COMPREHENSIVE ORGANOMETALLIC CHEMISTRY III

Editors-in-Chief
Robert H. Crabtree & D. Michael P. Mingos

Volume 10

APPLICATIONS II: TRANSITION METAL COMPOUNDS IN ORGANIC SYNTHESIS 1

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Elsevier Ltd.
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, UK

First edition 2007

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5.12 TECHNETIUM ORGANOMETALLICS

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Figure 17 of 12.03 ORGANOMETALLIC DERIVED METALS, COLLOIDS AND NANOPARTICLES

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Catalog Number: 2006934994

ISBN–13: 978-0-0804-4590-8
ISBN–10: 0-08-044590-X

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Printed and bound in Spain

06 07 08 09 10 10 9 8 7 6 5 4 3 2 1

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Preface

The availability of remarkably efficient search engines has made the access to the relevant literature and specific facts remarkably quick and efficient, but the information retrieved is not always refereed, checked or placed in its appropriate context. As Henry Kissinger [1] has remarked: "The computer has solved the problem of storing knowledge and making a vast amount of data available. Simultaneously, it exacts the price of shrinking [one's] perspective". In this latest edition of Comprehensive Organometallic Chemistry we have tried to engage the best minds in the field to sift the literature in their area of expertise and distill it down to produce a readable summary of the essential material. We have instructed them to be comprehensive in their coverage and authoritative in their approach and thereby maintain the standard and reputation of the original Comprehensive Organometallic Chemistry published in 1982 and the Second Edition published in 1995. Both editions were edited by Professors Abel, Stone and Wilkinson. This Third Edition of Comprehensive Organometallic Chemistry (COMC-III) builds on the two previous collections and incorporates a vast amount of new knowledge published since 1993, and simultaneously interprets the developments by providing general and significant insights by leading experts in the field.

Those seeking a structured entry into the impressive field of organometallic chemistry will find, either the desired information itself, or at least a reference to the primary or secondary literature that covers the point at issue. In the COMC tradition, we hope that this work will be useful not only to experts, but also to workers in allied fields who need to turn to organometallic chemistry to solve some pressing problem. With this in mind we have devoted the first volume to fundamental principles in order to provide a helpful entry into this important field for graduate students and scientists whose primary expertise lies in other areas. We also hope that readers will dip into this work and develop numerous research ideas or encounter a myriad of surprising results. Indeed, the applications of organometallic chemistry continue to expand at a prodigious rate, hence the significant increase in the number of volumes devoted to applications in COMC-III (to organic synthesis, to functional materials, as well as environmental and biological applications). Organic chemists have edited the volumes on organometallic chemistry towards organic synthesis now organized by reaction type so as to be readily accessible to the organic community. The new volume on applications covers a wide range of topics from optoelectronics to clusters and nano-particles.

The forthcoming availability of the whole COMC (1982), COMC-II (1995) through to COMC-III series in a web format will further enhance the utility of the series, providing a truly comprehensive data source and an unparalleled depth of coverage. With these new features, we hope that the combined efforts of the volume editors and individual authors have not only expanded the database of the subject but also provided an expanding perspective for all who use it.

The authors of individual chapters, the editors of the volumes and the editorial staff at Elsevier have made a tremendous effort to produce such a monumental work on schedule. We should like to thank them all most sincerely for working so well together as a team and we are sure the readership will appreciate the mature perspective and insight which they have provided for them.

D. Michael P. Mingos
Robert H. Crabtree

[1] H. Kissinger, Does America Need a Foreign Policy?, Touchstone Press, NY, 2002.

Editors-in-Chief

Michael Mingos has published more than 400 papers in inorganic, organometallic and theoretical chemistry. He has received numerous awards including the Corday-Morgan (1980) and Tilden (1988) Medals of the Royal Society of Chemistry, the Wilhelm Manchott Prize in 1995, the Michael Collins Award for Microwave Chemistry (1996) and was elected a Fellow of the Royal Society in 1992. He is perhaps best known for his contributions to the development of the polyhedral skeletal electron approach for inter-relating the structures of cluster compounds and their valence electron counts – commonly described as the Wade-Mingos Rules, but he has also developed a strong synthetic programme in cluster and supramolecular chemistry. He also pioneered the applications of microwave dielectric heating in organometallic and inorganic chemistry.

Currently Principal of St Edmund Hall and Professor of Inorganic Chemistry at the University of Oxford. He gained his B.Sc. at the University of Manchester (1965) and his D.Phil. at the University of Sussex (1968). He has subsequently received Honorary Degrees from both institutions. He became a Lecturer at Queen Mary College in 1971, before becoming a Fellow at Keble College, Oxford (1976–1992). In 1992 he moved to the Sir Edward Frankland BP Chair in Chemistry at Imperial College where he was elected Dean of the Royal College of Science in 1996.

His Editorial activities include a monograph on cluster chemistry, three undergraduate textbooks and many published reviews. He has also edited several books and served on the editorial boards of a number of international journals. He was Regional Editor of the Journal of Organometallic Chemistry from 1996 to 2006 and is Managing Editor of Structure and Bonding.

Robert Crabtree has published more than 400 papers in inorganic, organometallic and bioinorganic chemistry. He has received numerous awards including the Corday-Morgan (1984) Medal and Organometallic Chemistry Award (1991) of the Royal Society of Chemistry, the Organometallic Chemistry Award (1993) of the American Chemical Society, the Bailar Medal (U of Illinois, 2001), the Dow Lectureship (Berkeley, 2004) and the ISI Highly Cited Author Award (2000). He was chair of the inorganic chemistry division of the American Chemical Society (1998). He is known for the 'Crabtree catalyst' and contributions in alkane activation, sigma complexes, dihydrogen bonding, and molecular recognition in catalysis.

Currently Professor of Inorganic Chemistry at Yale University, he earned his B.A. at the University of Oxford (1970) and his D.Phil. at the University of Sussex (1973). He then became an Attaché de Recherche at the CNRS laboratory at Gif-sur-Yvette before moving to Yale in 1977.

His book, 'The Organometallic Chemistry of the Transition Metals' is now in its fourth edition (2005). He has also served on the editorial boards of a number of international journals. He was Regional Editor of the New Journal of Chemistry from 1998 to 2003 and is Editor-in-Chief of the 'Encyclopedia of Inorganic Chemistry'.

Editor of Volume 10

Iwao Ojima received his B.S., M.S., and Ph.D.(1973) degrees from the University of Tokyo, Japan. He joined the Sagami Institute of Chemical Research and held a position as Senior Research Fellow until 1983. He then joined the faculty at the Department of Chemistry, State University of New York at Stony Brook in 1983 and is currently a Distinguished Professor (1995–). He served as the Department Chairman from 1997 to 2003. He is the founding Director (2003) for the Institute of Chemical Biology and Drug Discovery (ICB&DD) at Stony Brook. He has a wide range of research interests in medicinal chemistry, including anticancer agents, anti-TB agents, antithrombotic agents, enzyme inhibitors, and medicinally relevant organofluorine compounds. He is a recipient of the Arthur C. Cope Scholar Award (1994) and the E. B. Hershberg Award (for important discovery of medicinally active substances) (2001) from the American Chemical Society; The Chemical Society of Japan Award (for distinguished achievements) (1999); and the Outstanding Inventor Award (2002) from the Research Foundation of the State University of New York. He is a Fellow of the J. S. Guggenheim Memorial Foundation, the American Association for the Advancement of Science, and The New York Academy of Sciences.

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10.01
C–H Bond Formation by Asymmetric and Stereoselective Hydrogenation

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10.01.1 Introduction

Molecular chirality plays a very important role in science and technology. The biological activities of pharmaceuticals, agrochemicals, fragrances, food additives, and other fine chemicals are often associated with their absolute configuration. The increasing demand in enantiomerically pure pharmaceuticals and fine chemicals has driven the development of asymmetric catalytic technologies.[1–21] Among all asymmetric catalytic methods, asymmetric hydrogenation, using small amounts of transition metal complexes and molecular hydrogen to reduce prochiral olefins, ketones, and imines, has become one of the most efficient, cost-effective, and environmental friendly

methods for constructing a vast array of structurally diverse chiral compounds.[3,3a–3m] During the past several decades, great attention has been devoted to discover new efficient catalysts for asymmetric hydrogenation, among them, transition metal complexes combined with chiral phosphorus ligands are the dominant choice of catalysts for asymmetric hydrogenation. This statement is fully confirmed by the award of the 2001 Nobel prize in chemistry to W. S. Knowles and R. Noyori for the work on asymmetric hydrogenation.

During the development of asymmetric hydrogenation in several decades, there are several remarkable significant milestones: (i) Kagan reported the first bisphosphine ligand, DIOP, for Rh-catalyzed asymmetric hydrogenation.[4,4a,4b] The successful applications of 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP) resulted in several significant directions for ligand design in asymmetric hydrogenation. Chelating bisphosphorus ligands could lead to superior enantioselectivity compared to monodentate phosphines. Additionally, P-chiral phosphorus ligands were not necessary for achieving high enantioselectivity, and ligands with backbone chirality can also provide excellent enantioselectivity in asymmetric hydrogenation. Furthermore, C_2-symmetry is an important structural feature for developing new efficient chiral ligands. (ii) Knowles made his significant discovery of a C_2-symmetric chelating bisphosphine ligand DIPAMP.[5,5a] Due to its high catalytic efficiency in Rh-catalyzed asymmetric hydrogenation of dehydroamino acids, DIPAMP was quickly employed in industrial production of L-dihydroxyphenylalanine (L-DOPA).[6] The success of practical synthesis of L-DOPA via asymmetric hydrogenation is a milestone work, and for this Knowles was awarded the Nobel prize in 2001.[3j] (iii) Noyori's research on 2,2-bis(diphenyl-phosphanyl)-1,1-binaphthyl (BINAP)–Ru catalysts for asymmetric hydrogenation opened up opportunities for efficient hydrogenations of a variety of substrates.[7,7a–7d] The initial application of Noyori's BINAP–Ru system was associated with olefin reduction, but soon the system was found to be useful for hydrogenation of ketones. Thus, a wide variety of prochiral olefin and ketone substrates were hydrogenated with excellent enantioselectivity. For this beautiful work, Noyori was awarded the Nobel prize in 2001. (iv) In the 1990s, significant progress was also achieved in Rh-catalyzed asymmetric hydrogenation with the introduction of some efficient chiral bisphosphorus ligands such as DuPhos and BPE developed by Burk *et al.*[8,8a] Excellent enantioselectivity was achieved in the hydrogenation of various functionalized olefins, and the scope of asymmetric hydrogenation was greatly expanded.

To date, following significant contributions by Knowles, Kagan, Noyori, and Burk *et al.*, thousands of efficient chiral phosphorus ligands with diverse structures have been developed for asymmetric hydrogenation, and their catalytic asymmetric hydrogenation processes have been extensively utilized in both academic research and industry.

10.01.2 Chiral Phosphorus Ligands

The development of efficient chiral phosphorus ligands has played an important role in the development of asymmetric hydrogenation. A historical overview of efficient chiral phosphorus ligands, to some extent, may also represent the development of asymmetric hydrogenation. Encouraged by the excellent results of many chiral ligands such as BINAP and DuPhos developed in 1980s and in the early 1990s, many research groups have devoted their efforts to designing and discovering new efficient chiral phosphorus ligands. Structural variation on the basis of known excellent ligand motif may often create new efficient chiral ligands. It may also help to understand the influence of structural, electronic, and steric properties of ligands to asymmetric hydrogenation. Although a number of new chiral ligands have been developed with great structural diversities, most of these ligands can be divided into several different categories.

10.01.2.1 Atropisomeric Biaryl Bisphosphine Ligands

In 1980, Noyori and Takaya reported an atropisomeric C_2-symmetric bisphosphine ligand—BINAP.[9] This ligand was first used in the Rh-catalyzed asymmetric hydrogenation of α-(acylamino)acrylic acids, and high selectivities were reported for some substrates.[10] However, the significant impact of BINAP in asymmetric hydrogenation did not gain too much attention until it was applied to the Ru chemistry. In 1986, Noyori and Takaya prepared a BINAP–Ru dicarboxylate complex for asymmetric hydrogenation of various functionalized olefins.[11,11a–11c] Subsequently, they discovered that the halogen-containing BINAP–Ru complexes were also efficient catalysts for asymmetric hydrogenation of a range of functionalized ketones.[12,12a–12c] In the mid–1990s, a major breakthrough was made on BINAP–Ru chemistry when Noyori discovered that the Ru–BINAP/diamine complexes are efficient catalysts for asymmetric hydrogenation of some unfunctionalized ketones.[13] This advancement addressed a long-standing challenging problem in asymmetric hydrogenation. Importantly, the catalytic system can selectively reduce ketones in the presence of carbon–carbon double or triple bonds.[14] Inspired by Noyori's work on the BINAP chemistry, other research groups developed many excellent atropisomeric biaryl bisphosphine ligands. For example, Miyashima reported 2,2′-bis(dicyclohexylphosphino)-6,6′-dimethyl-1,1′-biphenyl (BICHEP) ligand,

which was successfully applied to both Rh- and Ru-catalyzed asymmetric hydrogenation.[15,15a–15c] Schmid *et al.* reported biphenyl-2,2′-diyl-bis(dis(diipheylphosphine)) (BIPHEMP)[16] and MeO–2,2′-bis(diphenylphosphino)-6,6′-dimethoxy-1,1′-biphenyl (MeO–BIPHEP)[17] ligands, both of which were successfully applied to many Ru-catalyzed hydrogenations. Achiwa also developed several atropisomeric ligands such as BIMOP,[18] FUPMOP,[19] and 5,5′-dimethoxy-4,4′,6,6′-tetramethyl-2-diphenylphosphino-2′-dicyclohexylphosphino-1,1′-biphenyl (MOC–BIMOP).[20]

Modification of the electronic and steric properties of BINAP, BIPHEMP, and MeO–BIPHEP can lead to the development of new efficient atropisomeric ligands (Figure 1). In fact, Takaya has found that a modified BINAP

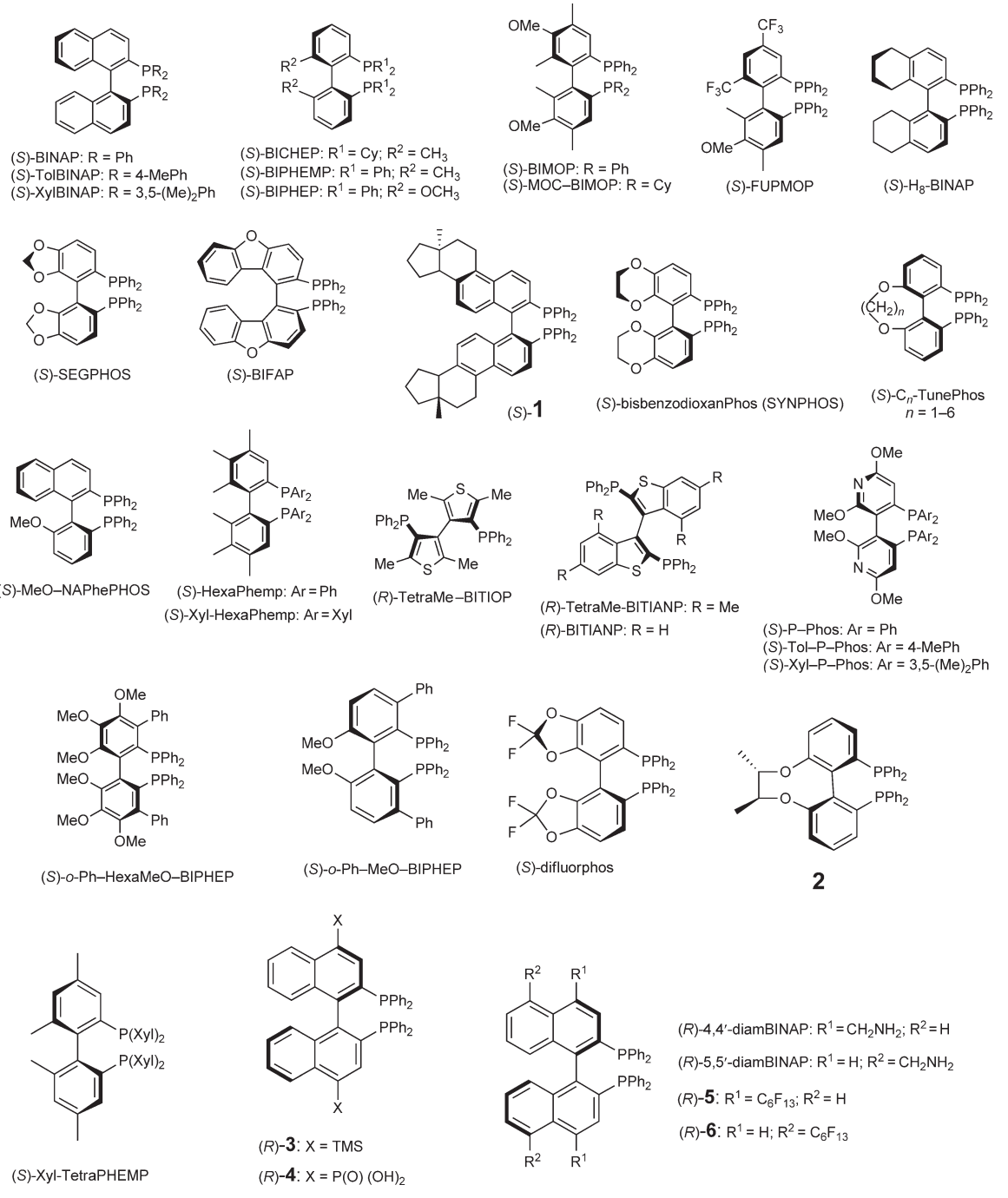


Figure 1 Atropisomeric biaryl bisphosphine ligands.

ligand, H_8–BINAP, provides better enantioselectivity than BINAP in Ru-catalyzed hydrogenation of unsaturated carboxylic acids.[21,21a] Mohr has developed a bis-steroidal bisphosphine **1**, which has shown similar catalytic results to BINAP in the Ru-catalyzed asymmetric hydrogenation.[22] Hiemstra has developed a dibenzofuran-based bisphosphine BIFAP, which has shown excellent enantioselectivity in Ru-catalyzed hydrogenation of methyl acetoacetate.[23] The dihedral angle of the biaryl backbone is expected to have strong influence on enantioselectivity. Another chiral biaryl bisphosphine ligand SEGPHOS was developed by Takasago International Corp. This ligand, which possesses a narrower dihedral angle than BINAP, has provided greater enantioselectivity than BINAP in the Ru-catalyzed hydrogenation of a wide variety of carbonyl compounds.[24,24a] Chan[25]and Genêt[25a,25b]have reported a closely related ligand bisbenzodioxanPhos (SYNPHOS) independently. In order to systematically investigate the influence of dihedral angle of biaryl ligands on enantioselectivity of reactions, Zhang has developed a series of TunePhos ligands with tunable dihedral angles. When the TunePhos ligands are applied to Ru-catalyzed asymmetric hydrogenation of β-keto esters, the obtained enantiomeric excess (ee) values fluctuate with the different dihedral angles of the TunePhos ligands.[26] C4-TunePhos shows comparable or superior enantioselectivity to BINAP in the Ru-catalyzed hydrogenation of β-keto esters. More applications of the TunePhos ligands have shown that different asymmetric catalytic reactions may require a different TunePhos ligand with a different dihedral angle. When TunePhos ligands were applied to the Ru-catalyzed hydrogenation of enol acetates, C2-TunePhos was the best ligand in terms of enantioselectivity.[27] However, C3-TunePhos provided the best stereoselectivities for synthesis of cyclic β-amino acids,[28] and hydrogenation of α-phthalimide ketones.[29] Genêt and Marinetti have developed a non-C_2-symmetric biaryl bisphosphine, MeO–NAPhePHOS, which has shown comparable results to C_2-symmetric biaryl bisphosphines in the Ru-catalyzed hydrogenation.[30]

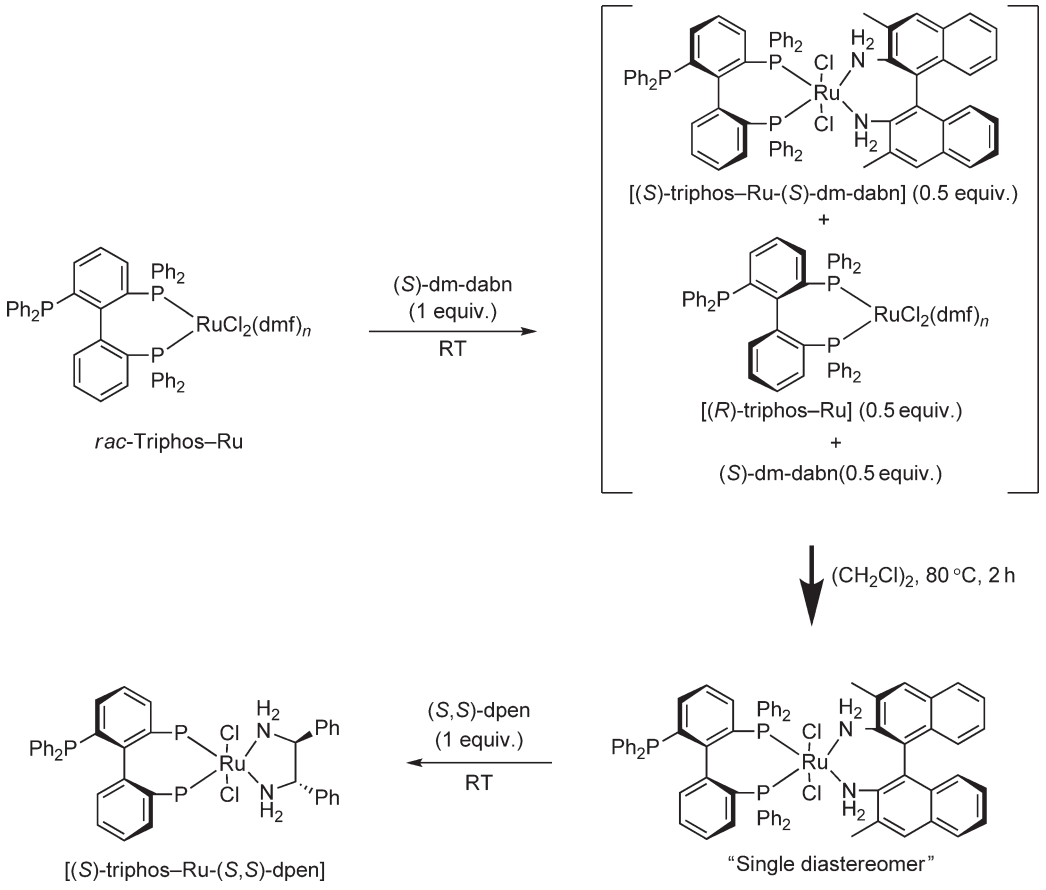
Structural variation of BINAP or MeO–BIPHEP can also be made on the aromatic rings of the biaryl backbone. For example, the aromatic rings can be replaced by five- or six-membered heteroaromatic rings. Sannicolò *et al.* have discovered a series of biheteroaryl bisphosphines such as BITIANP, TetraMe–BITIANP,[31,31a,31b] and TetraMe–BITIOP.[32] These ligands have shown comparably good results to BINAP in the Ru-catalyzed asymmetric hydrogenation. Chan has reported a dipyridylphosphine ligand P–Phos for Ru-catalyzed asymmetric hydrogenation, and high enantioselectivities and reactivities have been obtained for the hydrogenation of β-keto esters, α-arylacrylic acids, and simple ketones.[33,33a–33c]

An *ortho*-substituted BIPHEP ligand, *o*-Ph–HexaMeO–BIPHEP, has been developed by Zhang recently.[34] With two phenyl groups at *ortho*-positions of two diphenylphosphino groups, *o*-Ph–HexaMeO–BIPHEP is specially designed to restrict the rotation of the P–phenyl groups, which is considered to be detrimental for some enantioselective reactions. The design is effective when *o*-Ph–HexaMeO–BIPHEP is employed in the Rh-catalyzed asymmetric hydrogenation of cyclic enamides. While chiral ligands without *ortho*-substituents such as BINAP, BIPHEP, and HexaMeO–BIPHEP provide very poor selectivities, *o*-Ph–hexaMeO–BIPHEP shows excellent enantioselectivity for the hydrogenation of a series of cyclic enamides. Zhang also reported another *ortho*-substituted BIPHEP-type ligand—*o*-Ph–MeO–BIPHEP, which afforded excellent enantioselectivities in the hydrogenation of α-dehydroamino acids.[35]

Henschke and Casy prepared a biaryl bisphosphine ligand, HexaPhemp, which performed as good as or better than the corresponding BINAP ligands.[36] Dellis and Genêt have developed a new electrodeficient atropisomeric ligand based on an SEGPHOS backbone, difluorphos, which has a narrow dihedral angle and electrone-withdrawing substituents. The electrodeficiency was demonstrated to be crucial for high levels of enantioselectivities in the hydrogenation of some challenging β-keto esters.[37]

Chan has discovered a completely atropdiasteroselective synthesis of a biaryl diphosphine by asymmetric intramolecular Ullmann coupling or Fe(III)-promoted oxidative coupling. A chiral atropisomeric biaryl bisphosphine ligand **2** was synthesized through this central-to-axial chirality transfer.[38] Recently, a xylyl–biaryl bisphosphine ligand, Xyl-TetraPHEMP, was introduced by Moran, and is found to be effective for the Ru-catalyzed hydrogenation of aryl ketone.[39]

A family of tunable 4,4′-substituted BINAP was reported by Lin. 4,4′-$[SiMe_3]_2$–BINAP **3** and polar 4,4′-$[P(O)OH_2]_2$–BINAP **4** have shown high enantioselectivities (up to 99.6% ee) for the hydrogenation of a variety of β-aryl ketoesters.[40] 4,4′-$[SiMe_3]_2$–BINAP **3** is also effective for the asymmetric hydrogenation of α-phthalimide ketones and 1,3-diaryl diketones.[41] The 4,4′- bulky groups were proved to be responsible for the enhancement of enantioselectivity and diastereoselectivity in these reactions. Lemaire prepared 4,4′- or 5,5′-diamBINAP, with 4,4′- or 5,5′-diaminomethyl substituent, the hydrosoluble HBr salt of 4,4′- or 5,5′-diamBINAP–Ru complex afforded high enatioselectivity (>97% ee) for the water/organic solvent biphasic hydrogenation of β-keto esters.[42]Lemaire also reported 4,4′- or 5,5′-perfluoroalkylated BINAP, **5** and **6**, which showed the same activities and enantioselectivities as 4,4′- or 5,5′-diamBINAP for hydrogenation of β-keto esters.[43]



Scheme 1

As to most chiral atropisomeric ligand, resolution or asymmetric synthesis is requisite. Mikami developed a novel ligand-accelerated catalyst. The chirality of atropos, but achiral triphos ligand–Ru complex, can be controlled by chiral diamines. Using (*S*)-dm-dabn as controller, the single diastereomeric triphos–Ru complex was achieved through isomerization of (*R*)-triphos–Ru complex in dichloroethane at 80 °C (Scheme 1).[44]

Some derivatives have also been made on BINAP or BIPHEP ligands in order to make catalysts water soluble or recyclable (Figure 2). Literatures on homogeneous-supported catalysts in the field of asymmetric hydrogenation using BINAP derivatives have been recently reviewed.[45] Davis *et al.* have reported a sulfonated BINAP ligand, BINAP-4-SO_3Na, and found that its water-soluble Ru complex has comparable catalytic properties to the unmodified BINAP–Ru catalyst for hydrogenation of 2-acetamidoacrylic acid.[46,46a,46b] Schmid *et al.* have developed a water-soluble MeO–BIPHEP-type ligand, MeOBIPHEP–S. The ligand has the attachment of the sulfonato group at the *para*-position of each P–Phenyl groups to minimize the possible steric interactions of the sulfonato groups with the inner ligand sphere of a coordinated metal, and thus to retain the high enantioselectivity of the non-sulfonated catalyst. Indeed, MeOBIPHEP–S has shown similar high enantioselectivity and reacitivity to MeO–BIPHEP for Ru-catalyzed hydrogenation of unsaturated carboxylic acids.[47] By tethering BINAP with guanidine and PEG groups, Genêt has recently reported some recyclable BINAP ligands such as *Digm*-BINAP and PEG-*Am*-BINAP. The Ru catalysts of these ligands maintained high enantioselectivity after three or four times of recycles.[48] Many polymer-supported BINAP ligands have been developed. For instance, Bayston incorporated the BINAP framework onto an insoluble polymer (polystyrene). The resulting polymer-bound BINAP, after treatment with $[Ru(COD)(2\text{-methylallyl})_2]_2$ and HBr, provides high ee's in hydrogenation of β-keto esters and acrylic acids.[49] The polymer can be recycled as the catalyst for several times while high ee's are maintained. Noyori used the same polymer-bound BINAP to make a polymer-bound BINAP/diamine Ru catalyst, which has shown high ee's and turnover numbers for hydrogenation of simple ketones.[50] Chan has developed a

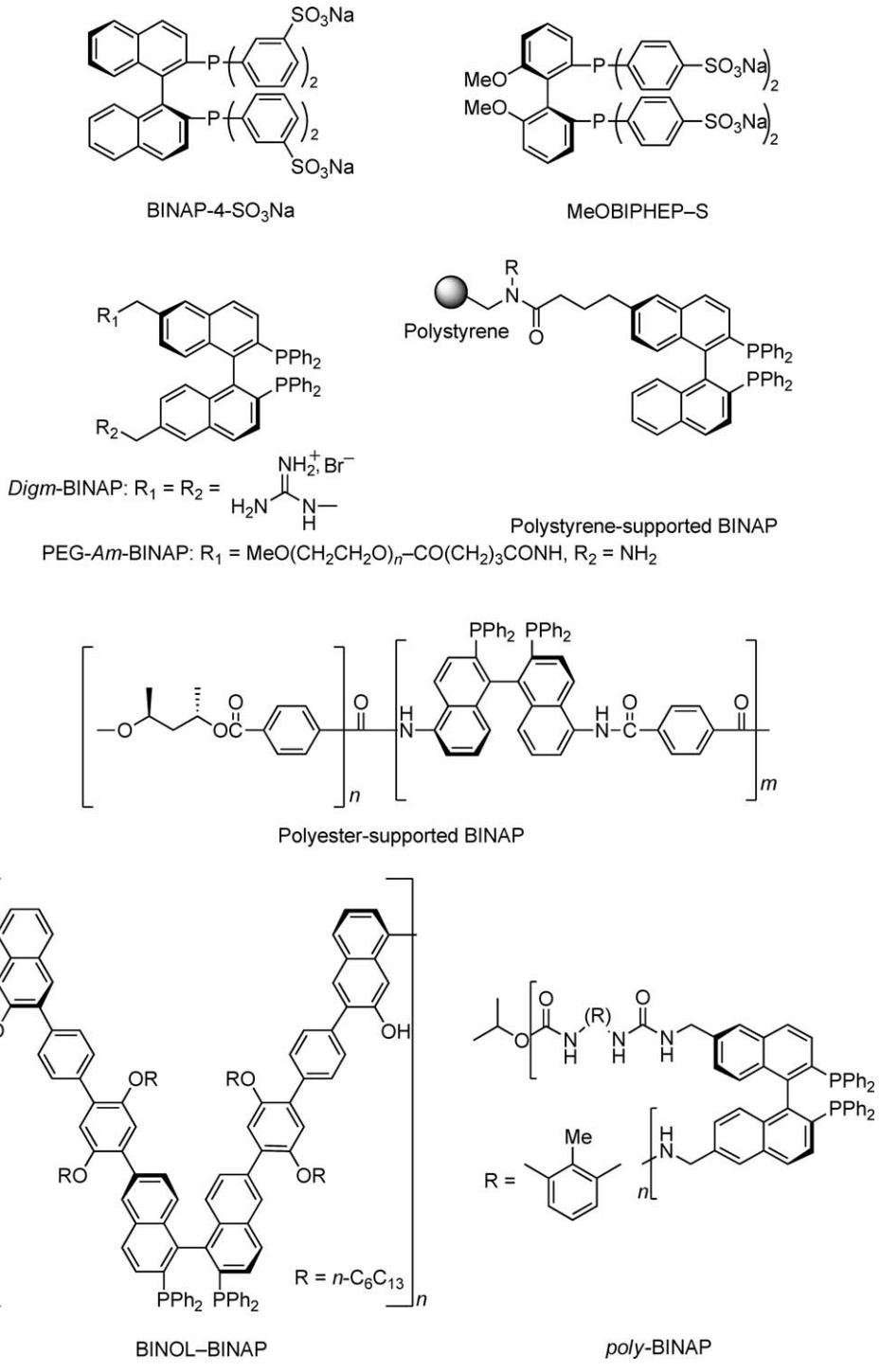


Figure 2 Water-soluble biphep ligand and polymer-supported BINAP ligands.

highly effective polyester-supported BINAP ligand through co-polymerization of chiral 5,5′-diaminoBINAP, chiral pentanediol, and terephthaloyl chloride.[51,51a] The ligand has been successfully applied repeatedly in the Ru-catalyzed asymmetric hydrogenation of 2-(6′-methoxy-2-naphthyl)acrylic acid. A dendrimer-supported BINAP ligand has also been reported.[52] Pu has developed several polymer-based chiral ligands such as poly(BINAP)

and BINOL–BINAP. These ligands have successfully been applied to the Rh-catalyzed hydrogenation of (*Z*)-methyl α-(benzamido)cinnamate and the Ru-catalyzed hydrogenation of simple ketones.[53,53a] Lemaire *et al.* have reported a polyNAP–Ru complex, which provides 99% ee in the hydrogenation of methyl acetoacetate even after four recycles of the catalyst.[54,54a,54b]

10.01.2.2 Chiral Bisphosphane Ligands through Modifications of DuPhos and BPE

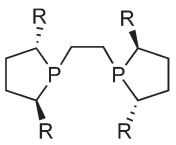
In the early 1990s, Burk introduced a new series of efficient chiral bisphospholane ligands BPE and DuPhos.[55,55a–55c] The invention of these ligands has expanded the scope of substrates in Rh-catalyzed enantioselective hydrogenation. For example, with Rh–DuPhos or Rh–BPE as catalysts, extremely high efficiencies have been observed in the asymmetric hydrogenation of α-(acylamino)acrylic acids, enamides, enol acetates, β-keto esters, unsaturated carboxylic acids, and itaconic acids.

Since Burk reported excellent results of DuPhos and BPE ligands in the asymmetric hydrogenation of functionalized olefins and ketones, many bisphosphanes have been developed based on the structural variations of DuPhos and BPE ligands (Figure 3). Börner,[56,56a] Zhang,[57,57a] and RajanBabu[58,58a] have independently reported a series of modified DuPhos and BPE ligands with ether, ketal, or hydroxyl groups at the 3- and 4-positions of the phospholanes. These types of ligands maintain the high efficiency of DuPhos or BPE in Rh-catalyzed hydrogenation. One major advantage of these ligands is their ease of preparation from D-manitol. The ligand with four hydroxy groups **10** also enabled the hydrogenation to be conducted in aqueous solution, and high enantioselectivities are maintained.[57,57a] Another water-soluble ligand BASPHOS **14**, bearing four hydroxyl groups, developed by Holz and Börner, also exhibits high efficiency for asymmetric hydrogenation in water.[59] Pilkington expanded the BPE ligand family to Ph–BPE. Ph–BPE exhibits enhanced activity and selectivity over the other BPE ligands in the Rh-catalyzed asymmetric hydrogenation of itaconate.[60] Structural variation can also be made on the backbone of DuPhos and BPE. Holz, and Börner have recently reported a bisphospholane ligand bearing a maleic anhydrid backbone, MalPhos, which has provided good enantioselectivities in the hydrogenation of (β-acylamino)acrylates.[61]

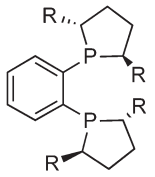
Merinetti reported a series of bisphosphetane ligands such as CnrPHOS and BPE-4 ligands.[62,62a–62e] Compared with their bisphospholane analogs DuPhos and BPE, CnrPHOS and BPE-4 provide only moderate enantioselectivity in the Rh-catalyzed hydrogenation of dehydroamino acid derivatives. However, these bisphosphetane ligands have shown excellent enantioselectivity in the Ru-catalyzed hydrogenation. Helmchen has developed a bisoxaphosphinane ligand **19** for the Rh-catalyzed hydrogenation of dehydroamino acid and itaconic acid derivatives and enantioselectivity up to 97% ee has been obtained.[63] Zhang has reported two bisdinaphthophosphepine analogs BINAPHANE and **20**, which have been applied to the Rh-catalyzed hydrogenation of enamides.[64,64a] These two ligands with axial chirality provide excellent enantioselectivity (up to 99% ee) for the hydrogenation of *E*/*Z*-isomeric mixtures of β-substituted arylenamides. A sterically bulky and conformationally rigid bisphosphane PennPhos has been developed by Zhang, and has different hydrogenation properties compared to other DuPhos-type ligands. With 2,6-lutidine and KBr as the additives, PennPhos has shown excellent enantioselectivity for the Rh-catalyzed hydrogenation of both aryl and alkyl methyl ketones.[65] The PennPhos ligand has also shown high efficiency in the Rh-catalyzed hydrogenation of cyclic enamides and cyclic enol acetates, which are difficult substrates for most DuPhos-type ligands.[66,66a] An improved BPE analog has been developed by incorporating two additional chiral carbon centers on the backbone. The matched (*R,R,R*)-1,2-bis(phospholano)cyclopentane **21** provides better enantioselectivity than BPE in the hydrogenation of dehydroamino acids.[67] By replacing one phospholane ring of Me–DuPhos with a disubstituted phosphino group, Saito *et al.* have developed a series of non-C_2-symmetric phosphine–phospholane ligands, UCAPs, for the Rh-catalyzed hydrogenation of enamides, and good enantioselectivities are obtained.[68]

10.01.2.3 Chiral Bisphosphane Ligands on the Modification of DIOP

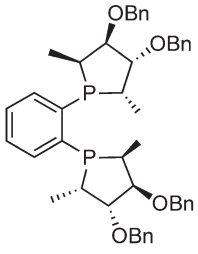
Kagan's pioneering work on the development of DIOP has brought significant impact on the design of new efficient chiral ligands for asymmetric hydrogenation.[4,4a,4b] However, DIOP itself only provides moderate to good enantioselectivity in the asymmetric hydrogenation of dehydroamino acid derivatives, and its applications to highly enantioselective asymmetric hydrogenation have rarely been disclosed. A possible reason is that the seven-membered chelate ring of DIOP metal complex is conformationally flexible. The conformational ambiguities in DIOP metal complexes as depicted in Figure 4 may be responsible for its moderate efficiency.



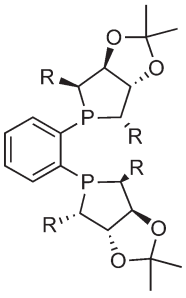
(*S*,*S*)-Me-BPE: R = Me
(*S*,*S*)-Et-BPE: R = Et
(*S*,*S*)-^{i}Pr-BPE: R = ^{i}Pr
(*S*,*S*)-Ph-BPE: R = Ph



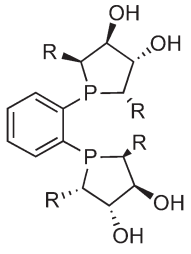
(S,*S*)-Me-DuPhos: R = Me
(*S*,*S*)-Et-DuPhos: R = Et
(*S*,*S*)-^{i}Pr-DuPhos: R = ^{i}Pr



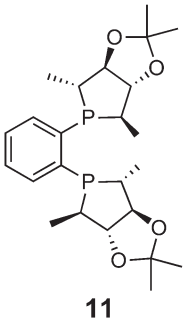
RoPHOS



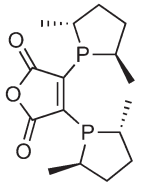
7: R = Me
8: R = Et



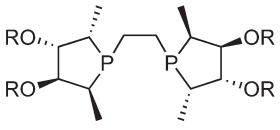
9: R = Me
10: R = Et



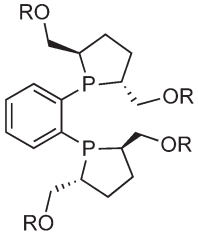
11



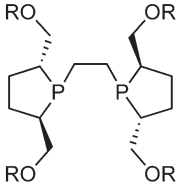
MalPHOS



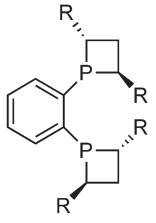
12: R = Bn
13: R = ^{t}Bu



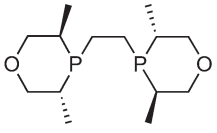
BASPHOS
14: R = H
15: R = Me
16: R = Bn



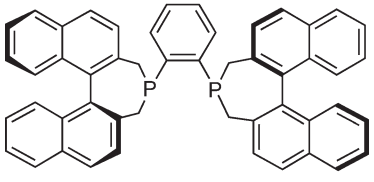
17: R = Me
18: R = Bn



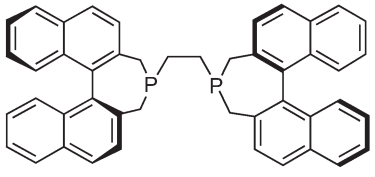
(*S*,*S*)-^{i}Pr-CnrPHOS: R = ^{i}Pr
(*S*,*S*)-Cy-CnrPHOS: R = Cy



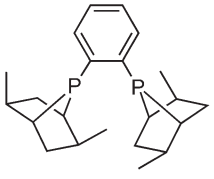
(*R*,*R*)-**19**



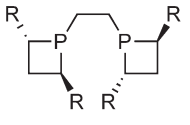
(*S*,*S*)-BINAPHANE



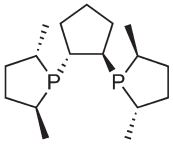
(*S*,*S*)-**20**



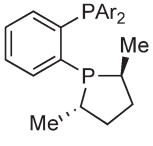
(*R*,*S*,*R*,*S*)-Me-PennPhos



(*S*,*S*)-^{i}Pr-BPE-4: R = ^{i}Pr
(*S*,*S*)-Cy-BPE-4: R = Cy



(*R*,*R*,*R*)-**21**



UCAPs
(*S*,*S*)-Me-UCAP-Ph: Ar = Ph
(*S*,*S*)-Me-UCAP-DTBM: Ar = 4-OMe-3,5-Me_2-$^{t}BuC_6H_2$
(*S*,*S*)-Me-UCAP-(1-Nap): Ar = 1-Np

Figure 3 Chiral bisphosphane ligands on the modifications of DuPhos and BPE.

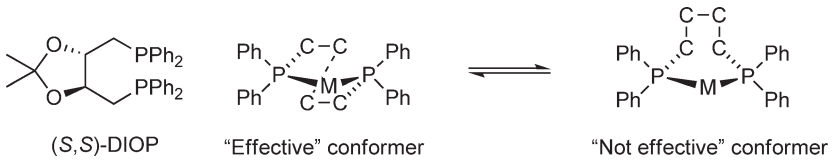


Figure 4 The conformational ambiguities in DIOP metal complexes.

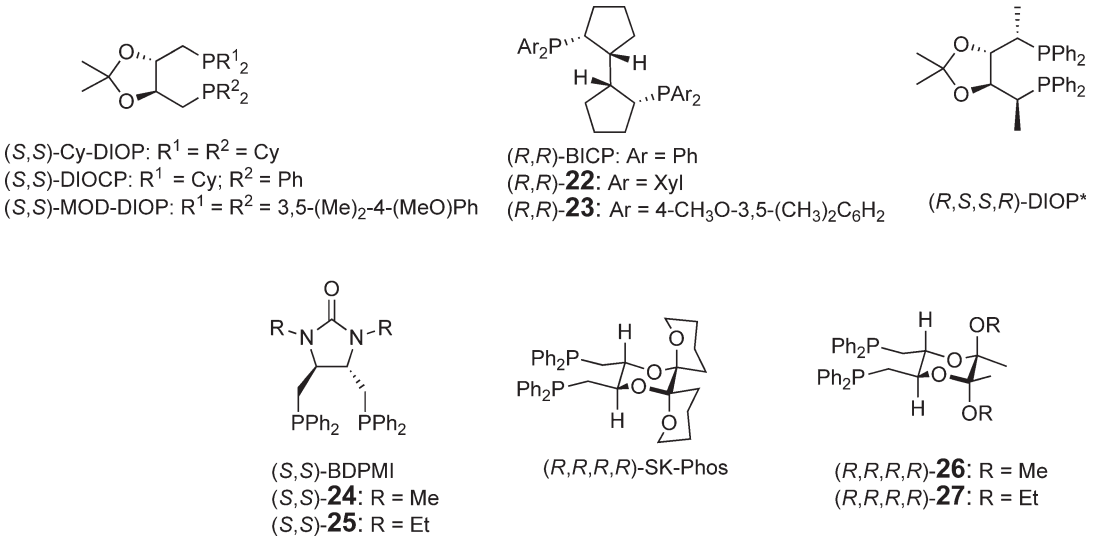


Figure 5 Chiral bisphosphane ligands on the modification of DIOP.

Achiwa successfully developed several modified DIOP ligands by varying the electronic and steric properties of DIOP. MOD–DIOP was applied in the asymmetric hydrogenation of itaconic acid derivatives and enantioselectivity up to 96% ee was obtained.[69,69a–69h]In order to rigidify the conformational flexibility of DIOP ligand, Zhang has introduced a rigid 1,4-diphosphane ligand BICP with two five-membered carbon rings on its backbone (Figure 5). BICP has been found to be efficient for the hydrogenation of α-dehydroamino acids, β-dehydroamino acids, arylenamides, and MOM-protected β-hydroxy enamides.[70,70a–70e] Genov introduced several BICP family ligands, **22** and **23**, and developed a new catalytic system comprising Ru–**22** or Ru–**23** complex in combination with non-chiral 2-(alkylthio)amine or 1,2-diamine and an alkoxide as a base for the highly enantioselective hydrogenation of aryl ketones.[71] Several rigidified DIOP-type ligands have been developed. Zhang[72,72a] and RajanBabu[73] have independently reported the development of DIOP* by introducing two alkyl substituents at the α-positions of the diphenylphosphine groups. It is found that the (*S,R,R,S*)-DIOP* provides excellent enantioselectivity in the Rh-catalyzed hydrogenation of arylenamides and MOM-protected β-hydroxy enamides.[72,72a] However, its isomeric ligand (*S,S,S,S*)-DIOP*, which was first synthesized by Kagan,[74] provides much lower enantioselectivity. It is believed that the two methyl groups of (*S,R,R,S*)-DIOP* orientate at pseudoequatorial positions in the "effective" conformer of the DIOP* metal complex, hence stabilizing the "effective" conformer to achieve high enantioselectivity. On the other hand, its isomeric ligand (*S,S,S,S*)-DIOP* has two methyl groups at pseudoaxial positions, which destabilize the "effective" conformer and lead to diminished ee's. Lee has developed 1,4-diphosphane-type ligands BDPMI with an imidazolidin-2-one backbone.[75,75a,75b] The *gauche*-steric interaction between the *N*-substituents and phosphanylmethyl group of the ligands may restrict the conformational flexibility of the seven-membered metal chelate ring. The BDPMI ligands have been successfully applied to the Rh-catalyzed hydrogenation of arylenamides and enantioselectivity up to 99% ee has been obtained. A series of 1,4-diphosphane ligands with a conformationally rigid 1,4-dioxane backbone such as ligands **26**, **27**, and SK-Phos have been developed by Zhang and found to be efficient (up to 99% ee) in the asymmetric hydrogenation of arylenamides and MOM-protected β-hydroxyl enamides.[76]

10.01.2.4 Chiral Ferrocene-based Bisphosphane Ligands

The initiatory successful ferrecene ligands include Hayashi–Kumada's ferrecene ligands BPPFA[77,77a,77b] and 1,1′-bis(diphenylphosphino)-2-(1-hydroxyethyl)ferrocene (BPPFOH),[78,78a] as well as Hayashi–Ito's ligand **28**.[79] Many excellent chiral ferrocene-based bisphosphane ligands with great structural variations have been developed recently (Figure 6). Ito has successfully developed a series of *trans*-chelating bisphosphane ligands TNF-related activation proteins (TRAPs), which have shown great capabilities for asymmetric hydrogenation.[80,80a–80g] EtTRAP and BuTRAP have shown excellent reactivity in the Rh-catalyzed hydrogenation of β,β-disubstituted

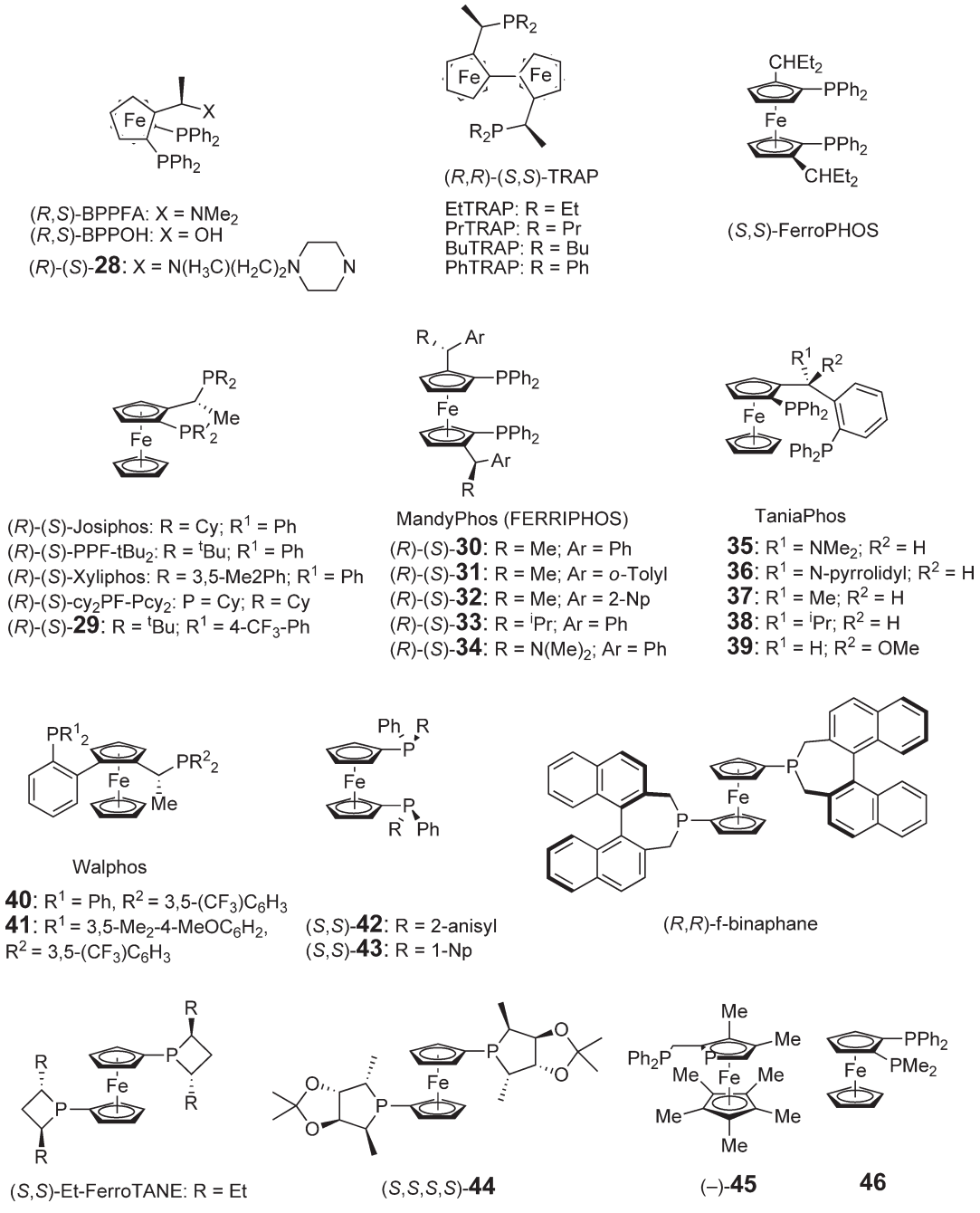


Figure 6 Chiral ferrocene-based bisphosphane ligands.

α-acetamidoacrylates, and enantioselectivity up to 88% ee has been obtained.[80a] The TRAP ligands have also been applied for the hydrogenation of β-oxy-α-acetamidoacrylates, and PrTRAP has been proved to be the best ligand in terms of enantioselectivity.[80d] In the presence of 10 mol. % of Et_3N or $CsCO_3$, a PhTRAP–Rh complex is able to hydrogenate *N*-acetyl-2-substituted indoline[80f] and *N*-tosyl-3-substituted indoline[80g] with high ee's.

Togni and Spindler have reported a class of non-C_2-symmetrical ferrocene-based bisphosphanes: Josiphos-type ligands.[81] Josiphos has been found to be effective for the Rh-catalyzed hydrogenation of α-acetamidocinnamate, dimethyl itaconate, and β-keto esters. Some excellent industrial applications have been realized with the Josiphos-type ligands. For example, PPF–*t*-Bu_2, a Josiphos-type ligand with di(*tert*-butyl)phosphino group, has been applied to the asymmetric hydrogenation for the commercial synthesis of (+)-biotin.[82] Another notable example is the application of XyliPhos to Ir-catalyzed hydrogenation of an imine for the synthesis of the herbicide (S)-metolachlor.[83,83a] Weissensteiner and Spindler have also reported a class of rigidified Josiphos-type ligands by incorporating a mono- or heteroannular bridge in the structure.[84,84a] However, their applications to the asymmetric hydrogenation are less efficient than the original Josiphos-type ligands. Haiso *et al.* have discovered a high yielding and highly enantioselective hydrogenation of unprotected enamine ester and amides using Rh–PPF–*t*-Bu_2 or Rh–**29** complex as catalyst.[85]

A C_2-symmetric bisphosphane FerroPhos has been developed by Kang and is found to be efficient for the Rh-catalyzed hydrogenation of α-dehydroamino acid derivatives.[86,86a] Knochel has independently reported a class of FERRIPHOS (MandyPhos) with similar structural features.[87,87a,87b] All these ligands have provided excellent enantioselectivities in the asymmetric hydrogenation of α-dehydroamino acids.

A series of non-C_2-symmetrical ferrocene-based 1,5-diphosphane ligands (TaniaPhos) has been developed by Knochel.[88,88a,88b] The ligands have been effectively used in Rh- or Ru-catalyzed asymmetric hydrogenations. The ligand **39**, which has an MeO group at the chiral carbon center, has shown excellent applications in the hydrogenation of several olefin and ketone substrates.[89] Weissensteiner and Spindler have reported a series of structurally different ferrocene-based 1,5-diphosphane ligands, WalPhos, which have shown good results in some Ru-catalyzed hydrogenations.[90]

Mezzetti[91] and Leeuwen/Widhal[92] have independently reported P-chiral ferrocenyl bisphosphines **42** and **43**. These two ligands have shown excellent enantioselectivity (up to 99% ee) for the asymmetric hydrogenation of α-dehydroamino acid derivatives.

Synthesis of chiral 1,1′-bis(phosphetano)ferrocenes (FerroTANE) has been independently reported by Marinetti[93] and Burk.[94] Et-FerroTANE has been successfully applied by Burk for the Rh-catalyzed hydrogenation of itaconates. It has also been suuccessfully employed in the hydrogenation of (*E*)-(β-acylamino)acrylate.[95] Zhang has reported a 1,1′-bis(phospholanyl)ferrocene ligand **44** with ketal substituents at the 3,4-positions. The ligand has shown excellent enantioselectivity in the hydrogenation of α-dehydroamino acid derivatives.[96] The ketal groups of the ligand are important for achieving high enantioselectivity, since the corresponding ligand without ketal groups only provides moderate ee's.[97] Zhang has also developed a 1,1′-bis(dinaphthophosphepinyl)ferrocene ligand, f-binaphane, which has been successfully applied to the Ir-catalyzed hydrogenation of acyclic arylimines.[98]

Fu has reported a planar-chiral bisphosphorus ligand **45** with a phosphaferrocene backbone. The ligand has provided enantioselectivity up to 96% ee in the hydrogenation of α-dehydroamino acid derivatives.[99] Another planar-chiral ferrocene-based bisphosphorus ligand **46** has been reported by Kagan recently and enantioselectivity up to 95% ee has been obtained in the reduction of dimethyl itaconate.[100]

10.01.2.5 P-chiral Bisphosphane Ligands

Knowles made his significant discovery of a C_2-symmetric chelating bisphosphine ligand DIPAMP.[5,5a] Due to its high catalytic efficiency in the Rh-catalyzed asymmetric hydrogenation of dehydroamino acids, the first P-chiral bisphosphane DIPAMP was quickly employed in the industrial production of L-DOPA.[6] However, the discovery of new efficient P-chiral bisphosphanes was slow partly because of the difficulties in ligand synthesis. It is not until Imamoto discovered a series of efficient P-chiral ligands such as BisP* that the development of P-chiral phosphorus ligands regains much attention (Figure 7).[101,101a,101b] The BisP* ligands have shown great activities and enantioselectivities in the hydrogenation of α-dehydroamino acids, enamides,[102] (*E*)-β-(acylamino)-acrylates,[103] and α,β-unsaturated-α-acyloxyphosphonates.[104] Mechanistic studies on asymmetric hydrogenation with ^{t}Bu–BisP*, as the ligand, by Gridnev and Imamoto illustrate that the Rh-catalyzed hydrogenation appears to proceed through a unique mechanism with this electron-rich phosphorus ligand. A dihydride pathway[105,105a,105b] is suggested, which is different from the classic unsaturated pathway[106,106a–106e,107,107a–107g] proposed by Halpern and Brown. In addition to Bisp*, several other P-chiral bisphosphanes such as MiniPhos,[108] 1,2-bis(isopropylmethylphosphino)benzene

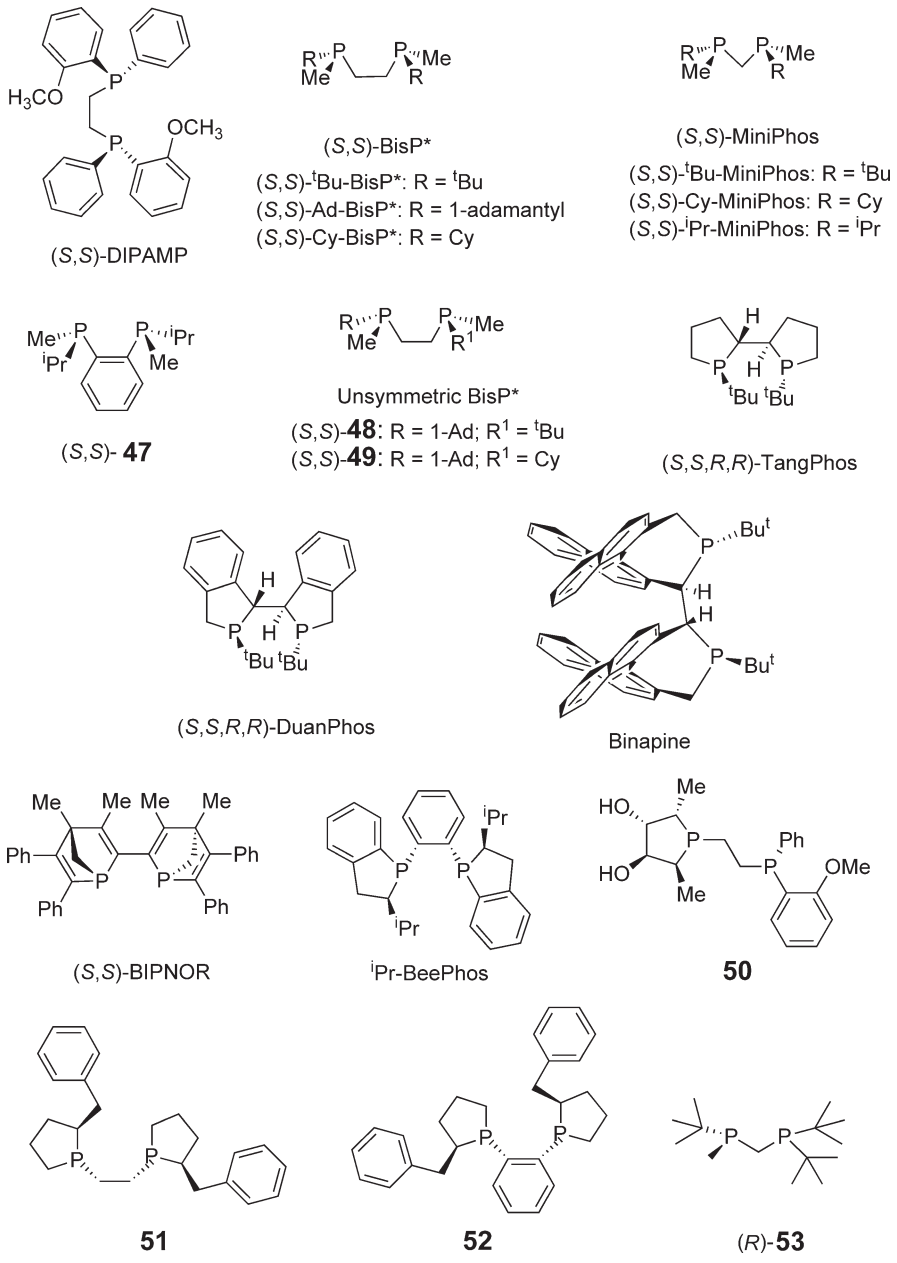


Figure 7 P-Chiral bisphosphane ligands.

47,[109] and unsymmetrical P-chiral BisP* (such as 48 and 49)[110,110a] have also been developed by Imamoto. Imamoto has developed P-chirogenic trialkylphosphonium salt from BISP* and MiniPhos. These air- stable salts were conveniently applied to the Rh-catalyzed asymmetric hydrogenation of enamides.[111] Zhang has recently reported a series of rigid P-chiral bisphospholane ligands, TangPhos,[112] BINAPINE,[113]and DuanPhos (Figure 7).[114] TangPhos has been found to be very efficient in the Rh-catalyzed hydrogenation of a variety of functionalized olefins such as α-dehydroamino acids, α-arylenamides, β-(acylamino)acrylates,[115] itaconic acids, and enol acetates.[116] The BINAPINE ligand on the other hand demonstrates excellent enantioselectivity and reactivity, with up to 10,000 turnover numbers, for the asymmetric hydrogenation of (*Z*)-aryl(β-acylamino)acrylates.[113] Using (−)-sparteine as a chirality-inducing base, only one enantiomer of TangPhos is readily accessible. In the same manner, another P-chiral ligand BisP* is also only available in one enantiomeric form. Both enantiomeric forms of DuanPhos are readily

available through resolution, and increased conformational rigidity makes DuanPhos a more enantioselective ligand overall than TangPhos for the enantioselective hydrogenation of various functionalized alkenes.[114] Recently, DuanPhos was found effective for the highly enantioselective hydrogenation of β-secondary amino ketones.[117] Mathey has reported a bisphosphane ligand BIPNOR, which contains two chiral bridgehead phosphorus centers.[118,118a] BIPNOR has shown high enantioselectivity in the hydrogenation of α-(acetomido)cinnamic acids and itaconic acids. Saito has reported a P-chiral bisphospholane ligand ^{i}Pr–BeePHOS, which has provided high enantioselectivity in the hydrogenation of enamide.[119] A hybrid P-chiral bisphosphane reported by Brown[120] has shown high selectivity for the asymmetric hydrogenation of itaconic acids (up to 95% ee).

Hoge introduced two P-chirogenic bisphospholane ligands, **51** and **52**, which have been applied to the hydrogenation of α-and β-acetamido dehydroamino acids with good enantioselectivities.[121,122] Recently, a three-hindered quadrant P-chirogenic ligand (*R*)-**53** was also reported by Hoge (Figure 7).[123] Using (*R*)-**53** –Rh as catalyst, both (*E*)- and (*Z*)-(β-acylamino)acrylates have been hydrogenated with high enantioselectivities.[124]

10.01.2.6 Other Bisphosphane Ligands

Some other efficient chiral bisphosphane ligands have been listed in Figure 8. Those include Achiwa's BPPM,[125] and a series of modified BPPM ligands such as BCPM and MOD–BPPM;[126,126a–126j] some excellent chiral

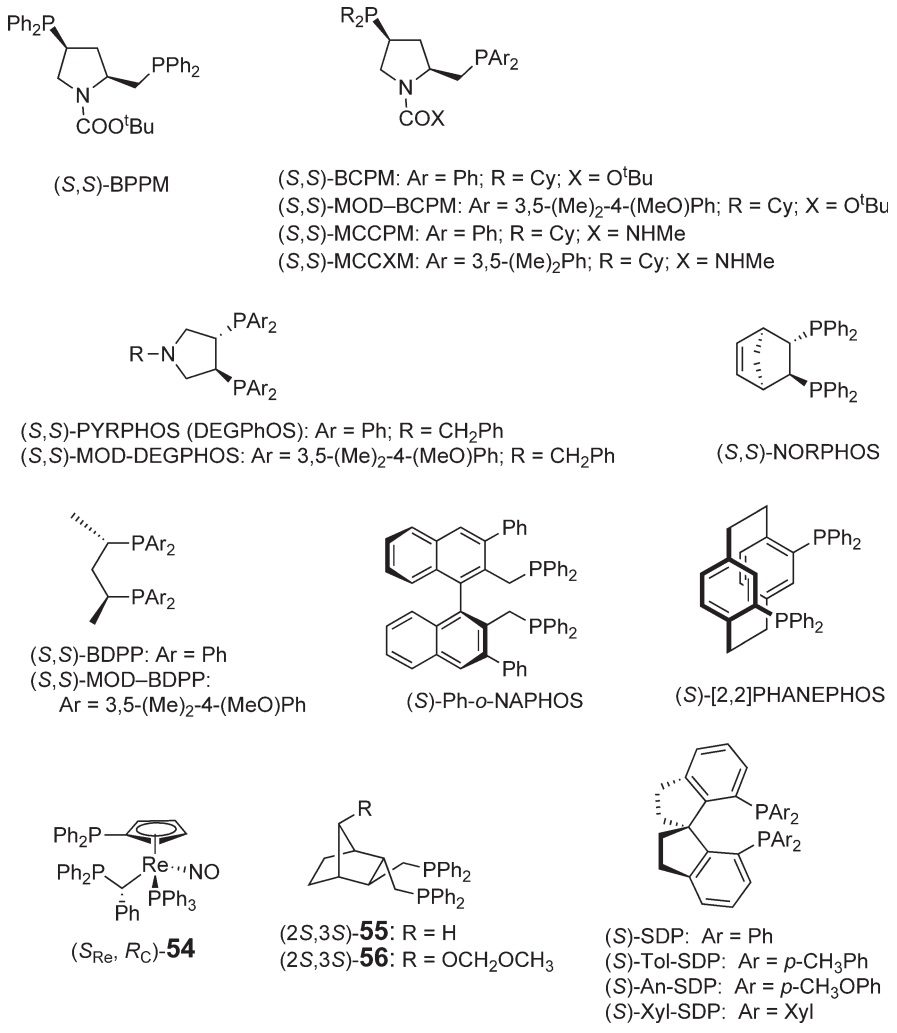


Figure 8 Other bisphosphane ligands.

1,2-bisphosphane ligands such as NORPHOS[127] and PYRPHOS (DEGUPHOS);[128,128a,128b] 1,3-bisphosphine ligands such as BDPP (SKEWPHOS).[129,129a,129b] Pye and Rossen have developed a planar-chiral bisphosphine ligand, [2.2]PHANEPHOS, based on a *para*-cyclophane backbone.[130,130a,130b] The ligand has shown excellent enantioselectivity in the Rh- or Ru-catalyzed hydrogenations. An *ortho*-phenyl-substituted NAPHOS ligand, Ph-*o*-NAPHOS, has been applied successfully to the Rh-catalyzed hydrogenation of α-dehydroamino acid derivatives.[131] Compared to NAPHOS, Ph-*o*-NAPHOS has a more rigid structure and provides higher enantioselectivities. A chiral bisphosphine ligand **54**, bearing a rhenium stereocenter in the backbone, has recently reported by Gladysz, and the ligand has provided good selectivity in the Rh-catalyzed hydrogenation of dehydroamino acid derivatives.[132] The chiral norbornane diphosphine ligands, **55** and **56**, were reported by Morimoto, and applied to the Rh-catalyed asymmetric hydrogenation.[133] Zhou reported a family of chiral *spiro*-bisphosphine ligand, SDP, containing 1,1′-*spiro*-biindane as a new scaffold, which are effective for the hydrogenation of simple ketones (Figure 8).[134]

10.01.2.7 Bisphosphinite, Bisphosphonite, and Bisphosphite Ligands

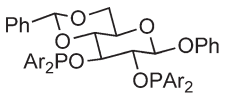
Compared to the rapid development of chiral bisphosphane ligands, the discovery of excellent bisphosphinites, bisphosphonites, or bisphosphites for asymmetric hydrogenation has been relatively slow due to their greater conformational flexibility and instability. Nevertheless, some efficient ligands have been discovered with rigid backbones (Figure 9). Selke[135,135a–135d] and RajanBabu[136,136a] have developed a series of bisphosphinites based on a sugar backbone. The phosphinite ligands derived from D-glucose have shown excellent enantioselectivity in the hydrogenation of α-dehydroamino acid derivatives. A major electronic effect has been identified in this system. High enantioselectivities are obtained with electron-rich bisphosphinites, while electron-deficient bisphosphinites provide much lower selectivities. Chan and Jiang have reported a rigid spirocyclic bisphosphinite ligand *spiro*-OP, which has been applied to the hydrogenation of α-dehydroamino acid derivatives.[137,137a] A bisphosphinite ligand DIMOP derived from D-manitol has also been developed by Chan and enantioselectivity up to 97% ee has been obtained in the hydrogenation of α-dehydroamino acids.[138] A water-soluble Rh complex associated with a bisphosphinite ligand **60** derived from a β,β-trehalose backbone is effective for the hydrogenation of α-dehydroamino acid derivatives in water or an aqueous/organic biphasic medium (up to 99.9% ee).[139] In order to rigidify the flexible structure of BINAPO, Zhang has recently reported a series of *o*-BINAPO ligands with substituents at 3,3′-positions of the binaphthyl group. Ph-*o*-BINAPO with phenyl groups at the 3,3′-positions is an efficient ligand for the hydrogenation of α-dehydroamino acid derivatives.[131] The *o*-BINAPO ligands have also been applied to the Ru-catalyzed hydrogenation of β-aryl-β-(acylamino)acrylates and enantioselectivity up to 99% ee has been obtained.[140]

Some excellent bisphosphonite ligands have also been developed. For example, Reetz has developed a binaphthol-derived ferrocene-based bisphosphonite ligand **61**, which has shown excellent reactivities and enantioselectivities in the Rh-catalyzed hydrogenation of itaconates and α-dehydroamino acid derivatives.[141] Zanotti-Gerosa developed a bisphosphonite ligand **62** on the basis of a *para*-cyclophane backbone. The ligand has been successfully applied to the asymmetric hydrogenation of α-dehydroamino acid derivatives and enantioselectivity up to 99% ee has been obtained. [142]

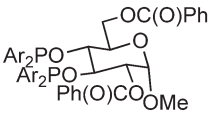
A few efficient bisphosphite ligands have been used for the asymmetric hydrogenation of itaconates or α-dehydroamino acid derivatives. Reetz has developed a series of C_2-symmetric bisphosphite ligands such as **63** based on the structure of 1,4:3,6-dianhydro-D-mannite.[143] The ligands have shown excellent enantioselectivities and reactivities in the asymmetric hydrogenation of itaconates. A series of non-C_2-symmetric bisphosphite ligands derived from D-glucose have been reported by Diéguez.[144] Ligand **64** has provided high enantioselectivity for the asymmetric hydrogenation of α-dehydroamino acid derivatives. Evans reported chiral mixed phosphorus/sulfur ligands, **65** and **66**. These ligands have shown high enantioselectivities for the Rh-catalyzed hydrogenation of α-dehydroamino acid derivatives (Figure 9).[145] Börner prepared air-stable enantiopure pyrophosphite ligand **67**, and applied it to the Rh-catalyzed hydrogenation.[146] Recently, Zhang introduced phosphine–phosphite ligand *o*-BINAPHOS, and phosphine–phosphinite ligand *o*-BIPNITE based on 3-phenyl BINOL. These ligands show excellent enantioselectivities for the Rh-hydrogenation of α-dehydroamino acid derivatives (Figure 9).[147]

10.01.2.8 Chelating Aminophosphine, Amidophosphine, and Phosphoramidites

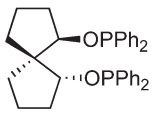
Several efficient amidophosphine– and aminophosphine–phosphinite ligands have been reported by Agbossou and Carpentier.[148,148a–148g] Amidophosphine–phosphinite ligands (*S*)-Cy,Cy-oxoProNOP and (*S*)-Cp,Cp-oxoProNOP



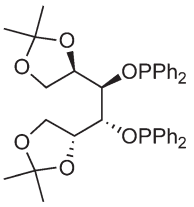
57: Ar = 3,5-$(TMS)_2$Ph
58: Ar = 3,5-$(Me)_2$Ph



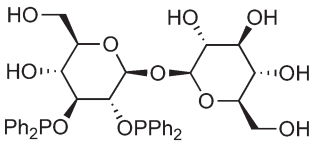
59: Ar = 3,5-$(Me)_2$Ph



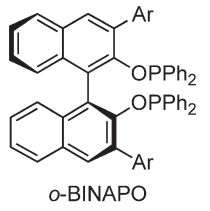
(*R*)-*spiro*-OP



DIMOP

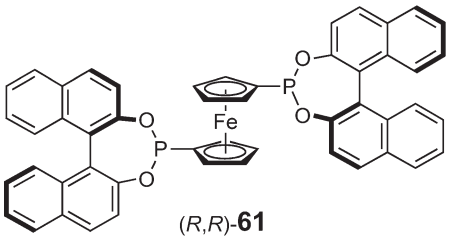


60

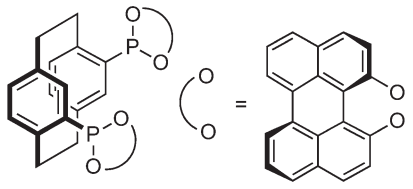


o-BINAPO

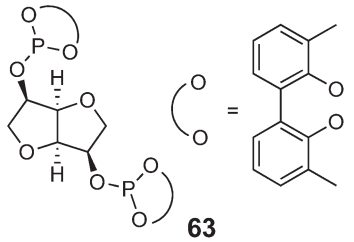
(*S*)-Ph-*o*-BINAPO: Ar = Ph
(*S*)-Xylyl-*o*-BINAPO: Ar = 3,5-Me_2Ph



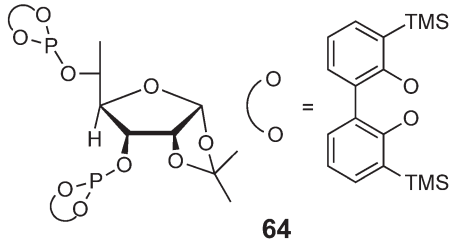
(*R*,*R*)-**61**



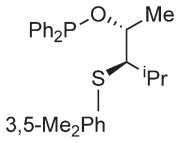
(*S*)-(*R*)-**62**



63



64



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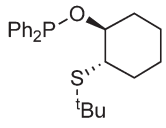

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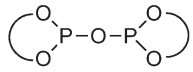
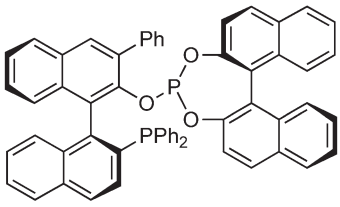
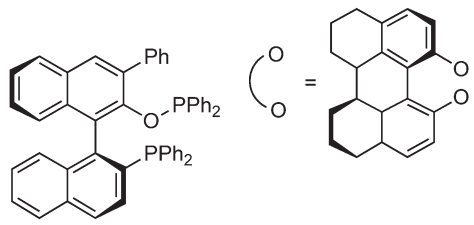


67



(*S*,*R*)-*o*-BINAPHOS



(*S*)-*o*-BIPNITE

Figure 9 Bisphosphinite, bisphosphonite, and bisphosphite ligands.

have been demonstrated to be efficient ligands for the Rh-catalyzed hydrogenation of dihydro-4,4-dimethyl-2,3-furandione, and enantioselectivity up to 98% ee has been obtained. Aminophosphine–phosphinite ligands (*S*)-Cp,Cp-IndoNOP and (*S*,2*S*)-Cr(CO)$_3$-Cp,Cp-IndoNOP are also effective for this substrate. The two ligands have also provided high enantioselectivity for the hydrogenation of *N*-benzoylformamide and 2-(*N*,*N*-dimethyl)aminoacetophenone. An aminophosphine–phosphinite ligand PINDOPHOS derived from pindolol has been applied for the asymmetric hydrogenation of α-dehydroamino acid derivatives and enantioselectivity up to 95% ee is obtained.[149] Another aminophosphine–phosphinite DPAMPP has been reported by Jiang and Mi recently,[150] and the ligand has shown excellent enantioselectivity for the hydrogenation of a series of α-dehydroamino acid derivatives. Some bisaminophosphine ligands such as H8-BDPAB and BDPAB have been reported by Chan and have been successfully applied for the hydrogenation of arylenamides.[151,151a] Xyl-BDPAB is also found to be an efficient ligand for the asymmetric hydrogenation of α-dehydroamino acid derivatives.[152] A series of mixed phosphine–phosphoramidite ligands QUINAPHOS, developed by Leitner, is efficient for the Rh-catalyzed hydrogenation of itaconic acid and α-dehydroamino acid derivatives.[153] A phosphite–phosphoroamidite ligand **68** developed by Diéguez is also effective for the asymmetric hydrogenation of α-dehydroamino acid derivatives.[154] Boaz has developed a family of ferrocene-based phosphine–aminophosphine ligands, BoPhoz. These air-stable ligands have shown excellent reactivities and selectivities for the hydrogenation of α-dehydroamino acid derivatives and itaconic acids.[155,155a] Zheng[156,156a] and Chan[157] have reported the modified BoPhos-type ligands **74** and **75**, respectively, which have shown excellent enantioselectivities (up to 99% ee) in the asymmetric hydrogenation of enamides, itaconates, α- and β-dehydroamino acid derivatives (Figure 10).

10.01.2.9 Chiral Monophosphorus Ligands

While more and more efficient chelating bisphosphorus ligands have been discovered, the development of monophosphorus ligands for asymmetric hydrogenation is slow.[158] However, this does not mean that monophosphorus ligands cannot be as effective as chelating bisphosphorus ligands for asymmetric hydrogenation. Recently, some monophosphorus ligands have been found to be very efficient for Rh-catalyzed asymmetric hydrogenation (Figure 11).[159,159a] Orpen and Pringle have reported a series of biarylphosphonite ligands, such as **76**, and have achieved up to 92% ee for the asymmetric hydrogenation of methyl (2-acetamide)acrylate.[160,160a] Wills also reported a BINOL-derived monophosphonite ligand **77**. Using Ru–**77**–Dpen complex as catalyst, high enantioselectivities (up to 99% ee) were achieved for the hydrogenation of simple ketones.[161] Reetz has developed a series of monophosphite ligands such as **78**–**80**, which have shown excellent reactivities and enantioselectivities for the hydrogenation of dimethyl itaconate.[162,162a] Helmchen prepared a BINOL-derived monophosphite ligands **81**, which is also very effective for hydrogenation of itaconates.[163] De Vries and Feringa has developed a phosphoramidite ligand named as MonoPhos, which has shown >99% ee in the asymmetric hydrogenation of dehydroamino acid derivatives.[164] The ligand is also effective for the asymmetric hydrogenation of arylenamides.[165,165a] Two similar phosphoramidite ligands **82** and **83** have shown excellent enantioseletivities in the Rh-catalyzed hydrogenation of (β-acylamino)acrylates.[166] Recently, Chan reported that a modified MonoPhos **84**, Rh–**84** complex provided high enantioselectivities (up to 99.9% ee) for the hydrogenation of enamides and α-dehydroamino acids.[167] Sarting from H$_8$–BINOL, Bakos has prepared a monodentate phosphite **85**. Using Rh–**85** complex, high reactivities and enantioselectivities (up to 40,000 tons, 96.9% ee) have been achieved for the hydrogenation of dimethyl itaconate.[168] Chan also reported an H$_8$–BINOL-based monodentate phosphoramidite, H$_8$–Monophos, which proved to be efficient for the asymmetric hydrogenation of enamides.[169] Some atropisomeric biphenyl-based monodentate phosphite ligands, for example, Ojima's **86**[170] and Chan's **87**,[171] were synthesized and applied to the asymmetric hydrogenation of dimethyl itaconate with very high efficiency. Chen *et al*. have developed a carbohydrate-derived monodentate phosphite **88**, which exhibited good enantioselectivities for the hydrogenation of enamides and dimethyl itaconates.[172] Zhou reported a monophosphoramidite ligand SIPHOS on the basis of a chiral 1,1′-*spiro*-biindane-7,7′-diol. Enantioselectivity up to 99% ee has been obtained in the asymmetric hydrogenation of α-dehydroamino acids, arylenamides, and itaconates.[173,173a,173b] Zhou also developed a monodentate *spiro*-phosphonite **89** derived from chiral SPINOL, which is efficient for the Rh-catalyzed hydrogenation of α- and β-dehydroamino acids.[174] Recently, Zhang has developed monodentate *spiro*-phosphoramidite ligand **90** from 9,9′-*spiro*-bixanthene-1,1′-diol.[175] Helmchen has reported a secondary monodentate phosphane **91**, which is also very effective for the hydrogenation of itaconates.[63]

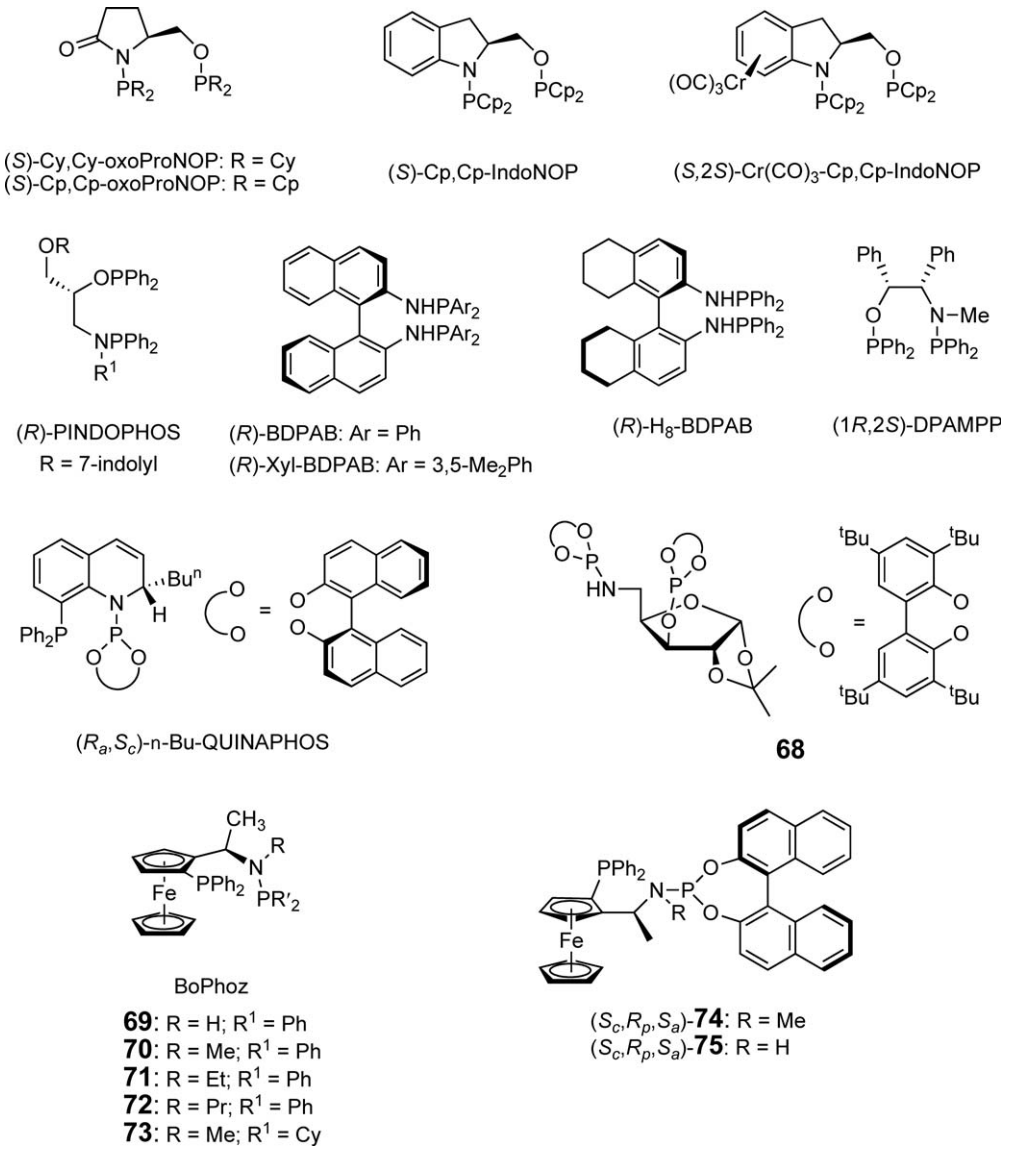


Figure 10 Chelating aminophosphine, amidophosphine, and phosphoramidites.

10.01.2.10 Chiral N, P Ligands

Although the Ir complex $[Ir(COD)(Py)PCy_3]^+PF_6^-$ was reported by Crabtree[176] as a highly active non-chiral catalyst for the hydrogenation of tri- and tetrasubstituted olefins over 20 years ago, the development of efficient chiral N, P ligands for the Ir-catalyzed asymmetric hydrogenation is slow until a set of Phox[177,177a–177c] ligands was applied by Pfaltz for the Ir-catalyzed hydrogenation of simple olefins (Figure 12).[178,178a,178b] The successful applications of Phox–Ir complexes to the asymmetric hydrogenation of unfunctionalized olefins have driven Pfaltz and his co-workers to develop several efficient N, P ligands such as phosphite–oxazoline **93**,[179] PyrPHOX,[180] phosphino–imidazolines (PHIM ligands),[181] phosphinite–oxazolines **96**∼**98**,[182] threonine-derived phosphinite–oxazolines **99** and **100**,[183] SimplePHOX.,[184] and pyridyl phosphite ligands **103–106**. [185] Burgess has also reported a series of JM-Phos[186] and imidazolylidene–oxazolines[187,187a] for the asymmetric hydrogenation of unfunctionalized olefins. Uemura has created chiral ferrocene N, P ligand **108** through diastereoselective *ortho*-lithiation of

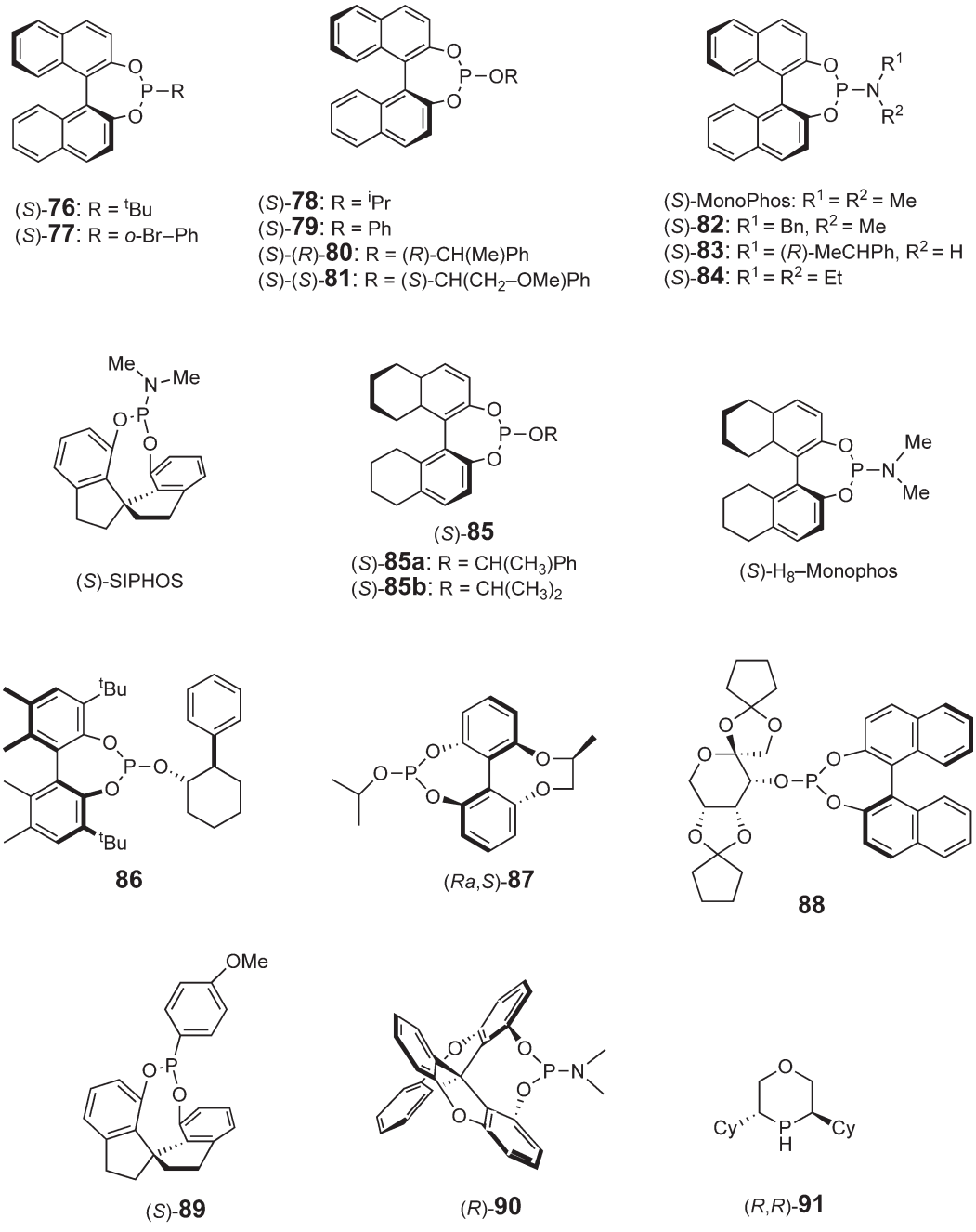


Figure 11 Chiral monophosphorous ligands.

oxazolinylferrocene.[188] Recently, Ir–**108** complex is applied to the asymmetric hydrogenation of quinolines, and enantioselectivity up to 92% ee was obtained.[188a] A set of phospholane–oxazoline ligands, **109**[189] and **110**,[190] has been recently developed by Zhang, and the ligands have provided excellent ee values in hydrogenation of unfunctionalized olefins and unsaturated esters.[189] A variety of heterocyclic N, P ligands have been developed for the Ir-catalyzed highly enantioselective hydrogenation of unfunctionized olefins, for example, Cozzi's HetPHOX **111**∼**114**, which bear thiophene or benzo[*b*]thiophene skeleton,[191] Gilbertson's proline-derived N, P ligand **115**,[192] and Knochel's **116** and **117**.[193] Ellman has reported P,N-sulfinylimine ligand **118** for the asymmetric hydrogenation of olefins.[194]

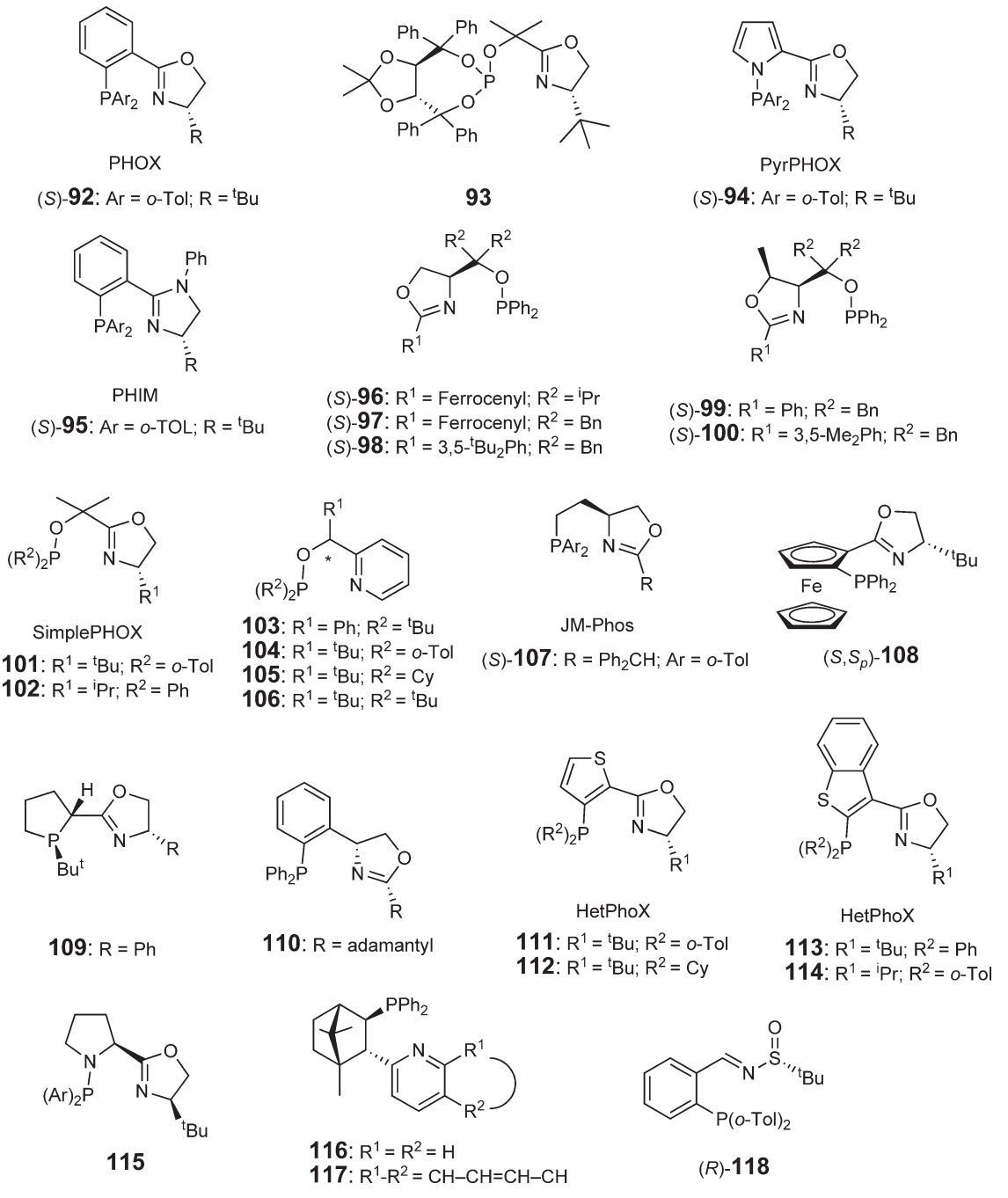


Figure 12 Chiral N, P ligands.

10.01.3 Applications of Chiral Phosphorus Ligands in Asymmetric Hydrogenation

10.01.3.1 Asymmetric Hydrogenation of Olefins

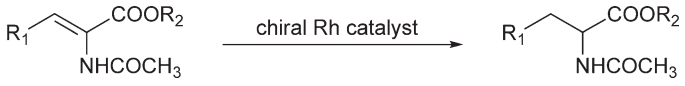
10.01.3.1.1 Hydrogenation of dehydroamino acid derivatives

Hydrogenation of α-dehydroamino acid derivatives has been a typical reaction to test the efficiency of new chiral phosphorus ligands. Indeed, a number of chiral phosphorus ligands with great structural diversity are found to be effective for the Rh-catalyzed hydrogenation of α-dehydroamino acid derivatives. Since (*Z*)-2-(acetamido)cinnamic

acid, 2-(acetamido)acrylic acid and their methyl esters are the most frequently used substrates, Table 1 lists some efficient examples (>95% ee) of the hydrogenation of these substrates with different chiral ligands. Generally, cationic Rh complexes and low hydrogenation pressure are applied for the hydrogenation reactions.

Several chiral ligands such as PYRPHOS,[128a] Et–DuPhos,[195] **44**,[96] TangPhos,[112] DPAMP,[144] and BoPhoz **70**[155,155a] have been demonstrated as very efficient ligands for the hydrogenation of α-dehydroamino acid derivatives in terms of both high enantioselectivity and reactivity, where the substrate-to-catalyst ratio as high as 50,000 : 1 can be achieved. DuPhos-type ligands such as Me–DuPhos, Et–DuPhos, **9** and **10**, are very efficient ligands for the hydrogenation of a wide variety of β-substituted α-dehydroamino acid derivatives. Various chiral α-amino acids-containing alkyl and substituted aryl groups can be produced with over 95% ee, even in supercritical CO_2.[196] With a TangPhos–Rh complex as the catalyst, enantioselectivity over 99% ee has been observed in hydrogenation of a series

Table 1 Asymmetric hydrogenation of (*Z*)-2-(acetamido) cinnamic acid, 2-(acetamido) acrylic acid and their methyl esters



A: R_1 = H, R_2 = H
B: R_1 = H, R_2 = CH_3
C: R_1 = Ph, R_2 = H
D: R_1 = Ph, R_2 = CH_3

Ligand	*Substrate*	*S/C ratio*	*Reaction conditions*	*Percent ee of product (confign.)*	*References*
(*R*,*R*)-DIPAMP	D	900	MeOH, 50 °C, 3 atm H_2	96 (*S*)	5
(*R*,*R*)-NORPHOS	C	95	MeOH, Rt, 1.1 atm H_2	96 (*R*)	127
(*R*,*R*)-PYRPHOS	D	50,000	MeOH, Rt, 61 atm H_2	96.5 (*S*)	128a
(*S*)-BINAP	D[a]	100	EtOH, Rt, 3 atm H_2	100 (*S*)	9
(*R*)-BICHEP	D[b]	1000	EtOH, Rt, 1 atm H_2	95 (*S*)	15b
(*S*)-*o*-Ph-MeO-BIPHEP	A	100	CH_2Cl_2, 25 °C, 25 psi H_2	>99 (*S*)	35
(*S*,*S*)-Et-DuPhos	B	50,440	MeOH, Rt, 2 atm H_2	>99 (*S*)	195
(*R*,*R*)-Ph-BPE	B	5,000	MeOH, 25 °C, 10 bar H_2	99 (*S*)	60
(*R*,*R*)-BICP	A	100	THF, Et_3N, Rt, 1 atm H_2	97.5 (*S*)	70
ROPHOS	D	100	MeOH, Rt, 1 atm H_2	98.4 (*S*)	56
10	C	100	MeOH, Rt, 3 atm H_2	>99 (*S*)	57a
14	A	100	H_2O, Rt, 50 psi H_2	>99 (*S*)	59
(*R*,*R*)-**19**	A	1000	MeOH, 20 °C, 1.1 atm H_2	97.4 (*R*)	63
(*R*,*R*,*R*)-**21**	D	1000	MeOH, 25 °C, 2 atm H_2	98 (*R*)	67
(*R*,*R*)-(*S*,*S*)-EtTRAP	B	100	CH_2Cl_2, 60 °C, 0.5 atm H_2	96 (*R*)	80a
(*R*)-(*S*)-JosiPhos	D	100	MeOH, 35 °C, 1atm H_2	96 (*S*)	81
(*S*,*S*)-FerroPhos	C	100	EtOH, Rt, 2 atm H_2	98.9 (*R*)	86
(*R*)-(*S*)-**30**	D	100	MeOH, Rt, 1 atm H_2	98.0 (*S*)	87
38	D	100	MeOH/toluene, 1 atm H_2	96.6 (*R*)	88
(*S*,*S*)-**43**	C	100	MeOH, 25 °C, 2 atm H_2	98.2 (*R*)	92
(*S*,*S*,*S*,*S*)-**44**	B	10,000	THF, Rt, 3 atm H_2	100 (*S*)	96
(*S*,*S*)-^{t}Bu-BisP*	D	500	MeOH, Rt, 2 atm H_2	99.9 (*R*)	101
(*S*,*S*)-^{t}Bu-MiniPhos	B	500	MeOH, Rt, 2 bar H_2	99.9 (*R*)	108
(*S*,*S*)-**47**	B	500	0 °C, 2 bar H_2	97 (*S*)	109
(*S*,*S*)-**48**	D	500	MeOH, Rt, 2 atm H_2	99.2 (*R*)	110
(*S*,*S*,*R*,*R*)-TangPhos	D	10,000	MeOH, Rt, 20 psi H_2	99.8 (*S*)	112
(*R*,*R*,*S*,*S*)-DuanPhos	B	10,000	MeOH, Rt, 20 psi H_2	>99 (*R*)	114
(−)-BIPNOR	C	100	EtOH, Rt, 3 atm H_2	>98 (*S*)	118
^{i}Pr-BeePhos	D	200	MeOH, 30 °C, 4 atm H_2	98 (*R*)	119
(*R*)-**53**	A	100	MeOH, Rt, 50 psi H_2	>99 (*R*)	123

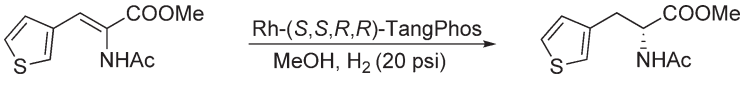
(*Continued*)

Table 1 (Continued)

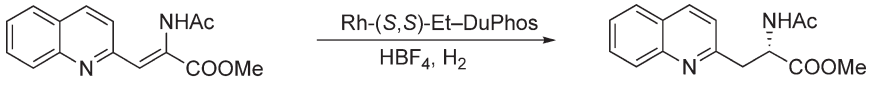
Ligand	*Substrate*	*S/C ratio*	*Reaction conditions*	*Percent ee of product (confign.)*	*References*
(*R*)-**53**	C	100	MeOH, Rt, 50 psi H_2	>99 (*R*)	123
(*R*)-PHANEPHOS	B	100	MeOH, Rt, 1atm H_2	99.6 (*R*)	130
(*S*)-Ph-o-NAPHOS	B	100	MeOH, Rt, 3 atm H_2	98.7 (*S*)	131
65	D	100	THF, Rt, 7.8 atm H_2	97 (*S*)	145
66	D	100	THF, Rt, 1.0 atm H_2	97 (*R*)	145
(*S*,*R*)-*o*-BINAPHOS	B	100	THF, Rt, 15 psi H_2	>99 (*S*)	147
(*S*,*R*)-*o*-BIPNITE	B	100	THF, Rt, 15 psi H_2	>99 (*S*)	147
(S_{Re}, R_C)-**54**	D	500	MeOH, 30 °C, 4atm H_2	97 (*R*)	132
58	C	1,000	THF, Rt, 30 psi H_2	99.0 (*S*)	136
(*R*)-spirOP	C	100	MeOH, Rt, 1atm H_2	97.9 (*R*)	137
DIMOP	A	500	acetone, Rt, 500 psi H_2	96.7 (*R*)	138
60	D	100	H_2O, Rt, 5 atm H_2[c]	99.9 (*S*)	139
(*S*)-Ph-*o*-BINAPO	B	100	MeOH, Rt, 3 atm H_2	99.9 (*S*)	131
(*R*,*R*)-**61**	B	1,000	CH_2Cl_2, Rt, 1.3 atm H_2	99.5 (*S*)	141
(*S*)-(*R*)-**62**	B	5,000	MeOH, Rt, 3.5 atm H_2	98.5 (*S*)	142
64	D	100	CH_2Cl_2, 25 °C, 5 atm H_2	98 (*S*)	144
(1*R*,2*S*)-DPAMPP	D	10,000	MeOH, Rt, 50 atm H_2	97 (*R*)	150a
(*S*)-Xyl-BDPAB	D	500	MeOH, Rt, 50 psi H_2	98 (*S*)	152
(*Ra*,*Rc*)-*n*-Bu-QUINAPHOS	B	1,000	CH_2Cl_2, Rt, 30 atm H_2	97.8 (*S*)	153
68	B	100	CH_2Cl_2, 5 °C, 30 atm H_2	>99 (*S*)	154
70	D	10,000	THF, Rt, 10 psi H_2	99.4 (*S*)	155,155a
(S_c,R_p,S_a)-**74**	D	100	CH_2Cl_2, Rt, 10 bar H_2	99.0 (*R*)	156
(*S*)-MonoPhos	B	20	EtOAc, Rt, 1 atm H_2	99.6 (*R*)	164
(*S*)-**84**	D	400	THF, Rt, 300 psi H_2	97.4 (*R*)	167
(*S*)-SIPHOS	D	200	CH_2Cl_2, Rt, 1atm H_2	96.4 (*S*)	173a
(*S*)-**89**	D	100	toluene, Rt, 10 bar H_2	99 (*S*)	174
(*R*)-**90**	D	100	Rt, 25 psi H_2	98.4 (*S*)	175

[a]Benzoyl derivative.
[b]Ethyl ester.
[c]Sodium dodecyl sulfate (10 mol%) is added.

of β-aryl-substituted dehydroamino acid derivatives.[112] An α-amino acid-containing thiophenyl group is also obtained with over 99% ee (Equation (1)). Hydrogenation of α-dehydroamino acid derivatives with strongly coordinating heteroaryl groups such as pyridyl is difficult, since the heteroaryl groups may potentially inhibit catalysis by coordinating with metal. This problem can be partially solved by converting the substrate into a protonated derivative with the addition of tetrafluoroboric acid.[197] For example, in the presence of tetrafluoroboric acid, 2-quinolylalanine is obtained with 94% ee via asymmetric hydrogenation with an Et–DuPhos–Rh catalyst (Equation (2)).[198] However, 2-pyridyl or 3-isoquinolylalanine cannot be obtained through a similar protocol.

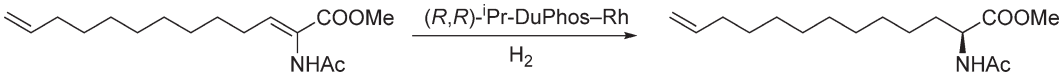


>99% ee (1)



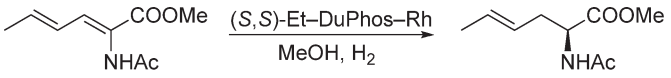
94% ee (2)

The Et–DuPhos–Rh system has shown good regioselectivity in the hydrogenation of substrates possessing two or more different alkene groups.[195] Since enamides are known to chelate to a cationic Rh–bisphosphine catalyst through the alkene and the carbonyl oxygen of the N-acyl group, this chelation directs the hydrogenation to occur preferentially at the enamide alkenes (Equation (3)). Indeed, over 99% regioselectivities have been observed in the hydrogenation of α,γ-dienamides with an Et–DuPhos–Rh catalyst, and a variety of chiral γ,δ-unsaturated amino acids can be obtained (Equation (4)).[199]



(3)

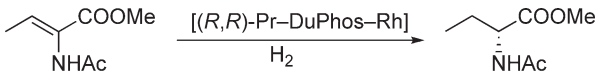
>99% ee, >95% regioselectivity



(4)

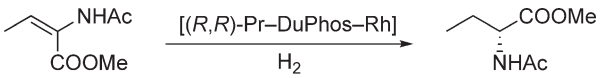
99% ee, 200 : 1 chemoselectivity

In contrast to the high enantioselectivity achieved for the (*Z*)-isomeric substrates, the hydrogenation of the (*E*)-isomeric substrates usually proceeds in a much lower rate and gives poor enantioselectivities.[200,200a] With the Rh–BINAP system as the catalyst and THF as the solvent, the hydrogenation of the (*Z*)- and (*E*)-isomeric substrates generates products with different configurations.[10] Remarkably, the DuPhos–Rh system provides excellent enantioselectivity for both (*Z*)- and (*E*)-isomeric substrates, and the hydrogenation products are formed with the same configuration (Equations (5) and (6)). This result is particularly important for the hydrogenation of alkyl dehydroamino acid derivatives, which are difficult to prepare in enantiomerically pure form.



(5)

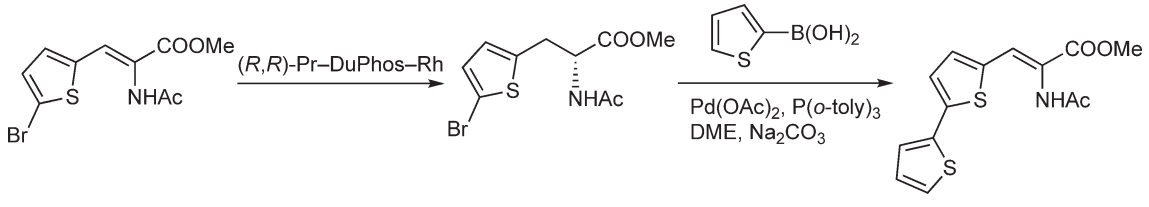
99.6% ee



(6)

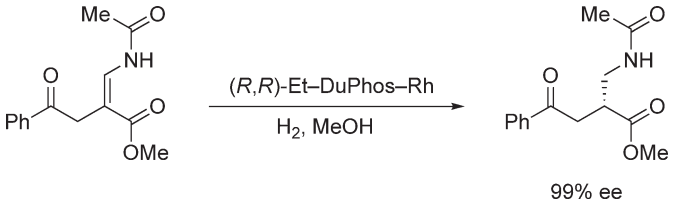
99.4% ee

Many synthetic utilities of the Rh-catalyzed hydrogenation of α-dehydroamino acid derivatives have been recently explored. For example, chiral α,β-diaminopropanoates can be efficiently synthesized via the asymmetric hydrogenation of α,β-diamidopropenoates with an Et–DuPhos–Rh catalyst (Equation (7)).[201] A tandem catalytic process involving the asymmetric hydrogenation of dehydroamino acid derivatives followed by a Suzuki coupling can provide a wide range of diverse α-amino acids, which have been used for the rapid synthesis of peptide analogs (Scheme 2).[202] A bis-dehydroamino acid derivative has been hydrogenated with an (*S,S*)-Me–DuPhos–Rh catalyst to yield an α,ω-diaminodicarboxylate with a 98 : 2 diasteromeric ratio. The product has been used for the synthesis of a peptidomimetic of the turn fragment in the helix–turn–helix DNA-binding protein motif

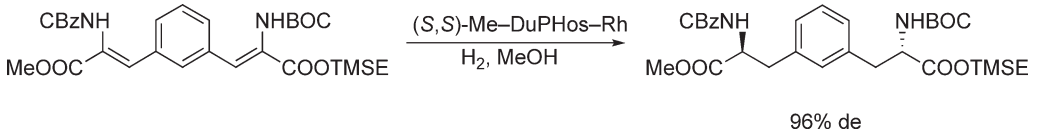


Scheme 2

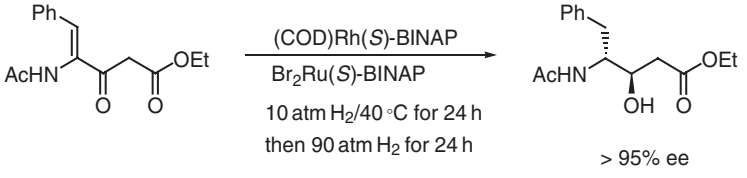
(Equation (8)).[203] Takahashi has reported a one-pot sequential asymmetric hydrogenation utilizing a BINAP–Rh and a BINAP–Ru catalyst to synthesize 4-amino-3-hydroxy-5-phenylpentanoic acids with over 95% ee. The process involves the hydrogenation of a dehydroamino acid with the BINAP–Rh catalyst, followed by the hydrogenation of a β-keto ester with the BINAP–Ru catalyst (Equation (9)).[204] (*R*)-metalaxyl, a highly active fungicide, has also been produced via asymmetric hydrogenation with a DuPhos–Rh catalyst (Equation (10)).[205] Using a DIPAMP–Rh complex as catalyst, a hindered pyridine-substituted α-dehydroamino acid derivative has been hydrogenated to give the corresponding chiral α-amino acid derivative with over 98% ee. The chiral product has been used for the synthesis of (*S*)-(−)-acromelobic acid (Scheme 3).[206] Hydrogenation of a tetrahydropyrazine derivative catalyzed by a PHANEPHOS–Rh complex at −40 °C gives an intermediate for the synthesis of Crixiran with 86% ee (Equation (11)).[130] An (*R*,*R*)-(*S*,*S*)-^{i}Bu–TRAP–Rh catalyst provides 97% ee for the hydrogenation of a tetrahydropyrazine carboxamide derivative (Equation (12)).[207] Interestingly, a related (*R*,*R*)-(*S*,*S*)-Me-TRAP–Rh catalyst provides the hydrogenation product with a different configuration. Hydrogenation of another tetrahydropyrazine carboxamide derivative catalyzed by an (*R*)-BINAP–Rh catalyst leads to the formation of a chiral product with 99% ee (Equation (13)).[208] Under the catalysis of Rh–BoPhoz **70** complex, high enantioselectivity (98.6% ee) was achieved in the hydrogenation of *N*-Boc cyclopropylalnine benzyl ester. Et–DuPhos is also efficient for this reaction (Equation (14)).[155a] A chiral unnatural α-amino acid, which is the key intermediate to vasopeptidase inhibtor BMS-189921, was obtained through Rh–Et–DuPhos-catalyzed asymmetric hydrogenation with 99% ee (Equation (15)).[209]



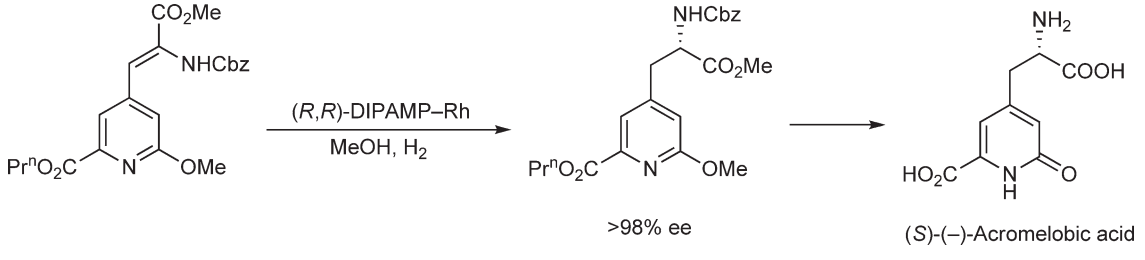
(7)



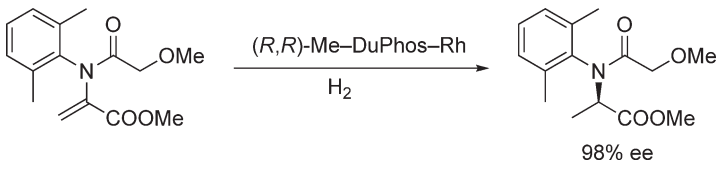
(8)



(9)



Scheme 3



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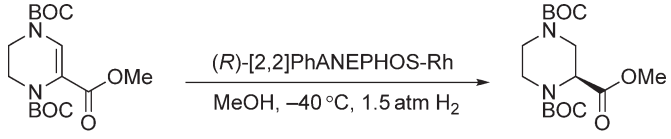
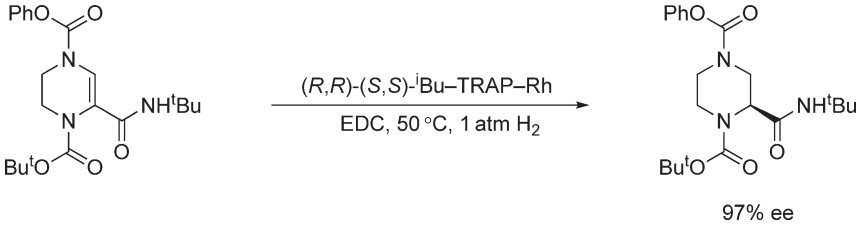


(11)



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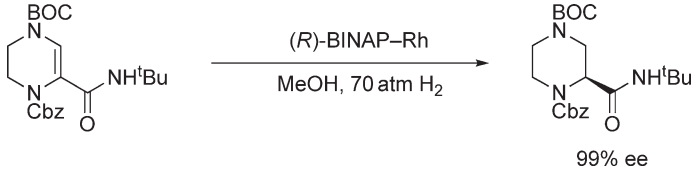

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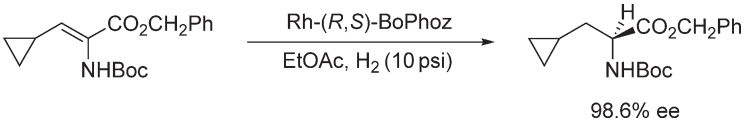

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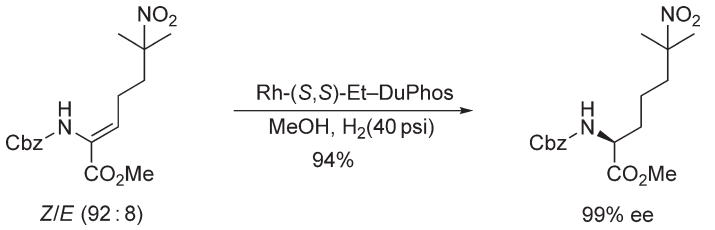
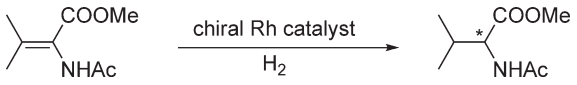


(15)

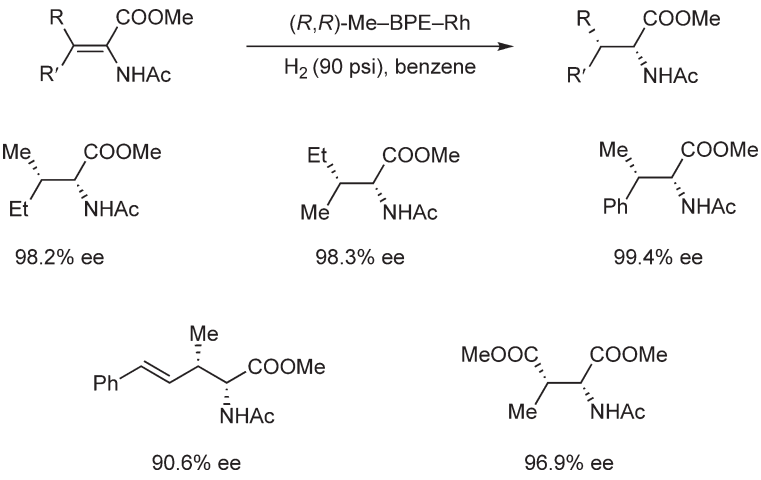
Hydrogenation of β,β-disubstituted α-dehydroamino acids remains a relatively challenging problem. Remarkably, the less bulky DuPhos or BPE-type ligands such as Me–DuPhos and Me–BPE, provide excellent enantioselectivity for a variety of this type of substrates.[210] The Rh complexes of chiral ligands such as BuTRAP,[80a] **44**,[96] Cy-BisP*,[101] MiniPhos,[108] and unsymmetrical BisP* **49**,[110a] have also shown high efficiencies for the reactions of some β,β-disubstituted α-dehydroamino acid substrates. Table 2 lists some examples of the efficient hydrogenation of β,β-dimethyl α-dehydroamino acid esters with different chiral phosphorus ligands.

When dissimilar groups occupy the two β-positions, two stereogenic centers are simultaneously established through hydrogenation. The Me–DuPhos–Rh or Me–BPE–Rh systems allow a series of both (*Z*)- and (*E*)-isomeric β,β-disubstituted α-dehydroamino acid derivatives to be hydrogenated with excellent enantioselectivity (Scheme 4). Good chemoselectivity is observed in the hydrogenation of substrates containing other olefin functionalities.[211] Thus, hydrogenation of β-substituted $\alpha,\beta,\gamma,\delta$-unsaturated amino acids with an Me–DuPhos–Rh or Me–BPE–Rh catalyst provides a series of β-substituted γ,δ-unsaturated amino acids with high ee.

Table 2 Asymmetric hydrogenation of β,β-dimethyl α-dehydroamino acid esters

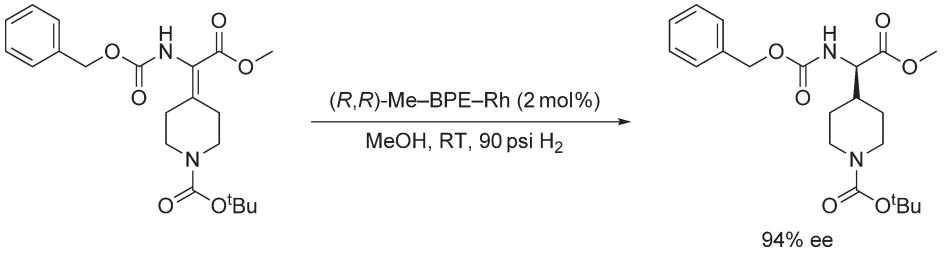


Ligand	*S/C ratio*	*Conditions*	*Percent ee of product (confign.)*	*References*
(*R*,*R*)-(*S*,*S*)-BuTRAP	100	^{i}PrOH, 15 °C, 1 atm H_2	88 (*S*)	80a
(*S*,*S*)-Me-DuPhos	500	benzene, 25 °C, 90 psi H_2	96.0 (*S*)	210
(*R*,*R*)-Me–BPE	500	benzene, 25 °C, 90 psi H_2	98.2 (*R*)	210
(*S*,*S*,*S*,*S*)-**44**	100	THF, Rt, 15 vpsi H_2	87.3 (*S*)	96
(*S*,*S*)-Cy-BisP*	500	MeOH, Rt, 6 atm H_2	90.9 (*R*)	101
(*S*,*S*)-^{t}Bu–MiniPhos	500	MeOH, Rt, 6 atm H_2	87 (*R*)	108
(*S*,*S*)-**47**	500	Rt, 6 atm H_2	87 (*S*)	109
(*S*,*S*)-**49**	100	MeOH, Rt, 20 atm H_2	96.1 (*R*)	110a



Scheme 4

Hydrogenation of a (*Z*)-dehydro-β-methyltryptophan derivative with an (*R*,*R*)-Me–DuPhos–Rh catalyst provides β-(2*R*,3*S*)-methyltryptophan with 97% ee.[212] A tetrasubstituted enamide containing a piperidine component is hydrogenated with an (*R*,*R*)-Me–BPE–Rh catalyst to give (*R*)-4-piperidinylglycine with 94% ee (Equation (16)).[213] The Pr–TRAP–Rh system provides excellent ee in the hydrogenation of (*Z*)-β-siloxy-α-(acetamido)acrylates and (*E*)-β-pivaloyloxy-α-(acetamido)acrylates (Equations (17) and (18)). By hydrogenation of both (*Z*)- and (*E*)-isomeric substrates of β-(acetylamino)-β-methyl-α-dehydroamino acid derivatives with Me–DuPhos–Rh catalysts, four isomers of *N*,*N*-protected 2,3-diaminobutanoic acid can be efficiently obtained with excellent ee (Equations (19) and (20)).[214] A Pr–TRAP–Rh catalyst is also applied for the hydrogenation of a series of (*E*)-β-(acylamino)-β-alkyl-α-dehydroamino acid derivatives and enantioselectivity up to 82% ee has been obtained.[80c]



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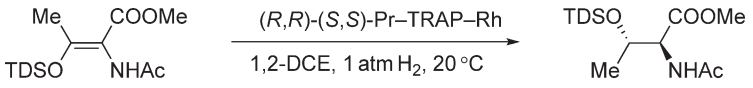
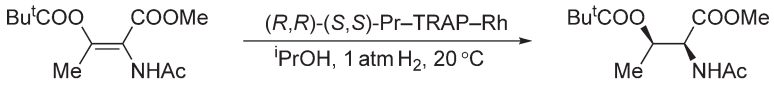
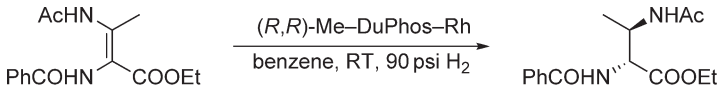


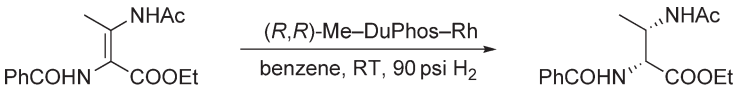
95% ee (17)



97% ee (18)



(Z) 96% ee (19)



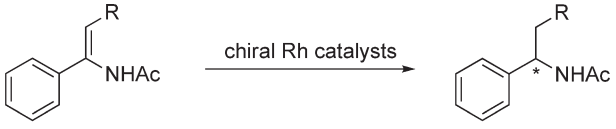
(E) >98% ee (20)

Compared to the great advance achieved in the Rh-catalyzed asymmetric hydrogenation, the Ru-catalyzed asymmetric hydrogenation of α-dehydroamino acid derivatives takes a different mechanistic pathway,[215] and little success has been made.

10.01.3.1.2 Hydrogenation of enamides

Rh-catalyzed hydrogenation of simple enamides has attracted much attention recently. With the development of more and more efficient chiral phosphorus ligands, extremely high ee can be obtained in the Rh-catalyzed hydrogenation of α-aryl enamides. *E*/*Z*-isomeric mixtures of β-substituted enamides can also be hydrogenated with excellent ee. Table 3 lists some efficient examples (>95% ee) of the hydrogenation of α-phenylenamide and *E*/*Z*-isomeric mixture of β-methyl-α-phenylenamide. A P-chiral ligand TangPhos has been demonstrated as an efficient

Table 3 Asymmetric hydrogenation of α-phenylenamide and *E*/*Z* isomeric mixture of β-methyl-α-phenylenamide



A: R = H
B: R = CH_3(*Z*/*E*)
C: R = ^{i}Pr (*Z*/*E*)

Ligand	*Substrate*	*S/C ratio*	*Reaction conditions*	*Percent ee of product (confign.)*	*References*
(*R*, *R*)-Me-BPE	A	500	MeOH, 22 °C, 6 psi H_2	95.2 (*R*)	216
	B	500	MeOH, 22 °C, 6 psi H_2	95.4 (*R*)	216
(*R*, *R*)-Ph-BPE	A	5,000	MeOH, 25 °C, 10 bar H_2	99 (*R*)	60
10	A	100	MeOH, Rt, 10 atm H_2	96 (*S*)	57a
(*S*,*S*)-BINAPHANE	B	100	CH_2Cl_2, Rt, 20 psi H_2	99.1 (*S*)	64
(*R*,*R*)-BICP	B	100	Toluene, Rt, 40 psi H_2	95.0 (*R*)	70a
(*R*,*S*,*S*,*R*)-DIOP*	A	50	MeOH, Rt, 10 bar H_2	98.8 (*R*)	72,72a
	B	50	MeOH, Rt, 10 bar H_2	97.3 (*R*)	72,72a
(*R*,*R*,*R*,*R*)-**26**	B	100	MeOH, Rt, 45 psi H_2	98 (*S*)	76
(*R*,*R*,*R*,*R*)-SK-Phos	B	100	MeOH, Rt, 45 psi H_2	97 (*S*)	76
(*S*,*S*)-**24**	A	100	CH_2Cl_2, Rt, 1 atm H_2	98.5 (*R*)	75

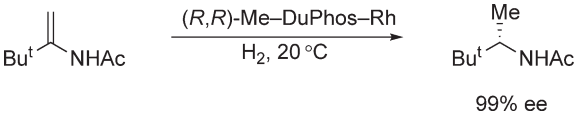
(*Continued*)

Table 3 (Continued)

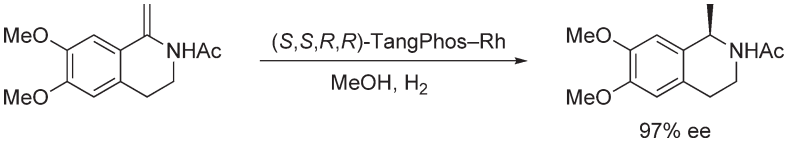
Ligand	*Substrate*	*S/C ratio*	*Reaction conditions*	*Percent ee of product (confign.)*	*References*
	B	100	CH_2Cl_2, Rt, 1 atm H_2	>99 (*R*)	75
39	A	100	MeOH/toluene, Rt, 1 atm H_2	96 (*S*)	93
(*S*,*S*)-^{t}Bu-BisP*	A	100	MeOH, Rt, 3 atm H_2	98 (*R*)	102
(*S*,*S*,*R*,*R*)-TangPhos	A	10,000	MeOH, Rt, 20 psi H_2	99.3 (*R*)	112
	B	100	MeOH, Rt, 20 psi H_2	98 (*R*)	112
(*R*,*R*,*S*,*S*)-DuanPhos	A	100	MeOH, Rt, 20 psi H_2	>99 (*R*)	114
	C	100	MeOH, Rt, 20 psi H_2	97 (*R*)	114
(*R*)-H_8-BDPAB	A	200	THF, 5 °C, 1 atm H_2	96.8 (*R*)	151
(S_c, R_p, S_a)-**74**	A	5000	CH_2Cl_2, Rt, 10 bar H_2	99.3 (*R*)	156
(*S*)-MonoPhos	A	100	CH_2Cl_2, −20 °C, 300 psi H_2	95 (*S*)	165,165a
(*S*)-**84**	A	100	THF, 5 °C, 300 psi H_2	99 (*R*)	167
(*S*)-H_8-MonoPhos	A	100	THF, −10 °C, 300 psi H_2	96 (*R*)	169
88	B	100	CH_2Cl_2, Rt, 10 atm H_2	96.7 (*S*)	172
(*S*)-SIPHOS	A	200	Toluene, 5 °C, 10 atm H_2	98.7 (*S*)	173

ligand for the Rh-catalyzed hydrogenation of enamides in terms of both enantioselectivity and reactivity, and turnover numbers up to 10,000 have been achieved.[112]

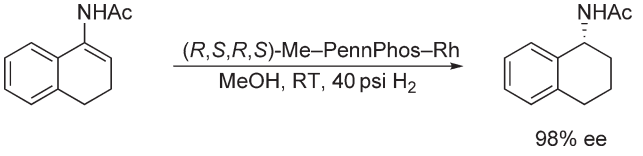
Some alkyl enamides such as *tert*-butylenamide or 1-admantylenamide can also be hydrogenated with a ^{t}Bu–BisP*–Rh catalyst or an Me–DuPhos–Rh catalyst[217] with 99% ee (Equation (21)). Notably, the configurations of the hydrogenation products of these bulky alkyl enamides are opposite to those of aryl enamides. Mechanistic study[218] by Gridnev and Imamoto[102] using NMR technique indicates that the hydrogenations of bulky alkyl enamides and aryl enamides involve different coordination pathways. Hydrogenation of *N*-acetyl-6,7-dimethoxy-1-methylene-1,2,3,4-tetrahydroquinoline can be catalyzed by a (*S*,*S*,*R*,*R*)-TangPhos–Rh complex to yield (*R*)-(−)-*N*-acetylsalsolidine with 97% ee (Equation (22)).[112] PennPhos,[66] *o*-Ph-HexaMeO–BIPHEP,[34] and Me–BPE[214] have shown high efficiencies in the Rh-catalyzed hydrogenation of cyclic enamides. A racemic cyclic enecarbamate has been hydrogenated with an *o*-Ph–HexaMeO–BIPHEP–Rh catalyst to yield the *cis*-chiral carbamate with 96% ee (Equation (24)).[34] The chiral product can be directly used for the synthesis of sertraline, an anti-depressant agent. A set of 2-substituted *N*-acetylindoles[80f] and 3-substituted *N*-acetylindoles[80g] can be efficiently hydrogenated by the Ph–TRAP–Rh system with excellent enantioselecitivities (Equations (25) and (26)). Hydrogenation of some tetrasubstituted enamides has also been reported. ^{t}Bu–BisP* and ^{t}Bu–MiniPhos have provided excellent ee for hydrogenation of a β,β- dimethyl-α-phenyl enamide derivatives (Equation (27)).[102] Using a PennPhos–Rh catalyst[66] or an *o*-Ph–BIPHEP–Rh catalyst,[34] tetrasubstituted enamides derived from 1-indanone and 1-tetralone have been hydrogenated with excellent ee.



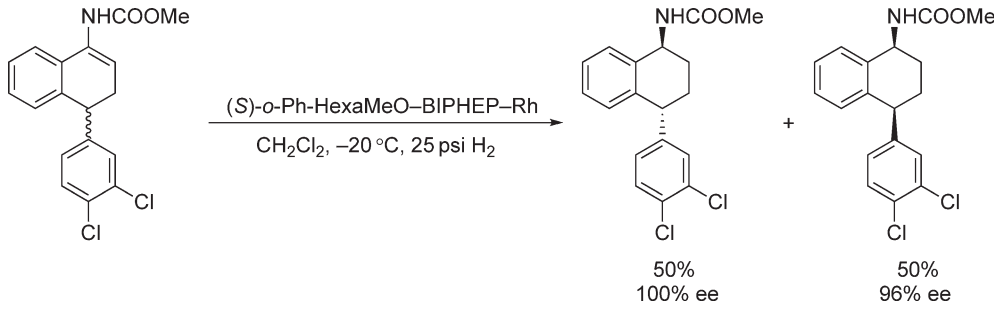
(21)



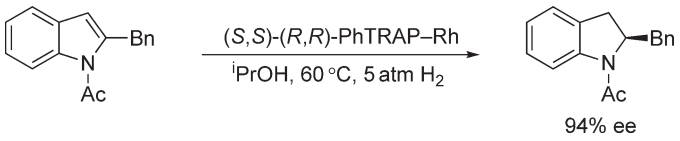
(22)



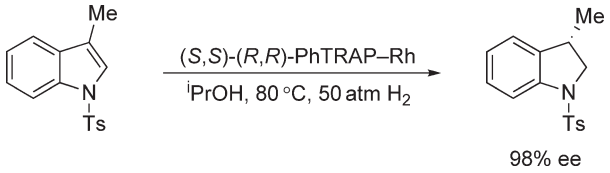
(23)



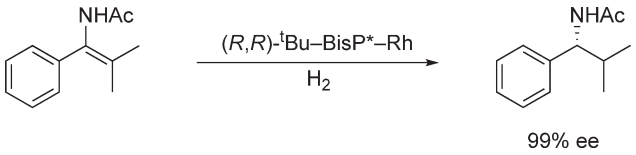
(24)



(25)

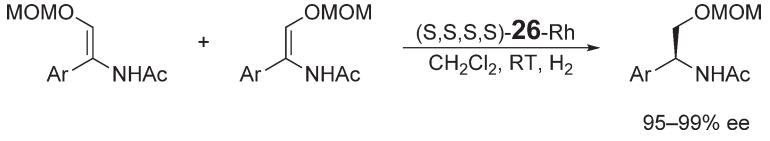


(26)



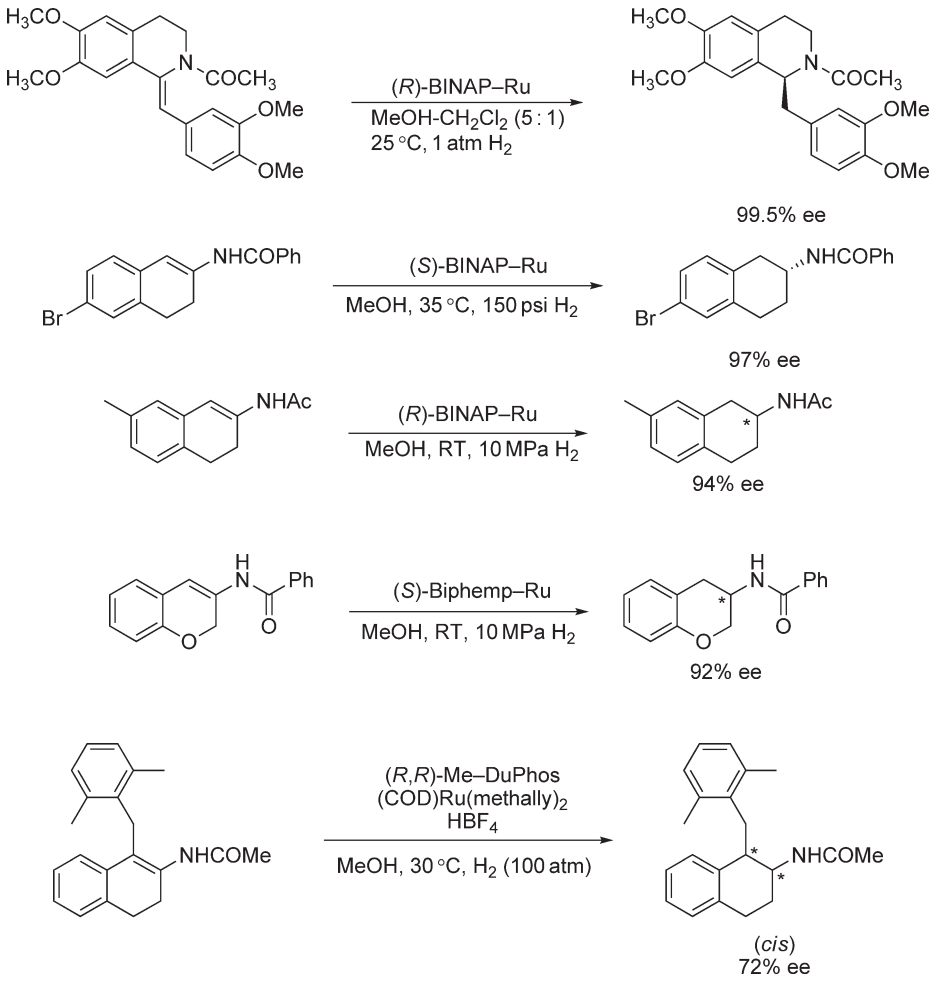
(27)

Hydrogenation of a series of *E*/*Z*-isomeric mixtures of α-arylenamides with a MOM-protected β-hydroxyl group catalyzed by a BICP–Rh complex or an Me–DuPhos complex leads to the formation of chiral β-amino alcohol derivatives with excellent enantioselectivities.[70b] A 1,4-diphosphane **26** with a rigid 1,4-dioxane backbone is also very effective for this transformation (Equation (28)).[76] DIOP*–Rh[72a] and Me–DuPhos–Rh[219] catalysts are also effective for this transformation.



(28)

Other than Rh chemistry, the Ru–BINAP system has shown excellent enantioselectivity in the hydrogenation of (*Z*)-*N*-acyl-1-alkylidenetetrahydroisoquindines. Thus, a series of chiral isoquinoline products can be efficiently synthesized (Equation (29)).[11,11a,220] Using Ru–BINAP catalyst, cyclic enamides, 6-bromotetralone–eneacetamide (Equation (30))[221] and 7-methyltetralone–eneacetamide (Equation (31))[222] are hydrogenated to give the corresponding chiral amide product with 97% and 94% ee, respectively. Ru–Biphemp catalyst also provided good selectivity (92% ee) for the asymmetric hydrogenation of a cyclic enamide derived from 3-chromanone (Equation (32)).[222] Hydrogenation of a series of tetrasubstituted enamides derived from 1-substituted-2-tetralones catalyzed by an Ru complex generated *in situ* from (COD)Ru(methallyl)$_2$, Me–DuPhos, and HBF_4 provides chiral amide products with up to 72% ee (Equation (33)).[223]

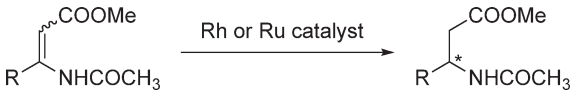


10.01.3.1.3 Hydrogenation of (β-acylamino) acrylates

Asymmetric hydrogenation of (β-acylamino)acrylates has gained much attention recently because the hydrogenation products, β-amino acid derivatives, are important building blocks for making chiral drugs.[224,224a–224g] Since both (*Z*)- and (*E*)-isomeric substrates are generally formed simultaneously through most synthetic methods, obtaining high enantioselectivities for both (*Z*)- and (*E*)-isomeric substrates is important for a practical synthesis of β-amino acid derivatives via asymmetric hydrogenation. Some Rh and Ru complexes with chiral phosphorus ligands such as BINAP,[225] DuPhos,[226] BICP,[70d] BDPMI,[75a] *o*-Ph–HexaMeO–BIPHEP,[34] ligand **2**,[38] DuanPhos,[114] (*R*)-**53**,[124] ^{t}Bu–BisP*,[103] TangPhos,[115] monophosphoramidite **82**,[166] phosphoramidite **75**,[156a] Et-FerroTANE,[95] Xyl–P–Phos,[33b] and MalPhos[61] have been found to be effective for the hydrogenation of (*E*)-3-alkyl-3-(acylamino)acrylates. However, only a few chiral ligands such as BDPMI[75a], TangPhos,[115] (*R*)-**53**,[124] and monophosphoramidite **83**[166] can provide the products with over 95% ee in the hydrogenation of (*Z*)-3-alkyl-3-(acylamino)acrylates (Table 4). With TangPhos–Rh catalyst, an *E*/*Z*-isomeric mixtures of methyl 3-acetamido-2-butenoate was hydrogenated in THF to give methyl(R)-3-acetamidobutanoate with 99.5% ee. (*R*)-**53** is also effective for the asymmetric hydrogenation of *E*/*Z*-isomeric mixtures of 3-alkyl-3-(acylamino)acrylates.[124] Mechanistic study of the hydrogenation of 3-alkyl-3-(acylamino)acrylates with an Rh–BisP* complex as the catalyst shows that the reaction proceeds via a monohydride intermediate with β-carbon atom bound to rhodium.[103]

Compared with 3-alkyl-3-(acylamino)acrylic acid derivatives, much less success has been obtained in the asymmetric hydrogenation of 3-aryl-3-(acylamino)acrylic acid derivatives. An Et–FerroTANE–Rh catalyst has provided up to 99% ee for the hydrogenation of a series of (*E*)-3-aryl-3-(acylamino)acrylates.[95] Since (*E*)-3-aryl-3-(acylamino)-acrylic acid derivatives are difficult to obtain in large scales compared to (*Z*)-3-aryl-3-(acylamino)acrylic acid

Table 4 Asymmetric hydrogenation of (β-acylamino) acrylates



Ligand	*R*	*Geometry*	*Reaction conditions*	*Percent ee of product (confign.)*	*References*
(*R*)-BINAP–Ru	CH_3	*E*	MeOH, 25 °C, 1 atm H_2	96 (*S*)	225
(*R*)-Xyl–P–Phos–Ru	CH_3	*E*	MeOH, 0 °C, 8 atm H_2	98.1 (*S*)	33b
(*S*,*S*)-Me–DuPhos–Rh	CH_3	*E*	MeOH, 25 °C, 1 atm H_2	98.2 (*S*)	226
(*R*,*R*)-BICP–Rh	CH_3	*E*	Toluene, Rt, 40 psi H_2	96.1 (*R*)	70d
(*S*,*S*)-**24**–Rh	CH_3[a]	*E*	CH_2Cl_2, Rt, 1 atm H_2	94.6 (*R*)	75a
(*S*,*S*)-^{t}Bu–BisP*–Rh	CH_3	*E*	THF, Rt, 3 atm H_2	98.7 (*R*)	103
(*S*,*S*)-MiniPhos–Rh	CH_3	*E*	THF, Rt, 3 atm H_2	96.4 (*R*)	103
(*S*,*S*,*S*,*S*)-TangPhos–Rh	CH_3	*E*	THF, Rt, 20 psi H_2	99.6 (*R*)	115
(*R*,*R*,*S*,*S*)-DuanPhos–Rh	CH_3	*E*	MeOH, Rt, 20 psi H_2	>99 (*R*)	114
(*R*)-**53**–Rh	CH_3	*E*	MeOH, Rt, 20 psi H_2	99 (*R*)	124
(*S*)-HexaPHEMP–Rh	CH_3	*E*	MeOH, Rt, 140 psi H_2	95 (*R*)	36
2-Rh	CH_3	*E*	MeOH, 0 °C, 250 psi H_2	97.7 (*S*)	38
2-Rh	^{i}Pr	*E*	MeOH, 0 °C, 250 psi H_2	98.8 (*S*)	38
(*R*,*R*)-MalPhos–Rh	CH_3	*E*	MeOH, 25 °C, 1 atm H_2	97.8 (*R*)	61
(*R*,*R*)-Et–FerroTANE–Rh	CH_3	*E*	MeOH, 25 °C, 1 atm H_2	99 (*R*)	95
(S_c, R_p, S_a)-**75**–Rh	CH_3	*E*	CH_2Cl_2, 5 °C, 10 bar H_2	98 (*R*)	156a
(*S*,*S*)-Me–DuPhos–Rh	CH_3	*Z*	MeOH, 25 °C, 1 atm H_2	87.8 (*S*)	226
(*S*,*S*)-**24**–Rh	CH_3[a]	*Z*	CH_2Cl_2, Rt, 100 psi H_2	95 (*R*)	75a
(*S*,*S*,*R*,*R*)-TangPhos–Rh	CH_3	*Z*	THF, Rt, 20 psi H_2	98.5 (*R*)	115
(*S*)-**83**–Rh	CH_3	*Z*	^{i}PrOH, Rt, 10 atm H_2	95 (*R*)	166
(*R*)-**53**–Rh	CH_3	*Z*	EtOAc, Rt, 20 psi H_2	98 (*R*)	124
(S_c, R_p, S_a)-**75**–Rh	CH_3	*Z*	CH_2Cl_2, 5 °C, 10 bar H_2	92 (*R*)	156a
(*S*,*S*,*R*,*R*)-TangPhos–Rh	CH_3	*E*/*Z*[b]	THF, Rt, 20 psi H_2	99.5 (*R*)	115
(*R*)-**53**–Rh	CH_3	*E*/*Z*[b]	THF, Rt, 20 psi H_2	98 (*R*)	124
(*R*,*R*)-Et–FerroTANE–Rh	Ph	*E*	MeOH, 25 °C, 1 atm H_2	>99 (*R*)	95
(*S*)-**83**–Rh	Ph[a]	*Z*	^{i}PrOH, Rt, 10 atm H_2	92 (*S*)	166
(*S*)-Xylyl-*o*-BINAPO–Ru	Ph	*Z*	EtOH, 50 °C, 80 psi H_2	99 (*S*)	140
(*S*)-Xylyl-*o*-BINAPO–Ru	*p*-F–Ph	*Z*	EtOH, 50 °C, 80 psi H_2	99 (*S*)	140
(*S*)-Xylyl-*o*-BINAPO–Ru	*p*-MeO–Ph	*Z*	EtOH, 50 °C, 80 psi H_2	99 (*S*)	140
(*S*,*S*,*R*,*R*)-TangPhos–Rh	Ph	*Z*	THF, Rt, 20 psi H_2	93.8 (*S*)	115
(*S*,*S*,*R*,*R*)-TangPhos–Rh	*p*-F–Ph	*Z*	THF, Rt, 20 psi H_2	95.0 (*S*)	115
(*S*,*S*,*R*,*R*)-TangPhos–Rh	*p*-MeO–Ph	*Z*	THF, Rt, 20 psi H_2	98.5 (*S*)	115
BINAPINE[c]–Rh	Ph	*Z*	THF, Rt, 20 psi H_2	99 (*S*)	113
BINAPINE[c]–Rh	*p*-F–Ph	*Z*	THF, Rt, 20 psi H_2	99 (*S*)	113
BINAPINE[c]–Rh	*p*-Me–Ph	*Z*	THF, Rt, 20 psi H_2	99 (*S*)	113
BINAPINE[c]–Rh	*p*-MeO–Ph	*Z*	THF, Rt, 20 psi H_2	99 (*S*)	113
(*R*,*R*,*S*,*S*)-DuanPhos–Rh	*p*-MeO–Ph	*Z*	MeOH, Rt, 20 psi H_2	92 (*S*)	114
(*R*,*R*,*S*,*S*)-DuanPhos–Rh	*p*-Cl–Ph	*Z*	MeOH, Rt, 20 psi H_2	92 (*S*)	114
(S_c, R_p, S_a)-**75**–Rh	*p*-MeO–Ph	*Z*	CH_2Cl_2, 5 °C, 10 bar H_2	98 (*R*)	156a
(S_c, R_p, S_a)-**75**–Rh	*p*-F–Ph	*Z*	CH_2Cl_2, 5 °C, 10 bar H_2	98 (*R*)	156a
(*S*)-**89**–Rh	*p*-MeO–Ph	*E*/*Z*	CH_2Cl_2, Rt, 100 bar H_2	98 (*R*)	174
(*S*)-**89**–Rh	*o*-MeO–Ph	*E*/*Z*	CH_2Cl_2, Rt, 100 bar H_2	95 (*R*)	174

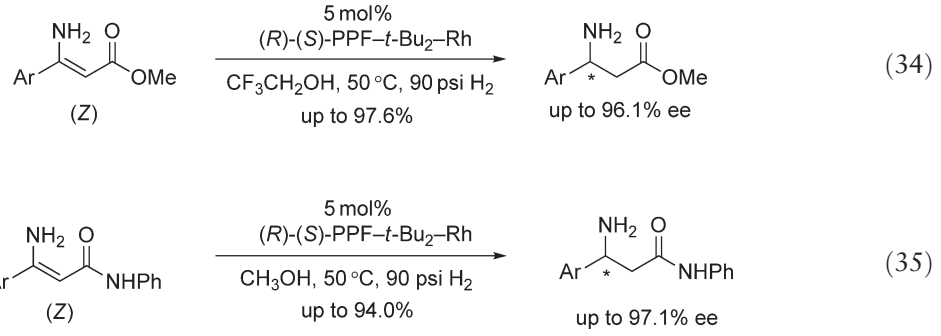
[a]ethyl ester.
[b]*E*/*Z* = 1 : 1.
[c]S/C ratio = 10,000.

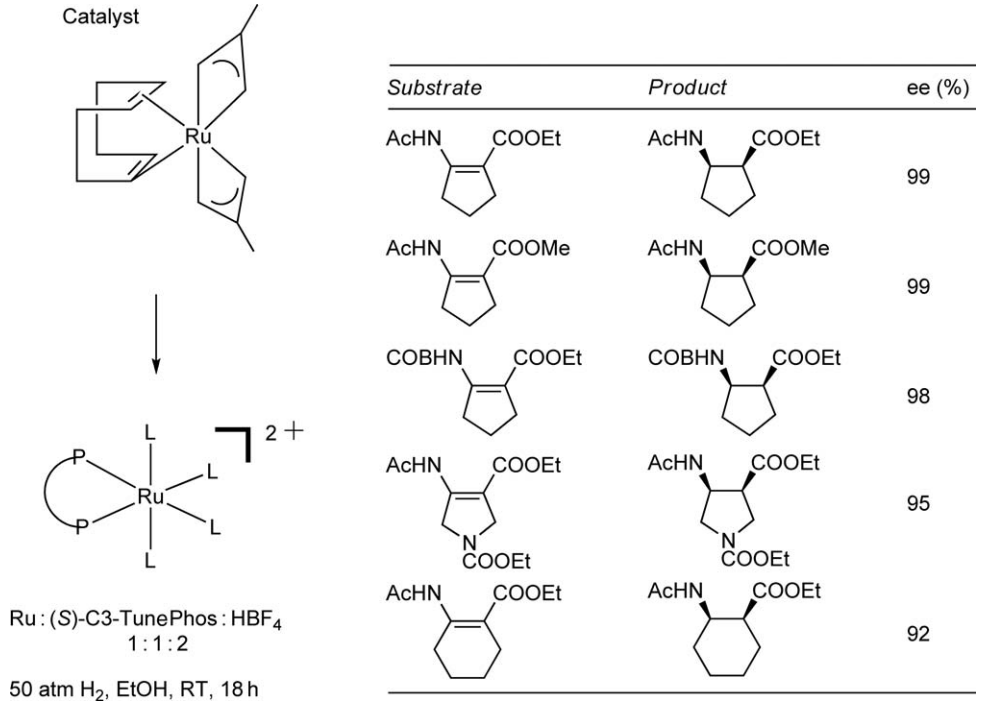
derivatives, achieving high enantioselectivities for the (*Z*)-isomeric substrates is more important for the practical synthesis of chiral 3-aryl-3-amino acids via the asymmetric hydrogenation. Few efficient ligands have been reported for the hydrogenation of (*Z*)-3-aryl-3-(acylamino)acrylates. Xylyl–BINAPO–Ru catalyst,[140] TangPhos–Rh catalyst,[115] BINAPINE–Rh,[113] and hybrid ferrocenylphosphine–phosphoramidite **75**[156a] are found to be effective for the reactions of a variety of (*Z*)-3-aryl-3-(acylamino)acrylates. Using a BINAPINE–Rh complex as catalyst, a wide

range of (*Z*)-3-aryl-3-(acylamino)acrylic acid derivatives was hydrogenated with both excellent enantioselectivities (96∼>99% ee) and reactivity, and turnover numbers up to 10,000 have been achieved. (Table 4).[113] A series of *E*/*Z*-mixture of 3-aryl-3-(acylamino)acrylic acid derivatives was reduced by the Rh complex of monodentate *spiro*-phosphonites **89**, and high enantioselectivities (up to 98% ee) were achieved.[174]

By employing Ru catalyst generated *in situ* from $Ru(COD)(methallyl)_2$, chiral phosphine ligand (*S*)-C3-TunePhos, and HBF_4, a series of cyclic 3-(acylamino)acrylate was hydrogenated with excellent ee. As shown in Scheme 5, 99% ee was obtained in the hydrogenation of both 2-acetylamino-cyclopent-1-enecarboxylic acid methyl ester and ethyl ester. A heterocyclic 3-(acylamino)acrylate is also hydrogenated to give *cis*-product with excellent enantioselectivity (95% ee). Hydrogenation of a cyclohexenyl substrate provided the *cis*-hydrogenation product with 92% ee.[28]

The *N*-acyl protecting group is considered indispensable to satisfy the chelation requirment with transtion metal, leading to high reactivity and enantioselectivity for the hydrogenation of unsaturated *β*-amino acid. Recently, Haiso *et al*. have discovered a novel asymmetric hydrogenation of unprotected enamine ester and amides. Using Rh–PPF–*t*-Bu_2 or Rh–**29** complex as catalyst, unprotected enamine ester and amides were reduced with high reactivity and enantioselectivity (Equations (34) and (35)).[85] Preliminary mechanistic studies suggested that the hydrogenation proceeds through a different intermediate, that is, an imine tautomer.



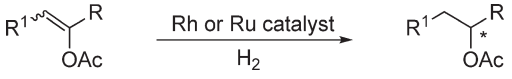


Scheme 5

10.01.3.1.4 Hydrogenation of enol esters

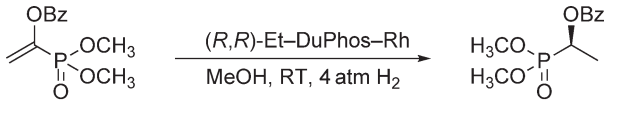
Enol esters have a similar structure to enamides. However, in contrast to many highly enantioselective examples of the asymmetric hydrogenation of enamides, only a few successful results have been reported for the hydrogenation of enol esters. One possible reason is that the acyl group of an enol ester has a weaker coordinating ability to the metal catalyst than that of the corresponding enamide substrate. Some Rh and Ru complexes associated with chiral phosphorus ligands such as DIPAMP,[227,228] DuPhos,[229,230] BINAP,[228] and FERRIPHOS **33**[87b] and TaniaPhos **39**[89] are effective for the asymmetric hydrogenation of 2-(acyloxy)acrylates (Table 5). A wide range of 2-(acyloxy)acrylates has been hydrogenated with an Et–DuPhos–Rh catalyst with excellent ee.[229] High selectivities are also obtained in the hydrogenation of the *E*/*Z*-isomeric mixtures of β-substituted substrates. The products can be easily converted into α-hydroxy esters and 1,2-diols. Asymmetric hydrogenation of a series of enol phosphates with a DuPhos–Rh or a BPE–Rh catalyst provides moderate to excellent ee (Equation (36)).[231] ^{t}Bu–MiniPhos–Rh and a ^{t}Bu–BisP*–Rh catalysts are also effective for the asymmetric hydrogenation of enol phosphates.[232] Some Rh or Ru catalysts with chiral phosphorus ligands such as DuPhos,[230] **10**,[57a] TangPhos,[116] BINAP,[233] and TunePhos[27] have been used for the asymmetric hydrogenation of aryl enol acetates without other functionalities (Table 5). A TangPhos–Rh catalyst provides enantioselectivities ranging from 92% ee to 99% ee for a diverse set of aryl enol acetates.[116] A C_2-TunePhos–Ru,[27] DuanPhos–Rh[114] and **2**–Ru[38] catalysts are found to be equally effective for this transformation. Hydrogenation of cyclic enol acetates is a challenging problem. Me–PennPhos is found to be efficient for the Rh-catalyzed hydrogenation of five- or six-membered ring cyclic enol acetates (Equation (37)).[66a] Hydrogenation of acyclic enol acetates is also possible. Vinylic, acetylenic,[234] and trifluoromethyl[235,235a] enol acetates have been hydrogenated with a DuPhos–Rh or BPE–Rh catalyst with excellent ee (Table 5).

Table 5 Asymmetric hydrogenation of α-(acyloxy) acrylates

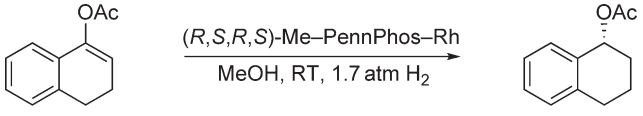


Catalyst	*R*	R^1	*Geometry*	*Reaction conditions*	*Percent ee of product (confign.)*	*References*
(*R*,*R*)-Et–DuPhos–Rh	CO_2Et	H	N/A	MeOH, Rt, 2 atm H_2	>99 (*R*)	230
(*R*)-(*S*)-**33**–Rh	CO_2Me	H	N/A	Acetone, Rt, 1 atm H_2	94.9 (*S*)	87b
(*R*)-(*S*)-**39**–Rh	CO_2Me	H	N/A	MeOH, Rt, 1 atm H_2	98 (*S*)	89
(*R*,*R*)-DIPAMP–Rh	CO_2Et	^{i}Pr	*E*/*Z*[a]	MeOH, Rt, 3 atm H_2	92 (*S*)	228
(*R*,*R*)-Et–DuPhos–Rh	CO_2Et	^{i}Pr	*E*/*Z*[b]	MeOH, Rt, 6 atm H_2	96.1 (*R*)	229
(*R*)-BINAP–Ru	CO_2Et	^{i}Pr	*E*/*Z*[a]	MeOH, 50 °C, 50 atm H_2	98 (*S*)	228
(*R*,*R*)-DIPAMP–Rh	CO_2Et	Ph	*Z*	MeOH, Rt, 3 atm H_2	88 (*S*)	228
(*R*,*R*)-Et–DuPhos–Rh	CO_2Et	Ph	*E*/*Z*[c]	MeOH, Rt, 3 atm H_2	95.6 (*R*)	229
(*S*,*S*)-Me–DuPhos–Rh	Ph	H	N/A	MeOH, Rt, 3 atm H_2	89 (*S*)	230
(*S*,*S*,*R*,*R*)-TangPhos–Rh	Ph	H	N/A	EtOAc, Rt, 20 psi H_2	96 (*R*)	116
(*R*,*R*,*S*,*S*)-DuanPhos–Rh	Ph	H	N/A	THF, Rt, 20 psi H_2	97 (*R*)	114
(*R*,*R*,*S*,*S*)-DuanPhos–Rh	2-Np	H	N/A	THF, Rt, 20 psi H_2	98 (*R*)	114
(*S*,*S*)-Me-DuPhos–Rh	1-Np	H	N/A	MeOH, Rt, 3 atm H_2	93 (*S*)	230
10–Rh	1-Np	H	N/A	MeOH, Rt, 3 atm H_2	95 (*S*)	57a
(*S*,*S*,*R*,*R*)-TangPhos–Rh	1-Np	H	N/A	EtOAc, Rt, 20 psi H_2	97 (*R*)	116
(*S*)-C2-TunePhos–Ru	1-Np	H	N/A	EtOH/CH_2Cl_2, Rt, 3 atm H_2	97.7 (*S*)	27
2–Rh	1-Np	H	N/A	EtOH/CH_2Cl_2, Rt, 50 psi H_2	96.7 (*R*)	38
2–Rh	*p*-FC_6H_4	H	N/A	EtOH/CH_2Cl_2, Rt, 50 psi H_2	97.1 (*R*)	38
(*R*,*R*)-Me–DuPhos–Rh	PhCH═CH (*E*)	H	N/A	THF, Rt, 2 atm H_2	94 (*R*)	234
(*R*,*R*)-Et–BPE–Rh	CF_3	H	N/A	MeOH, Rt, 2 atm H_2	>95 (*R*)	230

[a] *E*/*Z* = 70 : 30.
[b] *E*/*Z* = 6 : 1.
[c] *E*/*Z* = 9 : 1.

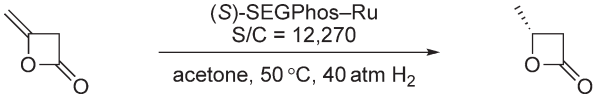


96% ee (36)

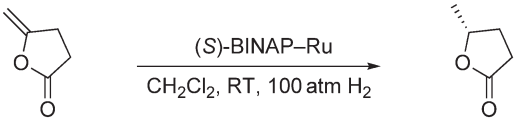


99.1% ee (37)

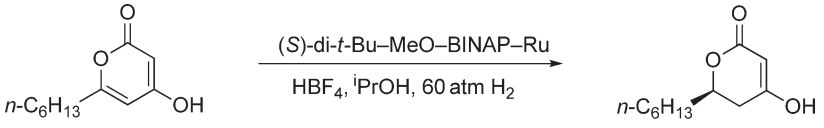
Although high hydrogen pressure is required, BINAP and its analogous ligands have shown superior results in the Ru-catalyzed hydrogenation of four- and five-membered cyclic lactones or carbonates bearing an exocyclic methylene group.[233] An (*S*)-SEGPHOS–Ru catalyst provides 93.8% ee in the hydrogenation of a diketene with high turnover numbers (Equation (38)).[236] With an (*S*)-BINAP–Ru catalyst, 94% ee is obtained in the hydrogenation of 4-methylene-γ-butyrolactone (Equation (39)). In the presence of a small amount of HBF_4, a di-*t*-Bu–MeOBIPHEP–Ru catalyst allows the hydrogenation of a 2-pyrone substrate with 97% ee (Equation (40)).[237]



93.8% ee (38)



94% ee (39)



97% ee (40)

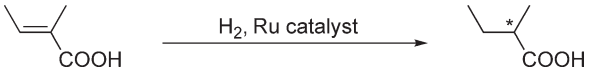
10.01.3.1.5 Hydrogenation of unsaturated acids and esters

10.01.3.1.5.(i) α,β-Unsaturated carboxylic acids

Significant advance has been achieved in the asymmetric hydrogenation of α,β-unsaturated carboxylic acids with chiral Ru catalysts. The Ru–BINAP–dicarboxylate complex has shown excellent enantioselectivities in the hydrogenation of some α,β-unsaturated carboxylic acids, albeit the catalytic efficiencies are still highly sensitive to the substrates, reaction temperature, and hydrogen pressure.[11c] Other atropisomeric ligands, such as H_8–BINAP,[238,238a] MeO–BIPHEP,[239] BIPHEMP,[239] P–Phos,[33,33a–33c] TetraMe–BITIANP,[31a] TetraMe–BITIOP,[32] are also effective for this transformation. Ru complexes prepared in different forms appear to exhibit slightly different efficiencies. Table 6 lists examples of the hydrogenation of tiglic acid with different metal–ligand complexes. The H_8–BINAP ligand with a larger dihedral angle gives superior results compared to the BINAP ligand.

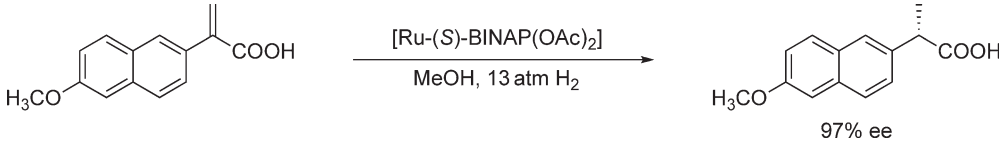
With a BINAP–Ru,[11c,240] H_8–BINAP–Ru,[238,238a] or P–Phos–Ru[33,33a–33c] catalyst, the anti-inflammatory drug (*S*)-ibuprofen and (*S*)-naproxen can be efficiently synthesized via asymmetric hydrogenation (Equation (41)). In the case of hydrogenation of 2-arylpropionic acids, high hydrogenation pressure and low temperature are required to achieve good enantioselectivity. With an (*R*)-BIPHEMP–Ru catalyst, (*S*)-2-(4-fluorophenyl)-3-methylbutanoic acid, a key intermediate for the synthesis of calcium antagonist, Mibefradil, can be obtained with 94% ee (Equation (42)).[241] Using (*R*)-**53**–Rh as catalyst, the asymmetric hydrogeanation of *tert*-butylammonium (3*Z*)-3-cyano-5-methyl-3-hexenoate produced the precursor to CI-1008 (pregabalin, a pharmaceutical for psychotic disorder, seizure disorder, and pain) with turnover numbers of 27,000 and 98% ee (Equation (43)).[123] An Rh–Me–DuPhos complex also provides

Table 6 Asymmetric hydrogenation of tiglic acid

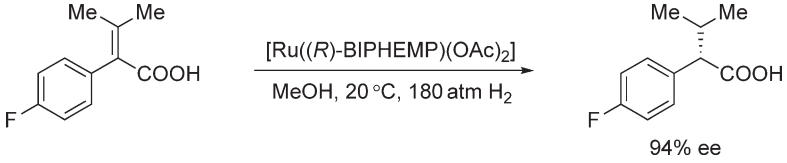


Catalyst	*S/C ratio*	*Reaction conditions*	*Percent ee of product (confign.)*	*References*
$Ru(OAc)_2$[(*R*)-BINAP]	100	MeOH, 15–30 °C, 4 atm H_2	91 (*R*)	11c
Ru[(*R*)-BINAP](2-methallyl)$_2$	100	MeOH, 20 °C, 4 atm H_2	90 (*R*)	239
$Ru(OAc)_2$[(*S*)-H8–BINAP]	200	MeOH, 10–25 C, 1.5 atm H_2	97 (*S*)	238
[(*R*)-MeO–BIPHEP]$RuBr_2$	100	MeOH, 20 °C, 1.4 atm H_2	92 (*R*)	239
$[NH_2Et_2]$[{RuCl[(*S*)-BIPHEMP]}$_2$(μ-Cl)$_3$]	100	MeOH, 20 °C, 4 atm H_2	98 (*S*)	239
Ru(*p*-cymene)[(−)-TetraMe–BITIANP)I_2]	500	MeOH, 25 °C, 10 atm H_2	92 (*S*)	31a
[Ru(−)-TetraMe-BITIOP](2-methally)$_2$]	3,000	MeOH, 25 °C, 10 atm H_2	94 (*R*)	32

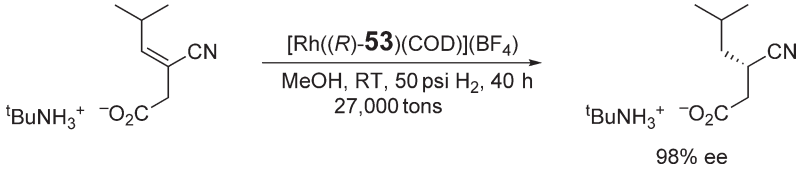
high enantioselectivity (97.7% ee, S/C = 100) for this reaction.[242] Using PhanePhos–Rh complex as catalyst, the asymmetric hydrogenation of an isomeric mixture ($E/Z = 19:1$) of 4,4′-diaryl-3-butenoate provided a chiral intermediate for an anti-depressant agent sertraline with 90% ee (Equation (44)).[243] Walphos was applied to the Rh-catalyzed hydrogenation of unsaturated carboxylic acid to yield a key synthon for renin inhibtor SPP100 with 95% ee and turnover numbers of 5,700 (Equation (45)).[90]



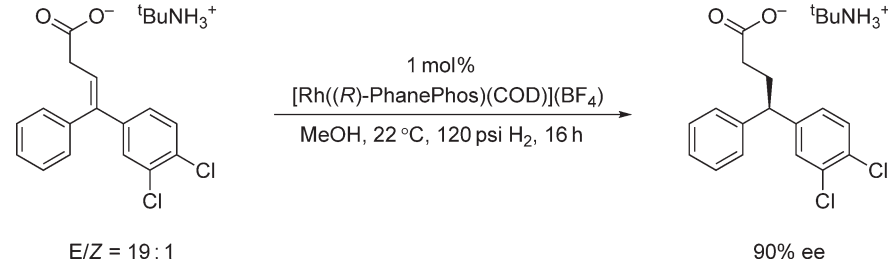
(41)



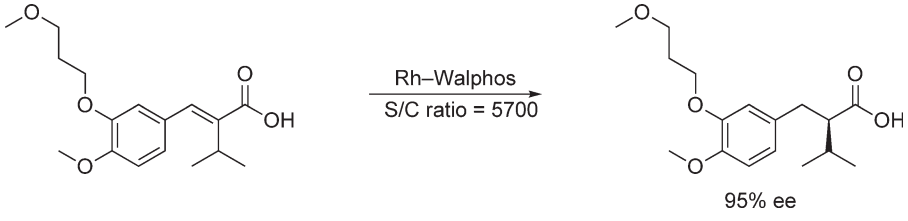
(42)



(43)

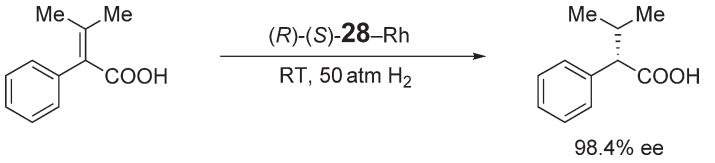


(44)



(45)

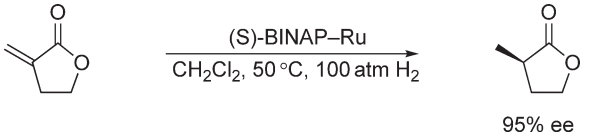
In contrast to successful results obtained with Ru catalysts, few systems have been reported on the Rh-catalyzed hydrogenation of α,β-unsaturated carboxylic acids. The (aminoalkyl)ferrocenylphosphine ligand **28** provides excellent reactivities and enantioselectivities in the Rh-catalyzed hydrogenation of trisubstituted acrylic acids.[79] The aminoalkyl side chain of the ligand is important to maintain the high reactivity and enantioselectivity. It is believed that the amino group of the ligand interacts with the carboxylic acid functionality of the substrate, hence facilitating the olefin coordination to the Rh center. When substrates with two different substituents at the β-positions are employed, the hydrogenation products with two chiral centers can be efficiently obtained. An (*R*)-(*S*)-**28**–Rh complex has also been employed for the synthesis of (*S*)-2-(4-fluorophenyl)-3-methylbutanoic acid, and 98% ee is obtained (Equation (46)).[241] An ^{i}Pr-DuPhos–Rh complex is also efficient for the hydrogenation of some α,β-unsaturated carboxylic acids such as tiglic acid.[8,8a]



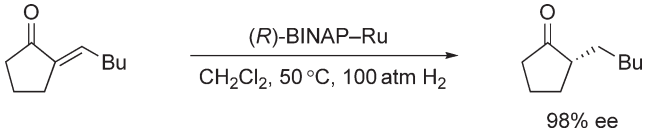
(46)

10.01.3.1.5.(ii) α,β-Unsaturated esters, amides, lactones, and ketones

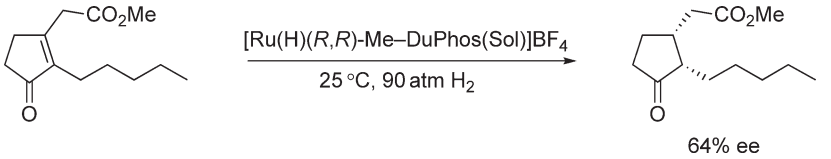
Limited progress has been achieved in the asymmetric hydrogenation of α,β-unsaturated carboxylic acid esters, amides, lactones, and ketones. The Ru–BINAP system is efficient for the hydrogenation of 2-methylene-γ-butyrolactone and 2-methylene–cyclopentanone (Equations (47) and (48)).[233,244] By using a protonated cationic (*R,R*)-Me–DuPhos–Ru complex as the catalyst, the hydrogenation of a vinylogous β-oxoester with a tetrasubstituted C═C bond provides (+)-*cis*-methyl dihydrojasmonate with 64% ee (Equation (49)).[245] With a dicationic (*S*)-di-*t*-Bu–MeOBIPHEP–Ru complex under a high hydrogen pressure, 3-ethoxypyrrolidinone is hydrogenated in isopropanol to give (*R*)-4-ethoxy-γ-lactam with 98% ee (Equation (50)).[47] Recent development of Ir–N, –P ligand systems allows the hydrogenation of β-methyl cinnamates with high enantioselectivities. Hydrogenation of ethyl β-methyl cinnamate with a cationic (*S*)-**100**–Ir complex as the catalyst provides the corresponding chiral acid with 94% ee.[183] A chiral phospholane–oxazoline ligand **109** is even more effective.[189] Its cationic Ir complex has allowed the synthesis of a set of chiral aryl 2-methyl butyric acid esters with ee ranging from 95% to 99% (Equation (51)). Using Ir–Phox complex as catalyst, a number of pharmaceutically interesting chiral 1-arylethylphosphonates were synthesized with 92∼95% ee through asymmetric hydrogenation (Equation (52)).[178b]



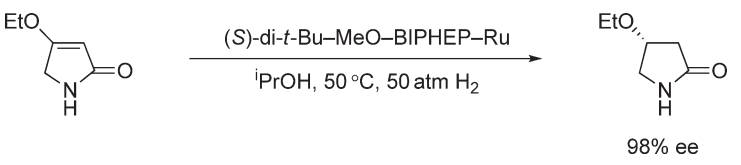
(47)



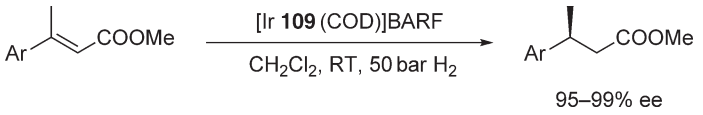
(48)



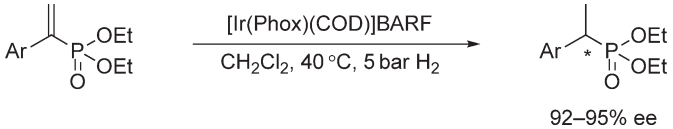
(49)



(50)



(51)



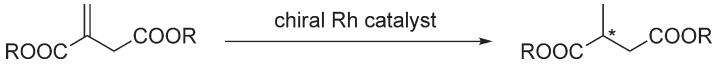
(52)

10.01.3.1.5.(iii) Itaconic acids and their derivatives

Many chiral phosphorus ligands have shown excellent reactivities and enantioselectivities in the Rh-catalyzed hydrogenation of itaconic acids or esters. Table 7 lists successful examples (over 95% ee) of hydrogenation of itaconic acid or dimethyl ester with different chiral phosphorus ligands. High reactivity is observed with electron-rich phosphane ligands such as BICHEP,[15b] Et–DuPhos,[247] Ph–BPE,[60] TangPhos,[116] and DuanPhos[114] as well as electron-deficient phosphite or phosphonite ligands such as **61**,[141] **63**,[143] and **74**[156] Some monophosphorus ligands such as MonoPhos,[165,165a] **80**,[162] and (*S*)-**85b**[168] are as equally efficient as bisphosphorus chelating ligands. A secondary phosphane **91**[63] is also effective. A bisphospholane ligand **10** with four hydroxyl groups allows the hydrogenation to proceed in aqueous solution.[57a]

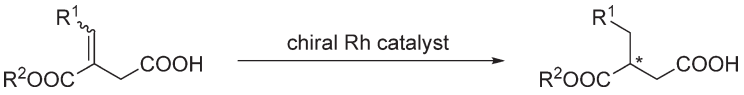
In contrast to the many successful examples for hydrogenation of the parent itaconic acid or its dimethyl ester, only a few ligands have been reported to be efficient for the hydrogenation of β-substituted itaconic acid derivatives. Rh complexes with chiral ligands such as MOD–DIOP,[69,69a–69h] BPPM,[246] Et–DuPhos,[247] and TangPhos[116] are

Table 7 Asymmetric hydrogenation of itaconic acid or dimethyl ester



Ligand	*R*	*S/C ratio*	*Reaction condition*	*Percent ee of product (confign.)*	*References*
(*R*)-BICHEP–Rh	H	1000	EtOH, 25 °C, 1 atm H_2	96 (*R*)	15b
(*R*,*R*)-Et-DuPhos	Me	10,000	MeOH, 25 °C, 5 atm H_2	98 (*R*)	247
(*R*,*R*)-Ph-BPE	Me	100,000	MeOH, 25 °C, 10 bar H_2	99 (*S*)	60
10	H	100	MeOH/H_2O(3 : 97), Rt, 10 atm H_2	>99 (*R*)	57a
13	Me	100	MeOH, Rt, 1 atm H_2	99.1 (*R*)	56
15	Me	100	MeOH, Rt, 1 atm H_2	97.9 (*R*)	59a
(*R*,*R*)-(*S*,*S*)-Et-TRAP	Me	200	CH_2Cl_2, reflux, 1atm H_2	96 (*S*)	80b
38	Me	100	MeOH, Rt, 1 atm H_2	98 (*S*)	88
39	Me	100	MeOH, Rt, 1 atm H_2	98 (*R*)	89
(*S*,*S*)-Et-FerroTANE	Me	200	MeOH, Rt, 5.5 atm H_2	98 (*R*)	94
(*S*,*S*,*S*,*S*)-**44**	H	100	MeOH, Rt, 80 psi H_2	99.5 (*R*)	96
46	Me	100	MeOH, Rt, 1atm H_2	95 (*R*)	100
(*S*,*S*)-Ad-BisP*	Me	500	MeOH, Rt, 1.6 atm H_2	99.6	101a
(*S*,*S*,*R*,*R*)-TangPhos	Me	5,000	THF, Rt, 20 psi H_2	99 (*S*)	116
(*R*,*R*,*S*,*S*)-DuanPhos	Me	100	THF, Rt, 20 psi H_2	>99 (*S*)	114
(*R*,*R*)-**61**	Me	5380	CH_2Cl_2, Rt, 1.3 bar H_2	>99.5 (*R*)	141
63	Me	1000	CH_2Cl_2, −10 °C, 0.3 bar H_2	98.7 (*R*)	143
70	H	100	MeOH, Rt, 300 psi H_2	97.4 (*R*)	155,155a
(S_c, R_p, S_a)-**74**	Me	10,000	CH_2Cl_2, Rt, 10 bar H_2	99.1 (*S*)	156
(*S*)-MonoPhos	H	20	CH_2Cl_2, 25 °C, 1 atm H_2	96.6 (*S*)	165,165a
(*S*)-(*R*)-**80**	Me	5000	CH_2Cl_2, 20 °C, 1.3 atm H_2	97.4 (*S*)	162
(*S*)-**85b**	Me	40,000	CH_2Cl_2, 23 °C, 20 bar H_2	96.9 (*S*)	168
86	Me	200	$ClCH_2CH_2Cl$, 50 °C, 100 psi H_2	99.6 (*R*)	170
(*Ra*, *S*)-**87**	Me	50	CH_2Cl_2, Rt, 3 bar H_2	96 (*R*)	171
88	Me	100	CH_2Cl_2, Rt, 10 atm H_2	99.4 (*R*)	172
(*R*,*R*)-**91**	H	100	^{i}PrOH, 20 °C, 1.1 atm H_2	96.0 (*S*)	63

Table 8 Asymmetric hydrogenation of β-substituted itaconic acid derivatives

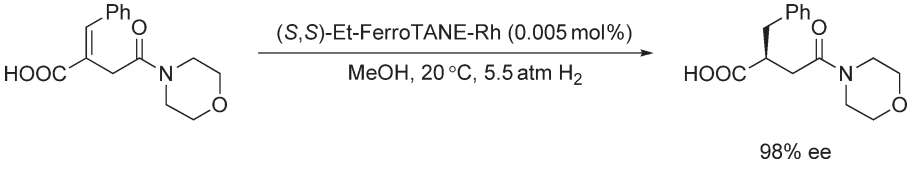


Ligand	R^1	R^2	*geometry, S/C ratio*	*Reaction conditions*	*Percent ee of product (confign.)*	*References*
(*R*,*R*)-MOD-DIOP	Ph	Me	*E*, 500	MeOH, NEt_3, 30 °C, 1atm H_2	96 (*S*)	69b
(*R*,*R*)-BPPM	Ph	H	*E*, 200	MeOH, NEt_3, 25 °C, 1atm H_2	94 (*R*)	246
(*S*,*S*)-Et-DuPhos	Ph	Me	*E*/*Z*, 3000	MeOH, Rt, 5.5 atm H_2[a]	97 (*S*)	247
(*S*,*S*,*R*,*R*)-TangPhos	ph	Me	*E*/*Z*, 200	THF, Rt, 20 psi H_2	95 (*S*)	116
(*S*,*S*)-Et-DuPhos	^{i}Pr	Me	*E*/*Z*, 3000	MeOH, Rt, 5.5 atm H_2[a]	99 (*R*)	247
(*S*,*S*,*R*,*R*)-TangPhos	^{i}Pr	Me	*E*/*Z*, 200	THF, Rt, 20 psi H_2	96 (*S*)	116
(*R*,*R*,*S*,*S*)-DuanPhos	^{i}Pr	Me	*E*/*Z*, 100	THF, Rt, 20 psi H_2	>99 (*S*)	114

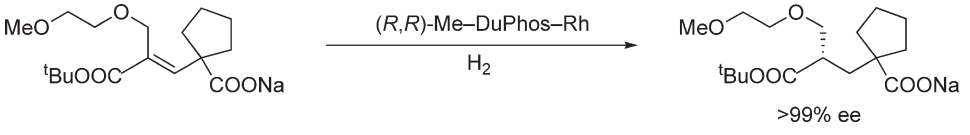
[a]10 mol% of NaOMe is added.

efficient for the hydrogenation of several β-substituted itaconic acid derivatives. Some examples are shown in Table 8. In the presence of a base such as sodium methoxide or tertiary amine, an Et–DuPhos–Rh complex has shown great enantioselectivities and reactivities in the hydrogenation of a series of β-aryl- or β-alkylitaconic acid monomethyl esters. The *E*/*Z*-isomeric mixtures of substrates can be directly used. High enantioselectivities have also been obtained with a TangPhos[116] or DuanPhos–Rh[114] catalysts in hydrogenation of a variety of β-aryl- or β-alkyl-substituted itaconic acid substrates.

A chiral 1,1′-diphosphetanylferrocene ligand, Et–FerroTANE, is very efficient for the hydrogenation of a series of β-aryl- or β-alkyl-substituted monoamidoitaconates.[94] For example, in the presence of 0.005 mol.% Et–FerroTANE–Rh catalyst, a β-phenyl(monoamido)itaconate is hydrogenated completely to give the chiral monoamidosuccinate with 98% ee (Equation (53)). A PYRPHOS ligand is also found to be effective for the hydrogenation of a β-aryl monoamidoitaconate.[246] With an Et–DuPhos–Rh catalyst, a unique olefin substrate has been hydrogenated to afford an important intermediate for the drug candoxatril with over 99% ee (Equation (54)).[248] An MeO–BIPHEP–Ru catalyst is also found to be very effective for this process when a mixed solvent (THF/H_2O) is applied.[249]



(53)

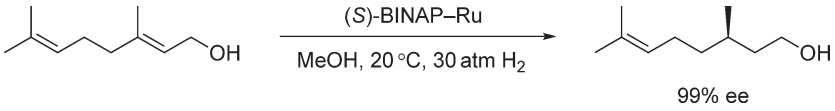


(54)

10.01.3.1.6 Hydrogenation of unsaturated alcohols

Asymmetric hydrogenation of unsaturated alcohols such as allylic and homoallylic alcohols was not very efficient until the discovery of the BINAP–Ru catalyst. With Ru(BINAP)$(OAc)_2$ as the catalyst, geraniol and nerol are successfully hydrogenated to give (*S*)- or (*R*)-citronellol in nearly quantitative yield with 96–99% ee (Equations (55) and (56)).[11b] The substrate to catalyst ratio up to 48,500 can be applied, and the other double bond at the C6 and C7 positions of the substrate is not reduced. A high hydrogen pressure is required for the high enantioselectivity in the hydrogenation of geraniol. Low hydrogen pressure facilitates the isomerization of geraniol to γ-geraniol, which leads to the hydrogenation product with opposite configuration, hence yielding a decreased ee.[250,250b] In addition to BINAP, other chiral atropisomeric ligands, such as MeO–BIPHEP,[17] TetraMe–BITIANP,[31a] and TetraMe–BITIOP,[32] are also effective for this transformation. The catalytic efficiency of the BINAP–Ru catalyst is strongly sensitive to the

substitution patterns of the allylic alcohols. Homoallylic alcohols can also be hydrogenated with high ee with the BINAP–Ru catalyst. Its application to the synthesis of (3*R*,7*R*)-3,7,11-trimethyldodecarol, an intermediate for the synthesis of α-tocopherol, is shown in equation (57). When racemic allylic alcohols are subjected to asymmetric hydrogenation, highly efficient kinetic resolution is achieved with a BINAP–Ru complex as the catalyst.[12b] A racemic 4-hydroxy-2-cyclopentenone is hydrogenated with an (*S*)-BINAP–Ru catalyst to leave the unreacted starting material with 98% ee at 68% conversion (Equation (58)). The chiral starting material serves as an important building block in the three-component coupling for prostaglandin synthesis.



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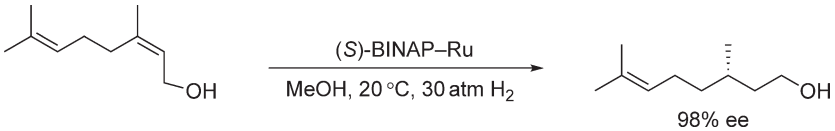
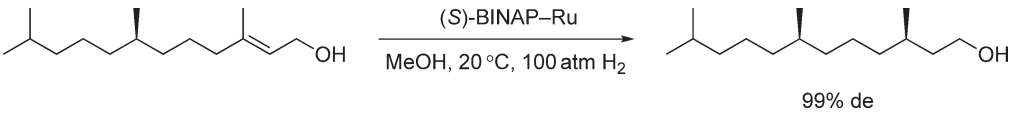
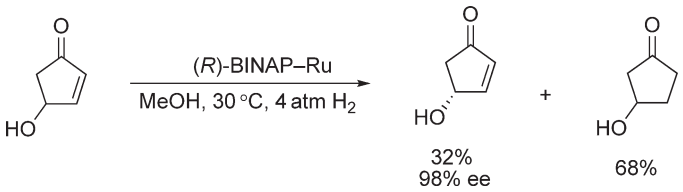


(56)



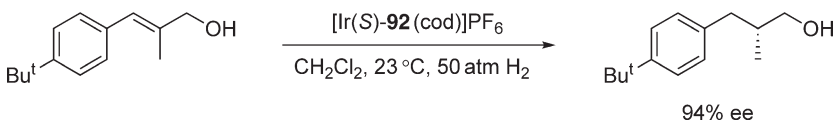
(57)



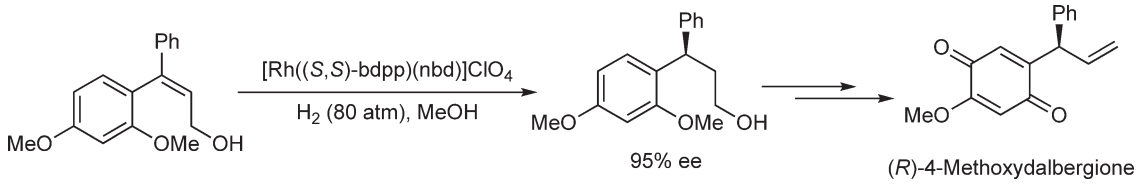
(58)

A chiral BDPP–Rh complex is an efficient catalyst for the hydrogenation of 3-(2′,4′-dimethoxyphenyl)-3-phenyl-2-propenol. The chiral alcohol product, with enantiomeric excess up to 95%, has been used for the synthesis of chiral 4-methoxydalbergione (Scheme 6).[251,251a]

The development of Ir-chiral N,P ligand system opens another promising way for the hydrogenation of allylic alcohol and its derivatives. For example, a cationic Phox–Ir complex catalyzes the hydrogenation of (*E*)-2-methyl-3-phenyl-9-propen-1-ol in a highly enantioselective fashion.[178] With 1 mol.% (*S*)-**92**–Ir catalyst, the hydrogenation proceeds completely to provide the chiral alcohol product in 96% ee. Under the same conditions, a *para*-^{t}Bu-substituted chiral alcohol derivative is obtained with 94% ee for the synthesis of lilial (Equation (59)). Heterocyclic N, P-ligand, HetPHOX **113**, is also efficient for this reaction.[191]



(59)

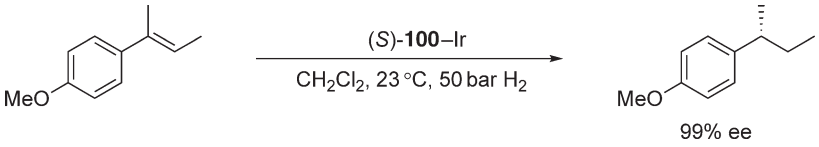


Scheme 6

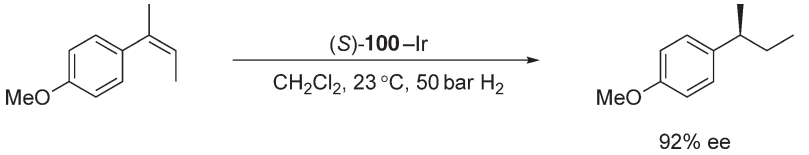
10.01.3.1.7 Hydrogenation of unfunctionalized olefins

Asymmetric hydrogenation of unfunctionalized olefins remains a challenging area since only limited success has been reached. Some chiral metallocene catalysts such as chiral titanocene[252] or zirconocene[253] have been found to be efficient for the hydrogenation of tri- or tetrasubstituted unfunctionalized olefins. With (EBTHI)TiH or (EBTHI)ZrH as the catalyst, a series of tri- or tetrasubstituted aryl alkenes have been hydrogenated with excellent enantioselectivity. Chiral cyclolanthanide complexes are also effective in the hydrogenation of 2-phenyl-1-butene at a low reaction temperature. Some Ru and Rh complexes with chiral bisphosphorus ligands have been tried with few successful results.[254,254a,254b] An Me–DuPhos–Ru complex in the presence of ^{t}BuOK has been applied for the hydrogenation of 3-phenylbutenes and enantioselectivity up to 89% ee is obtained.[255] Cationic Ir-chiral N, P ligand complexes have recently shown promising results in the enantioselective hydrogenation of unfunctionalized olefins. Several chiral N,P ligands have been developed and have provided excellent ee in the asymmetric hydrogenation of 2-methyl stilbene, as shown in Table 9.

A series of *para*-substituted (*E*)-methylstilbenes has been hydrogenated with a Phox–Ir catalyst with excellent enantioselectivities.[178,178a,178b] A threonine-derived phosphinite–oxazoline ligand (*S*)-**100** has provided high enantioselectivities for the hydrogenation of both (*E*)- and (*Z*)-2-(4-methoxyphenyl)-2-butene, although the configurations of the products are opposite (Equations (60) and (61)).[183] A terminal olefin 2-arylbutene is also hydrogenated at 0 °C under 1 atm of hydrogen to give the chiral product with 89% ee (Equation (62)). Hydrogenation of a tetrasubstituted olefin is catalyzed by a PHOX–Ir complex to give product with 81% ee and a complete conversion (Equation (63)).[178,178a,178b]

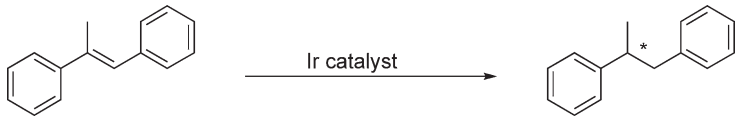


(60)

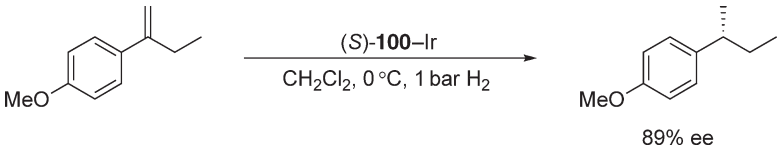


(61)

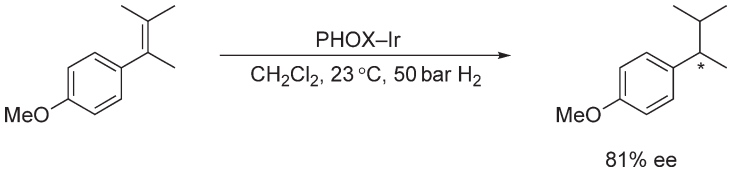
Table 9 Asymmetric hydrogenation of 2-methyl stilbene



Ligand	*S/C ratio*	*Reaction conditions*	*Percent ee of product (confign.)*	*References*
(*S*)-**92**	1000	CH_2Cl_2, 23 °C, 50 bar H_2	97 (*R*)	178
(*S*)-**94**	100	CH_2Cl_2, Rt, 50 bar H_2	99 (*R*)	180
(*S*)-**95**	100	CH_2Cl_2, 25 °C, 50 bar H_2	94 (*R*)	181
(*S*)-**98**	250	CH_2Cl_2, 23 °C, 50 bar H_2	98 (*R*)	182
(*S*)-**99**	5000	CH_2Cl_2, Rt, 50 bar H_2	99 (*R*)	183
(*S*)-**107**	500	CH_2Cl_2, 25 °C, 50 bar H_2	95 (*R*)	186
(*S*)-**105**	100	CH_2Cl_2, Rt, 50 bar H_2	96(*S*)	185
(*S*)-**106**	100	CH_2Cl_2, Rt, 50 bar H_2	97 (*S*)	185
109	100	CH_2Cl_2, Rt, 50 bar H_2	95 (*R*)	189
110	100	CH_2Cl_2, Rt, 100 bar H_2	99 (*R*)	190
HetPHOX **112**	100	CH_2Cl_2, Rt, 50 bar H_2	99	191
116	200	CH_2Cl_2, Rt, 50 bar H_2	95 (*S*)	193



(62)



(63)

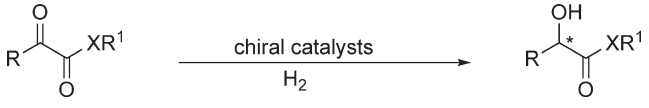
10.01.3.2 Asymmetric Hydrogenation of Ketones

10.01.3.2.1 Hydrogenation of functionalized ketones

10.01.3.2.1.(i) α-Keto esters

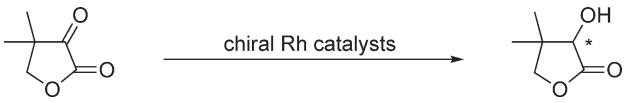
Asymmetric hydrogenation of α-keto esters has been studied with some Rh and Ru catalysts. Several neutral Rh catalysts with chiral ligands such as MCCPM,[126a,256] Cy,Cy-oxoProNOP,[148b,148c,148e] Cp,Cp-IndoNOP,[148f] and $Cr(CO)_3$-Cp,Cp-IndoNOP[148f] have shown excellent reactivities and enantioselectivities in the hydrogenation of some α-keto esters or amides. A cationic BoPhoz **73**–Rh complex is also effective for this transformation.[155,155a] Some Ru catalysts associated with chiral atropisomeric ligands such as BINAP,[257] BICHEP,[15c] MeOBIPHEP, TetraMe–BITIOP,[32] and TetraMe–BITIANP[31a] are also applicable (Table 10). A cyclic α-keto esters, dihydro-4,4-dimethyl-2,3-furandione, has been efficiently hydrogenated by several Rh catalysts with high turnover numbers (Table 11). The product, (*R*)-pantolactone, is a key intermediate for the synthesis of vitamin B and coenzyme A.

Table 10 Asymmetric hydrogenation of some α-keto esters or amides



Catalyst	*R*	*XR*^{1}	*S/C ratio*	*Reaction conditions*	*Percent ee of product (confign.)*	*References*
(*S*,*S*)-MCCPM-Rh	Me	OMe	2000	THF, 20 °C, 20 atm H_2	87 (*R*)	256
(−)-TetraMe-BITIANP–Ru	Me	OMe	600	MeOH, 25 °C, 100 atm H_2	88 (*S*)	31a
(*S*)-Cy,Cy-oxoProNOP–Rh	Me	OEt	200	Toluene, 20 °C, 50 atm H_2	95 (*R*)	148e
73-Rh	$Ph(CH_2)_2$	OEt	100	THF, Rt, 20 atm H_2	92.4 (*R*)	155,155a
(+)-TetraMe-BITIOP–Ru	$Ph(CH_2)_2$	OEt	462	EtOH, H_2O, 50 °C, 100 atm H_2, HBF_4	91 (*S*)	32
(*R*)-SEGPHOS–Ru	^{t}Bu	OEt	1,000	EtOH, 70 °C, 50 atm H_2	98.5 (*R*)	24,24a
(*R*)-BICHEP–Ru	Ph	OMe	100	EtOH, 25 °C, 5 tm H_2	>99 (*S*)	15c
(*S*)-MeO-BIPHEP–Ru	Ph	OMe		MeOH, 50 °C, 20 atm H_2	86 (*S*)	239
(*S*)-BINAP–Ru	4-MePh	OMe	150	MeOH, 30 °C, 100 atm H_2, HBF_4	93 (*S*)	257
(*S*)-Cp,Cp-IndoNOP–Rh	Ph	NHBn	200	Toluene, 20 °C, 1 atm H_2	91 (*S*)	148f
(*S*, 2*S*)-$Cr(CO)_3$-Cp,Cp-IndoNOP–Rh	Ph	NHBn	200	Toluene, 20 °C, 1 atm H_2	97 (*S*)	148g
(*R*)-BICHEP–Ru	Ph	NHBn	100	MeOH, 25 °C, 40 atm H_2	96 (*R*)	15d

Table 11 Asymmetric hydrogenation of dihydro-4,4-dimethyl-2,3-furandione

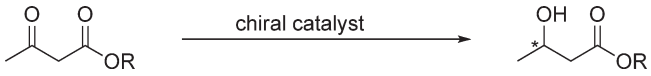


Ligand	*S/C ratio*	*Reaction conditions*	*Percent ee of product (confign.)*	*References*
(*S*,*S*)-BCPM–Rh	1,000	THF, 50 °C, 50 atm H_2	90.5 (*R*)	258
(*S*,*S*)-*m*-MePOPPM	150,000	Toluene, 40 °C, 12 atm H_2	95 (*R*)	259,259a, 259b
(*S*)-Cp,Cp-oxoProNOP	70,000	Toluene, 40 °C, 40 atm H_2	96 (*R*)	148c
(*S*)-Cp,Cp-IndoNOP	200	Toluene, 20 °C, 1 atm H_2	>99 (*R*)	148f
(*S*,2*S*)-Cr(CO)$_3$-Cp,Cp-IndoNOP	200	Toluene, 20 °C, 1 atm H_2	>99 (*R*)	148f
59	100	THF, Rt, 20 atm H_2	97.2 (*R*)	155, 155a

10.01.3.2.1.(ii) β-Keto esters

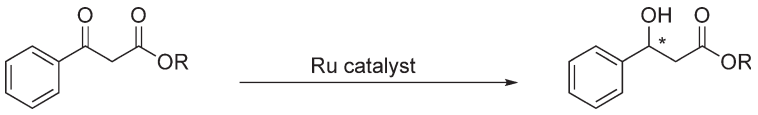
Asymmetric hydrogenation of β-keto esters has been very successful with chiral Ru catalysts, and a detailed review has been written on this subject.[260] With a BINAP–Ru catalyst, a variety of β-keto esters have been hydrogenated to give chiral β-hydroxyl esters with high enantioselectivities.[12] Several different Ru–BINAP complexes have been employed and similarly high enantionselectivities are found.[261,261a–261g] In addition to BINAP, many other chiral atropisomeric biaryl ligands are also very efficient for this transformation. Some other C_2-symmetric ligands such as BPE,[262] BisP*,[263] and PHANEPHOS,[130a] are also effective. A Josiphos–Rh complex has found to be effective for the hydrogenation of ethyl 3-oxobutanoate.[81] Some examples of the efficient hydrogenation of 3-oxobutanoic acid esters with different chiral phosphorus ligand systems are listed in Table 12.

Table 12 Asymmetric hydrogenation of 3-oxobutanoic acid esters



Catalyst	*R*	*S/C ratio*	*Reaction conditions*	*Percent ee of product (confign.)*	*References*
$RuCl_2$[(*R*)-BINAP]	Me	2,000	MeOH, 23 °C, 100 atm H_2	>99 (*R*)	12
$RuCl_2$[(*S*)-**1**) $(DMF)_n$	Me	1,260	MeOH, 100 °C, 100 atm H_2	99 (*S*)	261
$RuBr_2$[(*S*)-NAPhePHOS]	Me	100	MeOH, 50 °C, 50 atm H_2	97 (*S*)	30
Ru[(*R*)-BisbenzodioxanPhos]$Cl_2(DMF)_n$	Me	1,000	MeOH, 80 °C, 50 psi H_2	98.1 (*R*)	25,25a,25b
$RuCl_2$[(*S*)-BIFAP](DMF)$_n$	Me	1,000	MeOH, 70 °C, 100 atm H_2	100 (*S*)	23
Ru[(+)-(TetraMe-BITIANP)]$Cl_2(DMF)_n$	Et	1,000	MeOH, 70 °C, 100 atm H_2	99 (*R*)	31a
Ru(+)-(TetraMe-BITIOP)$Cl_2(DMF)_n$	Et	1,000	EtOH, 70 °C, 100 atm H_2	98 (*S*)	32
Ru[(*S*)-P-Phos)]$Cl_2(DMF)_n$	Me	400	MeOH/CH_2Cl_2, 70 °C, 50 psi H_2	98.5	33,33a–33c
Ru[(*R*)-C_4-TunePhos)$Cl_2(DMF)_n$	Me	100	MeOH, 60 °C, 750 psi H_2	99.1(*R*)	26
Ru[(*S*)-FUPMOP](*p*-cymene)I_2	Me	1,000	MeOH/CH_2Cl_2, 30–40 °C, 30 atm H_2	100 (*S*)	19
Ru[(*R*)-BIMOP)](*p*-cymene)I_2	Me	1000	MeOH/CH_2Cl_2, 30–40 °C, 30 atm H_2	99 (*R*)	18
Ru[(*R*)-MeO–BIPHEP)]Br_2	Me	100	MeOH, 50 °C, 20 atm H_2	>99 (*R*)	239
Ru[(*S*)-BIPHEMP)]Br_2	Me	100	MeOH, 80 °C, 10atm H_2	>99 (*S*)	239
Ru[(*R*)-difluorphos]Br_2	Me	100	MeOH, 50 °C, 4 bar H_2	99 (*S*)	37
{Ru[(*R*)-4,4′-diamBINAP]Br_2}$(Br^-)_2$	Me	1000	H_2O, 50 °C, 40 bar H_2	99 (*S*)	42
Ru[(*S*)-[2,2]PHANEPHOS](CF$_3$COO)$_2$	Me	250	MeOH/H_2O, TBAI, −5 °C, 50 psi H_2	96 (*R*)	130a
Ru(**35**)Br_2	Et	200	EtOH, 50 °C, 50 atm H_2	95.5 (*R*)	88
Ru[(*R*,*R*)-^{i}Pr-BPE]Br_2	Me	500	MeOH/H_2O, 35 °C, 60 psi H_2	99.3 (*S*)	262
Ru[(*S*,*S*)-^{t}Bu–BisP*] Br_2	Me	200	MeOH/H_2O, 70 °C, 6 atm H_2	98	263
(*R*)-(*S*)-Josiphos–Rh	Et	100	MeOH, Rt, 20 atm H_2	97 (*S*)	81

Table 13 Asymmetric hydrogenation of 3-oxo-3-phenylpropionic ester

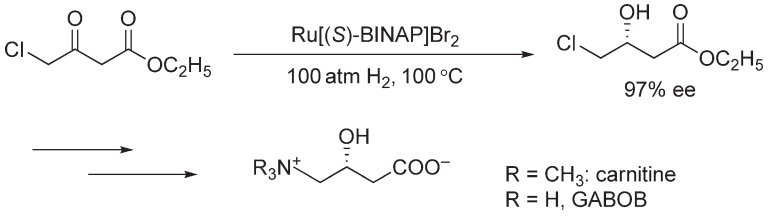


Catalyst	*R*	*S/C ratio*	*Reaction conditions*	*Percent ee of product (confign.)*	*References*
$RuBr_2$[(*R*)-BINAP]	Et	760	MeOH, 23–30 °C, 91 atm H_2	85 (*S*)	12
$RuBr_2$[(*R*)-MeO–BIPHEP]	Et	50	EtOH, 50 °C, 1 atm H_2	96 (*S*)	261b
Ru[(−)-TetraMe–BITIOP]Cl_2	Et	257	MeOH/H_2O, 45 °C, 100 atm H_2	93 (*S*)	32
$[NH_2Me_2]$[{RuCl[(*R*)-SEGPHOS]}$_2$(μ-Cl)$_3$]	Me	10,000	MeOH, 80 °C, 30 atm H_2	97.6 (*S*)	24a
Ru[(*R*)-difluorphos]Br_2	Et	100	EtOH, 80 °C, 10 bar H_2	92 (*S*)	37
Ru[(*R*)-**3**]Cl_2	Et	100	MeOH, Rt, 1400 psi H_2	99.5 (*S*)	40
{Ru[(*R*)-4,4′-diamBINAP]Br_2}(Br^-)$_2$	Me	1,000	H_2O, 50 °C, 40 bar H_2	99 (*S*)	42
Ru(**38**)Br_2	Et	200	MeOH, 50 °C, 50 atm H_2	96 (*S*)	88
Ru[(*R*)-Xyl-P-Phos)] (C_6H_6)Cl_2	Et	800	EtOH/CH_2Cl_2, 90 °C, 300 psi H_2	96.2 (*S*)	33
Ru[(*S*)-Xylyl-*o*-BINAPO)]Cl_2(DMF)$_n$	Et	100	EtOH/CH_2Cl_2, 50 °C, 80 psi H_2	99 (*R*)	140

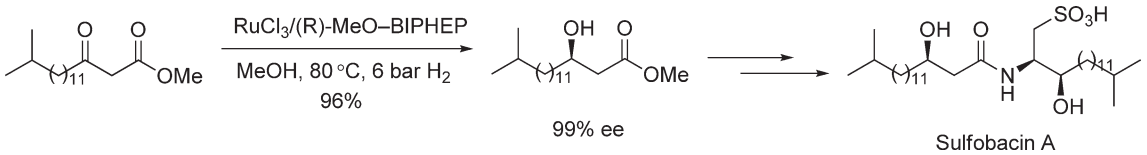
Although the BINAP–Ru(II) system has been recognized as an efficient and general catalyst for the hydrogenation of β-alkyl-β-keto esters, the enantioselectivity obtained in the hydrogenation of 3-oxo-3-phenylpropionic ester is low, providing the corresponding chiral 3-hydroxyl-3-phenylpropionic ester with 85% ee.[12] Many other atropisomeric ligands have provided better enantioselectivity for this substrate, as shown in Table 13. One bisphosphinite ligand *o*-Xylyl–BINAPO has provided excellent enantioselectivity up to 99% ee in the Ru-catalyzed hydrogenation of a series of β-aryl-β-keto esters.[140] The BINAP–Ru system is also efficient for hydrogenation of β-keto amide and β-keto thioesters.[12a,264,264a]

When a coordinative functional group such as a chloride or methoxy group exists in the proximity of the carbonyl group of a β-keto ester, lower enantioselectivity appears to be observed due to the competition of two different coordination patterns. 4-Benzyloxy- and 4-chloro-3-oxobutanoate are hydrogenated at room temperature with a BINAP–Ru catalyst to give alcohols with 78% ee and 56% ee, respectively.[265] However, the enantioselectivity can be dramatically improved when a higher reaction temperature is employed. In fact, 97% ee is observed when hydrogenation of 4-chloro-3-oxobutanoate is carried out at 100 °C (Scheme 7). The chiral product has allowed the efficient synthesis of γ-amino-β-hydroxybutyric acid (GABOB) and (*R*)-carnitine, a carrier of long-chain fatty acids through the mitochondrial membrane.

Using $RuCl_3$/(*R*)-MeO–BIPHEP catalytic system, the β-hydroxy ester, a key intermediate to vWF receptor antagonists Sulfobacin A, was produced through asymmetric hydrogenation in 96% yield and 99% ee (Scheme 8).[266] The

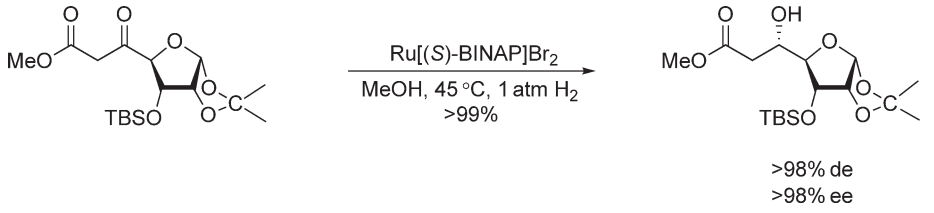


Scheme 7



Scheme 8

glycoside-derived β-hydroxy ester was generated via Ru(BINAP)Br_2-catalyzed hydrogenation of β-keto ester bearing a sugar moiety with >98% de and >98% ee (Equation (64)).[267]

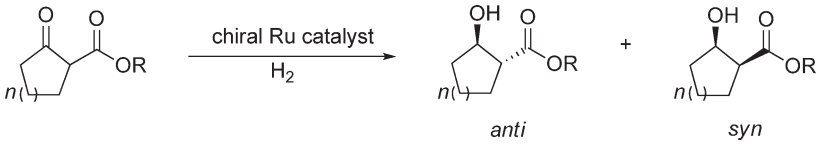


(64)

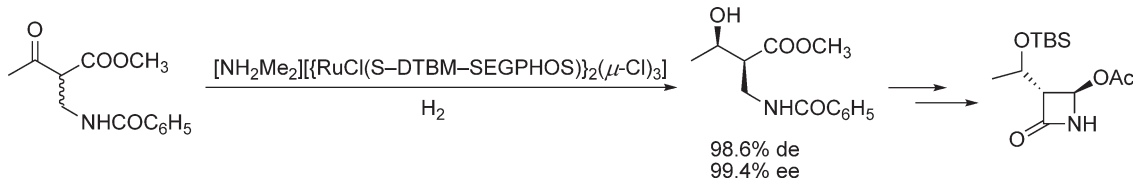
When a racemic α-monosubstituted β-keto ester is subjected to asymmetric hydrogenation, efficient dynamic resolution can be realized if the racemization of the substrates is fast and the chiral recognition of hydrogenation catalyst is good.[12c,268,268a] In fact, excellent dynamic kinetic resolution has been discovered in the hydrogenation of several α-monosubstituted β-keto esters with few Ru catalysts under suitable conditions. Hydrogenation of 2-alkoxycarbonylcycloalkanones has been a standard reaction to test the efficiency of different Ru catalysts (Table 14). The *anti*-hydrogenation product is preferentially formed, and 99% ee has been obtained for the *anti*-product when a TetraMe–BITIANP–Ru[31a] or TetraMe–BITIOP–Ru[32] complex is used as the catalyst. Reaction solvent and catalyst precursor dramatically affect both diastereoselectivity and enantioselectivity of the reaction.

Hydrogenation of a racemic 3-acetyltetrahydrofuran-2-one is successfully catalyzed by the BINAP–Ru system to give the *cis*-hydrogenation product with 97% ee and 99 : 1 diastereoselectivity (Equation (65)).[257] A TetraMe–BITIANP–Ru complex is also effective for this transformation.[31a] The BINAP–Ru system also provides efficient dynamic kinetic resolution in the hydrogenation of α-acylamino and α-amidomethyl β-keto esters.[12c,257,270] High enantioselectivities and diasteroselectivities are obtained for the *cis*-hydrogenation product. Excellent enantioselectivity and diastereoselectivity are obtained in the hydrogenation of 2-benzamidomethyl-3-oxobutanoate with a (−)-DTBM–SEGPHOS–Ru catalyst.[24a] The methyl (2*S*,3*R*)-2-benzamidomethyl-3-hydroxybutanoate is obtained with 99.4% ee and 98.6% de. The product can be transformed into a key intermediate of carbapenem antibiotics (Scheme 9). Excellent selectivities, 99% ee and 94% de, are obtained when a (−)-TetraMe–BITIOP–Ru complex is

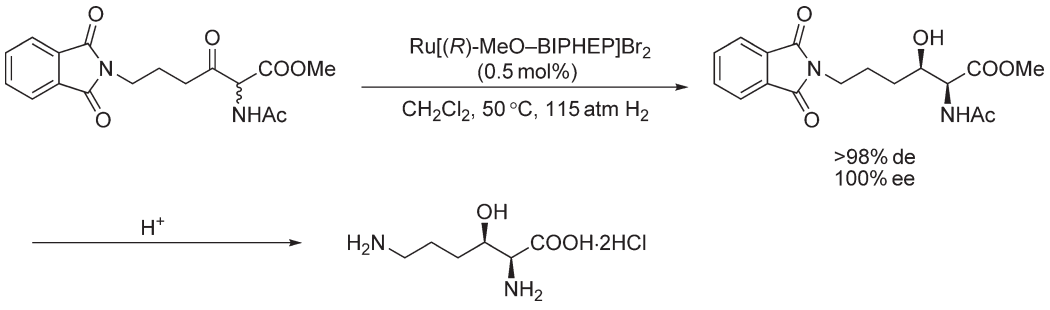
Table 14 Asymmetric hydrogenation of 2-alkoxycarbonylcycloalkanones



Catalyst	*n*	*R*	*S/C ratio*	*Reaction conditions*	*Anti : syn*	*Percent ee of the anti product (confign.)*	*References*
Ru[(*R*)-BINAP]Cl(C_6H_6)Cl	1	Me	1,170	CH_2Cl_2, 50 °C, 100 atm H_2	99 : 1	93 (*R*,*R*)	12c
Ru[(+)-(TetraMe-BITIANP)]$Cl_2(DMF)_n$	1	Me	1,000	MeOH, 70 °C, 100 atm H_2	93 : 7	99 (*R*,*R*)	31a
[Ru(+)-(TetraMe-BITIOP)(cymene)I]I	1	Me	1,000	MeOH, CF_3COOH, 80 °C, 100 atm H_2	94 : 6	99 (*S*,*S*)	32
Ru[(*R*)-C_4-TunaPhos)]$Cl_2(DMF)_n$	1	Me	200	MeOH, 60 °C, 750 psi H_2	N/A	96.8 (*R*,*R*)	26
Ru[(*R*)-MeO-BIPHEP)]$Cl_2(DMF)_n$	1	Me	200	MeOH, 60 °C, 750 psi H_2	N/A	97.5 (*R*,*R*)	26
Ru(**35**)Br_2	1	Et	200	CH_2Cl_2/EtOH, 50 °C, 50 atm H_2	99 : 1	90.9 (*R*,*R*)	88
Ru [(*R*,*R*)-^{i}Pr-BPE]Br_2	1	Me	500	MeOH/H_2O (9 : 1), 35 °C, 60 psi H_2	24 : 1	98.3 (*S*,*S*)	262
Ru[(*R*,*R*)-*t*-BuBisP*]Br_2	1	Me	200	MeOH/H_2O (10 : 1), 70 °C, 6 atm H_2	70 : 13	96	263
Ru[(*R*)-BINAP]Cl(C_6H_6)Cl	2	Et	500	CH_2Cl_2, 50 °C, 100 atm H_2	95 : 5	90 (*R*,*R*)	269
Ru[(*R*)-BINAP]Cl(C_6H_6)Cl	3	Et	500	CH_2Cl_2, 50 °C, 100 atm H_2	93 : 7	93 (*R*,*R*)	269

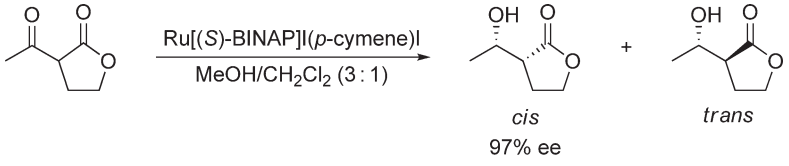


Scheme 9

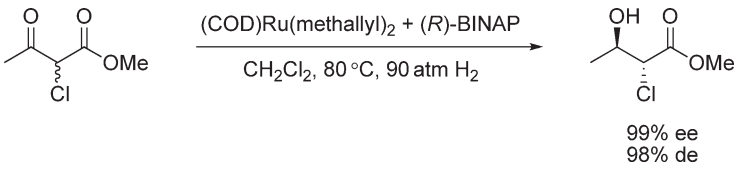


Scheme 10

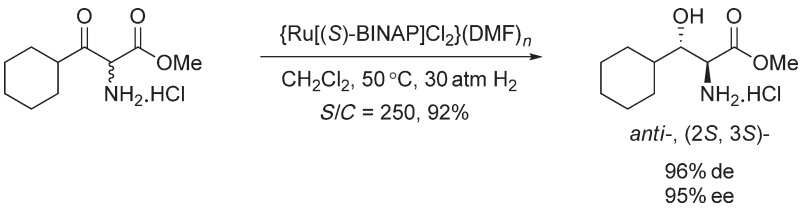
used as the catalyst.[32] When a BIPHEP–Ru complex is applied as catalyst to the hydrogenation of racemic methyl 2-acetamido-3-keto-6-phthalimidohexanoate for the synthesis of (2*S*,3*R*)-3-hydroxylysine, excellent enantioselectivity and diastereoselectivity are obtained (Scheme 10).[271] Efficient dynamic kinetic resolution is also observed in the hydrogenation of α-chloro-β-keto esters with *anti*-chlorohydrin as the major product.[272] With (COD)Ru(methallyl)$_2$-(*S*)-BINAP as the catalytic system and CH_2Cl_2 as the solvent, the hydrogenation of racemic ethyl 2-chloro-3-phenyl-3-oxopropionate provides the *anti*-chlorohydrin product with 99% ee and 98% de (Equation (66)). The product can be directly converted into chiral (2*S*,3*R*)-methylglycidate. Some catalytic systems have shown high *syn*-selectivity for the asymmetric hydrogenation of racemic α-amino β-keto esters through dynamic kinetic resolution, but few ligands provided *anti*-selective hydrogenation. Using Ru–BINAP complex as catalyst and hydrochloride salt of racemic α-amino β-keto esters as substrate, high enantioselectivities and diasteroselectivities are achieved for the *anti*-hydrogenation product (Equation (67)). The reverse *syn*/*anti*-selectivity was believed to be attributed to the unprotected amino group, which coordinated with Ru and served as a stronger directing substituent than the ester group.[273] Excellent dynamic kinetic resolution was observed for *anti*-selective hydrogenation of racemic α-phthalimide β-keto esters with Ru-C3-TunePhos as catalyst (Equation (68)).[29]



(65)



(66)



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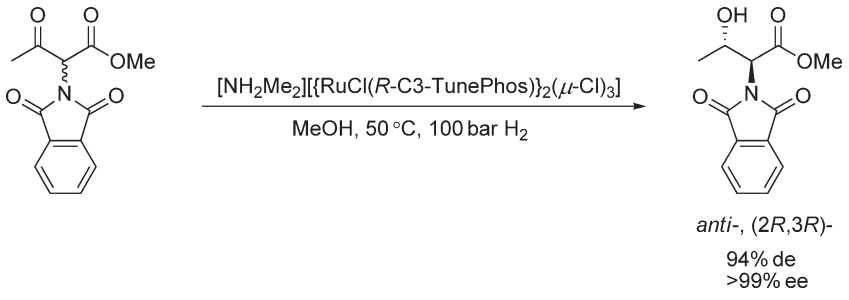
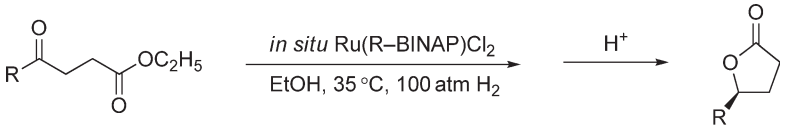


(68)

10.01.3.2.1.(iii) γ-Keto esters

γ-Keto esters can also be efficiently hydrogenated by chiral Ru catalysts associated with atropisomeric ligands with a prolonged reaction time.[274] For example, with an *in situ* formed Ru–BINAP catalyst from Ru(BINAP)$(OAc)_2$ and HCl, a series of chiral lactones can be efficiently synthesized through asymmetric hydrogenation of 4-oxo-carboxylates (Equation (69)). Hydrogenation of ethyl levulinate is performed with an (*R*)-SEGPHOS–Ru catalyst to give ethyl (R)-4-hydroxypentanoate with up to 99% ee.[24a]



(69)

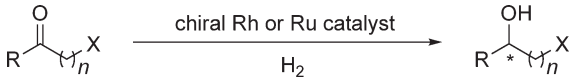
R = CH_3, C_2H_5, *n*-C_8H_{17}, C_6H_5

10.01.3.2.1.(iv) Amino ketones

Amino ketones or their hydrochloride salts can be effectively hydrogenated with chiral Rh or Ru catalysts (Table 15). The Rh catalysts combined with chiral phosphorus ligands such as BPPFOH,[78a] MCCPM,[126e–j] Cy,Cy-oxoProNOP,[148b,148d] Cp,Cp-oxoProNOP,[148b,148d] IndoNOP,[148f] and DuanPhos[117] have provided excellent enantioselectivities and reactivities in the hydrogenation of some α-, β-, or γ-alkyl amino ketone hydrochloride salts. For example, the hydrogenation of 2-diethylaminoacetophenone catalyzed by an MCCPM–Rh complex at 50 °C under 20 atm of hydrogen afford the chiral amino alcohol product with 96% ee and the S/C ratio of 100,000.[275] Using Rh–DuanPhosas as catalyst, a series of γ-secondary amino alcohol was synthesized with high enantioselectivities (up to >99% ee).[117] A BINAP–Ru catalyst has also shown excellent enantioselectivity in the hydrogenation of α-dimethylamino ketones under high hydrogen pressure.[12a,257] The *trans*-$RuCl_2$[(*R*)-XylBINAP][(*R*)-daipen] complex has been proved to be very efficient for the hydrogenation of a wide range of α-, β-, or γ-amino ketones.[276] High enantioselectivities and turnover numbers are achieved under mild conditions. Zhang's Ru-C3-TunePhos catalytic system has shown excellent enantioselectivity (>99% ee) and reactivity for the asymmetric hydrogenation of α-phthalimide ketones, and turnover numbers up to 10,000 have been achieved. (Table 15).[29] 4,4′-$[SiMe_3]_2$–BINAP **3** is also effective for this transformation.[41]

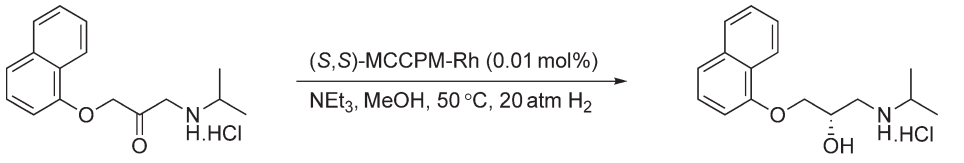
Excellent asymmetric hydrogenation of amino ketones has been applied for the syntheses of many chiral drugs. For example, the enantioselective hydrogenation of 3-aryloxy-2-oxo-1-propylamine derivatives can directly afford the 1-amino-3-aryloxy-2-propanol derivatives as chiral β-adrenergic blocking agents. This has been successfully accomplished with a neutral MCCPM–Rh complex as the catalyst. With 0.01 mol.% of an (*S*,*S*)-MCCPM–Rh complex,

Table 15 Asymmetric hydrogenation of α-phthalimide ketones



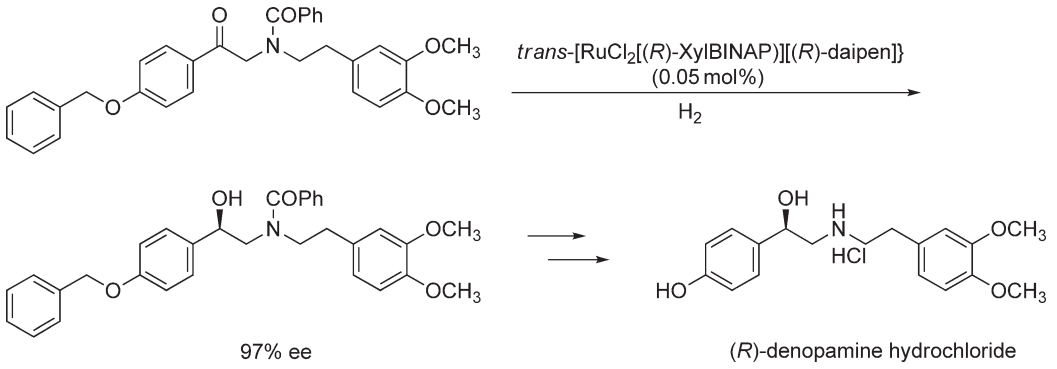
Catalyst	*R*	*n*	*X*	*S/C ratio*	*Reaction conditions*	*Percent ee of product (confign.)*	*References*
(*R*)-(*S*)-BPPFOH–Rh	(3,4)-$(OH)_2$Ph	1	NHMe·HCl	100	NEt_3, MeOH, Rt, 50 atm H_2	95 (*R*)	78a
(2*S*,4*S*)-MCCPM–Rh	Ph	1	NEt_2·HCl	100,000	NEt_3, MeOH, 50 °C, 20 atm H_2	96 (*S*)	275
(*S*)-Cp,Cp-oxoProNOP–Rh	Ph	1	NMe_2·HCl	200	MeOH, 20 °C, 50 atm H_2	96 (*S*)	148d
(*S*)-Cp,Cp-oxoProNOP–Rh	Me	1	NMe_2·HCl	200	MeOH, 20 °C, 50 atm H_2	97 (*S*)	148d
(*S*)-Cp,Cp-IndoNOP–Rh	Ph	1	NMe_2·HCl	200	Toluene, 20 °C, 50 atm H_2	99 (*S*)	148f
(*S*)-Cy,Cy-oxoProNOP–Rh	Ph	2	NMe_2·HCl	200	Toluene, 20 °C, 20 atm H_2	93 (*R*)	148f
(2*S*,4*S*)-MCCPM–Rh	Ph	2	N(Me)Bn·HCl	1,000	MeOH, 50 °C, 30 atm H_2	91 (*R*)	126f
(*S*)-Cy,Cy-oxoProNOP–Rh	Ph	3	NMe_2·HCl	200	Toluene, 80 °C, 50 atm H_2	92 (*R*)	148f
(S_c,R_p)-DuanPhos	4-Br-Ph	2	NHMe·HCl	200	MeOH, 50 °C, 50 bar H_2, K_2CO_3	>99 (*S*)	117
(S_c,R_p)-DuanPhos	4-OMePh	2	NHMe·HCl	200	MeOH, 50 °C, 50 bar H_2, K_2CO_3	>99 (*S*)	117
[Ru-(*S*)-BINAP]Br_2	Ph	1	NMe_2	490	MeOH, 20–32 °C, 100 atm H_2	95 (*S*)	12a
RuI[(*S*)-BINAP)](p-cymene)I	Me	1	NMe_2	1,100	CH_2Cl_2/MeOH, 30 °C, 105 atm H_2	99.4 (*S*)	257
trans-$RuCl_2$[(*R*)-XylBINAP][(*R*)-daipen]	Me	1	NMe_2	2,000	^{t}BuOK, ^{i}PrOH, 25 °C, 8 atm H_2	92 (*S*)	276
trans-$RuCl_2$[(*R*)-XylBINAP][(*R*)-daipen]	Ph	1	NMe_2	2,000	^{t}BuOK, ^{i}PrOH, 25 °C, 8 atm H_2	93 (*R*)	276
trans-$RuCl_2$[(*R*)-XylBINAP][(*R*)-daipen]	Ph	1	N(Ac)Me	2,000	^{t}BuOK, ^{i}PrOH, 25 °C, 8 atm H_2	99 (*R*)	276
trans-$RuCl_2$[(*R*)-XylBINAP][(*R*)-daipen]	Ph	1	N(Boc)Me	2,000	^{t}BuOK, ^{i}PrOH, 25 °C, 8 atm H_2	99 (*R*)	276
trans-$RuCl_2$[(*R*)-XylBINAP][(*R*)-daipen]	Ph	2	NMe_2	10,000	^{t}BuOK, ^{i}PrOH, 25 °C, 8 atm H_2	97.5 (*R*)	276
$[NH_2Me_2][\{RuCl[(S)$-TunePhos$]\}_2(\mu$-$Cl)_3]$	Ph	1	Phthalimide	100	EtOH, 80 °C, 1,500 psi H_2	98.5	29
$[NH_2Me_2][\{RuCl[(S)$-TunePhos$]\}_2(\mu$-$Cl)_3]$	Me	1	Phthalimide	10,000	EtOH, 80 °C, 100 bar H_2	>99 (*S*)	29
$[NH_2Me_2][\{RuCl[(R)$-**3**$]\}_2$-$(\mu$-$Cl)_3]$	Ph	1	Phthalimide	100	EtOH, 80 °C, 1,500 psi H_2	99	41

(*S*)-propranolol is obtained with 90.8% ee from the corresponding α-amino ketone substrate (Equation (70)).[126e] The *trans*-$RuCl_2$[(*R*)-XylBINAP][(*R*)-daipen] complex has been applied as a catalyst to the enantioselective synthesis of (*R*)-denopamine, a β_1-receptor agonist used for treatment of congestive heart failure (Scheme 11).[276] A γ-functionalized amino ketone is also hydrogenated efficiently with 99% ee to provide BMS181100, a potent antipsychotic agent (Equation (71)).[276] The chiral γ-secondary amino alcohols, key precursors to pharmarceuticals (*S*)-fluroxetine and (*S*)-duloxetine, were synthesized with Rh–DuanPhosas catalyst, and high enantioselectivities (up to >99% ee) and high turnover numbers (up to 6,000) were obtained (Scheme 12).[117]

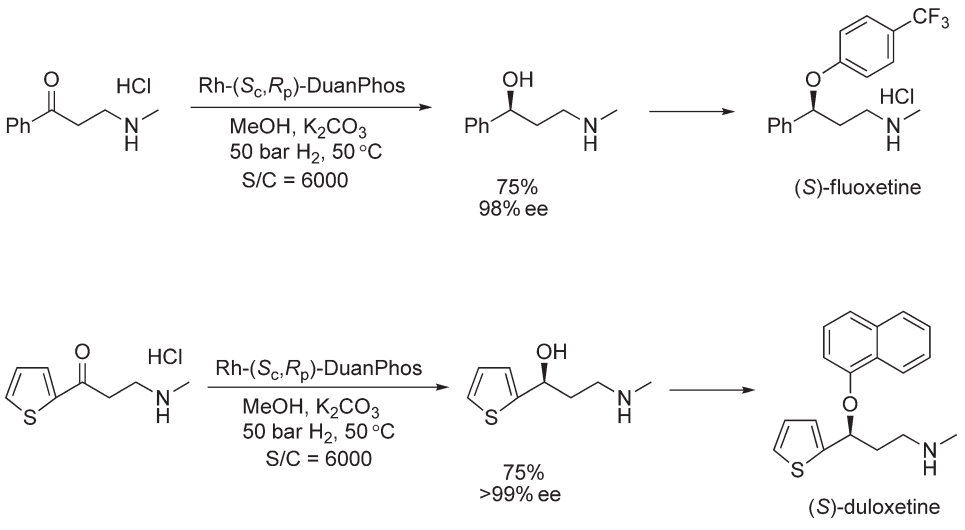


(70)

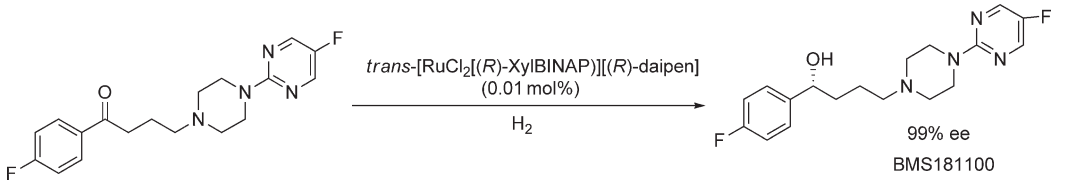
(*S*)-Propranolol hydrochloride



Scheme 11



Scheme 12



(71)

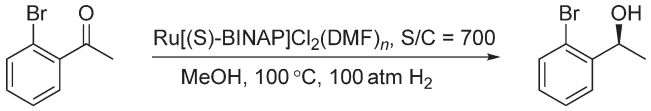
10.01.3.2.1.(v) Hydroxyl ketones, alkoxy ketones, phenylthio ketones, and *ortho*-haloaryl ketones

Enantioselective hydrogenation of α-, or β-hydroxylketones (Table 16) has been realized by a BINAP–Ru catalyst.[12a] An SEGPHOS–Ru complex has been demonstrated as a superior catalyst for the asymmetric hydrogenation of α-hydroxyl ketones.[24a] The chiral diol can be obtained with 98% ee and a substrate-to-catalyst ratio of 10,000. α-Alkoxy ketones can also be reduced with high enantioselectivity with an Ru–XylBINAP/DAIPEN complex as the catalyst.[3i] Although the alkoxy group of the substrates do not participate in coordination with the Ru catalyst, they possess a significant stereo-directing ability in achieving high enantioselectivity. For example, methoxyacetophenone is hydrogenated with an Ru-(*R*)-XylBINAP/(*R*)-DIPEN complex to provide the corresponding (*R*)-diol with 95% ee. Hydrogenation of an α,α'-dialkoxy ketones is catalyzed by the Ru–BINAP system to give chiral 1-*o*-octadecyl-3-*o*-trityl

Table 16 Asymmetric hydrogenation of α, or β-hydroxylketones

Catalyst	*R*	*n*	R^1	*S/C ratio*	*Reaction condition*	*Percent ee of product (confign.)*	*References*
$RuCl_2$[(*R*)-BINAP]	Me	1	H	230	MeOH, 20–32 °C, 93 atm H_2	92 (*R*)	12a
$[NH_2Me_2]$[{RuCl[(*R*)-SEGPHOS]}$_2(\mu$-Cl)$_3$]	Me	1	H	10,000	MeOH, 65 °C, 30 atm H_2	98.5 (*R*)	24a
$RuCl_2$[(*R*)-BINAP]	Me	2	H	900	EtOH, 20–32 °C, 70 atm H_2	98 (*R*)	12a
trans-Ru[(*R*)-XylBINAP][(*R*)-daipen]	Me	1	Ph	2,000	^{t}BuOK, ^{i}PrOH, 25–28 °C, 8 atm H_2	80 (*S*)	3i
trans-Ru [(*R*)-XylBINAP][(R)-daipen]	Ph	1	Me	2,000	^{t}BuOK, ^{i}PrOH, 25–28 °C, 8 atm H_2	95 (*R*)	3i

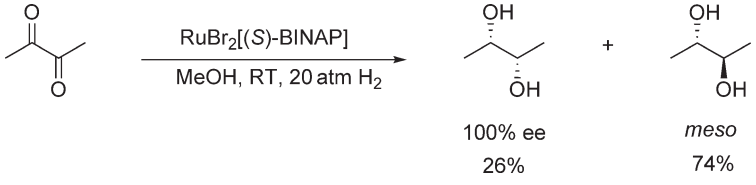
glycerol with over 96% ee.[277] A halogen atom at an appropriate position in the substrate can also exert great directing influence through interaction with Ru.[12a,261,278] Hydrogenation of *ortho*-haloaryl ketones can be catalyzed by the Ru–BINAP system with excellent ee's. For example, *ortho*-bromoacetophenone can be converted into the corresponding chiral alcohol with 96% ee (Equation (72)). However, this type of substrate can be hydrogenated more effectively with the Ru/chiral phosphine/diamine system.[279] Asymmetric hydrogenation of phenylthioketones has been realized with Ru catalysts. BINAP, MeO–BIPHEP,[280] BDPP[281] and Me–CnrPHOS,[62c] are efficient for this transformation (Table 17).



(72)

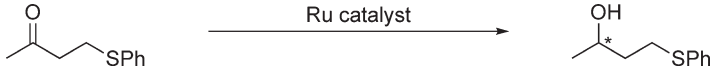
10.01.3.2.1.(vi) Diketones

Several chiral Ru complexes have been applied successfully for the asymmetric hydrogenation of α-, β-, and γ-diketones. Hydrogenation of an α-diketone, 2,3-butandione, catalyzed by an (*R*)-BINAP–Ru complex gives optically pure (*R*,*R*)-2,3-butanediol and the *meso*-diol in a ratio of 26 : 74 (Equation (73)).[12a]



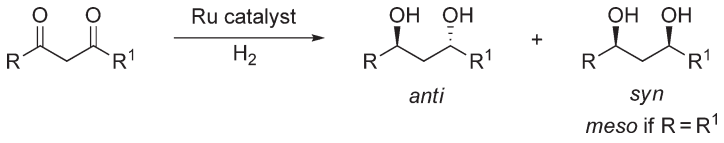
(73)

Table 17 Asymmetric hydrogenation of phenylthioketones



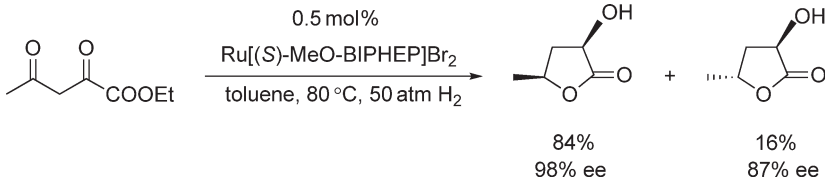
Catalyst	*S/C ratio*	*Reaction condition*	*Percent ee of product (confign.)*	*References*
Ru[(*S*)-MeO-BIPHEP]Br_2	50	MeOH, Rt, 30 atm H_2	98 (*S*)	280
Ru[(*S*)- BINAP]Br_2	50	MeOH, Rt, 30 atm H_2	96 (*S*)	280
Ru[(*S*,*S*)-BDPP]Br_2	100	MeOH, Rt, 30 atm H_2	94 (*S*)	281
Ru[(*S*,*S*)-^{i}Pr-CnrPhos]Br_2	100	MeOH, 80 °C, 80 atm H_2	97 (*S*)	62c

Table 18 Asymmetric hydrogenation of β-diketones



Ligand	*R*	*R*^{1}	*S/C ratio*	*Reaction condition*	*Percent de (anti vs. syn)*	*Percent ee of the anti-product (confign.)*	*References*
(*R*)-BINAP	Me	Me	2,000	MeOH, Rt, 72 atm H_2	98	100 (*R*,*R*)	12a
(*R*)-BIPHEMP	Me	Me	2,000	EtOH, 50 °C, 100 atm H_2	98	>99.9 (*R*,*R*)	283
(*S*,*S*)-BDPP	Me	Me	1,700	MeOH, 80 °C, 80 atm H_2	50	97 (*S*,*S*)	282
(*S*,*S*)-^{i}Pr-CnrPhos	Me	Me	50	MeOH, 80 °C, 70 atm H_2	>95	98 (*R*,*R*)	62c
(*S*,*S*)-Cy-BPE-4	Me	Me	100	MeOH, 80 °C, 80 atm H_2	95	98 (*R*,*R*)	62e
40	Me	Me	1,000	MeOH, 80 °C, 100 atm H_2	>98	97 (*R*,*R*)	90
(*S*,*S*)-^{i}Pr-CnrPhos	*i*Pr	*i*Pr	50	MeOH, 80 °C, 70 atm H_2	>95	98 (*S*,*S*)	62c
35	Ph	Ph	200	EtOH, 50 °C, 50 atm H_2	98	98.2 (*S*,*S*)	88
39	Ph	Ph	200	EtOH, 50 °C, 50 atm H_2	>95	>99.9 (*R*,*R*)	89
(*R*)-BINAP	$ClCH_2$	$ClCH_2$	314	MeOH, 105 °C, 85 atm H_2		92∼94 (*R*,*R*)	284
(*S*)-BINAP	Ph	Me	-	MeOH, Rt, 72 atm H_2	88	94 (*R*,*R*)	12a
35	Ph	Me	200	EtOH, 50 °C, 50 atm H_2	97.2	98.2 (*S*,*S*)	88
(*R*)-**3**	Ph	Ph	200	MeOH, 50 °C, 1,500 psi H_2	>99	>99 (*S*,*S*)	41
(*S*)-difluorphos	CF_3	CF_3	100	MeOH, 50 °C, 50 bar H_2	86	98 (*R*,*R*)	37

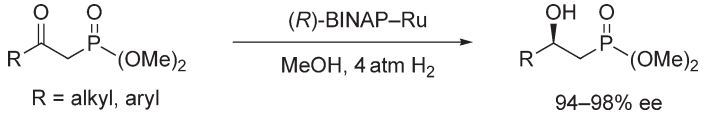
Asymmetric hydrogenation of β-diketones prefers to provide *anti*-1,3-diols (Table 18). When symmetric β-diketones are subjected to hydrogenation, chiral 1,3-diols are formed dominantly. Hydrogenation of 2,4-pentadione catalyzed by an (*R*)-BINAP–Ru catalyst gives enantiomerically pure (*R*,*R*)-2,4-pentadiol in 99% yield along with 1% of *meso*-compound.[12a] BDPP,[282] BIPHEMP,[283] ^{i}Pr–CnrPhos,[62c] Cy–BPE-4,[62e] and WalPhos **40**[90] are also very effective for this transformation. Various symmetric or asymmetric β-diketones have been hydrogenated with chiral Ru complexes associated with BINAP,[12a,284] MeO–BIPHEP,[285] **3**,[41] TaniaPhos **35**,[88] **39**,[89] and ^{i}Pr–CnrPhos[62c] to give chiral *anti*-diol products with excellent enantioselectivities and diastereoselectivity. The methodology has been used for the synthesis of important chiral intermediates and natural products. For example, ethyl 2,4-dioxovalerate is hydrogenated with an (*S*)-MeO–BIPHEP–Ru catalyst to give the *syn*-product (2*R*,4*S*)-α-hydroxyl-γ-butyrolactone in 84% yield and 98% ee, along with the *anti*-(2*R*,4*R*)-isomer in 87% ee and in 16% yield (Equation (74)).[285]



(74)

10.01.3.2.1.(vii) Keto phosphonates

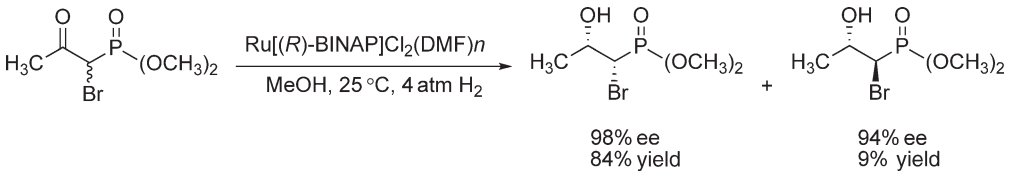
A series of β-keto phosphonates have been hydrogenated with the Ru–BINAP system to give various chiral β-hydroxyl phosphonates (Equation (75)).[286] An Ru–MeO–BIPHEP catalyst is also effective for this transformation.[287] β-Keto thiophosphonates can also be smoothly transformed into β-hydroxyl thiophosphonates with high ee.[287]



(75)

An efficient dynamic kinetic resolution is observed when an α-bromo- or α-acetylamino-β-keto phosphate is subjected to the hydrogenation with an Ru–BINAP catalyst under suitable conditions. With $RuCl_2$[(*S*)-BINAP](DMF)$_n$ (0.18 mM) as the catalyst, a racemic α-bromo-β-keto phosphonate is hydrogenated at 25 °C under

4 atm of hydrogen to give the *syn*-product (1*R*,2*S*)-α-bromo-β-hydroxy phosphonate with 98% ee (Equation (76)). The *syn*-product after acid-catalyzed hydrolysis followed by base treatment provides fosfomycin, an antibiotic reagent.[286] Hydrogenation of an α-acetylamino-β-keto phosphonate under similar conditions provides a *syn*-(1*R*,2*R*) product in 98% ee and an *anti*-(1*S*,2*R*) product with >90% ee and in a ratio of 97 : 3.[288]



(76)

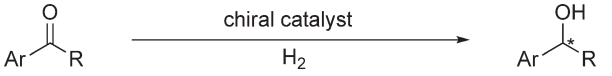
10.01.3.2.2 Hydrogenation of unfunctionalized ketones

Asymmetric hydrogenation of unfunctionalized ketones is a more challenging task than the hydrogenation of functionalized ketones.[289,3i] Due to lack of secondary coordination to the metal, most chiral Rh or Ru catalysts which are quite effective for functionalized ketones usually cannot provide high enantioselectivity and reactivity for the hydrogenation of unfunctionalized ketones. Nevertheless, the asymmetric hydrogenation of unfunctionalized ketones has been developed rapidly in the latest few years due to the discovery of several efficient catalytic systems. Two notable catalytic systems are the *trans*-[$RuCl_2$(diphosphane)(1,2-diamine)] complex developed by Noyori[13] and the Rh–PennPhos system reported by Zhang.[65] PennPhos is an electron-donating diphosphane with a bulky, rigid, and well-defined chiral backbone. Its Rh complex (combined with additives: 2,6-lutidine and KBr) has allowed efficient hydrogenation of simple aromatic and aliphatic ketones. The *trans*-[$RuCl_2$(bisphosphine)(1,2-diamine)] complex is an efficient catalyst for the hydrogenation of a variety of simple aryl ketones. With this catalyst, heteroaryl ketones can also be hydrogenated efficiently in a high substrate-to-catalyst ratio. The high specificity of the catalyst for the hydrogenation of ketones has allowed unsaturated ketones to be reduced into chiral alcohols, leaving olefin functionalities intact. Functionalized olefins such as alkoxy and amino ketones can also be hydrogenated with great enantioselectivity, which has been discussed before.[276,3i]

10.01.3.2.2.(i) Aromatic ketones

Enantioselective hydrogenation of simple aromatic ketones has been studied with some chiral Rh, Ir, and Ru catalysts (Table 19). The DIOP–Rh[290] and the DBPP–Rh[291,291a] complexes with a tertiary amine have been used in catalyzing the hydrogenation of acetophenone and moderate ee (80% and 87%, respectively) have been achieved. An Me–PennPhos–Rh complex has been applied for the hydrogenation of a set of aromatic ketones, and enantioselectivities as high as 96% ee have been achieved.[65] The additives 2,6-lutidine and KBr are very important for achieving the high selectivity, although the mechanism has not been fully understood. A BINAP–Ir(I)-aminophosphine system[292] and *trans*-[$RuCl_2$(BINAP)(1,4-diamine)]/^{t}BuOK combined catalyst[293] have been found to be effective for hydrogenation of some cyclic aromatic ketones. A series of substituted 1-tetralones, 1-indanones, or heteroatom-contained cyclic ketones have been reduced, and enantioselectivity up to 96% ee has been achieved. The *trans*-[$RuCl_2$(bisphosphine)(1,2-diamine)] catalyst, combined with ^{t}BuOK as the base and isopropanol as the solvent, is a very effective catalytic system for the hydrogenation of a diverse range of simple aromatic ketones.[294,295] Chiral BINAP, TolBINAP, or XylBINAP with a chiral diamine, such as dpen, daipen, is a good combination for the catalyst system. With *trans*-[$RuCl_2$(*S*)-Xyl–BINAP][(*S*)-DAIPEN] as the metal complex, ^{t}BuOK as the base, and ^{i}PrOH as the solvent, various substituted acetophenones and acetylnaphthalenes are reduced quantitatively with high enantioselectivity and turnover numbers. Chiral BICP,[67e] Xylyl–PHANEPHOS,[130b] Xyl–P–Phos,[296] Xyl–TetraPHEMP,[39] SDP,[134] and ligand **77**[161] combined with chiral diamines ligands are also effective for this catalyst system. A variety of *ortho*-substituted benzophenone derivatives can also be hydrogenated with excellent enantioselectivity by using the *trans*-[$RuCl_2$(*S*)-Xyl–BINAP][(*S*)-DAIPEN] complex as the catalyst.[279] Noyori has also reported the synthesis of *trans*-RuH(η^1-BH_4)(BINAP)(1,2-diamine) by reducing *trans*-[$RuCl_2$(*R*)-TolBINAP][(*R*,*R*)-dpen] with $NaBH_4$.[297] This complex can directly catalyze the hydrogenation of ketones under base-free conditions. Hydrogenation of a series of heteroaromatic ketones catalyzed by *trans*-[$RuCl_2$(*R*)-Xyl-BINAP][(*R*)-DAIPEN] provides excellent yields and enantioselectivities.[298] Genov has developed a new catalytic system comprising Ru–BICP family ligands **22** or **23**

Table 19 Asymmetric hydrogenation of simple aromatic ketones

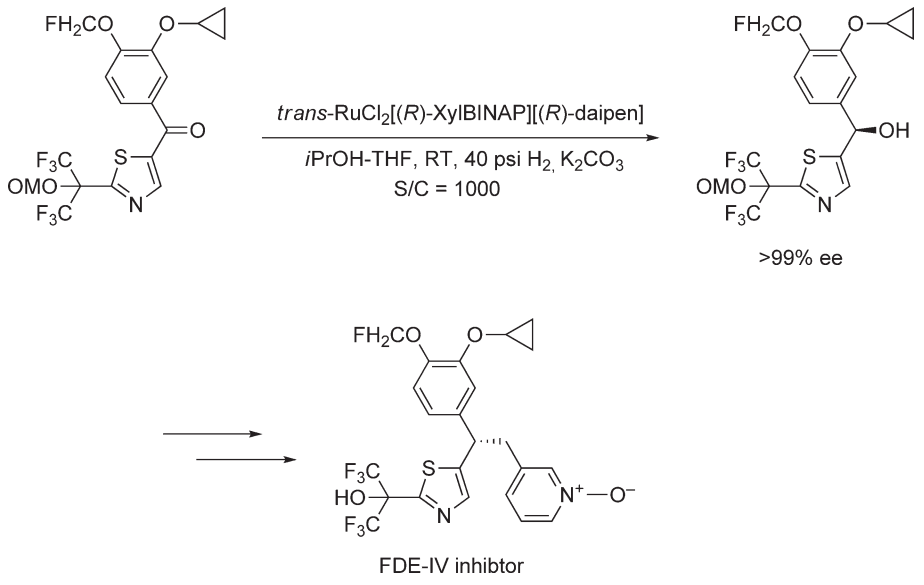


Catalyst	*Ar*	*R*	*S/C ratio*	*Reaction conditions*	*Yield (%)*	*Percent ee of product (confign.)*	*References*
$[RhCl(nbd)]_2$-(*S*,*S*)-DIOP + NEt_3	Ph	Me	200	MeOH, 50 °C, 69 atm H_2, 6 h	64	80	290
$[RhCl(nbd)]_2$-(*S*,*S*)-BDPP + NEt_3	Ph	Me	100	MeOH, 50 °C, 69 atm H_2, 24 h	72	82 (*S*)	291,291a
$[RhCl(cod)]_2$-(*R*,*S*,*R*,*S*)-Me-PennPhos + 2,6-lutidine	Ph	Me	100	MeOH, Rt, 30 atm H_2, 24 h	97	95 (*S*)	65
$[Ir\{(S)\text{-BINAP}\}(cod)]BF_4$ + $PPh(2\text{-}NMe_2Ph)$	Ph	Me	100	Dioxan–MeOH (5 : 1), 54–61 atm H_2, 60 °C, 126 h	63	54 (*S*)	300
trans-$RuCl_2$[(*S*)-XylBINAP][(*S*)-daipen] + ^{t}BuOK	Ph	Me	10,000	^{i}PrOH, 28–30 °C, 8 atm H_2, 60 h	97	99 (*R*)	295
trans-$RuH(\eta^1\text{-}BH_4)$[(*S*)-XylBINAP][(*S*,*S*)-dpen]	Ph	Me	10,000	^{i}PrOH, 45 °C, 8 atm H_2, 7 h	100	99 (*R*)	297
trans-$RuCl_2$[(*R*)-XylylPhanePhos][(*S*,*S*)-DPEN] + ^{t}BuOK	Ph	Me	20,000	^{i}PrOH, 18–20 °C, 8 atm H_2, 1.5 h	100	99 (*R*)	130b
trans-$RuCl_2$[(*R*)-Xyl-P–Phos][(*R*,*R*)-DPEN] + ^{t}BuOK	Ph	Me	100,000	^{i}PrOH, 25–28 °C, 500 psi H_2, 36 h	99.7	99.1 (*S*)	296
$[RhCl(cod)]_2$-(*R*,*S*,*R*,*S*)-Me–PennPhos + 2,6-lutidine + KBr	Ph	Et	100	MeOH, Rt, 30 atm H_2, 88 h	95	93 (*S*)	65
trans-$RuCl_2$[(*R*)-XylBINAP][(*R*,*R*)-DPEN] + ^{t}BuOK	Ph	Et	2,000	^{i}PrOH, 26–30 °C, 4 atm H_2, 15 h	100	99 (*S*)	3h
trans-$RuCl_2$[(*R*)-XylBINAP][(*R*,*R*)-DPEN] + ^{t}BuOK	Ph	Cyclo-C_3H_5	2,000	^{i}PrOH, 28–30 °C, 8 atm H_2, 14 h	99.7	96 (*R*)	3h
trans-$RuCl_2$[(*S*)-TolBINAP][(*S*,*S*)-DPEN] + ^{t}BuOK	1-Np	Me	100,000	^{i}PrOH, 24–30 °C, 10 atm H_2, 40 h	99.5	98 (*R*)	294
trans-$RuCl_2$[(*S*)-XylBINAP][(*S*)-daipen] + ^{t}BuOK	Ph	CF_3	11,000	^{i}PrOH, 26–30 °C, 10 atm H_2, 16 h	100	96 (*S*)	295
$RuCl_2$[(*R*,*R*)-BICP](TMEDA) + (*R*,*R*)-dpen + KOH	2-Thienyl	Me	500	^{i}PrOH, Rt 60 psi H_2, 24 h	100	93 (*S*)	67e
trans-$RuCl_2$[(*R*)-XylBINAP][(*R*)-daipen] + ^{t}BuOK	2-Thienyl	Me	5,000	^{i}PrOH, 25 °C, 8 atm H_2, 12 h	100	99 (*S*)	298

(*Continued*)

Table 19 (Continued)

Catalyst	*Ar*	*R*	*S/C ratio*	*Reaction conditions*	*Yield (%)*	*Percent ee of product (confign.)*	*References*
trans-$RuCl_2$[(*R*)-XylBINAP][(*R*)-daipen] + ^{t}BuOK + $B(O^iPr)_3$	2-Py	Me	2,000	^{i}PrOH, 25 °C, 8 atm H_2, 12 h	100	96 (*S*)	298
trans-$RuCl_2$[(*S*)-XylBINAP][(*S*)-daipen] + ^{t}BuOK	*o*-Me–Ph	Ph	2,000	^{i}PrOH, 28 °C, 8 atm H_2, 14 h	99	93 (*S*)	279
trans-$RuCl_2$[(*S*)-XylBINAP][(*S*)-daipen] + ^{t}BuOK	*o*-F-Ph	Ph	20,000	^{i}PrOH, 28 °C, 8 atm H_2, 14 h	99	97 (*S*)	279
trans-$RuCl_2$[(*S*)-XylBINAP][(*S*)-daipen] + ^{t}BuOK	Ferrocenyl	Ph	2,000	^{i}PrOH, 28 °C, 8 atm H_2, 14 h	100	95 (*S*)	279
trans-$RuCl_2$[(*S*)-Xyl–P–Phos]$_2$[(*S*,*S*)-DPEN] + ^{t}BuOK	*p*-Me-Ph	Me	2,000	^{i}PrOH, 22 °C, 10 bar H_2, 20 h	100	96 (*R*)	161
trans-$RuCl_2$[(*S*)-Xyl–SDP]$_2$[(*R*,*R*)-DPEN] + ^{t}BuOK	Ph	Et	5,000	^{i}PrOH, Rt, 50 atm H_2, 3.5 h	99	99.5 (*S*)	134
trans-$RuCl_2$[(*S*)-Xyl-SDP]$_2$[(*R*,*R*)-DPEN] + ^{t}BuOK	*p*-OMe-Ph	Me	5,000	^{i}PrOH, Rt, 50 atm H_2, 4.5 h	100	98 (*S*)	134
trans-$RuCl_2$[(*S*)-Xyl-SDP]$_2$[(*R*,*R*)-DPEN] + ^{t}BuOK	Ferrocenyl	Me	5,000	^{i}PrOH, Rt, 50 atm H_2, 5 h	100	98 (*S*)	134
trans-$RuCl_2$[(*R*)-Xyl-TetraPHEMP]$_2$ [(*R*)-daipen] + ^{t}BuOK	Ph	Me	15,000	^{i}PrOH, 30 °C, 10 bar H_2	>99	98 (*S*)	39
trans-$RuCl_2$[(*S*,*S*)-**23**]$_2$[^{t}Bu-thioethylamine] + ^{t}BuONa	3,5-$(CF_3)_2$–Ph	Me	1,000	^{n}BuOH, −10 °C, 7 atm H_2, 15 h	>99	93 (*S*)	71



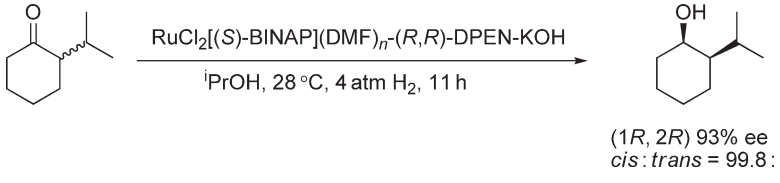
Scheme 13

complex in combination with non-chiral 2-(alkylthio)amine or 1,2-diamine and an alkoxide as a base for the highly enantioselective hydrogenation of aryl ketones.[71] A ternary system consisting with $RuCl_2$[(*R,R*)-BICP](tmeda), (*R,R*)-1,2-diphenylethylenediamine, and KOH hydrogenated an array of 2-acetylthiophene derivatives with up to 93% ee.[67e] Using *trans*-[$RuCl_2$(Xyl–BINAP)][(*S*)-DAIPEN]/base-combined catalyst, the asymmetric hydrogenation of aromatic–heteroaromatic ketones has been applied for the synthesis of chiral drugs, PDE-IV inhibtor (Scheme 13).[299]

10.01.3.2.2.(ii) Aliphatic ketones

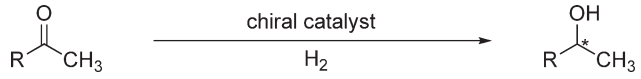
Asymmetric hydrogenation of simple aliphatic ketones remains a difficult area since it requires a chiral catalyst to effectively differentiate between two alkyl groups or between methyl and other alkyl group. The PennPhos–Rh system combined with 2,6-lutidine and KBr has given some promising results in the asymmetric hydrogenation of aliphatic ketones (Table 20).[65] With this catalytic system, the hydrogenation of *tert*-butyl methyl ketone provides the chiral alcohol with 94% ee. Isopropyl methyl ketone and *n*-butyl methyl ketone are also reduced into chiral alcohols with 85% ee and 75% ee, respectively. The cyclohexyl methyl ketone is hydrogenated by the PennPhos–Rh system with 92% ee. A cyclopropyl methyl ketone can be effectively hydrogenated by *trans*-$RuCl_2$[(*S*)-XylBINAP][(*S*)-daipen] with ^{t}BuOK as the base to give the *R* alcohol with 95% ee.[295] The Ru catalyst also provides a good ee (85%) for the hydrogenation of cyclohexyl methyl ketone.

A racemic 2-isopropylcyclohexanone has been hydrogenated with a ternary chiral Ru catalyst consisting of $RuCl_2$[(*S*)-BINAP](DMF)$_n$, (*R,R*)-DPEN, and KOH. An efficient dynamic kinetic resolution is observed with excellent enantioselectivity and *cis-trans*-ratio (Equation (77)).[301] The *cis*-(1*R*,-2*R*)-alcohol is obtained with 93% ee. With the same catalyst system, another good dynamic kinetic resolution is observed in the hydrogenation of (−)-menthone.[301] When a base-free catalyst, *trans*-RuH(η^1-BH_4)[(*S*)-XylBINAP][(*R,R*)-dpen], is used for the hydrogenation of racemic 1-isopropylcyclohexanone, a good kinetic resolution is observed.[297] After 53% conversion, the unreacted (*S*)-ketone is recovered with 91% ee along with the (1*R*,2*R*)-alcohol product with 85% ee (Equation (78)).

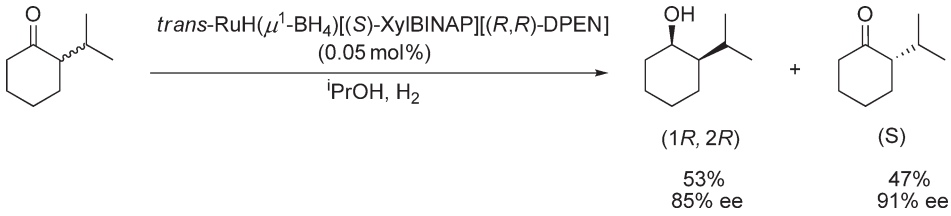


(77)

Table 20 Asymmetric hydrogenation of simple aliphatic ketones



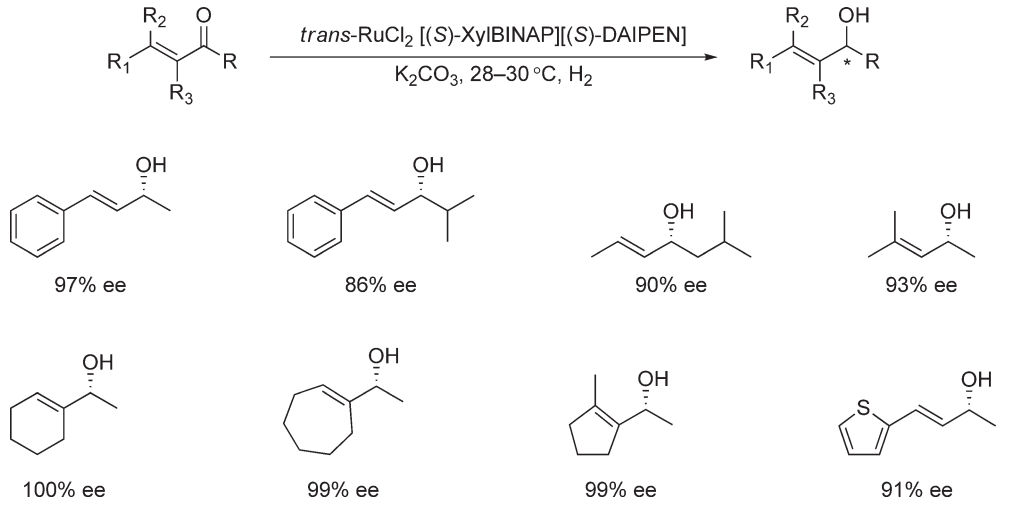
Catalyst	*R*	*S/C ratio*	*Reaction conditions*	*Yield (%)*	*Percent ee of product (confign.)*	*References*
[RhCl(cod)]$_2$-(*R,S,R,S*)-Me–PennPhos + 2,6-lutidine + KBr	^{n}Bu	100	MeOH, Rt, 30 atm H_2, 48 h	96	75 (*S*)	65
[RhCl(cod)]$_2$-(*R,S,R,S*)-Me–PennPhos + 2,6-lutidine + KBr	^{i}Bu	100	MeOH, Rt, 30 atm H_2, 75 h	66	85 (*S*)	65
[RhCl(cod)]$_2$-(*R,S,R,S*)-Me–PennPhos + 2,6-lutidine + KBr	^{i}Pr	100	MeOH, Rt, 30 atm H_2, 94 h	99	84 (*S*)	65
[RhCl(cod)]$_2$-(*R,S,R,S*)-Me–PennPhos + 2,6-lutidine + KBr	Cyclohexyl	100	MeOH, Rt, 30 atm H_2, 106 h	90	92 (*S*)	65
[RhCl(cod)]$_2$-(*R,S,R,S*)-Me–PennPhos + 2,6-lutidine + KBr	^{t}Bu	100	MeOH, Rt, 30 atm H_2, 96 h	51	94 (*S*)	65
trans-RuCl$_2$ [(*S*)-XylBINAP][(*S*)-daipen] + ^{t}BuOK	Cyclohexyl	11,000	^{i}PrOH, 28 °C, 8 atm H_2, 20 h	99	85 (*R*)	295
trans-RuCl$_2$ [(*S*)-XylBINAP][(*S*)-daipen] + ^{t}BuOK	CycloC$_3$H$_5$	11,000	^{i}PrOH, 28 °C, 8 atm H_2, 12 h	96	95 (*R*)	295



(78)

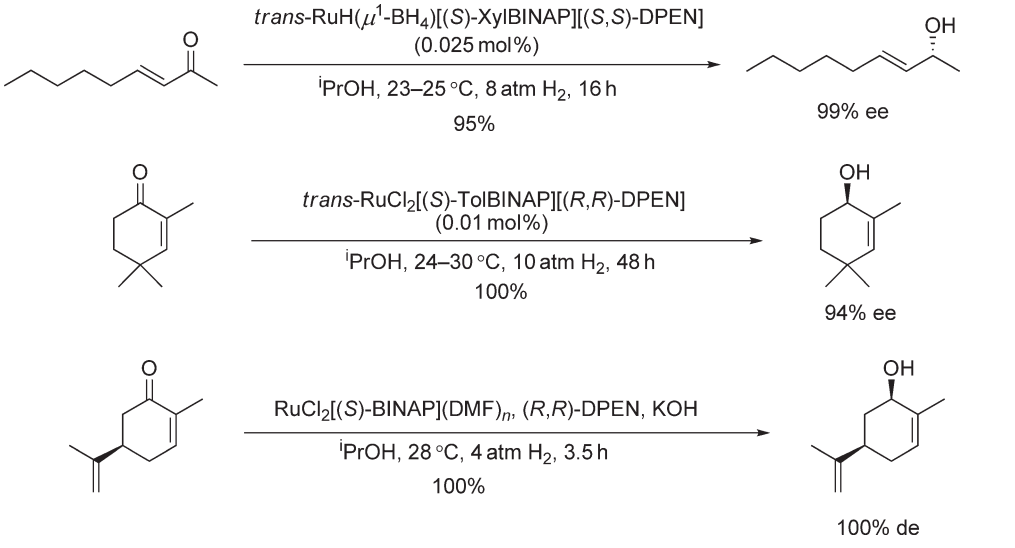
10.01.3.2.2.(iii) Unsaturated ketones

For a long time, hydrogenation of unsaturated ketones has been considered as a difficult area, since most of the present hydrogenation catalysts prefer to hydrogenate the C═C double bond rather than the C═O bond. The Ir–DIOP[302] and [Ir(BINAP)(COD)]BF_4^- aminophosphine systems[303] have shown excellent chemoselectivity for the hydrogenation of C═O bonds over C═C bonds, but only moderate ee has been obtained in the hydrogenation of 4-phenyl-3-buten-2-one or cyclic enones. The situation has changed dramatically, after Noyori developed the *trans*-$RuCl_2$(BINAP)(1,2-diamine) catalyst for hydrogenation of ketones. The *trans*-$RuCl_2$[(*S*)-XylBINAP][(*S*)-daipen] complex with K_2CO_3 as a base can efficiently hydrogenate a diverse array of α,β-unsaturated ketones with excellent chemoselectivity and enantioselectivity (Scheme 14).[295] The highly base-sensitive substrate 3-nonen-2-one can also be hydrogenated to give the corresponding (*R*)-allylic alcohol product in 95% yield and 99% ee by using a base-free catalyst *trans*-RuH(η^1-BH_4)[(*S*)-XylBINAP][(*S,S*)-dpen] (Equation (79)).[297] *Trans*-$RuCl_2$[(*S*)XylylPHANEPHOS][(*R,R*)-DPEN] with ^{t}BuOK is also effective for the transformation.[130b] Certain cyclic enones can also be hydrogenated with high enantioselectivity.[304] For example, the hydrogenation of 2,4,4-trimethyl-2-cyclohexenone, by using *trans*-$RuCl_2$[(*S*)-TolBINAP][(*R,R*)-dpen] and ^{t}BuOK as the catalyst system, gives (*R*)-2,4,4-trimethyl-2-cyclohexenol in 100% yield and 94% ee (Equation (80)). Interestingly, unlike the case of the hydrogenation of aryl ketones and acyclic α,β-unsaturated ketones where Ru-(*R*)-BINAP-(*R*)-diamine or Ru-(*S*)-BINAP-(*S*)-diamine provides best enantioselectivity, the hydrogenation of this cyclic hexenone requires ligand combination of (*R*)-BINAP-(*S*)-diamine or (*S*)-BINAP-(*R*)-diamine. The presence of a methyl group at the C-2 position is crucial for achieving high enantioselectivity since only moderate ee are obtained for the hydrogenation of 2-cyclohexen-1-one and 4,4-dimethyl-2-cyclohexen-1-one. By using the combination of $RuCl_2$[(*S*)-BINAP](DMF)$_n$, (*R,R*)-DPEN, and KOH as the catalyst system, (*R*)-carvone is hydrogenated into the *cis*-product (*R,R*)-carveol in 100% yield with perfect diastereoselectivity



Scheme 14

(Equation (81)), while the other two C═C double bonds in the structure are intact. Under the same reaction conditions, the racemic carvone is also resolved kinetically with a K_R/K_S ratio of 33 : 1. Asymmetric hydrogenation of α,β-acetylenic ketones to chiral propargylic alcohols is still unavailable.



10.01.3.3 Asymmetric Hydrogenation of Imines

Although great accomplishments have been achieved in the highly enantioselective hydrogenation of prochiral alkenes and ketones, relatively limited progress has been made in the asymmetric hydrogenation of prochiral imines.[305] A number of efficient asymmetric catalysts for the reduction of alkenes and ketones are unfortunately ineffective for the hydrogenation of related imine compounds. Currently, there are only a few efficient chiral catalyst systems available for the hydrogenation of imines. The recent development of some Ir complexes with chiral phosphanes, *trans*-[$RuCl_2$(bisphosphine)(1,2-diamine)] complex,[306,306a,307] chiral titanocene,[308a–308c] and zirconocene catalysts[309] provides great promise in this area. Some success has also been achieved in the asymmetric hydrogenation of functionalized C═N double bonds, such as *N*-acyl hydrozones, sulfonimides, and *N*-diphenylphosphinyl ketimines.

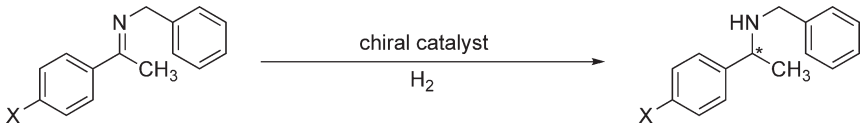
10.01.3.3.1 Hydrogenation of acyclic *N*-alkylimines

Although several chiral Rh, Ir, Ti, and Zr catalysts have been applied for the asymmetric hydrogenation of acyclic *N*-alkylimines, only limited success has been achieved for this transformation. Except a chiral titanocene catalyst which has shown moderate to good enantioselectivities for a variety of acyclic *N*-alkylimines,[308,308a–308c] most chiral Rh and Ir catalysts provide limited substrate scope such as acetophenone *N*-benzylimine and its derivatives; the employed substrates are generally a mixture of (*E*)- and (*Z*)-isomers. Some successful examples are listed in Table 21. With a halide additive KI, a neutral CycPhos–Rh complex has shown moderate to good enantioselectivities (up to 91% ee) in the hydrogenation of acetophenone *N*-benzylimine and its derivatives.[310] BDPP is also an effective ligand for this transformation. Enantioselectivity up to 83% ee is observed when acetophenone *N*-benzylimine is reduced by a neutral (*S*,*S*)-BDDP–Rh complex at 0 °C, although a low conversion is observed.[291a] A catalyst system consisted of a cationic (*S*,*S*)-BDPP complex, reversed micelles of sodium bis(2-ethylhexyl)sulfosuccinate (AOT), and 15-crown-5 provides a better ee (89% ee).[311] The best enantioselectivity (94% ee) for the hydrogenation of acetophenone *N*-benzylimine is obtained with a neutral monosulfonated (*S*,*S*)-BDPP–Rh complex in a mixed solvent (EtOAc/H_2O).[312] The *para*-chloro- and *para*-methoxy-substituted derivatives also provide over 90% ee. Interestingly, di-, tri-, tetrasulfonated (*S*,*S*)-BDPP ligands are much less enantioselective for this transformation.[313] Some chiral Ir systems such as [Ir(COD)Cl]/(*S*)-tolBINAP/$BnNH_2$[314] and Ir–Phox[315,315a] complex also provide moderate ee for the asymmetric hydrogenation of acetophenone *N*-benzylimine.

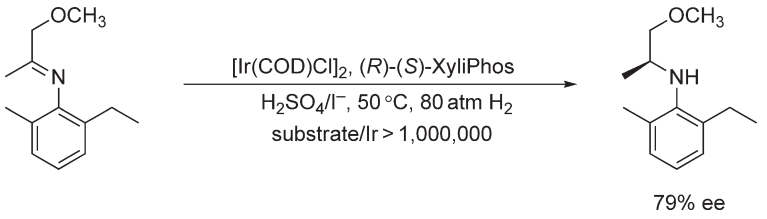
10.01.3.3.2 Hydrogenation of acyclic aromatic imines

Much advance has been achieved in the hydrogenation of acyclic aromatic imines. A notable example is the successful manufacture of (*S*)-metolachlor via asymmetric hydrogenation of an *N*-aryl ketimine.[83,83a] The hydrogenation is efficiently conducted with $[Ir(COD)Cl]_2$ and (*R*)-(*S*)-Xyliphos as the catalyst system in the presence of some acid and iodide. Under a hydrogen pressure of 80 atm at 50 °C with a substrate-to-catalyst ratio of >1,000,000, the hydrogenation is complete within 4 h with 79% ee and an initial turnover frequency (TOF) of 1,800,000 h^{-1} (Equation (82)). The enantiomeric purity of amine product, although only moderate, is enough for application as a herbicide. Some other chiral Ir complexes combined with (*S*,*S*)-BDPP or (*S*,*S*)-DIOP have shown enantioselectivity up to 90% ee in the hydrogenation of 1-methoxypropanone (2,6-dimethyl)anilineimine.[316,317a]

Table 21 Asymmetric hydrogenation of acyclic *N*-alkylimines

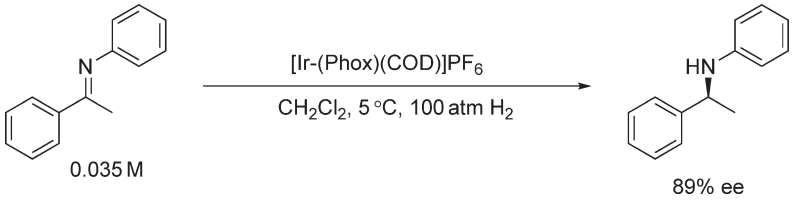


Catalyst	*X*	*S/C ratio*	*Additive*	*Reaction conditions*	*Yield (%)*	*Percent ee of product (confign.)*	*References*
$[Rh(NBD)Cl]_2$ + (*R*)-CycPhos	H	100	KI	Benzene/MeOH (1 : 1), 20 °C, 1,000 psi H_2, 90 h	>99	79 (*S*)	310
$[Rh(NBD)Cl]_2$ + (*R*)-Cycphos	OMe	100	KI	Benzene/MeOH (1 : 1), −25 °C, 1000 psi H_2, 144 h	>99	91 (*S*)	310
$[Rh(COD)Cl]_2$ + (*S*,*S*)-BDPP	H	100	$N(Et)_3$	MeOH, 0 °C, 70 atm H_2, 6 h	55	83 (*R*)	291a
$[Rh(COD)Cl]_2$ + (*S*,*S*)-BDPP	H	100		MeOH, 20 °C, 70 atm H_2, 6 h	96	84 (*R*)	312
$[Rh(COD)Cl]_2$ + monosulfonated (*S*,*S*)-BDPP	H	100		EtOAc/H_2O, 20 °C, 70 atm H_2	>98	94 (*R*)	312
$[Rh(COD)Cl]_2$ + monosulfonated (*S*,*S*)-BDPP	OMe	100		EtOAc/H_2O, 20 °C, 70 atm H_2	>98	92 (*R*)	312
$[Rh(COD)Cl]_2$ + monosulfonated (*S*,*S*)-BDPP	Cl	100		EtOAc/H_2O, 20 °C, 70 atm H_2	>98	92 (*R*)	312
[Rh(*S*,*S*)-BDPP(NBD)]ClO_4	H	100	15-crown-5	AOT/benzene, 8 °C, 70 atm H_2, 73 h	98	89 (*R*)	311
[Rh(*S*,*S*)-BDPP(NBD)]ClO_4	OMe	100		AOT/benzene, 4 °C, 70 atm H_2, 21 h	96	92 (*R*)	311
$[Ir(COD)Cl]_2$ + (*S*)-TolBINAP	H	100	$BnNH_2$	MeOH, 20 °C, 60 atm H_2, 18 h	100	70 (*R*)	314
[Ir(*S*)-N,P-ligand(NBD)]PF_6	H	100		CH_2Cl_2, 23 °C, 100 atm H_2	100	76 (*R*)	315,315a

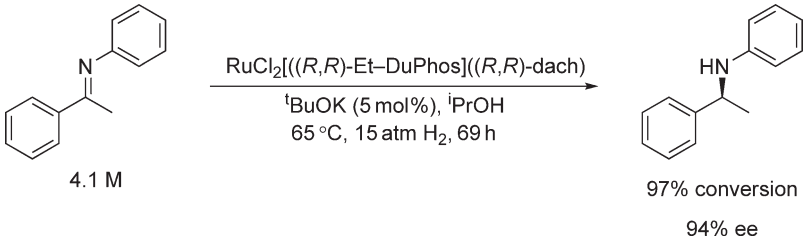


(82)

High enantioselectivities have been recently obtained in the hydrogenation of acetophenone *N*-aryl imine derivatives. Enantioselectivity up to 89% ee has been achieved in the hydrogenation of acetophenone aniline imine with a cationic Phox–Ir complex as the catalyst (Equation (83)).[315] The low concentration of substrate and catalyst is important for achieving high enantioselectivity, and the substrate-to-catalyst ratio as high as 1,000 can be employed. Supercritical carbon dioxide can also be used as the solvent instead of CH_2Cl_2, although a slightly lower selectivity is observed.[315a] A *trans*-[$RuCl_2$(bisphosphine)(1,2-diamine)] complex with Et–Duphos and dach as the ligand combination is also very effective,[306,306a] and enantioselectivity up to 94% ee has been obtained in the hydrogenation of acetophenone aniline imine under basic conditions (Equation (84)).[306] A neutral Ir-f-BINAPHANE complex[98] has provided excellent enantioselectivity in the hydrogenation of a series of acetophenone *N*-arylimine derivatives at −5 °C under 1,000 psi of hydrogen with I_2 as the additive (Table 22). The acetophenone aniline imine is hydrogenated to the corresponding amine with 95% ee. Enantioselectivity over 99% ee is achieved in the hydrogenation of acetonephenone 2,6-dimethyl aniline imine, although a lower conversion is observed. When acetophenone (2′-Me-6′-MeO–)aniline imine is subjected to hydrogenation, the corresponding chiral amine product is obtained, which after treatment with cerium ammonium nitrate provides chiral phenylethylamine with 98% ee (Equation (85)). The additive I_2 is beneficial to the enantioselectivity for the hydrogenation of *N*-phenyl or *N*-4′-methoxyphenylimines but detrimental for *N*-2′,6′-dimethylphenylimines. A BINAP–Pd complex has been successfully applied to the hydrogenation of a series of fluorinated α-iminoesters, and enantioselectivities up to 91% ee have been obtained.[318] The use of 2,2,2-trifluoroethanol as the solvent is important for achieving high enantioselectivities and reactivities (Equation (86)).

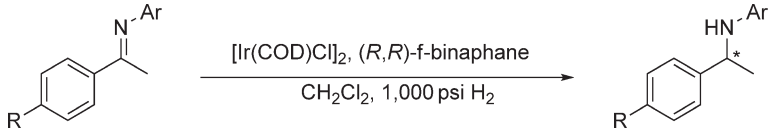


(83)

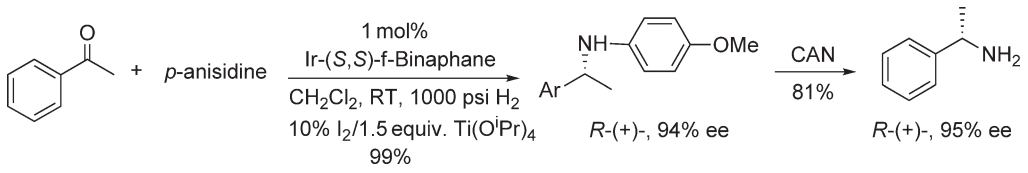


(84)

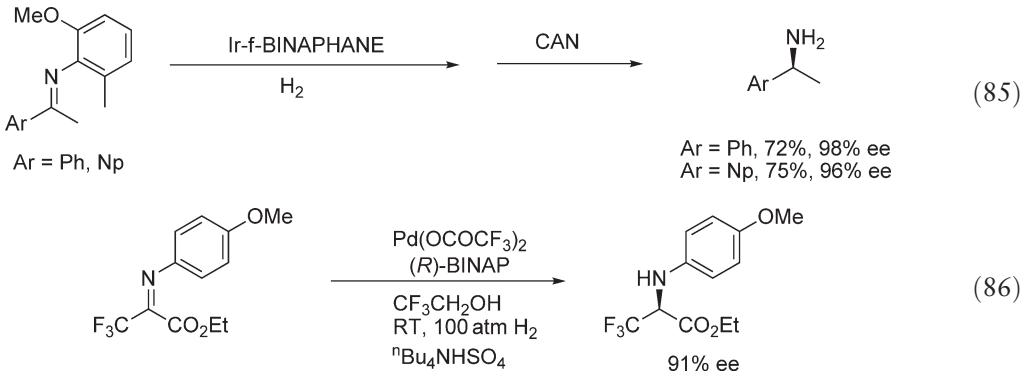
Table 22 Asymmetric hydrogenation of acyclic aromatic imines



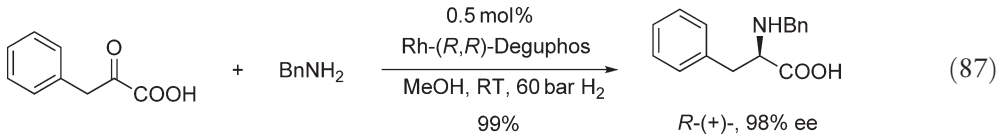
R	*Ar*	*S/C ratio*	*Reaction conditions*	*Conv.* (%)	*ee* (%)
H	Ph	100	I_2, −5 °C, 40 h	100	94
MeO	Ph	100	I_2, −5 °C, 24 h	100	95
H	2,6-Me_2Ph	100	Rt, 44 h	77	>99
MeO	2,6-Me_2Ph	100	Rt, 44 h	77	98
CF_3	2,6-Me_2Ph	100	Rt, 44 h	88	99



Scheme 15



Without isolating and purifying the imines, the asymmetric reductive amination of ketones or aldehydes with amines is a simple and practical way for the preparation of chiral amines. Using an Ir-f-Binaphane complex as the catalyst, complete conversions and high enantioselectivies (up to 96% ee) were achieved in the asymmetric reductive amination of aryl ketones in the presence of $Ti(O^iPr)_4$ and I_2. A simple and efficient method of synthesizing chiral primary amines has been realized (Scheme 15).[319] Rh–Deguphos has shown high eantioselectivity for reductive amination of α-keto acids, and a series of α-amino acids were produced with up to 98% ee (Equation (87)).[320]



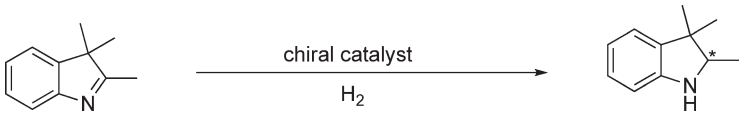
10.01.3.3.3 Hydrogenation of cyclic imines

The most efficient catalytic system to date for the hydrogenation of cyclic imines is a chiral titanocene catalyst developed by Buchwald.[308,308a–308c] This non-phosphorus-containing catalyst has shown excellent enantioselectivity for a diverse array of cyclic imines, albeit with a relatively high catalyst loading. Several Ir complexes associated with chiral phosphorus ligands such as DIOP, MOD–DIOP, BCPM, BINAP, BICP, and BDPP have shown good to excellent ee for hydrogenation of several cyclic imines, but they generally have very limited substrate scope. In many cases, the presence of some additives plays an important role in achieving high enantioselectivity.

Hydrogenation of 2,3,3-trimethylindolenine has been studied as a typical reaction (Table 23). An (*S*,*S*)-BDPP Ir(III) hydride complex has shown high reactivity for this reaction and the amine product is obtained with 80% ee.[317,317a] In the presence of an additive BiI_3, a neutral (2*S*,4*S*)-BCPM–Ir complex provides the hydrogenation product with 91% ee at −30 °C.[321] Without the additive, a much lower ee is obtained. At 0 °C, a neutral BICP–Ir complex with phthalimide as the additive provides 95% ee for this reaction.[322] *Trans*-[$RuCl_2$((*S*)-MeO–BIPHEP)((*S*,*S*)-ANDEN)] is also effective, and enantioselectivity up to 88% ee has been obtained, albeit with a low conversion.[318]

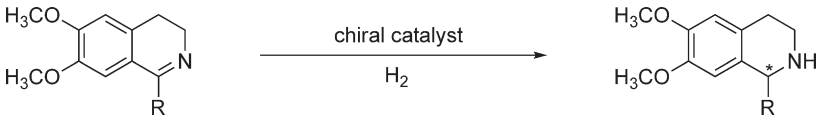
Asymmetric hydrogenation of 3,4-hydroisoquinolines with Ir-chiral phosphorus ligand complexes has been studied. Although the highest enantioselectivity to date is obtained with a chiral titanocene catalyst,[308,308a–308c] chiral BCPM–Ir or BINAP–Ir complexes with additive phthalimide or F_4-phthalimide have shown some good selectivity. Some examples are listed in Table 24.

Table 23 Asymmetric hydrogenation of 2,3,3-trimethylindolenine



Catalyst	*S/C ratio*	*Reaction conditions*	*Percent ee of product (sign)*	*References*
$[Ir((S,S)\text{-BDPP})HI_2]_2$	1000	THF/CH_2Cl_2(3 : 1), 30 °C, 39 atm H_2, 43 h	80 (+)	317,317a
$[Ir(COD)Cl]_2$ + (4*R*,5*R*)-MOD–DIOP + Bu_4NI	100	Benzene/MeOH(1 : 1), 20 °C, 100 atm H_2, 48 h	81.4 (+)	323
$[Ir(COD)Cl]_2$ + (2*S*,4*S*)-BCPM + BiI_3	100	Benzene/MeOH(1 : 1), −30 °C, 100 atm H_2, 90 h	91 (+)	310
$[Ir(COD)Cl]_2$ + (*R*,*R*)-BICP + Phthalimide	100	Toluene, 0 °C, 1,000 psi H_2, 100 h	95.1 (+)	322
$[RuCl_2((S)\text{-MeO–BIPHEP})((S,S)\text{-anden})]$	100	^{t}BuOK (1 equiv.), ^{i}PrOH, 50 °C, 15 atm H_2, 18 h	88	306

Table 24 Asymmetric hydrogenation of 3,4-hydroisoquinolines



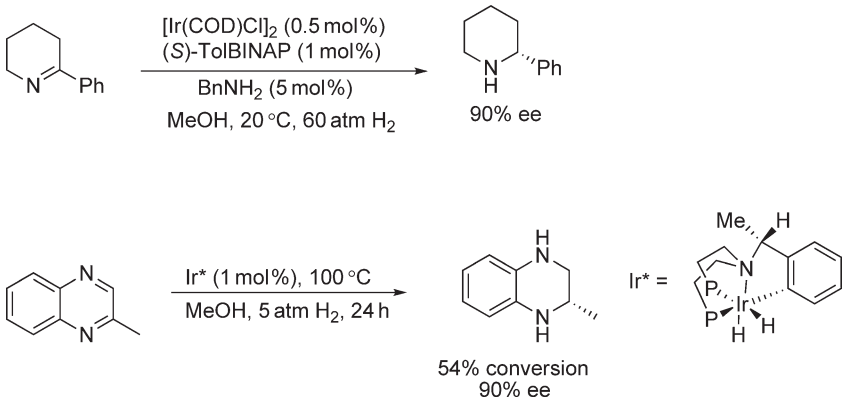
Catalyst	*R*	*S/C ratio*	*Reaction conditions*	*Percent ee of product (confign.)*	*References*
$[Ir(COD)Cl]_2$ + (*S*,*S*)-BCPM + phthalimide	Me	100	Toluene, 2–5 °C, 100 atm H_2, 24 h	85–93 (*S*)	324
$[Ir(COD)Cl]_2$ + (*S*)-BINAP + F_4-phthalimide	CH_2OBn	200	Toluene/MeOH, 2–5 °C, 100 atm H_2, 72 h	86 (*S*)	325
$[Ir(COD)Cl]_2$ + (*S*)-BINAP + F_4-phthalimide	$(CH_2)_3OBn$	200	Toluene/MeOH, 2–5 °C, 100 atm H_2, 72 h	89 (*S*)	325
$[Ir(COD)Cl]_2$ + (*S*,*S*)-BCPM + F_4-phthalimide	3,4-$(MeO)_2$–$PhCH_2$	100	Toluene, 5 °C, 100 atm H_2, 20 h	88 (*S*)	326
$[Ir(COD)Cl]_2$ + (*S*,*S*)-BCPM + phthalimide	3,4-$(MeO)_2$–$PhCH_2CH_2$	100	Toluene, 2 °C, 100 atm H_2, 22 h	87 (*S*)	326
$[Ir(COD)Cl]_2$ + (*S*)-BINAP + F_4-phthalimide	3,4-$(MeO)_2$–$PhCH_2CH_2$	100	Toluene/MeOH, 2 °C, 100 atm H_2, 40 h	86 (*S*)	326
$[Ir(COD)Cl]_2$ + (*S*,*S*)-BCPM + phthalimide	(*E*)-(3,4)–$(MeO)_2$–PhCH=CH	100	Toluene, 2 °C, 100 atm H_2, 24 h	86 (*S*)	326

An (*S*)-TolBINAP–Ir complex with a protic amine such as benzylzmine as the additive has been applied for the hydrogenation of 2-phenyl-3,4,5,6-tetrahydropyridine, and enantioselectivity up to 90% ee is obtained.[314] An *ortho*-metallated Ir dihydrid complex has been used in the hydrogenation of 2-methylquinoxaline, and enantiopurity up to 90% ee has been obtained for the 2-methyl-1,2,3,4-tetrahydroquinoxaline product (Scheme 16).[327]

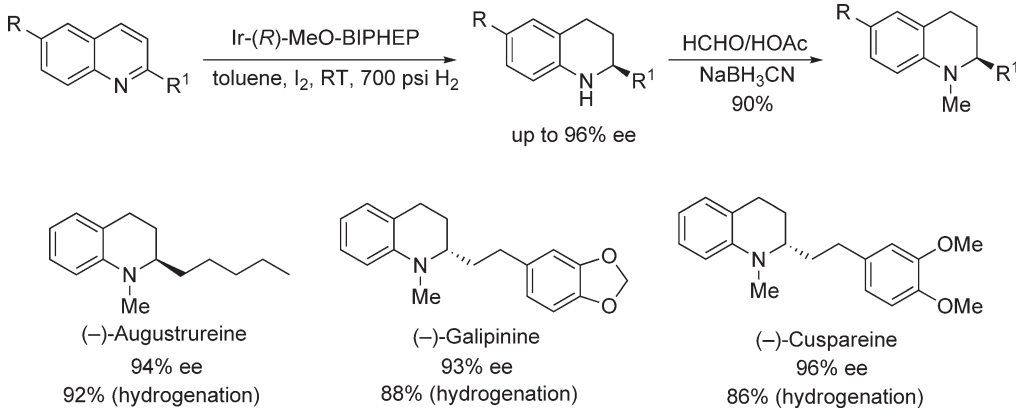
Using Ir/MeO–Biphep/I_2 catalyst system, a variety of substituted quinoline derivatives were hydrogenated in 95% yield and up to 96% ee. This method provided an efficient accesss to three naturally occurring alkaloids (Scheme 17).[328] Ferrocene N, P ligand **108** is also effective for the asymmetric hydrogenation of quinolines with up to 92% ee.[188a]

10.01.3.3.4 Hydrogenation of C=N–X substrates

When a heteroatom is directly connected with the nitrogen atom of a C=N double bond, the C=N double bond is generally activated and the hydrogenation may occur under mild conditions. Additionally, the functionality on the



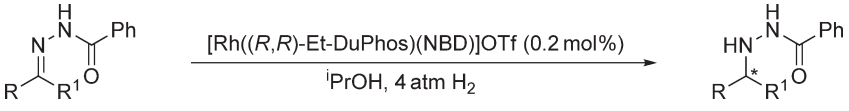
Scheme 16



Scheme 17

heteroatom may create a second coordination with the catalyst. Indeed, some successful results have been obtained in the hydrogenation of *N*-acylhydrozone, sulfonimide, and *N*-diphenylphosphinylketimines. An Et–DuPhos–Rh complex is efficient for the hydrogenation of a variety of *N*-acylhydrozone compounds.[329] As shown in Table 25, a series of *N*-aroylhydrozones are hydrogenated to form chiral *N*-benzoylhydrazine products with up to 97% ee; the hydrogen

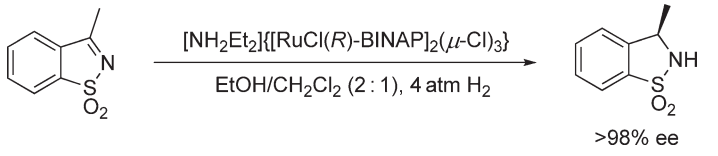
Table 25 Asymmetric hydrogenation of *N*-aroylhydrozones



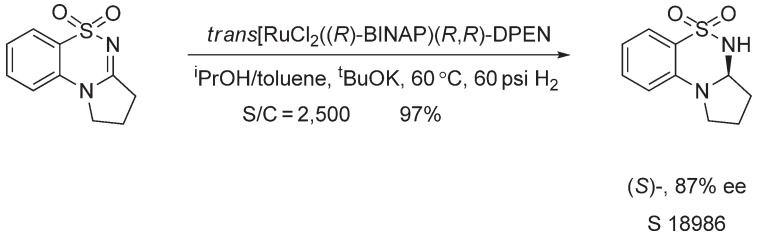
R	R^1	*Temp.* (°C)	*Time* (h)	*Percent ee of product (confign.)*
Ph	Me	−10	24	95 (*S*)
4-MeOPh	Me	0	24	88 (*S*)
4-EtO_2CPh	Me	0	12	96 (*S*)
4-NO_2Ph	Me	0	12	97 (*S*)
Ph	Et	−10	24	85 (*S*)
2-NP	Me	0	12	95 (*S*)
COOEt	Et	0	24	91 (*S*)
$PO(OEt)_2$	Ph	−10		90

pressure as low as 4 atm can be applied. The *N*-benzoyl hydrazines derived from α-keto esters are also hydrogenated with excellent enantioselectivity. The α-hydrazino acid products can be easily converted into chiral α-amino acids. Other *N*-benzoylhydrazine products can be converted into chiral amines by treatment with samarium diiodide.

Some success has been achieved in the asymmetric hydrogenation of *N*-tosylimines with a Ru–BINAP complex as the catalyst. Moderate to good enantioselectivities have been obtained for several *N*-tosylimines derived from arylketones, albeit with low conversion.[330] A BINAP–Ru dimer $[NH_2Et_2]\{[RuCl(R)\text{-BINAP}]_2(\mu\text{-Cl})_3\}$ is very efficient for the hydrogenation of a cyclic sulfonamide.[331] Under 4 atm of hydrogen, the hydrogenation proceeds completely to give the chiral sultam product with over 98% ee (Equation (88)). Using *trans*-$[RuCl_2((R)\text{-BINAP})((R,R)\text{-DPEN})]$ as catalyst, the chiral 2-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor positive modulator S 18986 was synthesized via hydrogenation of a cyclic *N*-sulfonylimine in 97% yield and 87% ee (Equation (89)).[332]



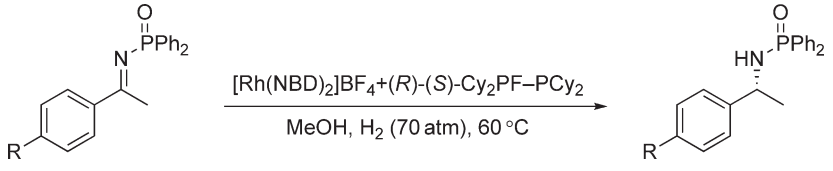
(88)



(89)

Asymmetric hydrogenation of *N*-diphenylphosphinylketimines has been achieved with an (*R*)-(*S*)-Cy_2PF–PCy_2–Rh complex as the catalyst (Table 26).[333] *N*-Diphenylphosphinyl acetophenone imine is hydrogenated completely with 99% ee at 60 °C under 70 bar of hydrogen. The reaction temperature is crucial for achieving high enantioselectivity. The strong basicity of the ligand is also responsible for both the reactivity and the enantioselectivity of the transformation. While *para*-Me- and *para*-CF_3-substituted acetophenone derivatives provide 97% ee and 93% ee, respectively, the enantioselectivities for *para*-MeO- and *para*-Cl-substituted derivatives are much lower. This dramatic difference has not been explained. The hydrogenation products can be readily transformed into chiral amines via acidic hydrolysis.

Table 26 Asymmetric hydrogenation of *N*-diphenylphosphinylketimines



R	*S/C ratio*	*Time* (h)	*Percent ee of product (confign.)*
H	500	1	99 (*R*)
OMe	100	19	62 (*R*)
Me	100	21	97 (*R*)
CF_3	100	18	93 (*R*)
Cl	100	53	30 (*R*)

10.01.4 Concluding Remarks

The development of chiral phosphorus ligands has made undoubtedly significant impact on the asymmetric hydrogenation. Transition metal catalysts with efficient chiral phosphorus ligands have enabled the synthesis of a variety of chiral products from prochiral olefins, ketones, and imines in a very efficient manner, and many practical hydrogenation processes have been exploited in industry for the synthesis of chiral drugs and fine chemicals.

However, there are still many challenges in the field of asymmetric hydrogenation. The current hydrogenation methods still cannot reduce numerous prochiral olefins, ketones, and imines with high ee and high turnover numbers. Expanding the substrate scope of asymmetric hydrogenation as well as enhance the efficiency of known hydrogenation processes remains an urgent and important task. More effort in searching new efficient chiral phosphorus ligands as well as new applications in asymmetric hydrogenation is needed and the advance in the field should be of great significance in catalytic asymmetric synthesis.

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10.02
C–H Bond Formation: Through Isomerization

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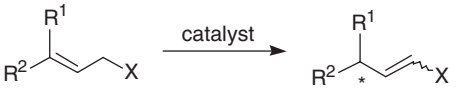
10.02.1 Introduction

Metal-catalyzed isomerization of olefinic double bonds has been extensively studied due to its high usefulness in organic synthesis.[1–3] The isomerization of olefinic double bonds occurs frequently in transition metal-catalyzed oligomerization, hydroformylation, hydrogenation, methathesis, and others. Thermodynamically, isomerization of terminal double bonds to internal double bonds is favorable. Although isomerization of multi-substituted internal double bonds to less substituted terminal double bonds is unfavorable, such reaction proceeds efficiently in the case of stabilization by some functional groups. Especially, metal-catalyzed isomerization of functionalized allylic compounds such as allylamines, allylic alcohols, and allyl ethers has been thoroughly investigated, and some asymmetric reactions, which have significant synthetic and industrial utility, have been developed (Equation (1)).

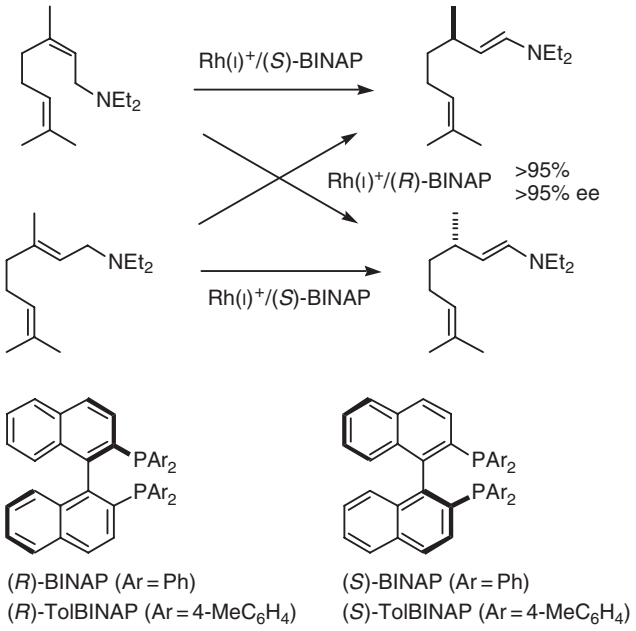


(1)

Various transition metal complexes, in particular of late transition metals, were reported to be effective catalysts for such double bond isomerization. Because organic synthesis is the focus of this volume, this section will cover the transition metal-catalyzed isomerization of alkenes, which has the significant synthetic and industrial utilities. This chapter will also include the synthetic application, asymmetric reactions,[4–6] and isomerization of alkynes, in particular, that of propargylic alcohols.

10.02.2 Allylamines

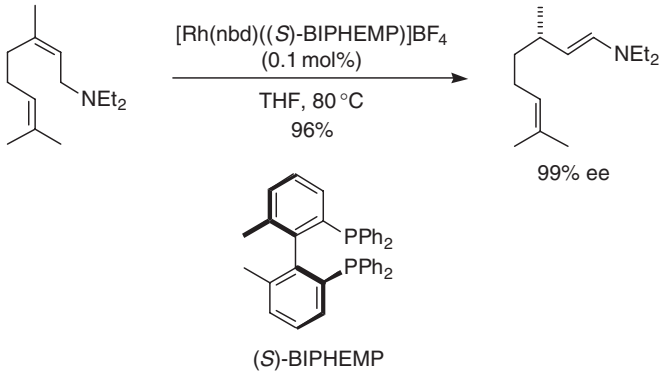
The transition metal-catalyzed asymmetric isomerization of allylamines has been studied extensively in perfumery industry due to its application to the synthesis of a wide variety of perfumery products.[7–11] Especially, asymmetric isomerization of geranylamine and nerylamine for the enantioselective synthesis of (*E*)- or (*Z*)-citronelylenamines, which can be hydrolyzed to give optically active citronellal, has been extensively studied. The isomerization of geranylamine and nerylamine was first tried by using low-valent cobalt complexes, prepared by reducing the cobalt ion with $AlHBu^{i}_{2}$ in the presence of (+)-DIOP (where DIOP = 2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane), which furnished citronelylenamines with modest yield and enantioselectivity.[12] On the other hand, the use of cationic rhodium(I)/BINAP complex (where BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl), $[Rh(BINAP)(solvent)_2]ClO_4$, furnished citronelylenamines in excellent yield and enantioselectivity (Scheme 1).[13,14]



Scheme 1

In order to establish the industrial application, $[Rh(BINAP)_2]ClO_4$ was developed as a new catalyst, which has excellent thermal stability allowing multiple repetition of the catalyst recovery. A further improvement of the catalyst was accomplished by the use of $[Rh(TolBINAP)_2]ClO_4$, which possessed a better solubility in organic solvents and achieved even higher optical yields (>98% ee) for the isomerization of allylamines such as geranylamine and nerylamine.[15]

Other than BINAP ligands, rhodium-catalyzed enantioselective isomerization of nerylamine was examined by using the BIPHEMP ligand (where BIPHEMP = (6,6′-dimethylbiphenyl-2,2′-diyl)bis(dis(diiphenylphosphine)), which afforded (*E*)-citronelylenamines in excellent yield and enantioselectivity (Equation (2)).[16]

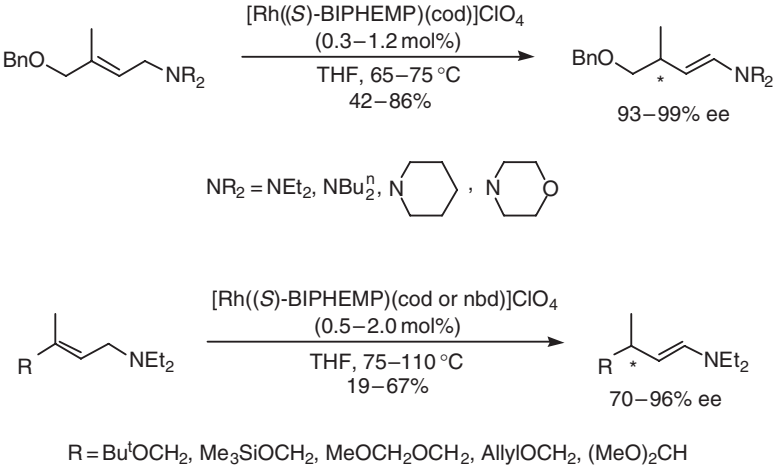


(2)

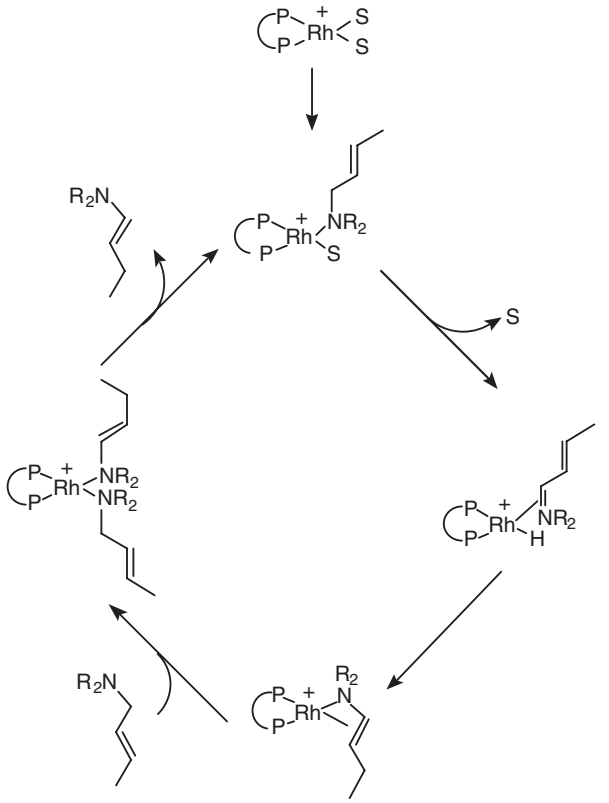
The enantioselective isomerization of bifunctional C_5-isoprenoid allylamines to optically active bifunctional aldehydes was developed by using $Rh(I)^+$/(*S*)-BIPHEMP as the catalyst (Scheme 2).[17] These aldehydes are useful optically active bifunctional building blocks for isoprenoid homologation.

The mechanism of this catalysis has been extensively studied. The catalytic process is initiated by the coordination of the nitrogen atom of an allylamine, followed by an intramolecular stereospecific 1,3-hydrogen shift (Scheme 3).[18]

The synthesis of a variety of chiral aliphatic aldehydes of high optical purity through the enantioselective isomerization of allylamines found many applications in organic synthesis. The enantioselective isomerization of diethylgeranylamine, which was prepared from myrcene, furnished (*R*,*E*)-diethylenamine in >98% yield with >98% ee. This enamine is converted to (−)-menthol stereospecifically in high chemical yield (yield of each step >92%, Scheme 4).[9,11]

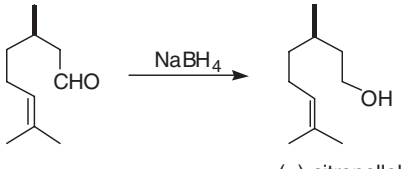


Scheme 2

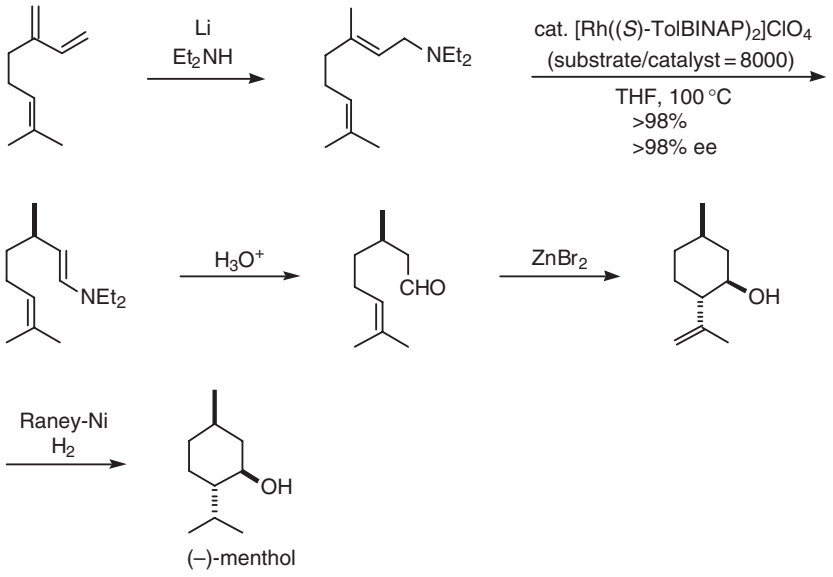


Scheme 3

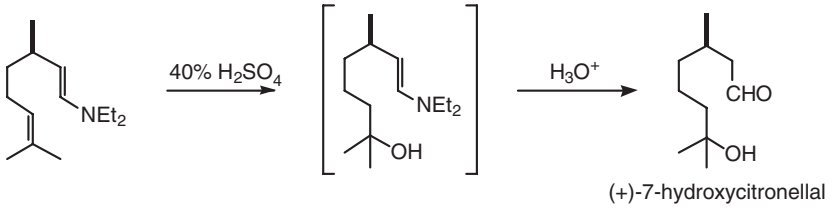
Catalytic hydrogenation of citronellal provides (+)-citronellol with high optical purity (Equation (3)).[9]



(3)



Scheme 4



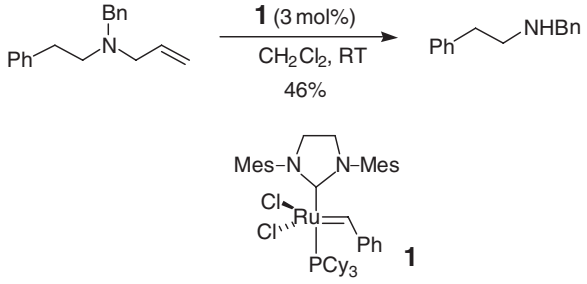
Scheme 5

Hydration of (*R*,*E*)-diethylenamine, followed by hydrolysis with sulfuric acid gives (+)-7-hydroxycitronellal, which is known as an artificial perfume with pleasant olfactory properties, with high optical purity (Scheme 5).[9]

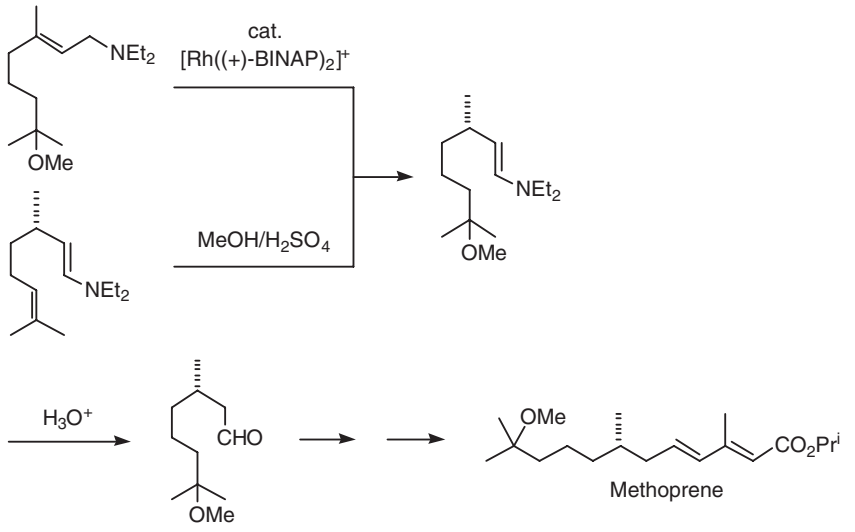
Methoprene is an insect growth regulator and it is also used as an insecticide for cockroaches. The enantioselective isomerization of 7-methoxygeranylamine in the presence of $[Rh((+)\text{-BINAP})_2]^+$ followed by acid hydrolysis provides the intermediate, 7-methoxycitronellal, in high yield with high optical purity (97%, 98% ee, Scheme 6).[9] Alternatively, methoxylation of (*S*)-citronellalenamine (98% ee) with methanol in the presence of 97% sulfuric acid followed by hydrolysis gives 7-methoxycitronellal in 79% yield without racemization (Scheme 6).[9]

The rhodium-catalyzed isomerization of allylamine can be used for the deprotection of *N*-allyl protective groups (Scheme 7).[19,20]

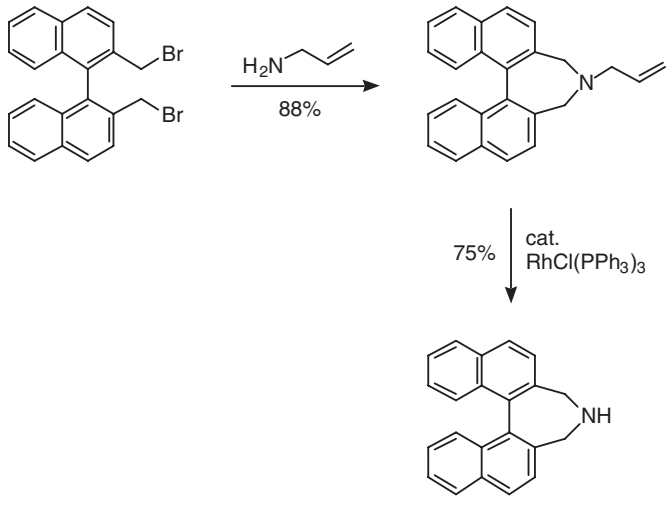
Ruthenium-carbenoid catalyst **1** promotes the isomerization of β,γ-unsaturated amines to the corresponding enamines (Equation (4)).[21] This reaction is useful in the deprotection of amines.



(4)

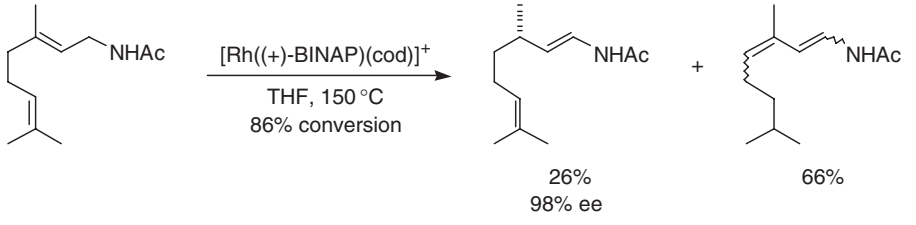


Scheme 6



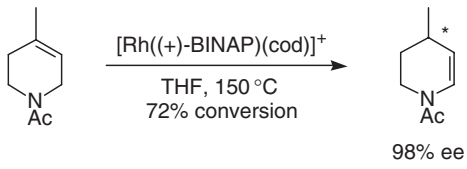
Scheme 7

Metal-catalyzed isomerization of allylamides is slower than that of allylamines. The isomerization was examined at higher temterature (>100 °C) using [Rh((+)-BINAP) (cod)]$^{+}$. Although the enantioselectivity was high, the yield of the desired enamide was low due to the formation of dienamide (Equation (5)).[9]



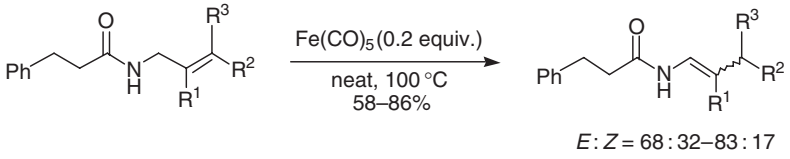
(5)

A cyclic allylamide was also isomerized at 150 °C using [Rh((+)-BINAP) (cod)]$^+$ to the corresponding enamide with high optical purity (Equation (6)).[9]



(6)

The catalytic isomerization of various *N*-allylamides to the corresponding enamides can be accomplished without solvent by the use of $Fe(CO)_5$ (Equation (7)).[22] This method is compatible with various functional groups including protected amino and hydroxy groups.

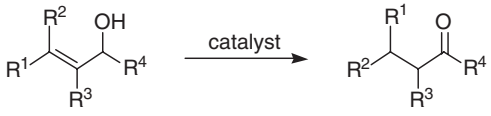


(7)

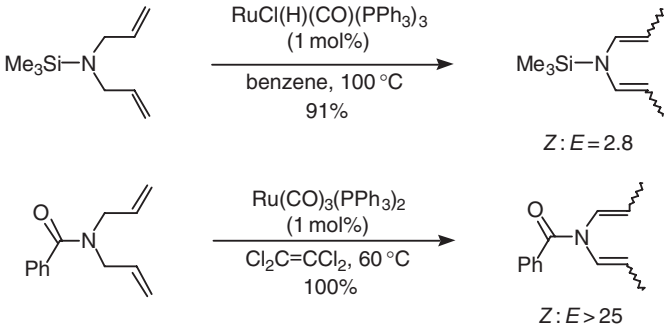
The isomerization of multifunctionalized allylamines and allylamides is efficiently catalyzed by various ruthenium complexes in high yield (Scheme 8).[23,24]

10.02.3 Allylic Alcohols

The isomerization of allylic alcohols provides an enol (or enolate) intermediate, which tautomerizes to afford the saturated carbonyl compound (Equation (8)). The isomerization of allylic alcohols to saturated carbonyl compounds is a useful synthetic process with high atom economy, which eliminates conventional two-step sequential oxidation and reduction.[25,26] A catalytic one-step transformation, which is equivalent to an internal reduction/oxidation process, is a conceptually attractive strategy due to easy access to allylic alcohols.[27–29] A variety of transition metal complexes have been employed for the isomerization of allylic alcohols, as shown below.

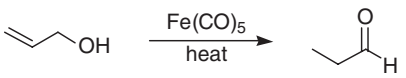


(8)



Scheme 8

Iron complex-catalyzed isomerization of allylic alcohols was found during the studies on the hydrolysis of π-allyliron tricarbonyl salts. The isomerization of allyl alcohol to propionaldehyde was observed on heating in the presence of $Fe(CO)_5$ (Equation (9)).[30]



(9)

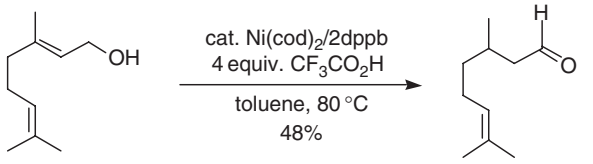
The scope and limitations of the $Fe(CO)_5$-catalyzed isomerization of allylic alcohols was investigated in detail. This study revealed that the treatment of secondary allylic alcohols with 10–20 mol% $Fe(CO)_5$ at 110–125 °C for 2–6 h gave isomerized ketones in 60–80% yield with >95% purity.[31]

Although the isomerization of allylic alcohols can be catalyzed by $Fe(CO)_5$ under thermal conditions, this reaction suffers from slow reaction rates, low yields, and high reaction temperature. To overcome these problems, photochemical activation of $Fe(CO)_5$ was investigated. By employing photochemical activation conditions, the isomerization of a wide variety of allylic alcohols proceeded in good to excellent yields using 1–10 mol% of $Fe(CO)_5$ in pentane (Scheme 9).[32]

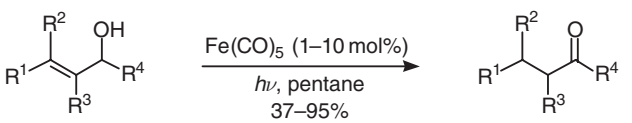
The process mentioned above was successfully applied to a short and efficient synthesis of two perfume compounds, cyclamen aldehyde and foliaver (Scheme 10).[32]

Allylic alcohols react with aldehydes, in the presence of catalytic amounts of $Fe(CO)_5$ under photochemical activation conditions, to give mainly aldol products (Scheme 11).[33] This novel tandem iosmerization–aldolization reaction is a process with a perfect atom economy, proceeding under neutral conditions.

Nickel complexes are also active catalyst for the isomerization of allylic alcohols. $Ni(dppb)_2$, prepared by mixing $Ni(cod)_2$/2dppb (2 equiv.), catalyzed the isomerization of geraniol to citronellal in the presence of CF_3CO_2H (4 equiv.) in toluene at 80 °C (Equation (10)).[34]

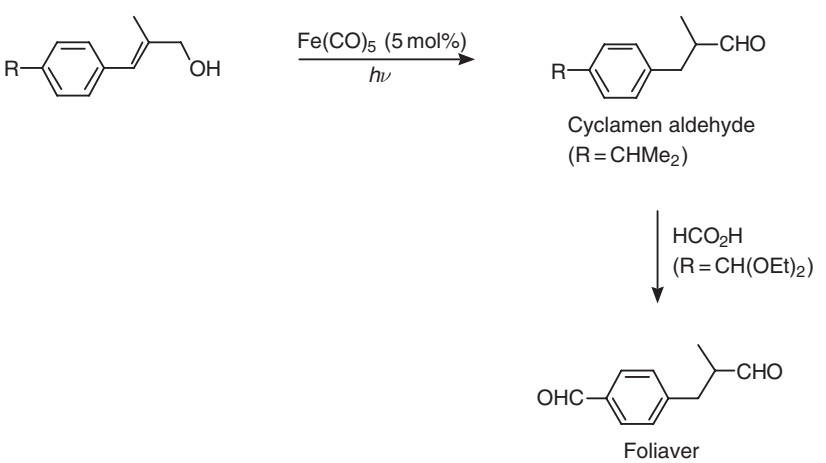


(10)

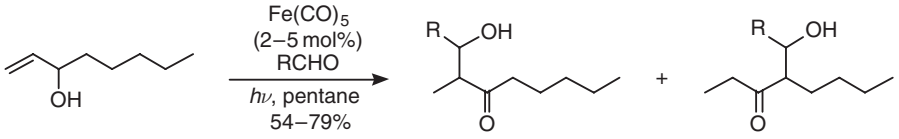


R^1, R^2, R^3 = H, Me, Ph, CO_2Me, CN, COPh
R^4 = H, Bu^n, n-C_5H_{11}, Ph

Scheme 9

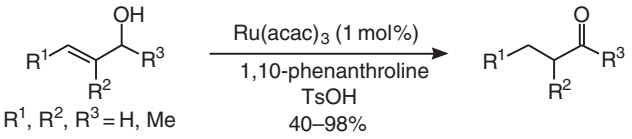


Scheme 10



RCHO = HCHO, CH_3CHO, Pr^i_2CHCHO, $PhCH_2CHO$, PhCHO, 5-acetoxymethyl-2-furaldehyde

Scheme 11



Scheme 12

Various ruthenium complexes catalyze the isomerization of allylic alcohols to saturated carbonyl compounds. $Ru(acac)_3$ is an effective catalyst for the isomerization of a wide range of allylic alcohols (Scheme 12).[35]

$CpRu(PPh_3)_2Cl$ and the corresponding indenyl complex are effective catalysts for isomerization of a wide range of allylic alcohols.[36,37] The reactions proceeded in good yield for a wide range of primary and secondary allylic alcohols using 5% catalyst and 10% Et_3NHPF_6 in dioxane at 100 °C (Scheme 13).

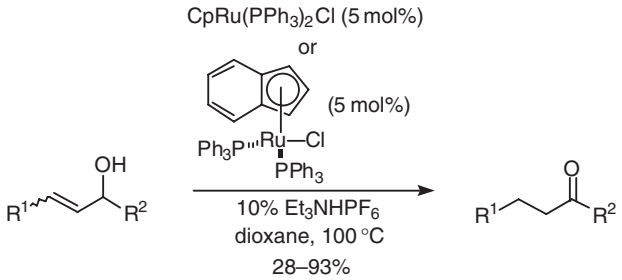
High chemoselectivity is observed in this ruthenium-catalyzed isomerization of allylic alcohols. Simple primary and secondary alcohols and isolated double bonds are not affected by these catalysts. Furthermore, free hydroxy group is essential for this catalysis. The reaction of 1-acetoxycyclododec-2-ene-4-ol furnished 4-acetoxycyclododecanone in high yield (Scheme 14).[37]

The plausible mechanism of this ruthenium-catalyzed isomerization of allylic alcohols is shown in Scheme 15. This reaction proceeds via dehydrogenation of an allylic alcohol to the corresponding unsaturated carbonyl compound followed by re-addition of the metal hydride to the double bond. This mechanism involves dissociation of one phosphine ligand. Indeed, the replacement of two triphenylphosphines by various bidentate ligands led to a significant decrease in the reactivity.[37]

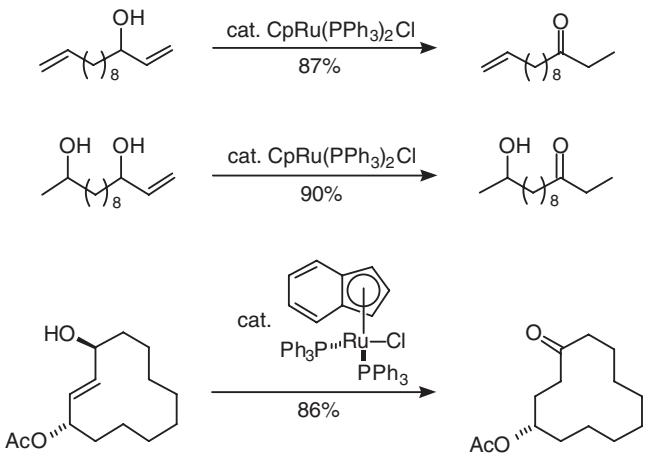
$[RuCp(PR_3)\ (CH_3CN)]PF_6$ type complexes (R = Me, Cy, Ph), which have labile ligands, would generate a $14e^-$ cationic ruthenium species readily. The reactions of a variety of disubstituted allylic alcohols furnished the corresponding carbonyl compounds in good to high yields using these catalysts (1 mol%) at 57 °C (Scheme 16).[38]

$Ru^{II}(H_2O)_6(tos)_2$ is an efficient catalyst for the isomerization of allylic alcohols and allylic ethers under mild conditions in aqueous media to yield the corresponding carbonyl compounds.[39]

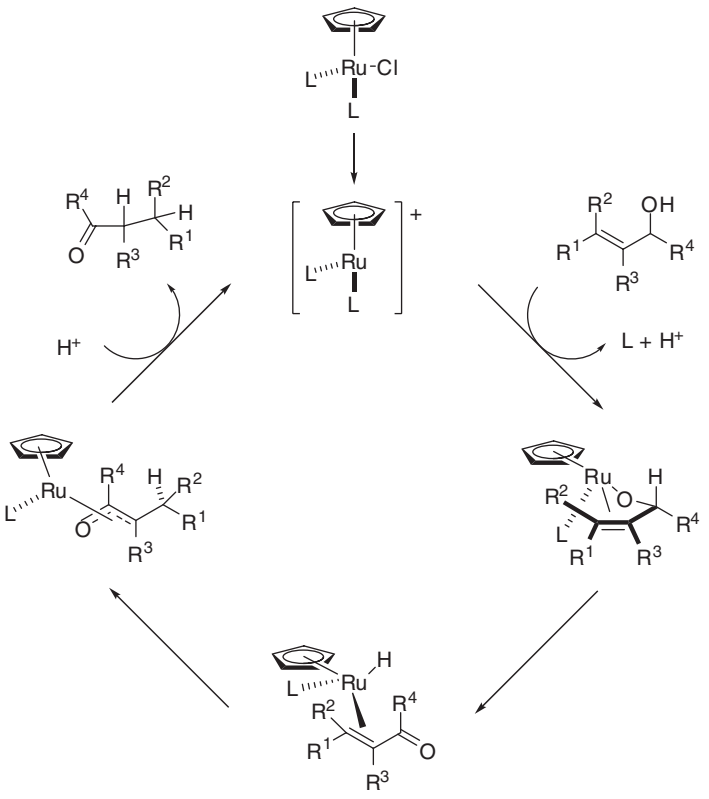
The ring-closing methathesis catalysts (10 mol% catalyst in refluxing toluene) are also effective for this transposition.[40,41] Both ester and ether functionalities appear compatible with these reaction conditions (Scheme 17).



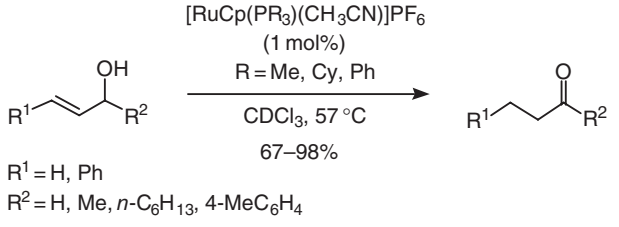
Scheme 13



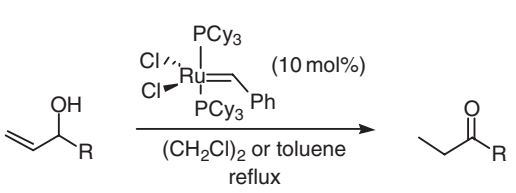
Scheme 14

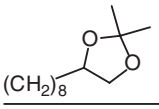


Scheme 15



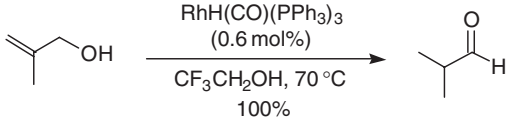
Scheme 16



R	*Yield* (%)
$(CH_2)_4CO_2Me$	67
	70

Scheme 17

A variety of rhodium complexes also catalyze the isomerization of allylic alcohols to saturated carbonyl compounds. $RhH(CO)(PPh_3)_3$ quantitatively isomerized methallyl alcohol to isobutylaldehyde at 70 °C in trifluoroethanol (Equation (11)).[42]

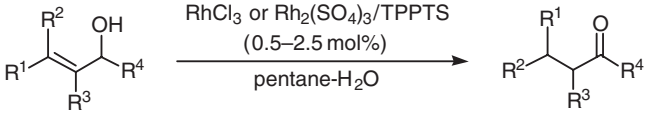


(11)

$RhCl_3$ or $Rh_2(SO_4)_3$ with water-soluble sulfonated triphenylphosphine (TPPTS) is effective catalyst for isomerization of allylic alcohols in a biphasic (pentane/water) system (Scheme 18).[43] As an extension, the use of microreactors for high throughput screening of catalytic reactions was reported.[44] This new technology was used for the screening of different rhodium- and ruthenium-based catalysts in the isomerization of 1-hexene-2-ol to ethyl propyl ketones. It was found that under these conditions, the $RhCl_3$/TPPTS system was the most efficient one in agreement with the previous results.

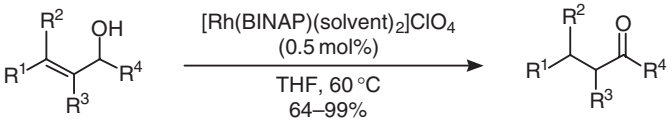
In parallel to the asymmetric catalytic isomerization of allylamines, [Rh(BINAP) $(solvent)_2]ClO_4$ is a very efficient catalyst for the isomerization of allylic alcohols.[9,11] By employing 0.5 mol% of the catalyst, good to excellent conversions were achieved even in the case of substrates that are more difficult to isomerize, such as allylic alcohols having two alkyl groups in the terminal position ($R^1 = R^2 = Me$) and 2-cyclohexen-1-ol (Scheme 19).

A very extensive and detailed study of the cationic rhodium(I)-catalyzed isomerization of allylic alcohols demonstrated that mono- and disubstituted allylic alcohols can be efficiently isomerized to the corresponding carbonyl compounds through the corresponding enol compounds (Scheme 20).[45] The isomerization using cationic rhodium(I)



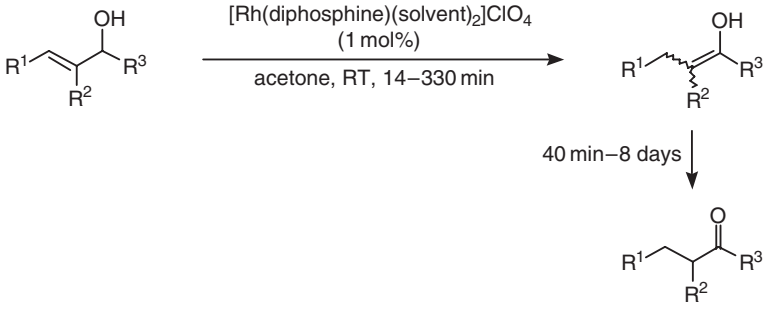
R^1 = H, Me, Pr^n, $CH_2CH_2CH{=}CMe_2$
R^2 = H, Me, Pr^n
R^3 = H
R^4 = H, Me, Pr^n, *n*-C_5H_{11}
R^1 = Me, R^3 = H, R^2R^4 = $-(CH_2)_3-$

Scheme 18



R^1, R^2, R^3, R^4 = H, Me
$R^1 = R^3$ = H, R^2R^4 = $-(CH_2)_3-$

Scheme 19

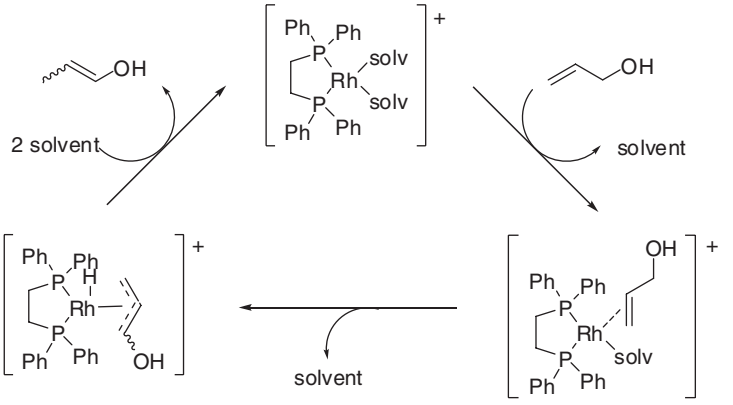


Scheme 20

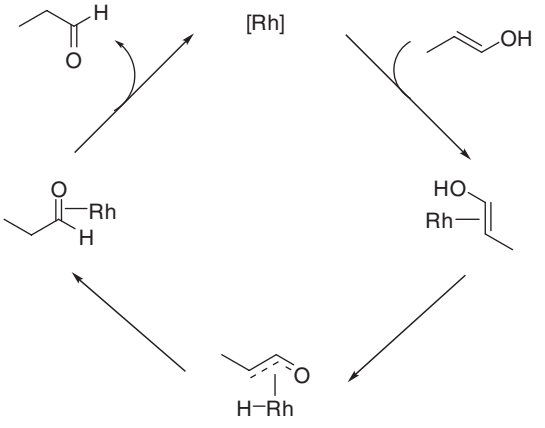
complexes is very attractive from a synthetic point of view due to its low catalyst loading (1 mol% catalyst) and mild reaction conditions (at room temperature or below).

The mechanistic study revealed that the isomerization of allylic alcohols to the corresponding enols proceeds through a π-allyl intermediate (Scheme 21), and the isomerization of the enols to the corresponding carbonyl compounds proceeds through an oxy-π-allyl intermediate (Scheme 22).[45]

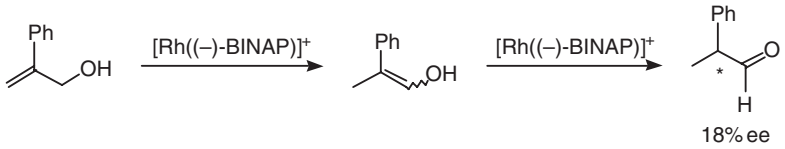
When the optically active catalyst [Rh((−)-BINAP)]$^+$ was employed, a prochiral substrate was transformed to the corresponding chiral aldehyde with 18% ee (Scheme 23).[45] Since the enantioselectivity-determining step in this



Scheme 21



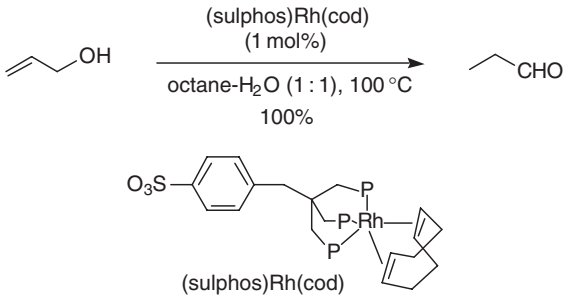
Scheme 22



Scheme 23

process is the conversion of the enol to the aldehyde, it is clear that isomerization does not proceed completely by heating and that the mechanism of the catalytic isomerization probably involves intimate association of the enol with the catalyst.

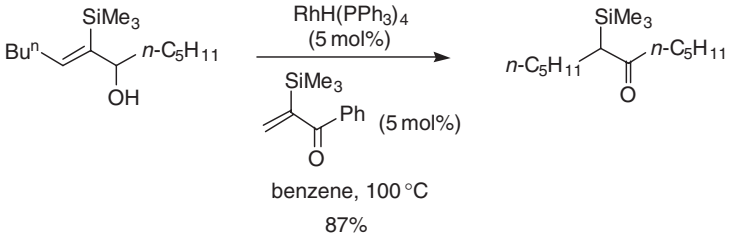
As part of a search for catalysts that can be used under biphasic conditions, zwitterionic Rh(sulphos)(cod) derivatives were studied. The isomerization of allyl alcohol proceeded within 1 h at 100 °C using only 1 mol% catalyst to give propanal in quantitative yield (Equation (12)).[46] After separation of the product, the catalyst could be recycled three times with a slight deactivation after each run.



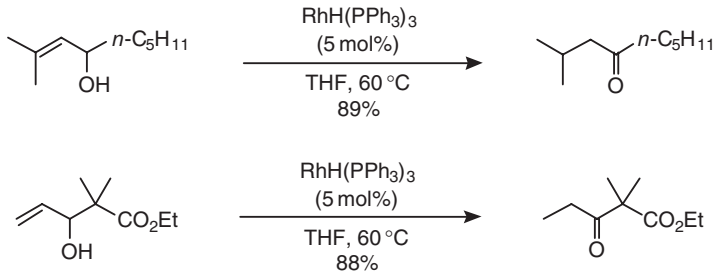
(12)

Although it is known that Wilkinson's catalyst does not efficiently isomerize allylic alcohols or allylic ethers, treatment of $RhCl(PPh_3)_3$ with *n*-BuLi furnishes the hydrido complex $RhH(PPh_3)_3$, which is a highly efficient catalyst for the isomerization of allylic alcohols.[47] A wide range of secondary allylic alcohols could be efficiently isomerized using 5 mol% $RhH(PPh_3)_3$ in refluxing THF (Scheme 24).

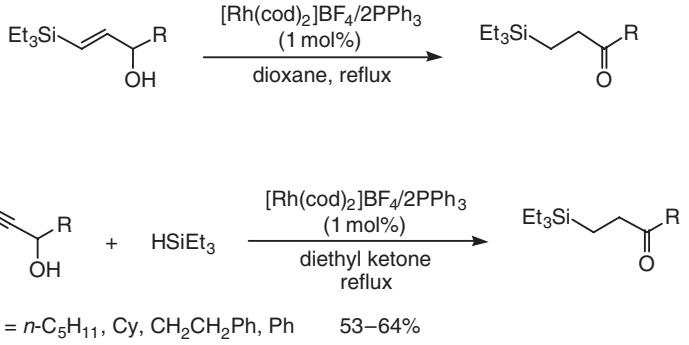
$RhH(PPh_3)_4$ efficiently isomerized α-silylallylic alcohols to α-silyl ketones in excellent yields, but only in the presence of an α-silyl enone as co-catalyst (Equation (13)).[48]



(13)



Scheme 24

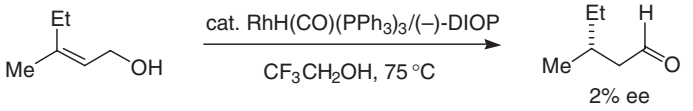


Scheme 25

For β-silylallylic alcohols, $[Rh(cod)_2]BF_4/2PPh_3$ is a more effective catalyst than $RhH(PPh_3)_4$ to afford β-silyl ketones in good yields (Scheme 1).[1] As an interesting extension of this reaction, a tandem hydrosilation–isomerization process, starting from propargylic alcohols, was reported (Scheme 25).[49]

Although the asymmetric isomerization of allylamines has been successfully accomplished by the use of a cationic rhodium(I)/BINAP complex, the corresponding reaction starting from allylic alcohols has had a limited success. In principle, the enantioselective isomerization of allylic alcohols to optically active aldehydes is more advantageous because of its high atom economy, which can eliminate the hydrolysis step of the corresponding enamines obtained by the isomerization of allylamines (Scheme 26).

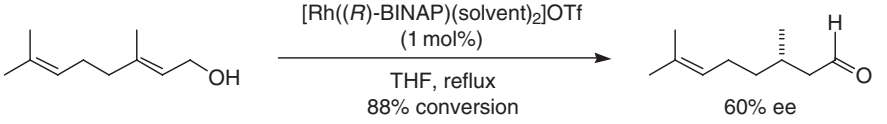
The first enantioselective isomerization of allylic alcohols was carried out by using $RhH(CO)(PPh_3)_3$/(−)-DIOP. However, the enantioselectivity was very low (Equation (14)).[50]



(14)

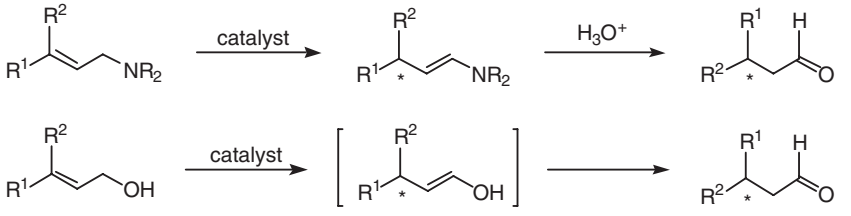
The enantioselective isomerization of allylic alcohols using cationic rhodium(I)/BINAP complex was reported.[9,11] Although the enantioselectivities were lower than those achieved by the isomerization of the corresponding enamines, 3,3′-disubstituted allylic alcohols were isomerized to the corresponding aldehydes in moderate yield and enantioselectivity (Scheme 27).

Changing the counterion from ClO_4^- to OTf^- improved the enantioselectivity in the case of geraniol as the substrate (from 37% ee to 60% ee, Equation (15)).[51]

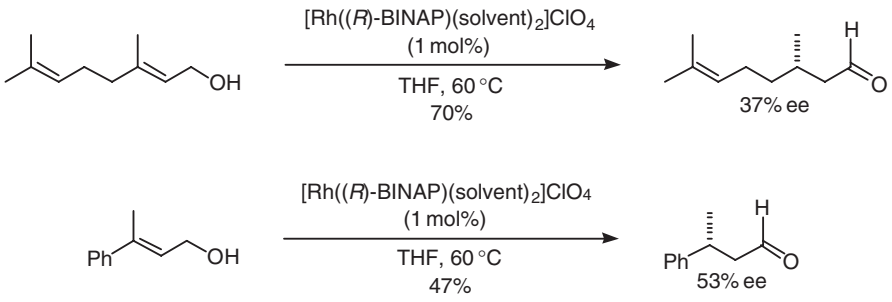


(15)

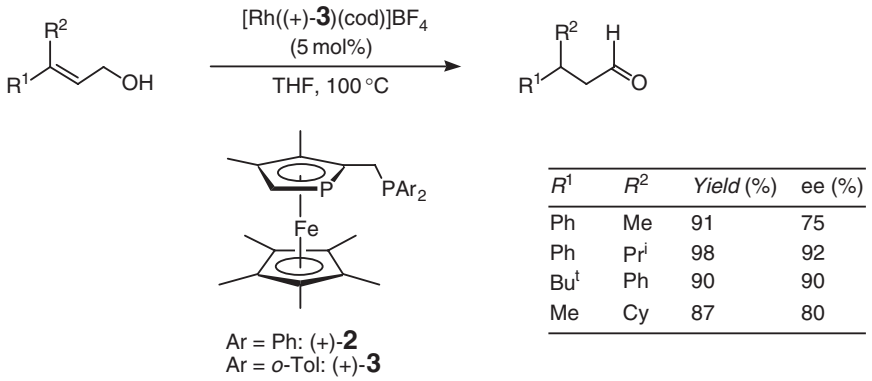
Further improved enantioselectivities were accomplished using cationic rhodium(I)/new chiral bidentate phosphaferrocene ligands. The isomerization of a variety of 3,3′-disubstituted allylic alcohols proceeds to give optically active aldehydes in good yields with good to excellent ee's (Scheme 28).[52,53] Phosphaferrocene ligand **3** is more useful than ligand **2** due to its high stability against air and moisture.[53]



Scheme 26



Scheme 27



R^1	R^2	*Yield* (%)	ee (%)
Ph	Me	91	75
Ph	Pr^i	98	92
Bu^t	Ph	90	90
Me	Cy	87	80

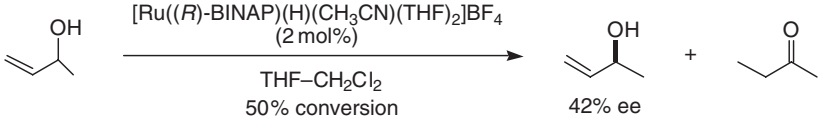
Scheme 28

Mechanistic study revealed that the reaction proceeds through intramolecular 1,3-hydrogen migration, and the chiral rhodium catalyst differentiates the enantiotopic C-1 hydrogens of allylic alcohols (Scheme 29).[53]

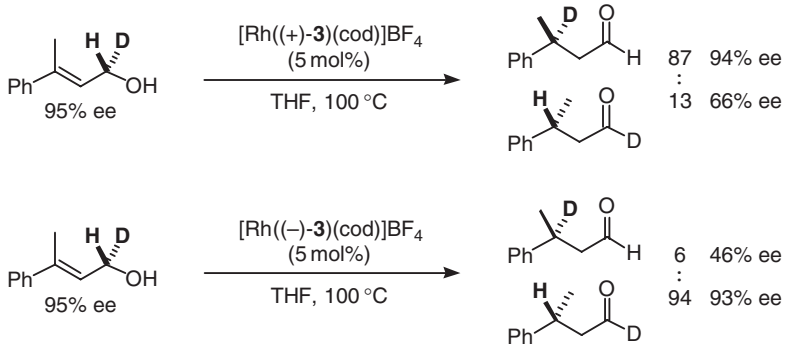
This asymmetric isomerization was successfully applied to the formal total synthesis of 7-hydroxycalamenene and 7-hydroxycalamenal, two naturally occurring sesquiterpenes in the cadinene family (Scheme 30).[52]

An efficient kinetic resolution of 4-hydroxy-2-cyclopentenone was achieved using [Rh((*R*)-BINAP)($CH_3OH)_2$]ClO_4 as catalyst.[1] The reaction proceeded with a 5 : 1 discrimination rate between the two enantiomers, and (*S*)-isomer, which is a useful intermediate in prostaglandin synthesis, was obtained with 91% ee at 72% conversion (Scheme 31).[54]

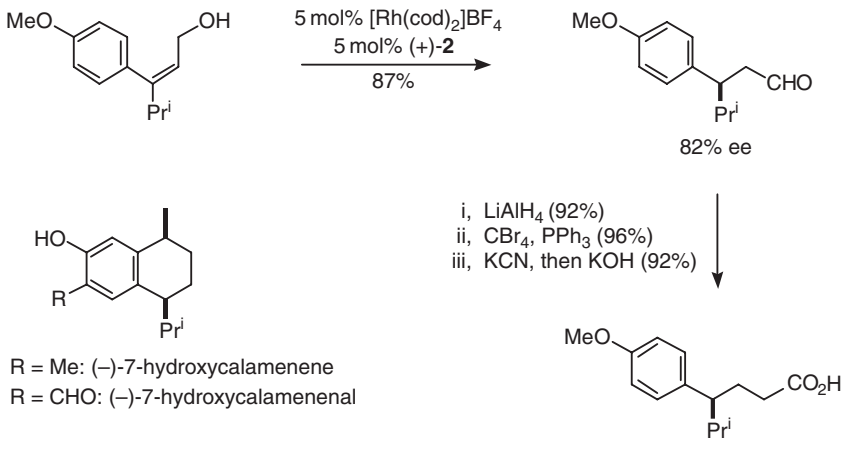
In the case of acyclic allylic alcohols, an efficient kinetic resolution of 1-buten-3-ol was achieved using [Ru((*R*)-BINAP)(H)(CH_3CN)($THF)_2$]BF_4 as catalyst (Equation (16)).[55]



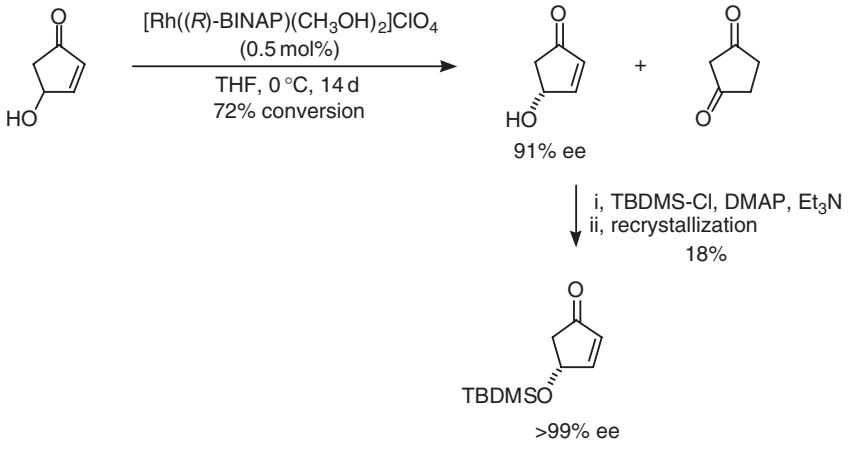
(16)



Scheme 29



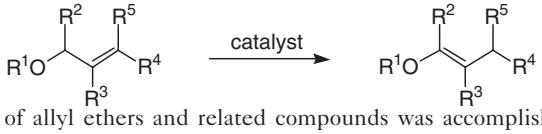
Scheme 30



Scheme 31

10.02.4 Allyl Ethers

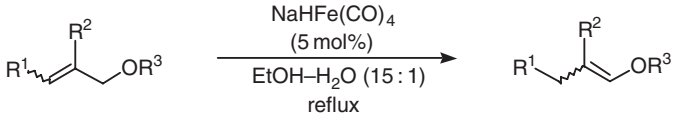
The isomerization of allyl ethers and allyl acetals to vinyl ethers or vinyl acetals, respectively, has found many applications in organic synthesis (Equation (17)). Various transition metal catalysts have been reported in the literature for the isomerization of allyl ethers and allyl acetals.



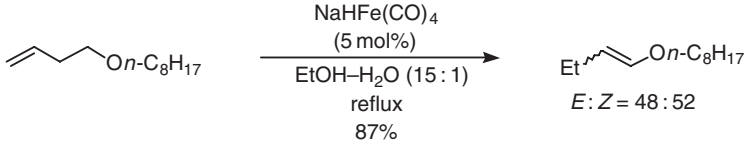
(17)

The efficient isomerization of allyl ethers and related compounds was accomplished by using $NaHFe(CO)_4$ as catalyst. Isomerization of a homoallyl ether was also carried out in high yield (Scheme 32).[56]

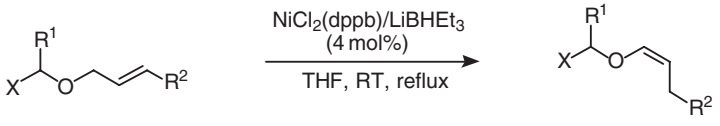
The double bond geometry resulting from the isomerization process is not an issue when the allyl moiety is used only as a protecting group. However, the *Z*-/*E*-selectivity of this process plays an important role especially when the vinylic products are used for the stereoselective reactions. A novel procedure for a highly *Z*-selective isomerization of acyclic allyl acetals and allyl ethers using $NiCl_2$(dppb) as catalyst through activation with superhydride (lithium triethylborohydride) was reported.[57] The applicability of this process is exemplified in the stereoselective synthesis of a substrate for Claisen rearrangement (allyl vinyl ether)[58] from a diallyl ether (Scheme 33).



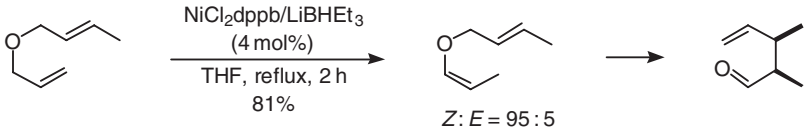
R^1	R^2	R^3	*Yield* (%)	(*E* : *Z*)
H	H	*n*-$C_{10}H_{21}$	96	(42 : 58)
H	H	Ph	86	(96 : 4)
Me	H	*n*-$C_{10}H_{21}$	96	(58 : 42)
H	Me	*n*-C_8H_{17} (50 h)	63	



Scheme 32

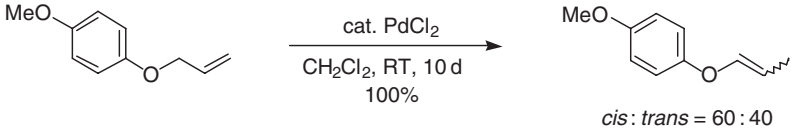


x	R^1	R^2	*Yield* (%)	(*Z* : *E*)
N(Me)Ac	Bu^t	H	83	(>99 : 1)
N(Me)Ac	Ph	Me	83	(96 : 4)
OMe	Bn	H	87	(95 : 5)
Ph	H	H	81	(95 : 5)



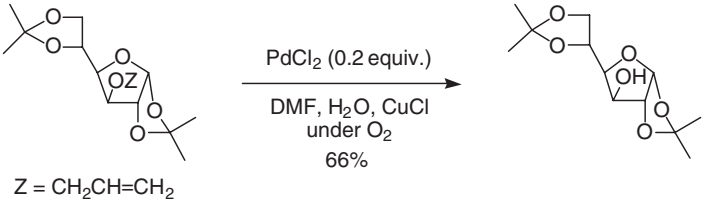
Scheme 33

Cis- and *trans*-1-propenyl 4-methoxyphenyl ethers, which were used for Diels–Alder reaction, were synthesized through $PdCl_2$-catalyzed isomerization of 4-methoxyphenyl allyl ether (Equation (18)).[59]



(18)

$PdCl_2$/CuCl catalyzes the deprotection of prop-2-enyl ethers in moderate yield under Wacker-oxidation conditions (Equation (19)).[60]

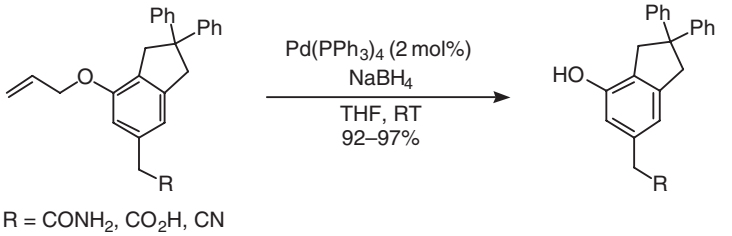


(19)

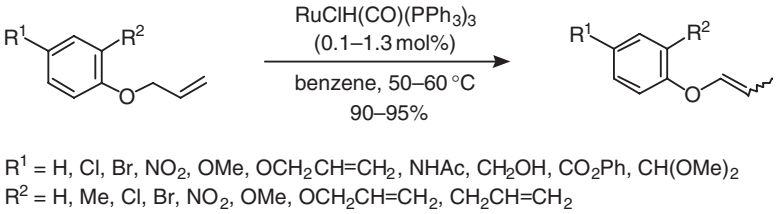
Reductive deprotection of allyl aryl ethers[1] can be accomplished by the use of $Pd(PPh_3)_4/NaBH_4$ in high yield (Scheme 34).[21,61]

The isomerization of allyl aryl ethers catalyzed by 0.1–1.3 mol% $RhCl(H)(CO)(PPh_3)_3$ in benzene at 50–60 °C gave *Z*-isomers as the major products (Scheme 35).[62]

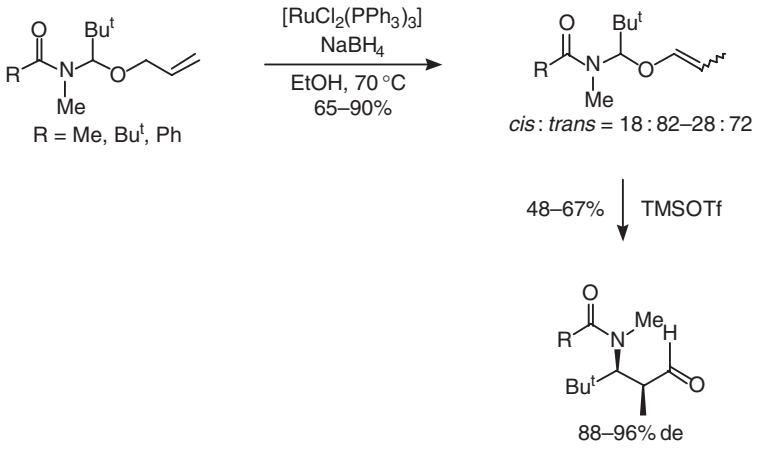
A diastereoselective synthesis of *β*-(*N*-acylamino)aldehydes was accomplished via ruthenium-catalyzed isomerization of *O*-vinyl-*N*,*O*-acetals followed by rearrangement in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) (Scheme 36).[63]



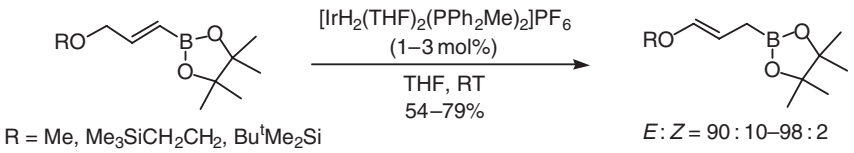
Scheme 34



Scheme 35



Scheme 36



Scheme 37

Isomerization of [(*E*)-3-alkoxy-1-propenyl]boronates to the corresponding γ-alkoxyallylboronates was catalyzed by ruthenium or iridium complexes.[64] $[IrH_2(THF)_2(PPh_2Me)_2]PF_6$ was the most efficient catalyst for selective preparation of (*E*)-γ-alkoxyallylboronates (Scheme 37).

The isomerization of multifunctionalized allyl silyl or allyl boryl ethers is efficiently catalyzed by a ruthenium complex in high yield (Scheme 38).[23,24]

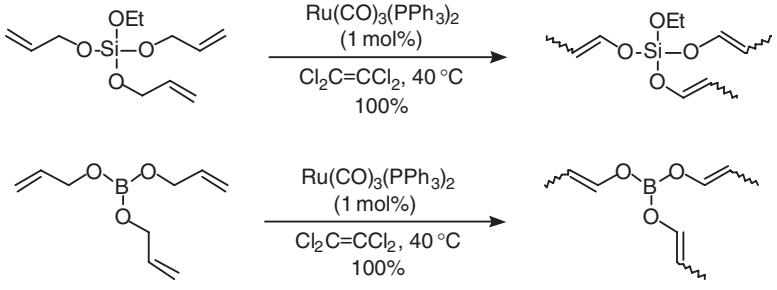
Ruthenium-carbenoid complex **1** catalyzed the isomerization of β,γ-unsaturated ethers to the corresponding vinyl ethers. This reaction is useful in the deprotection of allyl and homoallyl ethers (Scheme 39).[65]

The ruthenium-catalyzed isomerization of aryl allyl ethers or amines followed by ring-closing metathesis with ruthenium catalyst **1** furnishes fused benzo-heterocycles in good yield (Scheme 40).[66,67]

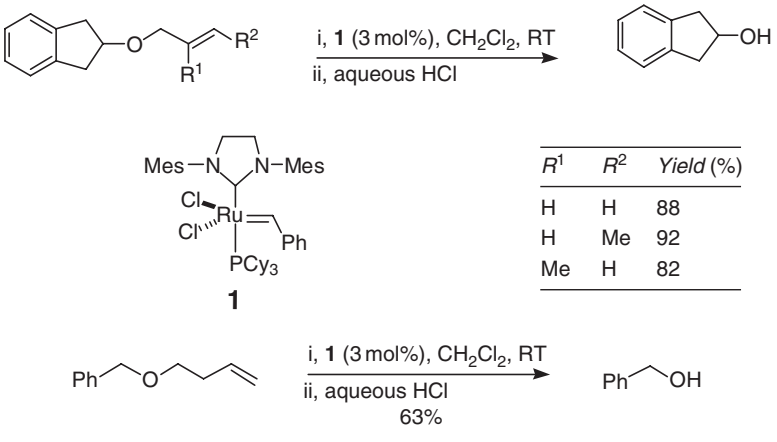
An olefin metathesis/double bond isomerization sequence can be promoted by the catalysis of *in situ* generated ruthenium hydride species from ruthenium complex **1** (Scheme 41).[68]

The isomerization of the double bonds conjugated with the ester moiety to enol ethers can be carried out using $RuCl(H)(CO)(PPh_3)_3$ as catalyst (Scheme 42).[69]

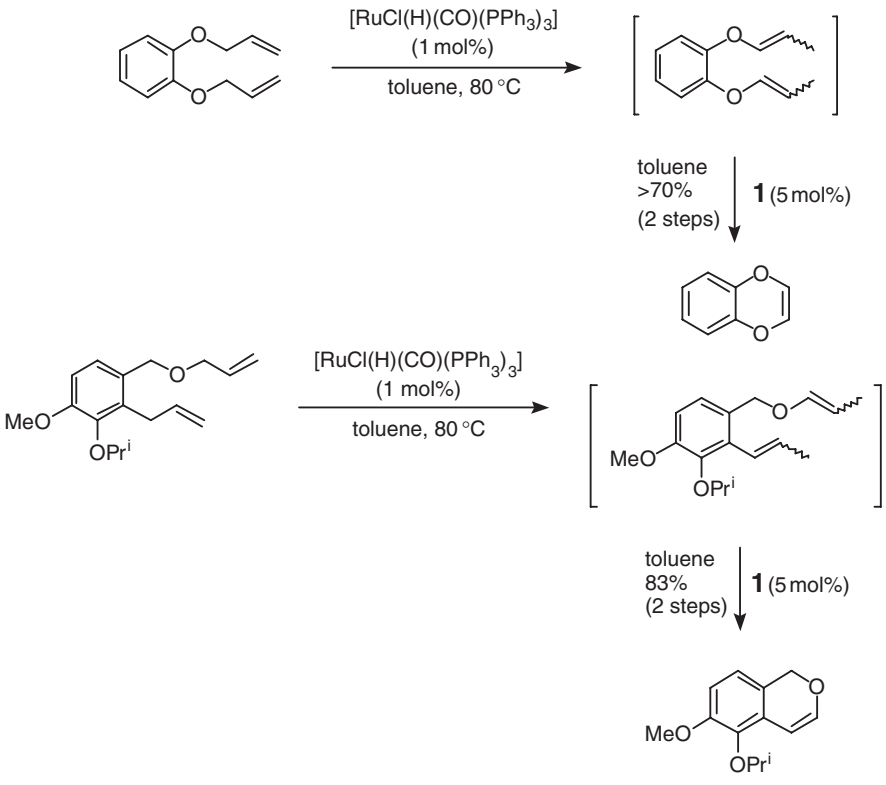
The stereoselective isomerization of allyl silyl ethers to (*E*)- or (*Z*)-silyl enol ethers was carried out in the presence of a cationic iridium(I) catalyst. The complex, prepared *in situ* by treating $[Ir(cod)_2]PF_6/2PPr_3$ with hydrogen, was



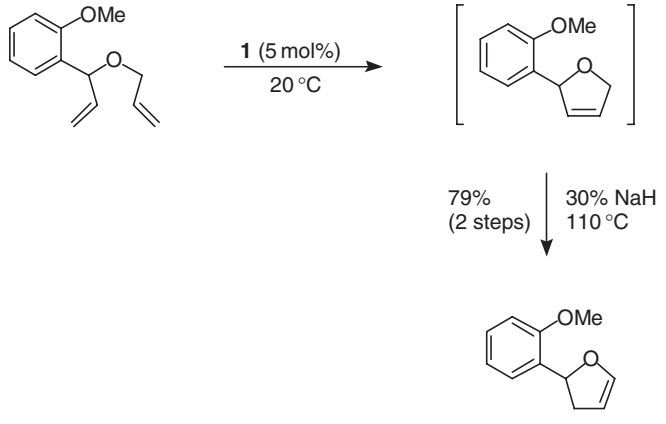
Scheme 38



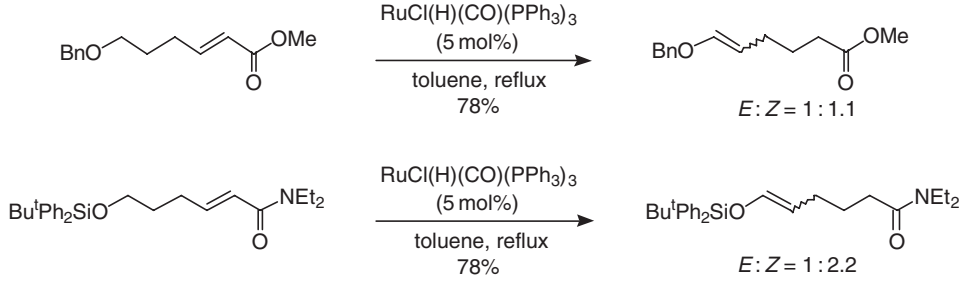
Scheme 39



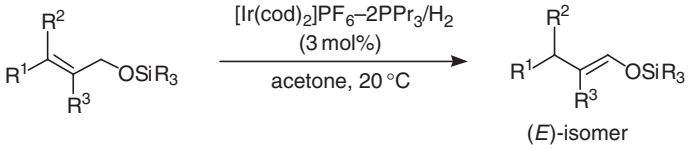
Scheme 40



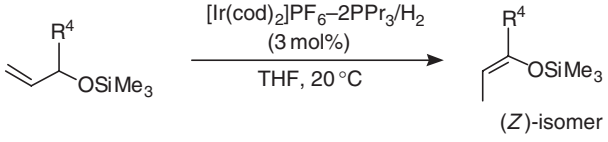
Scheme 41



Scheme 42



R^1, R^2, R^3 = H, Me, Pr^n, Ph
SiR_3 = $SiBu^tMe_2$, $SiPhMe_2$, $SiPh_2Me$, $SiMe_3$,



R^4 = Me, Et, Pr^i, $CH(CH_3)C_3H_7$, $CH(C_2H_5)C_2H_5$, Cy, Bu^t, n-C_5H_{11}, Ph

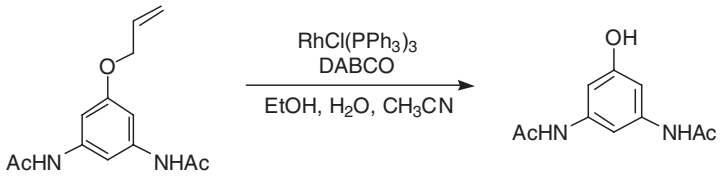
Scheme 43

found to be an excellent catalyst for the isomerization of primary and secondary allyl ethers in high yields. The primary silyl ethers produced (*E*)-enol ethers and the secondary allyl ethers afforded (*Z*)-enol ethers with high stereoselectivity (Scheme 43).[70,71]

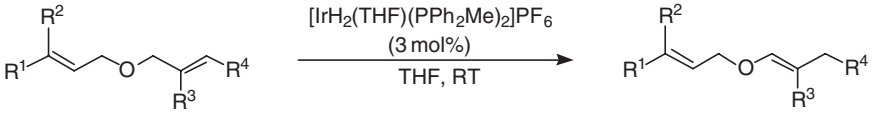
The stereoselective isomerization of unsymmetrical diallyl ethers to allyl (*E*)-vinyl ethers was also carried out in the presence of a cationic iridium(I) catalyst. The catalyst prepared *in situ* by treating $[Ir(cod)(PPh_2Me)_2]PF_6$ with hydrogen was found to be an excellent catalyst for the selective isomerization of a less substituted allyl group to an (*E*)-vinyl ether (Scheme 44).[72]

A polymer-supported iridium catalyst **4** has been prepared and used in the isomerization of the double bonds in aryl allyl ethers and aryl allylic compounds with excellent *trans*-selectivity and without conventional workup procedures (Scheme 45).[73]

$RhCl(PPh_3)_3$ is an effective catalyst for the deprotection of allyl ethers in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) (Equation (20)).[74,75] The role of the base is to prevent hydrolysis of prop-1-enyl ether to propanal, which poisons the catalyst.

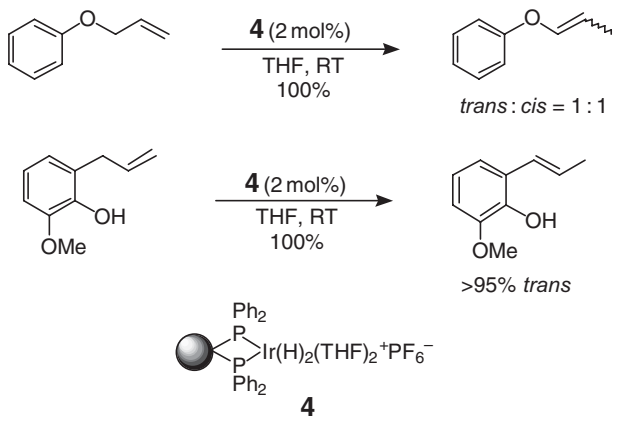


(20)

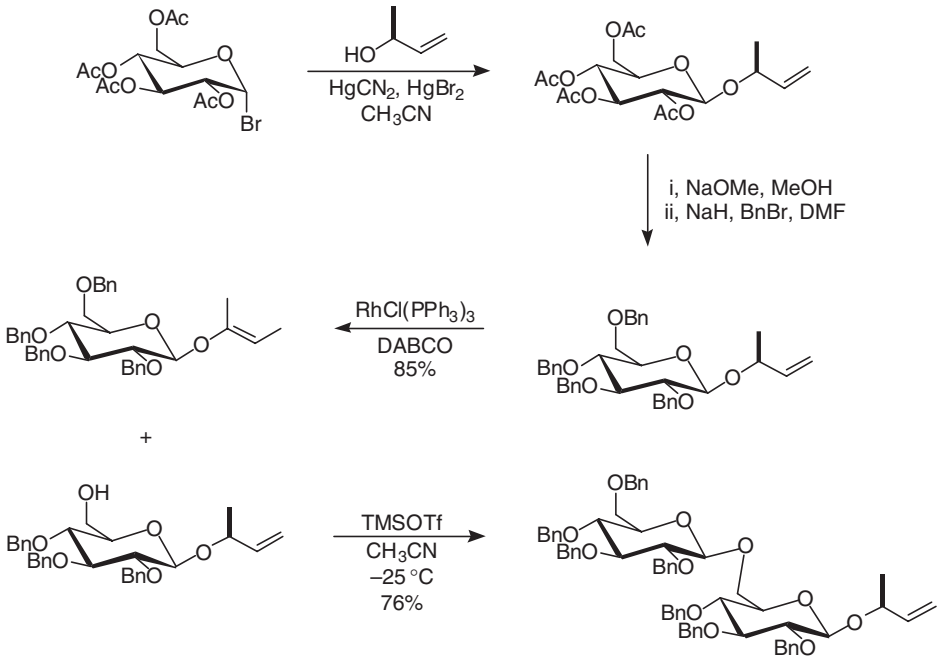


R^1	R^2	R^3	R^4	*Yield* (%)	(*E* : *Z*)
Ph	H	H	H	78	(96 : 4)
Ph	H	H	Me	60	(99 : 1)
Ph	H	Me	H	56	
Me	Me	H	H	65	(99 : 1)
Me	Me	H	Me	25	(*E* > 99)

Scheme 44



Scheme 45

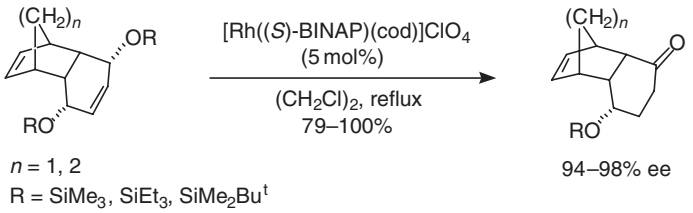


Scheme 46

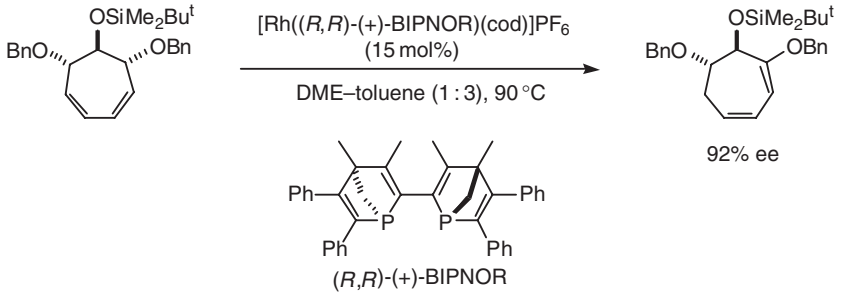
A novel latent-active glycosylation strategy was reported. This strategy is based on a rhodium-catalyzed isomerization of substituted allyl glycosides followed by a Lewis acid-mediated glycosylation reaction (Scheme 46).[76,77]

Several asymmetric isomerizations of allyl ethers have been accomplished by using chiral transition metal complexes. Desymmetrization of *meso*-2-ene-1,4-diol derivatives through enantioselective isomerization using [Rh((*S*)-BINAP)(cod)]ClO_4 as catalyst was investigated. Although the isomerization of *meso*-2-ene-1,4-diol gave the corresponding hydroxy ketones in quantitative yield and only 43.3% ee, the reaction of the corresponding *meso*-silyl ethers achieved 94–98% ee (Scheme 47).[78,79]

A similar desymmetrization of the dienyl ethers was accomplished using cationic rhodium(I)/BIPNOR complex. In this reaction, an oxygen-containing co-solvent was necessary, and the best result was obtained with a 3 : 1 mixture of toluene and 1,2-dimethoxyethane (glyme) (DME) (Equation (21)).[80]

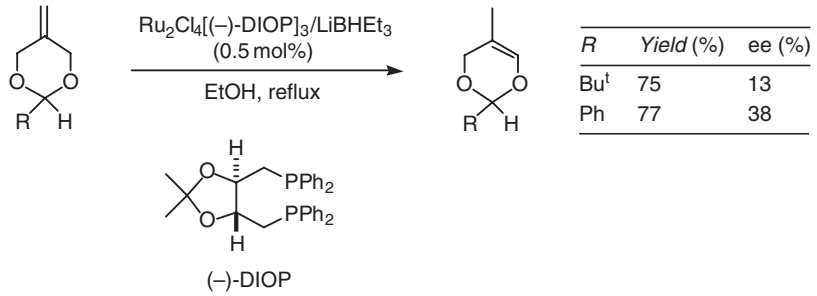


Scheme 47



(21)

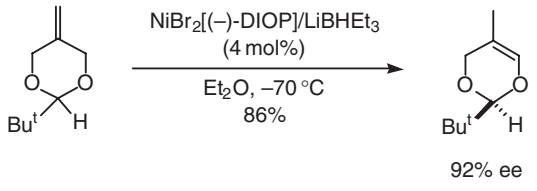
Desymmetrization of cyclic allyl acetals such as 2-substituted 4,7-hydrodioxepins or 5-methylene-1,3-dioxanes was investigated using ruthenium or nickel catalysts. The isomerization of the dioxanes was accomplished using Ru_2Cl_4(DIOP)/$LiBHEt_3$ in high yield with up to 38% ee (Equation (22)).[81]



R	*Yield* (%)	ee (%)
But	75	13
Ph	77	38

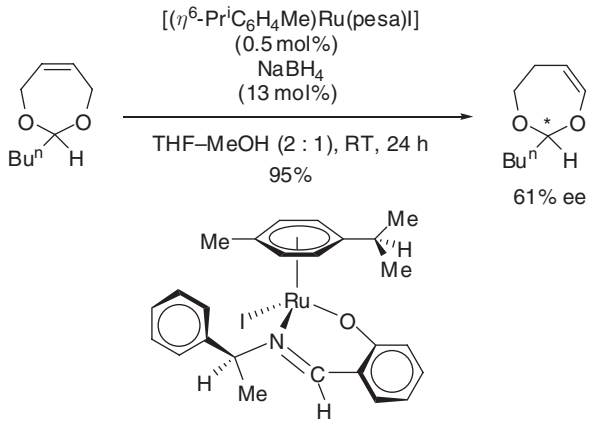
(22)

Desymmetrization of 5-methylene-1,3-dioxanes using $NiBr_2$(DIOP)/$LiBHEt_3$ improved the enantioselectivity up to 92% ee (Equation (23)).[82]



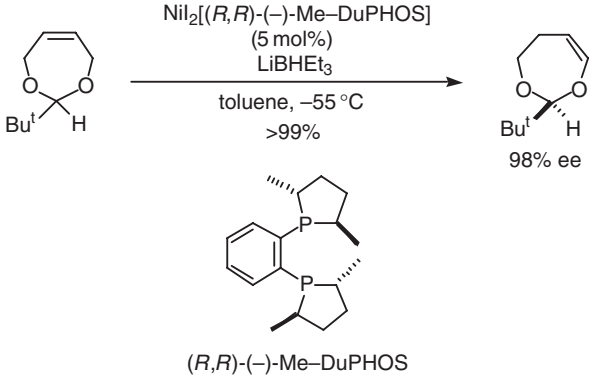
(23)

The isomerization of the dioxepins[83] was investigated using some chiral ruthenium complexes, and these catalysts gave moderate (up to 61% ee) enantioselectivities (Equation (24)).[84]



(24)

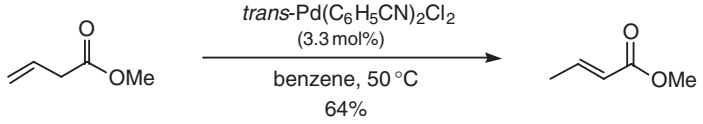
Excellent enantioselectivity (up to 98% ee) was realized by using NiI_2[Me-DuPHOS]/$LiBHEt_3$ as the catalyst at −55 °C (Equation (25)).[85]



(25)

10.02.5 Other Alkenes

Some synthetically useful isomerization reactions of alkenes, other than nitrogen- or oxygen-substituted allylic compounds, were reported by the use of a catalytic amount of transition metal complexes. The palladium complex, *trans*-$Pd(C_6H_5CN)_2Cl_2$, effectively catalyzed the stereoselective isomerization of β,γ-unsaturated esters to α,β-unsaturated esters (Equation (26)).[86]

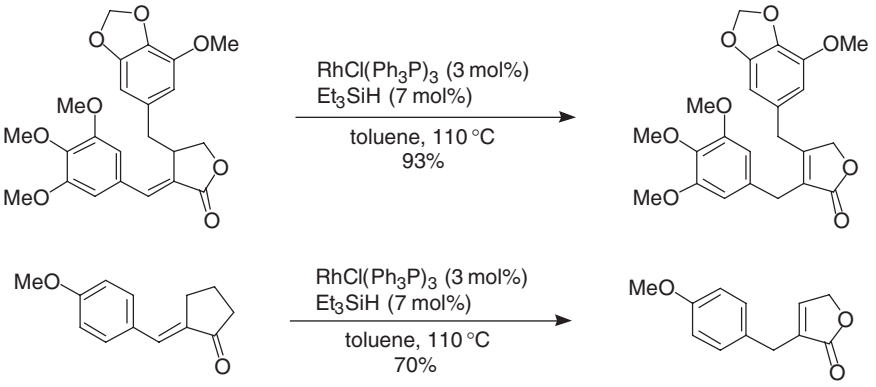


(26)

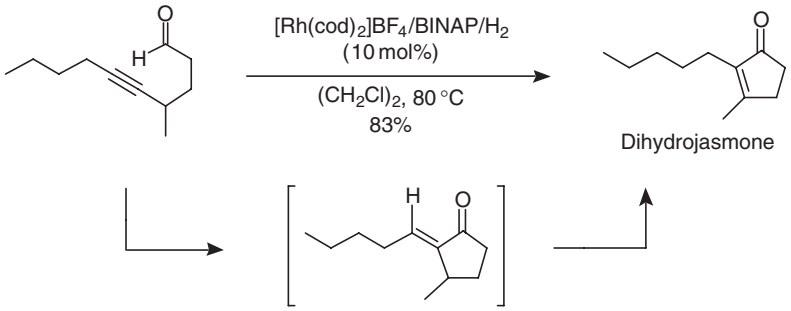
The isomerization of α-alkylidene cyclic carbonyl compounds to α,β-unsaturated cyclic carbonyl compounds was achieved by using catalytic amounts of $RhCl(PPh_3)_3$ and Et_3SiH (Scheme 48).[87]

Tandem hydroacylation–isomerization of 5-alkynals catalyzed by a cationic rhodium(I)/BINAP complex was applied to the short synthesis of dihydrojasmone (Scheme 49).[88]

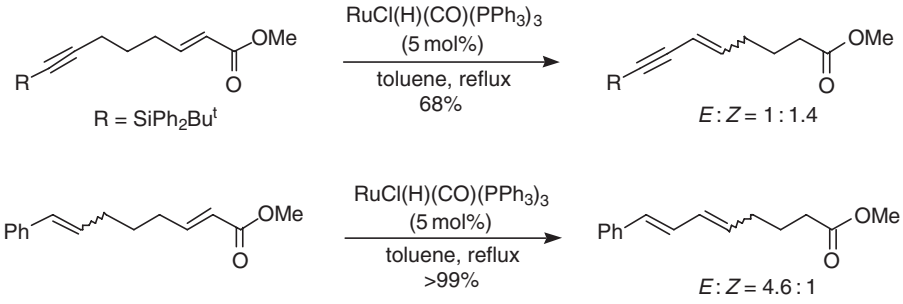
On the other hand, the isomerization of the double bond conjugated with the ester moiety to enynes and dienes can be carried out by using $RuClH(CO)(PPh_3)_3$ as catalyst (Scheme 50).[89]



Scheme 48



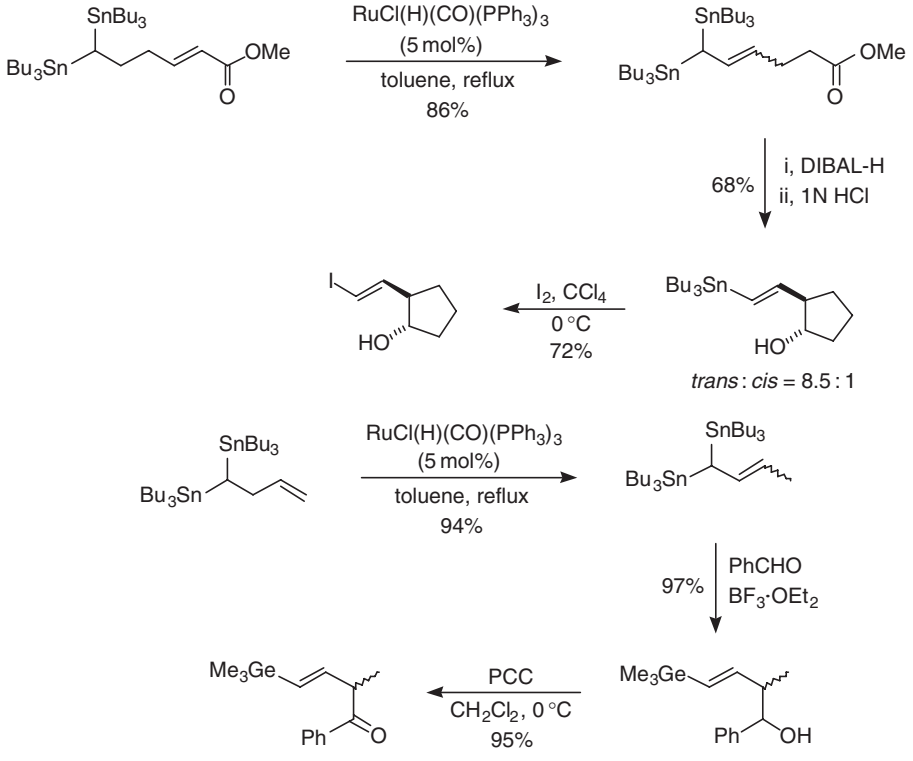
Scheme 49



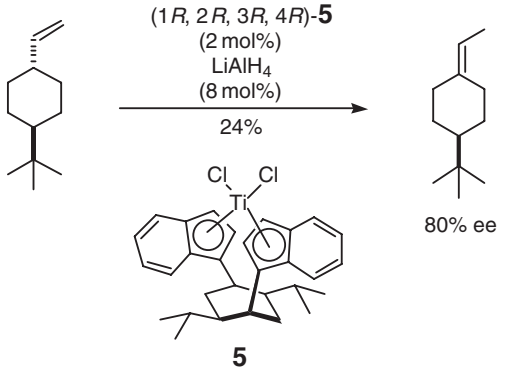
Scheme 50

Isomerization of bis(tributylstannyl)alkenyl compounds catalyzed by $RuCl(H)(CO)(PPh_3)_3$ gave the corresponding allylbis(tributyl)tin compounds in good yields (Scheme 51). These compounds are useful intermediates in organic synthesis.[89]

Although there are many reports on the enantioselective catalytic double bond isomerization of functionalized achiral alkenes, that of alkenes bearing an isolated double bond have had limited success. The use of a chiral bis(indenyl)titanium catalyst **5** containing a chiral bridging group realized the highly enantioselective isomerizations of unfunctionalized achiral alkenes with up to 80% ee (Equation (27)).[90]



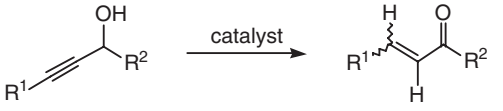
Scheme 51



(27)

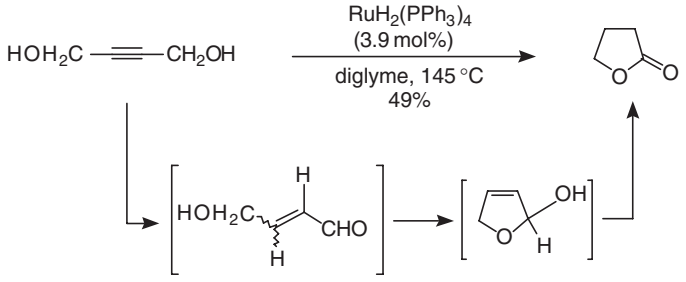
10.02.6 Propargylic Alcohols

α,β-Unsaturated carbonyl compounds are useful building blocks in organic synthesis. For the preparation of them, the isomerization of propargylic alcohols to the corresponding α,β-enones and α,β-enals is one of the most efficient methods because of an easy access to propargylic alcohols and high atom economy (Equation (28)).[25,26] However, such an isomerization reaction has not been extensively studied compared with the well-established reaction of allylic alcohols.



(28)

In 1982, the ruthenium-catalyzed isomerization of 2-butyne-1,4-diol to butyrolactone was reported. This reaction was proposed to proceed through initial isomerization of 2-butyne-1,4-diol to α,β-unsaturated aldehyde followed by cyclization and double bond isomerization (Scheme 52).[91]



Scheme 52

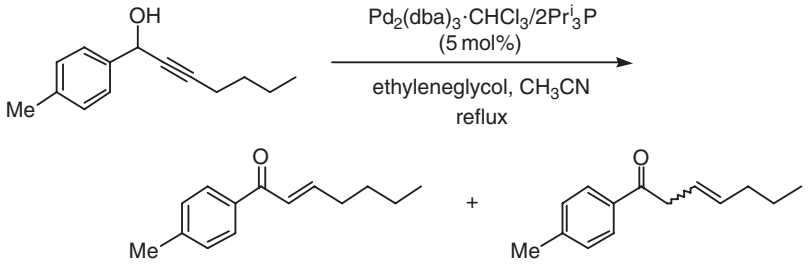
First example for the isomerization of propargylic alcohols to isolable α,β-enals was reported in 1989. A variety of prop-2-ynols can be isomerized to α,β-unsaturated aldehydes in the presence of a catalytic amount of $RuCl_2(PPh_3)_3$/Pr^i_3P (Scheme 53).[92]

The isomerization of propargylic alcohols to α,β-enones was also developed by using an iridium catalyst. A variety of secondary propargylic alcohols can be isomerized to the corresponding α,β-unsaturated ketones in the presence of 1 mol% $IrH_5(Pr^i_3P)_2$ (Scheme 54).[93]

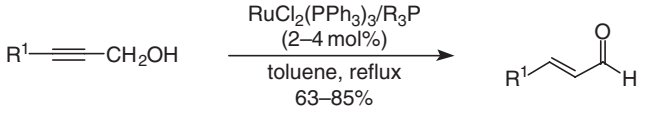
$Pd_2(dba)_3$-$CHCl_3$/Bu^n_3P catalyzes the isomerization of alkynediols to 1,4-diketones in high yield. Importantly, alkenyl-substituted alkynediols chemoselectively isomerized to the corresponding α,β-unsaturated 1,4-diketones (Scheme 55).[94]

This catalysis was successfully applied to the synthesis of 2,5-undecadione, a key intermediate in the synthesis of dihydrojasmone (Scheme 56).[94]

Unfortunately, alkynemono-ols failed to isomerize to the corresponding α,β-unasaturated ketones or aldehydes using this palladium catalyst under the same reaction conditions. However, in the presence of a catalytic amount of ethyleneglycol, $Pd_2(dba)_3$-$CHCl_3$/Pr^i_3P was able to isomerize alkynemono-ols to α,β-unsaturated ketones in high yields (Equation (29)).[95] In the presence of ethyleneglycol, an active palladium hydride species appears to be formed *in situ*.

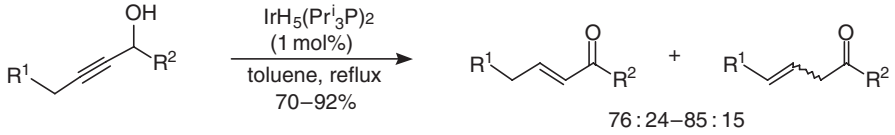


(29)



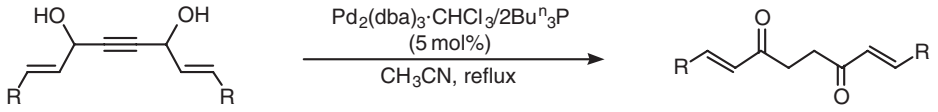
R^1 = Bu^n, *n*-C_5H_{11}, *n*-C_6H_{13}, *n*-C_7H_{15}, Ph
R = Pr^i, Bu^n

Scheme 53



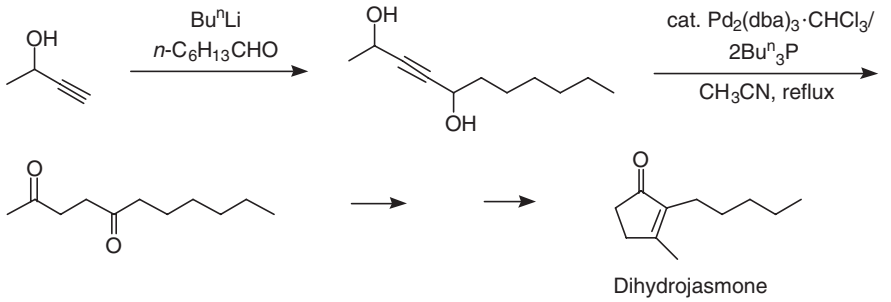
R^1 = Et, Pr^n, Pr^i, Bu^n, *n*-C_6H_{13}
R^2 = Me, Et, Ph

Scheme 54



R	*Yield* (%)
Me	72
Ph	93

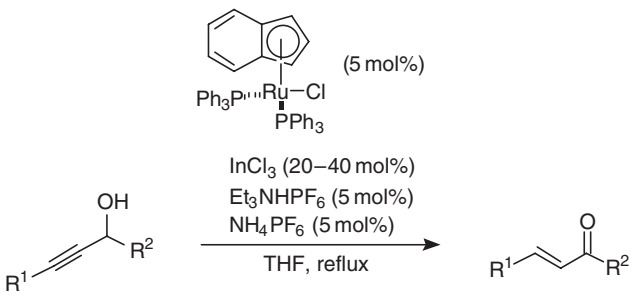
Scheme 55



Scheme 56

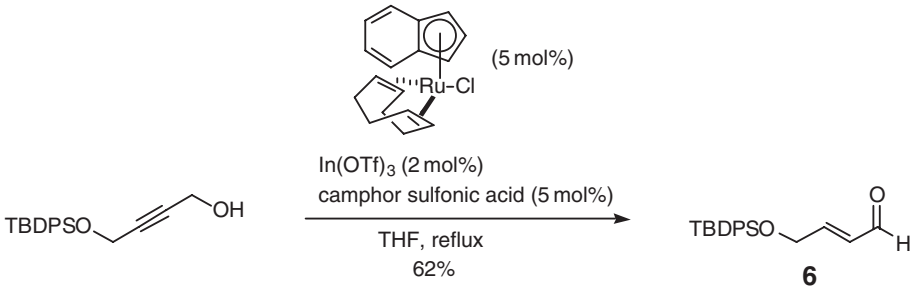
A ruthenium(II)-indenyl complex, which is an efficient catalyst for the isomerization of allylic alcohols, is also an effective catalyst for the isomerization of propargylic alcohols to both α,β-enals and α,β-enones (Scheme 57).[96] In this reaction, the addition of 20–40 mol% $InCl_3$ is highly effective. The reaction exhibits extraordinary chemoselectivity and a variety of functional groups are unaffected, which allows a highly efficient synthesis of dienals ($R^1 = Me_2C=CH$, $R^2 = H$).

This ruthenium-catalyzed isomerization of propargylic alcohols was successfully applied to the synthesis of α,β-enal **6**, a key intermediate in the total synthesis of sphingofungin analogs (Equation (30)).[97]



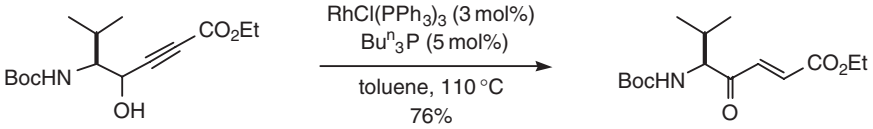
R^1	R^2	*Yield* (%)
$Ph(CH_2)_3$	H	88
$PhC(=O)(CH_2)_3$	H	80
$PhCH(OH)(CH_2)_6$	H	86
$Me_2C=CH$	H	67
$CH_3(CH_2)_3$	$(CH_2)_8CH=CH_2$	83

Scheme 57



(30)

Although there are many examples of rhodium-catalyzed isomerization of allylic alcohols, only one example of rhodium-catalyzed isomerization of a propargylic alcohol was reported. The isomerization of a γ-hydroxyalkynecarboxylate proceeded in the presence of 3 mol% $RhCl(PPh_3)_3$ and 5 mol% $Bu^n{}_3P$ in toluene at 110 °C to give the corresponding γ-ketoalkenoate (Equation (31)).[98]



(31)

10.02.7 Concluding Remarks

Metal-catalyzed C–H bond formation through isomerization, especially asymmetric variant of that, is highly useful in organic synthesis. The most successful example is no doubt the enantioselective isomerization of allylamines catalyzed by Rh(I)/TolBINAP complex, which was applied to the industrial synthesis of (−)-menthol. A highly enantioselective isomerization of allylic alcohols was also developed using Rh(I)/phosphaferrocene complex. Despite these successful examples, an enantioselective isomerization of unfunctionalized alkenes and metal-catalyzed isomerization of acetylenic triple bonds has not been extensively studied. Future developments of new catalysts and ligands for these reactions will enhance the synthetic utility of the metal-catalyzed isomerization reaction.

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10.03
Synthetic Reactions via C–H Bond Activation: C–C and C–E Bond Formation

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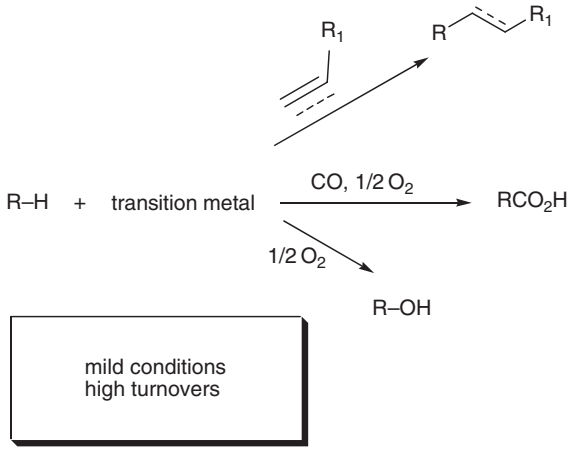
10.03.1 Introduction

One of the main goals in today's catalysis is to functionalize relatively cheap, plentiful feedstocks, such as alkanes in a selective and efficient manner. The importance of homogeneous catalysis in terms of carbon management, is highlighted in Refs: 1 and 1a. For example, methane is an abundant hydrocarbon, whose exploitation is hampered due to its low chemical reactivity (strength of the C–H bond $\sim 105\,\text{kcal mol}^{-1}$). Consequently, chemists are attempting to develop efficient, high turnover, catalytic processes to convert the former into useful synthetic intermediates, including methanol or acetic acid, employing mild conditions. The direct C–H activation of methane and other alkanes represents an atom-economical solution[2] and is an area of intense current scientific activity.[3] Moreover, in the case of higher alkanes, regio- and chemoselectivity issues become an important factor and the catalysts must be tolerant to the reaction conditions employed, which at times can be quite severe (strong acid, air, water, etc.) (Scheme 1).

The aim of this review is to present a selection of the more recent advances in C–H activation chemistry along with comparisons of earlier examples in order to track progress in a particular area. Wherever possible, the role, or perceived role, of the metal is presented. We will often adopt the term "C–H functionalization" according to the concept presented by Sames and co-workers, to describe a formal process, when there is an absence of conclusive mechanistic evidence since "the term "C–H activation" carries considerable mechanistic claim," see Ref: 83 here. The following areas will be covered, whenever a particular distinction is possible; both inter- and intramolecular functionalizations of the C–H bond of: (i) sp^3-hybridized carbon atoms, (ii) sp^2- and *sp*-hybridized carbon atoms. Emphasis will be on synthetic applications, which, as this section unfolds, have been particularly remarkable, as C–H functionalizations are now employed as key steps in the synthesis of bioactive molecules. References have been selected in terms of their relevance to the area of C–H functionalization, as well as their accessibility; consequently, patent literature or proceedings of meetings have not usually been included. We have not highlighted the important area of biomimetic catalysis and related porphyrin chemistry although this is discussed elsewhere. [4,5,5a] Selected areas



Scheme 1

of the literature from 1992 until early 2005 have been covered. For each chapter a list of reviews and a brief survey of some important findings in fundamental organometallic chemistry, which underpins the field of C–H activation chemistry, will precede some of the most significant synthetic developments in the field.

An important section of the C–H activation chemical literature, up until the early 2000s, has already been reviewed and excellent reviews are appearing at an exponential rate (*vide infra*).[6,6a–6g] This review will effectively serve as an update to our earlier work as well as cover a wider scope of metals and processes. An attempt, wherever possible, is made to avoid repetition. Undoubtedly, many important contributions are omitted in the area of C–H activation chemistry, for which the authors apologize, although this is inevitable in a review of this size due to space considerations. However, the reader is invited to consult the reviews and references cited hereafter, which should provide ample exposure to the area of C–H activation processes.

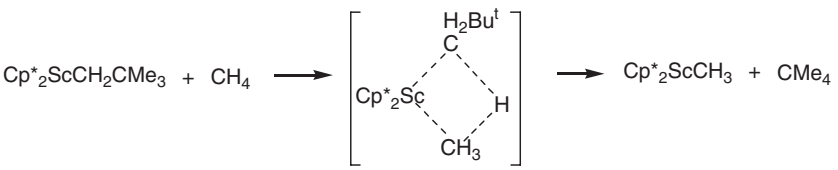
10.03.2 Functionalization of the C–H Bond of sp^3-Hybridized Carbon Atoms

10.03.2.1 Functionalization of Alkanes and Unactivated Alkyl Units

10.03.2.1.1 Organometallic aspects

The activation of alkanes represents a very important field, and a host of reviews and important publications have recently appeared.[7,7a–7t]

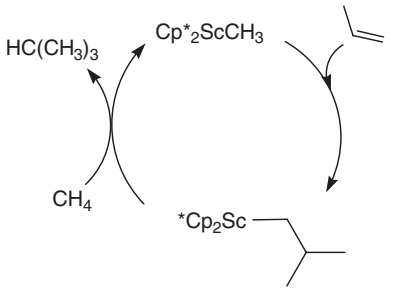
As stated in the introduction, outstanding advances in theoretical and fundamental organometallic chemistry have led to the design of complexes capable of activating C–H bonds, a few examples of which will follow. Supported by theoretical calculations, many groups have designed organometallic complexes capable of activating methane, the least reactive alkane. A recent example is the intermolecular C–H activation of methane mediated by scandium complexes via a σ-bond metathesis process (Equation (1)).[8]



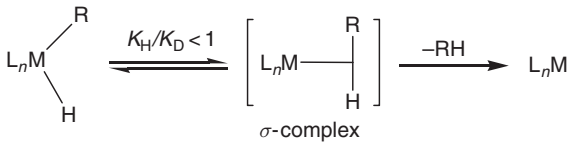
(1)

The organometallic product of the reaction (1) catalyzes the hydromethylation of propene, although insertion of the olefin into the Sc–CH_3 bond is slow and turnover numbers/turnover frequencies (TON and TOF) are low (Scheme 2).

The existence of σ-complex intermediates in C–H activation chemistry has been suggested to explain inverse kinetic isotope effects in reductive elimination processes whereby alkanes are formed from alkyl metal hydrides (Scheme 3).[9]

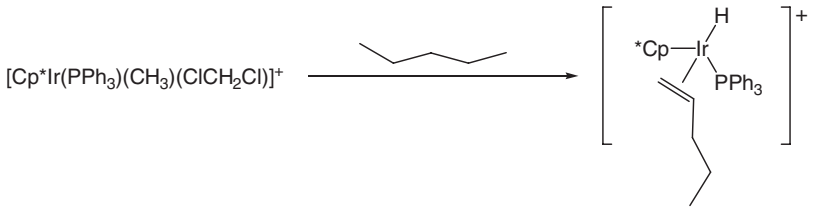


Scheme 2



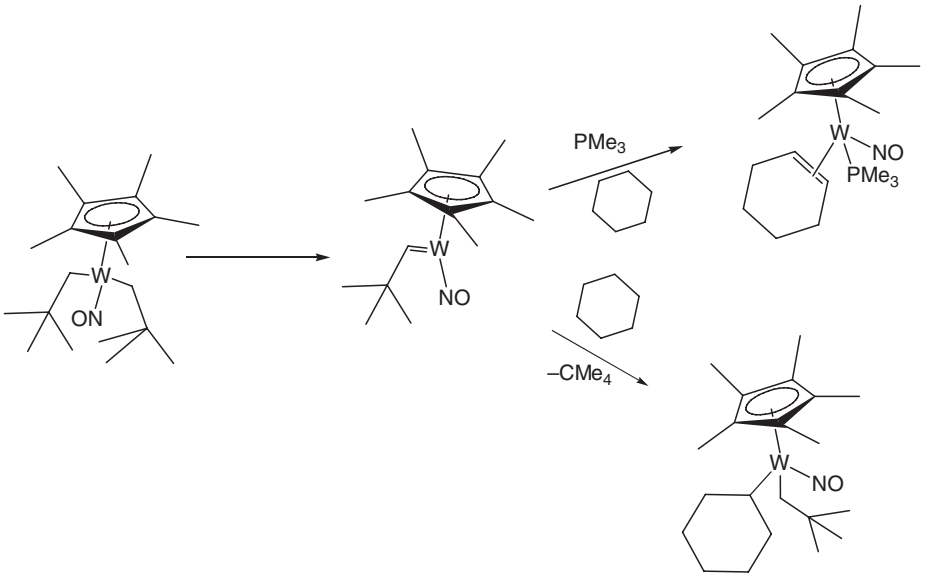
Scheme 3

Bergman's group showed that low-temperature selective C–H activations of *n*-alkanes could be achieved using cationic-solvated iridium complexes (Equation (2)).[10,10a]



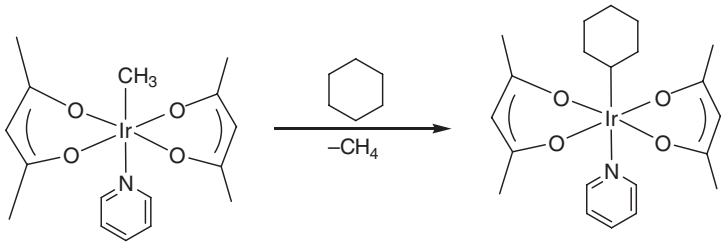
(2)

Other complexes have been reported to activate alkanes, including thermally generated tungsten neopentylidene analogs (Equation (3)).[11]



(3)

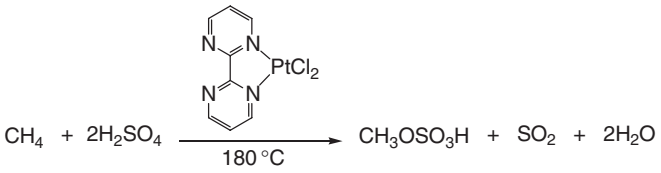
The activation of cyclohexane can also be achieved using an Ir(III) complex. The reactions with *n*-alkanes are unselective and a mixture of products, probably resulting from the activation of primary and secondary C–H bonds, is obtained (Equation (4)).[12]



(4)

10.03.2.1.2 Synthetic aspects

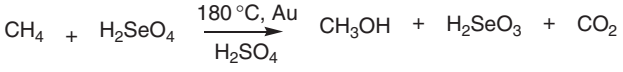
Homogeneous catalysts have been reported, which can oxidize methane to other functionalized products via C–H activation, involving an electrophilic substitution process. The conversion of methane into methyl bisulfate, using a platinum catalyst, in sulfuric acid, has been described. The researchers found that a bipyrimidine-based ligand could both stabilize and solubilize the cationic platinum species under the strong acidic conditions and TONs of >500 were observed (Equation (5)).[13]



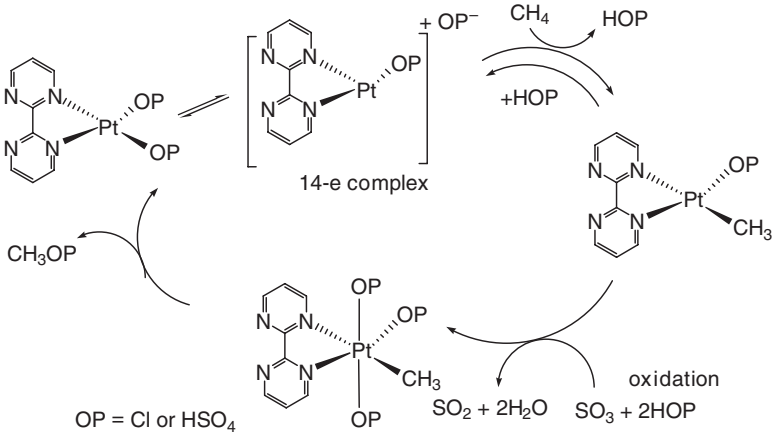
(5)

The process is thought to be electrophilic in nature via a coordinatively unsaturated, 14-electron intermediate (Scheme 4).

More recently, the direct synthesis of methanol from methane, using metallic gold as catalyst, was reported, involving a purported CH_3–Au intermediate. Selenic acid was used as a stoichiometric oxidant as it is known to oxidize gold metal. Moderate turnovers (30) were achieved (Equation (6)).[14]



(6)



Scheme 4

Acetic acid analogs can also be formed from a one-step C–H activation process using a palladium sulfate catalyst.[15] A free radical process was ruled out for this formal eight-electron oxidation due to the high selectivities observed (90% based on methane converted) (Equation (7)).

$$2CH_4 + 4[H_2SO_4\text{–}Pd(II)] \longrightarrow CH_3CO_2H + 4SO_2 + 6H_2O \quad (7)$$

A mechanism was proposed, which involved carbonylation (CO may be generated from methanol) of a Pd–CH_3 intermediate under the strongly acidic conditions (Equation (8)).

$$\left[Pd(II)(OSO_3H)_2\right] \xrightarrow{CH_4} \left[H_3C\text{—}Pd\text{—}OSO_3H\right] \xrightarrow{CO} \left[H_3C(OC)\text{—}Pd\text{—}OSO_3H\right] \xrightarrow{-Pd(0)} CH_3CO_2SO_3H \quad (8)$$

Other soft, electrophilic metals, including mercury(II) analogs, are also known to activate methane.[16]

Acetic acid can be synthesized from methane using an aqueous-phase homogeneous system comprising $RhCl_3$ as catalyst, CO and O_2.[17] Side-products included methanol and formic acid, although yields of acetic acid increased upon addition of either Pd/C or iodide ions. The active species is thought to be a CH_3–Rh(I) derivative, formed from the C–H activation of methane. The activation of ethane was also achieved, although selectivities were lower, with products including acetic and propionic acids and ethanol (Equation (9)).

$$CH_4 + CO \xrightarrow[H_2O,\ 1/2O_2]{100\,^\circ C,\ RhCl_3} CH_3CO_2H \quad (9)$$

The same group reported a palladium-mediated oxidation of methane to a methanol derivative employing a $CuCl_2$ and Pd/C-based catalyst system and dioxygen in a trifluoroacetic acid/water mixture.[18] A system was also described, which mediated the oxidation of ethane (Equation (10)).

$$\underset{550\ psi}{C_2H_6} \xrightarrow[\underset{150\,^\circ C}{H_2SO_4\ (98\%)}]{oxidant} CH_3OSO_3H + HO_3SCH_2CH_2OSO_3H \quad (10)$$

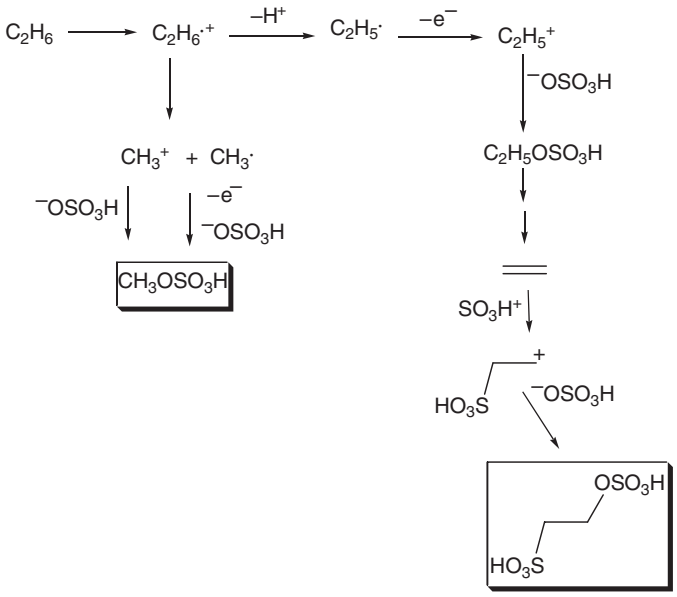
Oxidant = $HgSO_4$, $K_2S_2O_8$, $Ce(SO_4)_2$ (0.1 M solution)

The latter process proceeds via radicals and carbocation intermediates and methane bisulfate is the result of C–C bond cleavage (Scheme 5).[19]

Not all C–H activation chemistry is mediated by transition metal catalysts. Many of the research groups involved in transition metal catalysis for C–H activation have opted for alternative means of catalysis. The activation of methane and ethane in water by the hexaoxo-μ-peroxodisulfate(2−) ion ($S_2O_8^{2-}$) was studied and proceeds by hydrogen abstraction via an oxo radical. Methane gave rise to acetic acid in the absence of external carbon monoxide, suggesting a reaction of a methyl radical with CO formed *in situ*. Moreover, the addition of (external) CO to the reaction mixture led to an increase in yield of the acid product (Equation (11)).[20]

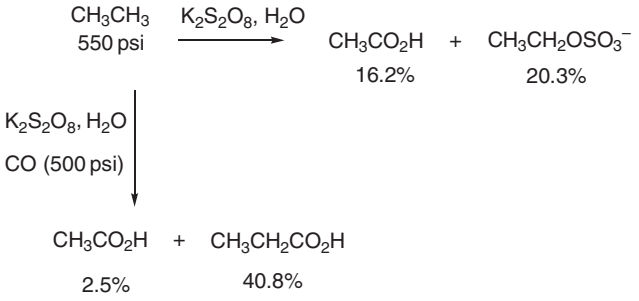
$$\underset{1000\ psi}{CH_4} \xrightarrow[5.5\%]{K_2S_2O_8,\ H_2O} CH_3CO_2H$$

$$\underset{700\ psi}{CH_4} + \underset{300\ psi}{CO} \xrightarrow[48.6\%]{K_2S_2O_8,\ H_2O} CH_3CO_2H \quad (11)$$



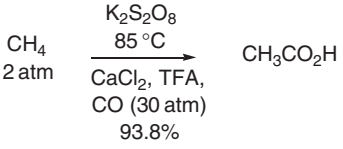
Scheme 5

With ethane, acetic or propionic acids could be formed (Equation (12)).



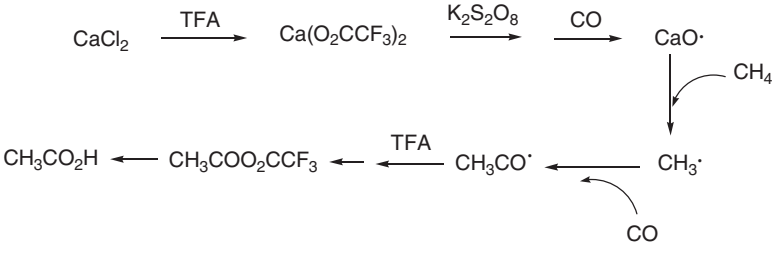
(12)

The Fujiwara group reported a transition metal free calcium-mediated transformation of methane into acetic acid, in the presence of $S_2O_8^{2-}$ (Equation (13)).



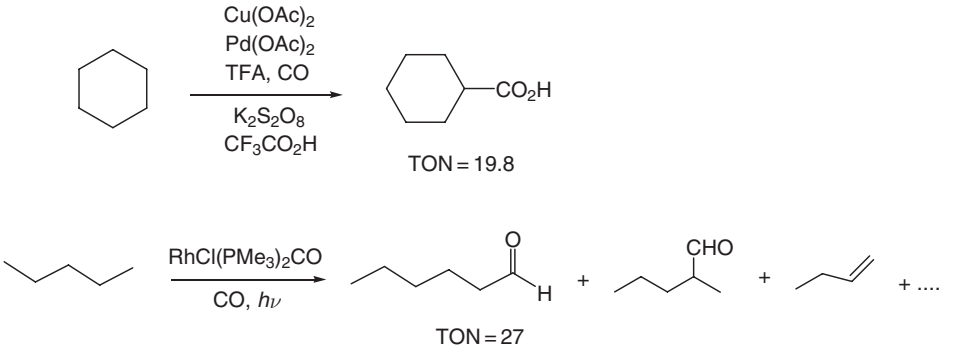
(13)

This reaction involves radicals, notably CaO˙, evidenced by the fact that when radical scavengers are added, little or no product is formed (Equation (14)).[21]



(14)

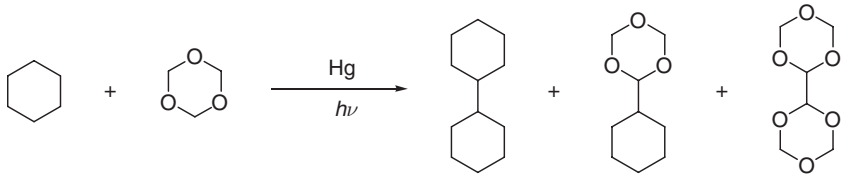
The thermally induced carboxylation of alkanes has been thoroughly investigated by the same group, who have developed a range catalysts, based on vanadium ($VO(acac)_2$) or palladium analogs.[22,22a,22b] Photochemically induced carbonylation of linear alkanes, to afford aldehydes, is also known (Equation (15)).[23,23a]



(15)

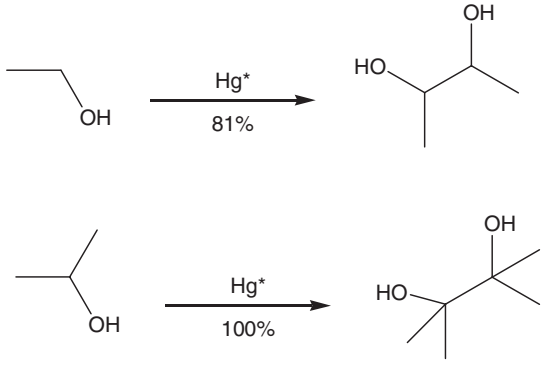
The primary C–H bond is often activated in these and related systems, whereas secondary C–H bonds are often intact, although in general chemistry the reactivity of a C–H bond is often in the order tertiary > secondary > primary.[24]

Other photochemical reactions have been reported as in the Mercat process involving gas-phase mercury-catalyzed oxidative homo- and cross-couplings (Equation (16)).[25,25a,25b]



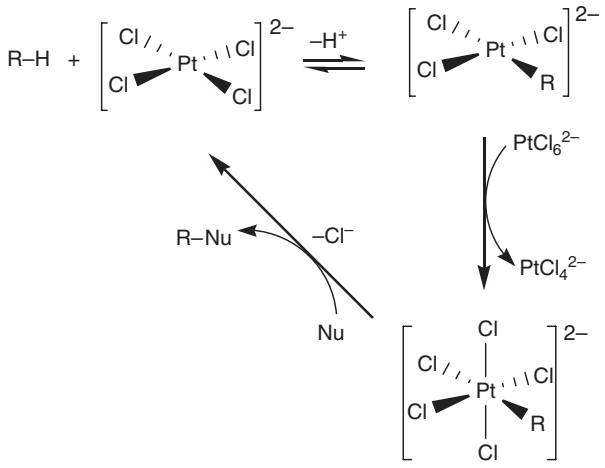
(16)

Similar mercury-photosensitized alcohol dehydrodimerizations leading to glycols have been documented (Equation (17)).[26]



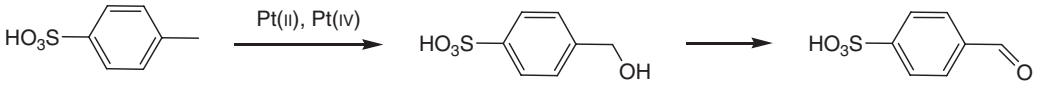
(17)

Synthetic organic chemistry applications employing alkane C–H functionalizations are now well established. For example, alkanes can be oxidized to alkyl halides and alcohols by the Shilov system employing electrophilic platinum salts. Much of the Pt(II)/Pt(IV) alkane activation chemistry discussed earlier has been based on Shilov chemistry. The mechanism has been investigated and is thought to involve the formation of a platinum(II) alkyl complex, possibly via a σ-complex. The Pt(II) complex is oxidized to Pt(IV) by electron transfer, and nucleophilic attack on the Pt(IV) intermediate yields the alkyl chloride or alcohol as well as regenerates the Pt(II) catalyst. This process is catalytic in Pt(II), although a stoichiometric Pt(IV) oxidant is often required (Scheme 6).[27,27a–27d]



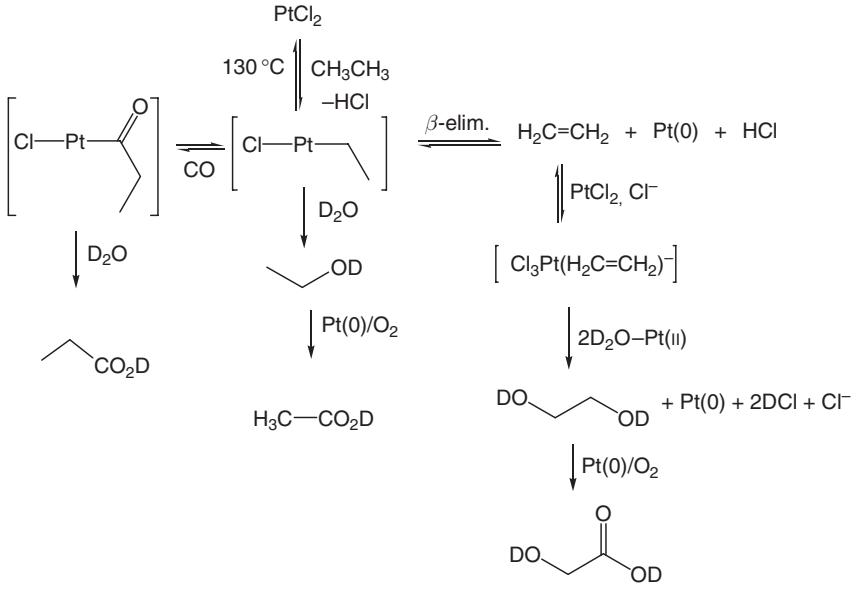
Scheme 6

The oxidation of *p*-toluenesulfonic acid to the corresponding alcohol and aldehyde was achieved using the Shilov system and when employing oxidants other than Pt(IV), including peroxydisulfate or phosphomolybdic acid, only moderate turnovers were observed (Equation (18)).[28]



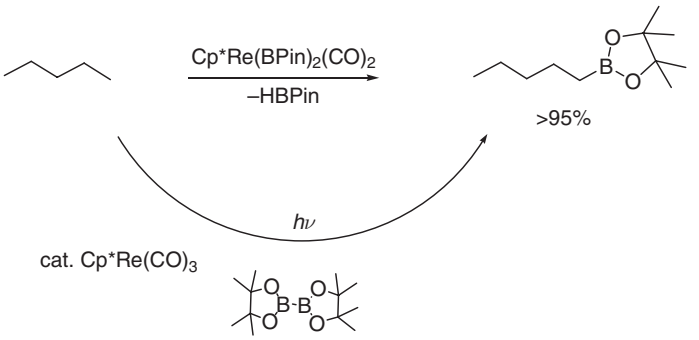
(18)

A mixture of Pt(II) and metallic Pt in an aqueous medium was shown to oxidize ethane to yield acetic and glycolic acids. A series of deuterium-exchange processes enabled a complex mechanism to be elucidated; metallic platinum catalyzes the oxidation of intermediate alcohols to acid products, whereas the Pt(II) salt activates the initial alkene (Scheme 7).[29]



Scheme 7

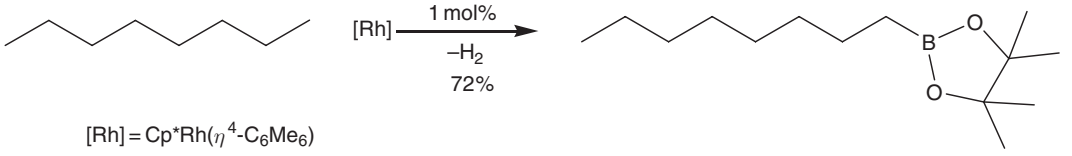
The regioselective borylation of alkanes can be achieved either catalytically or stoichiometrically using a host of metal complexes such as rhenium analogs. Such processes can be photochemically or thermally induced (Equation (19)).[30,30a–30c]



(19)

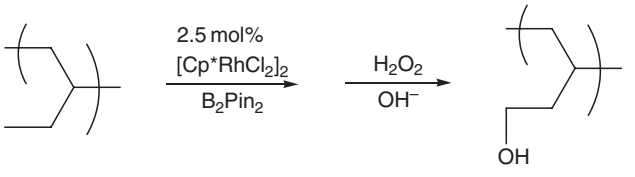
A mechanism has been proposed involving CO dissociation from the metal complex followed by oxidative addition of the diboron analog. This precedes the alkane functionalization process (Scheme 8).

Other derivatives can effect such functionalizations, including iron, ruthenium, rhodium, and tungsten complexes. Excellent regioselectivities were observed in catalytic thermal processes involving unfunctionalized alkanes and primary alkyl C–H bonds were functionalized (Equation (20)).[31]

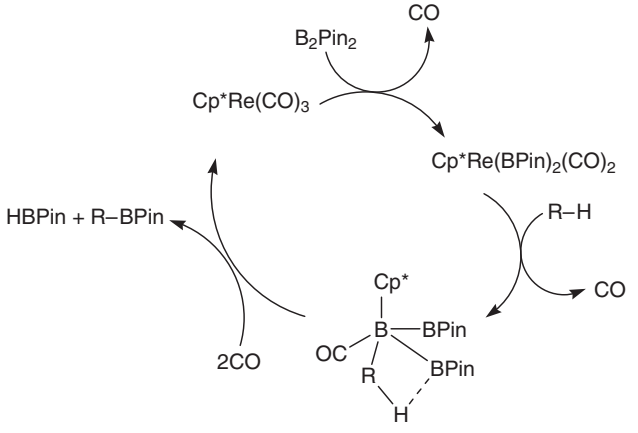


(20)

The regiospecific functionalization of polyolefins can be achieved in a similar fashion to yield organoboranes, which are then converted into alcohols (Equation (21)).[32]

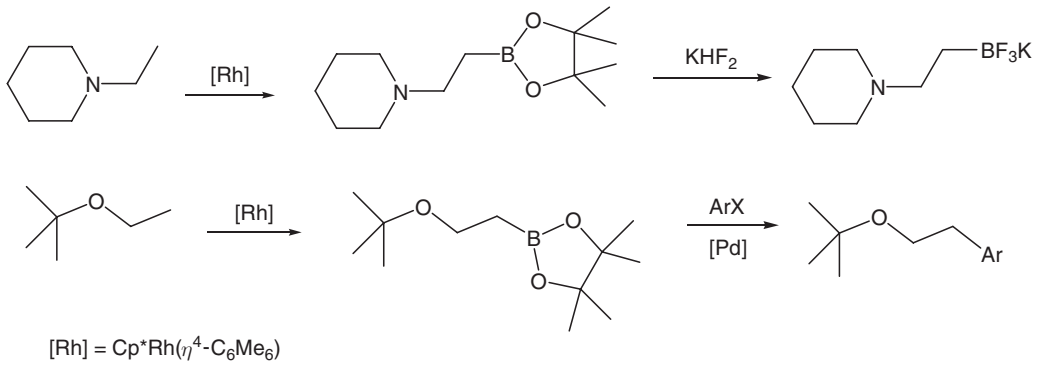


(21)



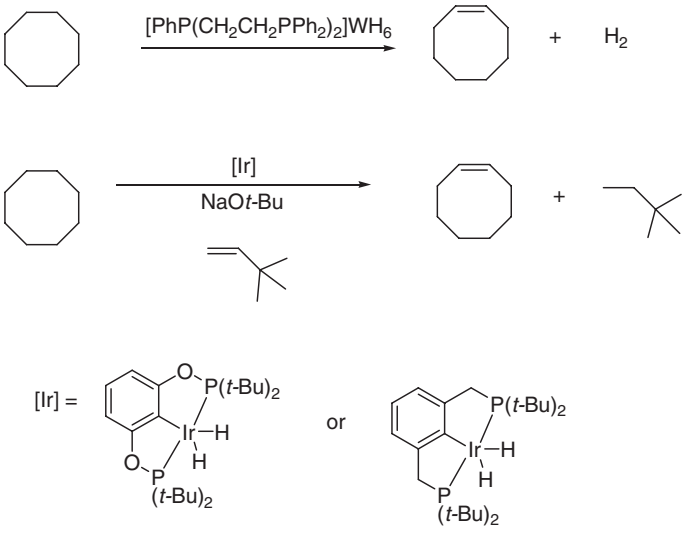
Scheme 8

The regiospecific functionalization of the terminal alkyl group of simple amines or ethers with bis(pinacolato)-diborane leads to organoboranes. The latter have manifold applications in organic synthesis since the catalytic borylation process can be combined with a functional group transformation step, including Suzuki–Miyaura couplings, for the synthesis of elaborated molecules. Curiously, functionalization of the C–H atoms α to the heteroatom was not observed (Equation (22)).[32a]



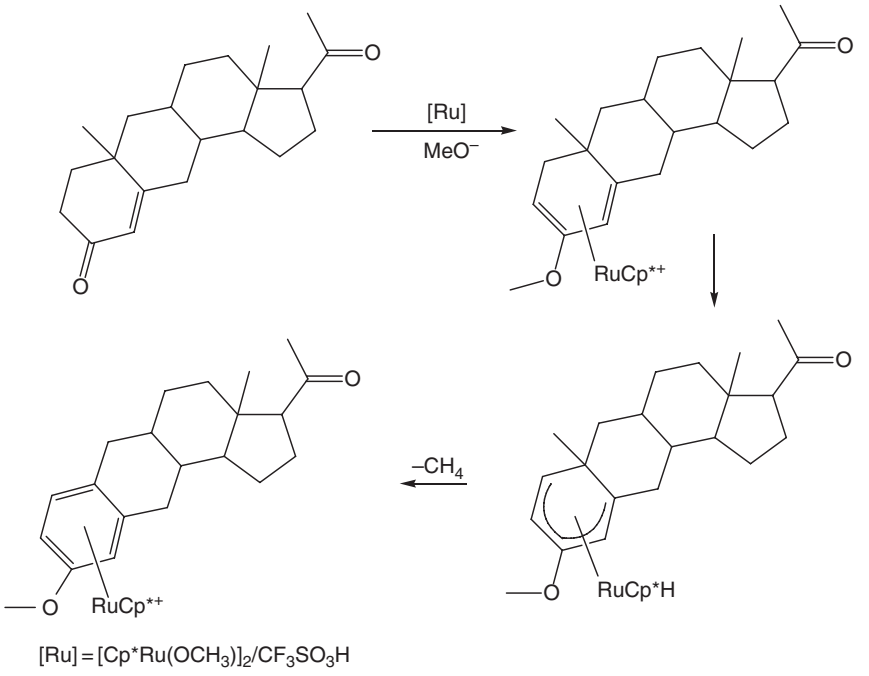
(22)

Another area of high research intensity is the catalytic dehydrogenation of alkanes to yield industrially important olefin derivatives by a formally endothermic (ca. 35 kcal mol^{-1}) loss of H_2. Recent results have concentrated on pincer iridium complexes, which catalytically dehydrogenate cycloalkanes, in the presence of a hydrogen accepting (sacrificial) olefin, with turnover numbers (TONs) of >1000 (Equation (23)) (see, e.g., Ref: 33, 33a–33e).



(23)

Related dehydrogenation processes are known as in the aromatization of the A ring of steroids, which was achieved by using the Cp^*Ru^+ fragment. Such a process occurs via a series of C–O, C–H and C–C bond activations (Equation (24)).[34]

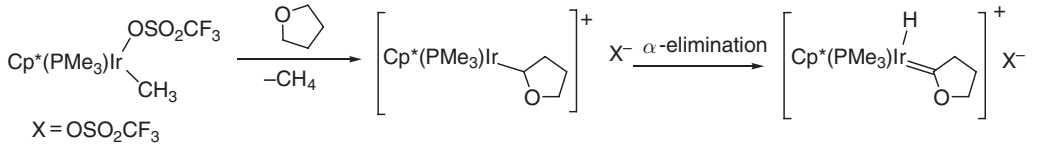


(24)

10.03.2.2 Functionalization of Activated Alkyl Groups

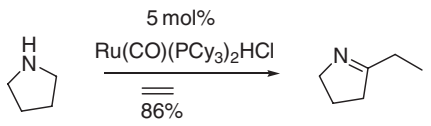
10.03.2.2.1 Intermolecular processes

Alkyl groups of compounds other than alkanes can be regioselectively functionalized using C–H activation chemistry. For example, acyclic and cyclic ethers can be activated by Ir(III) complexes to yield carbene complexes (Equation (25)).[35]



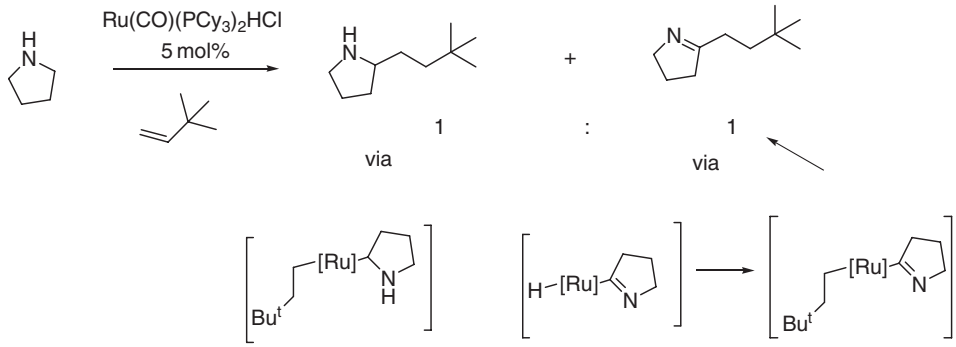
(25)

Ruthenium-catalyzed α-alkylations of amines have been reported (Equation (26)).



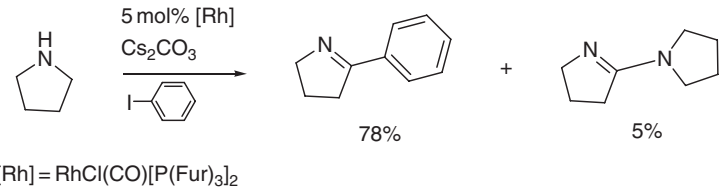
(26)

Both CH and N–H bond activations were mediated by the catalytically generated unsaturated ruthenium species (Equation (27)).[36]



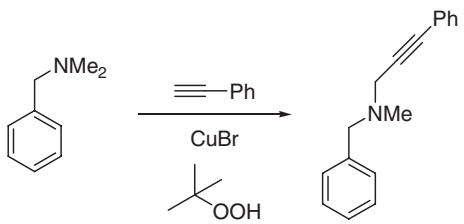
(27)

Rhodium-catalyzed oxidative C arylations of unprotected pyrroles have been reported, and the products were the result of both arylation and amination processes (Equation (28)).[37]



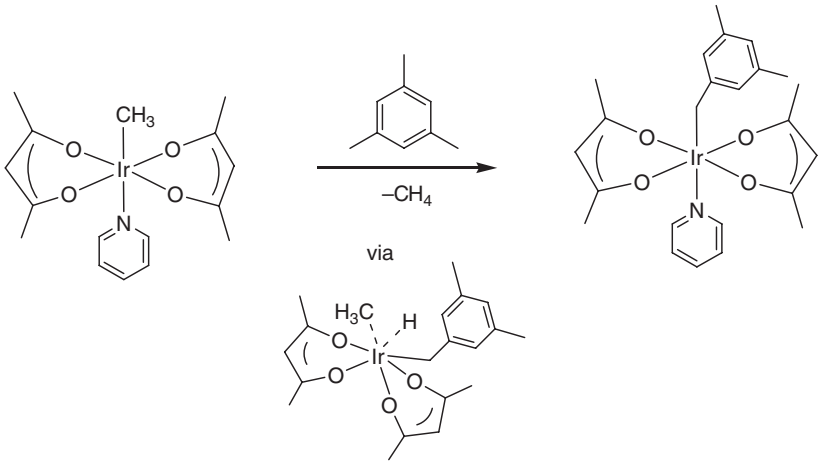
(28)

The selective functionalization of methylamines can be effected with catalytic amounts of copper bromide in the presence of peroxides. Both sp^3- and sp-bonds are functionalized in this reaction (Equation (29)).[38]



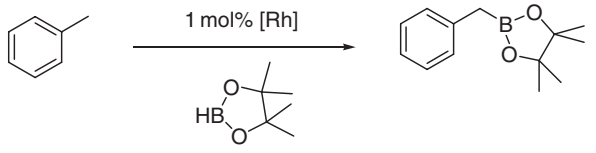
(29)

The intermolecular functionalization of benzylic and activated methylene sp^3-C–H bonds represents another burgeoning field in C–H activation chemistry. A recent sp^3-benzylic C–H functionalization was disclosed involving an Ir(III)acac analog. Such a reaction is retarded by pyridine addition, indicating that pyridine loss may initiate the C–H functionalization step. An Ir(V) intermediate has been postulated (Equation (30)).[12]



(30)

The functionalization of benzylic bonds, leading to synthetically important boronates, has been described (Equation (31)).

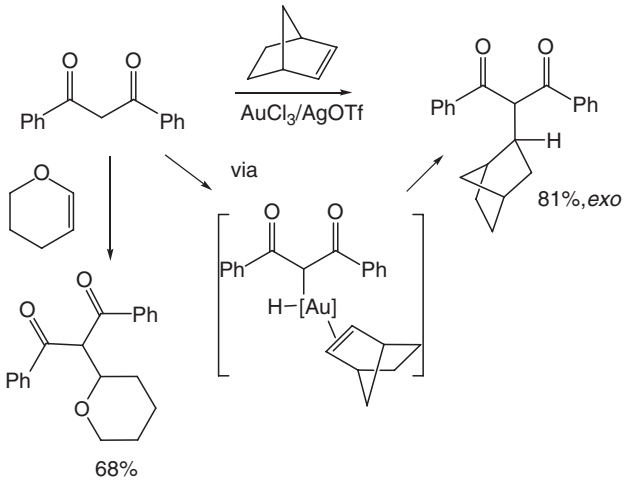


(31)

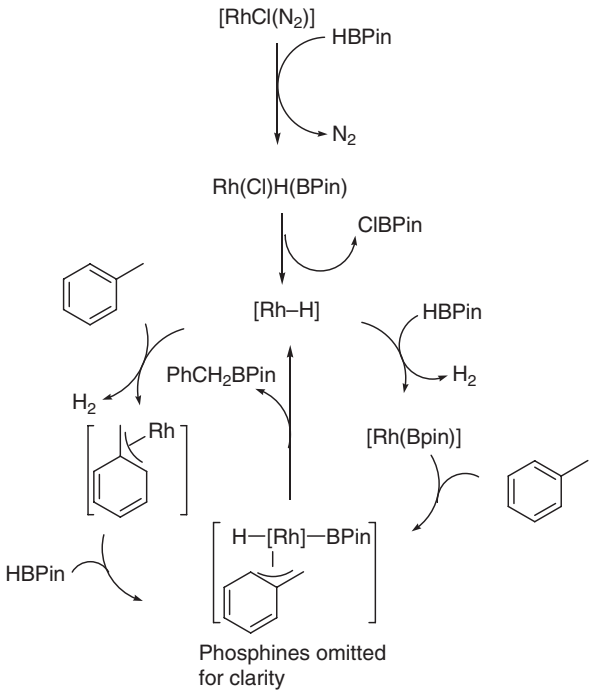
[Rh] = [RhCl(Pi-Pr$_3$)$_2$N$_2$]

A mechanism for this process has been postulated involving η^3-benzylrhodium intermediates (Scheme 9).[39]

Gold-catalyzed couplings of activated methylene derivatives with olefins have been postulated to proceed via an *in situ* formed Au(I) intermediate.[40,40a] Indeed, gold-mediated C–H functionalization processes are becoming very popular (Equation (32)). For other relevant papers on gold chemistry, see Refs: 41 and 41a.

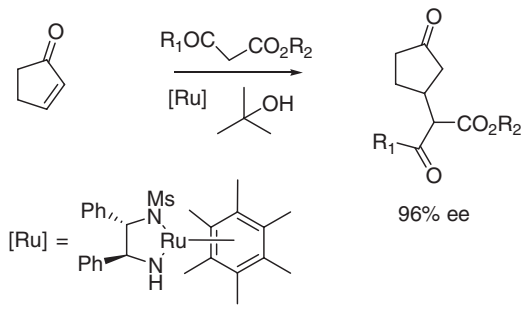


(32)



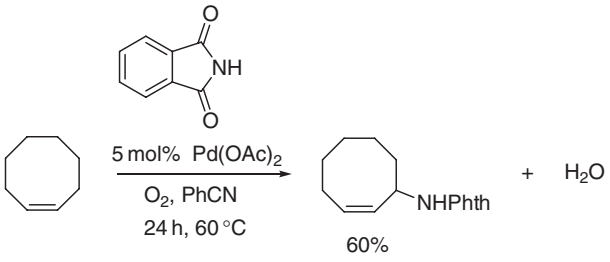
Scheme 9

Similar additions of β-keto esters to enones are catalyzed by ruthenium amides. With a chiral ligand, high levels of asymmetric induction are possible (Equation (33)).[42]



(33)

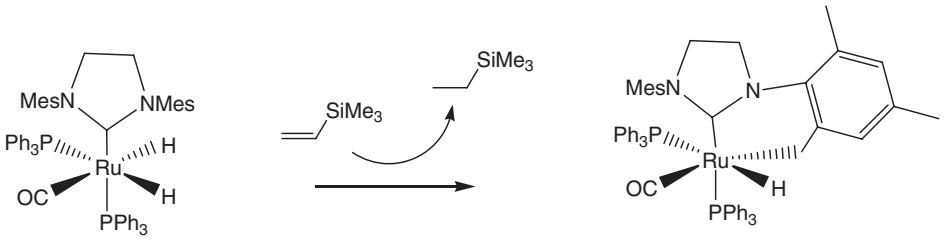
An alternative means of activating an activated sp^3-C–H bond is by the addition of a nucleophile to an allylic species as in aminations using catalytic amounts of Pd(II) (Equation (34)).[43]



(34)

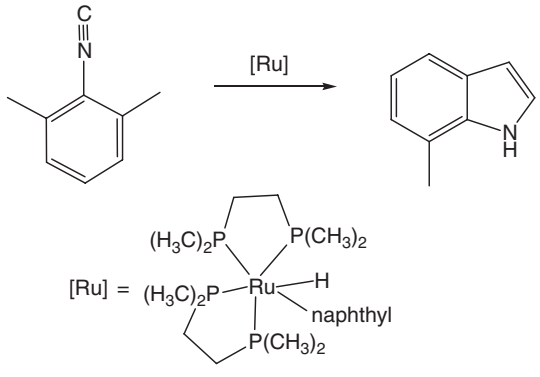
10.03.2.2.2 Intramolecular processes

Thermolysis of ruthenium carbene complexes leads to intramolecular sp^3-benzylic C–H functionalization in the presence of a hydrogen-accepting olefin (Equation (35)).[44,44a]



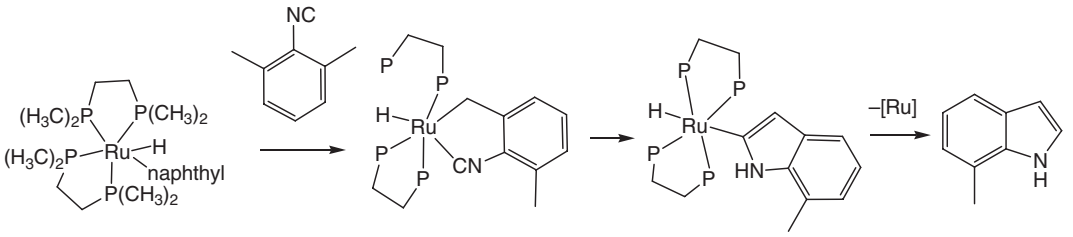
(35)

Indoles were synthesized by the intramolecular functionalization of a benzylic C–H bond. Hence, the reaction of 2,6-xylyl isocyanide with a ruthenium complex led to 7-methylindole (Equation (36)).[45]



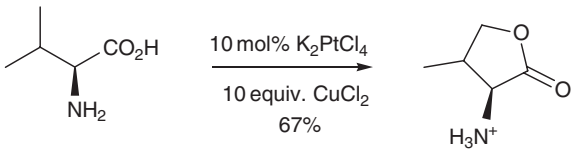
(36)

The bidentate ligand (dmpe) is believed to act in a hemilabile fashion, enabling a crucial intramolecular C–H activation to take place (Equation (37)).



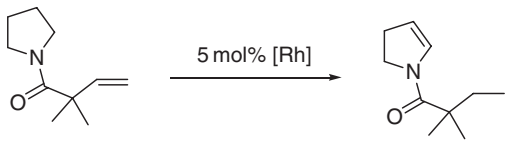
(37)

The directed C–H functionalization of amino acids in water is catalyzed by Pt(II) in the presence of a Cu(II) oxidant and is thought to proceed via a Pt(IV) intermediate (Shilov process). The reaction can be catalytic at 130 °C (Equation (38)).[46]



(38)

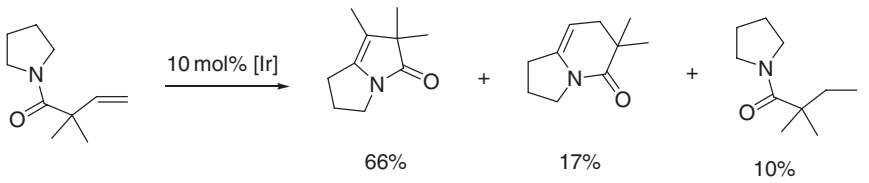
Directed intramolecular transfer hydrogenations are catalyzed by rhodium complexes with the pendant alkene acting as an internal sacrificial olefin (Equation (39)).



(39)

[Rh] = Cp*Rh(CH_2=CH–TMS)$_2$

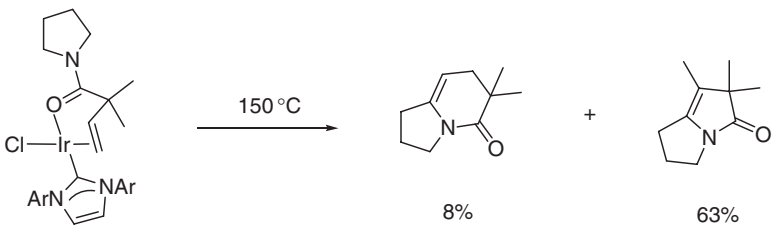
C–C bond formation can be favored over β-hydride elimination by changing the nature of the catalyst. Hence, cyclizations can be mediated by iridium carbene complexes resulting from a formal intramolecular cross-coupling of the alkene with an sp^3-C–H bond (Equation (40)).



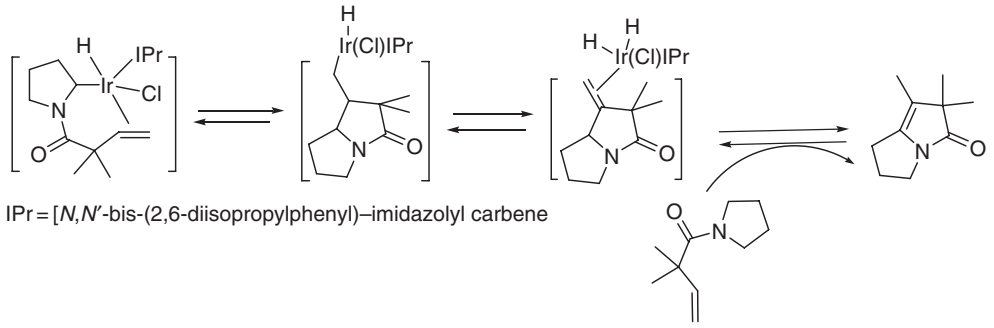
(40)

[Ir] = [Ir(coe)$_2$Cl]$_2$ + IPr carbene ligand + norbornene

A stoichiometric reaction, leading to a similar product distribution, lends support to a C–H activation process, giving rise to an iridium hydride intermediate (Equation (41)).



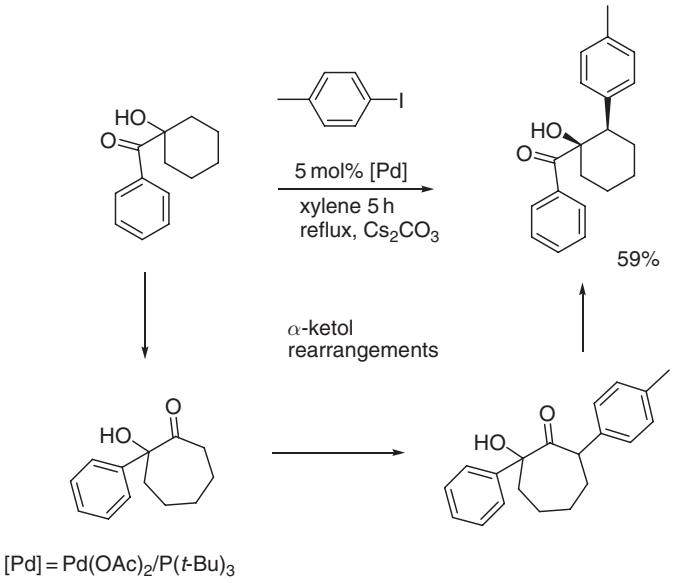
(41)



Scheme 10

The proposed mechanism for this reaction is shown in Scheme 10, and it is assumed that the labile cyclooctene (coe) ligand is displaced from the starting catalyst (Scheme 10).[47,47a]

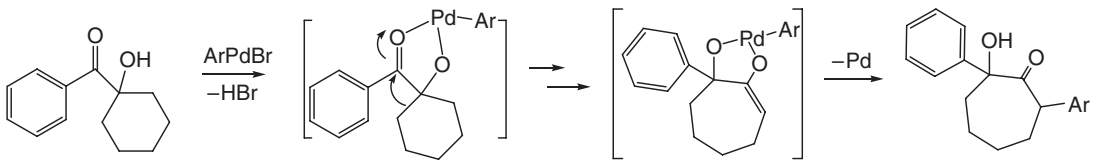
Palladium-catalyzed multiple arylations have been employed for the synthesis of elaborated carbocycles (Equation (42)).



(42)

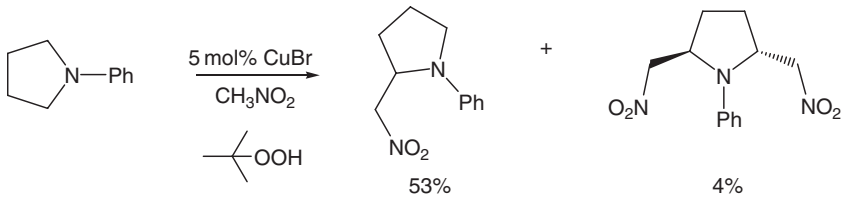
A general mechanism has been proposed (Scheme 11).[48]

Mannich-type chemistry and cross-dehydrogenative couplings between sp^3-C–H and sp-C–H bonds can be mediated by copper catalysis (Equations (43) and (44)).[49,49a] It is to be noted that the nitrogen atom mediates the

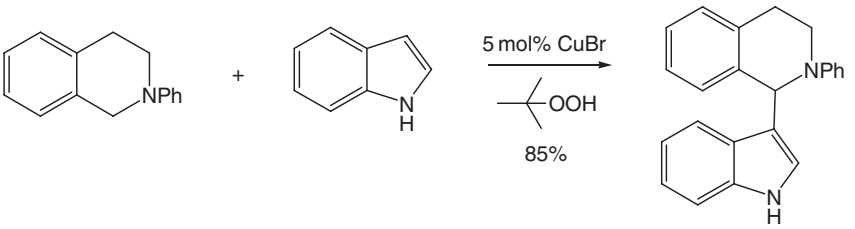


Scheme 11

addition of either the nitromethane or the indole to the α-position with respect to N in opposition to the borylation chemistry highlighted in Equation (22).

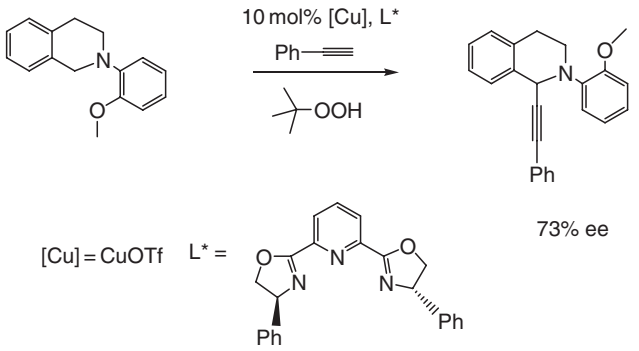


(43)



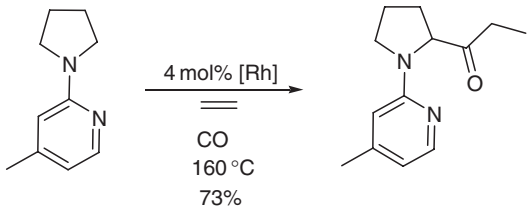
(44)

The copper-mediated stereoselective C–H functionalization of a prochiral benzyl sp^3 as well as an sp-C–H bonds leads to good enantioselectivities (Equation (45)).[50]



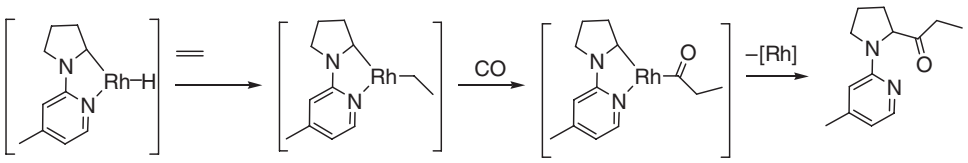
(45)

Carbonylations of sp^3-C–H bonds adjacent to a nitrogen atom have been reported using ethylene (10 atm), CO (15 atm), and a rhodium catalyst (Equation (46)).



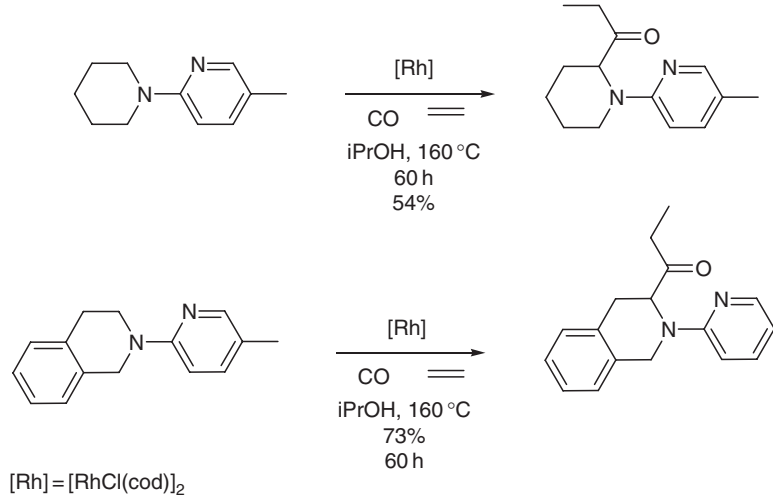
(46)

This proposed mechanism involves a rhodium hydride species (Scheme 12).



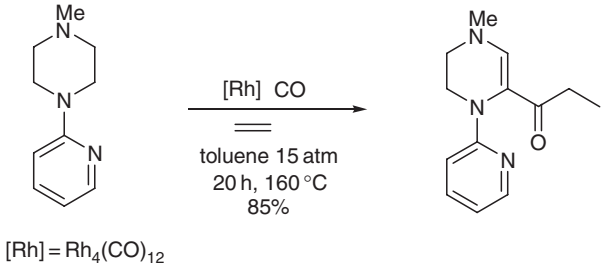
Scheme 12

This synthetically useful process, termed the Murai reaction and treated in detail in the next section for C–H activations of sp^2-hybridized carbon atoms, was extended to other substrates (Equation (47)).[51]



(47)

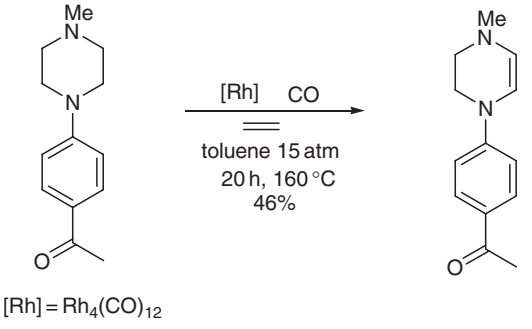
With *N*-(2-pyridinyl)piperazine substrates, both carbonylation and dehydrogenation occur (Equation (48)).



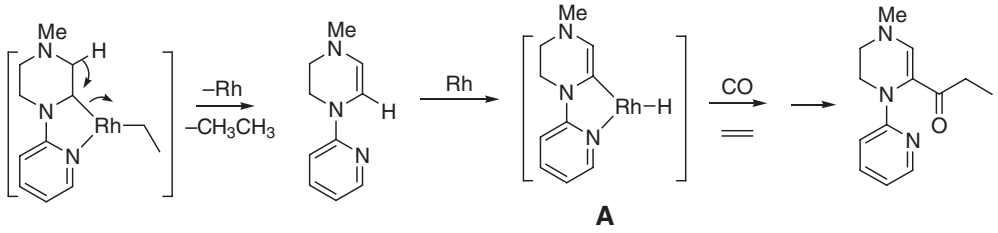
(48)

An explanation for the dehydrogenation process has been offered (Scheme 13). An alkylrhodium intermediate can undergo a β-elimination process to afford the unsaturated analog **A**, which is carbonylated by the usual process.

In the absence of a chelating group in the substrate, no carbonylation product was detected and an acceptable yield of the dehydrogenated product was reported (Equation (49)).[52]

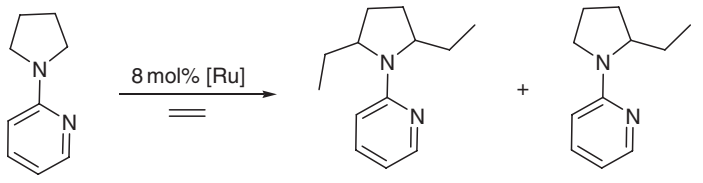


(49)

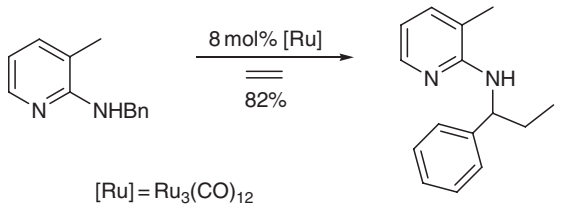


Scheme 13

Similar reactions, performed under low pressures of carbon monoxide, yield alkanes, without any carbonylation products (Equations (50) and (51)). A CO atmosphere prevented catalyst decomposition.[53]

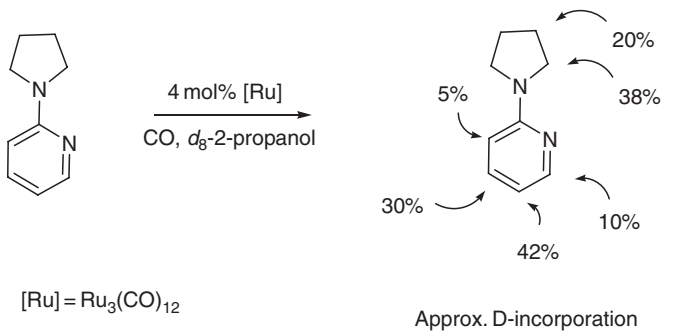


(50)



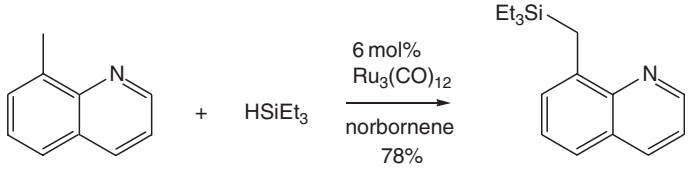
(51)

Exchange experiments (H/D) carried out under the conditions of catalysis but without ethylene showed that the C–H bond cleavage is facile and unselective (Equation (52)). However, such processes must be rapid and reversible.[52,54]

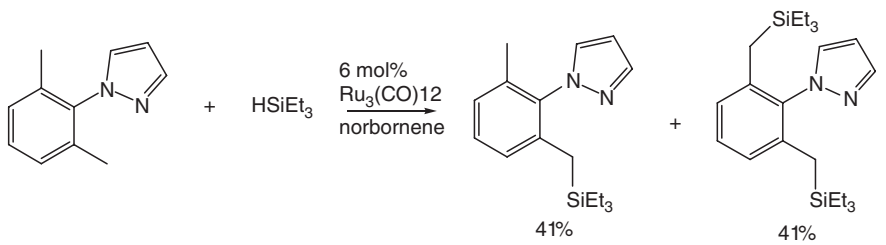


(52)

Directed sp^3-benzylic C–H functionalization can lead to C–Si bond formation with both mono- and bis-silylated compounds obtained (Equations (53) and (54)).



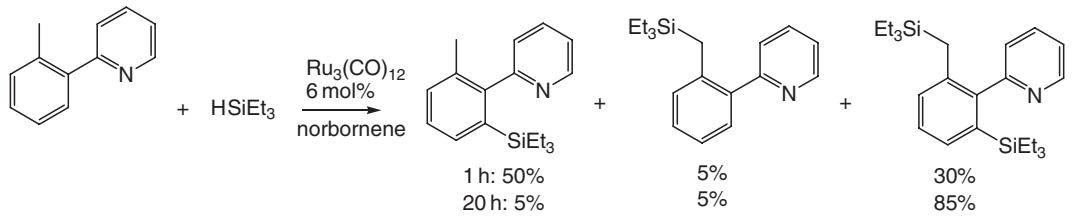
(53)



(54)

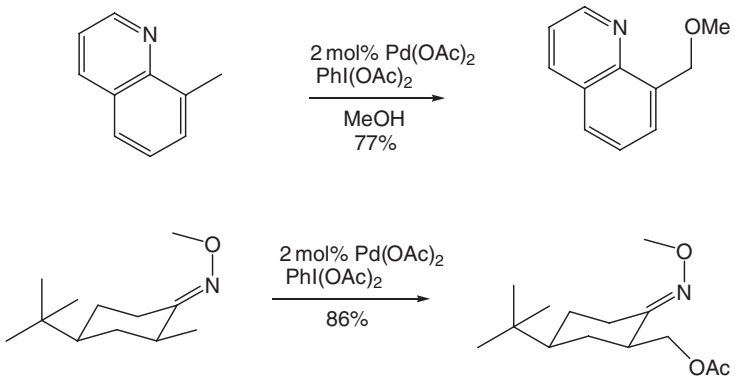
When aryl (sp^2) and benzylic (sp^3) C–H bonds are available, as in 2-(2-tolyl)pyridine, an Si–aryl bond is formed preferentially despite the higher dissociation energy for a C–H aryl bond compared with a benzylic C–H (110 vs. 90 kcal mol^{-1}).

Moreover, in this particular example, the distribution of mono- and bis-silylated products changes over time; improved yields of the mono-silylated (sp^2-functionalized product) are observed after 1 h reaction, whereas overnight reaction leads to a good yield of bis-C–H aryl- and C–H benzyl-activated product (Equation (55)).[55]



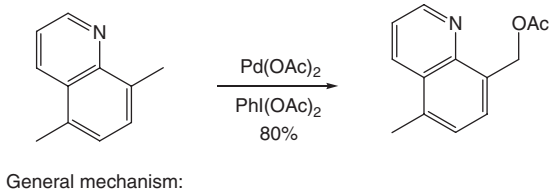
(55)

The chelation-directed oxidation of sp^2- as well as sp^3-C–H bonds using catalytic amounts of palladium has been reported (Equation (56)).[56,56a]

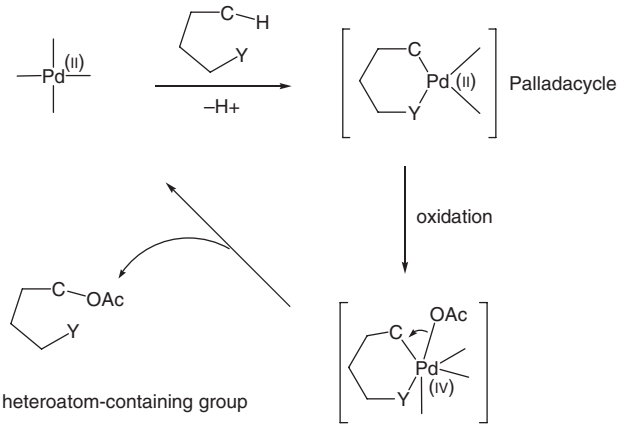


(56)

This process is likely to proceed via a palladacycle intermediate followed by a Pd(II) to Pd(IV) oxidation. Reductive elimination occurs with C–O bond formation and regeneration of the Pd(II) catalyst. Evidence for a palladacycle intermediate is supported by the high regioselectivity (8-Me group oxidized) observed for the oxidative functionalization of 5,8-dimethylquinoline, which, in the absence of a possibility of coordination, would otherwise contain two identical methyl groups (Equation (57)).[57]

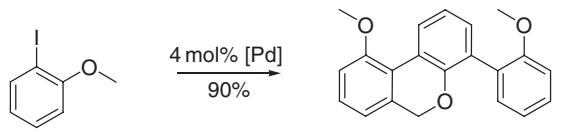


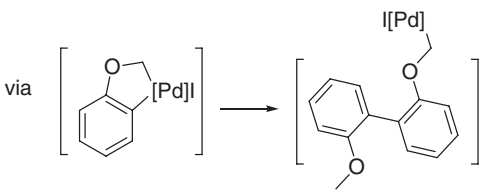
General mechanism:



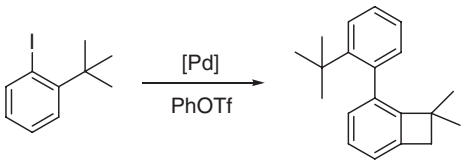
(57)

It is, hence, apparent that much progress has been made over the last decade in terms of sp^3-C–H functionalizations, since an earlier review by Dyker, who described synthetically useful transformations involving simple aromatic derivatives (Equations (58) and (59)).[58,58a,58b]





(58)



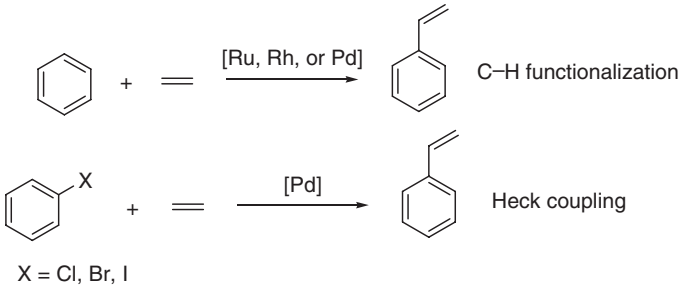
[Pd] = $Pd(OAc)_2$

(59)

10.03.3 Functionalization of the C–H Bond of sp^2- and sp-Hybridized Carbon Atoms

The functionalization of an aromatic sp^2-hybridized C–H bond represents a major challenge in organic synthesis, given the high C–H bond strength in arenes (110 kcal mol^{-1} in benzene). The formation of styrene by the direct addition of benzene to ethylene, through a C–H activation process, is a highly desirable goal, especially in terms of the potential industrial applications of this reaction. A considerable amount of effort has focused on this and similar reactions in order to form elaborated organic products with diverse structures and uses. The ultimate aim of achieving atom economy is achieved by avoiding Heck-type processes. Consequently, a C–C bond can be formed directly from a C–H bond as opposed to from a C–halogen bond (Scheme 14).[59,59a]

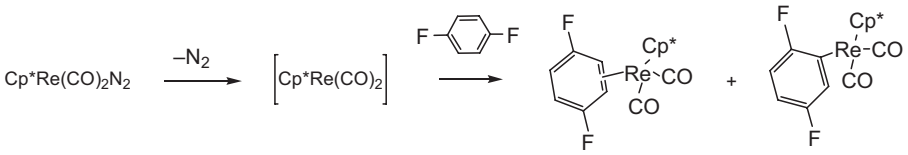
Directed sp^2-C–H functionalizations enable the catalytic transformation to be controlled by a coordinating group, often leading to *ortho*-functionalized products. These are extremely popular processes, and a selection of these reactions have been reviewed in Section 10.03.3.2.[60] In contrast, non-directed sp^2-C–H functionalization processes are invariably less selective but synthetically more desirable since a directing group is not required. Examples of selective non-directed sp^2-C–H functionalizations will be presented, where the regioselective outcome of the reaction is usually more difficult to control.



Scheme 14

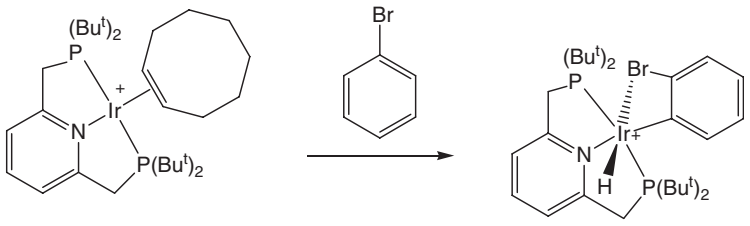
10.03.3.1 Intermolecular Functionalization

More mechanistic insight into the C–H functionalization process of arenes is provided by theoretical and experimental studies. Multifluorinated, electron poor, aromatic substrates readily undergo CH activation with coordinatively unsaturated rhenium complexes, attributed to the stronger C–Re bond in the product, whereas with monofluorinated analogs, the η^2-complex predominates (Equation (60)).[61]



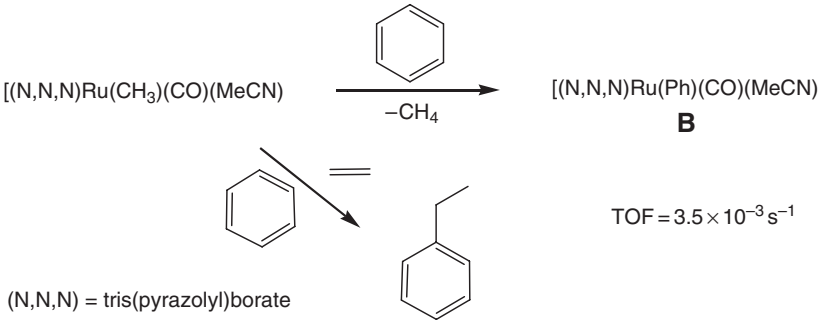
(60)

The *ortho*-C–H activation of haloarenes was achieved using an Ir(I) complex, with the halogen acting as a directing group (Equation (61)).[62]



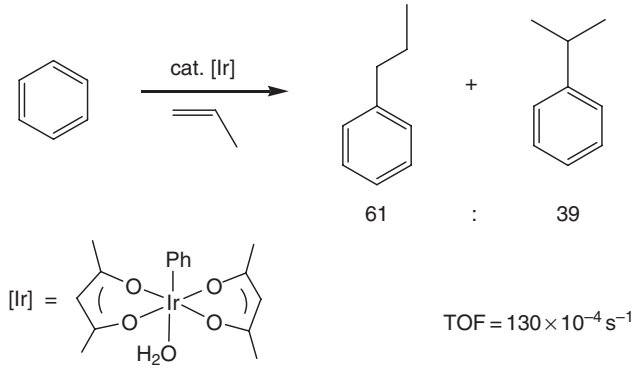
(61)

Hydridotris(pyrazolyl)borate (N,N,N)-containing ruthenium(II) complexes activate benzene in stoichiometric amounts to give the isolable complex **B**. A catalytic hydroarylation of ethylene led to ethylbenzene and a ca. 1 : 1 mixture of branched and linear alkylbenzenes was obtained when employing propylene (Equation (62)).[63,63a]



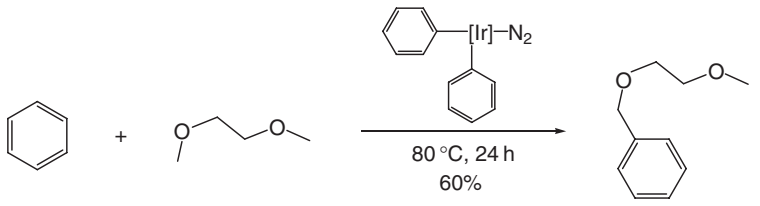
(62)

Homogeneous iridium(III) catalysts mediate arene C–H activations to form anti-Markovnikov products as in the hydroarylation of propene (Equation (63)).[64]



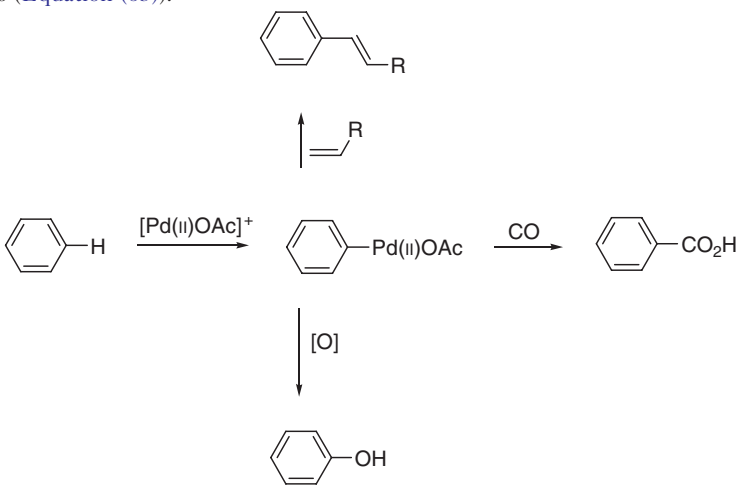
(63)

The C–C bond-forming coupling of solvent molecules via sp^2- and sp^3-C–H bond functionalizations can be achieved using an iridium complex based on the $TpMe_2$ ligand (hydridotris(3,5-dimethylpyrazolyl)borate) (Equation (64)).[65]



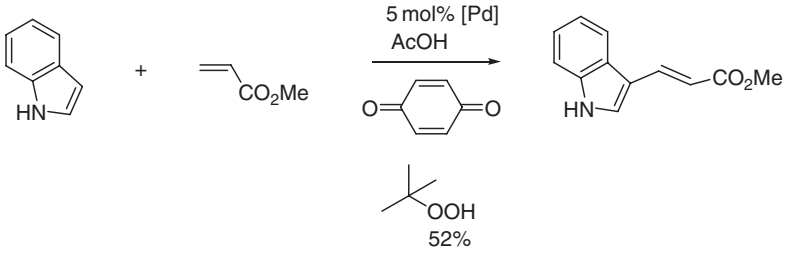
(64)

Fujiwara's research group have developed an array of catalytic arene functionalizations employing electrophilic palladium complexes (Equation (65)).[66]

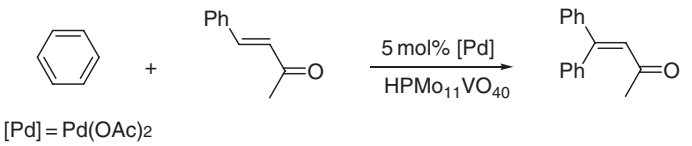


(65)

Palladium-catalyzed oxidative couplings of aromatic compounds with alkenes in air lead to cinnamate products with TONs attaining 280 (Equations (66) and (67)).[67,67a,67b]

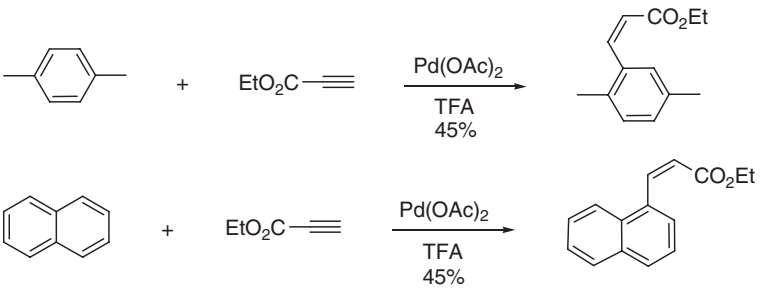


(66)

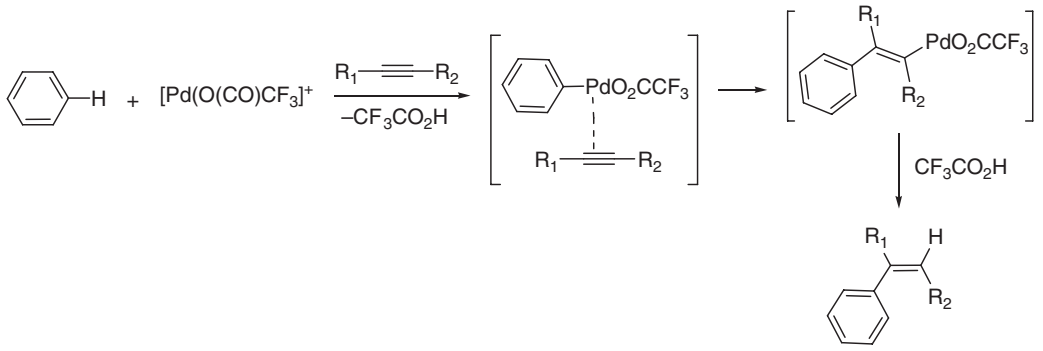


(67)

Stereo- and regioselective hydroarylations of alkynes are catalyzed by Pd(II) (or Pt(II)) agents (Equation (68)).



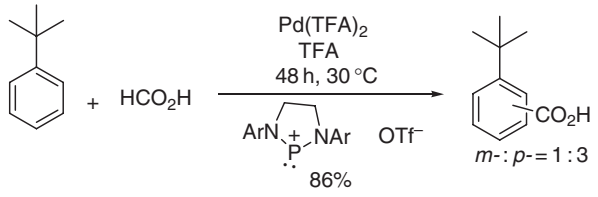
(68)



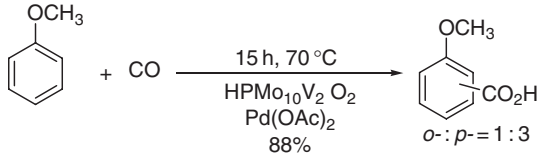
Scheme 15

An original mechanism involving the formation of an electrophilic Pd(II) species was proposed to explain the intermolecular *trans*-arylpalladation process (Scheme 15), although more recent work has suggested a Pd(0) pathway. [68,68a]

The non-directed carboxylation of arenes is mediated by Pd(II), although regioselectivities would appear to be poor (Equations (69) and (70)). Very recent examples include Refs: 69 and 69a.

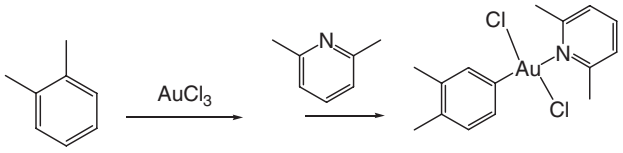


(69)



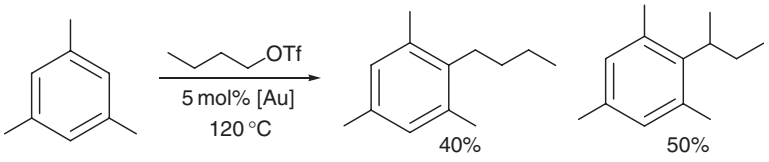
(70)

Aurations, mediated by Au(III), take place at relatively low temperature compared with the corresponding palladation processes. Kinetic products are often obtained via an electrophilic mechanism, displaying high levels of, steric-controlled, regioselectivity (Equation (71)).[70]

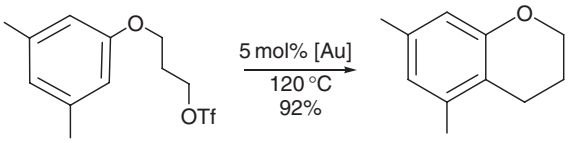


(71)

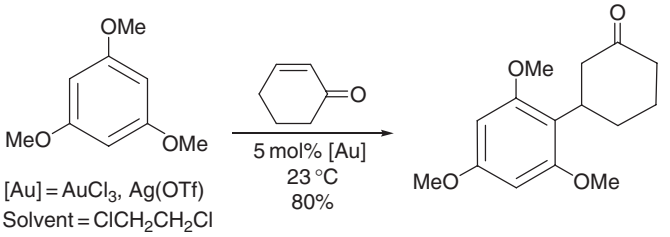
Gold-catalyzed direct C–H functionalizations enable the formation of polyalkylated arenes under mild conditions. In many cases, branched products are obtained. Two mechanisms are thought to operate; with electron-rich arenes, an S_N2-type mechanism via Au(III) leads to the linear product. The branched product is obtained via a Friedel–Craft-type alkylation. A silver salt is often added and is believed to generate a more electrophilic Au(III) species. Often regioselectivities are poor and symmetric arenes are employed. Intramolecular variants as well as Michael additions are also known (Equations (72)–(74)).[71,71a,71b]



(72)

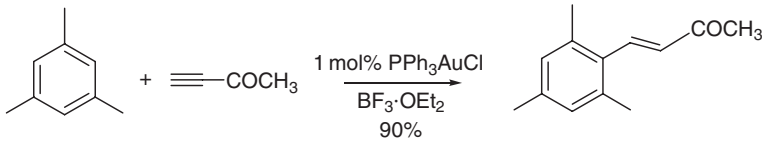


(73)

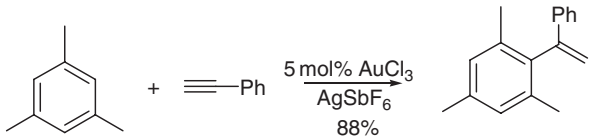


(74)

Hydroarylations of alkynes are catalyzed by gold complexes and these bear some resemblance to the Fujiwara Pd-catalyzed reaction. In general, when using gold chemistry, better *Z*/*E* selectivities are observed compared with palladium, lower catalyst loadings and milder conditions (neutral not TFA) are used. The mechanism involves the attack of ArH on the Au-coordinated alkyne. However, electron-poor acetylenes only appear to work with palladium chemistry (Equations (75) and (76)).[72]

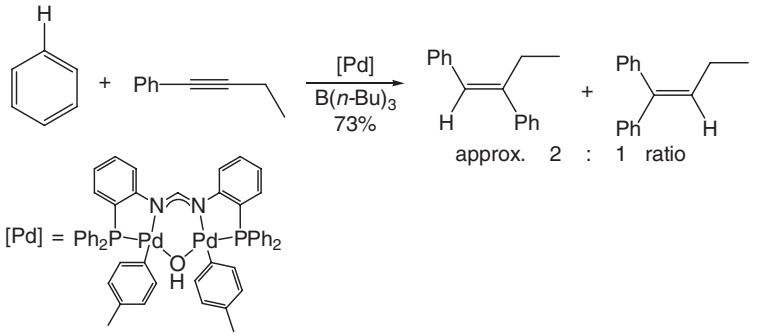


(75)



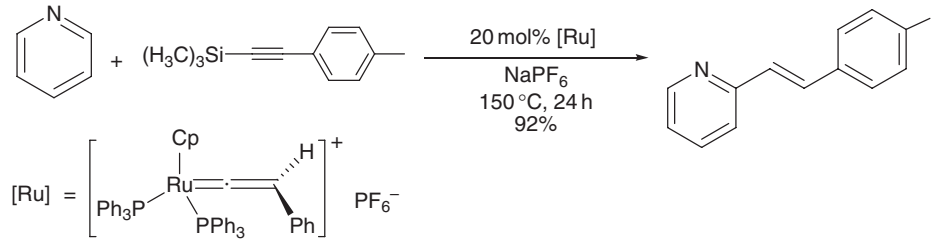
(76)

An aromatic C–H functionalization involving the *cis*-addition of benzene to internal alkynes is mediated by a bimetallic palladium complex in the presence of catalytic amounts of a borane. The mechanism of process remains to be clarified (Equation (77)).[73]



(77)

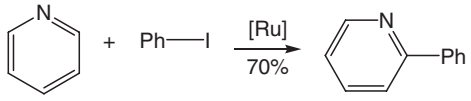
Pyridines can be functionalized by a range of metal complexes, notably ruthenium analogs. Ruthenium vinylidene complexes promote the reaction of pyridines with silylalkynes in both a regio- and stereoselective manner, affording 2-styrylpyridines (Equation (78)).



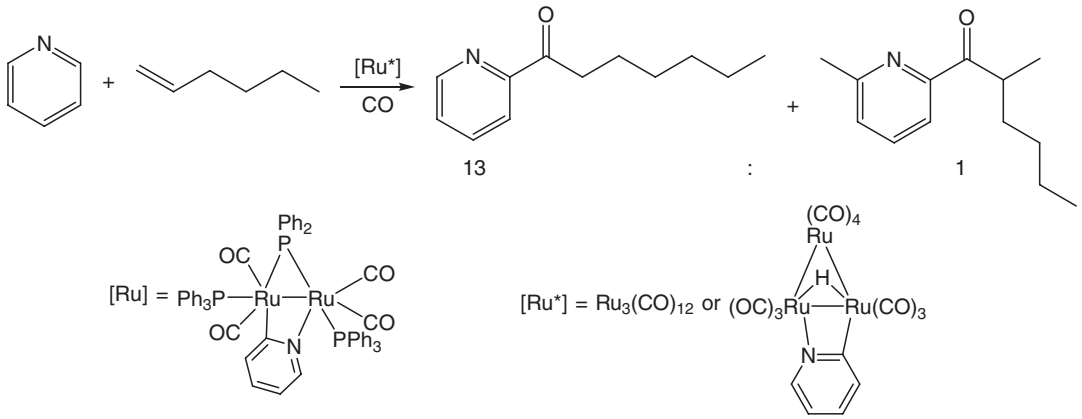
(78)

This is thought to proceed via an initial [2 + 2]-addition, followed by protonation of an allyl species. Phosphine decoordination from the metal is essential; when dppe is used instead of triphenylphosphine, no reaction takes place (Scheme 16).[74]

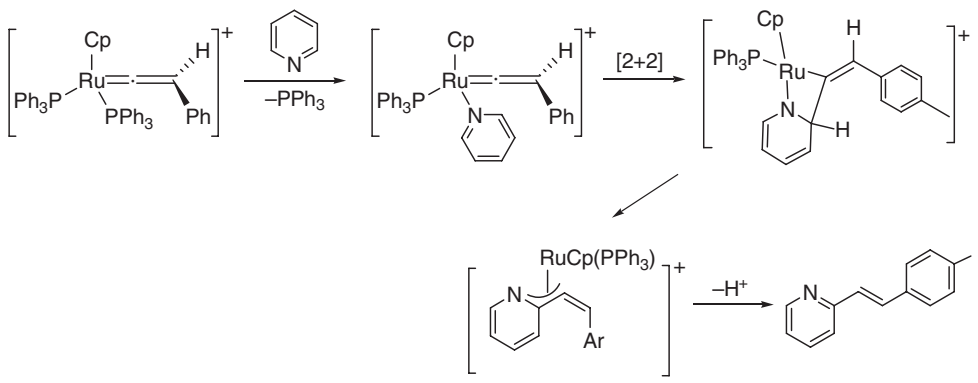
Other examples of pyridine functionalization reactions have been published, which are mediated by polynuclear metallic species (Equations (79) and (80)).[75,75a]



(79)

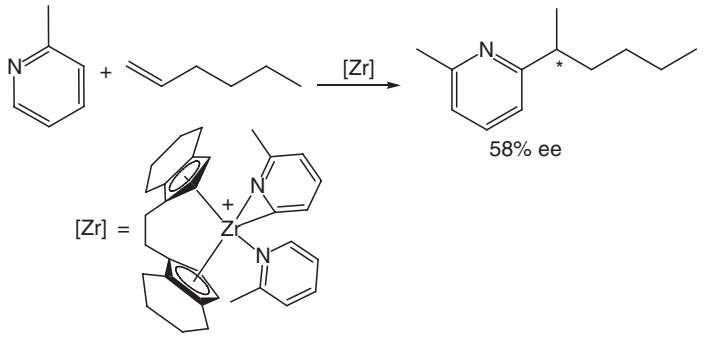


(80)



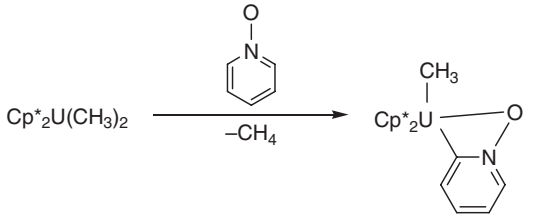
Scheme 16

Asymmetric induction was observed with a chiral zirconocene catalyst (Equation (81)).[76]



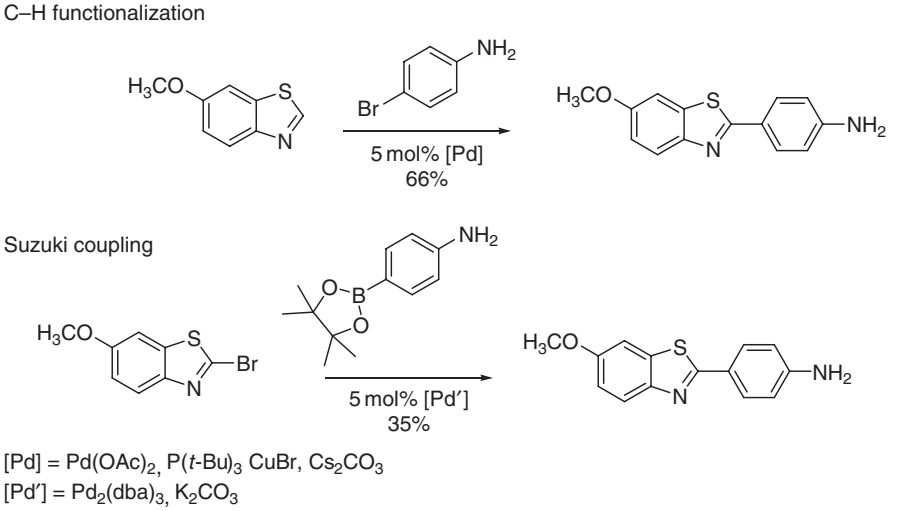
(81)

Actinides activate pyridine *N*-oxides to yield cyclometallated products. This may open up new synthetic opportunities (Equation (82)).[77]



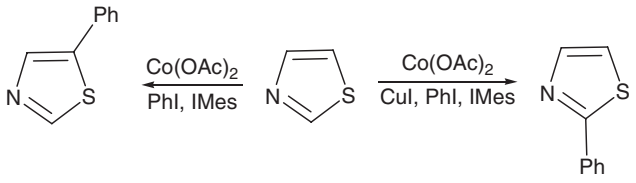
(82)

Synthetically viable C–H functionalizations have been employed in other heteroarene modifications, for example, for the efficient synthesis of 2-arylbenzothiazoles and benzoxazoles. Some of the products are precursors to radiolabels employed for the imaging of β-amyloid plaques for the diagnosis of Alzheimer's disease.[78] Curiously, the corresponding Suzuki coupling, employing the 2-bromobenzothiazole analog, gave inferior yields (Scheme 17).[79]



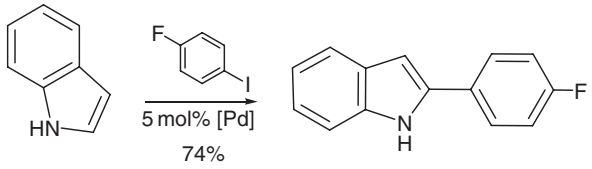
Scheme 17

In the search for more economical, tailored CH arylation processes, cheaper transition metals were employed for the arylation of thiazoles (Equation (83)).[80]

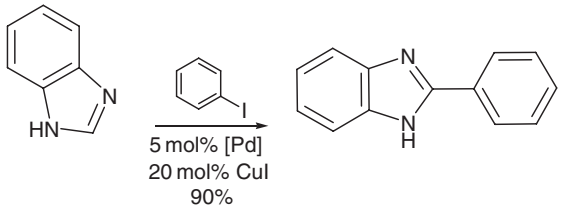


(83)

The arylation of common heteroarenes could be governed by the choice of conditions. Free (NH)-heteroarenes were C-arylated via selective catalytic C–H bond functionalizations. The key to these transformations was the use of MgO, which enabled the formation of a salt of the heteroarene, hence offering N-protection *in situ* (Equations (84) and (85)).[81,81a]

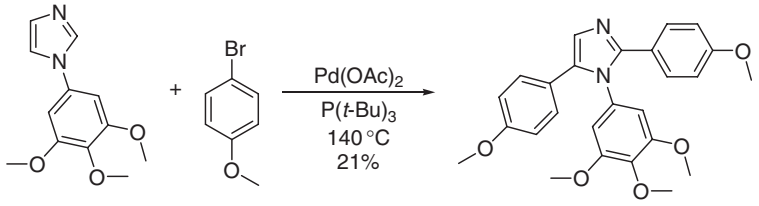


(84)



(85)

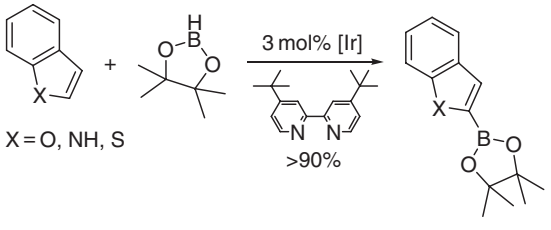
Related direct couplings of imidazoles have been reported and some of the analogs were tested for anticancer activity (Equation (86)).[82]



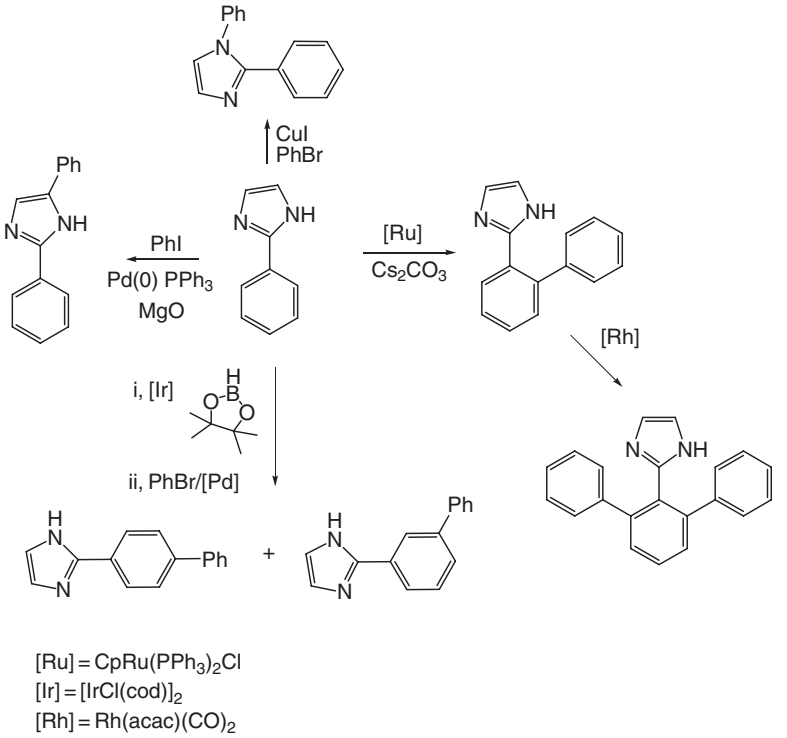
(86)

A remarkable series of CH functionalizations has been described whereby the regiochemical outcome of the reaction is determined by the catalyst employed. Directed and nondirected C–H functionalizations on 2-phenylimidazole were observed. This orthogonal approach is excellent for introducing diversity and may have applications in library generation in areas including medicinal chemistry (Scheme 18).[83]

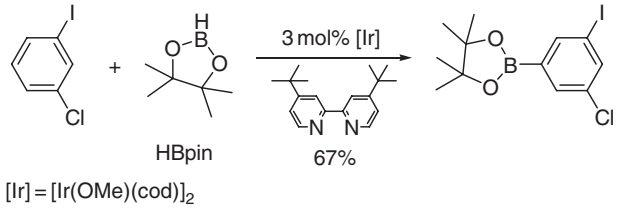
Remarkable carbon–boron bond-forming reactions are catalyzed by iridium complexes and proceed at room temperature with excellent regioselectivity, governed by steric factors. Heteroarenes are borylated in the 2-position and this reaction is generally tolerant of halide substituents on the arene (Equations (87) and (88)).



(87)

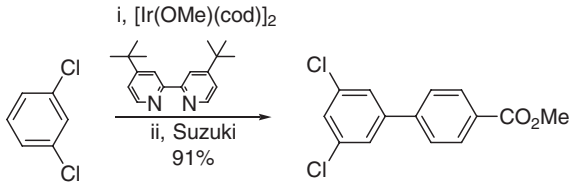


Scheme 18



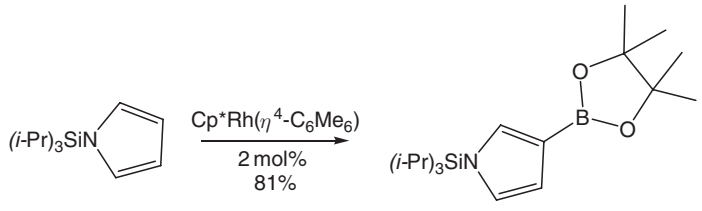
(88)

An ideal scenario combines this borylation strategy with further functionalization, including oxidation and coupling chemistry (Equation (89)).

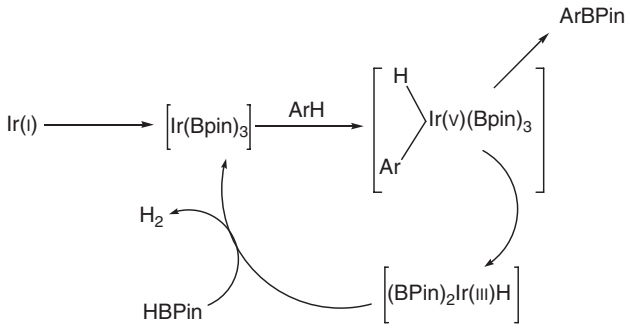


(89)

A mechanism involving Ir(III) and Ir(V) has been proposed (Scheme 19).[84,84a–84c]
Similar rhodium-mediated borylations are known (Equation (90)).[85]

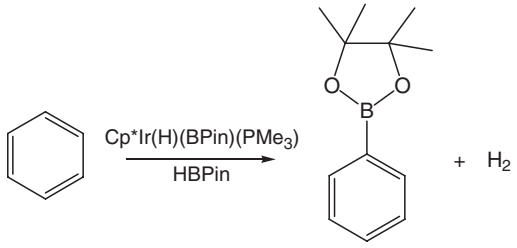


(90)

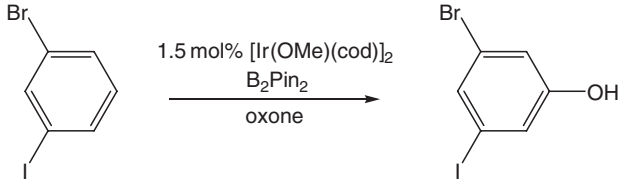


Scheme 19

Following on from stochiometric iridium-based C–H functionalizations, iridium-catalyzed reactions have been developed and can be combined with oxidation chemistry to enable the selective functionalization of aromatics. Moreover, these reactions can be performed under solventless conditions (Equations (91) and (92)).[86,86a–86c]

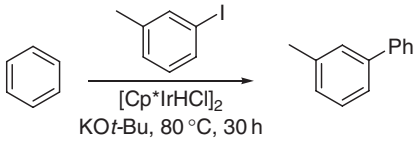


(91)



(92)

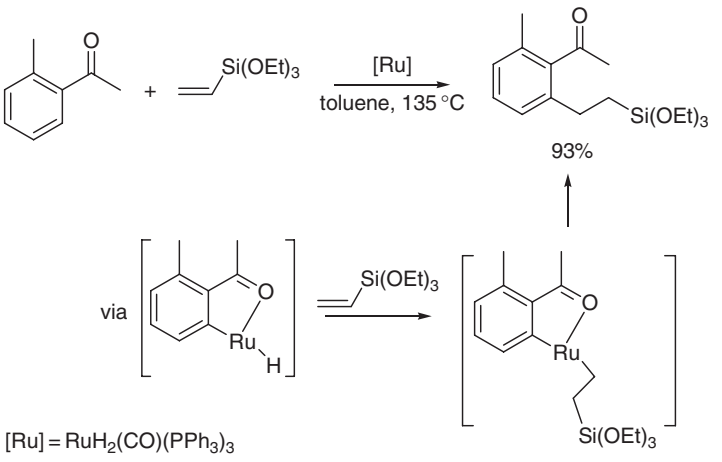
Non-directed C–H functionalizations of arenes can be mediated by Cp^*Ir complexes as in the catalytic synthesis of biphenyl analogs. Moderate TONs of ca. 10 have been reported (Equation (93)).[87]



(93)

10.03.3.2 Intramolecular Functionalization

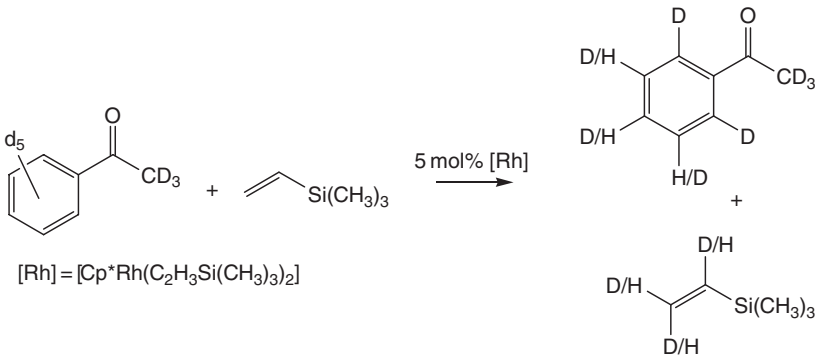
The selective intramolecular arene C–H/olefin coupling reaction (Murai reaction) represents one of the most important discoveries in catalytic C–H functionalization chemistry (Equation (94)).[88]



(94)

Site selection in these reactions is mainly sterically governed, but electronic effects can also be important (Scheme 20).

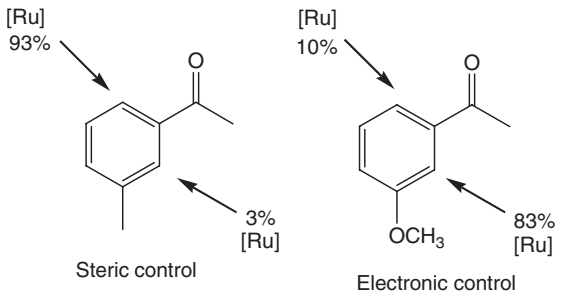
Brookhart's group has reported a related rhodium-catalyzed olefin insertion. To gain insight into the mechanism of this process, labeling studies were carried out under conditions where no coupling product was observed (^{1}H NMR study at 80 °C). Deuterium loss occurred in both *meta*- and *para*-sites of the aromatic group, and deuterium incorporation was observed in the olefin (Equation (95)).[89]



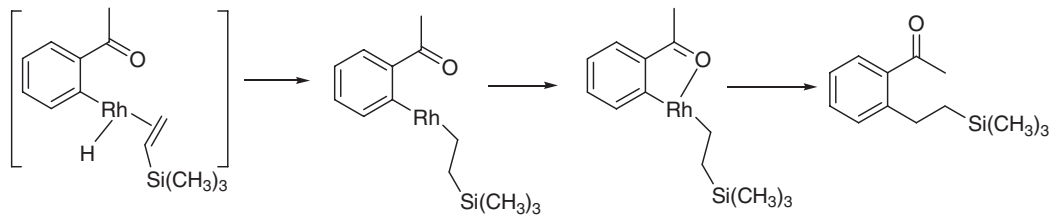
(95)

This study shows that the Rh catalyst indiscriminantely activates all aromatic sites of the substrate. Coordination to the metal lowers the energy barrier required for the C–C bond-forming step (reductive elimination) (Scheme 21).

Similar reactions were catalyzed by $RuH_2(CO)(PPh_3)_3$ and $Ru(PPh_3)_3(CO)(C_2H_4)$.[90,90a]

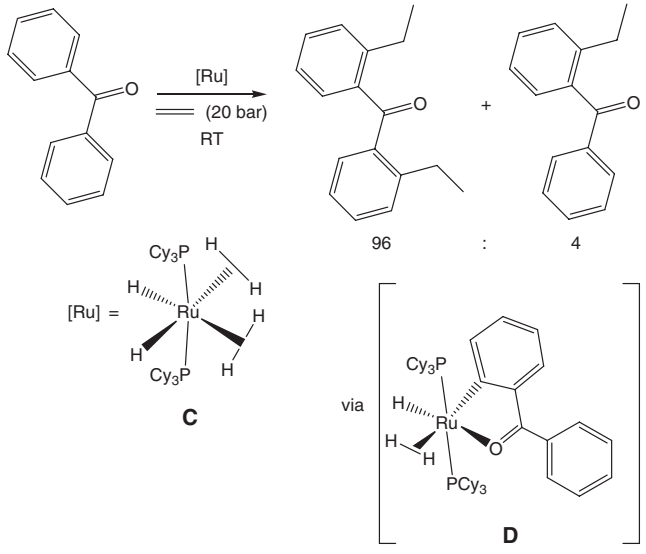


Scheme 20



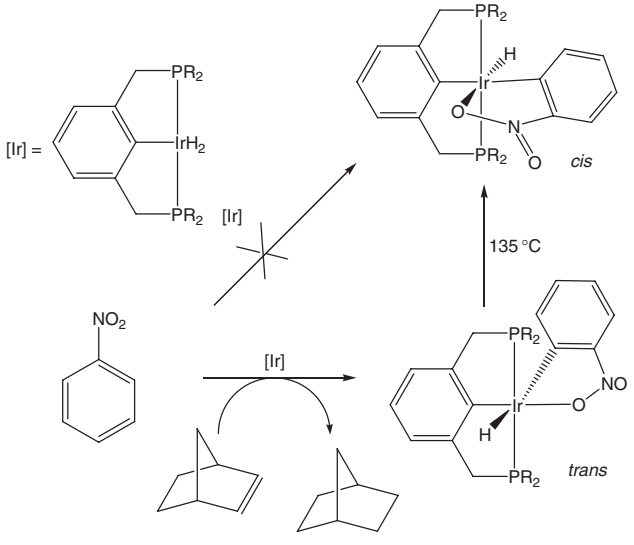
Scheme 21

A ruthenium dihydrogen complex **C** or a ruthenacycle **D**, which was proposed as a potential intermediate, catalyzed the insertion of ethylene into sp^2-C–H bonds, with TONs reaching 19 after 48 h of reaction and under very mild conditions (room temperature as opposed to the usual 135 °C) (Equation (96)).[91,91a–91c]



(96)

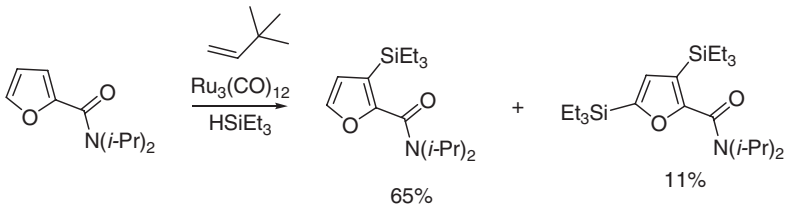
Structural studies on the nature of the organometallic intermediates following "chelation-assisted" CH additions of pincer iridium complexes have been carried out. The product was found to have an unexpected *trans*-disposition of the hydride with respect to the metallated aromatic group. This is not the expected direct outcome of a chelation-assisted reaction since coordination of oxygen to iridium prior to C–H activation would be expected to afford the *cis*-isomer (Equation (97)).



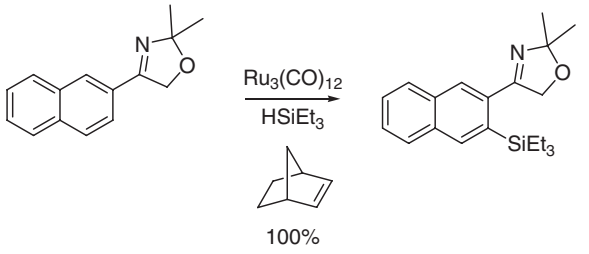
(97)

Low-temperature ^{31}P NMR studies showed that the reaction of (PCP)Ir with nitrobenzene leads to three products of the type (PCP)Ir(aryl)H and *meta*- and *para*-additions are kinetically favored. However, refluxing the *trans*-isomer afforded the *cis*-product, designated the thermodynamic product. Nevertheless, chelation to the metal still remains an important regiochemical factor in these reactions, which will be termed "chelation controlled" or "directed" hereafter.[92]

Silylations of aromatic analogs including heteroarenes are known, although in some instances a small amount of non-directed product is formed. The addition of a hydrogen scavenger was found to increase the yield of product (Equations (98) and (99)).[93]

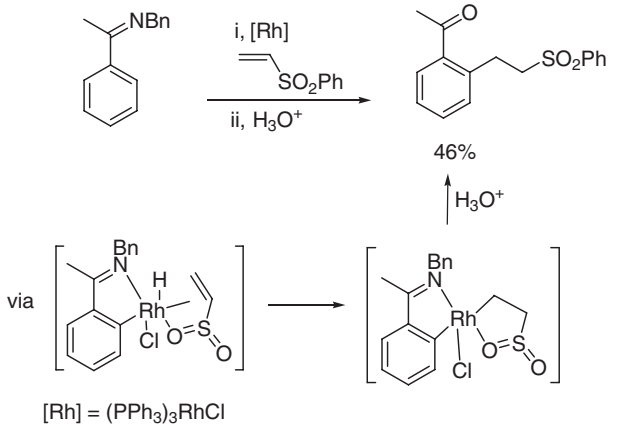


(98)



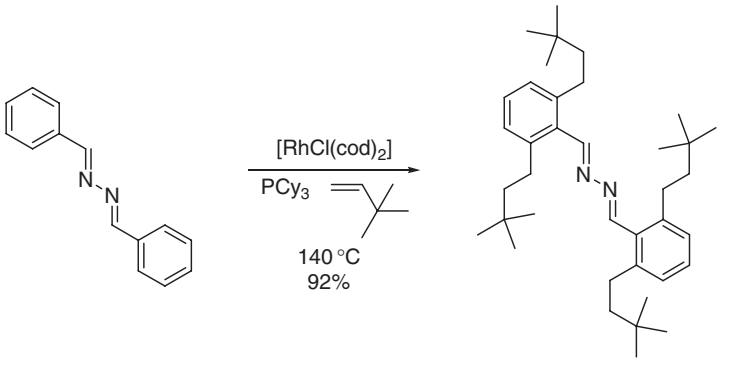
(99)

Directed rhodium-catalyzed Michael-type additions have recently been disclosed involving the *ortho*-alkylation of ketimines with functionalized olefins (Equation (100)).[94]



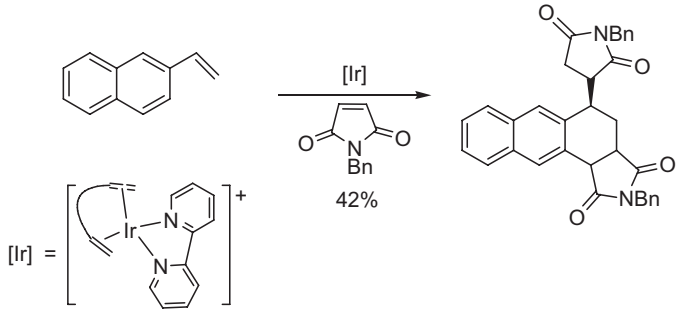
(100)

Multiple alkylations of azines can be achieved using a rhodium catalyst along with a phosphine ligand. Electron-rich azines give better results (Equation (101)).[95]



(101)

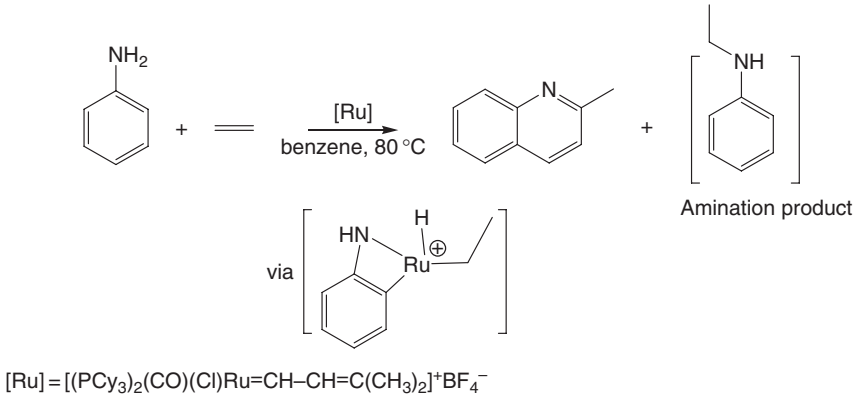
Double incorporation reactions of *N*-benzylmaleimide with styrene analogs are catalyzed by cationic iridium complexes (Equation (102)).



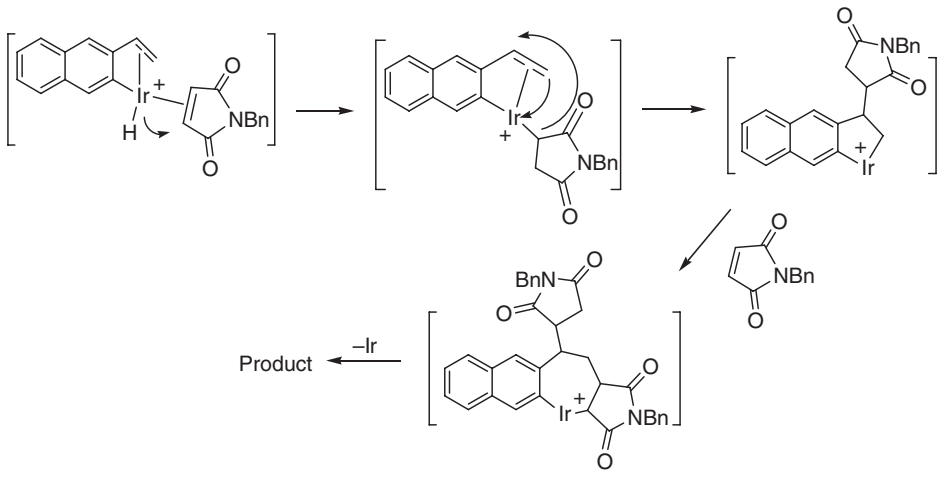
(102)

The reaction is thought to proceed via an iridium hydride, with the olefin group acting as a directing group. Metallacycle intermediates have also been implicated in this reaction (Scheme 22).[96]

Arylamine couplings with ethylene are catalyzed by ruthenium complexes (Equation (103)).[97]

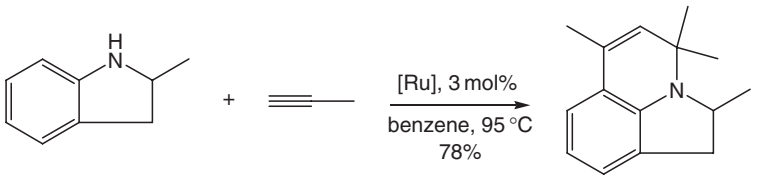


(103)

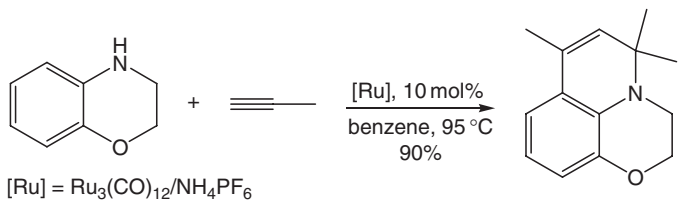


Scheme 22

Related alkyne couplings yield tricyclic quinolines via a regioselective amination/C–H functionalization pathway (Equations (104) and (105)).[98]

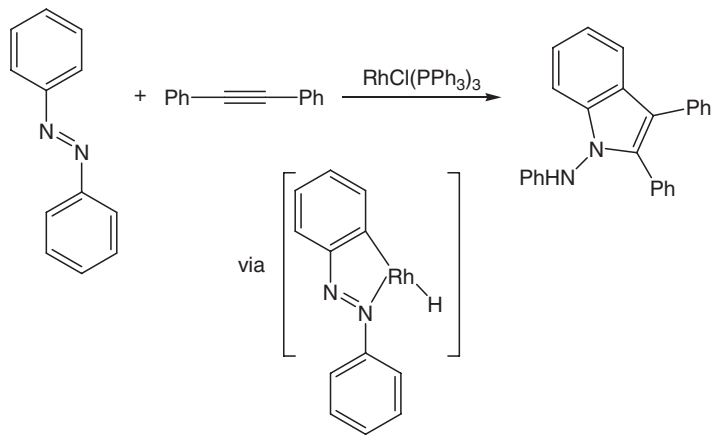


(104)



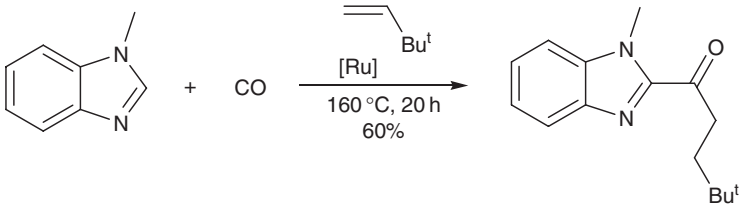
(105)

Indoles can be formed by metal-catalyzed cyclizations of azobenzenes on disubstituted alkynes (Equation (106)). [99]

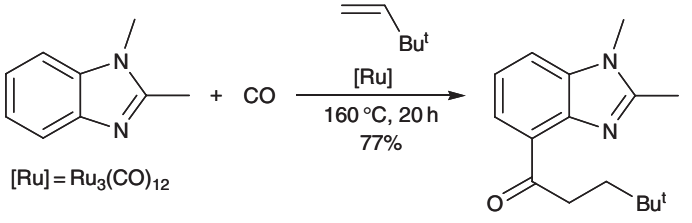


(106)

Ruthenium-catalyzed carbonylations of a variety of heterocycles have been disclosed. With benzimidazole derivatives, the regioselectivity changes upon introduction of a C(2) substituent (Equations (107) and (108)).[100]

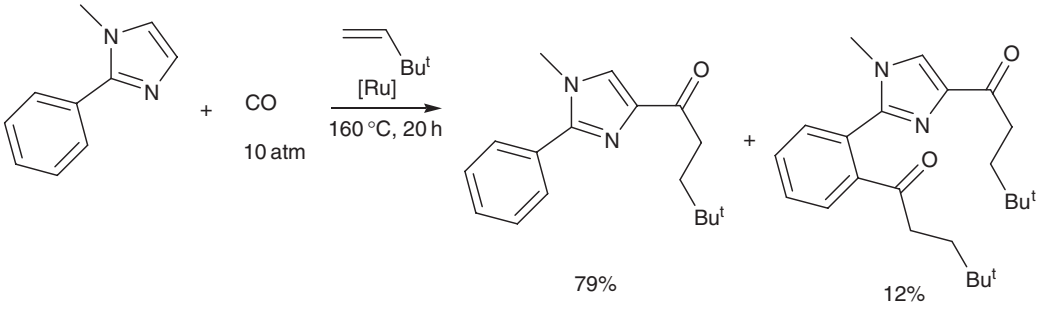


(107)

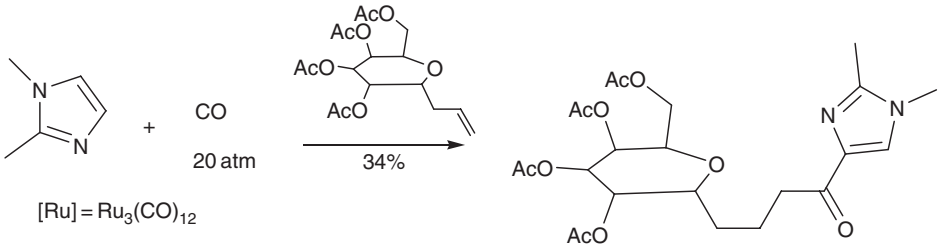


(108)

This has been extended with success to other elaborated substrates, with impressive results (Equations (109) and (110)).[101,101a]

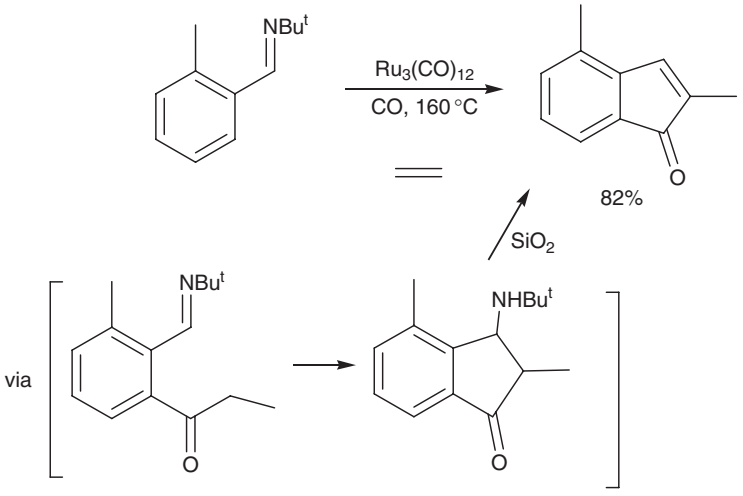


(109)



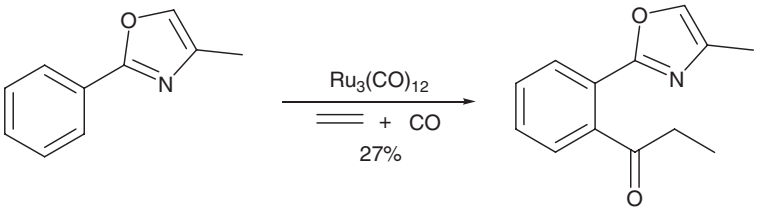
(110)

Indenones can be synthesized from the carbonylation of aromatic imines (Equation (111)).[102]

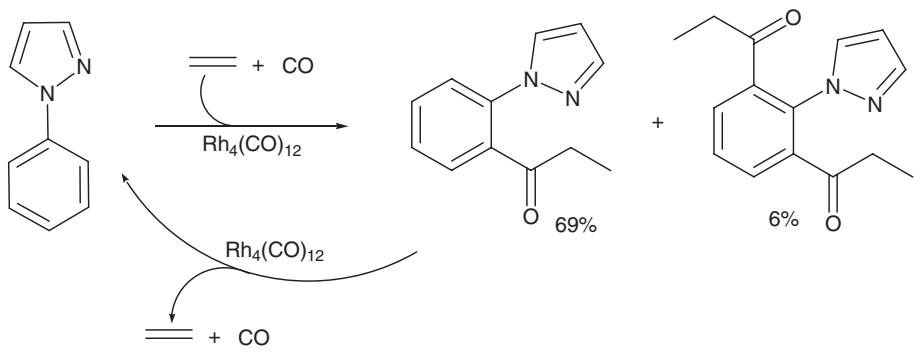


(111)

Ruthenium- and rhodium-catalyzed reactions lead to aryl ketones, and in some cases these processes are reversible (Equations (112) and (113)).[103]

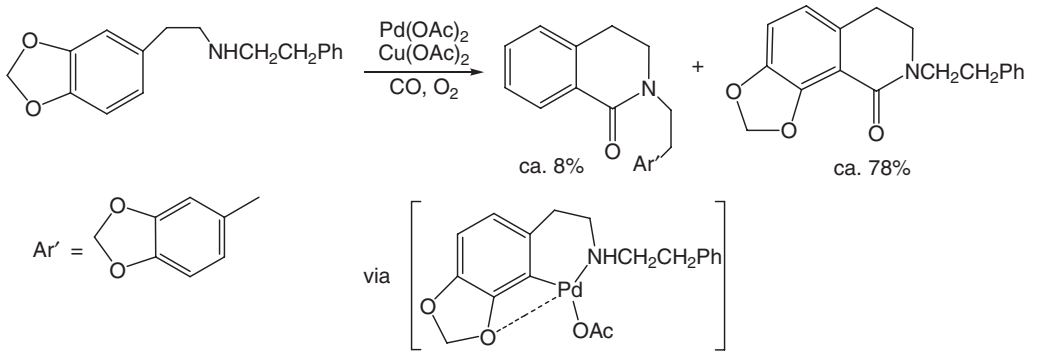


(112)



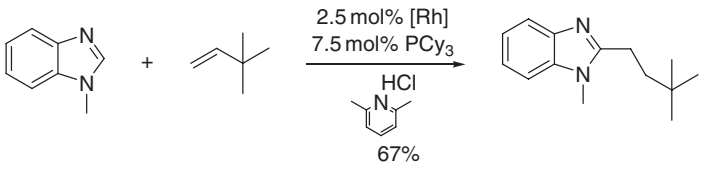
(113)

Carbonylations involving catalytic amounts of Pd(II) and substoichiometric Cu(II) have been developed for the synthesis of lactams. This Wacker-type process is assumed to proceed via C–H functionalization involving a palladacycle intermediate; such a hypothesis is backed by the high degree of regioselectivity attained, when using a bis-chelating substrate (Equation (114)).[104]

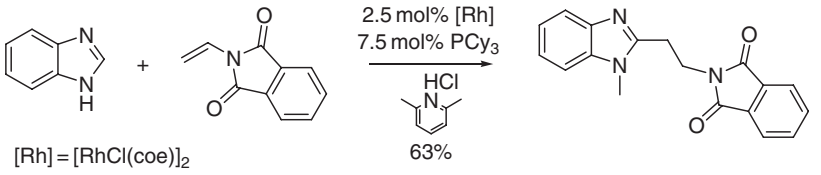


(114)

C–H functionalizations of benzimidazoles have been described and are thought to involve an Rh(III) hydride. Hydrochloride salts of bulky electron-rich phosphines were found to be useful additives (Equations (115) and (116)).[105]

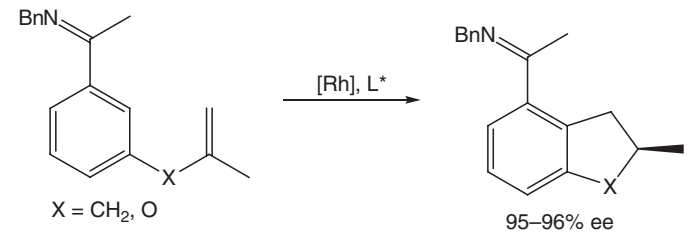


(115)

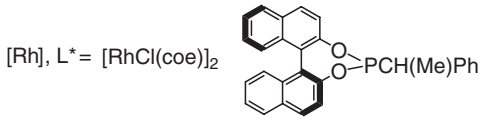


(116)

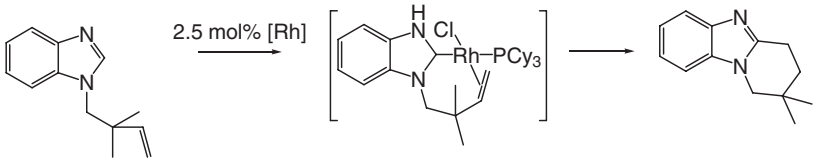
Stereoselective catalytic cyclizations are now known, with excellent enantioselectivities observed (Equation (117)).[106]



(117)

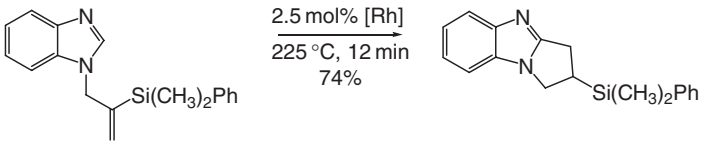


A rhodium-catalyzed intramolecular C–H functionalization has been employed for the synthesis of bicyclic imidazoles. The alkene acts as an anchor to the metal, directing the C–H functionalization process, which involves the formation of an Rh(I) carbene intermediate (Equation (118)).[107]

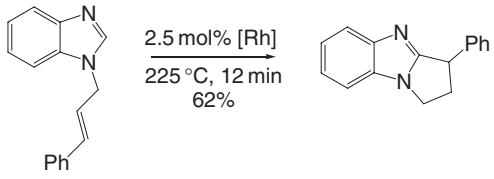


(118)

Such reactions are accelerated in a microwave, with reactions times reduced to <20 min (Equation (119) and (120)).[108]

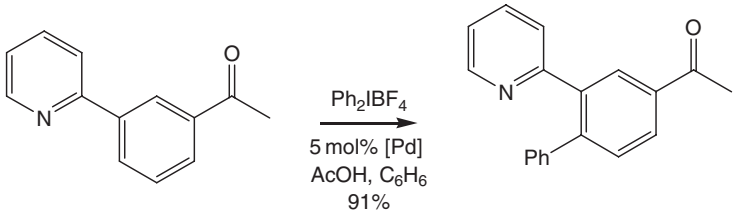


(119)

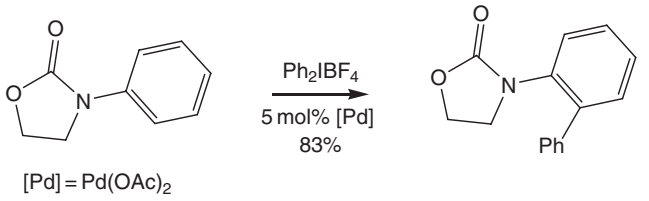


(120)

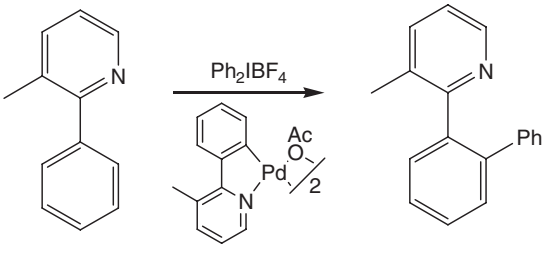
Palladium-catalyzed directed intramolecular activations of aryl C–H bonds have been reported, as in the phenylation of heterocycle analogs. Palladacycles are proposed intermediates, acting as effective catalysts, and the mechanism is likely to proceed via oxidation of Pd(II) to Pd(IV) by the iodonium salt, as for the Equation (57), which described the activation of benzylic sp^3-CH bonds (Equations (121)–(123).[109]



(121)

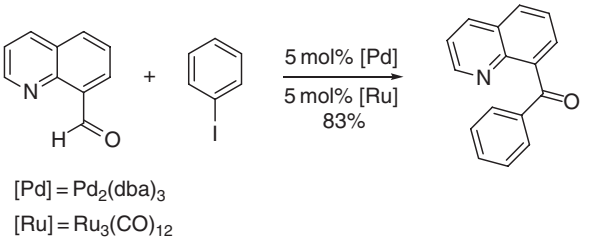


(122)



(123)

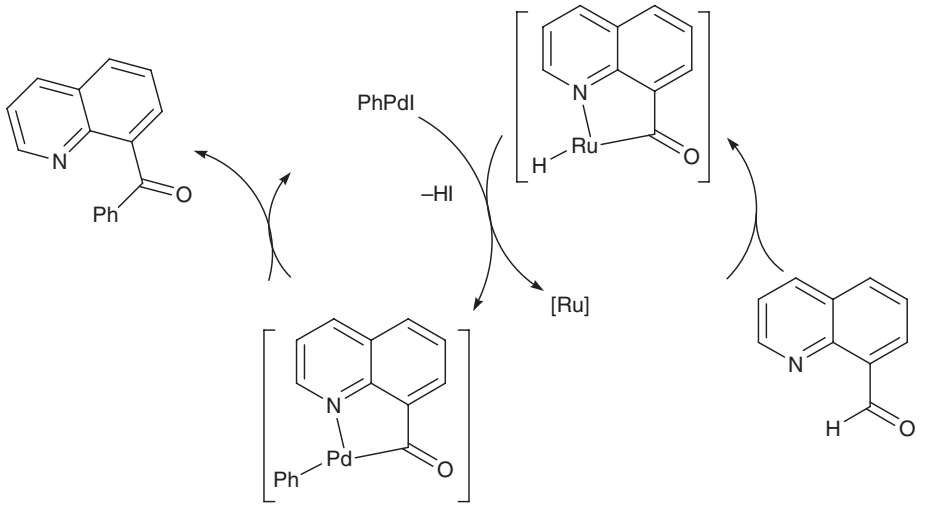
Cooperative Ru/Pd catalysis enabled the coupling of aldehydes to aryl iodides (Equation (124)).



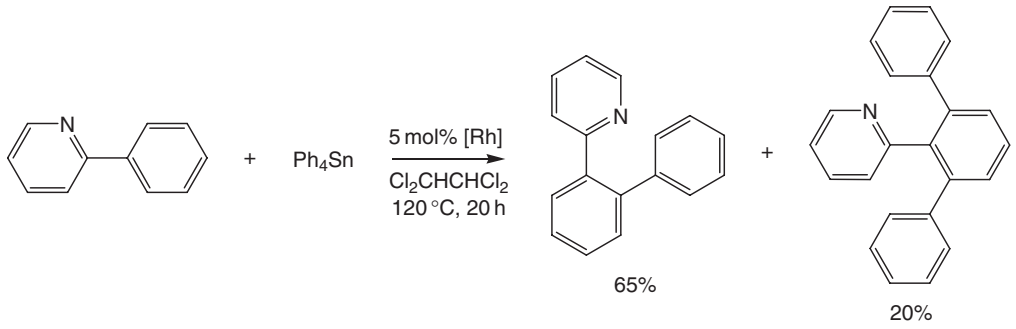
(124)

A mechanism was proposed for this reaction (Scheme 23).[110]

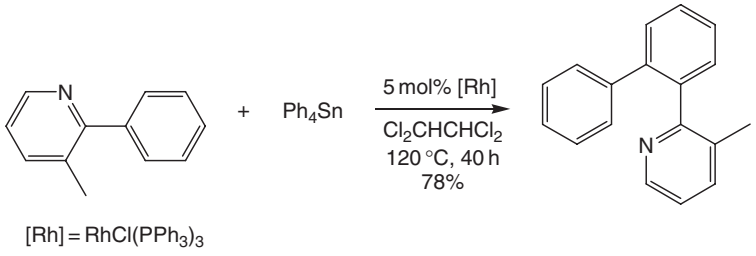
The *ortho*-arylation of 2-arylpyridines with aryltin reagents is mediated by Wilkinson's catalyst. This cross-coupling procedure occurs at high temperatures and consequently, the prevention of double phenylation represents a major hurdle, which is often achieved by adding a methyl group to either the pyridine or aryl group (Equations (125) and (126)).[111]



Scheme 23

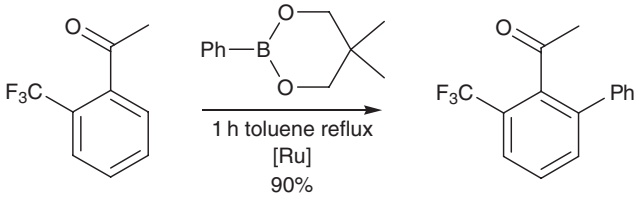


(125)

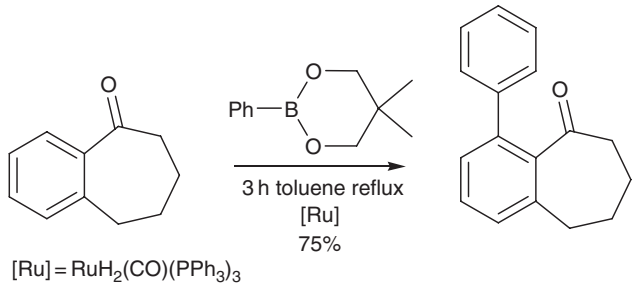


(126)

Ruthenium-catalyzed arylations of aromatic ketones were reported employing the transmetallation of boronic esters (Equations (127) and (128)).[112]



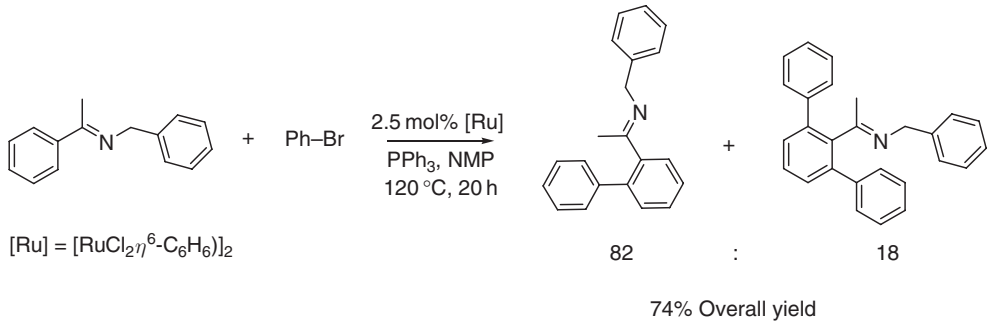
(127)



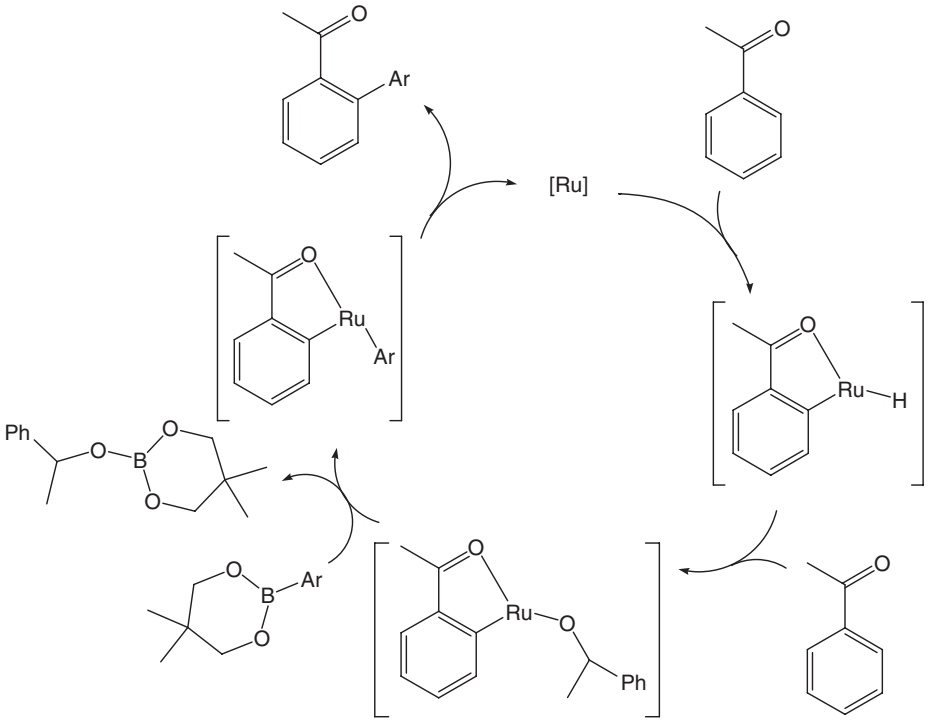
(128)

A reasonable mechanism for this reaction follows in Scheme 24.

Aromatic imines can be *ortho*-arylated and alkenylated using ruthenium catalysis (Equation (129)).[113]

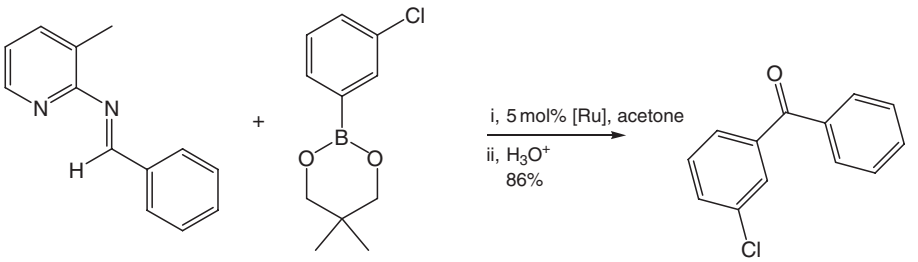


(129)



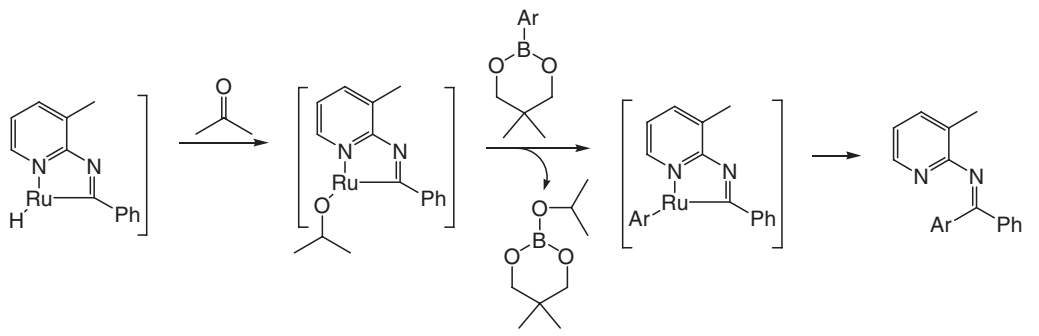
Scheme 24

An ingenious strategy developed by Jun's group makes use of a chelating 3-picolin-2-yl group for performing C–C bond forming reactions. In the particular example shown, for the synthesis of aromatic ketones, methylvinyl ketone is added to suppress unwanted reductive amination processes (Equation (130)).



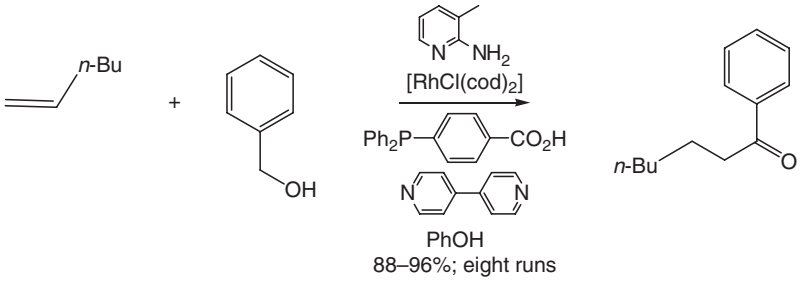
(130)

A mechanism has been proposed for this, and related transformations, involving a chelation assisted C–H bond functionalization. Following hydride addition to the solvent, acetone, and a transmetallation reaction, reductive elimination yields the ketimine. Hydrolysis of the latter affords the ketone (Equation (131)).[114,114a]



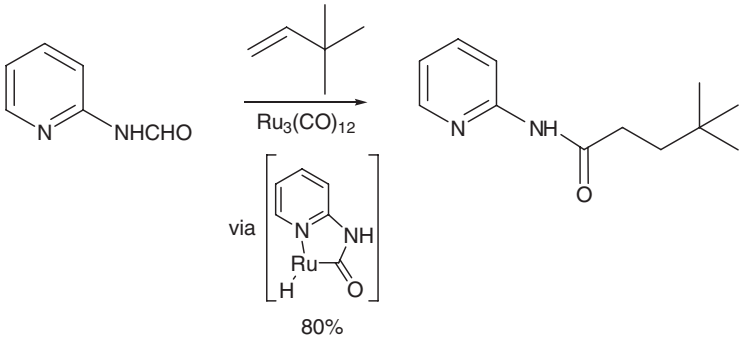
(131)

A recyclable system for the directed rhodium-catalyzed hydroacylation of olefins was reported using a homogeneous phenol and 4,4′-dipyridyl solvent system at 150 °C. High yields were obtained even after eight cycles and the ketone product was obtained after decantation (Equation (132)).[115]



(132)

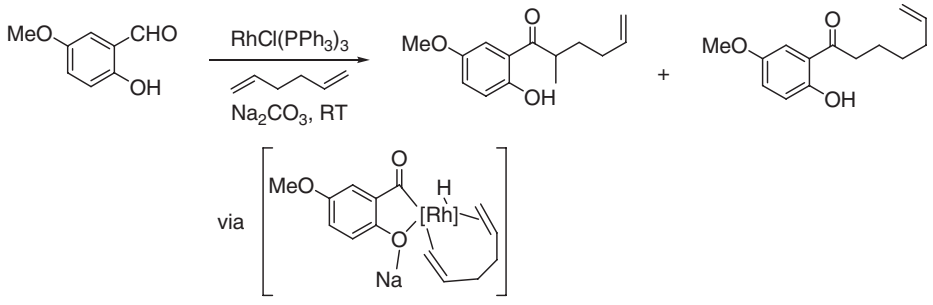
Hydroamidations have been reported involving the ruthenium-catalyzed chelation assisted activation of formamide (Equation (133)).[116]



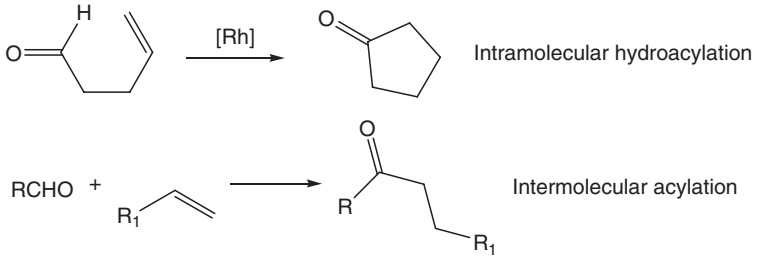
(133)

Although intermolecular hydroacylations have been known for over 30 years, attempts to carry out intermolecular versions have traditionally been hampered due to competitive decarbonylation processes (Scheme 25).

However, the decarbonylation reaction can be suppressed by the use of specially tailored chelating groups. Intermolecular processes involving dienes and salicylaldehydes are now known, and are thought to proceed via a double chelation mechanism, akin to the Jun-type system. Rhodium-catalyzed reactions lead to hydroacylated products, under relatively mild conditions (Equation (134)).[117]

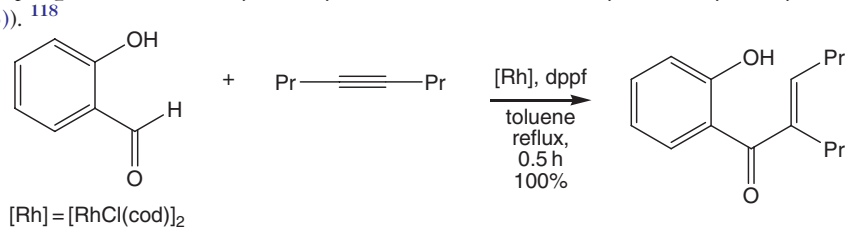


(134)



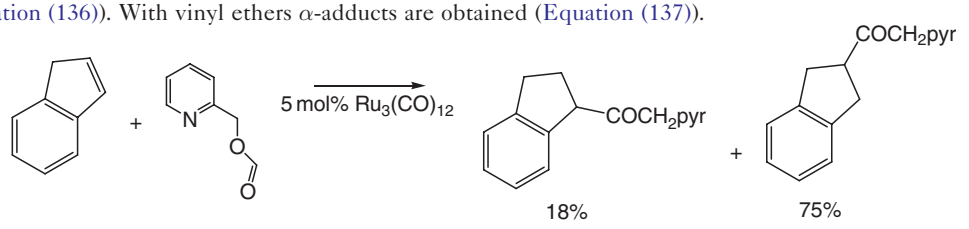
Scheme 25

A similar coupling reaction of salicyl aldehydes with disubstituted alkynes, catalyzed by rhodium, is known (Equation (135)). [118]

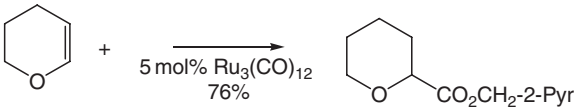


(135)

Directed ruthenium-catalyzed hydroesterifications of alkenes, employing 2-pyridylmethyl formate, leads to esters (Equation (136)). With vinyl ethers α-adducts are obtained (Equation (137)).

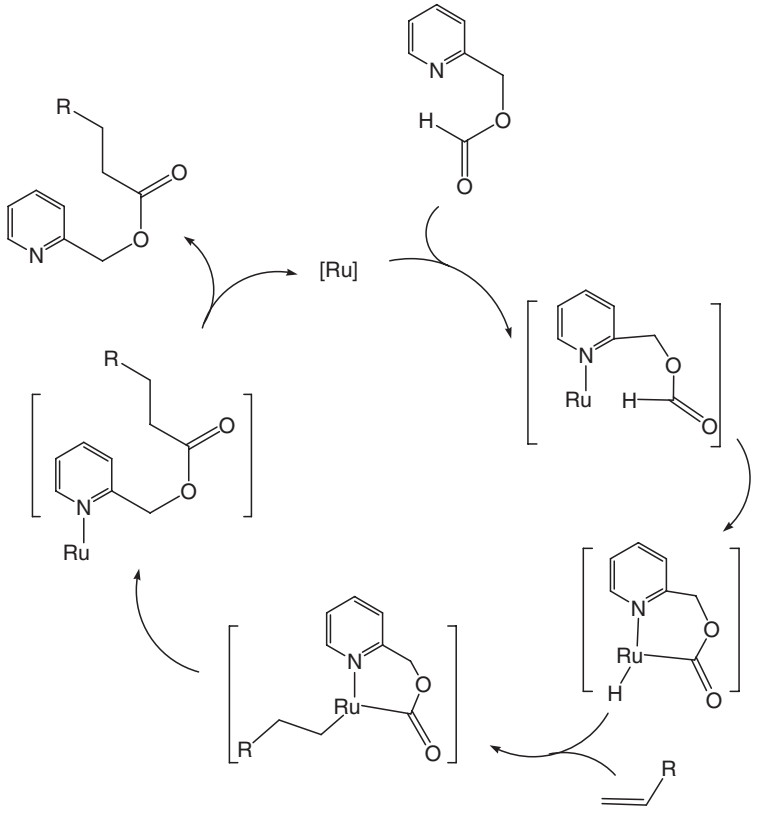


(136)



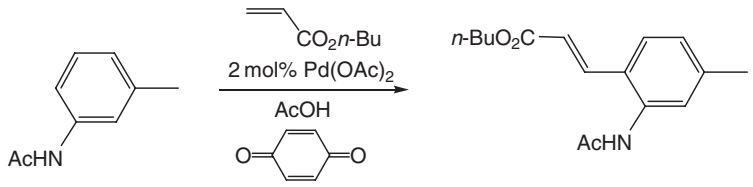
(137)

The mechanism for this process is presumed to involve activation of the formyl C–H bond, following pyridine coordination, by the Ru catalyst, which may be mononuclear or in a cluster form. Such chelation suppresses a decarbonylation route (Scheme 26).[119]



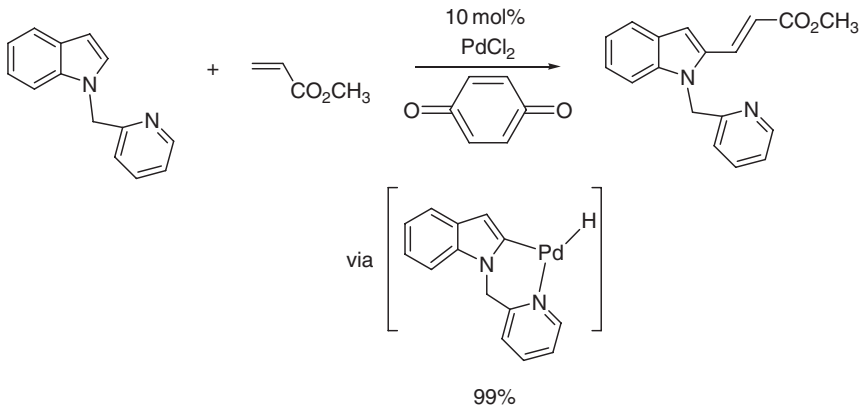
Scheme 26

Palladium-catalyzed room-temperature *ortho*-alkenylations of anilides have been recently reported, employing benzoquinone as a stoichiometric oxidant. A kinetic isotope effect k_H/k_D of 3 points to a slow C–H functionalization step. Electron-rich acetanilides react faster whereas anilines are unreactive (Equation (138)).[120]



(138)

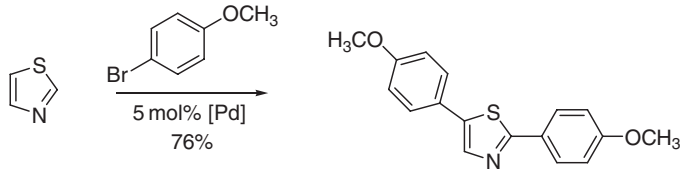
A similar strategy enabled the 2-alkenylation of indoles using catalytic palladium chemistry (Equation (139)).[121]



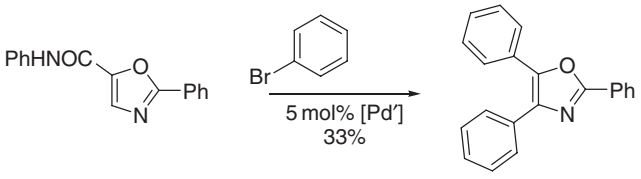
99%

(139)

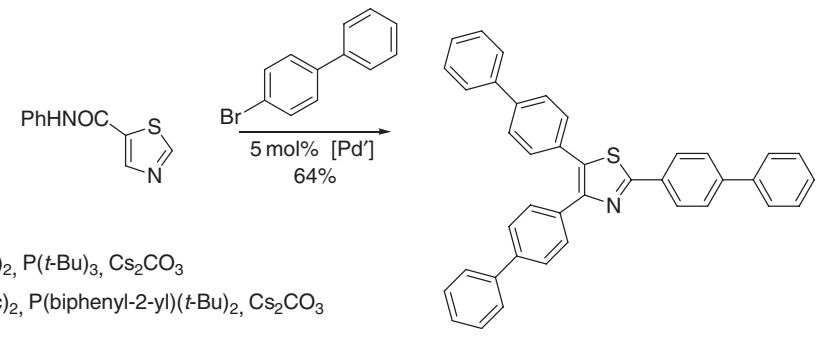
Other heterocycle analogs have been made by multiple arylations and in some cases a carbamoyl-directing group is cleaved during the reaction (Equations (140)–(142)).[122] (For other multiple arylations, see Refs: 122b–122d.)



(140)



(141)

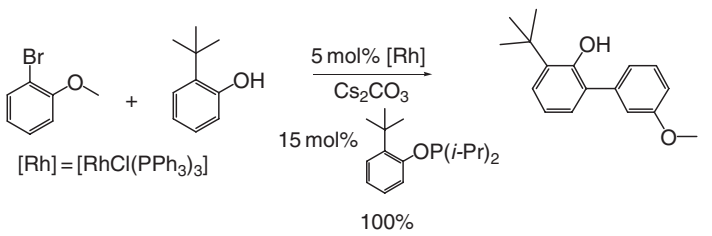


(142)

[Pd] = $Pd(OAc)_2$, P(*t*-Bu)$_3$, Cs_2CO_3

[Pd′] = $Pd(OAc)_2$, P(biphenyl-2-yl)(*t*-Bu)$_2$, Cs_2CO_3

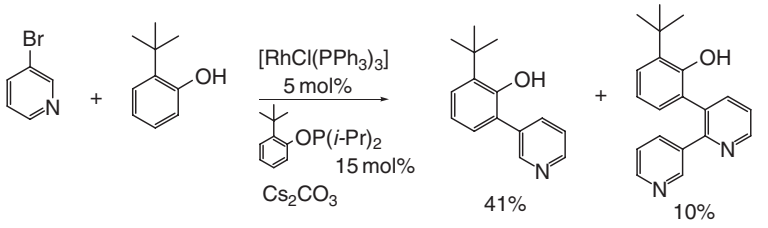
The directed synthesis of biaryls can be achieved using rhodium-based catalysts along with a phosphinite co-ligand (Equation (143)).



(143)

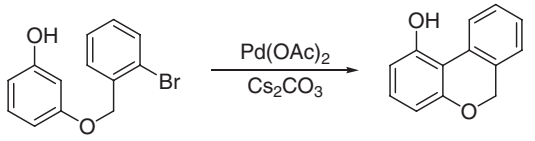
The reaction involves a key transesterification of the phenol with the phosphinite ligand. Orthometallation of the resulting phosphinite leads to a metallacycle. After reductive elimination, the biaryl product is formed and undergoes a transesterification to afford the phenol product (Scheme 27).[123]

In some cases multiple arylation products are obtained (Equation (144)).

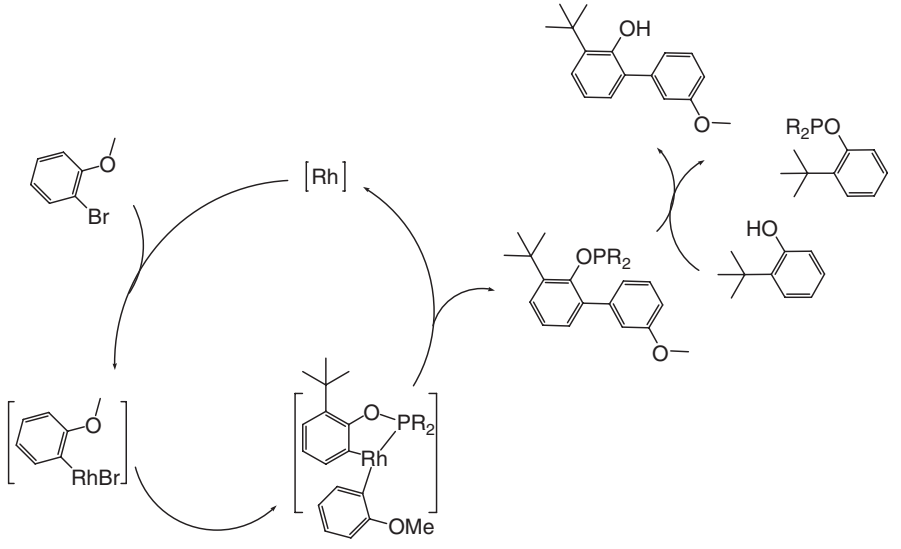


(144)

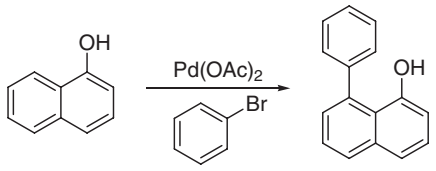
This adds to other reports of intra- and intermolecular arylations of phenolic derivatives (Equations (145)–(147)).[124,124a–124c]



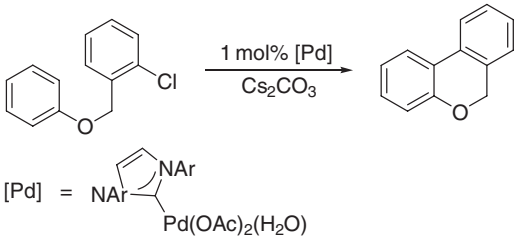
(145)



Scheme 27

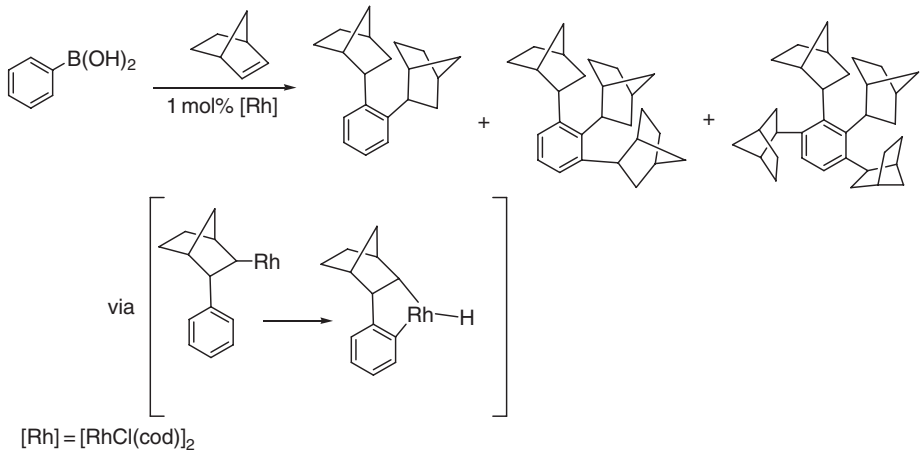


(146)



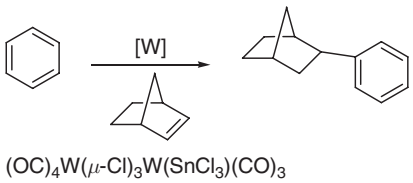
(147)

"Merry-go-round" processes involving multiple C–H functionalizations and carbometallations have been described. In the example depicted, a rhodium hydride continues to be formed until steric factors prevail. The 2-norbornene moiety acts as a directing group (Equation (148)).[125]



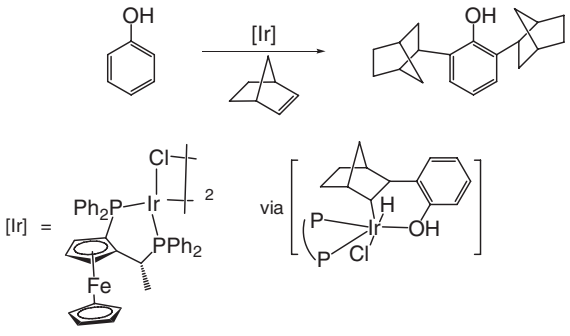
(148)

Tungsten complexes also catalyze similar reactions (Equation (149)).[126]



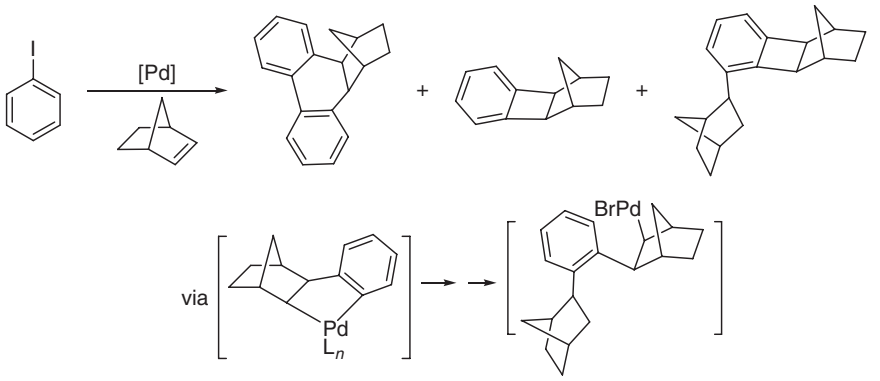
(149)

Solventless arylations of norbornene have been reported recently with low ee's (4.5%), in the presence of a chiral diphosphene ligand (Equation (150)).[127]



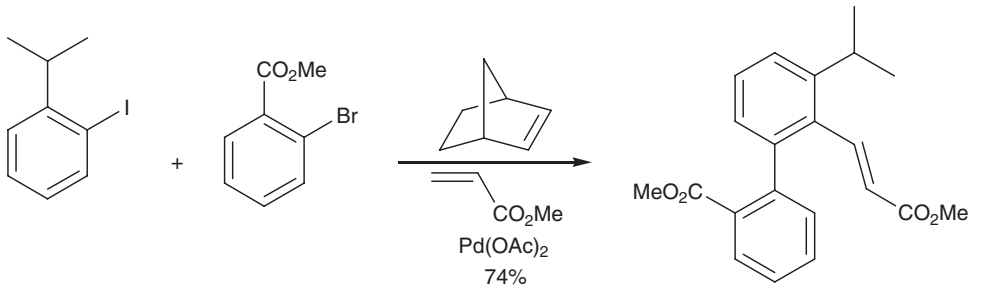
(150)

Catellani's group have exploited the use of palladacycles for the synthesis of a host of interesting molecules. Here, palladium-containing intermediates, which cannot β-eliminate easily, are used to perform further annulations. Palladium(IV) species are involved (Equation (151)).[128]

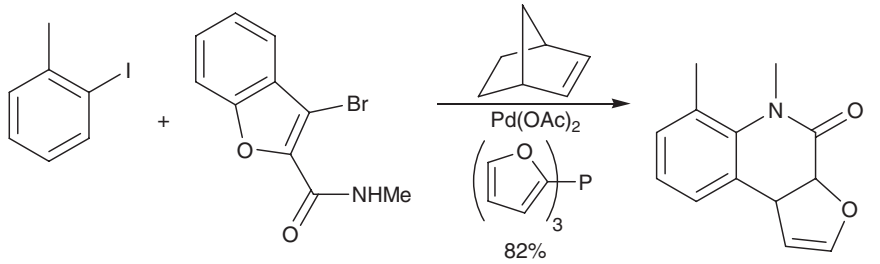


(151)

Both multiple-coupled products and interesting fused heterocycles can be synthesized using this methodology (Equations (152) and (153)).[129,129a–129c]

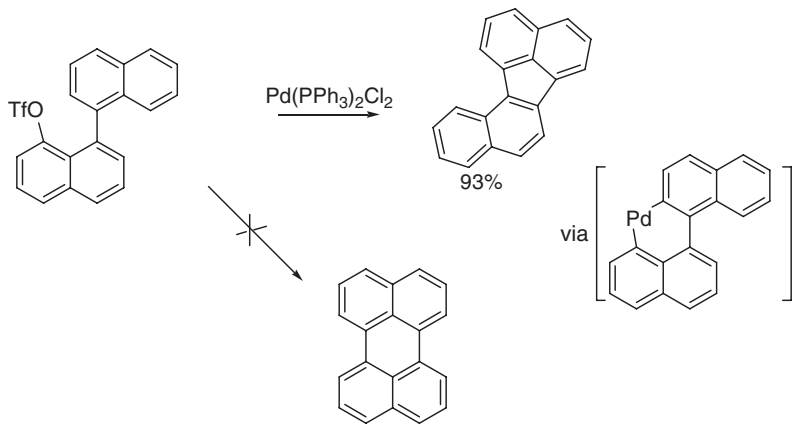


(152)

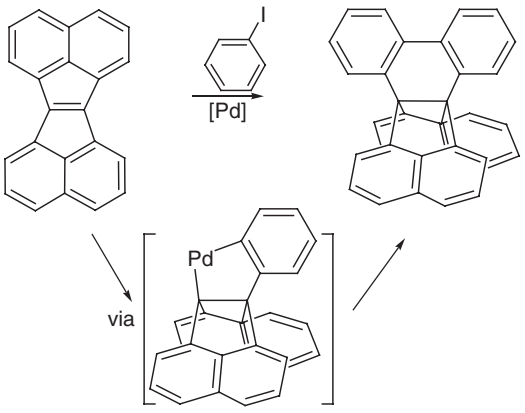


(153)

Related, earlier examples involve the formation of palladacycle intermediates (Equations (154) and (155)).

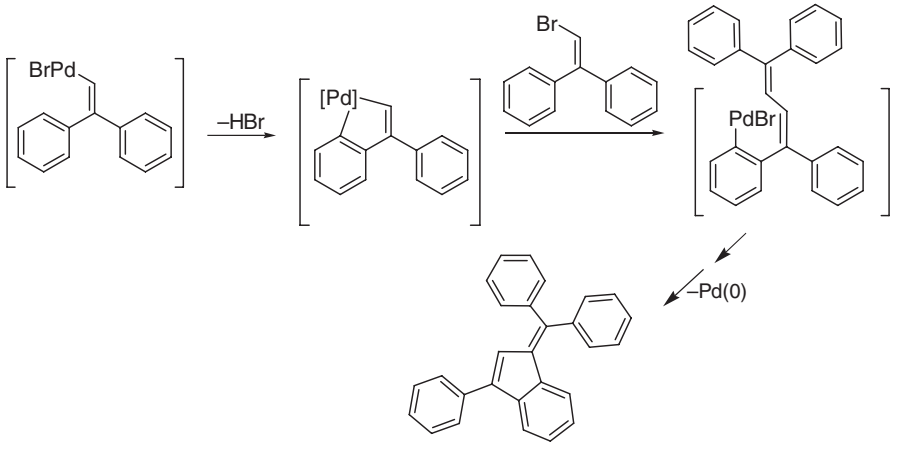


(154)



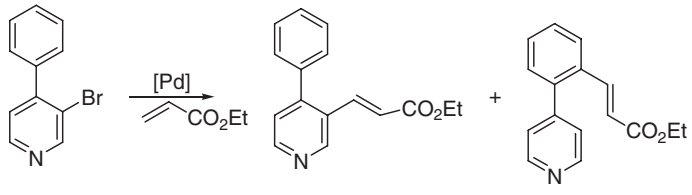
(155)

In certain cases a reductive elimination is prevented due to the unfavorable formation of the antiaromatic benzocyclobutadiene (Equation (155)). Annulated fulvenes and pentalenes are accessible by this methodology, in excellent yields (Equation (156)).[130,130a–130d]



(156)

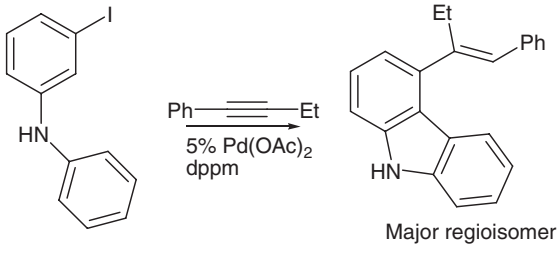
Many reactions have been recently reported, which involve palladium migration along an aromatic skeleton. For example, a Heck-type process led to the anticipated 3-substituted pyridyl, Heck product as well as a "crossover" product (Equation (157)).



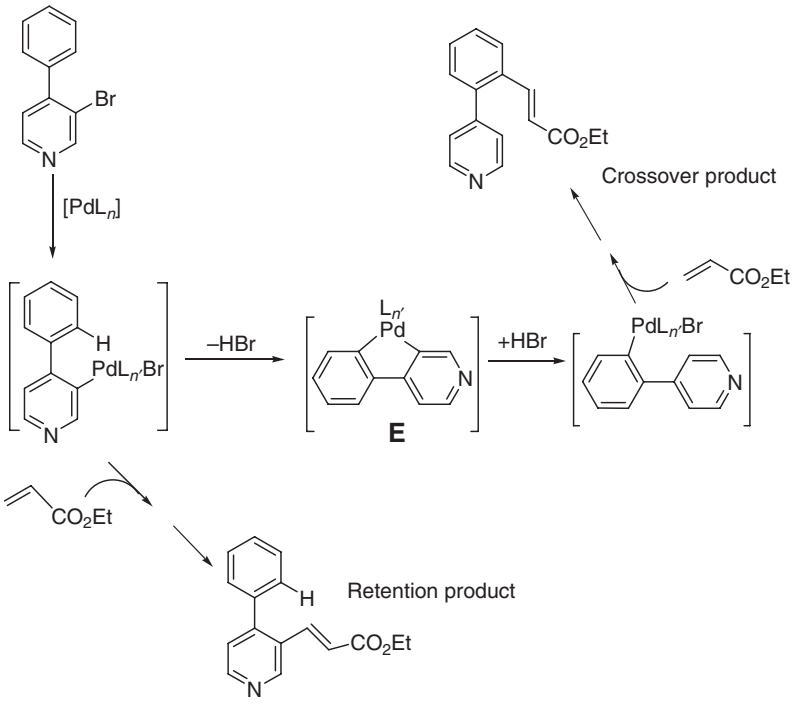
(157)

A mechanism involving a palladacycle **E** has been proposed to explain the formation of such a crossover product (Scheme 28).[131]

Carbazoles are also synthesized by a concomitant Pd migration/cross-coupling process involving the coupling of *N*-(3-iodophenyl)anilines with disubstituted alkynes (Equation (158)).[132]



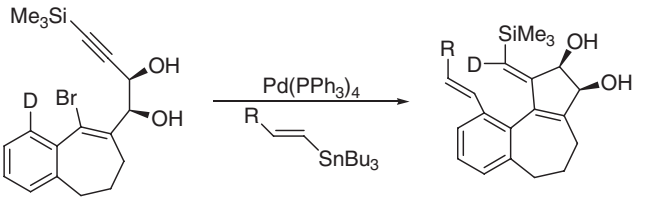
(158)



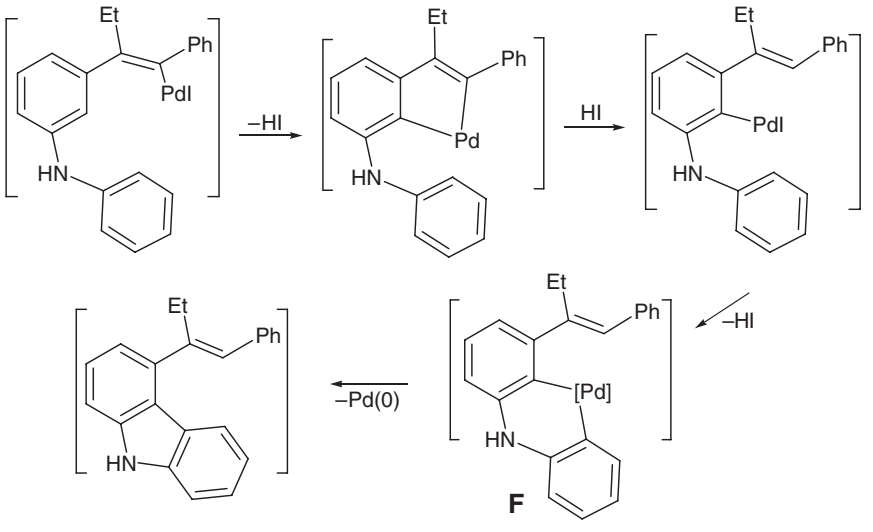
Scheme 28

A palladacyclic intermediate **F** was proposed to explain this unusual reaction sequence (Scheme 29).

A palladium-mediated Stille-C–H functionalization process was recently disclosed. Deuteration of the fused arene led to 92% D-incorporation in the vinylsilane product, suggesting a Pd-migration process (Equation (159)).[133]

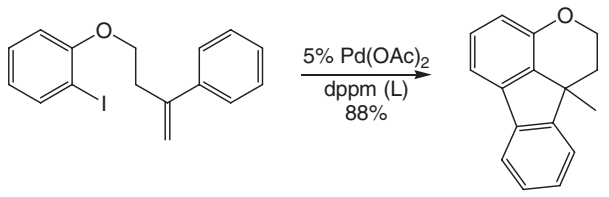


(159)



Scheme 29

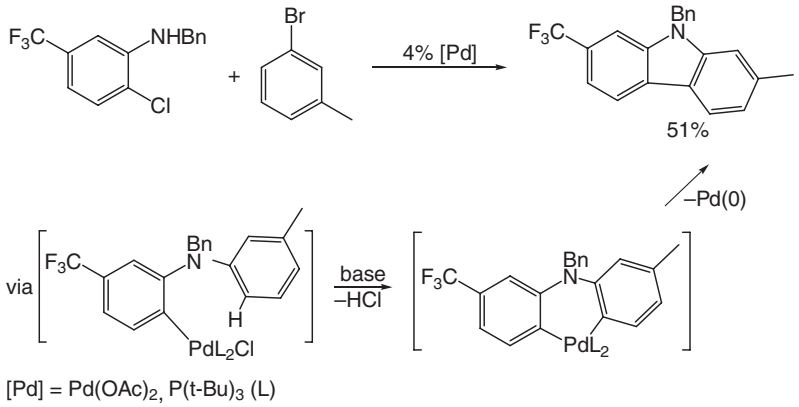
A cascade reaction involving multiple C–H functionalizations has been employed for the formation of bicyclic heterocycles with palladium catalysis (Equation (160)).[134]



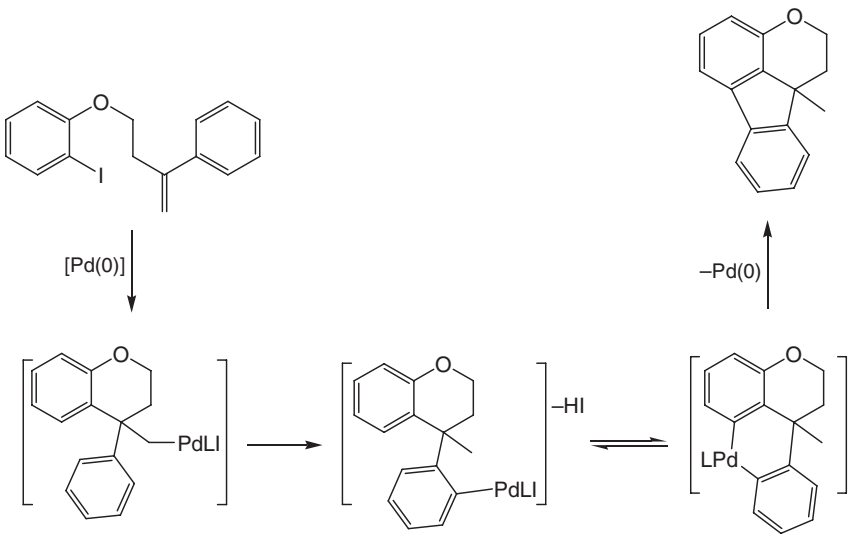
(160)

The proposed mechanism involves the initial oxidative addition of Pd(0) followed by a series of palladium migrations (Scheme 30).

Intramolecular C–H arylations have been described and are mediated by a variety of palladium complexes, affording a host of heterocyclic products. Carbazoles can be synthesized by a sequential amination/C–H functionalization process (Equation (161)).[135]

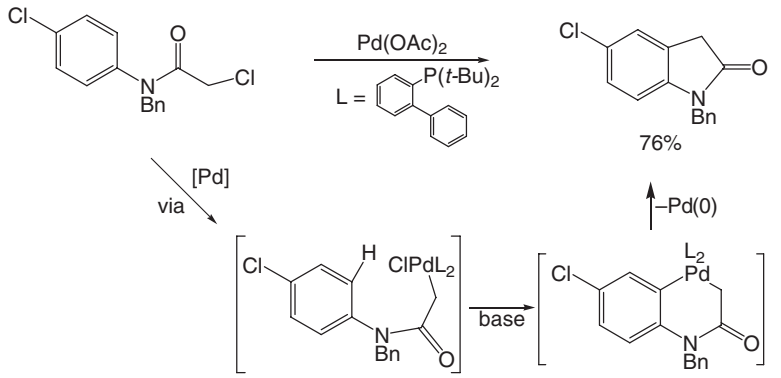


(161)



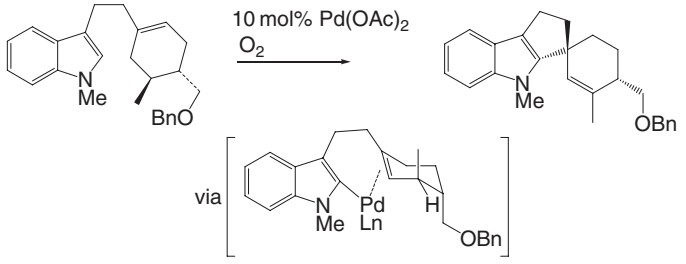
Scheme 30

The above reaction is complementary to a related heterocyclization process, which may proceed by a C–H functionalization of the aryl group (Equation (162)).[136]



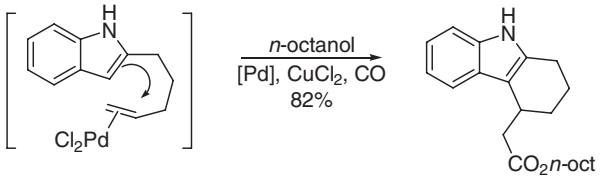
(162)

A palladium-catalyzed aerobic oxidative annulation of indoles, in the presence of ethyl nicotinate, has been disclosed.[137,137a] The stereochemical outcome of this reaction indicates that an initial C–H functionalization at C(2) of the indole, followed by *syn*-carbopalladation and *syn*-β-H-elimination, operates (Equation (163)).[137] This process has also been employed for the synthesis of benzofuran analogs.[137a]



(163)

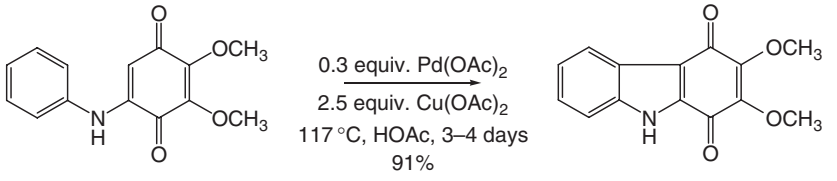
This is opposed to attack of the indole onto the Pd-coordinated, hence activated, olefin (Equation (164)).[138]



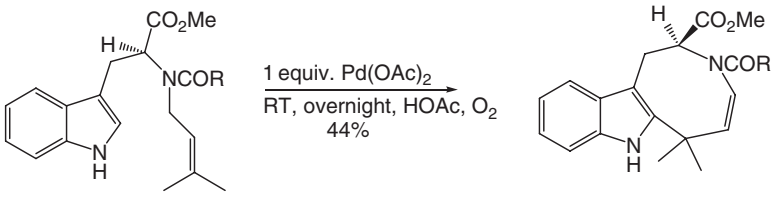
(164)

[Pd] = $PdCl_2(CH_3CN)_2$

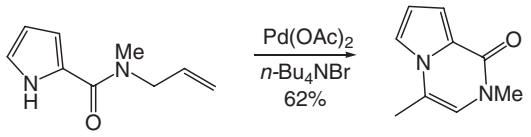
An earlier example of a palladium-catalyzed oxidative coupling was employed in the synthesis of an important intermediate in the synthesis of the antioxidant carbazoquinocin C (Equation (165)). High catalyst loadings, long reaction times, and rather harsh conditions were employed. A more recent stoichiometric cyclization occurred under milder conditions, affording an intermediate in the synthesis of Okaramine N (Equation (166)). Another recent example led to the formation of pyrrolo-pyrazines (Equation (167)).[139,139a,139b]



(165)

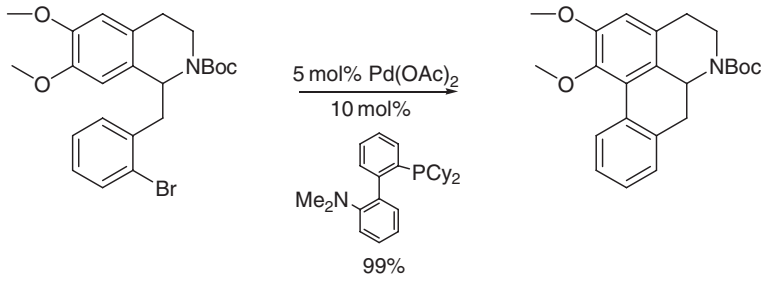


(166)

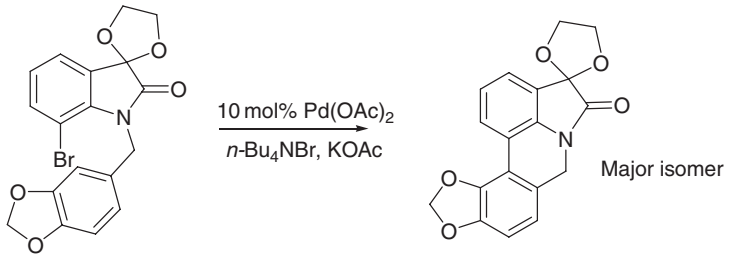


(167)

Intramolecular arylations have been used to form alkaloids (Equations (168) and (169)).[140,140a]

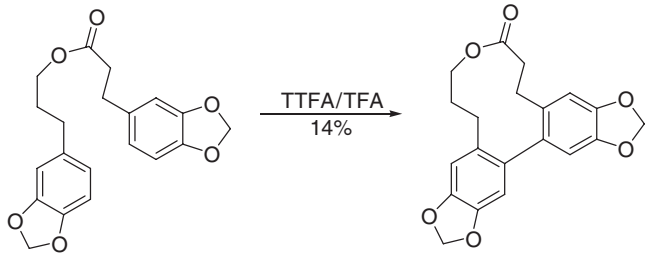


(168)

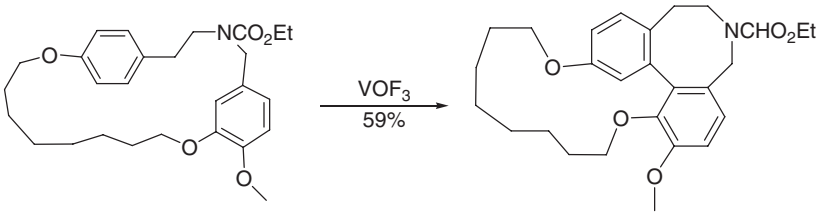


(169)

Double C–H functionalizations involving biphenyl couplings can be mediated by other transition metal complexes (e.g., VOF_3, RuO_2/TFA, Fe(III), TTFA (Tl_2O_3/TFA)), or by light. An early review highlighted this chemistry (Equations (170) and (171)).[141]

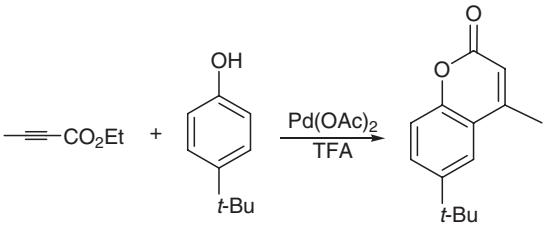


(170)

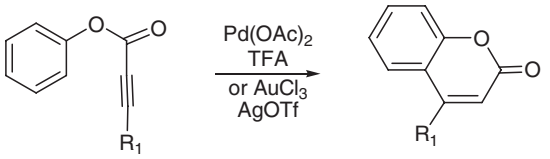


(171)

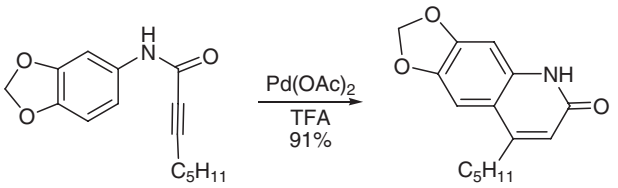
Coumarins and quinolinones can be formed by hydroarylation reactions of alkynes (Equations (172)–(174)).[71,142,142a]



(172)

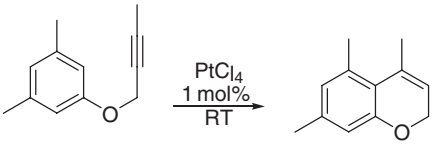


(173)

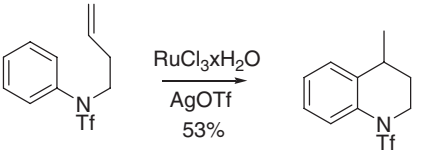


(174)

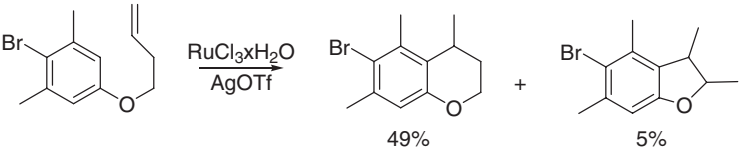
Similar intramolecular hydroarylations of alkynes and alkenes, which obviate the need for a halide or triflate group on the aryl ring, are now well established. Sames' group screened over 60 potential catalysts and over 200 reaction conditions, and found that Ru(III) complexes and a silver salt were optimal. This process appears to tolerate steric hindrance and halogen substrates on the arene (Equations (175)–(177)). The reaction is thought to involve alkene–Ru coordination and an electrophilic pathway rather than a formal C–H activation of the arene followed by alkene hydrometallation, and advocates the necessary cautious approach to labeling this reaction as a C–H functionalization process.[143,143a,143b]



(175)

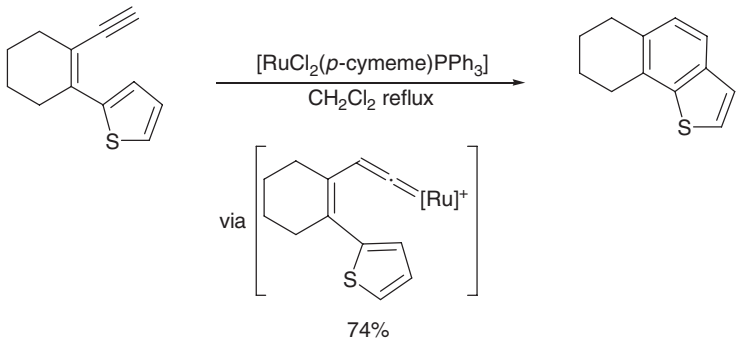


(176)



(177)

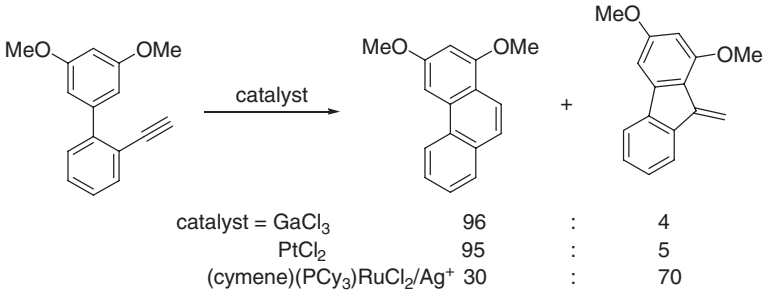
Electrocyclizations of arenes and alkynes lead to interesting fused systems via vinylidene intermediates (Equation (178)).[144]



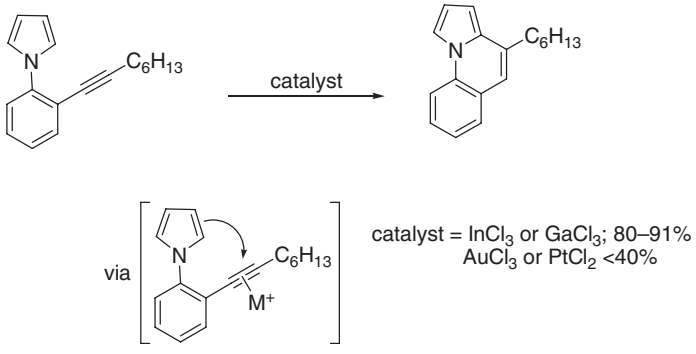
(178)

An excellent recent review covers metal-catalyzed alkyne hydroarylations in detail.[145]

Catalytic quantities of transition- or non-transition metals promote the cyclization of 2-alkynynylbiphenyl analogs to phenanthrene or fulvene analogs. The mechanism is thought to involve activation of the alkyne by metal coordination, prior to cyclization (Equations (179) and (180)).[146]

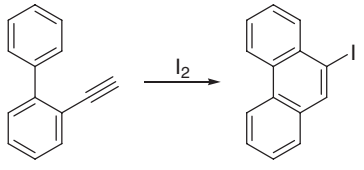


(179)



(180)

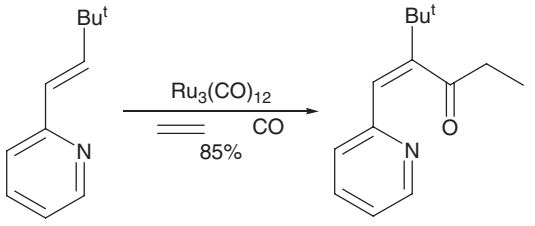
Iodine (or ICl, NBS, $Ipyr_2BF_4$) promotes similar cyclizations, probably via an electrophilic mechanism (Equation (181)).[147,147a]



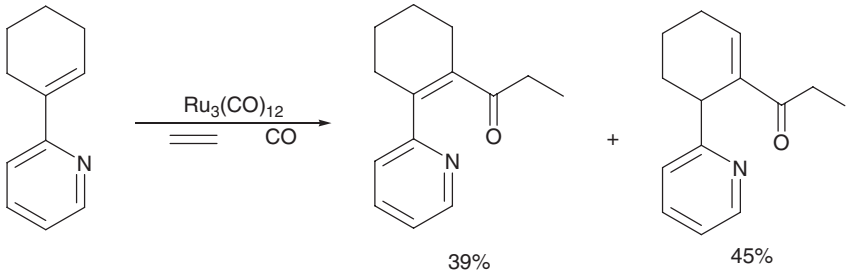
(181)

10.03.3.3 Functionalization of Olefins

Carbonylations at olefinic sp^2-C–H bonds have been exploited (Equations (182) and (183)).[148]

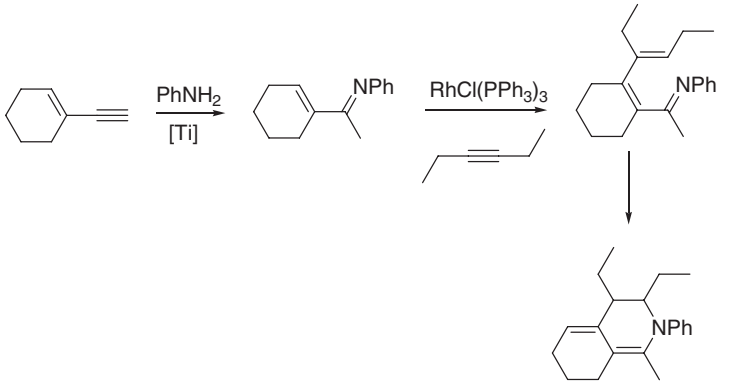


(182)



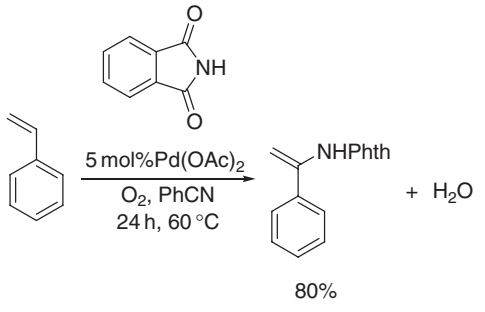
(183)

A titanium-mediated amination followed by a directed rhodium-catalyzed C–H functionalization of an olefinic C–H leads to heterocycles (Equation (184)).[149]



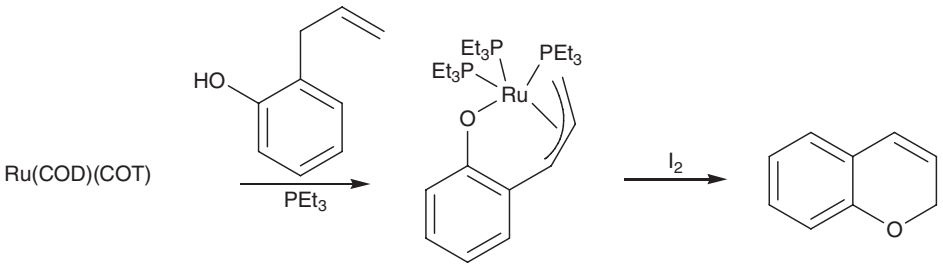
(184)

Oxidative aminations of olefins have recently been reported (Equation (185)).[43]



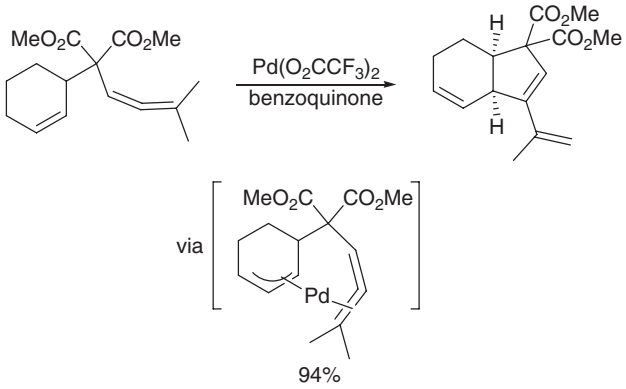
(185)

Allyl phenyl ethers are activated by a ruthenium(0) complex, ultimately affording a *2H*-benzopyran (Equation (186)).[150]



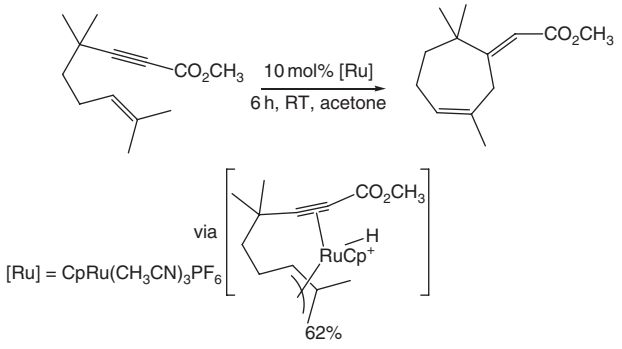
(186)

Oxidative cyclizations involving π-allyl complexes have been reported and are thought to involve *syn*-CH cleavage (Equation (187)).[151]



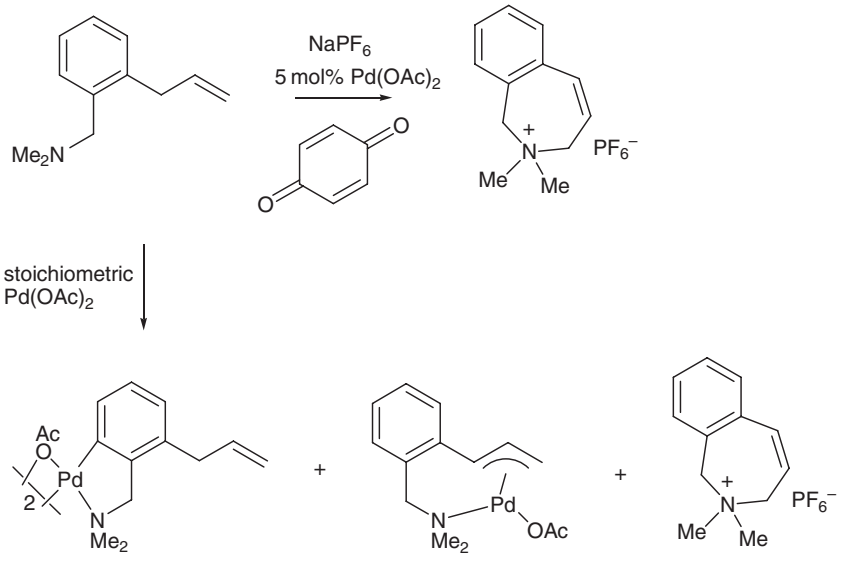
(187)

Michael additions of π-allyl species to alkynes were employed for the synthesis of elaborated carbocycles as in the ruthenium-catalyzed cycloisomerization of 1,6-enynes (Equation (188)).[152]



(188)

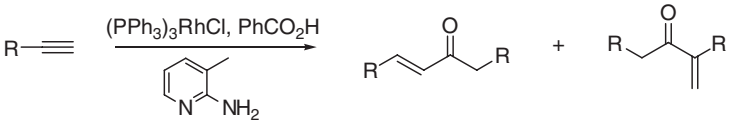
Other allylic functionalizations have been reported. The catalytic heteroannulation of allylic benzylamines leads to heterocyclic products, whereas a stoichiometric version of this reaction leads to both allylic and aryl functionalization (Equation (189)).[153,153a]



(189)

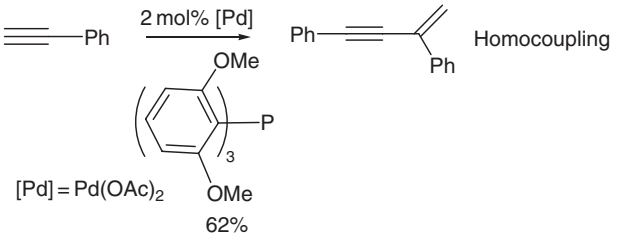
10.03.3.4 Functionalization of Alkynes

The rhodium-catalyzed intermolecular hydrative dimerization of 1-alkynes leads to α,β-unsaturated ketones (Equation (190)).[154]



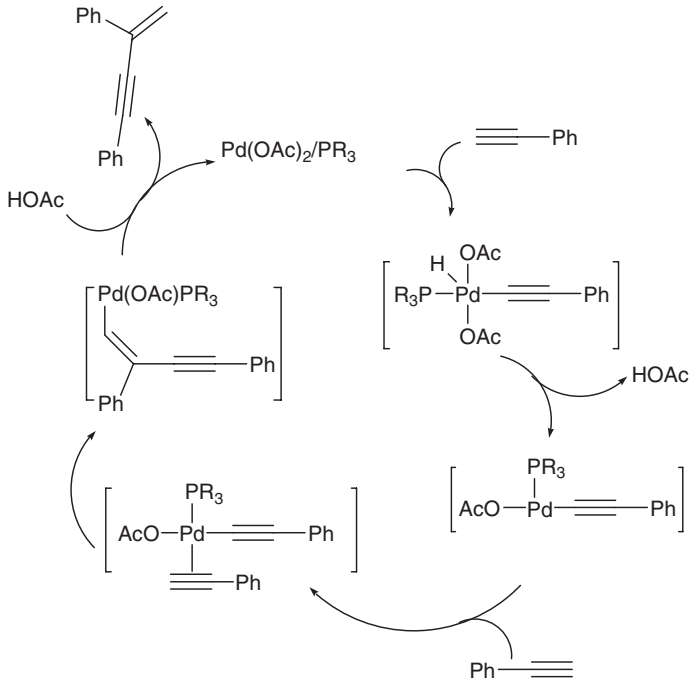
(190)

Trost's group examined the possibility of carrying out cross-coupling reactions of alkynes and transformed this into a very powerful synthetic method. Either homocoupling or perhaps, more interesting, heterocoupling procedures were performed using catalytic amounts of a palladium salt (Equation (191)).



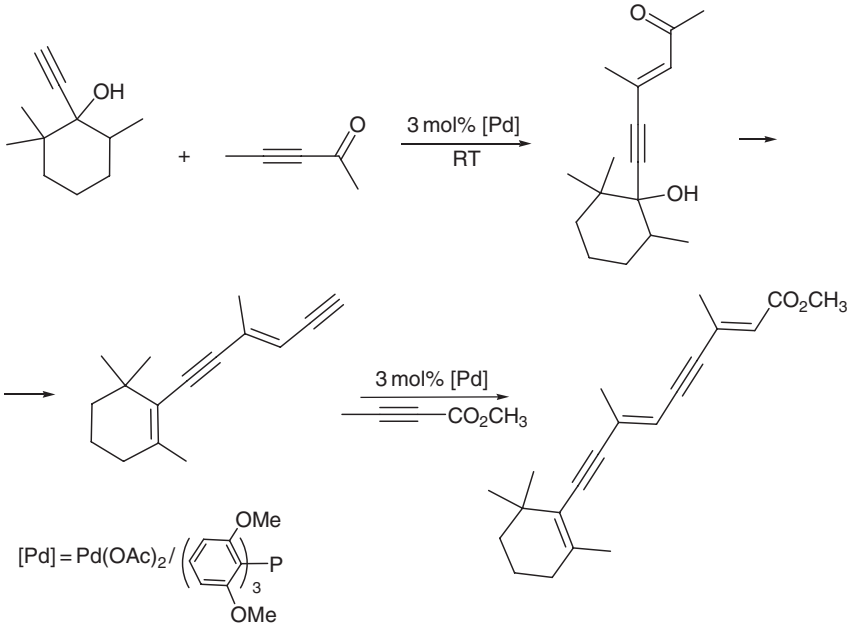
(191)

These reactions probably proceed via C–H activation of the terminal alkyne (Scheme 31).



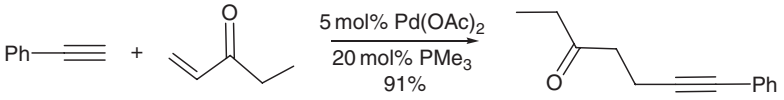
Scheme 31

A retinoid analog was synthesized using the cross-coupling method (Equation (192)).[155]



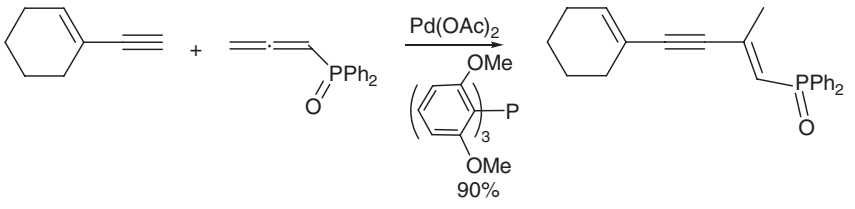
(192)

The addition of 1-alkynes to α,β-unsaturated ketones in water is catalyzed by a palladium(II)/phosphine combination. Deuteration studies suggest that this reaction proceeds via carbometallation of the olefinic moiety by an alkynylpalladium intermediate (Equation (193)).[156]



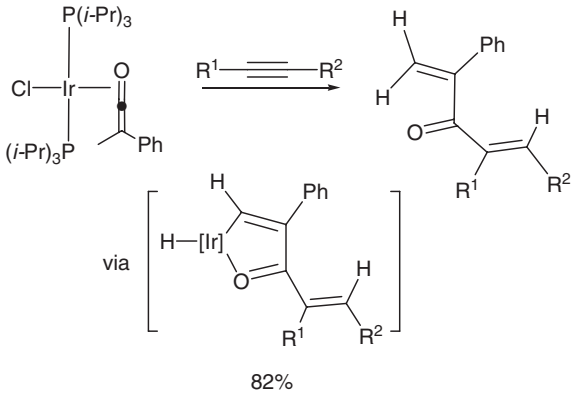
(193)

The addition of terminal alkynes to allenylphosphine oxides is catalyzed by palladium complexes (Equation (194)).[157]



(194)

A stoichiometric double C–H functionalization mediated by an iridium ketene complex leads to 1,4-dien-3-ones, assumed to proceed via two C–H functionalizations at the same carbon atom (Equation (195)).[158]

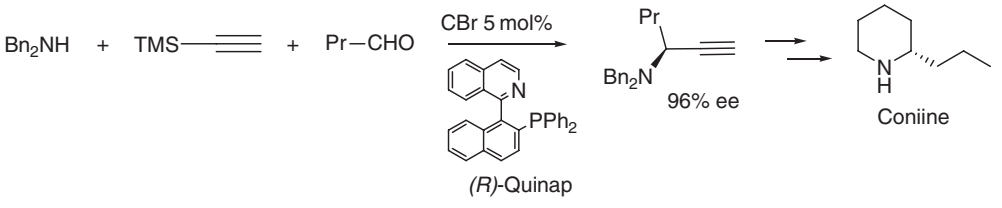


(195)

10.03.4 Application to Organic Syntheses

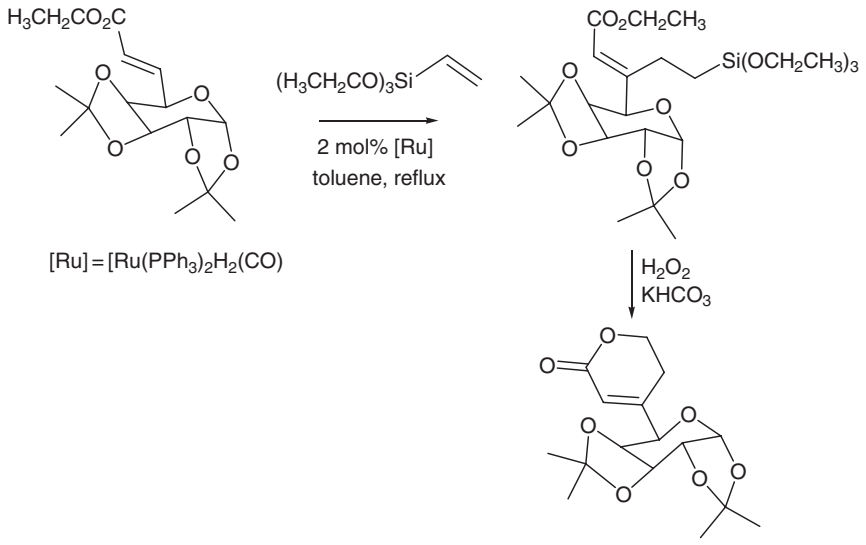
Chemists are exploiting catalytic C–H functionalization methodology for the synthesis of natural products or molecules of increasing complexity often with high degrees of regio-, chemo- and stereoselectivities.

A copper-catalyzed one-pot three-component atom-economical C–H functionalization process was used to form enantioenriched propargylamines. This protocol was also employed for the synthesis of the alkaloid (*S*)-(+)-coniine (Equation (196)).[159,159a]



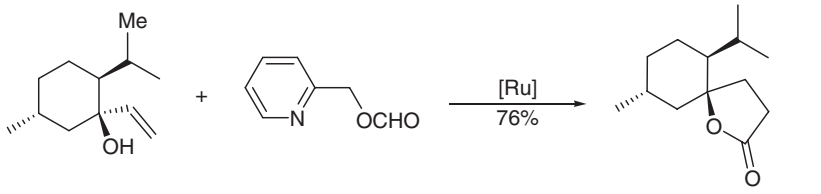
(196)

Stereoselective Murai-type couplings can be carried out on conjugated alkene systems. Such a procedure was employed in the synthesis of the elaborated lactone **G** (Equation (197)).[160]

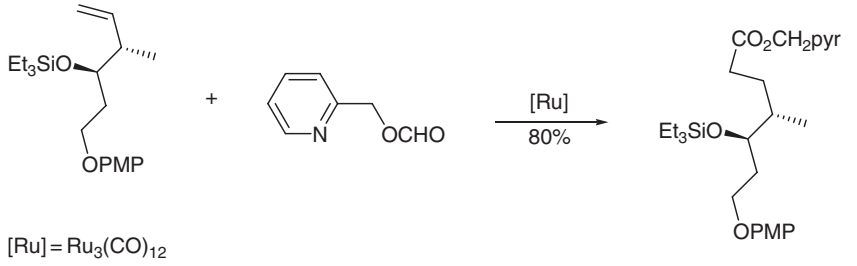


(197)

Ruthenium-catalyzed hydroesterification/lactonizations are also known (Equation (198) and (199)).[161]



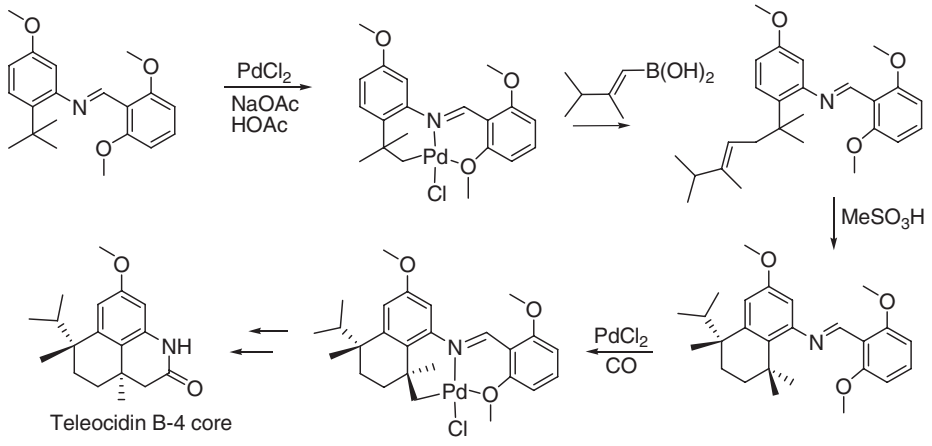
(198)



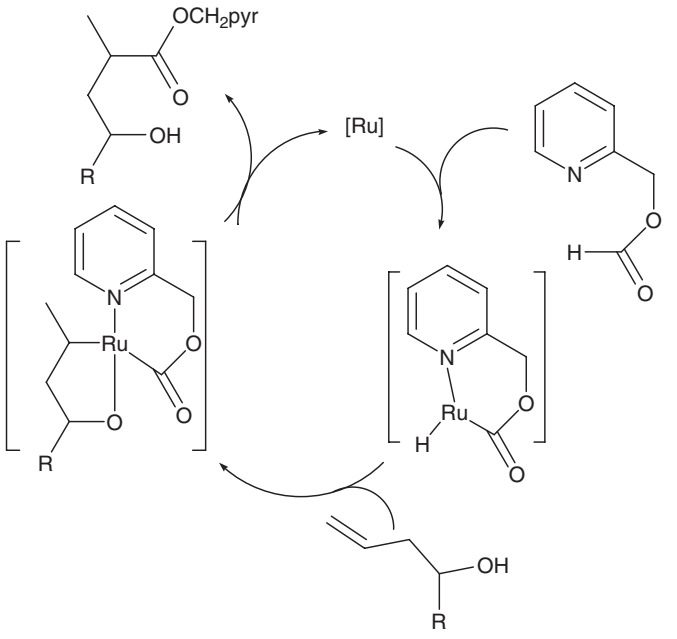
(199)

A general mechanism for these transformations has been proposed, involving chelation-induced C–H activation (Scheme 32).

A series of remarkable stoichiometric CH functionalization reactions have been employed, including transmetallation with a vinylboronic acid moiety, to synthesize the core of teleocidin B-4 (Equation (200)).[162]

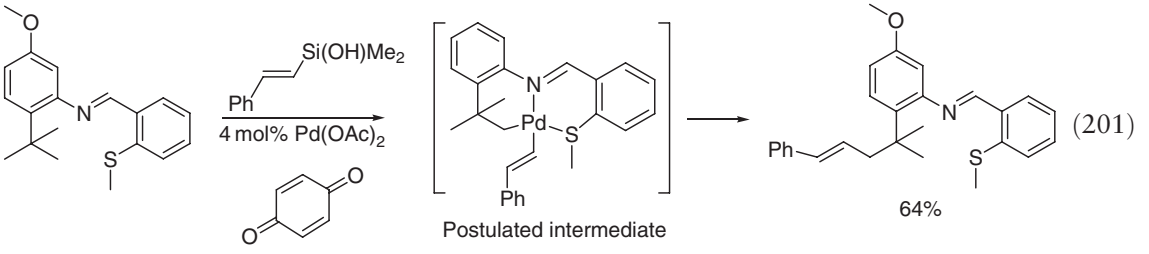


(200)



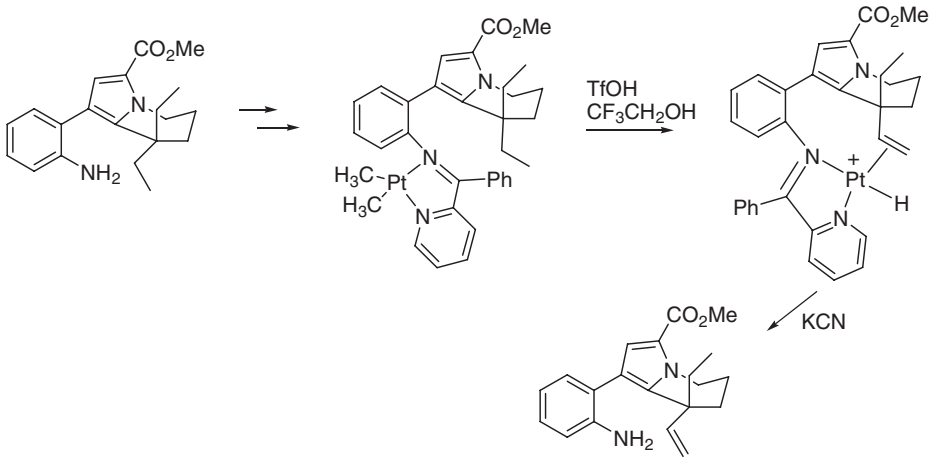
Scheme 32

A catalytic variant of this process exists, enabling C–C bond formation involving palladacyclic intermediates (Equation (201)).[163]



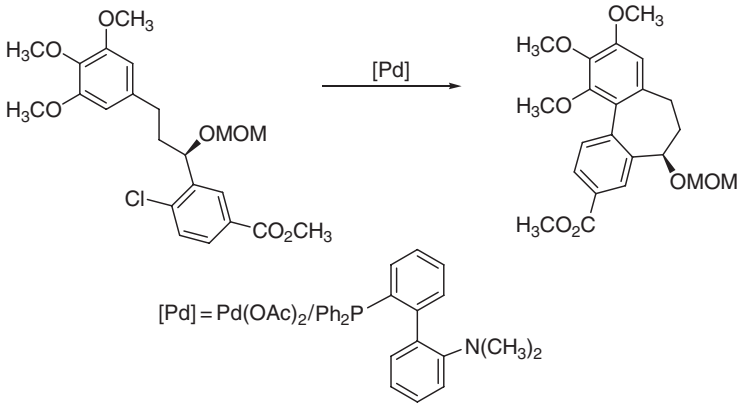
(201)

Intramolecular C–H functionalizations were employed for the synthesis of a precursor to (−)-rhazinilam, an antitumor agent. Using a chiral auxiliary good ee's were achieved (Equation (202)).[164]



(202)

An allocolchicine synthesis relied on an intramolecular arylation of an aryl chloride (Equation (203)).[165]



(203)

10.03.5 Conclusion

We hope to have demonstrated that the area of catalytic C–H functionalization chemistry has now established itself as an extremely useful scientific discipline, with potential applications ranging from industrial catalysis to organic synthesis. Theoretical, mechanistic, and synthetic organometallic chemistry gratifyingly continues to flourish, and new reaction mechanisms and novel transition metal complexes should open new avenues for atom-economical catalytic applications. Key achievements over the past 10 years include alkane functionalization employing Shilov-type and other chemistries, catalytic borylation of arenes and alkanes, as well as the functionalization of aromatic and heteroarenes by C–H functionalization chemistry, as opposed to more traditional Heck/Suzuki methodologies. Natural product total synthesis employing C–H functionalization heralds a new dawn for transition metal-mediated organic synthesis.

However, there still remain limitations to C–H functionalization chemistry in order to achieve the goal of high turnover, selective, clean catalysis employing mild conditions. It is hoped that these issues will be addressed and at least some of the obstacles will be overcome in the next decade.

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10.04
Synthetic Reactions via C–H Bond Activation: Carbene and Nitrene C–H Insertion

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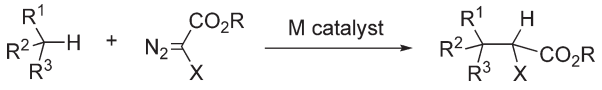
10.04.1 Introduction

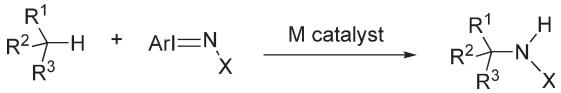
Effective methods for the functionalization of unactivated C–H bonds offer opportunities for developing new strategies for organic synthesis.[1–6] C–H activation has been a very active area of research for the organometallic community. A number of metal complexes have been discovered that will effectively functionalize a C–H bond by oxidative addition of the metal across the C–H bond.[7–22] Several of these methods have been developed into catalytic processes and are being recognized as emerging new strategic reactions for organic synthesis.[15,23–34]

An alternative organometallic approach for functionalizing C–H bonds is by means of metal carbene- or metal nitrene-induced C–H insertions (Equations (1) and (2)).[35,36] A major advantage of this approach over other methods is that the reaction is routinely catalytic and by using chiral catalysts, high enantioselectivity can be achieved. One of the major challenges with the metal carbene- and metal nitrene-induced C–H insertion is controlling the

regiochemistry of the process. Over the last decade, considerable progress has been made in this area such that the metal carbene and metal nitrene C–H insertions can be considered as the most general methods to date for regio-, diastereo-, and enantioselective C–H functionalization.[35,36]



(1)



(2)

Since the edition of COMC(1995), the intermolecular C–H insertion chemistry of metal carbenes and metal nitrenes has undergone explosive growth.[35–45] The early studies on intermolecular C–H insertions of metal carbenes established the basic concept with various systems but the reaction was not considered to have much synthetic utility.[46–48] The major problems with the reaction were the limited chemoselectivity in the process and the high tendency of the standard carbenoid, derived from ethyl diazoacetate, to undergo carbene dimerization instead of the C–H insertion reaction. Two major advances have been made in the last 10 years, which have overcome these problems. The first is the development of copper and silver scorpionate complexes as highly effective catalysts for the C–H insertion chemistry of ethyl diazoacetate.[49–61] The second is the discovery that donor/acceptor-substituted metal carbenes are much more chemoselective than the conventional metal carbenes.[37–43] The C–H insertion chemistry has now been developed to such a stage that it can be considered as a competing strategic reaction to some of the classic transformations of organic synthesis. The full synthetic potential of this chemistry is described in Section 10.04.2.

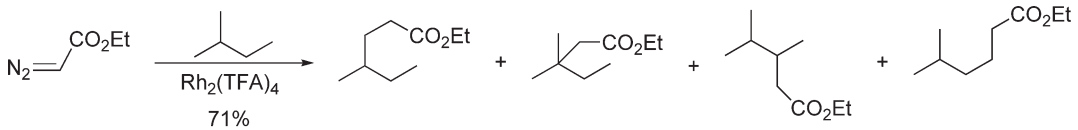
The intramolecular C–H insertion of metal carbenes was a well-established reaction at the time of the edition of COMC(1995), and the general reactivity profile has already been discussed.[62] The regiochemical issues can be effectively controlled because the formation of five-membered rings is generally favored. A few examples of highly enantioselective transformations were discussed in the previous edition.[62] Since then, the enantioselective intramolecular C–H insertion has become broadly applicable with the advent of a range of new chiral catalysts.[63–70] Furthermore, it has become recognized that other ring sizes can be formed by judicious choice of substrate and catalyst. These new developments and applications in synthesis are described in Section 10.04.3.

In recent years, the related C–H insertion chemistry of nitrenes has gained considerable momentum.[36] Effective chiral catalysts have been developed as well as new methods for generation of the nitrene precursors. Even more impressive has been the application of this chemistry to the synthesis of complex natural products. The scope of this chemistry is described in Section 10.04.4.

10.04.2 Intermolecular Carbene C–H Insertion

10.04.2.1 C–H Insertion of Alkanes

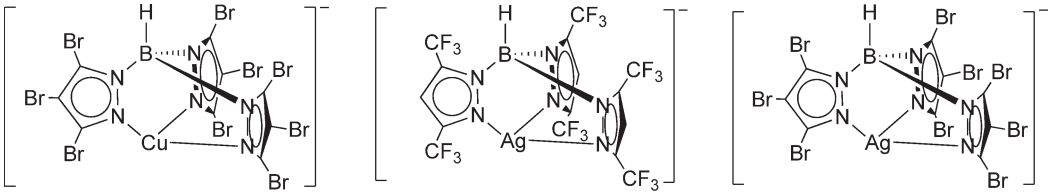
The selective C–H functionalization of alkanes has been a long-standing goal of the organometallic community. The intermolecular C–H insertion chemistry has arguably become, over the last decade, one of the most efficient processes for such a functionalization. Although there are several early papers on the C–H functionalization of alkanes by ethyl diazoacetate,[71–74] the reaction was not considered initially to be of broad synthetic utility.[46] An illustrative example from the early literature is the reaction of ethyl diazoacetate with 2-methylbutane, catalyzed by rhodium trifluoroacetate, in which all four possible products were formed (Equation (3)).[72,73] The product ratio could be influenced by the nature of the catalyst but the formation of mixtures could not be effectively controlled.



(3)

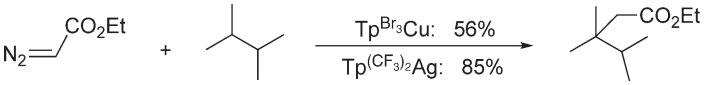
A major advance in the intermolecular C–H insertion chemistry of ethyl diazoacetate was the discovery that copper and silver scorpionate catalysts gave very clean transformations.[50–61] The regioselectivity of the C–H insertion was

much better than what had been previously achieved with rhodium catalysts. The most effective copper scorpionate catalyst was the tribromo derivative $Tp^{Br_3}Cu$, while the silver catalyst containing trifluoromethyl groups, $Tp^{(CF_3)_2}Ag$, gave fairly similar selectivity. The silver tribromo catalyst $Tp^{Br_3}Ag$ appeared to be much more electron deficient than the other two and the resulting C–H functionalization chemistry was less regioselective.

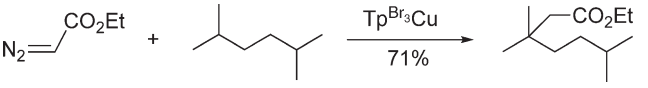


$Tp^{Br_3}Cu$ $Tp^{(CF_3)_2}Ag$ $Tp^{Br_3}Ag$

The C–H functionalization of certain hydrocarbons, catalyzed by either $Tp^{Br_3}Cu$ or $Tp^{(CF_3)_2}Ag$, can be highly regioselective. Representative examples are the reactions with 2,3-dimethylbutane (Equation (4)) and 2,5-dimethylhexane (Equation (5)).[49,56] In these cases, C–H insertion into the tertiary C–H site was favored over reactions at the primary and sterically crowded secondary C–H sites.

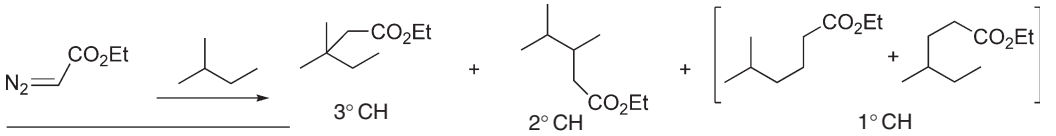


(4)



(5)

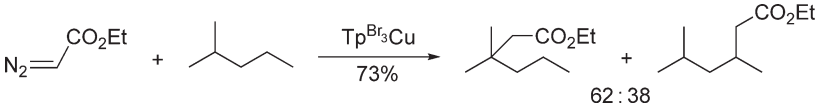
The regioselectivity of the C–H insertion is very dependent on the nature of the catalysts. A good example of this is the reaction of 2-methylbutane (Equation (6)).[56] As can be seen in the reactions with 2-methylbutane, the silver and copper catalysts $Tp^{Br_3}Cu$ and $Tp^{(CF_3)_2}Ag$ resulted in competitive C–H insertions at the tertiary and secondary C–H bonds. In contrast, the more electrophilic silver catalyst $Tp^{Br_3}Ag$ was less discriminating and all four possible products were formed, comparable to the earlier results with the rhodium catalysts.



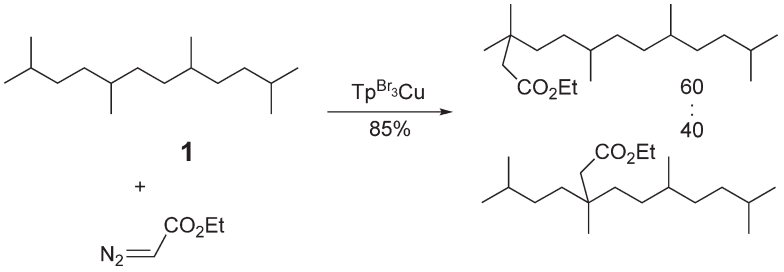
	3° : 2° : 1°
$Tp^{Br_3}Cu$:	80 : 20 : 0
$Tp^{(CF_3)_2}Ag$:	35 : 65 : 0
$Tp^{Br_3}Ag$:	21 : 36 : 41

(6)

The reactivity between a tertiary C–H site and a sterically accessible, secondary C–H site is relatively even in the reactions catalyzed by $Tp^{Br_3}Cu$. This can be seen in the reaction with 2-methylpentane (Equation (7)),[38,49,56] which gave rise to a mixture of only two products. No insertion into the methyl or the sterically crowded methylene C–H bonds was seen. The C–H insertion has the possibility of selectively functionalizing relatively complex alkanes. An impressive example is the C–H insertion to **1** (Equation (8)).[56] A mixture of two alkylation products derived from insertion at the tertiary C–H bonds was obtained. This transformation has been extended to the selective functionalization of hydrocarbon polymers.[75]

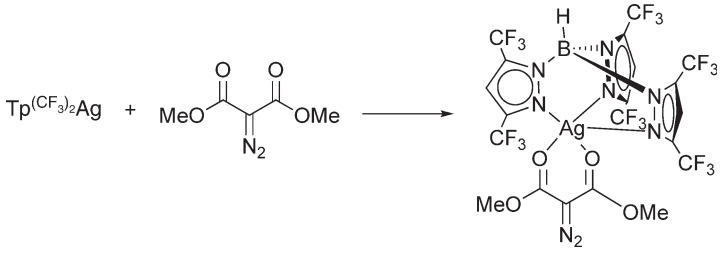


(7)



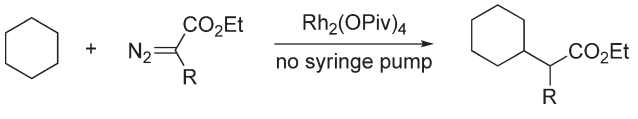
(8)

So far, the reports on copper and silver scorpionate catalysis are limited to ethyl diazoacetate as the carbenoid precursor, and it is questionable whether these catalysts can be used with other classes of diazo compounds. The reaction of the more stable methyl diazomalonate resulted in the formation of a remarkable O-bound diazo complex, which was thermally stable (Equation (9)).[76]



(9)

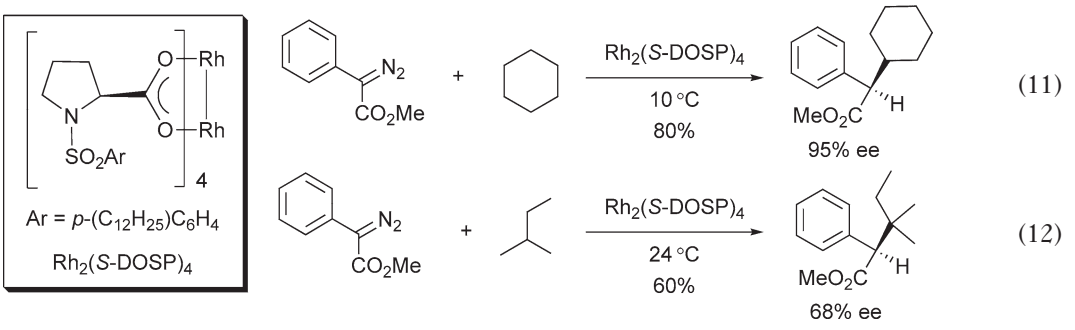
An alternative strategy for selective intermolecular C–H insertions has been the use of rhodium carbenoid systems that are more stable than the conventional carbenoids derived from ethyl diazoacetate. Carbenoids derived from aryldiazoacetates and vinyldiazoacetates, so-called donor/acceptor-substituted carbenoids, have been found to display a very different reactivity profile compared to the traditional carbenoids.[44] A clear example of this effect is the rhodium pivalate-catalyzed C–H insertion into cyclohexane.[77] The reaction with ethyl diazoacetate gave the product only in 10% yield, while the parallel reaction with ethyl phenyldiazoacetate gave the product in 94% yield (Equation (10)). In the first case, carbene dimerization was the dominant reaction, while this was not observed with the donor/acceptor-substituted carbenoids.



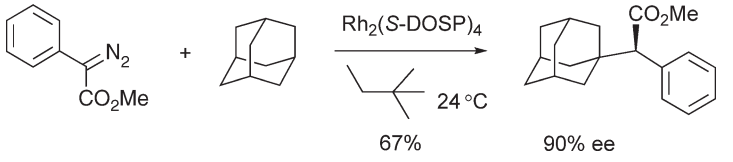
R	*Yield* (%)
H	10
Ph	94

(10)

The rhodium(II) prolinate catalyst, Rh_2(*S*-DOSP)$_4$, has been shown to be very effective in enantioselective transformations of donor/acceptor-substituted carbenoids. The Rh_2(*S*-DOSP)$_4$-catalyzed reaction of methyl phenyldiazoacetate, with cyclohexane as solvent, generated the C–H activation product in 95% ee (Equation (11)).[78] This reaction could be extended to a range of substituted aryldiazoacetates (*ortho*-, *meta*- or *para*-substituted) and other cycloalkanes. The yields and enantioselectivities were routinely high, although more vigorous reaction conditions were required for the *p*-methoxyphenyl derivative, presumably because this carbenoid would be less electrophilic than the other carbenoids. The donor/acceptor-substituted carbenoids display much higher regioselectivity than the carbenoid derived from ethyl diazoacetate. This is readily seen in the reaction of methyl phenyldiazoacetate with 2-methylbutane as solvent (Equation (12)).[78] The only C–H insertion product was derived from an attack at the tertiary C–H bond. This is in sharp contrast to the rhodium carboxylate-catalyzed reactions with ethyl diazoacetate, which gave a mixture of all four possible products.[72,73] Even the improved copper and silver scorpionate catalysts gave a mixture of at least two products in the ethyl diazoacetate reaction.[38,49,56]



The C–H activation chemistry can also be conducted on solid hydrocarbons, such as adamantane (Equation (13)).[78] A suitably inert solvent for such a reaction is 2,2-dimethylbutane. Rh_2(*S*-DOSP)$_4$-catalyzed decomposition of methyl phenyldiazoacetate in the presence of 2 equiv. of adamantane generated the C–H insertion product in 90% ee.



10.04.2.2 C–H Insertion as a Strategic Reaction

The C–H insertion of the donor/acceptor-substituted carbenoids is a general method for C–C bond formation. As will be discussed later, the chemistry is highly stereoselective and of broad synthetic utility. Consequently, the reaction can be considered as a strategic equivalent to several of the classic C–C bond formation methods of organic synthesis (Figure 1). Most notably, the carbenoid C–H insertion is strategically equivalent to an enolate disconnection, but depending on the functionality in the targets, the C–H insertion can be considered equivalent to other traditional disconnections. In order to illustrate the full synthetic potential of this chemistry, the reactions will be subdivided according to their equivalent classic reaction.

10.04.2.2.1 Enolate alkylation equivalent

The C–H insertion into alkanes described above is a surrogate of enolate alkylation (Figure 2). The two strategic reactions are complementary, because enolate alkylation is preferred at primary alkyl halides while the C–H activation tends to preferentially occur at tertiary C–H bonds.

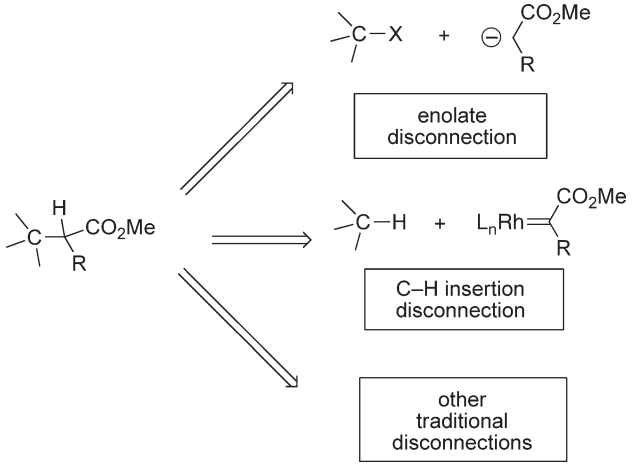


Figure 1 C–H insertion as a strategic reaction.

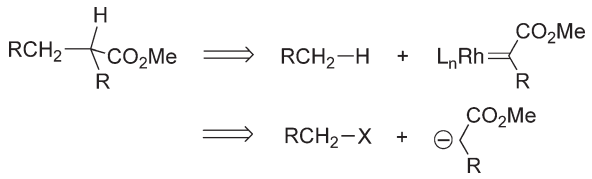
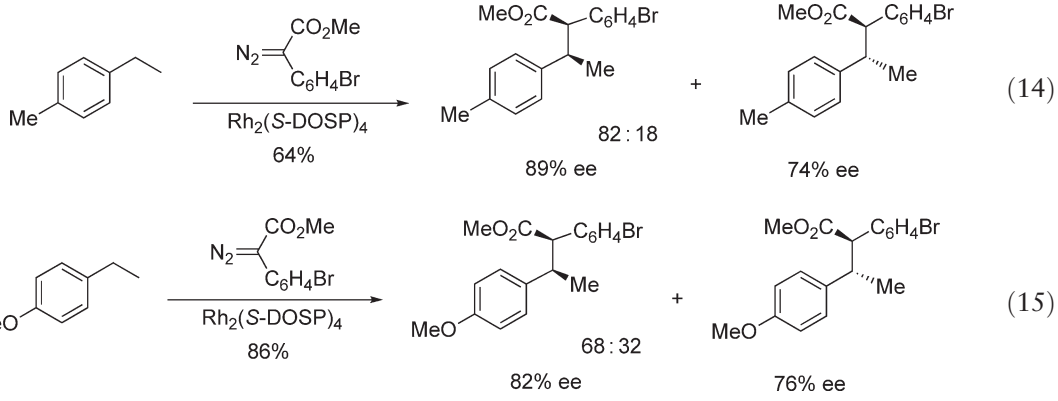


Figure 2 C–H insertion as an enolate alkylation equivalent.

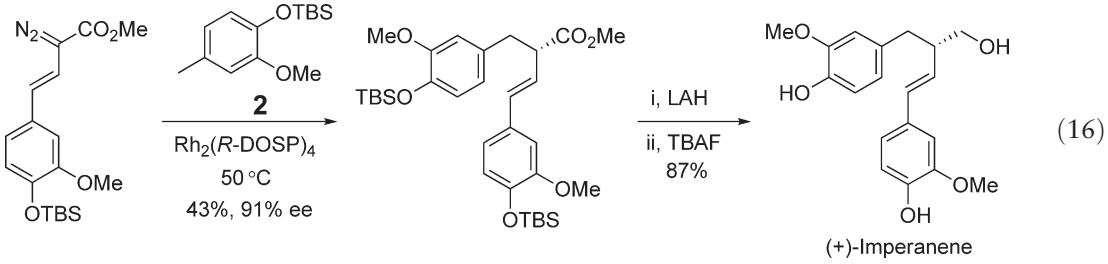
Insertion reactions at benzylic C–H bonds are another class of surrogate reactions of enolate alkylation. Illustrative examples of benzylic C–H functionalization with methyl 4-bromophenyldiazoacetate are shown in Equations (14) and (15).[79] The reaction with 4-ethyltoluene demonstrated the impressive selectivity favoring reaction at the methylene C–H bond over the methyl C–H bond (Equation (14)).[79] No side-reactions due to electrophilic reactions on the aromatic ring were seen as long as the benzene ring was at least 1,4-disubstituted. A higher yielding reaction was observed with 4-ethylanisole (Equation (15)), and a Hammet study showed that there was a buildup of positive charge on the benzylic carbon during the C–H insertion event.[79] Thus, electronic effects have a very important influence on the regioselectivity of the C–H functionalization. As will become more evident later, steric factors are also very important in the chemistry of the donor/acceptor carbenoids.



(14)

(15)

The benzylic C–H activation has been effectively applied to the enantioselective synthesis of (+)-imperanene (Equation (16)).[80] The key step was the Rh_2(*R*-DOSP)$_4$-catalyzed functionalization of the benzylic methyl C–H bond in arene **2**. An impressive feature of this transformation was that both the carbenoid and substrate contained very electron-rich aromatic rings, which were compatible with the highly electrophilic carbenoids because they were still sterically protected.



(16)

10.04.2.2.2 Aldol reaction equivalent

C–H insertion α to oxygen results in the formation of β-hydroxyester derivatives that are generally prepared from aldol reactions (Figure 3). For the C–H insertion chemistry to be a viable surrogate of the aldol reaction, the reaction would need to be highly diastereoselective and enantioselective.

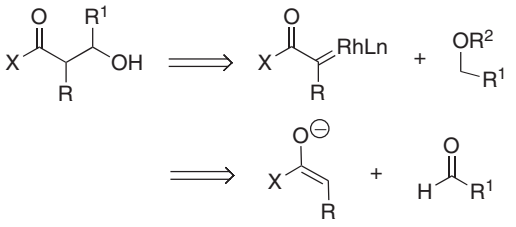
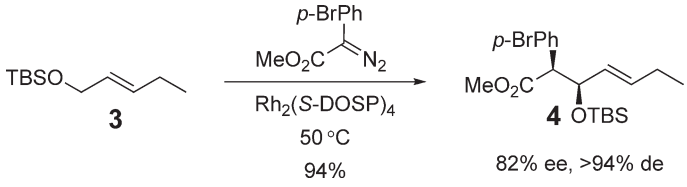
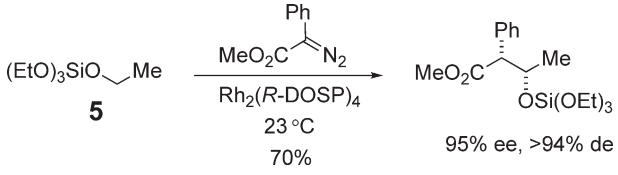


Figure 3 C–H Activation as an aldol reaction equivalent.

Several classes of silyl ethers have been shown to be excellent substrates for the C–H insertion chemistry of donor/acceptor-substituted carbenoids.[81] Effective C–H insertions predominantly occur at methylene sites. Primary sites are not sufficiently activated electronically while tertiary sites are sterically too crowded. Rh_2(*S*-DOSP)$_4$-catalyzed functionalization of the allyl silyl ether **3** resulted in a highly diastereoselective transformation, leading to the formation of the β-hydroxyester **4** in 94% yield and 82% ee (Equation (17)).[81] This example illustrates the regioselectivity of this chemistry, because **3** contains two allylic sites but only the methylene site adjacent to the siloxy group was functionalized. Even better substrates are the commercially available tetraalkoxysilanes such as **5**, because with these substrates, the high diastereoselectivity was retained while the enantioselectivity was increased (Equation (18)).[81]

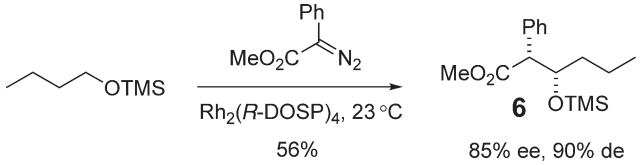


(17)

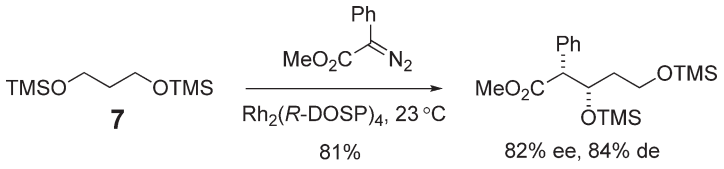


(18)

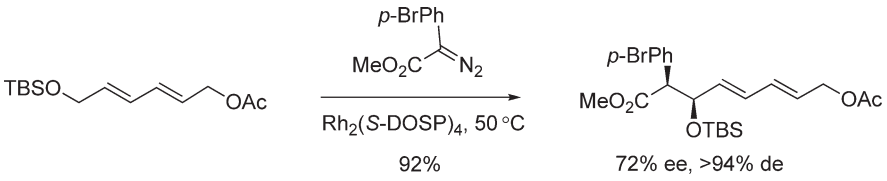
The C–H activation can also be conducted on the silyl derivatives of simple alcohols. C–H Insertion on the TMS derivative of butanol generated the β-hydroxy ester **6** in 56% yield and 85% ee (Equation (19)).[82] Similarly, the reaction of the bis-silylated diol **7** generated the C–H insertion product (Equation (20)). As only the siloxy group electronically activates these substrates, the most efficient reaction was achieved when a small silyl derivative was used. Indeed, an alcohol protected by a *tert*-butyldiphenylsilyl group was over 100 times less reactive than that protected by a trimethylsilyl group. Thus, the site of C–H functionalization in a complex substrate could be controlled by simply modifying the types of alcohol-protecting groups that are used. A specific example of the effect of different protecting groups is shown in Equation (21).[82] The acetoxy group is electron-withdrawing and would disfavor C–H insertion occurring adjacent to it. Consequently, the C–H insertion occurred exclusively at the siloxy position. The donor/acceptor-substituted carbenoid did not react with (*E*,*E*)-diene because it was sterically protected.



(19)



(20)

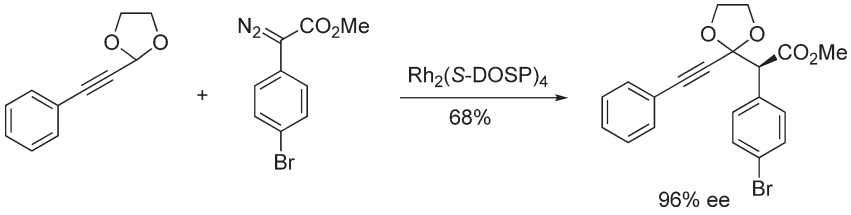


(21)

10.04.2.2.3 Claisen condensation equivalent

C–H functionalization at acetal C–H bonds generates protected forms of β-ketoesters (Figure 4). β-Ketoesters are often formed by Claisen condensation, but the asymmetric version is not a viable process, because the products would very likely racemize under the reaction conditions. Therefore, the C–H insertion equivalent to the Claisen condensation is very attractive, because the resulting β-ketoester is protected, which allows for the enantioselective version to be feasible (Figure 4).

The C–H insertion of acetals generates protected forms of β-ketoesters, as illustrated in Equation (22).[83] Effective reactions were possible with aryl, vinyl, and alkynyl ketals, but ketals of saturated aldehydes were not viable substrates.



(22)

10.04.2.2.4 Mannich reaction equivalent

C–H activation α to nitrogen generates β-amino acid derivatives (Figure 5). Therefore, the reaction can be considered to be a surrogate of the Mannich reaction.

A significant example of the C–H activation is the direct synthesis of the pharmaceutical agent *threo*-methylphenidate (Equation (23)).[84] The most effective catalyst for this reaction was Rh_2(*S*-biDOSP)$_2$, the bridged version of the standard prolinate catalyst. A 3 : 1 mixture of diastereomers was produced, from which the active ingredient *threo*-methylphenidate could be isolated in 52% yield and 86% ee. The stereochemical outcome of the C–H insertion was very dependent on the ring size. Rh_2(*S*-DOSP)$_4$-catalyzed reaction of methyl phenyldiazoacetate with *N*-Boc-pyrrolidine generated the *erythro* product with excellent stereocontrol (94% ee, 92% de; Equation (24)).[84] Thus, the major diastereomer of the product switches from the reaction of *N*-Boc-piperidine to *N*-Boc-pyrrolidine.

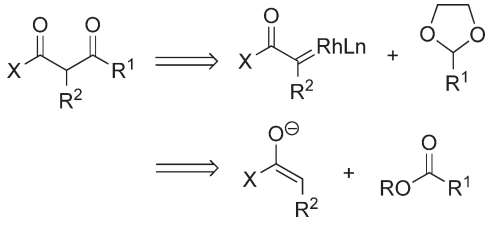


Figure 4 C–H activation as a Claisen condensation equivalent.

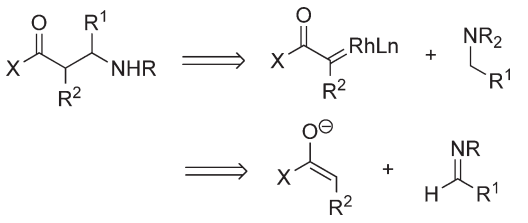
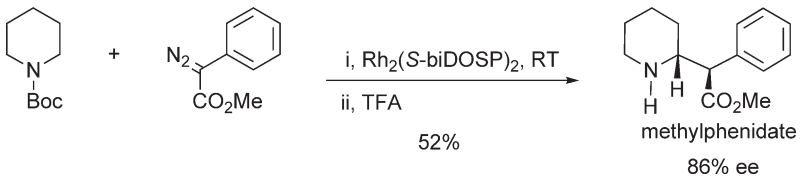
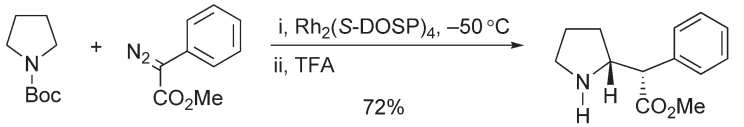


Figure 5 C–H activation as a Mannich reaction equivalent.

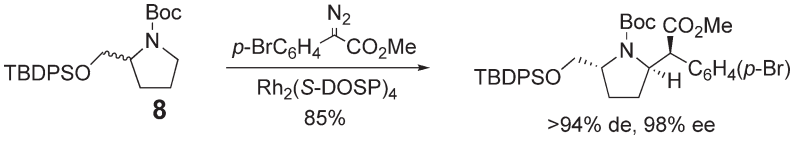


(23)

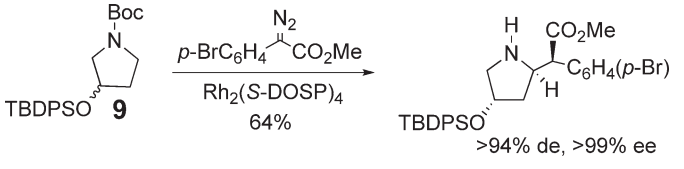


(24)

The reaction can be extended to more elaborate systems as shown in the reactions of the substituted pyrrolidines (Equations (25) and (26)).[85,86] Even though the 2-substituted pyrrolidine **8** has three electronically activated sites, two are sterically crowded. Furthermore, the Rh_2(*S*-DOSP)$_4$-catalyzed C–H insertion exhibited extreme stereodifferentiation, such that only one enantiomer of **8** was reactive under the reaction conditions. Consequently, a high level of kinetic resolution was observed, and the C–H insertion product was produced with 98% ee (Equation (25)).[85] Similar reactivity was seen in the reaction of the 3-substituted pyrrolidine **9**. In some regards, this reaction is even more impressive, because there was selective insertion into one of the two available methylene groups adjacent to nitrogen (Equation (26)).[85]

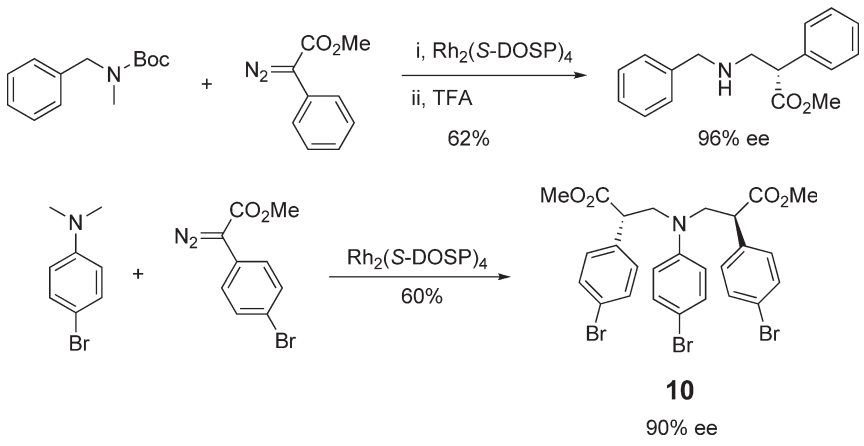


(25)



(26)

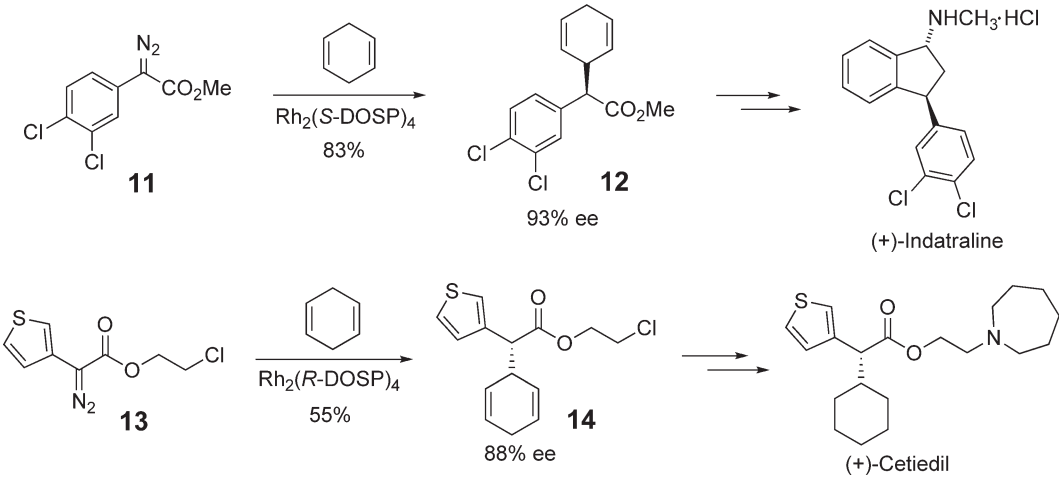
The C–H insertion α to nitrogen can be extended to acyclic systems. The reaction with *N*-benzyl-*N*-methylamine is an excellent example of the interplay between steric and electronic effects. The benzylic position would be electronically the most activated, but due to the steric crowding, the C–H insertion occurred exclusively at the *N*-methyl site (Equation (27)).[86] This is a general method for generating α-aryl-β-amino acid derivatives. The *N*,*N*-dimethylamino group undergoes a very favorable C–H insertion by the donor/acceptor-substituted carbenoids. Indeed, the reaction is so favorable that double C–H insertion was readily achieved to form the elaborated C_2-symmetric amine **10** (Equation (28)).[87]



10.04.2.2.5 Claisen rearrangement equivalent

The C–H functionalization protocol is not limited to the development of surrogate chemistry to enolate transformations. The C–H activation at allylic C–H bonds readily generates γ,δ-unsaturated esters, the products of the classic Claisen rearrangement (Figure 6).

The allylic C–H functionalization has been effectively used for the syntheses of pharmaceutical targets. The reaction of the 3,4-dichlorophenyl derivative **11** with 1,4-cyclohexadiene generated the C–H insertion product **12** with 93% ee, which was then readily converted to (+)-indatraline using conventional chemistry (Equation (29)).[88] The thiophenyl derivative **13** was also capable of a C–H insertion to form **14** with 88% ee. A few trivial steps converted **14** to the cholinergic agent (+)-cetiedil (Equation (30)).[89]



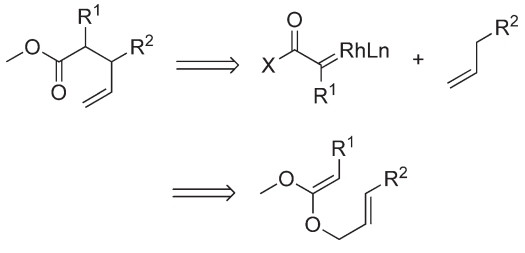
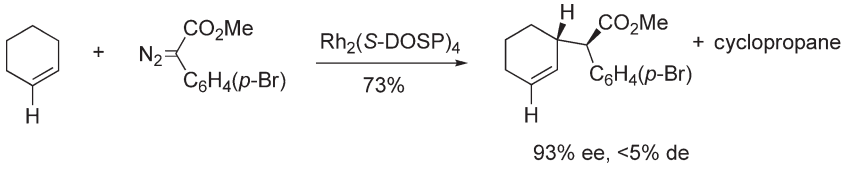
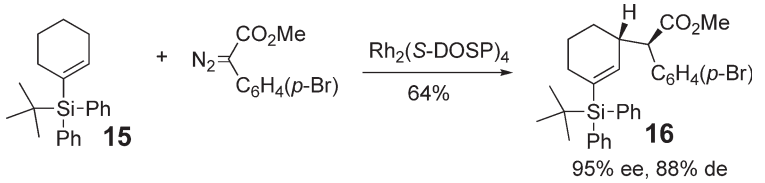


Figure 6 C–H activation as a Claisen rearrangement equivalent.

The reaction of aryldiazoacetates with cyclohexene is a good example of the influence of steric effects on the chemistry of the donor/acceptor-substituted rhodium carbenoids. The Rh_2(*S*-DOSP)$_4$-catalyzed reaction with cyclohexene resulted in the formation of a mixture of the cyclopropane and the C–H insertion products. The enantioselectivity of the C–H insertion was high but the diastereoselectivity was very low (Equation (31)).[90] In contrast, the introduction of a silyl group on the cyclohexene, as in **15**, totally blocked the cyclopropanation, and, furthermore, added sufficient size differentiation between the two substituents at the methylene site to make the reaction to form **16** proceed with high diastereoselectivity (Equation (32)).[90] The allylic C–H insertion is applicable to a wide array of cyclic and acyclic substrates, and even systems capable of achieving high levels of kinetic resolution are known.[90]



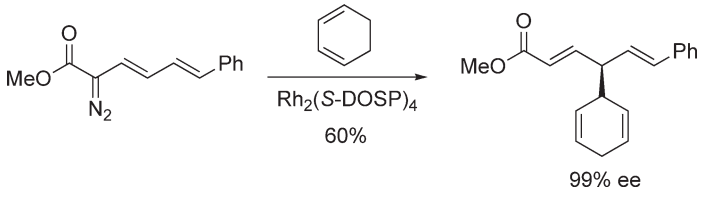
(31)



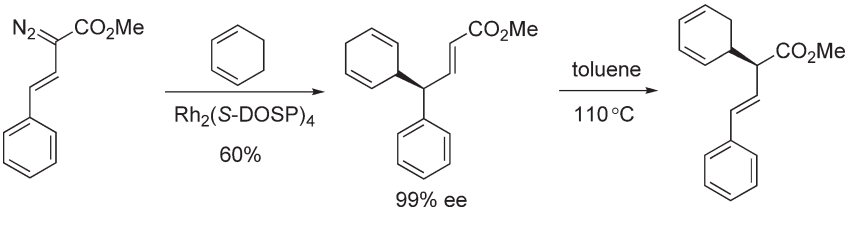
(32)

10.04.2.3 Combined C–H Activation/Cope Rearrangement

The C–H insertion chemistry of vinyldiazoacetates at allylic C–H sites results in a very unusual transformation.[91–93] Instead of the expected C–H insertion, a rearranged product is formed. This is readily seen in the reaction of the dienyldiazoacetate with 1,3-cyclohexadiene, which generated a product with both sets of double bonds out of conjugation (Equation (33)).[91] Similar reactions were seen with cycloheptatriene as substrate.[94] The most logical explanation for this transformation would be a C–H insertion followed by a Cope rearrangement. The reaction is actually more complicated as was seen in the reaction of methyl phenylvinyldiazoacetate with 1,3-cyclohexadiene (Equation (34)).[91] The C–H insertion product was not an intermediate in this reaction because it was stable under the reaction conditions. Under forcing conditions, the isolated product rearranged to the C–H insertion product (single diastereomer of undefined stereochemistry). Consequently, the transformation has been called a combined C–H activation/Cope rearrangement and can be considered an interrupted C–H insertion process. That is, the reaction begins forming the C–H insertion product, but before the process is completed, the Cope rearrangement process intercepts it.



(33)



(34)

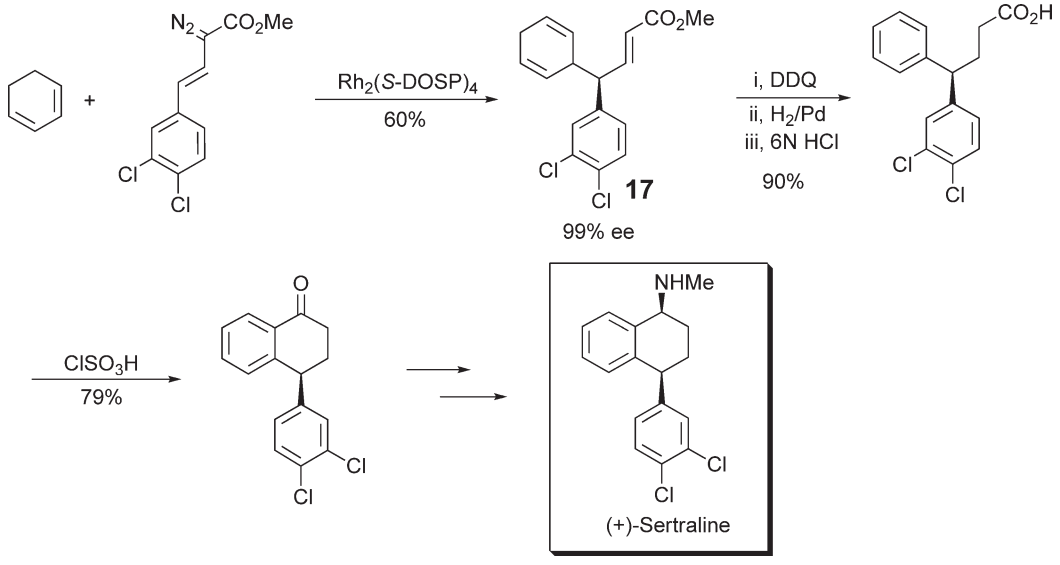
10.04.2.3.1 Combined C–H activation/Cope rearrangement as a strategic reaction

The combined C–H activation/Cope rearrangement generates a new C–H bond in a highly stereoselective manner and, therefore, has the potential to be a strategic reaction in synthesis. An example of this is the enantioselective synthesis of (+)-sertraline as shown in Scheme 1.[91] The C–H insertion step proceeded smoothly to form **17** with 99% ee. The conversion of **17** to (+)-sertraline could be readily achieved using conventional steps.

10.04.2.3.2 Tandem Claisen rearrangement/Cope rearrangement equivalent

The carbenoid C–H insertion chemistry has the possibility of achieving strategic reactions that are not feasible using conventional chemistry. A good example of this is the tandem Claisen rearrangement/Cope rearrangement equivalent shown in Figure 7. This is conceptually a very attractive process for converting a chiral alcohol to a C–C bond with control of two stereocenters. Unfortunately, the Cope rearrangement is not energetically favorable, but the combined C–H activation/Cope rearrangement would lead to the same products.

A hallmark of the combined C–H activation/Cope rearrangement is the highly diastereoselective and enantioselective nature of the transformation. Good examples of this are the reactions of vinylcarbenoids with the cyclohexene derivatives **18** (Scheme 2) and the unsaturated lactone **19** (Scheme 3). In the case of the cyclohexene derivatives, the combined C–H activation/Cope rearrangement products were produced with >98% de and 95–99% ee, although the direct C–H insertion was a competing reaction. High stereoselectivity was also exhibited in the reaction with the unsaturated lactone **19** (>98% de, 98–99% ee), but in this case, some direct C–H insertion and cyclopropanation also occurred as competing reactions.



Scheme 1

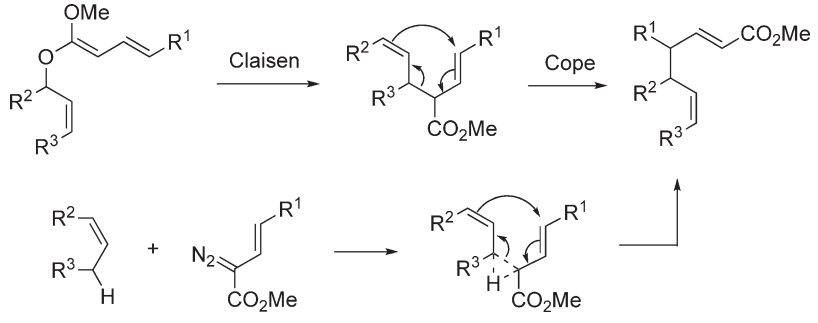
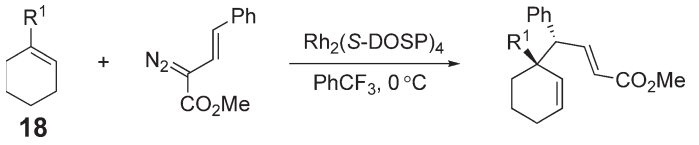
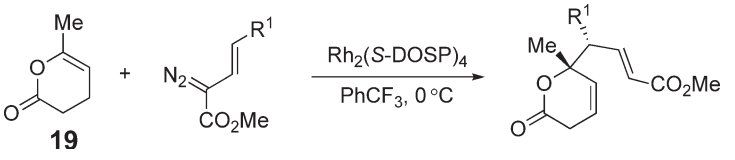


Figure 7 Tandem Claisen rearrangement/Cope rearrangement equivalent.



R^1	*Yield* (%)	*de* (%)	*ee* (%)
Me	68	>98	97
Me_2CH	31	>98	95
OAc	55	>98	98
OTMS	44	>98	99

Scheme 2

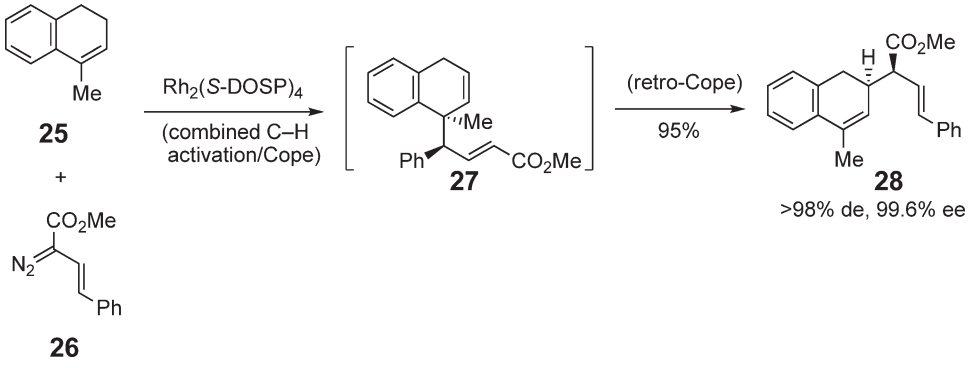


R^1	*Yield* (%)	*de* (%)	*ee* (%)
Ph	87	>98	99
CH=CHPh	82	>98	99
$CH=CH_2$	55	>98	99
p-BrC_6H_4	56	>98	99
CH_3CH_2	20	>98	98

Scheme 3

The combined C–H activation/Cope rearrangement has been used as the key step in the synthesis of the natural product (+)-erogorgiaene **24** (Scheme 4).[95] Rh_2(*R*-DOSP)$_4$-catalyzed reaction of vinyldiazoacetate **21** with dihydronaphthalene **20** resulted in enantiodifferentiation to form **23** with 90% ee. The other enantiomer of the dihydronaphthalene preferentially formed the cyclopropane **22**. Due to the high diastereoselectivity of the combined C–H activation/Cope rearrangement, a single diastereomer of **23** was formed with the correct configuration for (+)-erogorgiaene **24**. The total synthesis of (+)-erogorgiaene **24** was completed using conventional synthetic steps.

Dihydronaphthalenes are remarkable substrates for the combined C–H activation/Cope rearrangement, but under certain circumstances, further cascade reactions can occur. This was seen in the Rh_2(*S*-DOSP)$_4$-catalyzed reaction of vinyldiazoacetate **26** with dihydronaphthalene **25** (Equation (35)).[96] In this case, the isolated product was the formal C–H insertion product. The reaction proceeded through a combined C–H activation/Cope rearrangement to form **27**, followed by the reverse Cope rearrangement. As both steps were highly stereoselective, the formal C–H insertion product **28** was produced with very high stereoselectivity (>98% de, 99.6% ee).[96]



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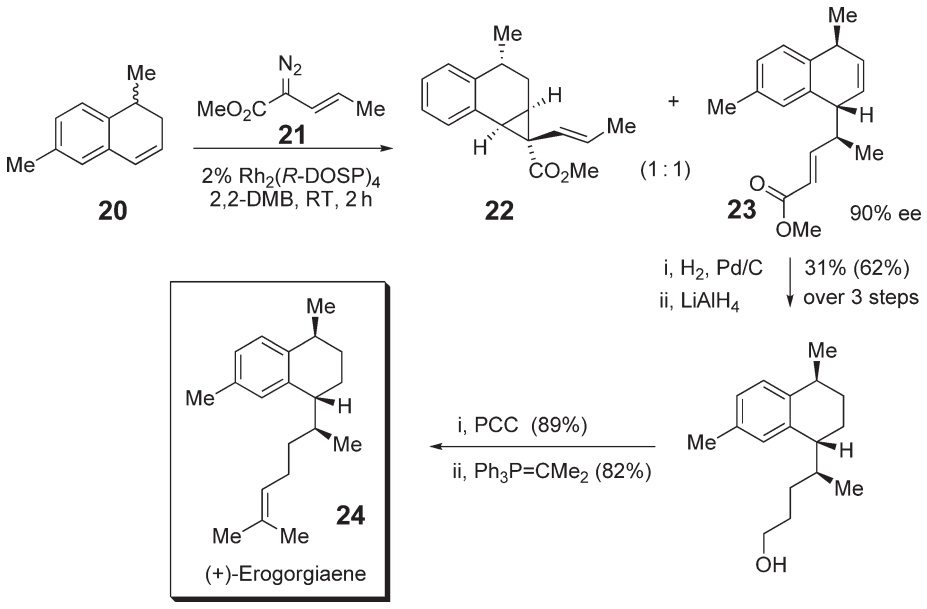
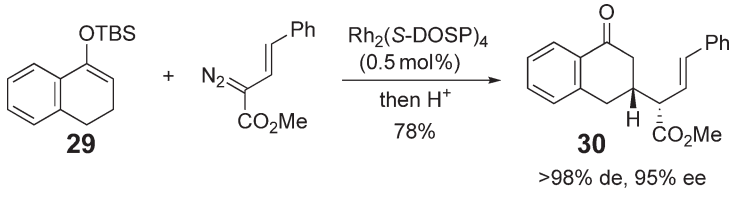
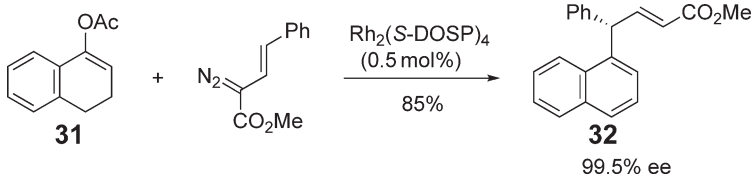


Scheme 4

The reaction with the siloxy derivative **29** is an interesting example because the product **30** is a 1,5-dicarbonyl derivative (Equation (36)).[96] 1,5-Dicarbonyls are classically prepared by a Michael addition, but the synthesis of **30** by a Michael addition is not possible because it would require addition to the keto form of 1-naphthol. The acetoxy derivative **31** resulted in a different outcome, leading to the direct synthesis of the naphthalene derivative **32** (Equation (37)).[96] In this case, the combined C–H activation/Cope rearrangement intermediate was aromatized by elimination of acetic acid before undergoing a reverse Cope rearrangement.

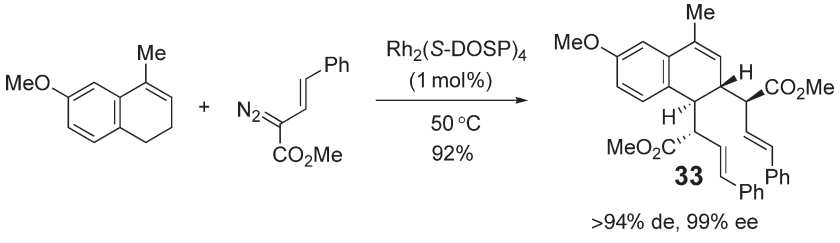


(36)



(37)

In certain cases, the C–H activation/Cope rearrangement is so favorable that double C–H functionalization can occur as illustrated in Equation (38). The product **33** was formed in 99% ee with excellent control of stereochemistry at four centers due to the involvement of a cascade process rather than a direct C–H insertion.

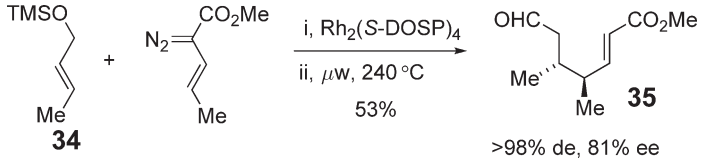


(38)

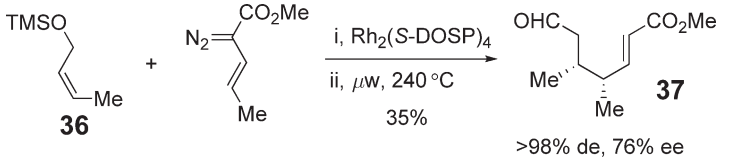
10.04.2.3.3 Tandem aldol reaction/siloxy-Cope rearrangement equivalent

The tandem aldol reaction/siloxy-Cope rearrangement has been developed as a general synthetic strategy applicable to the syntheses of a range of target systems (Figure 8).[97,98] The aldol reaction is usually conducted with chiral auxiliaries and the use of a siloxy-Cope rearrangement ensures that the second step goes to completion. A catalytic enantioselective equivalent of this reaction would be the combined C–H activation/oxy-Cope rearrangement on allyl silyl ethers.

Many types of allyl silyl ethers reacted with vinyldiazoacetates to give mixtures of the C–H activation and the C–H activation/Cope rearrangement products.[92] Subsequent heating of the crude product under microwave conditions converted the C–H activation product to the combined C–H activation/Cope rearrangement product. Due to the driving force of the siloxy-Cope rearrangement, the C–H insertion product was no longer thermodynamically the most stable. Illustrative examples of the reaction with allyl silyl ethers are shown in Equations (39) and (40).[92] The relative configuration of the products **35** and **37** was governed by the alkene geometry of the starting allyl silyl ethers **34** and **36**, respectively.



(39)



(40)

In summary, the intermolecular C–H insertion chemistry of transient metal carbenoids has undergone tremendous growth in the last 10 years. It now can be realistically considered as a viable alternative to many of the classic methodologies used in organic synthesis.

10.04.3 Intramolecular Carbene C–H Insertion

Intramolecular C–H insertion reactions of metal carbenoids have been widely used for the stereoselective construction of substituted lactams, lactones, cyclopentanones, benzofurans, and benzopyrans. Several excellent reviews have been published covering the general aspects of intramolecular C–H insertion by metal carbenoids.[46,47,62,71,99–104] The following section highlights the major advances made since 1994, especially in asymmetric intramolecular C–H insertion.

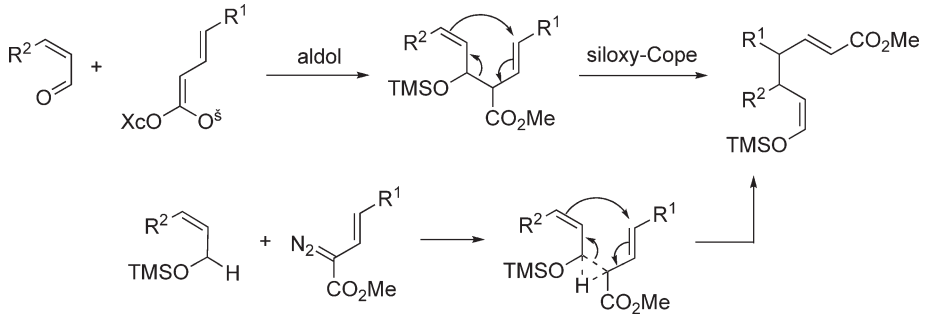


Figure 8 Tandem aldol reaction/siloxy-Cope rearrangement equivalent.

10.04.3.1 Carbene Precursors and Catalysts

The carbenoid intermediates could be divided into three major groups according to the carbenoid functionality: donor/acceptor, acceptor, and acceptor/acceptor (Figure 9). As shown above, the recent success of the intermolecular C–H insertion is due to the introduction of the highly chemoselective donor/acceptor-substituted carbenoids and the common precursors are aryldiazoacetates and vinyldiazoacetates.[35] The second group, acceptor-substituted carbenoids, are derived from diazo compounds with a single electron-withdrawing substituent (Figure 9).[46,47] Nitrogen extrusion from these diazo compounds can be achieved with a variety of catalysts to generate a highly reactive metallocarbenoid species. A major problem that needs to be avoided with this class of carbenoid is the formation of carbene dimers. Acceptor-substituted carbenoids have been widely applied to intramolecular C–H insertion reactions where the high reactivity can be tamed by entropic factors.[46,47] The third group, acceptor/acceptor-substituted carbenoids, are derived from diazo compounds with two electron-withdrawing substituents (Figure 9).[47] This includes carbenoids derived from diazoacetoacetates, diazomalonates, diazodiketones, diazoacetoacetamides, and α-methoxycarbonyl-α-diazoacetamides. Due to the added stabilization of the diazo compound by the presence of the second electron-withdrawing group, very active catalysts are required to decompose the diazo compound.[46] Again, intramolecular C–H insertion reactions are the most synthetically useful for the acceptor/acceptor-substituted carbenoids.

Activation of a C–H bond requires a metallocarbenoid of suitable reactivity and electrophilicity.[105–115] Most of the early literature on metal-catalyzed carbenoid reactions used copper complexes as the catalysts.[46,116] Several chiral complexes with C_2-symmetric ligands have been explored for selective C–H insertion in the last decade.[117–127] However, only a few isolated cases have been reported of impressive asymmetric induction in copper-catalyzed C–H insertion reactions.[118,124] The scope of carbenoid-induced C–H insertion expanded greatly with the introduction of dirhodium complexes as catalysts. Building on initial findings from achiral catalysts, four types of chiral rhodium(II) complexes have been developed for enantioselective catalysis in C–H activation reactions. They are rhodium(II) carboxylates, rhodium(II) carboxamidates, rhodium(II) phosphates, and *ortho*-metallated arylphosphine rhodium(II) complexes.

Rhodium(II) carboxylates are kinetically very active at decomposing diazo compounds, much more so than copper or rhodium(II) carboxamidate catalysts.[40,101] Originally, the dirhodium tetracarboxylate framework was not considered to be a promising scaffold for the design of chiral catalysts,[40] but major advances have been made in the past few years that refute this viewpoint. McKervey and co-workers explored a variety of *N*-protected *L*-proline derivatives for enantioselective C–H activation reactions. The most successful catalyst that McKervey developed was the *N*-benzenesulfonyl-protected Rh_2(*S*-BSP)$_4$ **39a**.[119,128] Davies then discovered that dirhodium tetraprolinates were exceptional chiral catalysts for the donor/acceptor-substituted carbenoids, even though these catalysts gave low to moderate enantioselectivity with other carbenoid systems. As the prolinate catalysts gave enhanced asymmetric induction in reactions conducted in nonpolar solvents, the hydrocarbon-soluble prolinate catalysts, *N*-*p*-*tert*-butylbenzenesulfonyl derivative Rh_2(*S*-TBSP)$_4$ **39b** and *N*-*p*-dodecylbenzenesulfonyl derivative Rh_2(*S*-DOSP)$_4$ **39c**, were

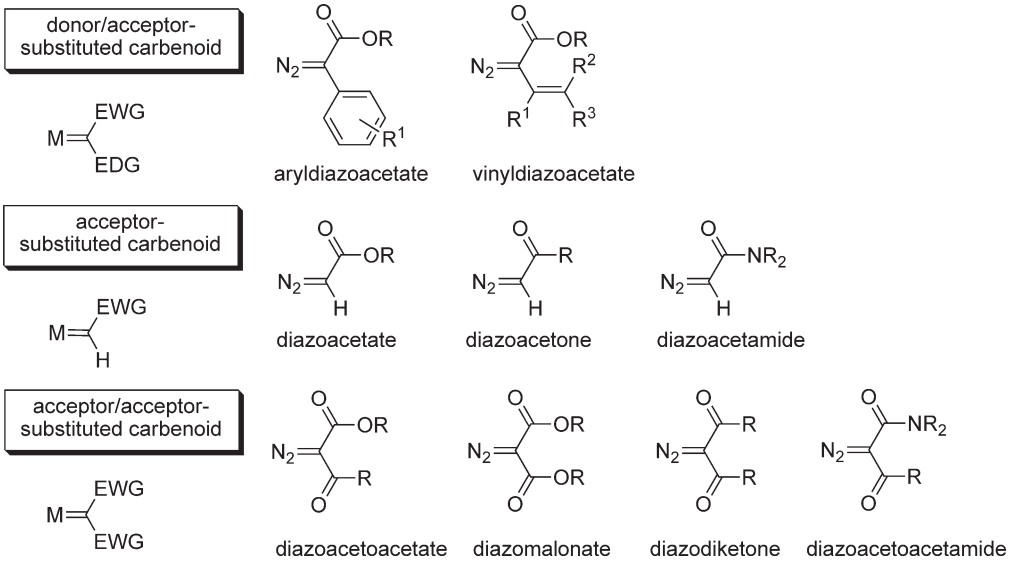
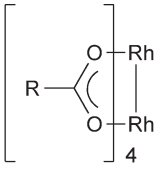
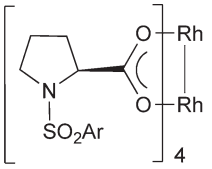


Figure 9 Classification of carbenoid intermediates and common precursors.

developed.[37,129,130] Spectacular results in intermolecular C–H activation chemistry have been observed with these prolinate catalysts, especially Rh_2(*S*-DOSP)$_4$, which has been found to maintain catalytic activity even at −78 °C.[40,41,43]

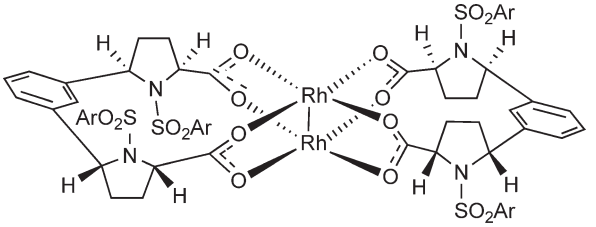




38a: R = CH_3 $Rh_2(OAc)_4$
38b: R = $(CH_2)_6CH_3$ $Rh_2(OOct)_4$
38c: R = $C(CH_3)_3$ $Rh_2(OPiv)_4$
38d: R = CF_3 $Rh_2(TFA)_4$
38e: R = C_3F_7 $Rh_2(pfb)_4$

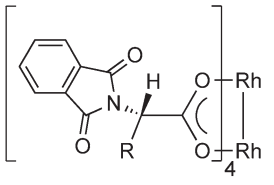
39a: Ar = C_6H_5 Rh_2(*S*-BSP)$_4$
39b: Ar = *p*-$Bu^tC_6H_4$ Rh_2(*S*-TBSP)$_4$
39c: Ar = *p*-$(C_{12}H_{25})C_6H_4$ Rh_2(*S*-DOSP)$_4$

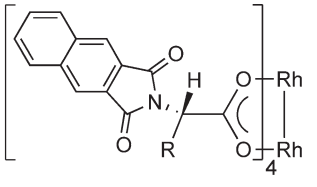
The enhancement of stereocontrol in hydrocarbon solvents has been proposed to be the result of a solvent-induced orientation of the prolinate ligands leading to a complex of overall D_2 symmetry.[131] From these findings, a second generation of catalysts was developed possessing a rigid bridged structure, which could therefore give optimum asymmetric induction even in non-hydrocarbon solvents. The most prominent catalysts in C–H activation chemistry have been Rh_2(*S*-biTISP)$_2$ **40a** and Rh_2(*S*-biDOSP)$_2$ **40b**.[132,133] These catalysts are essentially locked in a D_2-symmetric conformation with the *N*-arylsulfonyl groups orientated in an "up–down–up–down" arrangement.[40,129]



40a: Ar = 2,4,6-tri-$Pr^iC_6H_2$ Rh_2(*S*-biTISP)$_2$
40b: Ar = *p*-$(C_{12}H_{25})C_6H_4$ Rh_2(*S*-biDOSP)$_2$

Hashimoto and Ikegami developed dirhodium(II) tetracarboxylates **41** incorporating *N*-phthaloyl-(*S*)-amino acids as ligands.[134] Recently, a set of second-generation catalysts **42** were developed in which the phthalimido wall has been extended by an additional benzene ring.[135] The catalysts have a C_2-symmetric conformation with the phthalimido groups aligned in a "down–down–up–up" arrangement. The bulky Rh_2(*S*-PTTL)$_4$ has been the most universally successful of this breed of catalyst, being proficient in the intramolecular cyclizations of aryldiazoacetates into methylene sites,[136] certain α-diazo-β-ketoesters,[137] and the generation of γ-lactams from α-methoxycarbonyl-α-diazoacetamide precursors.[138] The methyl-substituted Rh_2(*S*-PTA)$_4$ is most adept at β-lactam formation from α-methoxycarbonyl-α-diazoacetamides, and Rh_2(*S*-PTPA)$_4$ has found relative success in catalyzing the cyclizations of α-diazo-β-ketoesters.[139] A (*S*)-2-benzyloxyphenylacetic acid-based catalyst also developed by Hashimoto and Ikegami proved not to be especially effective at asymmetric induction in C–H activation chemistry.[134]

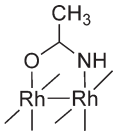




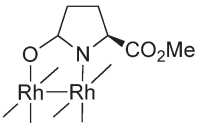
41a: R = Bn Rh_2(*S*-PTPA)$_4$
41b: R = Bu^t Rh_2(*S*-PTTL)$_4$
41c: R = Me Rh_2(*S*-PTA)$_4$

42a: R = Bn Rh_2(*S*-BPTPA)$_4$
42b: R = Bu^t Rh_2(*S*-BPTTL)$_4$
42c: R = Me Rh_2(*S*-BPTA)$_4$

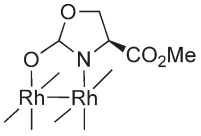
Doyle's rhodium(II) carboxamidate complexes are undisputedly the best catalysts for enantioselective cyclizations of acceptor-substituted carbenoids derived from diazo esters and diazoacetamides, displaying outstanding regio- and stereocontrol.[46,65,66,105,140,141] These carboxamidate catalysts consist of four classes of complexes: pyrrolidinones **44**,[142,143] oxazolidinones **45**,[144,145] imidazolidinones **46**,[144,146] and azetidinones **47**.[142–144,146–150] A number of Doyle's catalysts have proved to be effective in particular intramolecular transformations with specific substrate types.[105] The imidazolidinone-based catalysts Rh_2(*S*-MPPIM)$_4$ and Rh_2(*S*-MACIM)$_4$ produce excellent regio- and stereocontrol in cyclizations of acceptor-substituted diazoacetates owing to the restricted access available to the reacting carbenoid center due to the pendant acyl chains on the chiral ligands. With more sterically encumbered diazoacetates, the more open structures of the pyrrolidinone-based catalyst Rh_2(*S*-MEPY)$_4$ or the oxazolidinone-based catalyst Rh_2(*S*-MEOX)$_4$ tend to provide greater regio- and stereoselectivity. The enhanced reactivity of the azetidinone-based complexes compared to the other classes of carboxamidates means that catalysts such as Rh_2(*S*-IBAZ)$_4$ and Rh_2(*S*-MEAZ)$_4$ are reactive enough to decompose aryldiazoacetates and generate β- or γ-lactones with moderate to good enantiocontrol.[151,152]



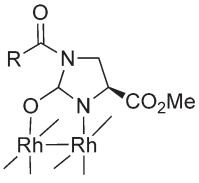
43 Rh_2(acam)$_4$



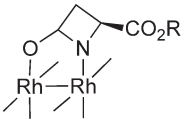
44 Rh_2(5*S*-MEPY)$_4$



45 Rh_2(5*S*-MEOX)$_4$

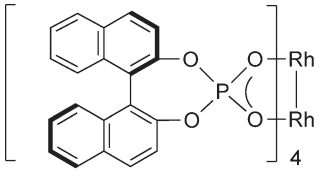


46a: R = CH_3 Rh_2(4*S*-MACIM)$_4$
46b: R = $BnCH_2$ Rh_2(4*S*-MPPIM)$_4$

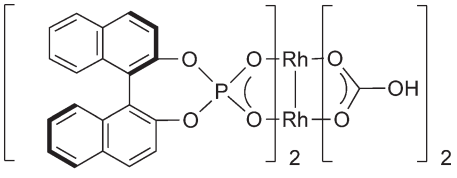


47a: R = CH_3 Rh_2(4*S*-MEAZ)$_4$
47b: R = Bu^i Rh_2(4*S*-IBAZ)$_4$

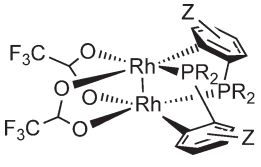
Chiral rhodium(II) binaphtholphosphates have been developed independently by McKervey and Pirrung. McKervey prepared Rh_2(*S*-BNP)$_2$(HCO_3)$_2$ **49** and Pirrung prepared Rh_2(*R*-BNP)$_4$ **48**, both of which have had limited use to date in C–H activation chemistry.[153,154] Lahuerta, Perez-Prieto, and co-workers recently introduced a family of novel rhodium(II) catalysts **50**; the chirality of these catalysts did not originate from chiral ligands but instead was inherent in the system.[155–159] The complexes possess C_2 symmetry and consist of two *ortho*-metallated arylphosphines and two carboxylate ligands in a *cis*-arrangement. These catalysts have had reasonable success in the cyclization reactions of acceptor-substituted diazoketone systems.[155]



48 Rh_2(*R*-BNP)$_4$



49 Rh_2(*R*-BNP)$_2$(HCO_3)$_2$



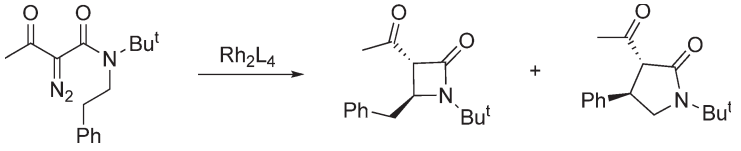
50a: R = C_6H_5; Z = H
50b: R = *p*-MeC_6H_4; Z = *p*-CH_3
50c: R = *m*-MeC_6H_4; Z = *m*-CH_3
50d: R = *p*-FC_6H_4; Z = *p*-F
50e: R = 3,5-$Me_2C_6H_4$; Z = 3,5-CH_3

10.04.3.2 Lactam Formation

Transition metal-catalyzed intramolecular C–H insertion reactions of diazoacetamides constitute a powerful methodology for the preparation of highly valuable heterocyclic compounds, among which β- and γ-lactams are especially noteworthy, since they are common scaffolds in numerous natural-product syntheses.[160,161] An extensive literature is available on this subject, including several reviews emphasizing various aspects of this chemistry.[35,47,68,99,108,162] The intramolecular C–H insertion of carbenoids derived from diazoacetamides typically results in a competition between β- and γ-lactam formation.[163–165] β-Lactam formation is favorable because of the activating influence of the amide nitrogen, whereas the γ-lactam is the generally favored ring size for intramolecular C–H insertion. However, the stereo-, regio-, and enantioselectivity could be affected by different catalysts and different framework of diazoacetamide.

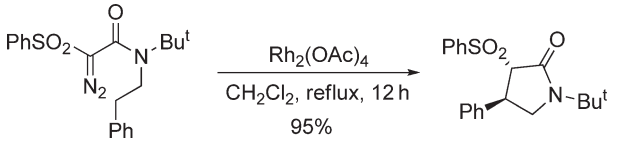
As the most effective catalysts for intramolecular C–H insertion, the dirhodium(II) carboxylates and the rhodium(II) carboxamides are especially important for their different electrophilic profiles. Electron-withdrawing ligands such as the rhodium(II) perfluorobutyrate [Rh_2(pfb)$_4$] augment the catalyst's electrophilic character, increasing the reactivity toward diazo decomposition. Catalysts with electron-donating bridged ligands such as rhodium(II) acetamide [Rh_2(acam)$_4$] **43** are often recognized as more selective, but on the other hand higher reactivity is required from the diazo compound in order to form the reactive metal carbene.

Explorations of the regioselectivity of different catalysts have been performed by Padwa[109] and Doyle[163] and other groups.[166–172] As shown in Equation (41), the selectivity was improved in favor of the γ-lactam when a Rh catalyst with an electron-donating ligand was used. Presumably, the electron-donating ligand would stabilize the electrophilic carbenoid carbon, thereby causing the insertion reaction to proceed through a relatively late transition state with a resulting increase in selectivity.[173] Inspired by these results, rather than using the α-diazo-α-acetoacetamides as precursors, Jung and co-workers demonstrated intramolecular C–H insertion reaction of α-diazo-α-(phenylsulfonyl)acetamides which proceeded with high regio- and stereoselectivities to afford highly functionalized γ-lactams (Equation (42)).[174–177]



(41)

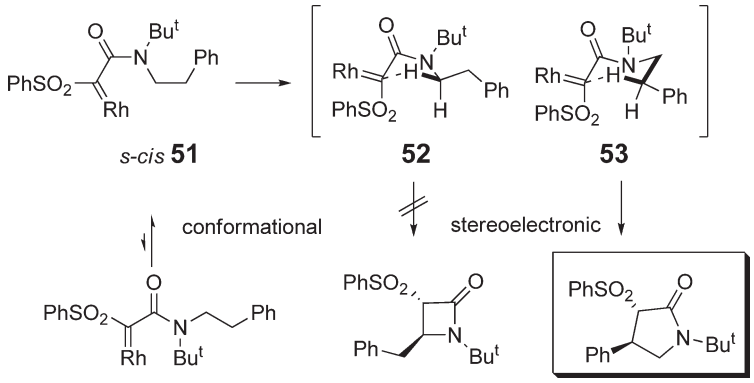
	Yield (%)	*Ratio*		
Rh_2(pfb)$_4$	85	56	:	44
Rh_2(OAc)$_4$	94	49	:	51
Rh_2(acam)$_4$	90	30	:	70



(42)

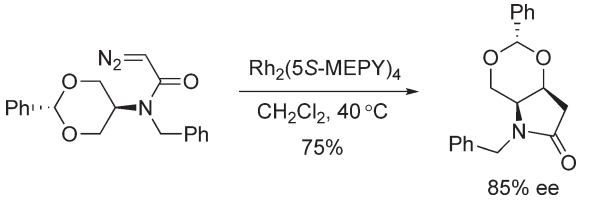
The outstanding regio- and stereoselectivities are rationalized in Scheme 5. During the insertion reaction, the conformationally restricted metallocarbenoid **51** would adopt a *s-cis*-conformer as a result of the severe non-bonded interaction between the *tert*-butyl group and the carbonyl substituents present in the *s-trans*-conformer (conformational effect). Only the *s-cis*-conformer is suitable for cyclization, and the two regioisomeric β- and γ-lactams can be obtained through transition states **52** and **53**, respectively. As a result of the extra stabilization by a phenylsulfonyl group, the cyclization would occur through the stereoelectronically favorable transition state **53** (stereoelectronic effect). The formation of *trans*-stereochemistry at C-3/C-4 was also explained by the adopted chairlike transition state **53**, where the C–Rh bond would be aligned with the target C–H bond and the phenyl group would occupy a pseudoequatorial position.[178] Similar influence was reported by Gois and Afonso using a phosphoryl moiety as an α-substituent.[167]

The dirhodium(II)-catalyzed asymmetric C–H insertion has been recognized as a powerful procedure for the preparation of many interesting compounds.[35,43,68,179] Doyle *et al.* developed an efficient procedure for the enantioselective syntheses of lactams.[180–182] The acyclic terminal diazoacetamides gave moderate enantioselectivity

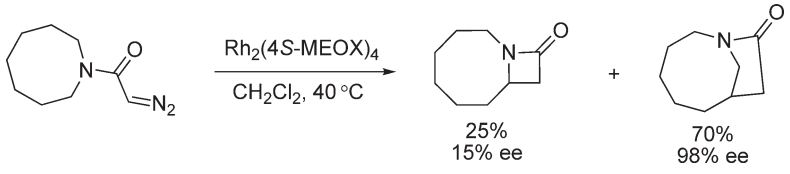


Scheme 5

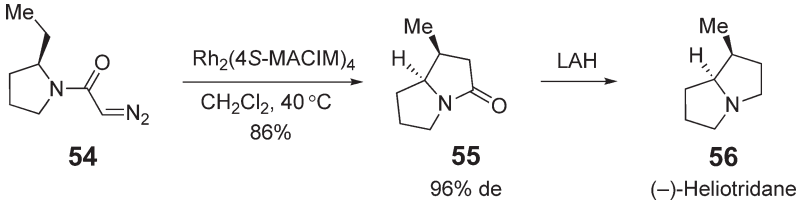
(Equation (43)).[180,181] Nevertheless, the related azacyclic systems display exceptional levels of enantiocontrol in certain cases (Equation (44)).[182] γ-Lactam formation is strongly preferred with the corresponding 2-substituted pyrrolidine system.[126] Indeed, exceptional double diastereodifferentiation can be obtained in Rh_2(MACIM)$_4$-catalyzed cyclizations of enantiopure diazoacetopyrrolidines, enabling easy access to pyrrolizidine bases such as (−)-heliotridane **56** (Equation (45)). The matched reaction of Rh_2(4*S*-MACIM)$_4$ with **54** displayed remarkable regioselectivity, forming exclusively **55** in 86–95% yield with great preference for the *cis*-isomer (92–96% de). The mismatched reaction with the corresponding (*R*)-enantiomer produced **55** with 50% de. This reaction is uniquely suited for rhodium(II) carboxamidates, because the rhodium(II) carboxylate catalysts Rh_2(*S*-BSP)$_4$ and Rh_2(*S*-PTPA)$_4$ gave low yields and poor selectivities.



(43)



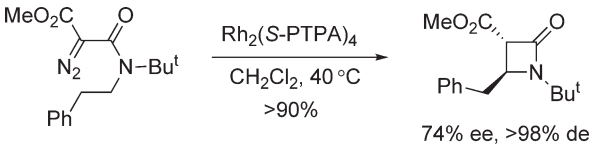
(44)



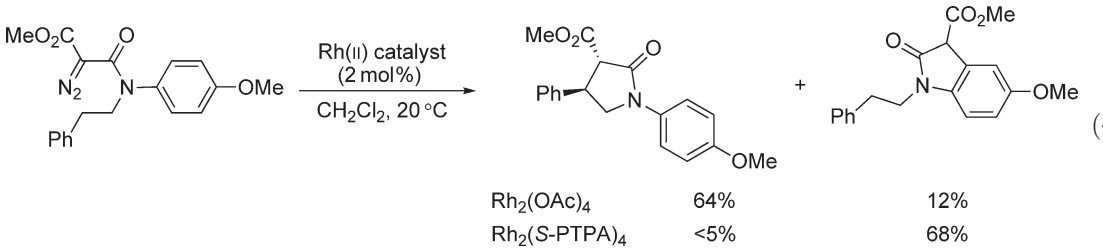
(45)

Expanding on the initial findings of Wee,[183–185] Hashimoto and co-workers discovered that the regioselectivity of the C–H activation reaction of diazo compounds containing two acceptor groups could to some extent be controlled by careful choice of the *N*-protecting group.[138,186] For example, formation of the β-lactam was completely suppressed by substituting the bulky *tert*-butyl group for a *p*-methoxyphenyl (PMP) group (Equations (46) and (47)). Unfortunately, due to the high electron density of the PMP unit, aromatic C–H insertion was favored over benzylic C–H activation. Protecting the nitrogen with the less electron-rich *p*-nitrophenyl group discouraged the electrophilic aromatic substitution pathway, enabling exclusive formation of *trans*-3,4-pyrrolidinone **57** with no trace of the β-lactam product (Equation (48)). Hashimoto demonstrated the synthetic utility of the *N*-*p*-nitrophenyl substituent as a site-control element in the syntheses of some pharmaceutically relevant targets. The $GABA_B$ receptor agonist,

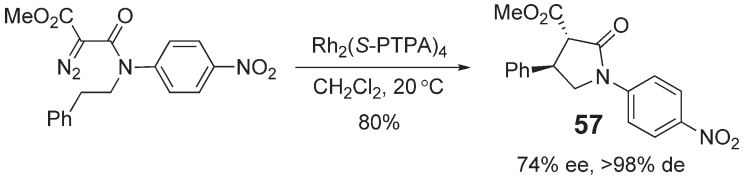
(*R*)-(−)-baclofen **58**,[138] and phosphodiesterase type IV inhibitor, (*R*)-(−)-rolipram **59**,[187] were efficiently prepared with an intramolecular C–H insertion being used as a key step (Equations (49) and (50)).



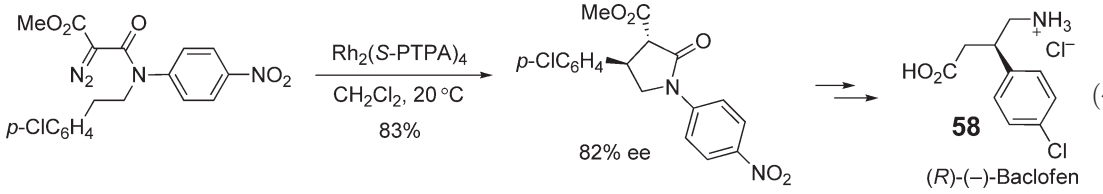
(46)



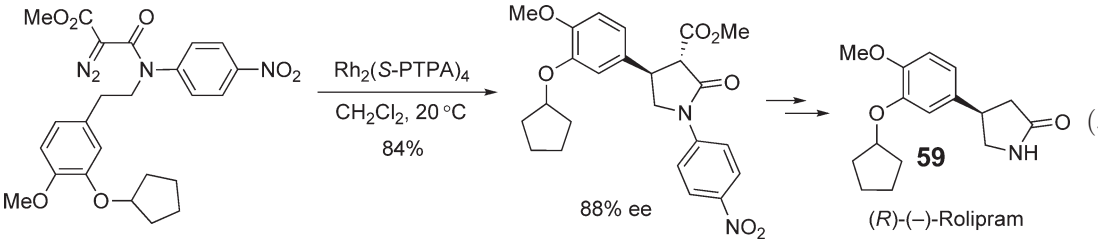
(47)



(48)

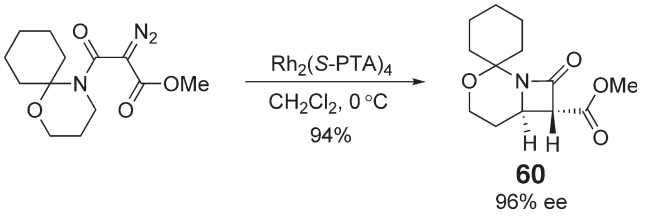


(49)

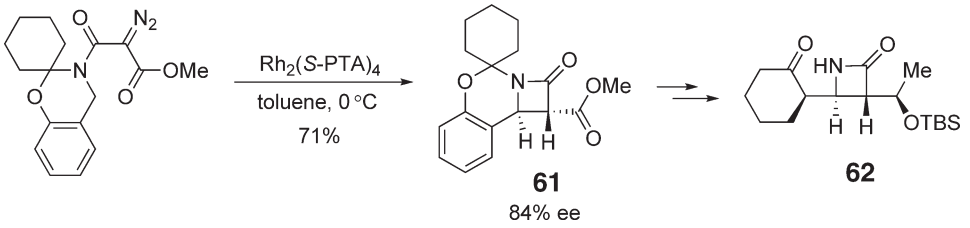


(50)

In an attempt to improve the enantioselectivity, following the precedent from Ponsford and Southgate,[188] Hashimoto demonstrated that the tetrahydro-1,3-oxazine system gave great selectivity in the C–H activation reaction. Indeed, highly selective formation of the β-lactam **60** was accomplished in up to 94% yield and 96% ee using Rh_2(*S*-PTA)$_4$ (Equation (51)).[189] This strategy was applied in a novel approach to a key intermediate **61** in the synthesis of trinem **62** (Equation (52)).[190,191]

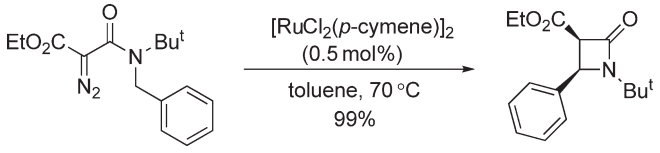


(51)

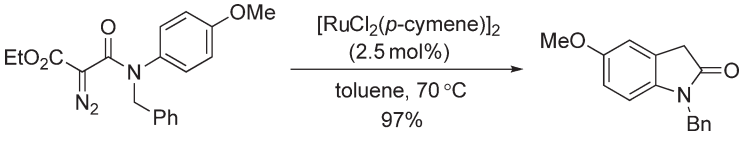


(52)

Recently, Yu and co-workers developed an operationally simple catalytic system based on $[RuCl_2(p\text{-cymene})]_2$ for stereoselective cyclization of α-diazoacetamides by intramolecular carbenoid C–H insertion.[192] β-Lactams were produced in excellent yields and >99% *cis*-stereoselectivity (Equation (53)). The Ru-catalyzed reactions can be performed without the need for slow addition of diazo compounds and inert atmosphere. With α-diazoanilide as a substrate, the carbenoid insertion was directed selectively to an aromatic C–H bond leading to γ-lactam formation (Equation (54)).



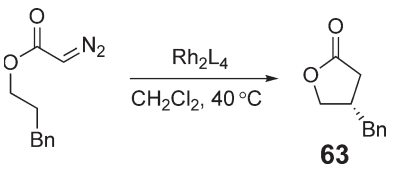
(53)



(54)

10.04.3.3 Lactone Formation

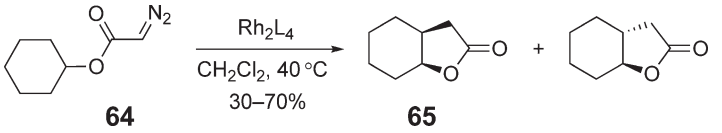
The intramolecular C–H insertion reactions of diazoacetates to generate lactones are well established. Electronic factors that control product formation, including the preference for five-membered rings and C–H bond reactivity, $3° > 2° \gg 1°$, operate with diazo esters in much the same manner as with diazoacetamides. The most effective catalysts for enantiocontrolled C–H insertion reactions are the chiral dirhodium(II) carboxamidate catalysts developed by Doyle and co-workers.[68,105,179,193] The first-generation catalysts, the pyrrolidinone $Rh_2(MEPY)_4$ and the oxazolidinone $Rh_2(MEOX)_4$, which are great catalysts for intramolecular cyclopropanation, gave moderate asymmetric induction in the formation of γ-butyrolactone **63**, whereas the second-generation imidazolidinone catalyst $Rh_2(MPPIM)_4$ was far superior (Equation (55)).[181,194–198] The unrivaled success of $Rh_2(MPPIM)_4$ is thought to be due to the greater steric influence of the *N*-3-phenylpropanoyl attachment, which provides greater control over the orientations of the carbenoid intermediate than with the more open structures of $Rh_2(MEPY)_4$ and $Rh_2(MEOX)_4$.[199] In the reaction of cyclohexyl diazoacetate **64**, both the first-generation and the second-generation catalysts gave high enantioselectivity. However, the second generation catalysts, which are the more sterically encumbered imidazolidinone catalysts $Rh_2(4S\text{-MPPIM})_4$ and $Rh_2(4S\text{-MACIM})_4$, provide exceptional diastereoselectivity for the *cis*-isomer **65** (Equation (56)).[200] This remarkable diastereocontrol is thought to stem from the *N*-acyl appendages on the chiral ligands of $Rh_2(4S\text{-MPPIM})_4$ and $Rh_2(4S\text{-MACIM})_4$, which restrict the trajectory of the substrate C–H bond and effectively fix the carbenoid center in a single orientation.[201] Similar results are seen in the cyclizations of secondary alkyl diazoacetates (Equation (57))[201–203] and seven- or eight-membered-ring cycloalkyl diazoacetates (Equation (58)), with the $Rh_2(4S\text{-MPPIM})_4$- or $Rh_2(4S\text{-MACIM})_4$-catalyzed process affording excellent stereoselectivity.[200] In cyclopentyl diazoacetates, the reactions are highly selective for the *cis*-isomer irrespective of the choice of catalyst, but only sterically demanding catalysts such as $Rh_2(4S\text{-MPPIM})_4$ produce outstanding asymmetric induction (Equation (59)).[201,204] The corresponding $Rh_2(4S\text{-MEOX})_4$- or $Rh_2(5S\text{-MEPY})_4$-mediated processes give much poorer diastereoselectivity. However, the open framework of the oxazolidinone catalyst $Rh_2(4S\text{-MEOX})_4$ is particularly suited for sterically demanding diazoacetates. The $Rh_2(4S\text{-MEOX})_4$-mediated reaction of adamantane derivatives **66** and **68** through C–H insertion at tertiary and secondary sites to form **67** and **69**, respectively, was accomplished with excellent enantioinduction (Equations (60) and (61)).



63

Catalyst	*Yield* (%)	*ee* (%)
Rh_2(5*R*-MEPY)$_4$	23%	72% (*R*)
Rh_2(4*S*-MEOX)$_4$	42%	51% (*S*)
Rh_2(4*R*-MPPIM)$_4$	56%	91% (*R*)

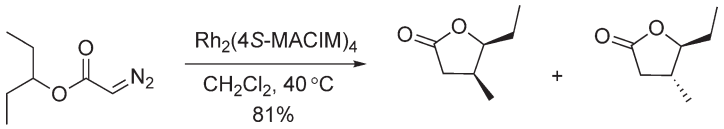
(55)



64 **65**

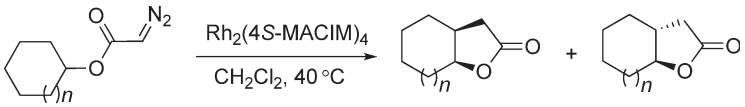
Catalyst	*Ratio*	
$Rh_2(OAc)_4$	40	60
Rh_2(5*S*-MEPY)$_4$	75 (97% ee)	25 (90% ee)
Rh_2(4*S*-MEOX)$_4$	55 (96% ee)	45 (95% ee)
Rh_2(4*S*-MPPIM)$_4$	96 (98% ee)	4 (–)
Rh_2(4*S*-MACIM)$_4$	99 (97% ee)	1 (65% ee)

(56)



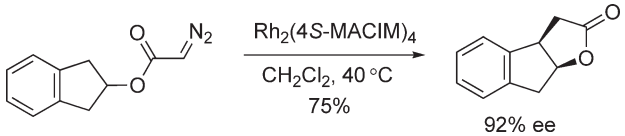
97 (99% ee) 3 (–)

(57)



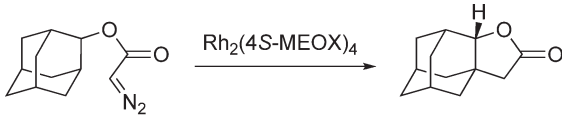
n = 2 75%	99 (96% ee)	1(61% ee)
n = 3 62%	99 (97% ee)	1(59% ee)

(58)



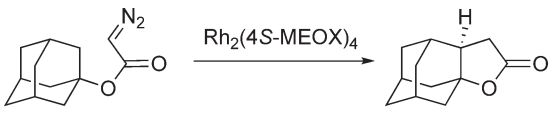
92% ee

(59)



66 **67**
98% ee

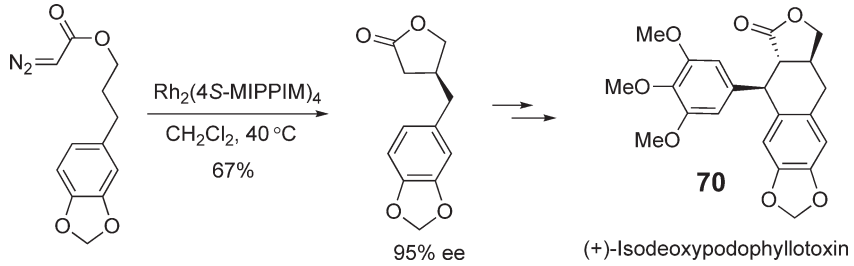
(60)



68 **69**
90% ee

(61)

Asymmetric catalysis with $Rh_2(4S\text{-MPPIM})_4$ has been used to prepare a wide variety of lignans such as (+)-isodeoxypodophyllotoxin **70** (Equation (62))[202,203] and (−)-enterolactone **71** (Equation (63)).[194] The chemistry has also been utilized in the synthesis of (*S*)-(+)-imperanene **72** (Equation (64))[197] and (*R*)-(−)-baclofen **73** (Equation (65)).[198] Enantioselectivities of 91–96% ee have been obtained for a broad range of applications.



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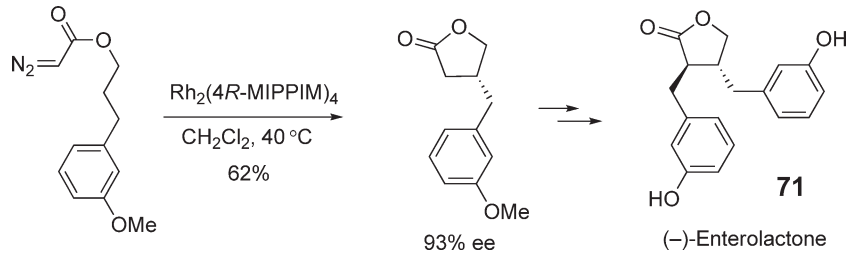

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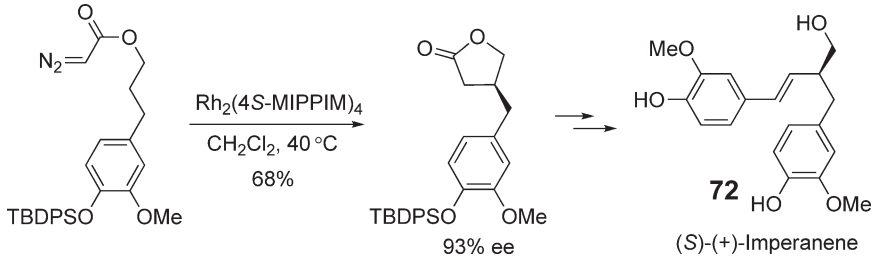
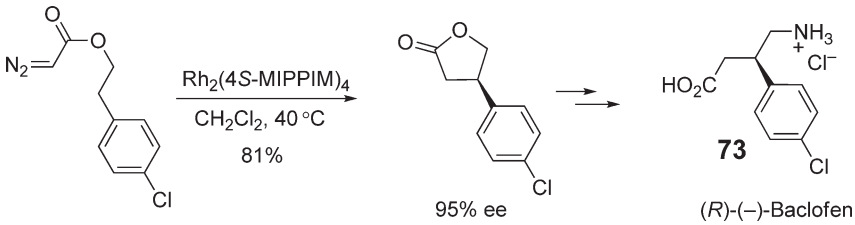
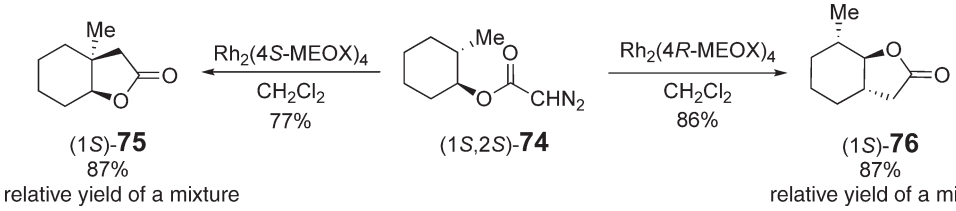


(64)

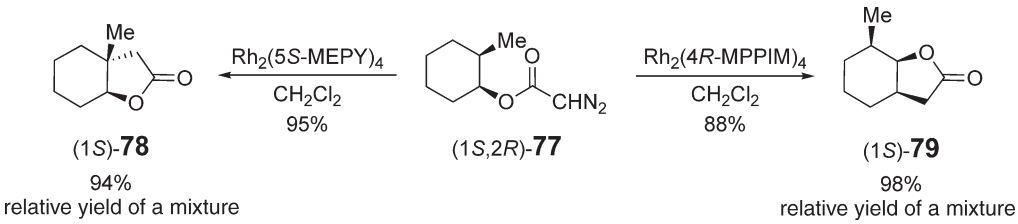


(65)

Effective double stereodifferentiation is possible in intramolecular C–H insertion.[199] For example, catalytic decomposition of enantiopure (1*S*,2*S*)-diazoacetate **74** by $Rh_2(4S\text{-MEOX})_4$ directed the reaction toward the preferential formation of γ-lactone (1*S*)-**75**, whereas the corresponding reaction catalyzed by $Rh_2(4R\text{-MEOX})_4$ prefers initially forming γ-lactone (1*S*)-**76** (Equation (66)). Similarly, treatment of (1*S*,2*R*)-diazoacetate **77** with $Rh_2(5S\text{-MEPY})_4$ or $Rh_2(4R\text{-MPPIM})_4$ gave (1*S*)-**78** or (1*S*)-**79**, respectively (Equation (67)).[199]

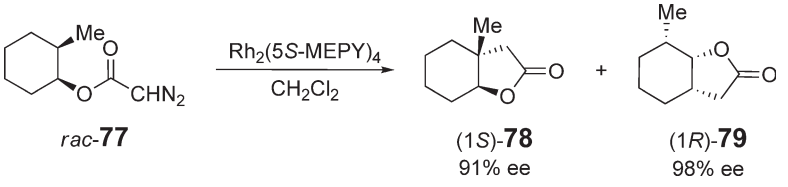


(66)



(67)

Having established that pure enantiomer (1*S*,2*R*)-**77** was capable of undergoing remarkably regioselective and diastereoselective C–H activation, it followed that highly efficient enantiomeric differentiation of *rac*-**77** could be accomplished.[199] Hence, the Rh_2(5*S*-MEPY)$_4$-catalyzed reaction of *rac*-**77** effectively gave close to a 1 : 1 mixture of enantioenriched (1*S*)-**78** (91% ee) and (1*R*)-**79** (98% ee) (Equation (68)). Other equally spectacular examples of diastereo- and regiocontrol via chiral rhodium carboxamide catalysts in cyclic and acyclic diazoacetate systems have been reported.[152,199,200,203–205]

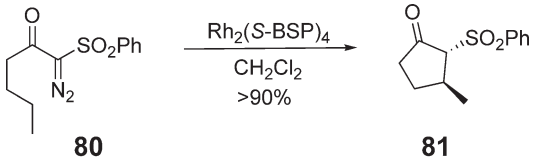


(68)

Rhodium(II) carboxamidates are clearly superior to all other types of catalysts in effecting highly chemo-, regio-, diastereo-, and enantioselective intramolecular C–H activation reactions of carbenoids derived from diazoacetates. Specifically, Rh_2(4*S*-MPPIM)$_4$ is the catalyst of choice for C–H activation reactions of simple primary and secondary alkyl diazoacetates. Likewise, Rh_2(4*S*-MACIM)$_4$ thus far has been the most successful catalyst with tertiary alkyl diazoacetates, whereas for primary acceptor-substituted diazoacetates with a pendant olefin side chain, Rh_2(4*S*-MEOX)$_4$ has proved to be highly selective.

10.04.3.4 Cyclopentanone Formation

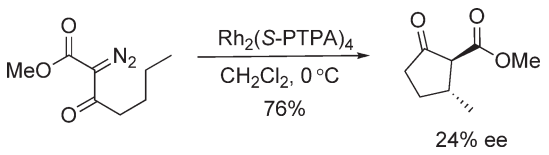
Wenkert and co-workers were the first to disclose the use of $Rh_2(OAc)_4$ for C–H insertion leading to cyclopentanone formation.[206] Then the versatility of this methodology was developed by Taber,[207–210] Stork, and Nakatani.[211] The first reported example of asymmetric induction was by McKervey and co-workers in 1990 and involved the Rh_2(*S*-BSP)$_4$-catalyzed decomposition of α-diazo-β-ketosulfone **80** (Equation (69)).[212] Cyclopentanone **81** was obtained in an excellent yield as a mixture of *cis*- and *trans*-isomers, although with poor enantioselectivity (12% ee).



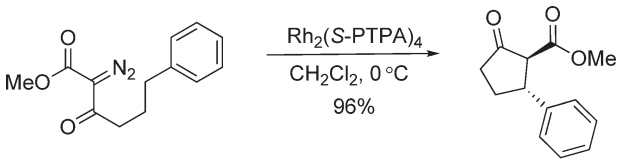
80 **81**
12% ee

(69)

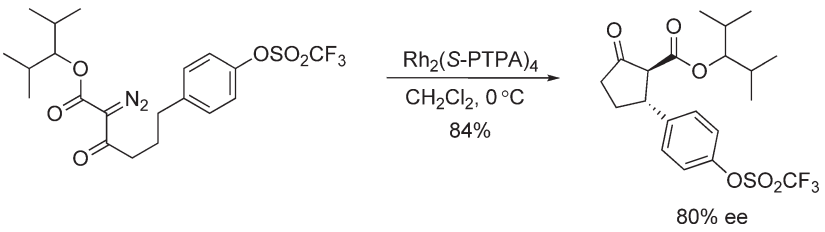
Diazo compounds containing two acceptor groups such as diazoketosulfones and diazoketoesters are less reactive toward metal-catalyzed diazo decomposition than unsubstituted α-diazocarbonyls, so much so that most rhodium(II) carboxamidate complexes are unable to effect nitrogen extrusion in these systems at ambient temperatures and typically require temperatures up to 80 °C.[117,148] Rhodium(II) carboxylates, however, are much more kinetically active than their carboxamidate counterparts and are capable of decomposing diazo compounds containing two acceptor groups even at temperatures below 23 °C.[40,101] The most effective catalysts for intramolecular C–H activation of carbenoids derived from α-diazo-β-ketoesters have been the *N*-phthaloyl amino acid catalysts developed by Ikegami and Hashimoto.[111,134,139,213,214] The enantioselectivity of the C–H activation process was found to be very dependent upon the size of the ester group and the nature of the substituents at the site of insertion. (Equations (70)–(72)). The highest levels of asymmetric induction occurred with substrates containing very large ester groups, and when the insertion occurred at benzylic sites in which the benzene ring had an electron-withdrawing substituent (Equation (72)).



(70)



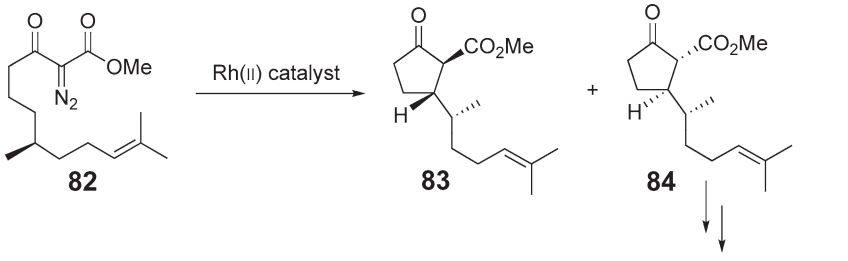
(71)



(72)

In the total synthesis of the *anti*-proliferative marine secosteroid (−)-astrogorgiadiol **85**, Taber and Malcolm screened several chiral rhodium catalysts in an attempt to enhance the diastereoselectivity for the cyclization of enantiopure α-diazo-β-ketoester **82** (Scheme 6).[215] The bridged prolinate catalyst Rh_2(*S*-biTISP)$_2$ gave the best levels of diastereocontrol, affording the key intermediate **84** with up to 58% de, albeit in modest yield. The *ent*-**82** was also tested with the same range of catalysts. Only under the influence of Rh_2(*S*-biTISP)$_2$ was the reaction found to be catalyst controlled. In all other cases, the chirality inherent in the starting diazoacetoacetate **82** dominated the outcome of the reaction.

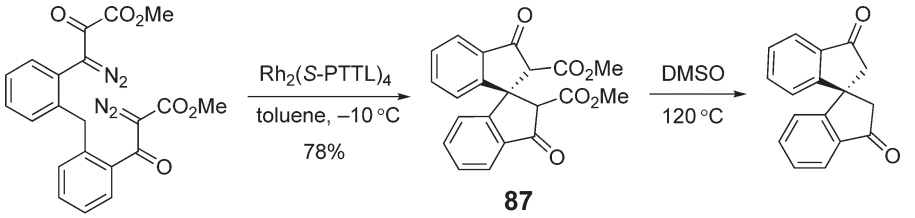
A very impressive example of the synthetic utility of this chemistry is the one-pot enantioselective double C–H activation reaction of **86** to generate chiral spiran **87** (Equation (73)).[172] In this case, the phthalimide catalyst Rh_2(*S*-PTPA)$_4$ was not especially effective (25% ee), but much better results were obtained with the bulkier Rh_2(*S*-PTTL)$_4$ catalyst (up to 80% ee). This catalyst has also been successfully used in the enantiotopically selective aromatic C–H insertions of diazo ketoesters (Equation (74)).[216] Moreover, dirhodium(II) tetrakis[*N*-tetrafluorophthaloyl-(*S*)-*tert*-leucinate], Rh_2(*S*-TFPTTL)$_4$, in which the phthalimido hydrogen atoms of the parent dirhodium(II) complex are substituted by fluorine atoms, dramatically enhances the reactivity and enantioselectivity (up to 97% ee). Catalysis



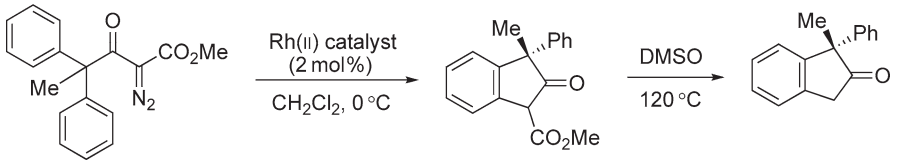
Catalyst	*Yield*	*Ratio* **83 : 84**
$Rh_2(OAc)_4$	92	43 : 57
Rh_2(*S*-PTPA)$_4$	98	26 : 74
Rh_2(5*S*-MEPY)$_4$	66	43 : 57
Rh_2(*S*-DOSP)$_4$	94	36 : 64
Rh_2(*S*-biTISP)$_2$	38	21 : 79

Scheme 6

with the use of 0.001 mol% of Rh_2(*S*-TFPTTL)$_4$ has achieved the highest turnover number (up to 98,000 with the methyl substituent) ever recorded for chiral dirhodium(II) complex-catalyzed carbene transformations, without compromising the yield or enantioselectivity of the process.[216]



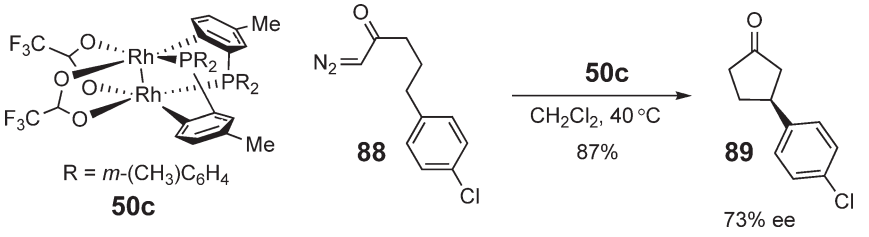
(73)



(74)

Catalyst	*Time*	*Yield* (%)	*ee* (%)
Rh_2(*S*-PTTL)$_4$	1 h	89%	92% ee
Rh_2(*S*-TFPTTL)$_4$	2 min	90%	97% ee

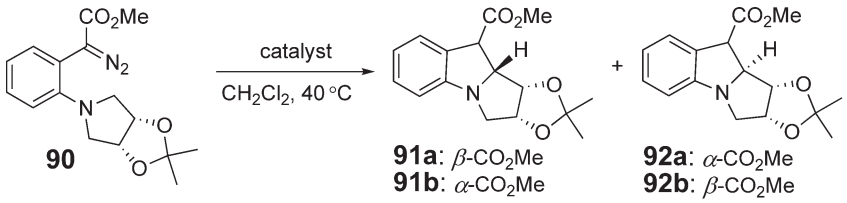
Carbenoids derived from diazoketones are notoriously reactive, and harnessing this reactivity in enantioselective processes has generally proved to be problematic.[119,120,204,217] A significant development in this field was the introduction of a family of *ortho*-metallated arylphosphine rhodium(II) catalysts by Lahuerta, Perez-Prieto, and co-workers, which in certain cases proved to be effective in mediating the cyclization of a number of diazoketones.[155,158,159,218] The reactions displayed wide variations in yield and enantioselectivity with the assorted ligated rhodium complexes used, and no catalyst proved to be consistently effective.[155] This underscores the importance of judicious choice of ligands when C–H activation reactions are conducted. The reactions were also highly sensitive to the influence of the substituents adjacent to the site of insertion, with electron-withdrawing groups tending to give the highest enantioinduction. For instance, the reaction of **88** catalyzed by catalyst **50c** generated the cyclopentanone **89** with 73% ee (Equation (75)). Presumably, the electron-withdrawing nature of the *para*-chloro substituent afforded a less activated benzylic site, which therefore experienced a later, and thus more selective, transition state when interacting with the electrophilic rhodium carbenoid.



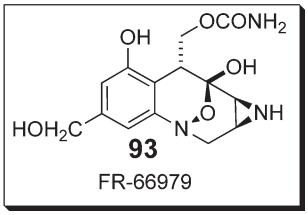
(75)

10.04.3.5 Dihydrobenzofuran and Dihydrobenzopyran Formation

The intramolecular C–H insertion of aryldiazoacetates is a very powerful strategy for synthesizing heterocyclic rings such as dihydrobenzofurans and dihydrobenzopyrans. The first effective asymmetric copper-catalyzed C–H activation reaction was reported by the group of Sulikowski in the synthesis of the anti-tumor antibiotic FR-66979 **93** (Scheme 7).[123,219] The C–H insertion of the aryldiazoacetate **90** formed four diastereomeric products **91a**, **91b**, **92a**,

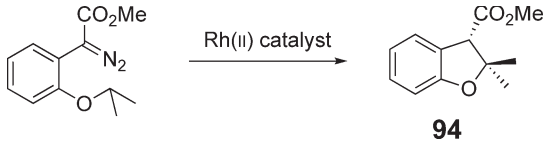


Catalyst	Yield (%)	Ratio 91a:91b:92a:92b	ee (%) 91	ee (%) 92
$Rh_2(OAc)_4$	95	37:13:45:5		
$Rh_2(5S\text{-MEPY})_4$	88	2:37:3:58	0	0
$Rh_2(S\text{-TBSP})_4$	95	30:10:54:6	11	10



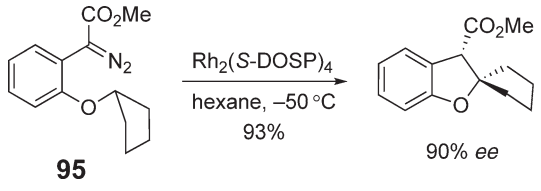
Scheme 7

and **92b**, and very low enantioselectivity (10–11% ee) was obtained using $Rh_2(S\text{-TBSP})_4$, although the rhodium prolinate catalysts were known to be very efficient in intermolecular C–H insertions of aryldiazoacetates. Intrigued by these results, independent studies by Davies[220] and Hashimoto[136] addressed C–H activation of aryldiazoacetates possessing an *ortho*-alkoxy substituent. $Rh_2(S\text{-DOSP})_4$ proved to be the catalyst of choice for C–H activation at a tertiary site (Equation (76)), giving **94** in an excellent 98% yield and 94% ee.[220] The $Rh_2(S\text{-PTTL})_4$-catalyzed reaction gave **94** with low asymmetric induction (22% ee).[136] Interestingly, although the $Rh_2(S\text{-DOSP})_4$-catalyzed reaction of cyclopentyl derivative **95** proceeded in excellent yield (Equation (77)), the reaction of the corresponding cyclohexyl derivative gave the desired spirocycle in only 12% yield, with carbene dimerization being the predominant product.[220] The low yield is thought to result from conformational restrictions associated with the cyclohexane system. In the methylene insertion of **96**, both $Rh_2(S\text{-PTTL})_4$ and $Rh_2(S\text{-DOSP})_4$ gave high diastereoselectivity, but $Rh_2(S\text{-PTTL})_4$ formed **97** with higher enantioselectivity (Equation (78)).



Catalyst	Yield (%)	ee (%)
$Rh_2(S\text{-DOSP})_4$	98	94
$Rh_2(S\text{-PTTL})_4$	88	22

(76)



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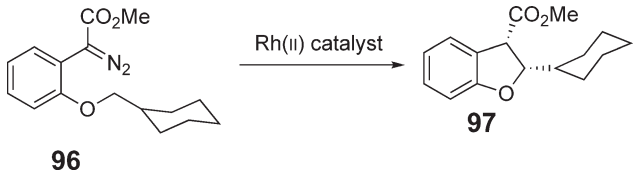
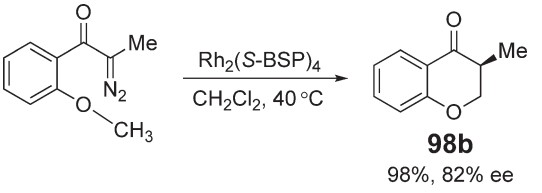


(78)

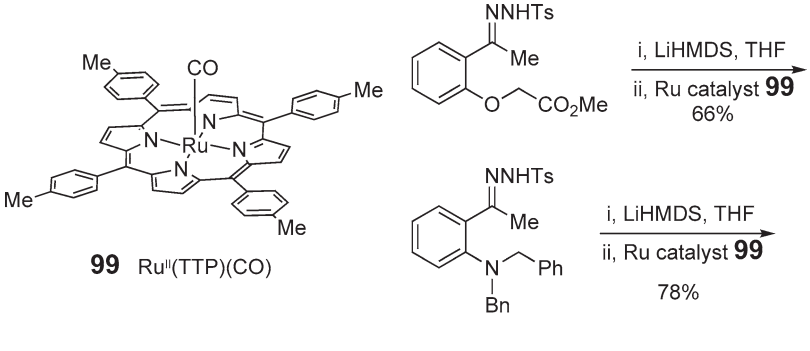
Catalyst	Yield (%)	de (%)	ee (%)
$Rh_2(S\text{-DOSP})_4$	72	95	63
$Rh_2(S\text{-PTTL})_4$	63	92	96

McKervey and co-workers studied C–H activation in a number of α-diazoketone species as a means of constructing a variety of chromanone derivatives. The formation of dihydrobenzopyran **98** was found to be catalyst-dependent, with highly electrophilic copper complexes generating solely products arising from sigmatropic rearrangement. In contrast, the considerably less electrophilic $Rh_2(5S\text{-MEPY})_4$ complex proved to be completely ineffective, unable to generate a suitably reactive carbenoid species to undergo C–H activation. Of the dirhodium(II) and copper(I) complexes tested, the tetraprolinate catalyst $Rh_2(S\text{-BSP})_4$ proved to be the most effective, generating **98b** with 82% ee (Equations (79) and (80)). Recently, Che reported a ruthenium porphyrin-catalyzed stereoselective intramolecular carbenoid C–H insertion.[221] *cis*-Disubstituted oxygen and nitrogen heterocycles have been synthesized very efficiently (Equations (81) and (82)). Most notably, these reactions are carried out with the carbenoid system lacking an acceptor group.

(79)



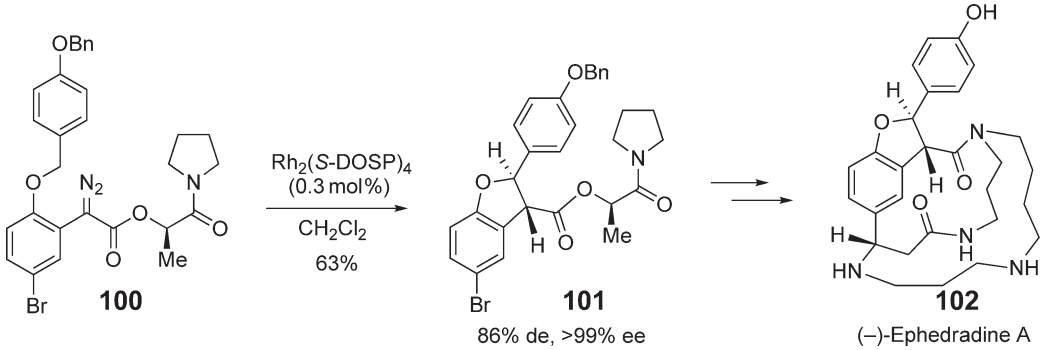
(80)



(81)

(82)

A very impressive application of this chemistry is the total synthesis of (−)-ephedradine A **102**.[222] The key intermediate *trans*-2-aryl-2,3-dihydrobenzofuran-3-carboxylic acid ester **101** was synthesized by intramolecular C–H insertion reaction. Upon treatment with a catalytic amount of $Rh_2(S\text{-DOSP})_4$, aryl diazo ester **100** possessing a chiral auxiliary underwent a C–H insertion reaction to give **101** in 63% yield and 86% de (Equation (83)).



(83)

10.04.4 Nitrene C–H Insertion

Nitrenes are neutral, electron deficient, and very reactive intermediates, containing six electrons in their outer shell. The four non-bonding electrons can be arranged either as two lone electron pairs, an electrophilic singlet nitrene, or as a lone pair and an unpaired biradical, a triplet nitrene. Triplet-state nitrenes react non-stereospecifically with C–H bonds by abstracting hydrogen atoms, forming two separate radicals which eventually couple. Singlet-state nitrenes can undergo direct insertion into a C–H bond with complete stereochemical fidelity.[223,224]

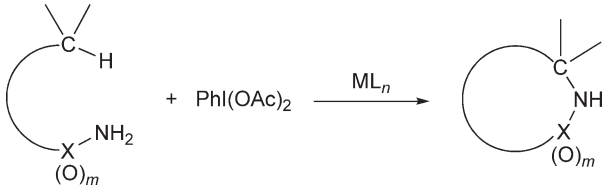
The transition metal-catalyzed C–H insertion reaction of carbenes to organic compounds is a well-established synthetic method, as shown in the first two sections in this chapter. However, nitrene C–H insertion, the corresponding reaction of carbene analog, is much less known. In the past decade, considerable advances have been made in the development of this chemistry into a generally useful C–H amination process by using improved catalysts and protocols, in which readily available amines or amides are used as the starting substrates. [36,67,225–229] Moreover, several examples of the application of this chemistry in total synthesis have been reported.[230–235]

10.04.4.1 Nitrene Precursors and Catalysts

Nitrenes can be generated from many precursors such as azides, isocyanates, ylides, heterocycles, and nitro compounds.[236,237] Amongst these, azides are the most convenient precursors since they are easily prepared and can be decomposed by heat, light or a suitable catalyst. Despite considerable endeavors, no one has yet provided a synthetically viable method to use azides as sources of nitrenes.[237] The breakthrough of nitrene chemistry was the recognization of the value of *N*-arenesulfonyl iminoiodinanes ($ArSO_2N{=}IPh$) as nitrene precursors by Breslow[238,239] and Mansuy.[240–243] They reported inter- and intramolecular C–H insertions by tosylimino phenyliodinane (TsN=IPh) in the presence of Mn(III) or Fe(III) porphyrins or $[Rh_2(OAc)_4]$. Subsequently, Müller demonstrated the intermolecular amination using *p*-nitrophenylsulfonyl iminoiodinane (NsN=IPh) as the nitrene source.[229,244–246]

TsN=IPh NsN=IPh

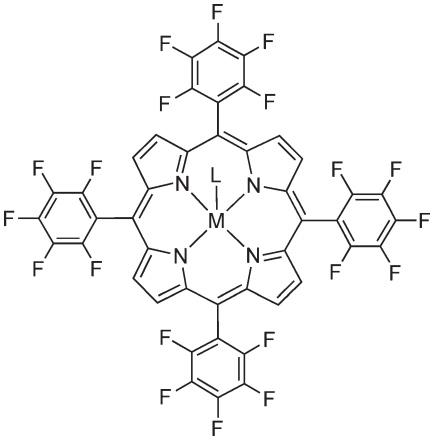
The iminoiodinanes PhI=NR, the most wisely used nitrene sources so far, are prepared from $PhI(OAc)_2$ and RNH_2. However, the variation of R groups is very limited; usually, R is $ArSO_2$. In a very few cases, the PhI=NR amidation procedure can be applied to intramolecular C–H insertion.[229,239,247,248] In 2000, Che demonstrated that $PhI(OAc)_2$ and $TsNH_2$ can replace the capricious TsN=IPh reagent for C–H insertion reactions with manganese and ruthenium porphyrins.[249] A similar discovery was made by Du Bois for intramolecular C–H amination of carbamate and sulfamate esters with rhodium (II) catalysts.[250,251] This "$PhI(OAc)_2 + RNH_2$" protocol is applicable to a wide variety of RNH_2 compounds and extended to intramolecular nitrene C–H insertion (Equation (84)).[252]



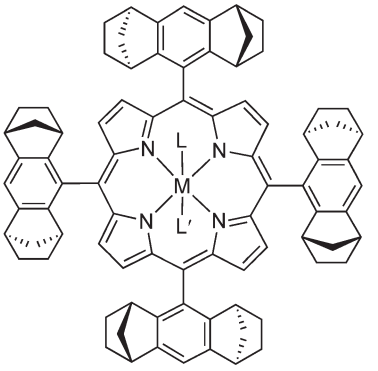
(84)

As shown in the previous two sections, rhodium(II) dimers are superior catalysts for metal carbene C–H insertion reactions. For nitrene C–H insertion reactions, many catalysts found to be effective for carbene transfer are also effective for these reactions. Particularly, $Rh_2(OAc)_4$ has demonstrated great effectiveness in the inter- and intramolecular nitrene C–H insertions. The exploration of enantioselective C–H amination using chiral rhodium catalysts has been reported by several groups.[225,244,253–255] Hashimoto's dirhodium tetrakis[*N*-tetrachlorophthaloyl-(*S*)-*tert*-leucinate], Rh_2(*S*-TCPTTL)$_4$,[253] and Pirrung's binaphthylphosphate-derived rhodium complex, Rh_2(*R*-BNP)$_4$ **48**,[244] afforded moderate enantiomeric excess for amidation of benzylic C–H bonds with NsN=IPh.

Metal porphyrins have been employed for intermolecular C–H amination with allylic, benzylic, and some saturated hydrocarbons using $ArSO_2N{=}IPh$ reagents.[238,240] More recently, Ru- and Mn-tetrakis(pentafluorophenyl)porphyrins **103** and **104** have been applied as catalysts to this reaction. High yields and good substrate conversions have been achieved. [249,256] The chiral ruthenium(II) and manganese(III) porphyrins **105** and **106** have been reported to catalyze the asymmetric amidation of saturated C–H bonds of ethylbenzene and ethylnaphthalenes to the corresponding amides in up to 85% yield with 45–58% ee.[257]

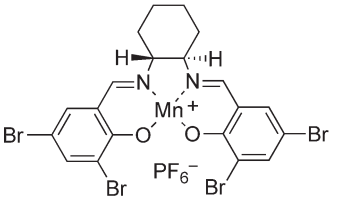


103: M = Ru(II); L = CO
104: M = Mn(III); L = Cl

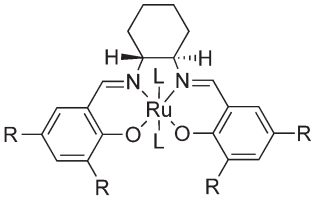


105: M = Ru(II); L = CO; L′ = EtOH
106: M = Mn(III); L = HO^-; L′ = MeOH

An asymmetric C–H insertion using a chiral 3,3′,5,5′-tetrabromosubstituted (salen)manganese(III) complex **107** with TsN=IPh afforded insertion products with ee up to 89%.[258] Che reported the first amidation of steroids such as cholesteryl acetate with (salen)ruthenium(II) complexes **108**.[259]



107

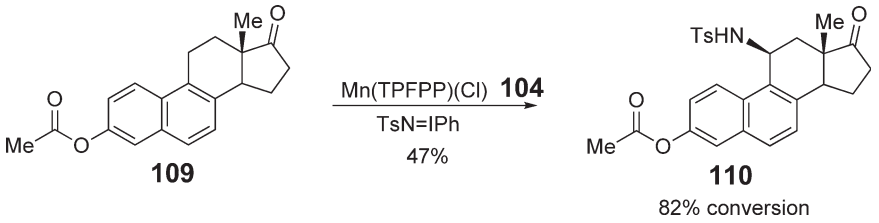


108 L = PPh_3, R = NO_2, I, Br

10.04.4.2 Manganese-catalyzed Nitrene C–H Insertion

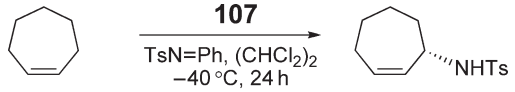
The metal-mediated amidation of saturated C–H bonds with a nitrene source was pioneered in 1982 by Breslow and Gellman, who successfully amidated cyclohexane with TsN=IPh in the presence of iron or manganese porphyrins.[238,239] Thereafter, Mansuy and co-workers demonstrated that iron and, particularly, manganese porphyrins can catalyze TsN=IPh amidation of adamantane or allylic amidation of alkenes in up to 70% yields.[240,242,243,260] However, all these amidation systems require the synthesis of a nitrene precursor $PhI{=}NR$ from $PhI(OAc)_2$ and NH_2R. In 2000, Che and co-workers reported that Mn(TPFPP)(Cl) **104**, which bears an electron-deficient porphyrin macrocycle *meso*-tetrakis(pentafluorophenyl)porphyrinato dianion (TPFPP), served as a good catalyst toward TsN=IPh amidation of a variety of hydrocarbons, including ethylbenzene, indan, adamantane, cyclohexene, tetrahydrofuran, 1,2-dihydronaphthalene, 2-ethylnaphthalene, and 3-hexene with high turnover numbers. More importantly, they demonstrated that $PhI(OAc)_2$ and NH_2R (R = Ts, Ns, and SO_2Me) can replace the capricious $ArSO_2N{=}IPh$ reagent as nitrene source.[249] The amidations of ethylbenzene, indan, adamantane, cyclohexene, and tetrahydrofuran directly with $PhI(OAc)_2$ and NH_2Ts as amidating reagents were explored by employing catalyst **104** (Table 1). In dichloromethane at 40 °C, with a **104**: substrate: $PhI(OAc)_2$: NH_2Ts molar ratio of 1 : 100 : 125 : 150,

the corresponding *N*-substituted amides were obtained in 72–90% yields within 2 h with good to excellent substrate conversions (Table 1). At the same time, independently, Breslow reported the amidation of equilenin acetate **109** with TsN=IPh catalyzed by catalyst **104** (Equation (85)).[261]

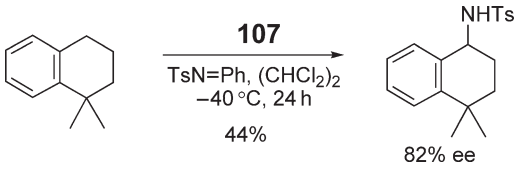


(85)

Chiral manganese complexes have been used to perform the enantioselective amidation of saturated C–H bonds.[256–258,262] Cationic Mn(salen) **107** showed good catalytic activity and moderate enantioselectivity. Typical examples are shown in Equations (86)–(88). High enantioselectivity of 89% ee was obtained in the reaction of 1,1-dimethylindan (Equation (88)).[258] Chiral manganese(III) porphyrin **106** was used in the enantioselective amidation as well; nevertheless, the best enantioselectivity was only 54% (Equation (89)).[256,257]

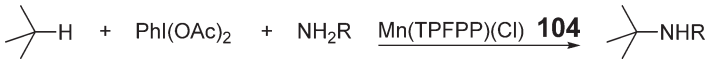


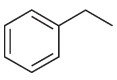
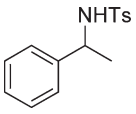
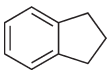
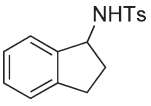
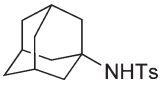
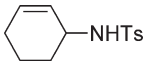
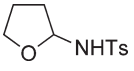
(86)

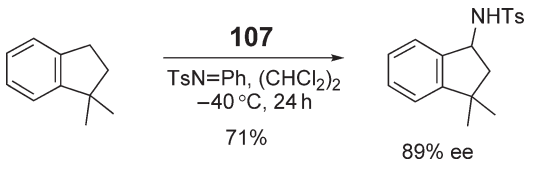


(87)

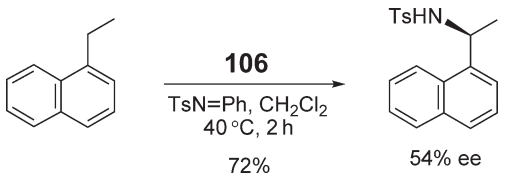
Table 1 Amidation of saturated C–H bonds with $PhI(OAc)_2$ and NH_2Ts catalyzed by Mn(TPFPP)(C1) **104**



Entry	*Substrate*	*Product*	*Conversion (%)*	*Yield (%)*
1			58	81
2			88	90
3			36	72
4			86	83
5			91	85



(88)

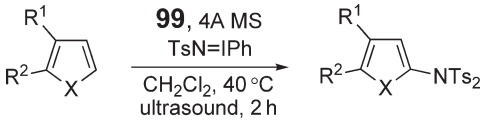


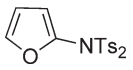
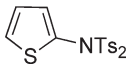
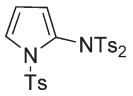
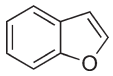
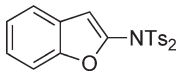
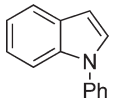
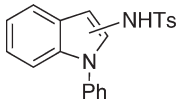
(89)

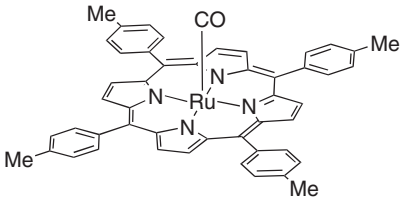
10.04.4.3 Ruthenium-catalyzed Nitrene C–H Insertion

In company with manganese porphyrin complex, ruthenium porphyrins have already shown great catalytic activity in the intermolecular amidation of saturated C–H bonds.[252,257,259,263] However, examples of amidation of aromatic C(sp^2)–H bonds are sparse in the literature.[51] Although reactions of these heterocycles with metallocarbenoids to give cyclopropanes are known,[264,265] examples of protocols for catalytic amidation of heteroarenes have limited precedent in the literature. In 2004, Che and co-workers described amidation of C(sp^2)–H bonds of heteroarenes such as furan, pyrrole, and thiophene using ruthenium(II) porphyrin **99** as a catalyst and TsN=IPh as a nitrogen source. The results are summarized in Table 2.[288] Most of the substrates gave moderate to good yield and only the *N*,*N*-ditosylamidated product was obtained. With *N*-phenylindole as a substrate, the Ru-catalyzed amidation with 1.5 equiv. of TsNI=Ph afforded *N*-monotosylamide as a 1 : 1 mixture of 2- and 3-regioisomers in 64% yield (entry 5, Table 2).

Table 2 [Ru^{II}(TTP)(CO)]-catalyzed amidation of aromatic heterocycles with PhI=NTs

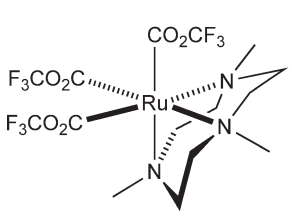


Entry	*Substrate*	*Product*	*Percent yield*/(*conversion*)
1			73(99)
2			33(56)
3			80(22)
4			58(50)
5			64(99)

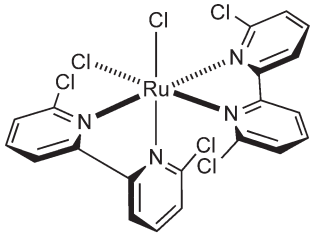


99 $Ru^{II}(TTP)(CO)$

Non-porphyrin ruthenium complexes $[Ru^{III}(Me_3tacn)(CF_3CO_2)_3 \cdot H_2O]$ **111** ($Me_3tacn = N,N',N'$-trimethyl-1,4,7-triazacyclononane) and *cis*-$[Ru^{II}(6,6'\text{-}Cl_2bpy)_2Cl_2]$ **112** (6,6′-Cl_2bpy=6,6′-dichloro-2,2′-bipyridine) have been investigated in nitrene C–H insertions.[266] With TsN=IPh as nitrogen source, both catalysts efficiently promote the amidation of adamantane, cyclohexene, ethylbenzene, cumene, indan, tetralin, and diphenylmethane to afford *N*-substituted sulfonamides in 80–93% yields with high selectivity. Selected examples are shown in Table 3. Competitive amidations of *para*-substituted ethylbenzenes and kinetic isotope effect studies for the amidation of cyclohexene/cyclohexene-d_{10} suggest that the amidation processes probably proceed via the hydrogen abstraction by a reactive Ru=NTs species to form a carboradical intermediate. The amidation with $PhI(OAc)_2/TsNH_2$ gave results comparable to those obtained with TsN=IPh. Extension of the "$PhI(OAc)_2/TsNH_2$ + catalyst **111** or **112**" protocol to $MeSO_2NH_2$ and $PhCONH_2$ with ethylbenzene as substrate produced the corresponding *N*-substituted amides in up to 89% yield.[266]

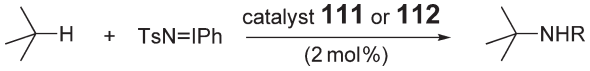


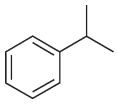
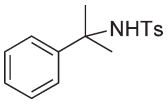
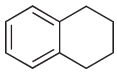
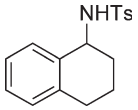
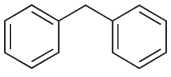
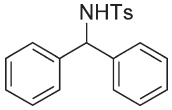
$Ru^{III}(Me_3tacn)(CF_3CO_2)_3$
111



cis-$[Ru^{II}(6,6'\text{-}Cl_2bpy)_2Cl_2]$
112

Table 3 Amidation of saturated C–H bonds with PhI=NTs catalyzed by complexes **111** or **112**



Entry	*Substrate*	*Product*	*Catalyst*	*Percent yield/(conversion)*
1			**111** **112**	80(38) 90(40)
2			**111** **112**	86(57) 84(50)
3			**111** **112**	90(61) 89(58)

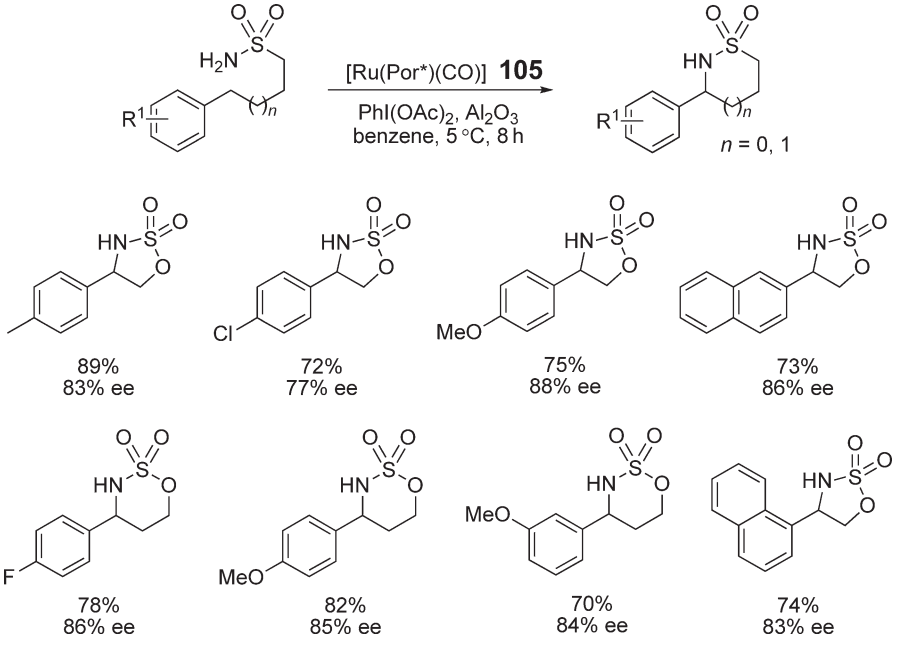
The Du Bois group demonstrated that reactions of a series of carbamates ($-OCONH_2$)[250] and sulfamate esters ($-OSO_2NH_2$)[251] with $PhI(OAc)_2$ was catalyzed by dirhodium complexes. These reactions occur by the direct intramolecular amidation of saturated C–H bonds and afford oxazolidinones and cyclic sulfamidates, respectively, with high regioselectivity and good to excellent diastereoselectivity. Furthermore, these reactions are stereospecific, allowing syntheses of enantiomerically pure amidation products from enantiomerically pure carbamates or sulfamate esters, which have found great utility in the syntheses of natural products, manzacidins A and C.[234] However, it remains a challenge to realize asymmetric intramolecular amidation of saturated C–H bonds from prochiral RNH_2 substrates. Che reported the first metal-catalyzed enantioselective intramolecular amidation of prochiral sulfamate esters by employing chiral ruthenium porphyrin [Ru(Por*)(CO)] **105** as a catalyst.[252,267] Cyclic sulfamidates, very important intermediates in organic synthesis,[268,269] have been obtained in 70–89% yields and 77–88% ee (Scheme 8).

10.04.4.4 Rhodium(II)-catalyzed Nitrene C–H Insertion

10.04.4.4.1 Intramolecular nitrene C–H insertion

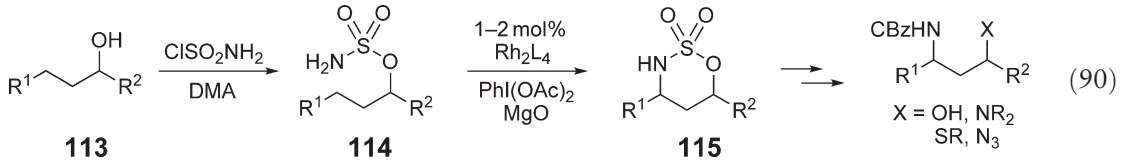
After Breslow and Gellman reported the first nitrene C–H insertions by an iminoiodinane reagent in the 1980s,[238] the intermolecular nitrene C–H insertion has been extensively studied. Meanwhile, the intramolecular nitrene C–H insertion received almost no attention for about twenty years. A major breakthrough in this area came from the work of Du Bois and Espino in 2001.[36,250] Thus, simple carbamates were transformed into oxazolidinones via a regioselective intramolecular rhodium-catalyzed C–H insertion mediated by $PhI(OAc)_2$. A key element of this reaction was the need for a base additive in order to scavenge the generated acetic acid detrimental to the catalytic activity of rhodium complexes. Magnesium oxide was found to be optimal for this. The formation of five-membered rings is strongly favored. In addition to benzylic and allylic C–H centers, carbamate insertions occur smoothly at saturated 2° and 3° sites (Scheme 9).[250] The C–N bond formation is stereospecific, consistent with the formation of a metallonitrene or nitrenoid intermediate, rather than a free carbamoylnitrene, mediated by an iodine(III) species.[226]

When sulfamate esters **114** are used as substrates, six-membered-ring formation is favored, and results in the selective formation of 1,2,3-oxathiazinane-2,2-dioxide heterocycles **115**.[251] Nevertheless, five-membered cyclic sulfamidates could be obtained when no alternative cyclization was possible. 1,3-Amino alcohols and related β-amino acids are thus readily accessible from the same simple alcohols **113** by converting them into sulfamates **114** (Equation (90)). Furthermore, in comparison to the carbamate reaction (Scheme 9), the sulfamate substrates have



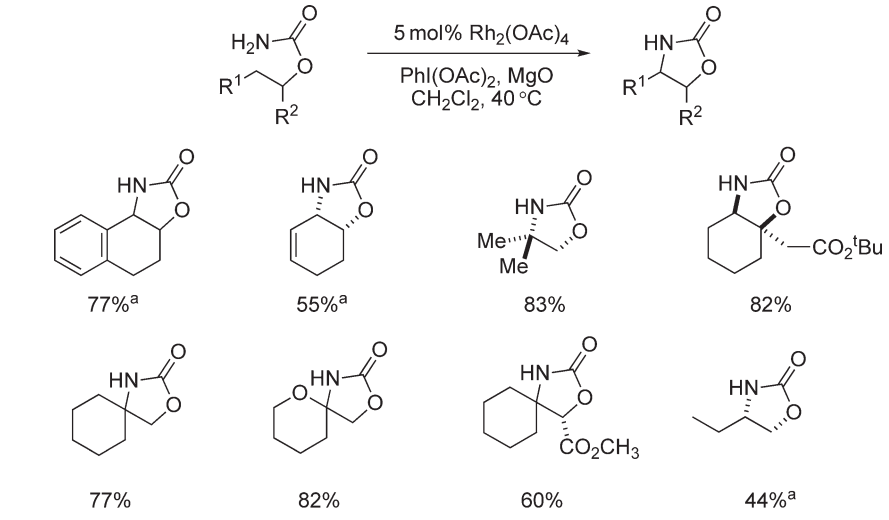
Scheme 8

much faster turnover rates. Thus, the catalyst loading could be reduced to 1–2 mol% for these reactions. In addition to their improved efficiency, the range of sulfamate structures that may be employed with this amination method is greater than with carbamates (Scheme 10).



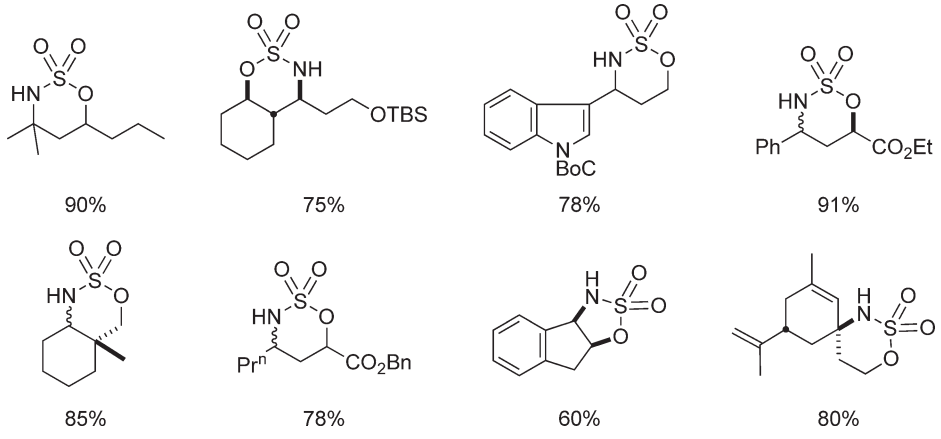
(90)

A very elegant expansion of the synthetic utility of this intramolecular amination was the insertion reactions into ethereal C–H bonds.[270–272] Du Bois and co-workers have exploited this reactivity to prepare cyclic sulfamates that are then used as iminium ion equivalents. Upon treatment with a suitable Lewis acid, nucleophilic addition reactions



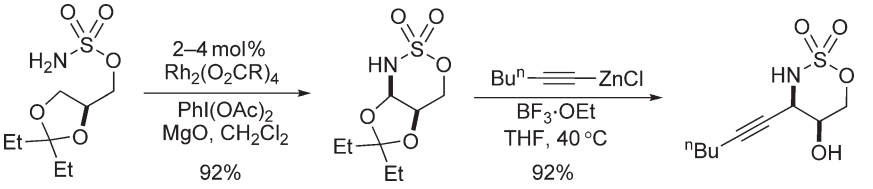
[a]$Rh_2(tpa)_4$ was used as catalyst: tpa = triphenylacetate.

Scheme 9



Scheme 10

to oxathiazinane *N,O*-acetals proceed smoothly with zinc acetylides, allylsilanes, and silyl enol ethers to form the corresponding 1,3-amino alcohols (Equation (91)).

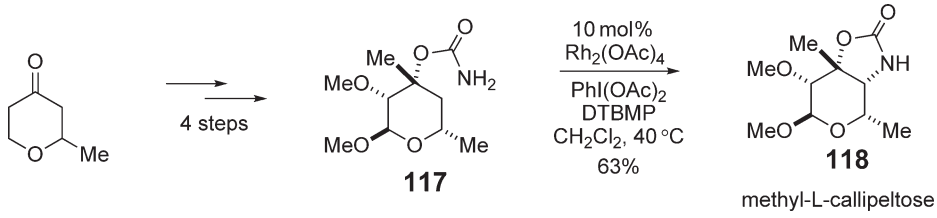


(91)

Du Bois originally used rhodium(II) acetate and rhodium triphenylacetate (tpa) as catalysts and found that regio- and diastereocontrol was influenced by the catalysts, but neither was particularly effective when low catalyst loadings were used. Inspired by the bridged dirhodium catalysts which have been developed for carbenoid chemistry,[40,273,274] a second generation catalyst $Rh_2(esp)_2$ **116** (esp = $\alpha,\alpha,\alpha',\alpha'$-tetramethyl-1,3-benzenedipropionate) was designed which was capable of much higher turnover numbers (Scheme 11).[275] Furthermore, this catalyst was effective in intermolecular reactions.

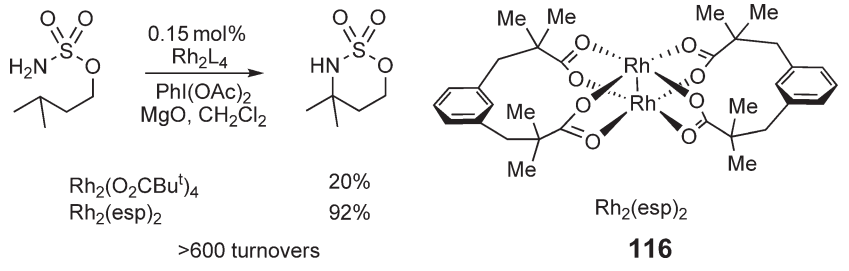
10.04.4.4.2 Applications in total synthesis

The intramolecular insertion reactions of nitrenoids into C–H bonds as described above provide an attractive alternative to conventional methods of amine formation. Both carbamate and sulfamate C–H insertions have been applied successfully to the total syntheses of natural products.[230–234] The first application of carbamate C–H insertion was reported by Trost in the total synthesis of methyl-L-callipeltose **118** (Equation (92)).[230] Intermolecular C–H insertion of carbamate **117** using 10 mol% $Rh_2(OAc)_4$, $PhI(OAc)_4$, and DTBMP (2,6-di-*tert*-butyl-4-methylpyridine) in dichloromethane (40 °C) furnished methyl-L-callipeltose **118** in 63% yield. In an another independent total synthesis of **118**, Panek performed this step in refluxing benzene and improved the yield to 93%.[231]



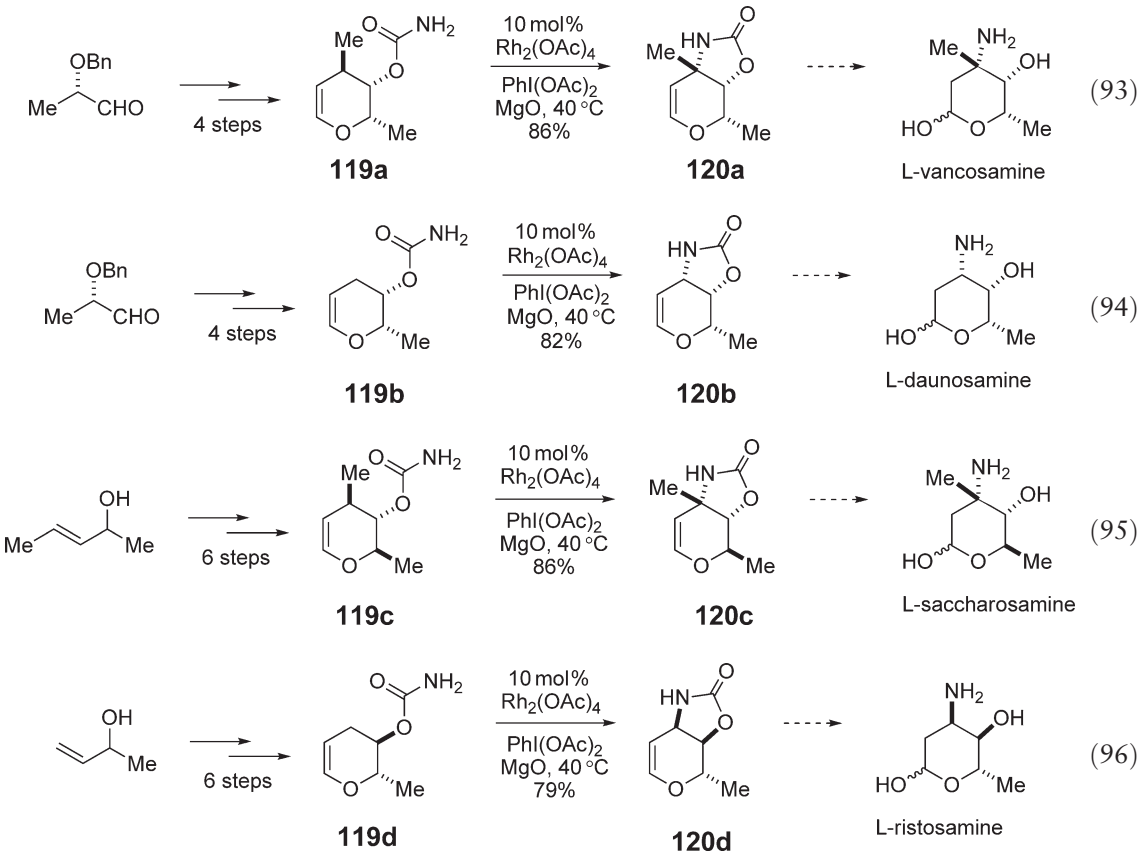
(92)

Protected 3-amino glycols are versatile synthetic intermediates that may serve as precursors for amino glycal reagents, for 2-deoxy sugars and 2-oxygenated sugars, and for glycosylated antibiotics and peptides.[276–278] Historically, the preparation of 3-amino glycal synthons has relied on the modification of simple glycosides.[279] Parker has outlined an elegant, enantioselective syntheses of carbamate-protected 3-amino glycols **120** from non-carbohydrate precursors using the rhodium nitrene C–H insertion as the crucial step (Equations (93)–(96)).[232,235] Intermolecular C–H insertion of carbamate **119**, which is constructed by tungsten-catalyzed cycloisomerization, is performed with 10 mol% $Rh_2(OAc)_4$ and proceeds stereospecifically to give the oxazolidinone **120**. Using this



Scheme 11

strategy, protected glycals of L-vancosamine (Equation (93)), L-daunosamine (Equation (94)), D-saccharosamine (Equation (95)), and L-ristosamine (Equation (96)) have been efficiently obtained.

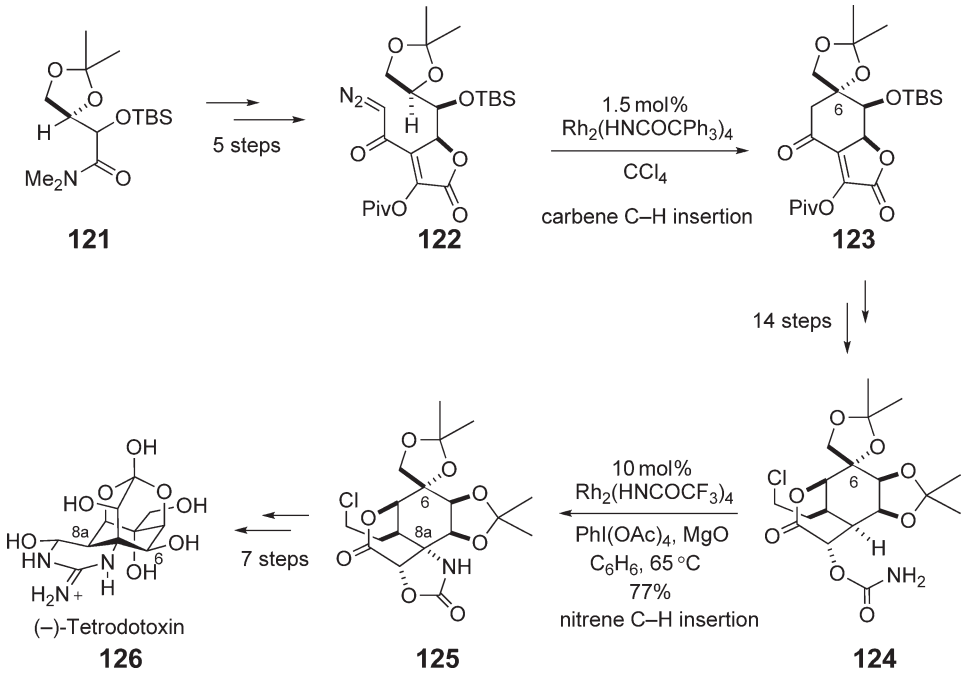


The signature application for the C–H insertion in synthesis is probably the total synthesis of (−)-tetrodotoxin **126** by Du Bois and Hinman.[233] Two stereospecific C–H activation steps, rhodium-catalyzed carbene C–H insertion and carbamate-based nitrene C–H insertion, have been used to install the two tetrasubstituted centers C6 and C8a (Scheme 12). Diazoketone **122** was treated with 1.5 mol% $Rh_2(HNCOCPh_3)_4$, and cyclic ketone **123** was selectively formed in high yield without purification. The reaction of carbamate **124** with 10 mol% $Rh_2(HNCOCF_3)_4$, $PhI(OAc)_4$, and MgO in C_6H_6 solvent furnished the insertion product **125** in 77% yield.

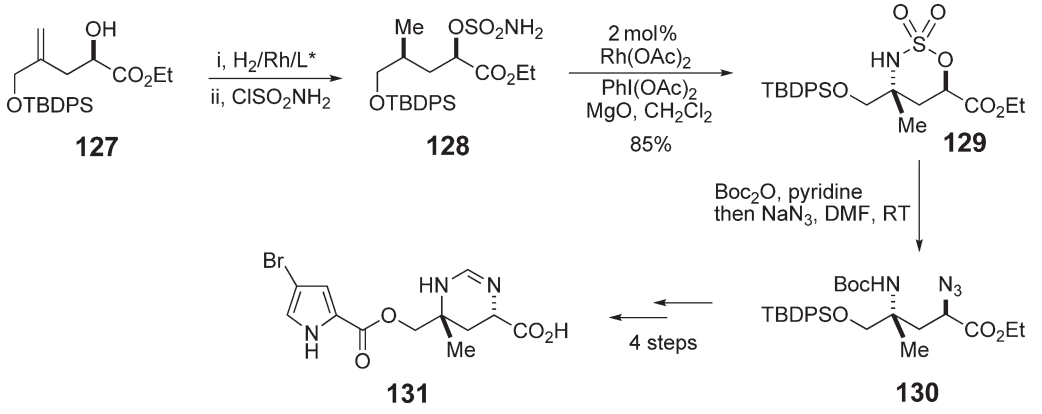
The sulfamate ester variant of this chemistry has already been shown to be a very powerful protocol for the syntheses of 1,3-amino alcohols and related β-amino acids (Equation (90)), as well as iminium ion equivalents (Equation (91)). The further showcases of this chemistry are the total syntheses of the bromopyrrole alkaloids, manzacidins A and C (Scheme 13).[234] The cyclic sulfamidate **129** was obtained diastereospecifically from sulfamate **128** using intramolecular rhodium-catalyzed C–H insertion. It was then found to react with sodium azide in *N*,*N*-dimethylformamide at room temperature after introduction of the Boc-activating group to afford the 1,3-diamino precursor **130** in 78% yield over 3 steps. Four subsequent manipulations afford the target structure **131**.

10.04.4.5 Catalysis by Other Metals

The first metal-catalyzed nitrogen atom-transfer process was reported by Kwart and Khan, who demonstrated that copper powder promoted the decomposition of benzenesulfonyl azide when heated in cyclohexene.[280] Evans has demonstrated that Cu(I) and Cu(II) triflate and perchlorate salts are efficient catalysts for the aziridination of olefins employing TsN=IPh as the nitrene precursor.[281] Subsequent to this finding, intensive effort has focused on the identification of new achiral and chiral copper complexes that serve competently to mediate this event.[225,228] However, very few examples of copper catalysts have been used in nitrene C–H insertion reactions.[247,282–284] Katsuki and co-workers reported the benzylic and allylic amination by treatment of alkenes or alkylarenes with *t*-butyl *N*-(*p*-toluenesulfonyl)peroxycarbamate

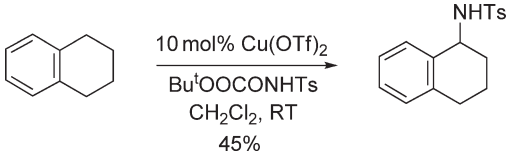


Scheme 12

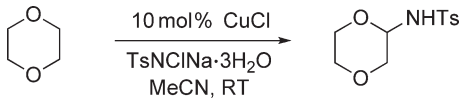


Scheme 13

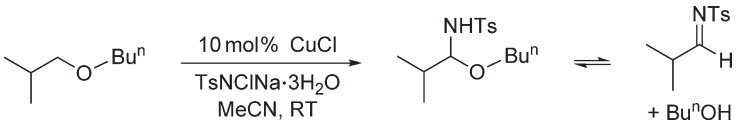
in the presence of Cu(II) triflate (Equation (97)). [282] Amination of C–H bonds activated by other oxygen atoms is facile with chloramine-T as nitrene source and copper(I) chloride in acetonitrile as catalyst.[284] For cyclic ethers, the hemiaminal products are generally stable, and can be isolated pure (Equation (98)). For acyclic ethers, the hemiaminal products, as expected, fragment with elimination of alcohol to yield imines (Equation (99)).



(97)



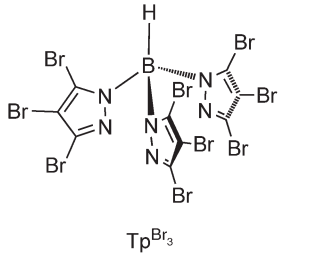
(98)

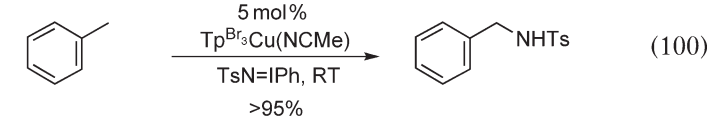


(99)

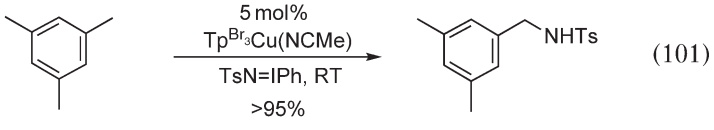
As shown in the manganese- and ruthenium-catalyzed intermolecular nitrene insertions, most of these results supposed the transfer of a nitrene group from iminoiodanes of formula PhI=NR to substrates that contain a somewhat activated carbon–hydrogen bond (Scheme 14). Allylic or benzylic C–H bonds, C–H bonds α to oxygen, and very recently, C(sp^2)–H bonds of heterocycles have been the preferred reaction sites for the above catalytic systems, whereas very few examples of the tosylamidation of unactivated C–H bonds have been reported to date.

Perez and co-workers reported the electron-deficient copper homoscorpionate catalyst Tp^{Br3}Cu(NCMe)-catalyzed nitrene insertion into C–H bonds of toluene, mesitylene, and cyclohexane, which are very unreactive substrates (Equations (100)–(102)).[51] In contrast to the former reports,[238,239,263] they obtained very high yields for these products. Furthermore, the first direct amination of benzene has been achieved and has generated the aniline derivative in an acceptable yield (Equation (103)). Recently, a cationic copper(I) complex **132**-catalyzed nitrene transformation to the C–H bonds of the electron-rich arene was reported by Sadighi and co-workers (Equation (104)).[285]

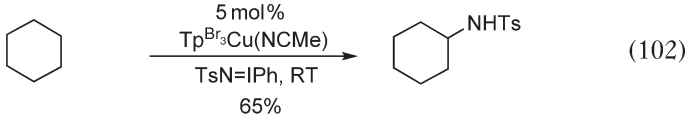




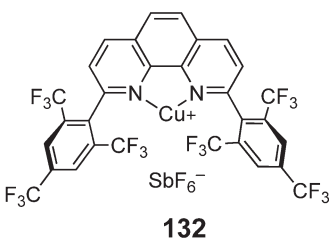
(100)



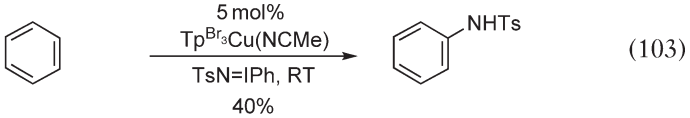
(101)



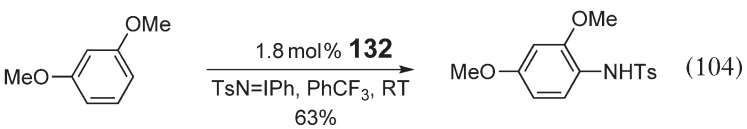
(102)



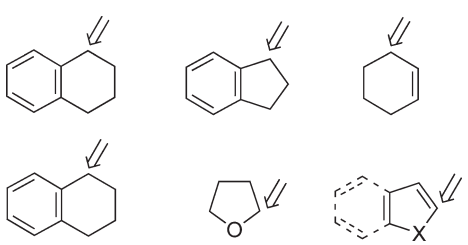
132



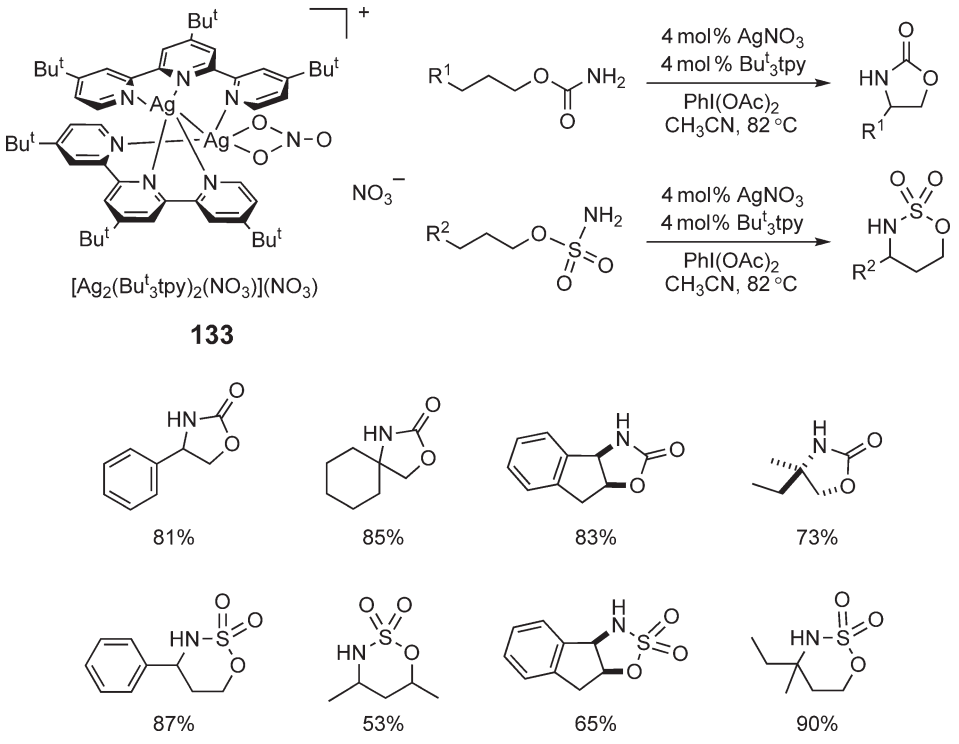
(103)



(104)



Scheme 14 Usual substrates employed in the metal-catalyzed intermolecular nitrene C–H insertion.



Scheme 15

Cui and He demonstrated a very interesting silver-catalyzed intramolecular amidation of saturated C–H bonds.[286] The catalyst they used is a novel disilver compound **133** (Scheme 15), which has been shown to efficiently catalyze the aziridination of olefins.[287] The same compound generated *in situ* could catalyze the activation of saturated C–H bonds of the substrates without olefin moieties. A range of carbamates and sulfamates were tested as shown in Scheme 8. Five-membered-ring and six-membered-ring insertion products were generated preferentially from carbamates and sulfamates, respectively. Good to excellent yields comparable to or better than those found with other catalytic systems[250,251,272] were observed with the silver catalyst **133**. Control experiments indicate that the silver-catalyzed reaction is stereospecific and provides support for the involvement of a nitrene-type oxidation in the reaction.

In summary, metal carbene and metal nitrene C–H functionalizations have undergone explosive growth over the last decade. Major advances have been made in both intermolecular and intramolecular versions of this chemistry. The reactions represent new strategic methods for synthesis, and with the foundation set, it is expected that the chemistry will be even more broadly used in synthesis in the future.

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10.05
Synthetic Reactions via C–H Bond Activation: Oxidation of C–H Bonds

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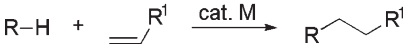
10.05.1 Introduction

This chapter mainly treats transition metal-catalyzed direct functionalization of carbon–hydrogen bonds in organic compounds. This methodology is emphasized by focusing on important functionalizations for synthetic use. The contents reviewed here are as follows: (i) alkylation of C–H bonds, (ii) alkenylation of C–H bonds, (iii) arylation of C–H bonds, (iv) carbonylation of C–H bonds, (v) hydroxylation and the related reactions, and (vi) other reactions and applications.

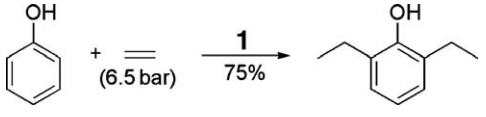
10.05.2 Alkylation of C–H Bonds

The C–H bond activation followed by addition to a double bond leads to the formation of alkylated compounds (Equation (1)). This reaction involves aromatic, aliphatic, olefinic, and acetylenic C–H bonds.

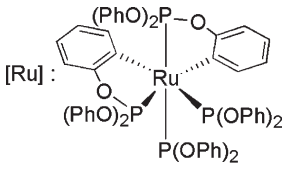


(1)

The addition to a double bond is observed in aromatic substrates where the reaction is assisted by chelation. The initial success of such reactions was achieved with the double alkylation of phenol with ethene (Equation (2)).[1] This reaction occurs at the *ortho*-positions selectively by using an orthometallated ruthenium phosphate complex **1**.

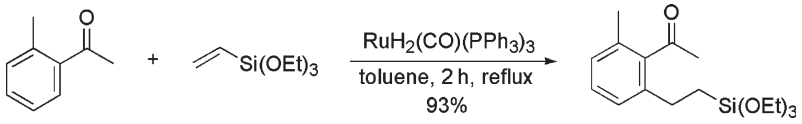


(2)



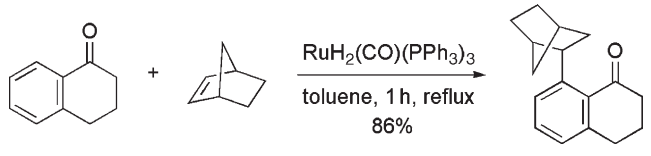
1

The reaction of aromatic ketones with olefins catalyzed by $RuH_2(CO)(PPh_3)_3$ was found to proceed with a high efficiency and a high selectivity (Equation (3)).[2] In this reaction, alkylation takes place regioselectively at the *ortho*-position of aromatic ketones. This direct alkylation process reduces the reaction steps for synthesis by the conventional methods. As shown in Scheme 1, this catalytic reaction is initiated by coordination of ruthenium on the carbonyl oxygen of the ketone:[3,3a] This chelation brings ruthenium very close to the *ortho*-C–H bond, causing the efficient catalytic reaction and the high regioselectivity. The enone structure is essential to this catalytic reaction, which proceeds with a stepwise mechanism. The ruthenium coordinated on the carbonyl oxygen attacks at the *ortho*-carbon nucleophilically, followed by the migration of hydride to the ruthenium.

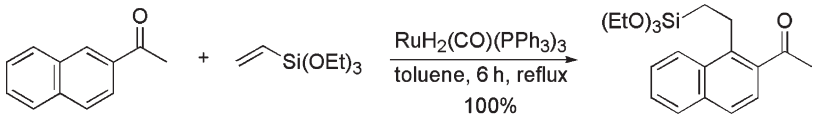


(3)

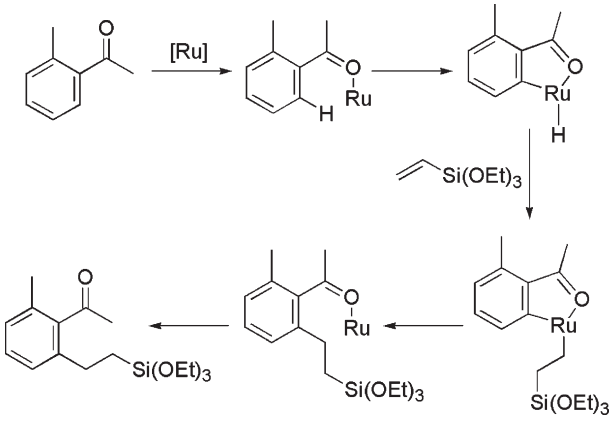
Examples shown in Equations (4)–(7) indicate that this reaction is generally applicable with regard to the carbonyl component: cyclic aromatic ketones, naphthyl ketones, and heteroaromatic ketones. Various olefins including vinylsilanes, norbornene, and aromatic olefins can be used in this reaction. Also, this reaction demonstrates the high functionality tolerance, and shows a high selectivity for alkylation as shown in Table 1.[4,4a] The reaction proceeds well even in the presence of electron-donating substituents such as amino and methoxy groups and electron-withdrawing groups such as trifluoromethyl, cyano, and ester groups.



(4)

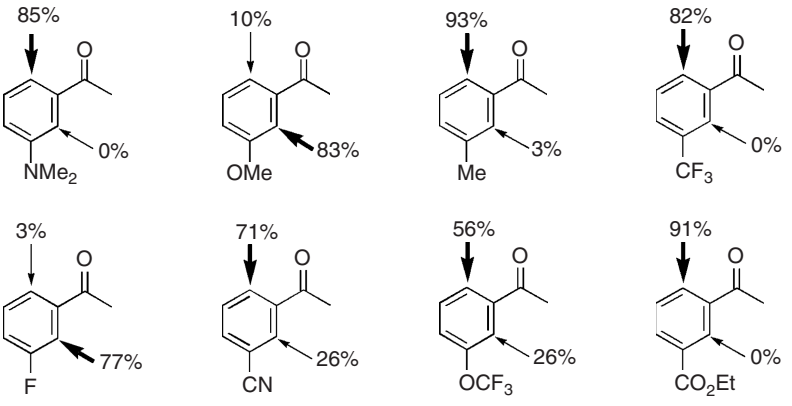


(5)

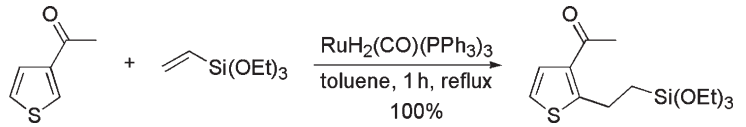


Scheme 1

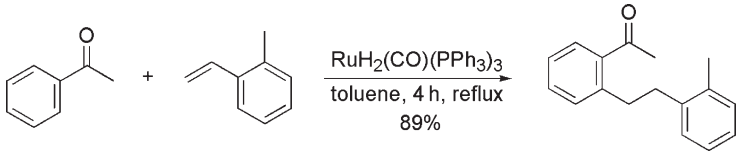
Table 1 Selectivity controlled by substituents[a]



[a]Percentages refer to yields of isomers from the reaction with (triethoxy)vinylsilane.

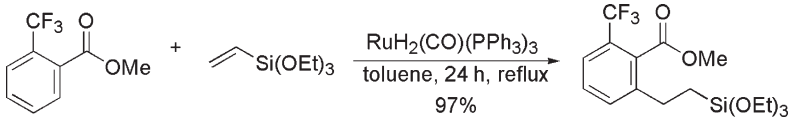


(6)



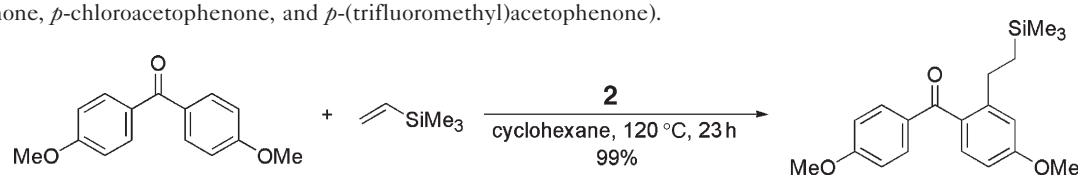
(7)

The use of ester and formyl groups for this reaction is also possible. The reaction of methyl benzoates with olefins proceeds when the benzoates have electron-withdrawing substituents such as trifluoromethyl, cyano, and ester groups (Equation (8)).[5,5a] In the case of aldehydes, the reaction requires sterically hindered substituents such as *tert*-butyl and trimethylsilyl groups.[6]

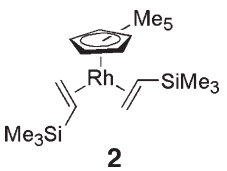


(8)

The *ortho*-alkylation of aromatic ketones with olefins can also be achieved by using the rhodium bis-olefin complex $[C_5Me_5Rh(C_2H_3SiMe_3)_2]$ **2**, as shown in Equation (9).[7] This reaction is applied to a series of olefins (allyltrimethylsilane, 1-pentene, norbornene, 2,2′-dimethyl-3-butene, cyclopentene, and vinyl ethyl ether) and aromatic ketones (benzophenone, 4,4′-dimethoxybenzophenone, 3,3′-bis(trifluoromethyl)benzophenone, dibenzosuberone, acetophenone, *p*-chloroacetophenone, and *p*-(trifluoromethyl)acetophenone).

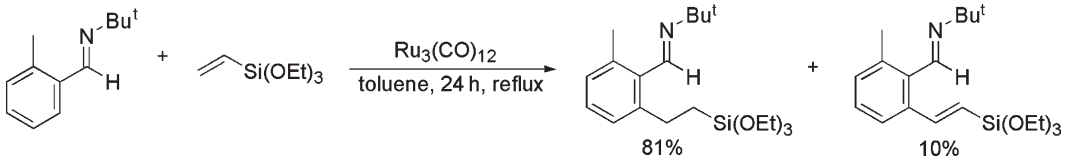


(9)

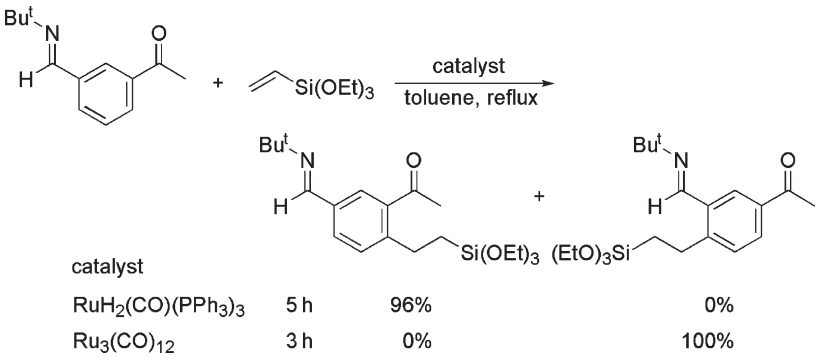


2

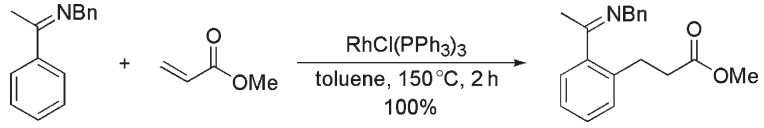
Nitrogen functionality also assists the alkylation of *ortho*-C–H bonds of aromatics, as shown in Equations (10)–(12). In the case of aromatic imines, $Ru_3(CO)_{12}$ exhibits a high catalytic activity.[8–10] This reaction gives the alkylation product together with the alkenylation product in the reaction with triethoxyvinylsilane. Rhodium catalysts show the same activity to give the alkylation product.[11,12,12a] For example, the Rh(I)-catalyzed reaction of the imine of aromatic ketones with methyl acrylate and functionalized alkenes gives the corresponding *ortho*-alkylated ketones in high yields.[12a] Interestingly, the regioselectivity by using ruthenium catalysts is observed when the aromatic compound bearing acetyl and imino groups is employed in the alkylation reaction.[9] Further, hydrazone nitrogen is also available for alkylation using Ru and Rh catalysts.[10]



(10)

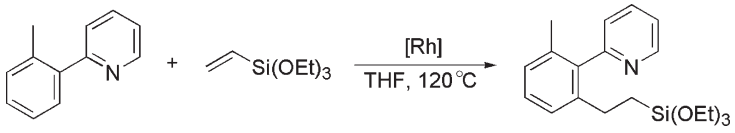


(11)



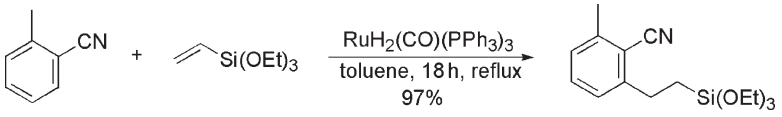
(12)

The sp^2 nitrogen in a pyridine ring can activate a C–H bond of 2-arylpyridines (Equation (13)). The alkylation of the 2-arylpyridine is satisfactorily catalyzed by rhodium catalysts such as $[RhCl(coe)_2]_2/PCy_3$ and $[RhCl(coe)_2]_2/PPh_3$.[13,13a]



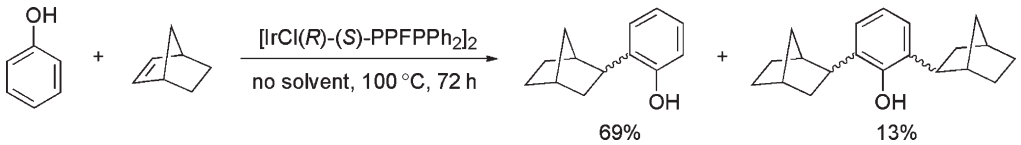
(13)

In addition to coordination by heteroatoms, the π-bond of cyano group also participates the activation of C–H bonds (Equation (14)).[14] The ruthenium-catalyzed alkylation of benzonitriles with triethylvinylsilane proceeds at the *ortho*-position predominantly.



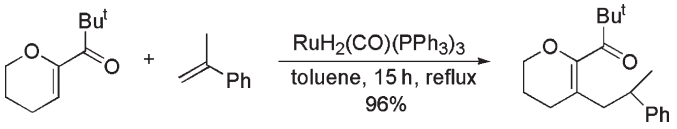
(14)

Hydroxyl group assists the *ortho*-alkylation of phenols (Equation (15)).[15] The reaction of phenols with norbornenes using Ir catalysts gives the corresponding *ortho*-alkylation products.



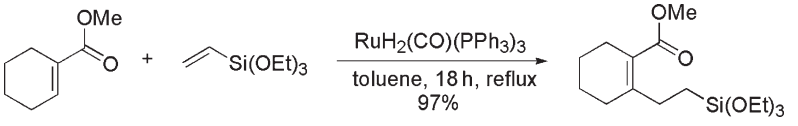
(15)

The alkylation of olefinic C–H bonds proceeds when conjugated enones are employed in the ruthenium-catalyzed reaction with alkenes, as shown in Equation (16).[16,17] Among the acylcyclohexenes, 1-pivaloyl-1-cyclohexene exhibits a high reactivity and the presence of an oxygen atom at the allylic position in the six-membered ring increases the reactivity of the enones. Some terminal olefins, for example, triethoxyvinylsilane, allyltrimethylsilane, methyl methacrylate, and vinylcyclohexane, are applicable for the alkylation of the olefinic C–H bonds. Acyclic enones also undergo this alkylation.

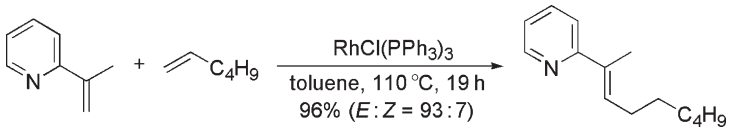


(16)

A similar type of alkylation using a conjugated ester proceeds with olefins by using $RuH_2(CO)(PPh_3)_3$ (Equation (17)).[18] Both cyclic and acyclic conjugated esters can be applied to the alkylation reaction with olefins. This reaction tolerates various functional groups on the ester moiety. The rhodium-catalyzed reaction of 2-isopropenylpyridine gives the alkylation product (Equation (18)), in which the stereochemistry around the double bond is inverted with respect to the thermodynamically favorable *E*-isomer.[19,19a–19d]

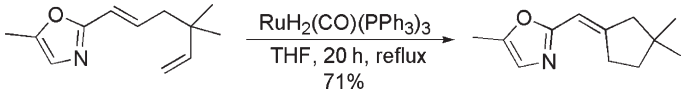


(17)

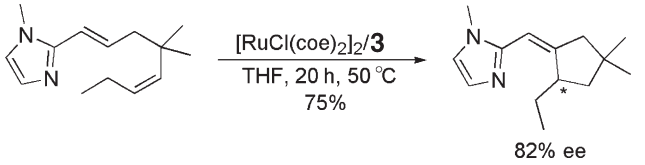


(18)

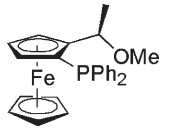
This alkylation reaction can be applied to intramolecular alkylation affording cyclic products, as shown in Equations (19)–(21). The reaction of 2-vinylpyridines with 1,5- or 1,6-dienes results in the formation of five- or six-membered carbocycles with good efficiency.[20,20a,20b] In addition to pyridine functionality, oxozole and imidazole rings can be applied to this intramolecular cyclization. When the reaction is conducted in the presence of a monodentate chiral ferrocenylphosphine and $[RhCl(coe)_2]_2$, enantiomerically enriched carbocycles are obtained. A similar type of intramolecular cyclization is applied to *N*-heterocycles.[21,21a,21b] The microwave irradiation strongly accelerates the rhodium-catalyzed intramolecular cyclization of a benzimidazole C–H bond to pendant alkenes. The cyclic products are formed in moderate to excellent yields with reaction times less than 20 min.[22]



(19)



(20)



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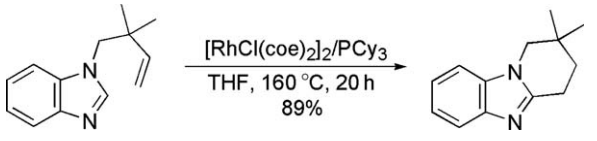
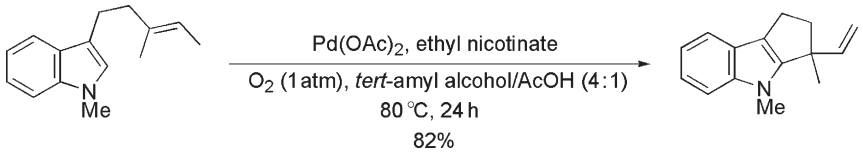
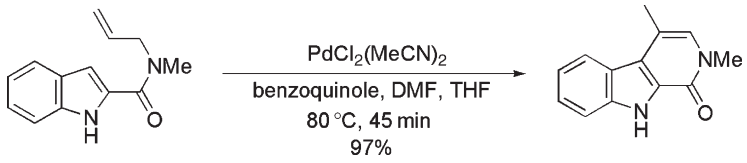


(21)

The oxidative annulations of indoles are achieved by using a $Pd(OAc)_2$/pyryidine catalytic system.[23] The reaction of indoles bearing olefin moieties in the presence of $Pd(OAc)_2$ and ethyl nicotinate under an atmosphere of oxygen in toluene undergoes the oxidative cyclization to give the annulation product having an olefin moiety (Equation (22)). The indole 2-*N*-allylcarboxamides derived from indole-2-carboxylic acid undergo the intramolecular oxidative cyclization with the aid of $PdCl_2(MeCN)_2$ to afford β-carbolinones in high yields (Equation (23)).[24]

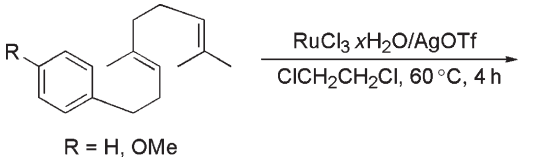


(22)



(23)

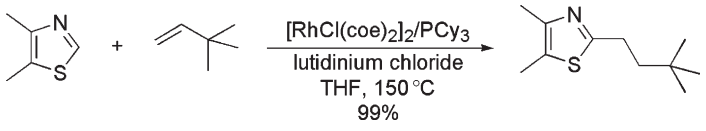
A similar intramolecular alkylation of arene–ene substrates is catalyzed by $RuCl_3$/AgOTf, providing good to excellent yields of cyclization products (chromanes, tetralins, terpenoids, and dihydrocoumarins).[25] This method is applied to the synthesis of tricyclic terpenoids, which are formed in nearly quantitative yields with high stereoselectivities (*trans*:*cis* various between 99:1 and 99:2), as shown in Equation (24).



R	*Yield* (%)
H	99
OMe	95

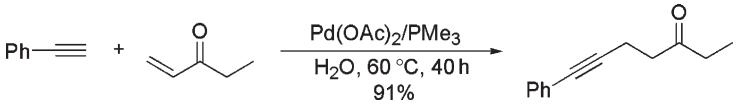
(24)

The alkylation of the C–H bonds occurs even in the CH═N moiety of five-membered heteroaromatic compounds such as thiazoles, benzimidazoles, and oxazoles (Equation (25)).[26,26a] This intermolecular alkylation without chelation assistance is very interesting.

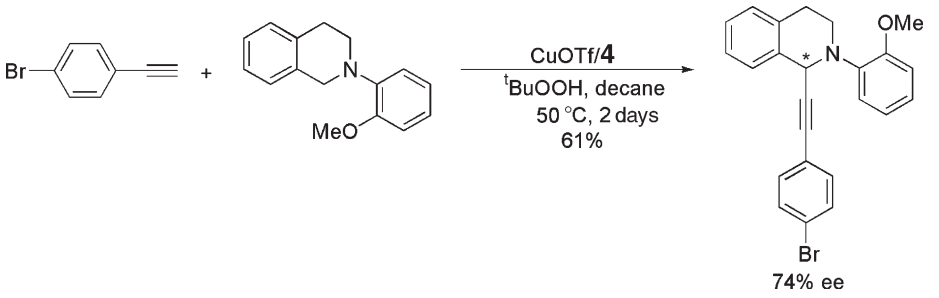


(25)

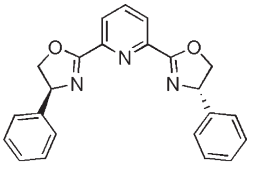
Even the *sp* C–H bonds of terminal alkynes are activated by transition metals to add olefins. Michael addition of terminal alkynes to butenone is achieved by using a binuclear catalyst $[Ru(\mu\text{-}O_2CH)(CO)_2(PPh_3)]_2$.[27] The reaction of phenylacetylene with butanone in the presence of the binuclear Rh catalyst in acetonitrile at 100 °C for 20 h gives 6-phenylhex-5-yn-2-one in 74% yield. A wide range of terminal alkynes can add to conjugated enones in a 1,4-fashion using $[RuCl_2(p\text{-cymene})]_2$ as a catalyst in the presence of catalytic amounts of pyrrolidine.[28] A similar conjugated addition of terminal alkynes to Meldrum's acid-derived olefins occurs in water in the presence of $Cu(OAc)_2$ catalyst.[29] The addition of terminal alkynes to vinyl ketones is catalyzed by $Pd(OAc)_2/PMe_3$, affording the corresponding γ,δ-alkynyl ketones in high yields (Equation (26)).[30] The coupling reaction of the *sp* C–H bond with the α C–H bond of tertiary amines catalyzed by $CuBr_2$ occurs in the presence of *tert*-butyl hydroperoxide to give the corresponding propargyl amines.[31] This method is applied to the enantioselective coupling reaction of terminal alkynes with tetrahydroisoquinolines (Equation (27)).[32] Pd-catalyzed addition of terminal alkynes to alkynoates also occurs. The reaction of 1-heptyne to methyl 5-hydroxy-2-pentynoate takes place in the presence of $Pd(OAc)_2$ and tris(2,6-dimethoxyphenyl)phosphine to give the dihydropyran derivative in 61% yield (Equation (28)).[33,33a]



(26)



(27)



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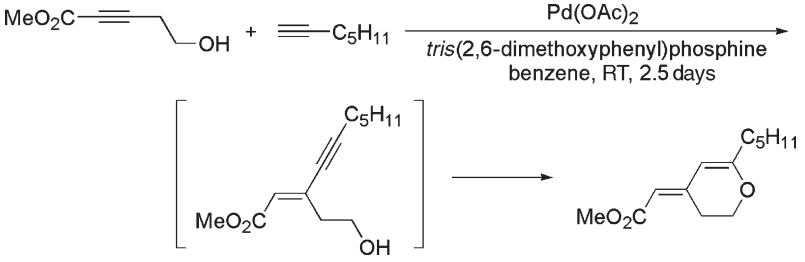
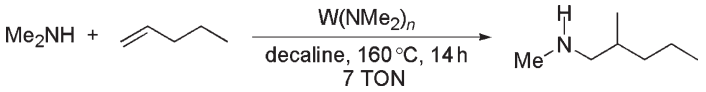


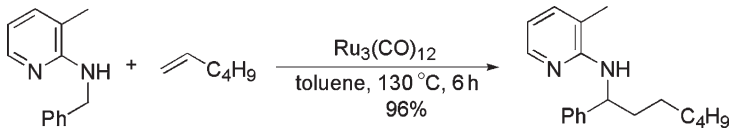
(28)

Alkylation of sp^3 C–H bonds adjacent to a heteroatom such as nitrogen and oxygen is possible. The early works using tungsten or iridium complexes involved the reaction of dimethylamine with 1-pentene (Equation (29)) and the alkylation of a C–H bond adjacent to oxygen with *tert*-butylethylene.[34,34a,34b]

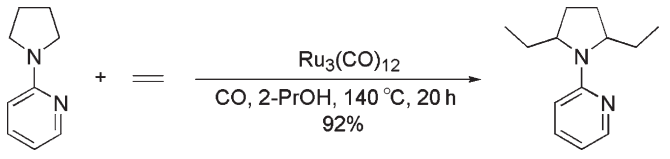


(29)

The alkylation of the sp^3 C–H bonds adjacent to a heteroatom becomes more practical when the chelation assistance exists in the reaction system. The ruthenium-catalyzed alkylation of the sp^3 C–H bond occurs in the reaction of benzyl(3-methylpyridin-2-yl)amine with 1-hexene (Equation (30)).[35] The coordination of the pyridine nitrogen to the ruthenium complex assists the C–H bond cleavage. The ruthenium-catalyzed alkylation is much improved by use of 2-propanol as a solvent.[36] The reaction of 2-(2-pyrrolidyl)pyridine with ethene affords the double alkylation product (Equation (31)).

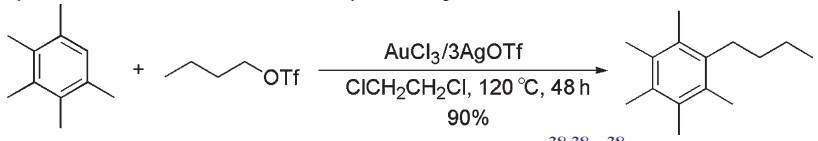


(30)



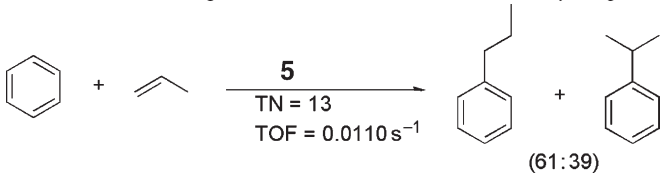
(31)

The reaction of pentamethylbenzene with butyl triflate catalyzed by $AuCl_3$/3AgOTf gives a linear product, butylpentamethylbenzene, in high yield (Equation (32)).[37] The formation of the linear product and the quenching experiment with NaCl leading to chloropentamethylbenzene suggest the involvement of the phenylgold(III) species as the reactive intermediate, which reacts with alkyl sulfonate ester to give the final alkylated product. The intramolecular alkylation can be used to construct cyclic compounds.

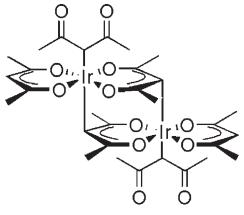


(32)

The most fundamental reaction is the alkylation of benzene with ethene.[38,38a–38c] Arylation of inactivated alkenes with inactivated arenes proceeds with the aid of a binuclear Ir(III) catalyst, [Ir(μ-acac-O,O,C^3)(acac-O,O)(acac-C^3)]$_2$, to afford anti-Markovnikov hydroarylation products (Equation (33)). The iridium-catalyzed reaction of benzene with ethene at 180 °C for 3 h gives ethylbenzene (TN = 455, TOF = 0.0421 s^{-1}). The reaction of benzene with propene leads to the formation of *n*-propylbenzene and isopropylbenzene in 61% and 39% selectivities (TN = 13, TOF = 0.0110 s^{-1}). The catalytic reaction of the dinuclear Ir complex is shown to proceed via the formation of a mononuclear bis-acac-O,O phenyl-Ir(III) species.[38b] The interesting aspect is the lack of β-hydride elimination from the aryliridium intermediates giving the olefinic products. The reaction of substituted arenes with olefins provides a mixture of regioisomers. For example, the reaction of toluene with ethene affords *m*- and *p*-isomers in 63% and 37% selectivity, respectively.

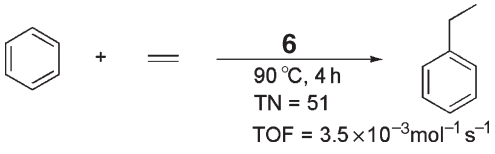


(33)

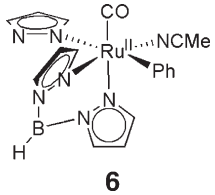


5

The hydroarylation of olefins is also achieved by using a ruthenium catalyst, TpRu(CO)(NCMe)(Ph) (Tp = hydridotris(pyrazolyl)borate) (Equation (34)).[39] The reaction of benzene with ethene is catalyzed by the ruthenium complex to give ethylbenzene (TN = 51, TOF = 3.5×10^{-3} mol^{-1} s^{-1} at 90 °C for 4 h). The ruthenium-catalyzed reaction of benzene with propene gives the hydroarylation products with a 1.6 : 1.0 ratio of *n*-propyl to isopropylbenzene, with 14 catalytic turnovers after 19 h.



(34)

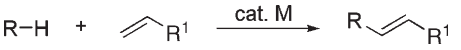


6

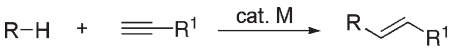
Theoretical studies on the Ir- and Ru-catalyzed hydroarylations are also conducted.[40,40a,40b]

10.05.3 Alkenylation of C–H Bonds

Formally there are two types of alkenylation of C–H bonds, coupling (Equation (35)) and addition reactions (Equation (36)).

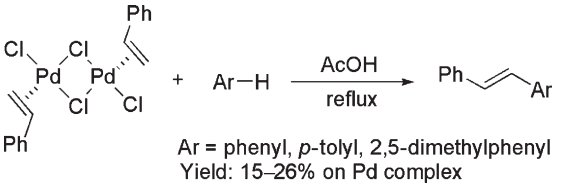


(35)

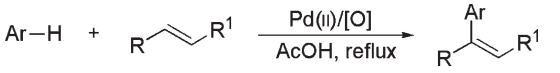


(36)

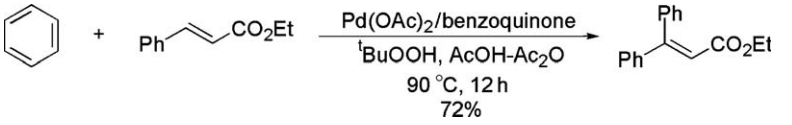
With the initial discovery of the stoichiometric coupling reaction of Pd(II)–olefin complexes with arenes (Equation (37)), the reaction has been made catalytic in the presence of catalytic amounts of $Pd(OAc)_2$ and an oxidant such as Ag(I), Cu(II), O_2, *t*-BuO_2H, and $PhCO_3Bu$-*t* (Equation (38)).[41,41a–41f] The catalytic reaction is very general to substrates, and a broad spectrum of arenes, heteroarenes, and olefins is compatible with the reaction (10–90% yield; turnover number, TON, 3–280). The reaction is one of the earliest examples of direct alkenylation of aromatic C–H bonds via C–H bond activation. The highest turnover number (up to 280) is obtained in the presence of benzoquinone as co-catalyst and *t*-BuOOH as oxidant (Equation (39)).[41f] By this reaction, ethyl 3-phenylcinnamate can be prepared efficiently from ethyl cinnamate and benzene. The presence of molybdovanadophosphoric acid ($H_7PMo_8V_4O_{40}$) as co-catalyst facilitates the catalytic reaction of benzene with olefins under dioxygen (1 atm).[42] The first asymmetric version of this reaction has been achieved by using Pd-chiral sulfonylamino–oxazoline complexes.[43] Furthermore, a similar coupling reaction between anilides and acrylates gives butyl (*E*)-3-(2-(acetylamino)phenyl)-propenoates via *ortho*-C–H bond activation (Equation (40)).[44]



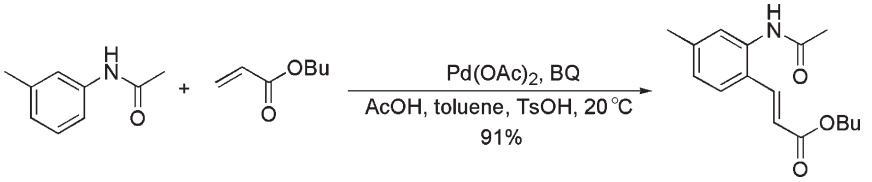
(37)



(38)



(39)

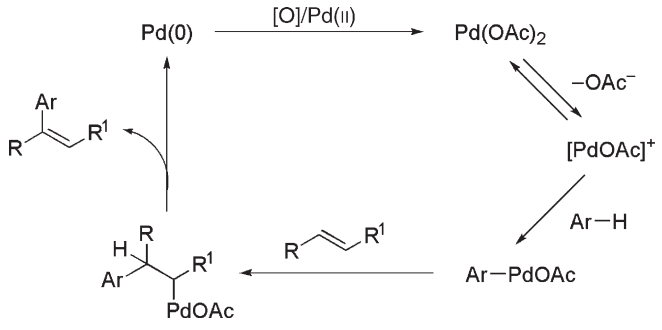


(40)

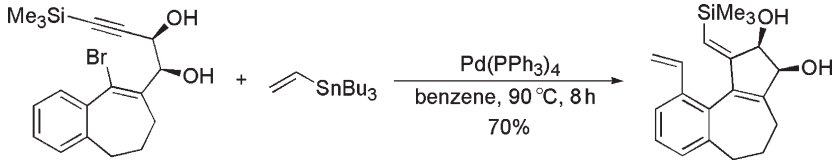
σ-Aryl–Pd complexes formed via electrophilic substitution of aromatic C–H bonds by cationic $[PdOAc]^+$ species have been proved to be the intermediates in the catalytic cycle, shown in Scheme 2. The complexes have been isolated as stable tripalladium(II) complexes with dialkylsulfide ligands, which react with styrene and CO to give stilbene and benzoic acid, respectively.

Rhodium complexes catalyze the oxidative coupling of benzene with ethene to produce styrene directly.[45,45a,45b] Using $Rh(ppy)_2(OAc)$ (ppyH = 2-phenylpyridine), the reaction of benzene with ethene in the presence of O_2 and $Cu(OAc)_2$ in benzene and acetic acid at 180 °C gives styrene and vinyl acetate in 77% and 23% selectivities, respectively.

The palladium-catalyzed reaction of *anti*-propargylic-1,2-diols derived from benzosuberone with vinylstannanes undergoes an efficient 5-*exo*-*dig* carbocyclopalladation producing the basic 5–7–6 core structures of natural products. The reaction of the *anti*-propargylic-1,2-diol with vinyltributylstannane in benzene in the presence of $Pd(PPh_3)_4$ as catalyst gives the styrene derivative (Equation (41)).[46]

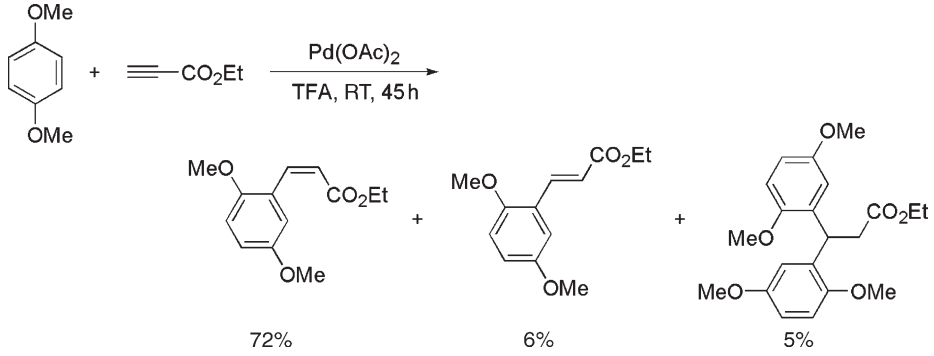


Scheme 2

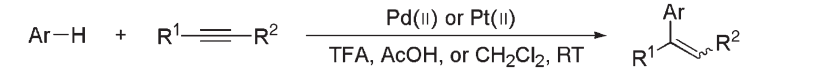


(41)

Addition of a C–H bond to carbon–carbon triple bonds gives alkenes that are regarded as the products derived by alkenylation of the C–H bond. The reaction of arenes with ethyl propiolate in trifluoroacetic acid (TFA) gives addition products, that is the alkenylation products of arenes (Equation (42)).[47,47a–47e] The alkenylation of arenes with propiolates is regio- and stereoselective, and very general with respect to arenes and alkynes, affording *cis*-arylalkenes in most cases (50–98% yield on alkyne) (Equation (43)). Various arenes, including those bearing OH or Br groups, undergo the alkenylation reaction with terminal and internal alkynes. The reaction of electron-rich arenes (donor) with electron-poor alkynes (acceptor) affords good yields, indicating that the reaction is electrophilic in nature. In some cases, the Pt(II) catalyst shows lower activity but better selectivity than Pd(II) catalysts.



(42)

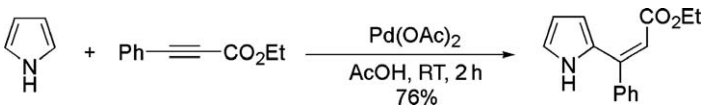


(43)

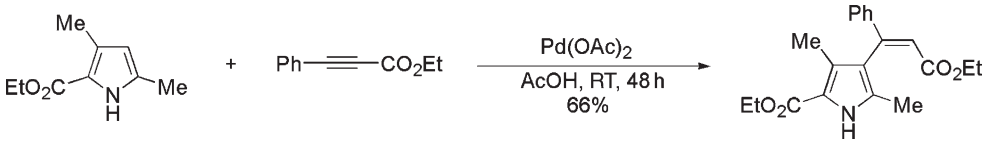
R^1 = H, Ph, CO_2Et, alkyl
R^2 = H, Ph, CO_2Et, CHO, COMe, alkyl
Ar–H: arenes and hetroarenes

Yield: 50–98% on alkyne

The reactions of heteroaromatic compounds such as furans, pyrroles, and indoles with alkynoates proceed under very mild conditions (in acetic acid or even in neutral solvents such as CH_2Cl_2 at room temperature). For example, the reaction of pyrrole with ethyl phenylpropiolate gives the 2-alkenylated pyrrole (Equation (44)).[47c] This reaction is applied to the direct synthesis of a β-alkenylpyrrole, the pyrrole fragment of haemin (Equation (45)).[47d] The present reaction provides a very convenient method for functionalization of arenes and heteroarenes.

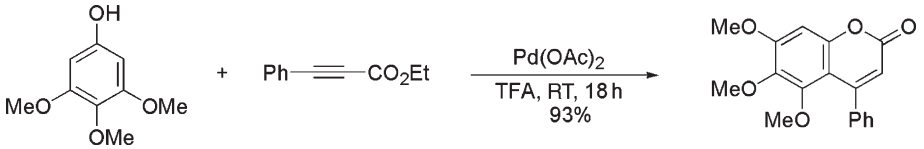


(44)

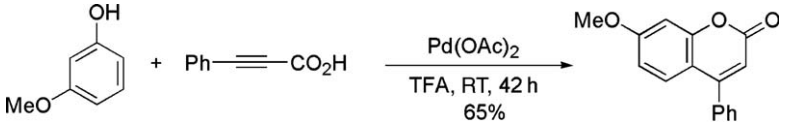


(45)

The intermolecular reaction of phenols with propiolic esters occurs in the presence of a $Pd(OAc)_2$ catalyst to afford coumarin derivatives directly.[48,48a] An exclusive formation of 5,6,7-trimethoxy-4-phenylcoumarin is observed in the $Pd(OAc)_2$-catalyzed reaction of 3,4,5-trimethoxyphenol with ethyl phenylpropiolate in TFA (Equation (46)). Coumarin derivatives are obtained in high yields in the cases of electron-rich phenols, such as 3,4-methylenedioxyphenol, 3-methoxyphenol, 2-naphthol, and 3,5-dimethylphenol. A similar direct route to coumarin derivatives is accomplished by the reaction of phenols with propiolic acids (Equation (47)).[49] A similar reaction proceeds in formic acid at room temperature for the synthesis of coumarins.[50,50a] Interestingly, Pd(0), rather than Pd(II), is involved in this reaction.



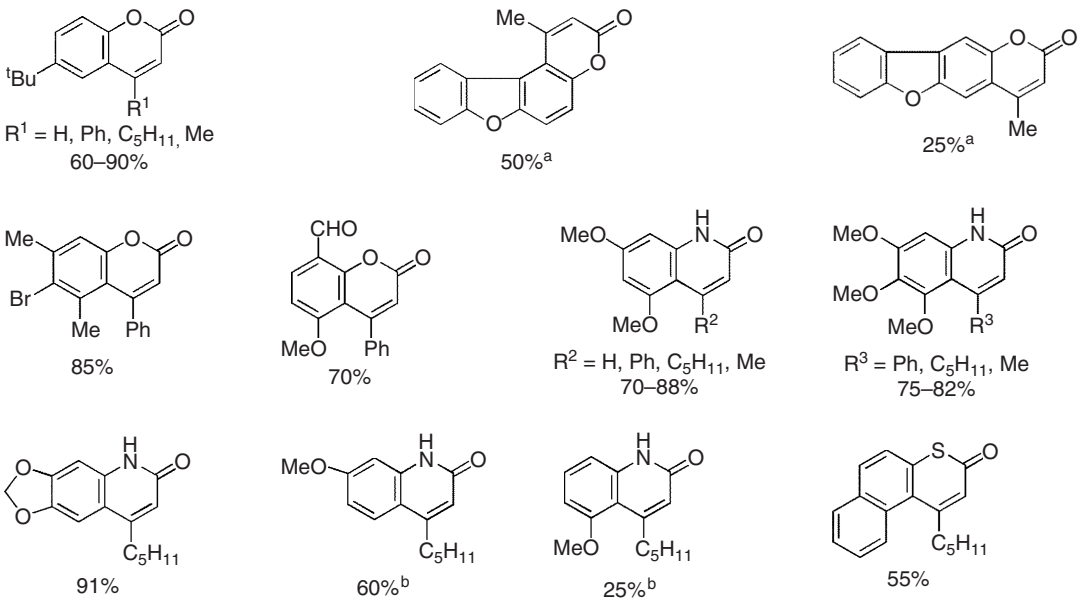
(46)



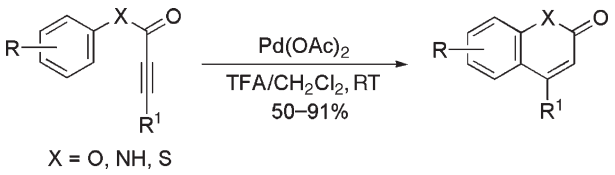
(47)

The intramolecular version of this reaction provides a general method for the preparation of biologically active heterocycles such as coumarins, quinolinones, and thiocoumarins (yield, 50–91%) (Equation (48) and Table 2).[47,47b] The reaction tolerates various functional groups such as Br, CHO, etc.

Table 2 Heterocyclic compounds from Pd-catalyzed intramolecular reactions

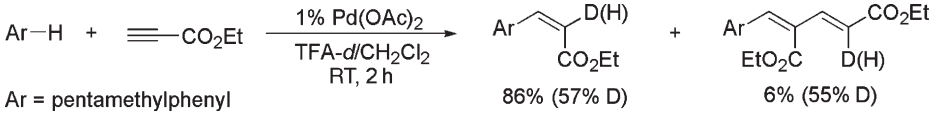


[a,b] The two regioisomers from the same starting materials, respectively.

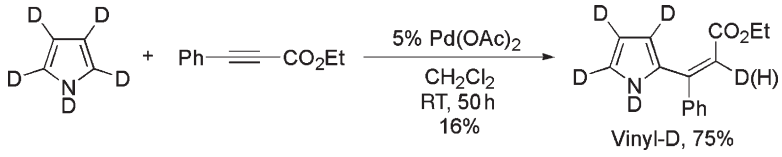


(48)

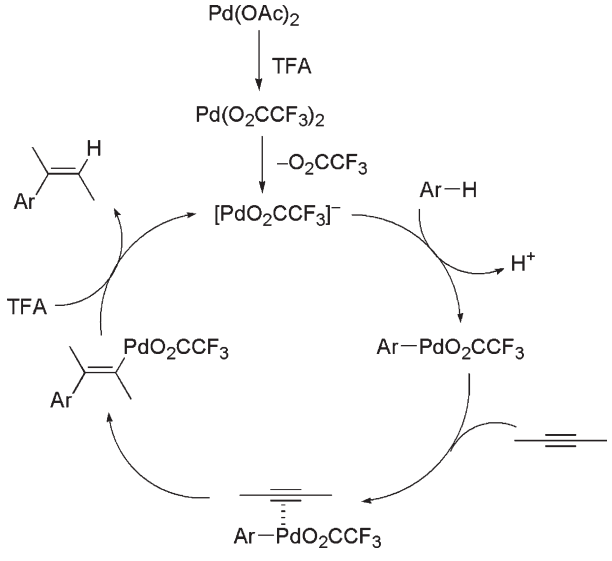
Isotope experiments reveal that D atoms have been incorporated into the vinyl position of adducts either in inter- or intramolecular reactions when the reaction was run in TFA-*d* (Equation (49)).[47a] The reaction of heteroarenes with alkynoates in AcOD gives the similar results. Also, the addition of heteroaromatic C–D bonds to C–C triple bonds and a large isotope effect ($k_H/k_D = 3$) between pyrrole and pyrrole-d_5 in the reaction with ethyl phenylpropiolate have been observed (Equation (50)). Thus, a possible mechanism involving σ-aryl–Pd complexes similar to those involved in the coupling reactions of arenes with olefins has been suggested. This mechanism is shown in Scheme 3. The facile formation of such Pd–aryl complexes from Pd(II) and arenes in TFA has been indicated by the coupling reaction of arenes with arenes, and also demonstrated by the formation of aromatic acids from simple arenes with carbon monoxide, and both at room temperature. Although the *trans*-insertion of aryl–Pd complexes to C–C triple bonds is not well understood, a similar *trans*-insertion has been reported in several reactions of alkynes,[51,52,52a–52d] including photoinduced *trans*-hydrophenylation of alkynes by benzene with an Rh catalyst.[51] The formation of vinyl–Pd complexes has been suggested by the formation of adducts of two alkynes and one arene. The use of TFA as solvent facilitates the generation of highly cationic $[Pd(II)O_2CCF_3]^+$ species to form σ-aryl–Pd complexes through electrophilic substitution of aromatic C–H bonds.



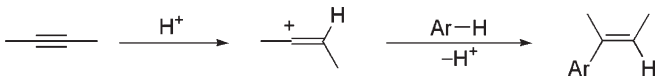
(49)



(50)



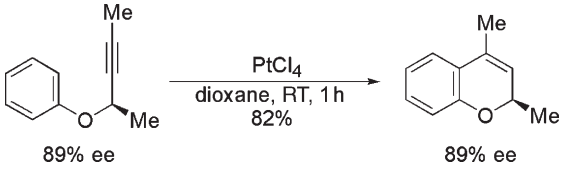
Scheme 3



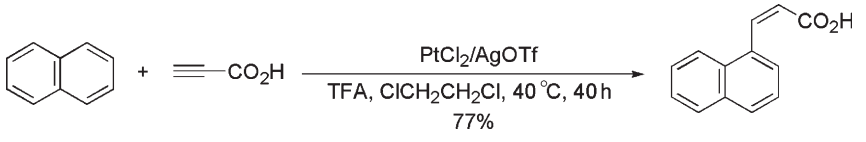
Scheme 4

On the other hand, the involvement of vinyl cationic species in the reaction cannot be ruled out in some cases, as shown in Scheme 4. In this context, it was found that the reaction of 3-butyn-2-one with mesitylene can occur without $Pd(OAc)_2$, clearly indicating the involvement of vinyl cations generated from alkynes and H^+ in this reaction.[47a] The yield difference in the presence and in the absence of $Pd(OAc)_2$ may be explained by the competition between $[Pd(II)O_2CF_3]^+$ and vinyl cationic species in the electrophilic substitution of aromatic C–H bonds. Recent kinetic isotope experiments suggest a mechanism involving alkyne coordination to Pd(II) followed by electrophilic aromatic substitution.[47e]

Other transition metals such as gold and platinum can serve for hydroarylation of alkynes. $AuCl_3$/3AgOTf is utilized as a catalyst for the hydroarylation of electron-deficient alkynes such as propiolic acid, its ethyl ester, and ethyl phenylpropiolate.[53] The electron-rich arenes can be efficiently functionalized by this method. The intramolecular reaction of aryl propiolates under similar conditions gives coumarin derivatives. The behaviors are similar to the palladium catalysts. $PtCl_4$ also proves to be an intramolecular hydroarylation catalyst.[54,54a] The $PtCl_4$-catalyzed reaction of arene–alkyne substrates provides the cyclized products such as chromenes (Equation (51)), dihydroquinolines, and coumarins. Moreover, $PtCl_2$/AgOTf enhances the efficiency and selectivity for the hydroarylation of propiolic acids and their esters with arenes (Equation (52)).[55] This reaction provides better yields of hydroarylation products in the case of relatively less reactive arenes such as *p*-xylene and naphthalene.

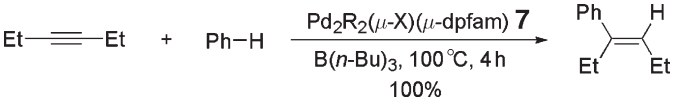


(51)

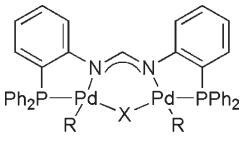


(52)

Dinuclear palladium complexes catalyze *cis*-hydroarylation of alkynes with arenes.[56] The reaction of 3-hexyne with benzene in the presence of a dinulear palladium complex $Pd_2R_2(\mu\text{-OH})(\mu\text{-dpfam})$ [dpfam = *N*,*N*′-bis[2-(diphenylphosphino)phenyl]formamidinate, R = *p*-Tol] and tri(*n*-butyl)borane at 100 °C for 4 h affords (*E*)-3-phenyl-3-hexene quantitatively (Equation (53)). The hydroarylation of 3-hexyne with monosubstituted benzenes (*E*)-3-aryl-3-hexenes with a ~2 : 1 ratio of the *meta*- and *para*-isomers. This regioselectivity is different from that of the hydroarylation of diphenylacetylene catalyzed by $Rh_4(CO)_{12}$.[57]



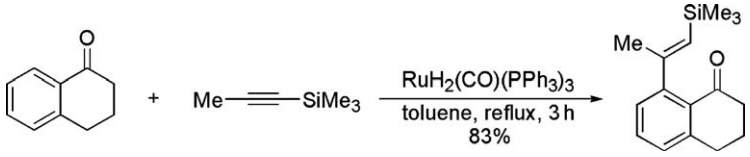
(53)



(R = *p*-Tol, X = OH)

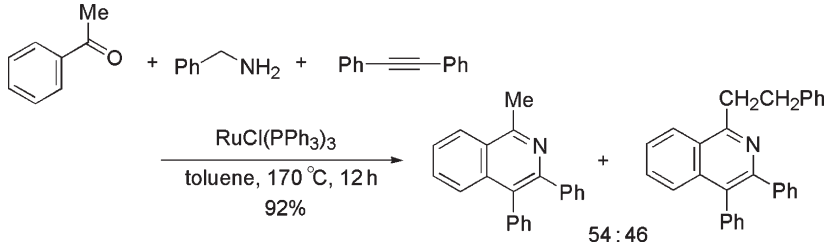
7

The regioselective alkenylation of aromatic rings is observed in the addition of aromatic C–H bonds in aromatic ketones to acetylenes.[58,58a] The reaction of trimethylsilyl-substituted acetylenes with aromatic ketones gives the corresponding alkenylation product with high regioselectivity in high yields (Equation (54)). Addition of olefinic C–H bonds in conjugate eneones to internal acetylenes also occurs with the aid of the same catalyst. The reaction of pivaloylcyclohexene with diphenylacetylene gives the corresponding dienone in high yield. 2-Phenylpyridines undergo the regioselective *ortho*-alkenylation with internal alkynes by $RhCl(PPh_3)_3$ catalyst.[59] Similarly, the regioselective alkenylation of 1-naphthols with alkynes proceeds in the presence of $[IrCl(cod)]_2$ catalyst.[60] In this reaction, the alkenylation takes place exclusively at the *peri*-position.



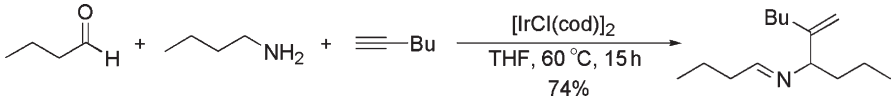
(54)

Similarly, ketimines (benzylimines of aromatic ketones) undergo the rhodium-catalyzed *ortho*-alkenylation with alkynes to give *ortho*-alkenylated aromatic ketones after hydrolysis.[61] This method is applied to an efficient one-pot synthesis of isoquinoline derivatives by using aromatic ketones, benzylamine, and alkynes under Rh catalysis (Equation (55)).



(55)

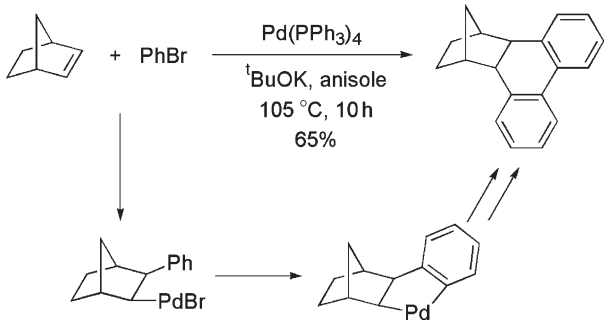
Interestingly, the alkenylation of sp^3 C–H bond is observed in the iridium-catalyzed coupling reaction of aldehydes, amines, and alkynes (Equation (56)).[62]



(56)

10.05.4 Arylation of C–H Bonds

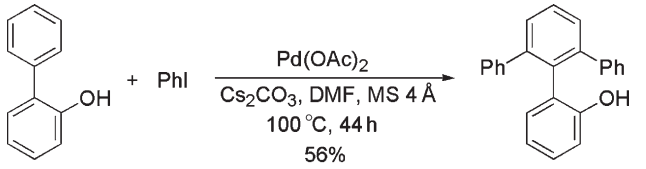
Arylation of C–H bonds is achieved by coupling reactions of C–H bonds with aromatic compounds such as halides, triflates, and organometallic reagents. Early works in this field involve the reaction of aryl halides with norbornene. As shown in Scheme 5, the coupling reaction of bromobenzene with norbornene in the presence of $Pd(PPh_3)_4$ as a



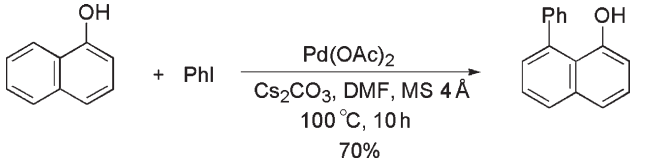
Scheme 5

catalyst gives hexahydromethanotriphenylenes in which cyclopalladation precedes the C–H bond activation.[63,63a–63e] Depending on the reaction conditions, the coupling reaction affords at least four different types of products: the 1 : 2 product, the 1 : 1 product, 1 : 3 product, and 2 : 2 product.[64]

The palladium-catalyzed arylation of 2-phenylphenols and naphthols shows an interesting feature of arylation of C–H bonds, leading to the formation of an (aryl)(aryloxy)palladium(II) intermediate.[65,65a,65b] The phenolates are suitable as precoordinating groups. The reaction of 2-hydroxybiphenyl with an excess of iodobenzene occurs regioselectively at the two *ortho*-positions of phenyl group under palladium catalysis (Equation (57)). In the case of 1-naphthol, the *peri*-position is phenylated (Equation (58)).

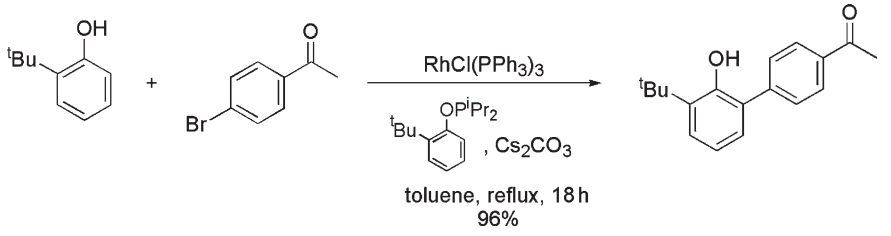


(57)



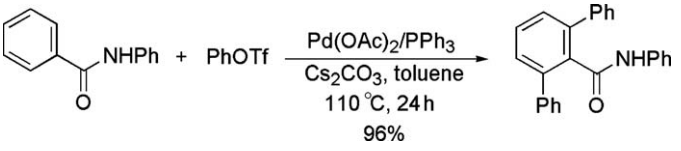
(58)

The rhodium-catalyzed arylation of phenols with aryl halides occurs in the presence of phosphinites [$PR_2(OAr)$] as a co-catalyst (Equation (59)).[66] The phosphorus atom coordinates to the rhodium atom to facilitate the electrophilic substitution with the rhodium(III) species at the *ortho*-position.



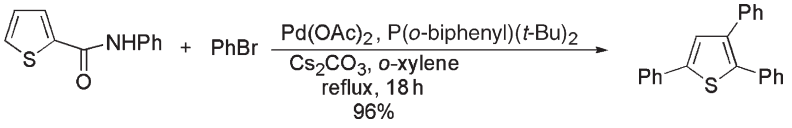
(59)

The palladium-catalyzed arylations of aromatic carbonyl compounds such as ketones,[67,67a] amides (Equation (60)),[68] and aldehydes[69] with aryl halides and triflates give the multiple arylation products similarly.



(60)

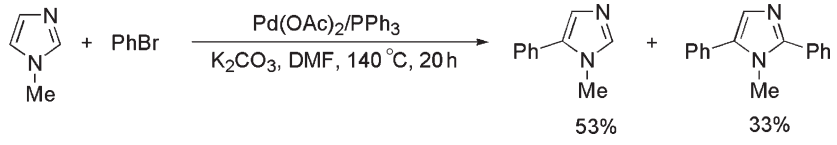
An interesting decarbamoylative arylation is observed when the reaction of secondary 2-thiophenecarboxamides with bromobenzene is conducted in the presence of $Pd(OAc)_2$ and a bulky phosphine [P(*o*-biphenyl)(*t*-Bu)$_2$] (Equation (61)).[70] However, the arylation occurs at the 2-position without the removal of the ester moiety when the reaction of 3-carboethoxyfuran with an aryl bromide is conducted.[71]



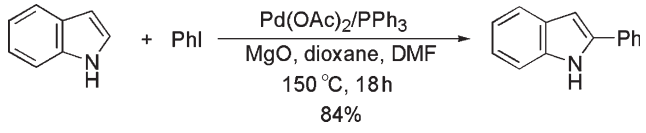
(61)

The arylation of heteroaromatic compounds is also achieved by aryl–aryl coupling reaction. The arylation of *N*-methylimidazole with bromobenzene occurs under palladium catalysis (Equation (62)).[72] The arylation of thiazole with aryl iodide occurs at the 2-position under $PdCl_2(PPh_3)_2$/CuI catalysis.[73] In this case, tetrabutylammonium fluoride improves the activity of the catalyst. Alternatively, thiazoles and benzothiazole are efficiently arylated

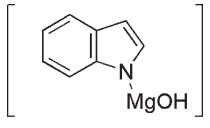
with aryl bromides at the 2-and/or 5-position(s) in the presence of $Pd(OAc)_2$ and a bulky ligand, $P(t\text{-}Bu)_3$ or P(biphenyl-2-yl)(t-Bu)$_2$, using Cs_2CO_3 as base.[73a] The C2 arylation of *N*-substituted indoles also occurs under the similar catalytic system, $Pd(OAc)_2/PPh_3$, using CsOAc as a base.[74] Decreasing the catalyst loading (0.5 mol.% Pd) favors the C2 arylation reaction. In the case of free (NH)-heterocycles including pyrrole, pyrazole, imidazole, and indole, the presence of MgO in the $Pd(OAc)_2/PPh_3$ catalysis affords the C-arylation products 2-phenylpyrrole, 3-phenylpyrazole, 4-phenylimidazole, and 2-phenylindole (Equation (63)), respectively.[75] The formation of an indolylmagnesium salt **8** by MgO leads to high selectivity and reactivity. Moreover, the general procedure for arylation of pyrroles is provided by using sodium salts of pyrroles.[76] The *in situ* generated pyrrolylzinc chloride from pyrrolylsodium and $ZnCl_2$ gives the C2 arylation product with the aid of $Pd(OAc)_2$ catalyst and 2-(di-*tert*-butylphosphino)biphenyl ligand (Equation (64)). This arylation takes place with a wide range of aryl halides, including aryl chlorides and aryl bromides, at low catalyst loadings and under mild conditions. A high degree of steric hindrance is also tolerated. The palladium-catalyzed coupling reaction of a bromomethylindole with 1,2-dimethoxybenzene is also observed.[77,77a]



(62)



(63)



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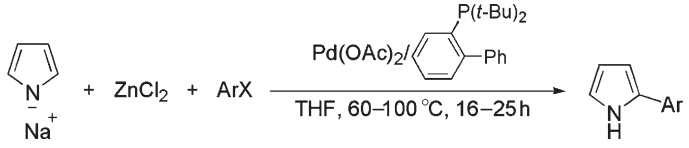
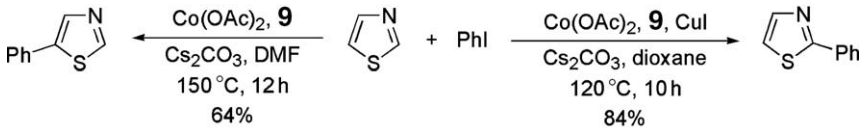
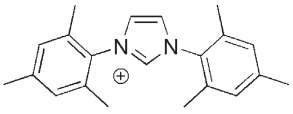


(64)

In addition to palladium catalysts, $Co(OAc)_2$ shows a catalytic activity for the arylation of heterocycles, including thiazole, oxazole, imidazole, benzothiazole, benzoxazole, and benzimidazole.[78] As shown in Scheme 6, the catalytic system $Co(OAc)_2$/**9**/Cs_2CO_3 gives C5 phenylated thiazole, while the bimetallic system $Co(OAc)_2$/CuI/**9**/Cs_2CO_3 furnishes the C2 phenylated thiazole. The rhodium-catalyzed reaction of heterocycles such as benzimidazoles, benzoxazole, dihydroquinazoline, and oxazoline provides the arylation product with the aid of $[RhCl(coe)]_2/PCy_3$ catalyst.[79] The intermediacy of an isolable *N*-heterocyle carbene complex is proposed.

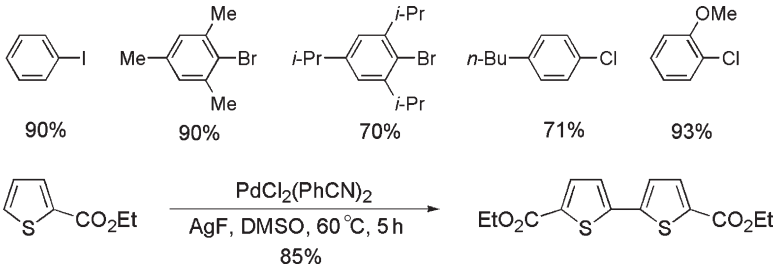


Scheme 6



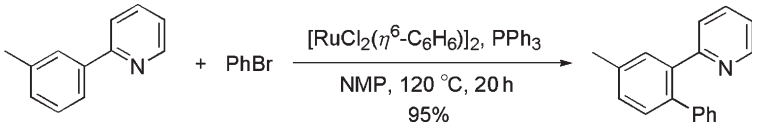
9

An interesting catalytic C–H homocoupling reaction of thiophenes, benzothiophene, and 2-(4-methoxyphenyl)thiazole is achieved by $PdCl_2(PhCN)_2$ catalyst in the presence of AgF in DMSO.[80] The coupling reaction of ethyl thiophene-2-carboxylate proceeds to give 5,5′-bis(ethoxycarbonyl)-2,2′-bithiophene in 85% yield (Equation (65)). The reaction of 2-bromothiophene gives the coupling product (5,5′-dibromo-2,2′-bithiophene) at the 5-position in 77% yield, while the bromo group does not react at all.



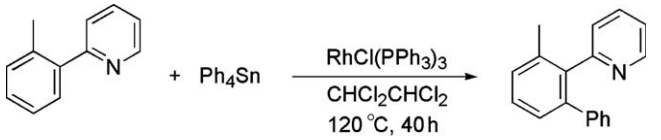
(65)

The regioselective arylation occurs when the reaction of 2-arylpyridines with aryl halides is conducted with the aid of the ruthenium(II)–phosphine complex as catalyst (Equation (66)).[81] The *ortho*-position to the 2-pyridyl group is arylated predominantly. The aromatic imines are also arylated with the same catalytic system.[82]

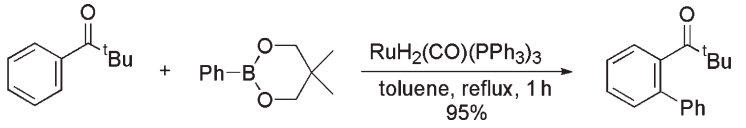


(66)

In addition to aryl halides and triflates, organometallic reagents can be utilized for the catalytic arylation reaction. The rhodium-catalyzed arylation of arylpyridines proceeds with the use of tetraarylstannanes (Equation (67)).[83] The ruthenium-catalyzed reaction of aromatic ketones with arylboronates affords the *ortho*-arylated aromatic ketones (Equation (68)).[84]



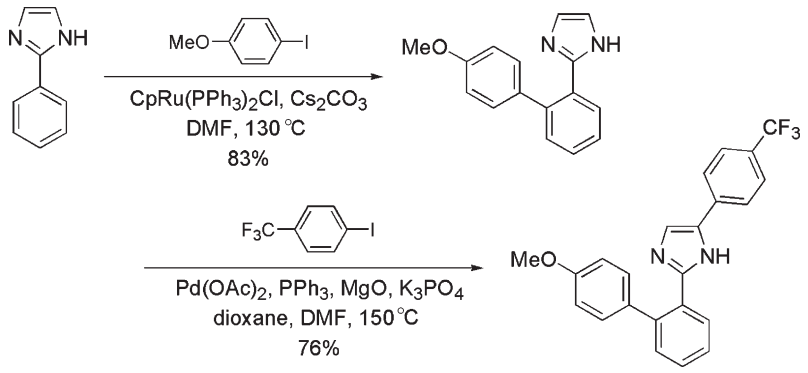
(67)



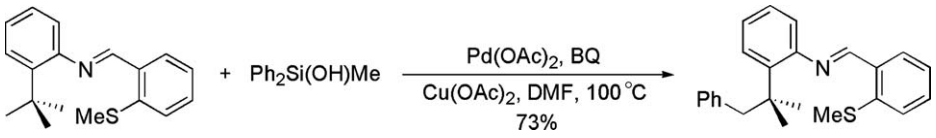
(68)

Scheme 7 shows that the method of sequential arylation with a high selectivity, using 2-phenylimidazole motif, proves to be applicable for pharmaceuticals and fluorescent and chemiluminescent probes.[85] The direct 4-arylation of free 2-phenylimidazole is achieved with iodoarenes as the aryl donors in the presence of palladium catalyst (Pd/PPh_3) and MgO as the base. A complete switch from C4 to C2′ arylation is accomplished using a ruthenium catalyst $[CpRu(PPh_3)_2Cl]$ and Cs_2CO_3.

The catalytic arylation of alkane moiety also occurs in the reaction of an aromatic imine bearing *tert*-butyl group with $Ph_2Si(OH)Me$ under a $Pd(OAc)_2/Cu(OAc)_2/BQ$ catalysis (Equation (69)).[86,86a]



Scheme 7

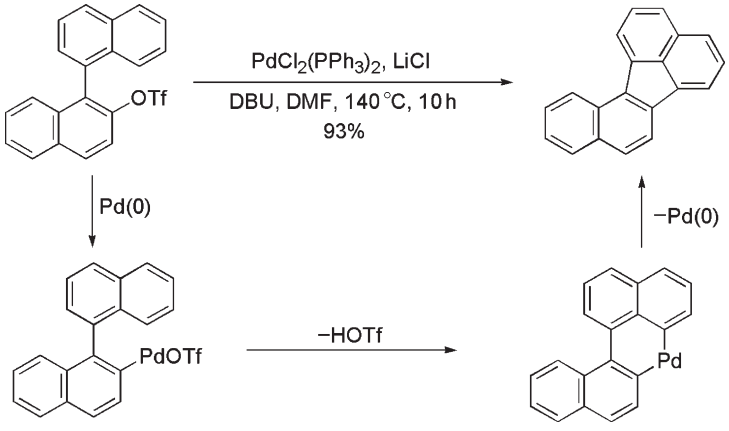


(69)

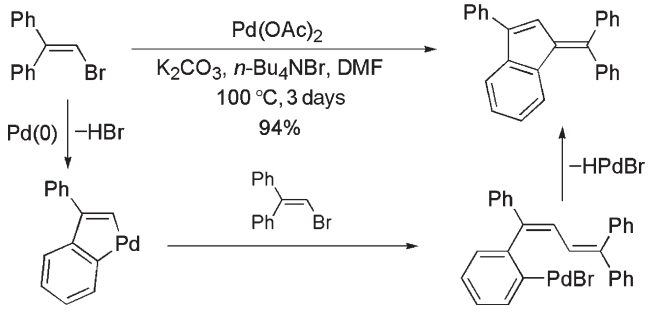
Intramolecular arylation of C–H bonds gives cyclic aromatic compounds. In this intramolecular arylation, the carbon–palladium σ-bond is first formed by the oxidative addition of Pd(0) species and then the resulting electrophilic Pd(II) species undergoes the intramolecular C–H bond activation leading to the formation of the palladacycle, which finally affords the cyclic aromatic compounds via reductive elimination.[87] For example, the fluoroanthene derivative is formed by the palladium-catalyzed reaction of the binaphthyl triflate, as shown in Scheme 8.[88] This type of intramolecular arylation is applied to the construction of five- and six-membered carbocyclic and heterocyclic systems.[89,89a–89e]

In the case of 2-bromo-1,1-diphenylethene (Scheme 9),[90] the resulting five-membered palladacycle adds a further equivalent of the starting material because a highly strained and antiaromatic benzocyclobutadiene would be formed. Finally, the ring closure via the reductive elimination gives the product. A similar reaction is observed in the case of 11-(bromomethylene)dibenzoheptatriene.[91]

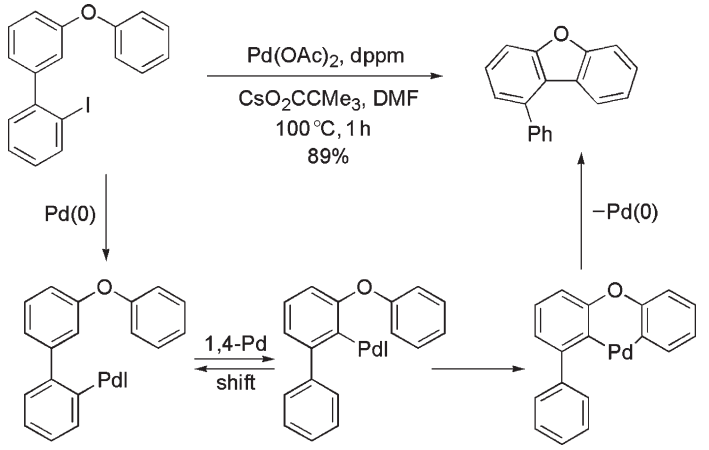
Sequential 1,4-palladium migration followed by intramolecular arylation provides complex fused polycycles.[92,92a] The reaction of 2-iodo-3′-phenoxybiphenyl in the presence of $Pd(OAc)_2$, diphenylphosphinomethane (dppm), and CsO_2CCMe_3 in DMF gives 4-phenyldibenzofuran in 89% yield (Scheme 10). The palladium-catalyzed reaction of *N*-(3-iodophenyl)anilines with alkynes affords substituted carbazoles in good yields (Equation (70)).[93] This process proceeds by carbopalladation of the alkyne, heteroatom-directed vinylic to arylpalladium migration, and ring closure involving two consecutive C–H activation processes.



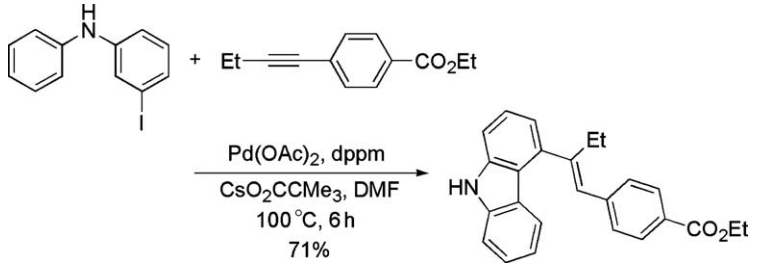
Scheme 8



Scheme 9

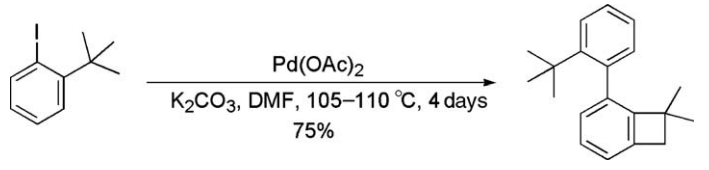


Scheme 10



(70)

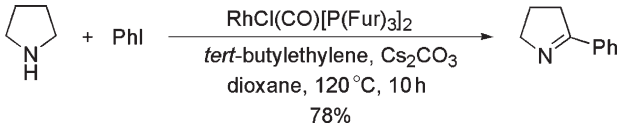
The intramolecular arylation of sp^3 C–H bonds is observed in the reaction of 1-*tert*-butyl-2-iodobenzene under palladium catalysis (Equation (71)).[94,94a,94b] The oxidative addition of ArI to Pd(0) gives an ArPdI species, which undergoes the electrophilic substitution at the *tert*-butyl group to afford the palladacycle. To this palladacycle, another molecule of ArI oxidatively adds, giving the Pd(IV) complex.



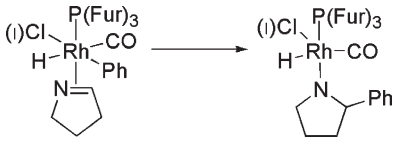
(71)

The oxidative C-arylation of five- to eight-membered (NH)-heterocycles such as pyrrolidine, piperidine, morpholine, etc., is observed in the reaction with iodoarenes in the presence of a rhodium catalyst, $RhCl(CO)[P(Fur)_3]_2$.[95]

The rhodium-catalyzed reaction of pyrrolidine with iodobenzene gives 2-phenylpyrroline in a high yield (Equation (72)). This reaction involves the formation of an imine rhodium hydride complex and phenylation (Equation (73)).

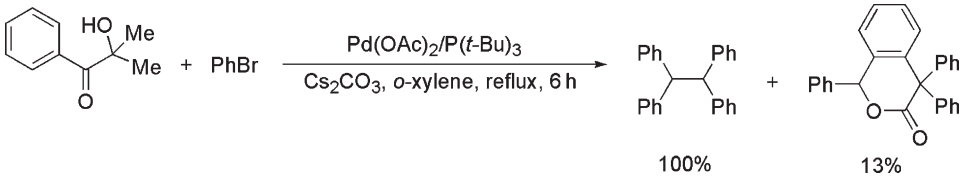


(72)



(73)

Palladium-catalyzed reaction of 2-hydroxy-2-methylpropiophenone with aryl bromides shows a unique multiple arylation via successive C–C and C–H bond cleavages, giving tetraarylethanes.[96] For example, the reaction of 2-hydroxy-2-methylpropiophenone with bromobenzene in the presence of $Pd(OAc)_2$, $P(t\text{-}Bu)_3$, and Cs_2CO_3 gives 1,1,2,2-tetraphenylethane quantitatively, together with 1,4,4-triphenyl-7-methylisochroman-3-one (13% yield) (Equation (74)).

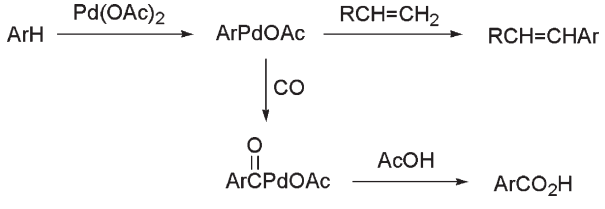


(74)

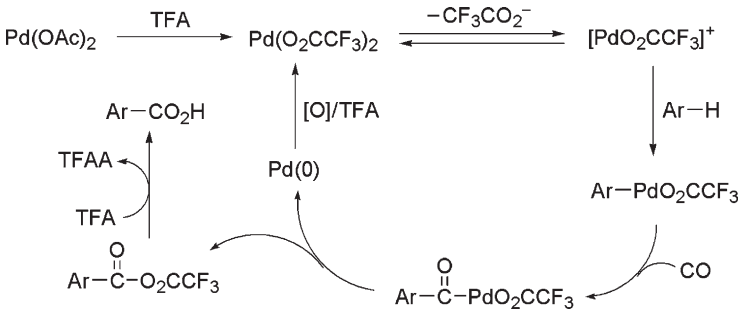
10.05.5 Carbonylation of C–H Bonds

In the palladium-catalyzed coupling reactions of arenes with alkenes, the σ-arylpalladium complexes react with CO to give aromatic acids in AcOH, as shown in Scheme 11.[97,97a–97c] This carboxylation reaction of arenes with CO proceeds catalytically with respect to Pd at room temperature under atmospheric pressure of CO, when $K_2S_2O_8$ is added as an oxidant and TFA is employed as a solvent.

The direct carboxylation of arenes with CO in the presence of a stoichiometric amount of $Pd(OAc)_2$ was reported in 1980.[98] The reaction can be made catalytic in the presence of oxidants such as O_2, *t*-BuOOH, alkyl halides, and $K_2S_2O_8$.[99,99a–99c] The reaction can be used to carboxylate arenes and heteroarenes such as furan and thiophene. The reaction provides a very convenient and atom-economic method for the synthesis of aromatic acids directly from simple arenes, offering a useful alternative to the carbonylation of aryl halides with CO catalyzed by transition metal compounds.[100] The carboxylation of arenes proceeds in high yields when TFA is used as solvent in the presence of $K_2S_2O_8$ as oxidant under mild conditions (room temperature and 1 atm of CO).[99b,99c] Benzene and chlorobenzene are converted to the corresponding benzoic acids quantitatively in the presence of 10% $Pd(OAc)_2$ (Equation (75)). A possible mechanism for the reaction is outlined in Scheme 12. The reaction proceeds via electrophilic metallation of aromatic C–H bonds by cationic $[PdO_2CCF_3]^+$ species to give σ-aryl–Pd complexes, which undergo CO insertion to afford aroylpalladium(II) complexes. The subsequent reductive elimination provides aromatic acids via reductive elimination of Pd and acid anhydride exchange. Pd(0) would be reoxidized to Pd(II) by $K_2S_2O_8$. The presence of TFA

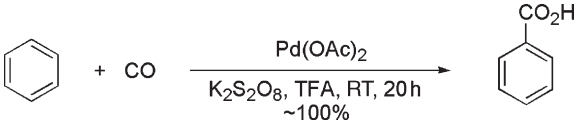


Scheme 11



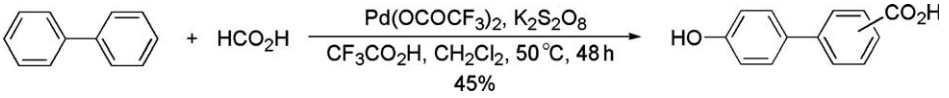
Scheme 12

facilitates the generation of the highly electrophilic cationic $[PdO_2CCF_3]^+$ species. Therefore, in the presence of TFA, the reaction occurs at room temperature.



(75)

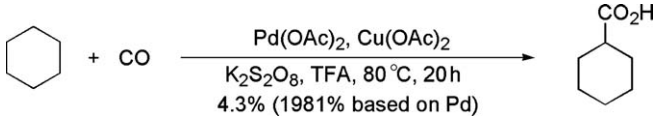
The reaction of biphenyl with formic acid and $K_2S_2O_8$ in a mixture of CF_3CO_2H and CH_2Cl_2, using $Pd(OCOCF_3)_2$ as a catalyst, gives hydroxyl-biphenylcarboxylic acid in 45% yield (Equation (76)).[101] The hydroxylation and carboxylation proceeds on one molecule. This reaction is applied to the palladium-catalyzed carboxylation of benzenes using formic acid as a carbonyl source.



(76)

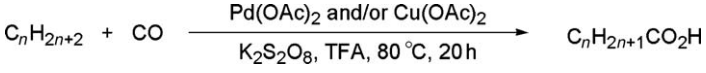
Although the activation and functionalization of C–H bonds of alkanes are the important, promising routes for synthesis of functionalized materials, it is difficult to achieve the functionalization of alkanes because they are unreactive due to the low reactivity of alkane C–H bonds. Carboxylation of alkanes to carboxylic acids is one of the interesting and important functionalization processes.

Cyclohexane was carboxylated with CO using $Pd(OAc)_2$ catalyst in the presence of $K_2S_2O_8$ as an oxidant in TFA at 80 °C.[102,102a,102b] Addition of $Cu(OAc)_2$ among metal additives such as Fe, $FeCl_2$, $Co(OAc)_2$, $Ni(OAc)_2$, $Cu(OAc)_2$, and $Zn(OAc)_2$ showed a drastic effect on the formation of cyclohexanecarboxylic acid. The best result was obtained in the reaction using $Pd(OAc)_2$ (0.1 mmol), $Cu(OAc)_2$ (0.2 mmol), and $K_2S_2O_8$ (9 mmol), giving 1981% yield of cyclohexanecarboxylic acid based on $Pd(OAc)_2$ (4.3% yield based on cyclohexane) (Equation (77)).



(77)

Gaseous alkanes such as methane, ethane, and propane were also carboxylated to give acetic, propionic, and butyric acids, respectively, as shown in Table 3.[102,103,103a] Ethane and propane were best carboxylated by the mixed catalyst of $Pd(OAc)_2$ and $Cu(OAc)_2$, while methane was not effectively carboxylated by the same catalytic system. In the case of methane, $Cu(OAc)_2$ gave the best result among the catalysts employed. However, the yield of acetic acid based on methane is low (Equation (78)).



(78)

Table 3 Carboxylation of methane, ethane, and propane with CO[a]

Alkane	*Carboxylic acid*	*Catalyst and yield (%)*[b]		
		$Pd(OAc)_2$–$Cu(OAc)_2$	*$Pd(OAc)_2$*	*$Cu(OAc)_2$*
Propane	Butyric acid[c]	7100 (8.7)	1760 (2.1)	1900 (2.2)
Ethane	Propionic acid	7600 (2.1)	440 (0.2)	700 (0.3)
Methane	Acetic acid	1300 (0.4)	100 (0.03)	2960 (0.9)

[a]Propane (10 atm), ethane (30 atm), methane (40 atm), $Pd(OAc)_2$ (0.05 mmol), $Cu(OAc)_2$ (0.05 mmol), $K_2S_2O_8$ (10 mmol), TFA (5 mL), and CO (20 atm).
[b]Based on the catalyst. Values in parentheses are based on alkanes.
[c]A mixture of isobutyric and butyric acids (4 : 1).

Recently, it was found that vanadium catalysts were very active in the carboxylation of alkanes, and the $VO(acac)_2$ catalyst in the presence of $K_2S_2O_8$ and TFA afforded acetic acid almost quantitatively from methane and CO.[104] The reaction of methane (5 atm) with CO (20 atm) at 80 °C for 20 h gave acetic acid in 93% yield based on methane (Equation (79)). Other vanadium compounds such as V_2O_3, V_2O_5, and $NaVO_3$ and various vanadium-containing heteropolyacids ($H_5PV_2Mo_{10}O_{40}$, $H_4PVW_{11}O_{40}$, and $H_5SiVW_{11}O_{40}$) also showed a high activity as the catalyst.

$$\underset{(5\ \text{atm})}{CH_4} + \underset{(20\ \text{atm})}{CO} \xrightarrow[\substack{K_2S_2O_8,\ \text{TFA},\ 80\ ^\circ\text{C},\ 20\ \text{h} \\ 93\%\ \text{based on}\ CH_4}]{VO(acac)_2\ (5\ \text{mol}\%)} CH_3CO_2H \tag{79}$$

Interestingly, $Co(OAc)_2$ has been found to be an efficient catalyst for the carboxylation of propane.[105,105a] For example, the reaction of propane (1 atm) with CO (30 atm) in the presence of $Co(OAc)_2$ (0.1 mmol) and $K_2S_2O_8$ (10 mmol) in TFA gave butyric acids in 58% yields based on propane (Equation (80)).

$$\underset{(1\ \text{atm})}{CH_3CH_2CH_3} + \underset{(30\ \text{atm})}{CO} \xrightarrow[K_2S_2O_8,\ \text{TFA},\ 70\ ^\circ\text{C},\ 15\ \text{h}]{Co(OAc)_2\ (0.1\ \text{mmol})} \underset{45\%}{CH_3\overset{\overset{CH_3}{|}}{C}HCO_2H} + \underset{13\%}{CH_3CH_2CH_2CO_2H} + \underset{32\%}{CH_3\overset{\overset{CH_3}{|}}{C}HOCOCF_3} \tag{80}$$

In TFA, methane and CO could be converted to acetic acid by a catalytic system of $Mo/CaCl_2/K_2S_2O_8$/TFA (Equation (81)).[106] The best result (89.4% of acetic acid) was obtained in the reaction of methane (20 atm) and CO (50 atm) using the catalytic system at 85 °C for 20 h.

$$CH_4 + CO \xrightarrow[K_2S_2O_8,\ \text{TFA}]{Mo/CaCl_2} CH_3CO_2H \tag{81}$$

Interestingly, it was found that the reaction of methane, without CO, in the presence of $VO(acac)_2$, $K_2S_2O_8$, and TFA gave acetic acid (Equation (82)).[107] The reaction of $^{13}CH_4$ afforded $^{13}CH_3$ $^{13}CO_2H$. This result suggests that the carbon source of acetic acid is methane.

$$2CH_4 \xrightarrow[\substack{K_2S_2O_8,\ \text{TFA},\ 80\ ^\circ\text{C},\ 20\ \text{h} \\ 71\%\ \text{based on}\ CH_4}]{VO(acac)_2} CH_3CO_2H \tag{82}$$

The oxovanadium(v) complex $VO(N(CH_2CH_2O)_3)$ **10** and amavadine $Ca[V(ON(CHC(CH_3)COO)_2)_2]$ **11** also showed a high activity for the conversion of methane into acetic acid in the absence of CO,[108] as shown in Table 4. Although the detailed mechanism is not clear, the isotope experiment using $^{13}CH_4$ in this study suggests that CH_4 is the source for the methyl group of acetic acid and the carbon source of the carboxylic acid group is TFA (Equation (83)).

$$CH_4 \xrightarrow[K_2S_2O_8,\ \text{TFA}]{V\ \text{cat.}} CH_3CO_2H \tag{83}$$

Table 4 Carboxylation of methane in the presence or absence of CO[a]

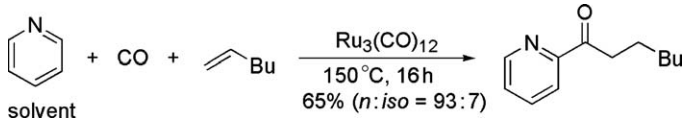
Catalyst[b]	*Methane* (atm)	*CO* (atm)	*TON*[c]	*Yield*[d] (%)
10	5		10.0	21.4
10	5	5	10.9	23.5
10	12	15	28.2	25.6
11	5		13.4	29.4
11	5	15	12.0	54.3

[a]Metal complex catalyst (0.0625 mmol), $K_2S_2O_8$ (12.5 mmol), TFA (23 mL), 80 °C, 20 h.
[b]$VO(N(CH_2CH_2O)_3)$ **10**, $Ca[V(ON(CH(CH_3)COO)_2)_2]$ **11**.
[c]Turnover number.
[d]Based on methane.

Since the direct carbonylation of C–H bonds with CO leading to aldehydes is endothermic, the reaction is conducted under photochemical conditions.[109,109a–109e] On the other hand, the direct coupling of a C–H bond, CO, and an olefin leading to a ketone is exothermic and can proceed under thermal reaction conditions.

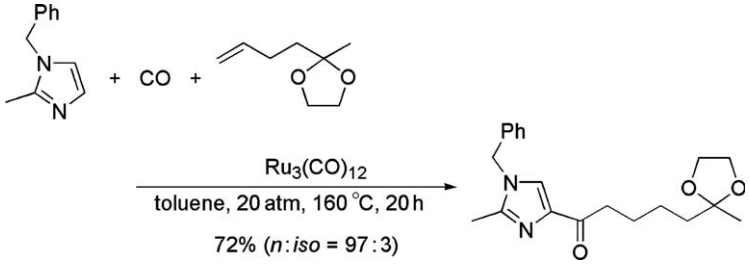
The first example of the three-component coupling reaction was conducted by using benzene, ethene, and CO in the presence of an Rh catalyst.[110,110a] However, this reaction gives styrene as a major product and the carbonylation product, propiophenone, is minor.

The direct carbonylation of heterocycles with CO and olefins proceeds efficiently. The reaction of pyridine, CO, and 1-hexene in the presence of $Ru_3(CO)_{12}$ at 150 °C gives α-acylated pyridines (Equation (84)).[111,111a] A number of olefins including ethene and 1-eicosene can be used in this carbonylation reaction.

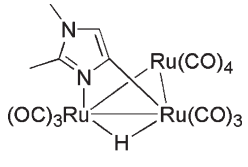


(84)

The carbonylation of imidazole derivatives with several olefins takes place in high yields with the aid of an $Ru_3(CO)_{12}$ catalyst.[112,112a] The carbonylation occurs exclusively at the α-position to the sp^2 nitrogen (Equation (85)). A wide range of olefins can be utilized in this reaction, and a variety of functional groups are compatible under the reaction conditions. The (μ-H)triruthenium clusters such as **12** are proposed as a key species in this carbonylation reaction. Other five-membered *N*-heteroaromatic compounds, such as pyrazoles, oxazoles, and thiazoles, can be used for the carbonylation reactions, where the carbonylation takes place at the α-C–H bond to the sp^2 nitrogen.

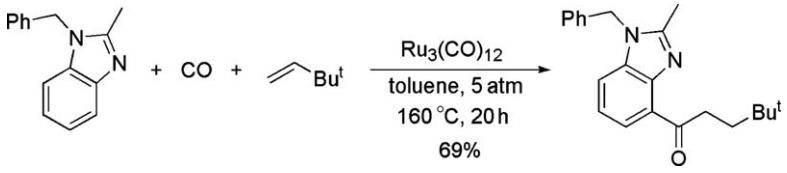


(85)



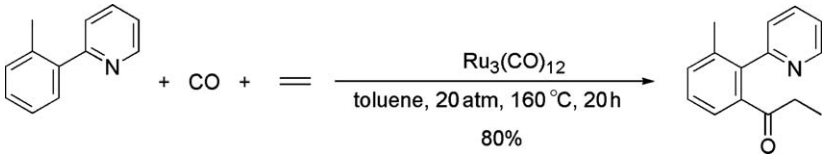
12

The carbonylation at the β-C–H bond to the sp^2 ring nitrogen is also achieved by $Ru_3(CO)_{12}$ catalyst.[113] The $Ru_3(CO)_{12}$-catalyzed reaction of 1-benzyl-2-methylbenzimidazole with olefin and CO affords the corresponding β-acylated product in high yield (Equation (86)).

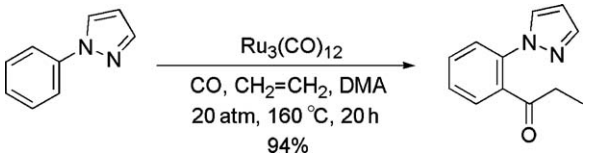


(86)

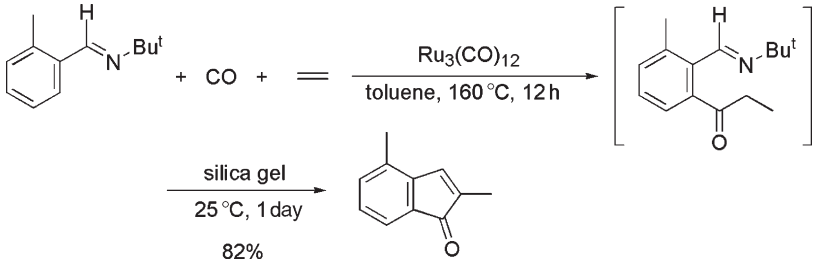
In the reaction of phenylpyridine with CO and ethene, the *ortho*-C–H bond (γ to the sp^2 nitrogen) in the benzene ring undergoes the carbonylation.[114] The ruthenium-catalyzed reaction of 2-(2-methylphenyl)pyridine with CO (20 atm) and ethene gives 3-methyl-2-(2-pyridyl)propiophenone in 80% yield (Equation (87)). In the reaction of *m*-substituted substrates, such as those bearing Me, OMe, CF_3, and COOMe, the carbonylation takes place exclusively at the less hindered C–H bond, irrespective of the electronic nature of the substituents. An oxazoline ring instead of a pyridine ring is also an effective directing group for the γ-carbonylation of the benzene ring.[115] The reaction of 1-arylpyrazoles with CO and ethene in the presence of $Ru_3(CO)_{12}$ results in regioselective carbonylation at the *ortho*-C–H bonds.[116,116a] The ruthenium-catalyzed reaction of 1-phenyl-1*H*-pyrazole with CO and ethene in *N*,*N*-dimethylacetamide (DMA) gives 1-[2-(1*H*-pyrazolyl)phenyl]-1-propanone in 94% yield (Equation (88)). In the reaction of aromatic aldimines, indenones are formed by intramolecular aldol-type condensation of the resulting carbonylation products (Equation (89)).[117]



(87)

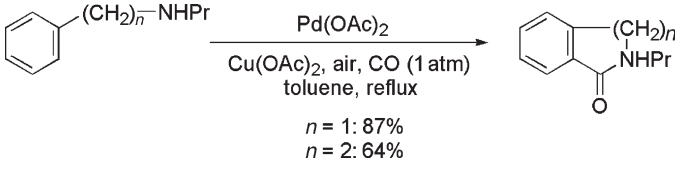


(88)



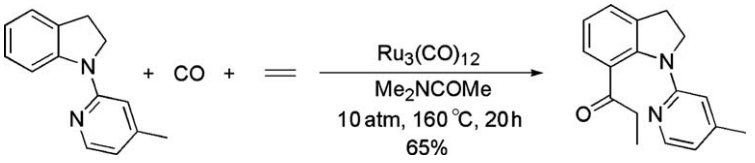
(89)

The palladium(II)-catalyzed direct carbonylation proceeds with remarkable site selectivity to afford a variety of five- or six-membered benzolactams from *N*-alkyl-ω-arylalkylamines in a phosphine-free catalytic system using $Pd(OAc)_2$ and $Cu(OAc)_2$ in an atmosphere of CO gas containing air (Equation (90)).[118]



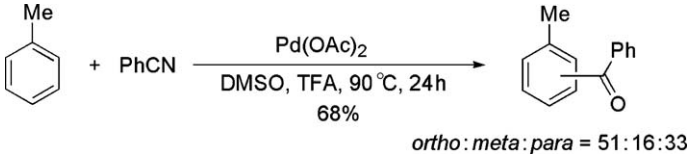
(90)

The carbonylation of a C–H bond at the δ-position to the sp^2 nitrogen proceeds with the aid of $Ru_3(CO)_{12}$ as catalyst (Equation (91)).[119] The reactivity appears to be sensitive to the polarity of the solvent. The choice of DMA as the solvent is crucial for the reaction to proceed efficiently.



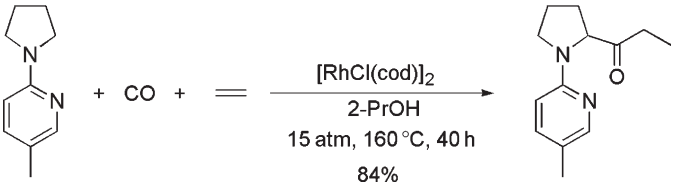
(91)

The Pd-catalyzed reaction of simple arenes and nitriles provides a useful synthesis of aromatic ketones.[120] The reaction of toluene and benzonitrile in the presence of $Pd(OAc)_2$ as a catalyst in DMSO and TFA gives diarylketones (Equation (92)). The presence of DMSO is essential in this reaction.



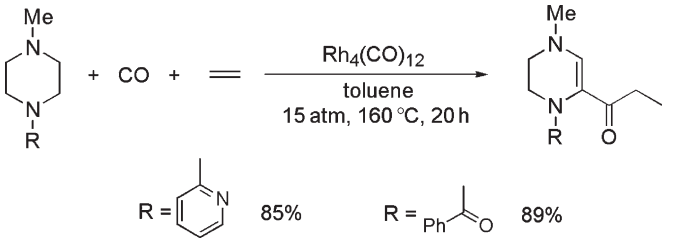
(92)

The carbonylation of the sp^3 C–H bond adjacent to a nitrogen atom is also possible by means of chelation-assisted C–H bond activation.[121] The carbonylation reaction of *N*-(2-pyridyl)pyrrolidine occurs at the α-position of the pyrrolidine ring by using $[RhCl(cod)]_2$ as a catalyst and 2-propanol as a solvent. Cyclic amines exhibit a high reactivity (up to 84%) (Equation (93)), while acyclic amines show relatively low reactivity (18%). The use of $Ru_3(CO)_{12}$ as a catalyst does not result in a carbonylation reaction, but instead the addition of the sp^3 C–H bond across the olefin bond to give an alkylation product, as mentioned before (Section 10.05.4).



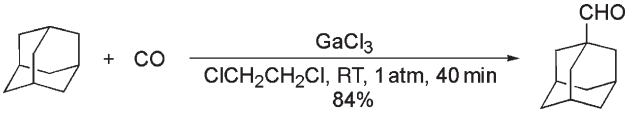
(93)

The reaction of *N*-(2-pyridinyl)piperazines with CO and ethene in the presence of $Rh_4(CO)_{12}$ involves two discrete reactions: (i) dehydrogenation of the piperazine ring leading to an olefin and (ii) carbonylation at a C–H bond in the resulting olefin (Equation (94)).[122] Interestingly, $Ru_3(CO)_{12}$ is ineffective for the carbonylation. An acyl group can also serve as a directing group for the carbonylation at the α-C–H bond.[123]



(94)

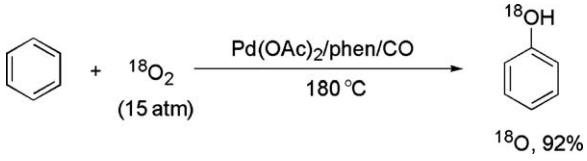
Although the formation of aldehydes by the superacid-mediated carbonylation reaction of saturated alkanes is achieved in superacidic media such as CF_3SO_3H, $B(OSO_2CF_3)_3$-CF_3SO_3H and SbF_5-CF_3SO_3H,[124] Lewis acids such as $AlCl_3$,[125] $CH_2Br_2/AlBr_3$,[126,126a,126b] and $GaCl_3$[127] promote the carbonylation of alkanes. The reaction of adamantane and $GaCl_3$ in 1,2-chloroethane under 1 atm of CO at room temperature gives 1-adamantanecarboaldehyde in 84% yield (Equation (95)). The formation of 1-adamantyl cation by the abstraction of hydride by $GaCl_3$ followed by the reaction with CO is proposed.



(95)

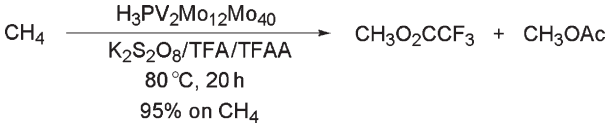
10.05.6 Hydroxylation and the Related Reactions

The reaction of arenes (ArH) with $Pd(OAc)_2$ gives the aryl–Pd σ-complex, ArPdOAc, which reacts with O_2 to give phenols, ArOH, as shown in Scheme 13. Direct synthesis of phenol from benzene and O_2 has been achieved by using the $Pd(OAc)_2$/1,10-phenanthroline(phen)/CO/AcOH system at 180 °C (Equation (96)).[128,128a,128b] The reaction involves the formation of σ-aryl–Pd complexes from electrophilic substitution of aromatic C–H bonds by $[AcOPd\text{-}phen]^+$ species, which should react with O_2. The combination of CO and 1,10-phenanthroline with $Pd(OAc)_2$ is crucial to the reaction. The reaction requires carbon monoxide as the co-reductant; thus, the catalytic system is similar to monooxygenases in some aspects.[129,129a] The direct synthesis of phenols from arenes is of the greatest interest to chemical industry, and the findings of other new catalytic systems have been reported.[130,130a]



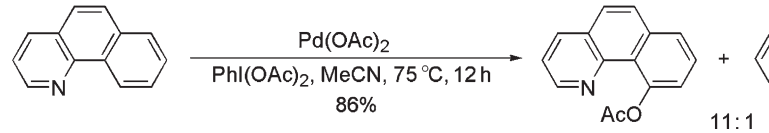
(96)

Various transition metal catalysts have been investigated for the conversion of alkanes to alcohol derivatives in strong acids by many research groups, especially for converting the abundant, but the least reactive, methane to methanol derivatives. The first electrophilic activation and conversion of methane to a methanol derivative is achieved by using H_2O_2 in TFA, using the Pd(II)/TFA system.[131] The highly efficient esterifications of methane occur when the reaction is conducted by using the Hg(II)/H_2SO_4 and Pt(II)/H_2SO_4 catalyst systems. The reactions are electrophilic in nature to give esters in high yields (43% and 72% yields, respectively).[132,132a] Recently, the vanadium-containing heteropolyacids were found to be very active in this transformation.[133,133a] Methane is converted to methyl trifluoroacetate in 95% yield along with a small amount of methyl acetate in a mixture of solvents TFA/TFAA (80 °C, 20 h) (Equation (97)). Heteropolyacids as catalysts in various catalytic reactions have been well documented.[134] Also, simple $Cu(OAc)_2$ has been found to be very active as a catalyst in this reaction. A possible mechanism involving the formation of methyl radical via abstraction of H atom by V(V)═O from methane and subsequent oxidation of methyl radical has been suggested.

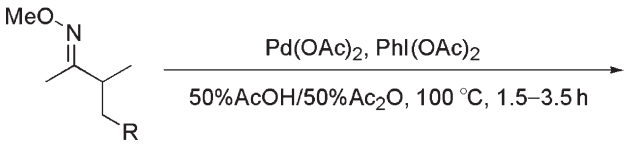


(97)

The palladium-catalyzed reaction of benzo[*h*]quinoline in the presence of $PhI(OAc)_2$ as an oxidant in MeCN gives an 11 : 1 mixture of 10-acetoxy- and 10-hydroxybenzo[*h*]quinolines in 86% yield (Equation (98)).[135] This chelation-directed oxidation can be extended to the benzylic C–H bond of 8-methylquinoline. The inactivated sp^3 C–H bonds of oximes and pyridines undergo the same palladium-catalyzed oxidation with $PhI(OAc)_2$ (Equation (99)).[136]

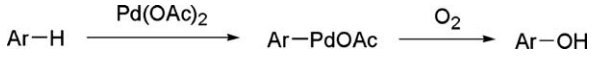


(98)

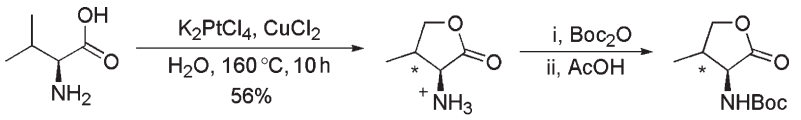


R	*Yield* (%)
HR	74
Me	78

(99)



Scheme 13



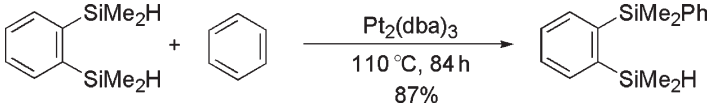
Scheme 14

Selective hydroxylation of α-amino acids in water is achieved with the aid of $K_2PtCl_4/CuCl_2$. The reaction of L-valine with $K_2PtCl_4/CuCl_2$ at 160 °C for 10 h affords the cyclized lactones, which are converted to *N*-Boc-lactones (Scheme 14).[137]

10.05.7 Other Reactions and Applications

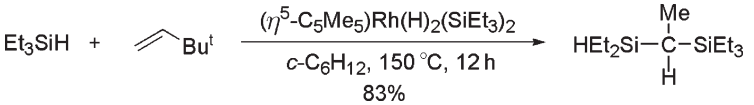
10.05.7.1 Silylation of C–H Bonds

Catalytic dehydrogenative silylation reactions of arenes and alkanes with hydrosilanes need photoirradiation or the co-presence of an efficient hydrogen acceptor. The first example of the dehydrogenative silylation is the reaction of benzene with pentamethyldisiloxane using an $IrCl(CO)(PPh_3)_2$ catalyst under thermal reaction conditions in the absence of a hydrogen acceptor.[138] This reaction requires a prolonged reaction period (49 days) to obtain relatively higher total yields of phenylated products. The selective silylation of arenes with *o*-bis(dimethylsilyl)benzene occurs in the presence of $Pt_2(dba)_3$ complex as a catalyst, giving the monoarylated hydrosilanes in high yields (Equation (100)).[139] In this reaction, the bis(silyl)platinum appears to function as the active catalyst species. The reactivities of the arenes decrease in the following order: anisole > chlorobenzene > benzene > toluene.

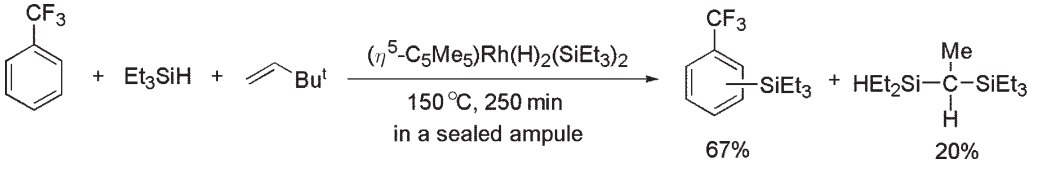


(100)

The reaction of triethylsilane in the presence of *tert*-butylethylene as the hydrogen acceptor using $(\eta^6\text{-}C_6Me_6)Rh(H)_2(SiEt_3)_2$ as catalyst affords the self-dehydrogenative silylated product (Equation (101)).[140] The $(\eta^5\text{-}C_5Me_5)Rh(H)_2(SiEt_3)_2$ and $(\eta^6\text{-}C_6Me_6)Rh(H)_2(SiEt_3)_2$ complexes are also effective for the dehydrogenative silylation of arenes with triethylsilane (Equation (102)).[141] In this reaction, the carbosilane dimer is formed in addition to the arylsilane.

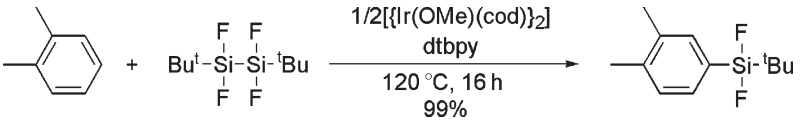


(101)



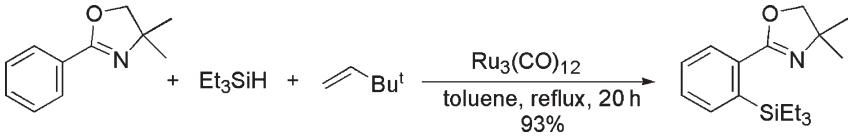
(102)

The iridium complex composed of 1/2[{Ir(OMe)(cod)$_2$}] and 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) shows a high catalytic activity for aromatic C–H silylation of arenes by 1,2-di-*tert*-butyl-1,1,2,2,-tetrafluorodisilane.[142] The reaction of 1,2-dimethylbenzene with 1,2-di-*tert*-butyl-1,1,2,2,-tetrafluorodisilane in the presence of 1/2[{Ir(OMe)(cod)$_2$}] and dtbpy gives 4-silyl-1,2-dimethylbenzene in 99% yield (Equation (103)), which can be utilized for other functionalizations such as arylation and alkylation.



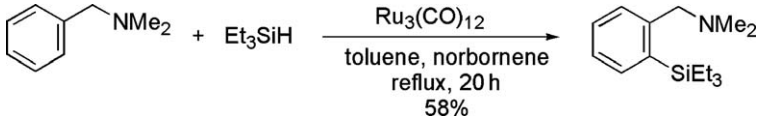
(103)

In the case of the reaction of aryloxazolines with hydrosilanes, the silylation occurs exclusively at the *ortho*-position to the oxazoline ring.[143,143a] When the reaction of aryloxazolines with triethylsilane is conducted in the presence of *tert*-butylethylene as a hydrogen acceptor with the aid of $Ru_3(CO)_{12}$ as catalyst, the silylation proceeds effectively at the *ortho*-position to the oxazoline group (Equation (104)). A variety of functional groups such as ester, amide, and imino groups, and sp^2 nitrogen in pyridine, imidazole, pyrazole, triazole, and tetrazole rings can be used as a directing group.



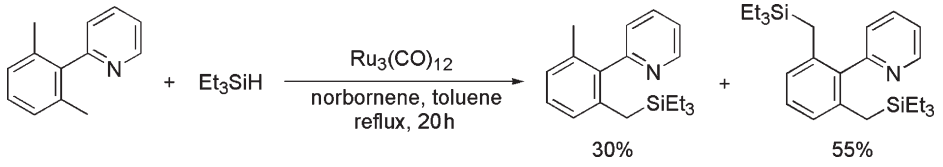
(104)

Interestingly, nitrogen atom participates in the activation of C–H bonds even in the absence of π-conjugation. The silylation of *N*,*N*-dimethylbenzylamine with triethylsilane gives the *ortho*-silylation product (Equation (105)).[144]



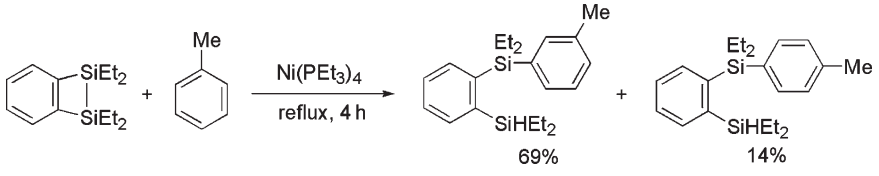
(105)

The silylation of benzylic C–H bonds is achieved by using $Ru_3(CO)_{12}$ catalyst in the presence of norbornene as a hydrogen acceptor.[145] The reaction of 2-(2,6-dimethylphenyl)pyridine with triethylsilane in the presence of $Ru_3(CO)_{12}$ catalyst and norbornene affords mono- and disilylation products in 30% and 55% yields, respectively (Equation (106)). The reaction of 2-(2-tolyl)pyridine shows that the silylation of the aromatic C–H bond is more facile than that of the benzylic C–H bond.

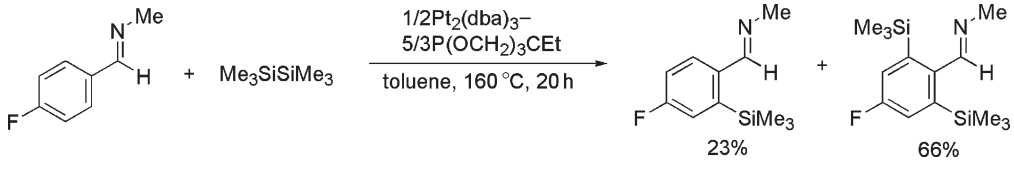


(106)

Disilanes are also effective as silylation reagents. The $Ni(PEt_3)_4$-catalyzed reaction of aromatic compounds with 3,4-benzo-1,1,2,2-tetraethyl-1,2-disilacyclobutene gives the 1-(diethylarylsilyl)-2-(diethylsilyl)benzene (Equation (107)).[146,146a–146e] In this reaction, the *o*-quinodisilane–nickel complex is involved as a key intermediate. The regioselective silylation of aromatic imines with hexaorganosilanes proceeds via chelation-assisted C–H bond activation by a platinum complex (Equation (108)).[147,147a] The electron-withdrawing groups at the *para*-position enhance the yields of the silylation products.

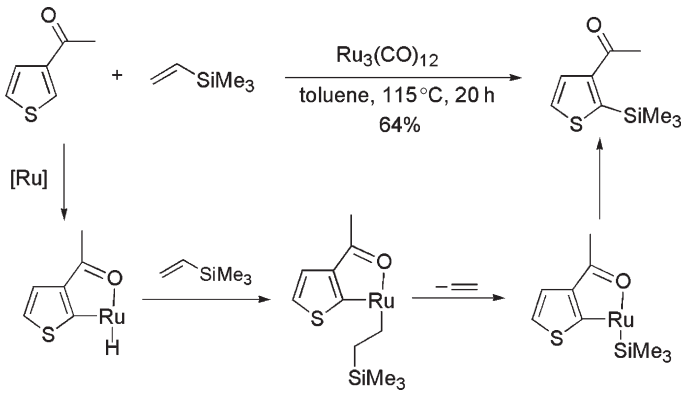


(107)



(108)

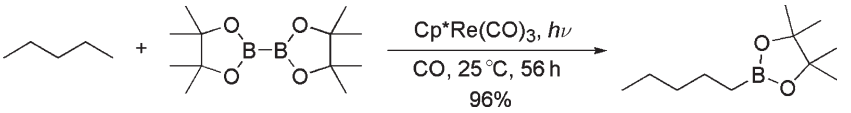
Triorganovinylsilanes can be used as silylating reagents. In this case, the vinyl moiety functions as a hydrogen acceptor. The $Ru_3(CO)_{12}$-catalyzed reaction of 3-acetylthiophene with trimethylvinylsilane affords 3-acetyl-2-(trimethylsilyl)thiophene in 64% yield, as shown in Scheme 15.[148] This reaction involves a β-silyl elimination, yielding a metal species.



Scheme 15

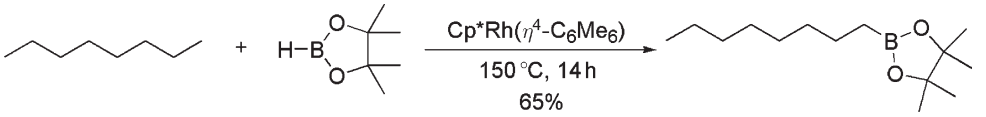
10.05.7.2 Borylation of C–H Bonds

Direct borylation of C–H bonds is very important in organic synthesis because the boryl functionality can be transformed to a hydroxyl group by oxidation and various types of functional materials by carbon–carbon bond formation. The first example of the borylation of C–H bonds is the reaction of arenes with a stoichiometric amount of transition metal boryl complex under photochemical conditions to give the corresponding arylboron compounds.[149] The borylation of an sp^3 C–H bond in an alkane is achieved by using $Cp^*W(CO)_2B(OR)_2$ [$(OR)_2 = 1,2\text{-}O_2(C_6H_2\text{-}3,5\text{-}(CH_3)_2)$] under photochemical conditions.[150] The catalytic borylation reaction of pentane with 4,4,4′,4′,5,5,5′,5′-octamethyl-2,2′-bi-1,3,2-dioxaobolane (B_2pin_2) using $Cp^*Re(CO)_3$ as catalyst is accomplished under photochemical conditions (Equation (109)).[151] The borylation occurs exclusively at the methyl C–H bonds. The co-presence of CO is necessary to suppress the deactivation of the catalyst.



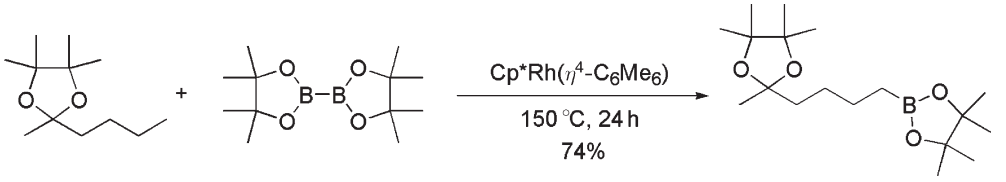
(109)

Furthermore, the borylation is achieved under thermal reaction conditions. The reaction of octane with B_2pin_2 using $Cp^*Rh(\eta^4\text{-}C_6Me_6)$ as a catalyst at 150 °C gives *n*-octylborane with perfect regioselectivity in high yield (Equation (110)).[152,152a] Pinacol borane (Hbpin) can also be used as a borylating reagent. The boryl complexes, $Cp^*Rh(H)_2(Bpin)_2$ and $Cp^*Rh(H)(Bpin)_3$, are observed in the catalytic reactions and react with alkanes and arenes to form the alkyl- and arylboronate esters.[153] This experimental result and the theoretical calculations suggest that the C–H bond cleavage process occurs by a metal-assisted σ-bond metathesis mechanism.



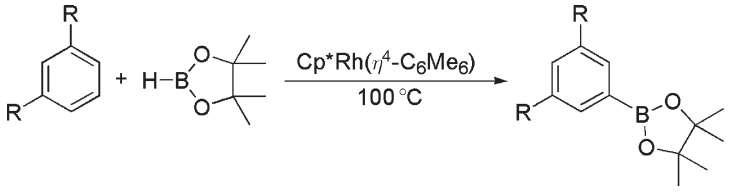
(110)

The rhodium-catalyzed borylation of methyl C–H bonds is compatible with several moieties containing oxygen, nitrogen, and fluorine.[154] For example, the reaction of pinacol acetal of 2-hexanone with bis(pinacolato)diborane (B_2pin_2) in the presence of $Cp^*Rh(\eta^4\text{-}C_6Me_6)$ catalyst gives the alkylboronate ester in 74% yield (Equation (111)). The rhodium-catalyzed C–H activation and borylation occur at the least hindered and least electron-rich methyl group.



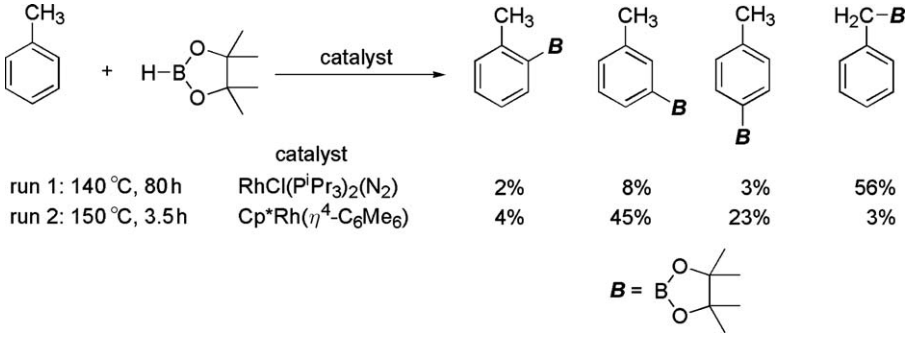
(111)

The borylation of arenes causes the inevitable problem of regioselectivity. The reaction of monosubstituted arenes with hydroboranes yields a mixture of regioisomers. In the reaction of 1,3-disubstituted arenes, for example, 1,3-dichloro-, 1,3-dibromo-, and 1,3-bis(trifluoromethyl)benzenes, the borylation occurs at the 5-position selectively (Equation (112)).[155,155a–155c] In the reaction of toluene with pinacol borane, the $RhCl(P^iPr_3)_2(N_2)$ catalyst favors the borylation of the benzylic C–H bond, while the $Cp^*Rh(\eta^4\text{-}C_6Me_6)$ catalyst results in the borylation of the aromatic C–H bonds (Equation (113)).[155,155a–155c,156] The presence of dtbpy dramatically improves the activity of the iridium catalyst for the borylation of aromatic and heteroaromatic C–H bonds.[157,157a,157b]



R	*Time* (h)	*Yield* (%)
Cl	14	89
Br	17	92
CF_3	10	88

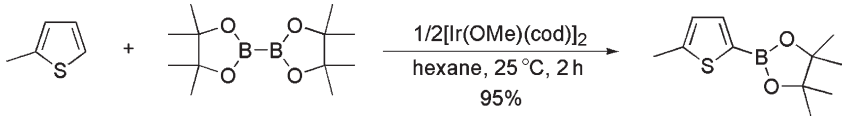
(112)



	catalyst				
run 1: 140 °C, 80 h	$RhCl(P^iPr_3)_2(N_2)$	2%	8%	3%	56%
run 2: 150 °C, 3.5 h	$Cp^*Rh(\eta^4\text{-}C_6Me_6)$	4%	45%	23%	3%

(113)

The borylation of five-membered heteroarenes with HBpin or B_2pin_2 is achieved with the aid of $1/2[IrCl(cod)]_2$, $1/2[Ir(OMe)(cod)]_2$, or $Cp^*Rh(\eta^4\text{-}C_6M_6)$.[158,158a] The borylation regioselectively occurs at the α-C–H bonds and the regioselectivity can be controlled by a sterically hindered substituent. Among the above catalysts, the complex generated from $1/2[Ir(OMe)(cod)]_2$ and dtbpy catalyzes more efficiently the direct borylation of 2-substituted heteroarenes such as thiophenes, furans, and pyrroles (Equation (114)).[159] Similar borylation of thiophene, furan, and pyrrole regioselectively provides 2,5-bis(boryl)heterocycles.

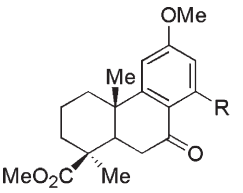


(114)

10.05.7.3 Application

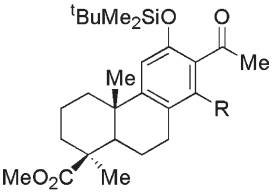
Synthetic reactions via C–H bond activation have been applied to the synthesis of natural products and the related molecules, development of functional materials, and functionalization of polymers.

The *ortho*-alkenylation of aromatic ketones catalyzed by a ruthenium complex is applied to the functionalization of diterpenoid analogs, methyl 12-methoxy-7-oxoopodocarpa-8,11,13-trien-19-oate **13** and methyl 13-acetyl-12-[(*tert*-butyldimethylsilyl)oxy]podocarpa-8,11,13-trien-19-oate **14**.[160] The reaction of the terpenoid analogs **13** and **14** (R = H) with 1-phenyl-2-trimethylsilylethyne in the presence of $RuH_2(CO)(PPh_3)_3$ in toluene gives the corresponding alkenylation products **13** and **14** ($R = C(Ph)=CHSiMe_3$) in good yields. The alkenylated diterpenoids are transformed to tetracyclic molecules on treatment with trimethyl orthoformate.



R = H, C(Ph)=CHSiMe$_3$

13

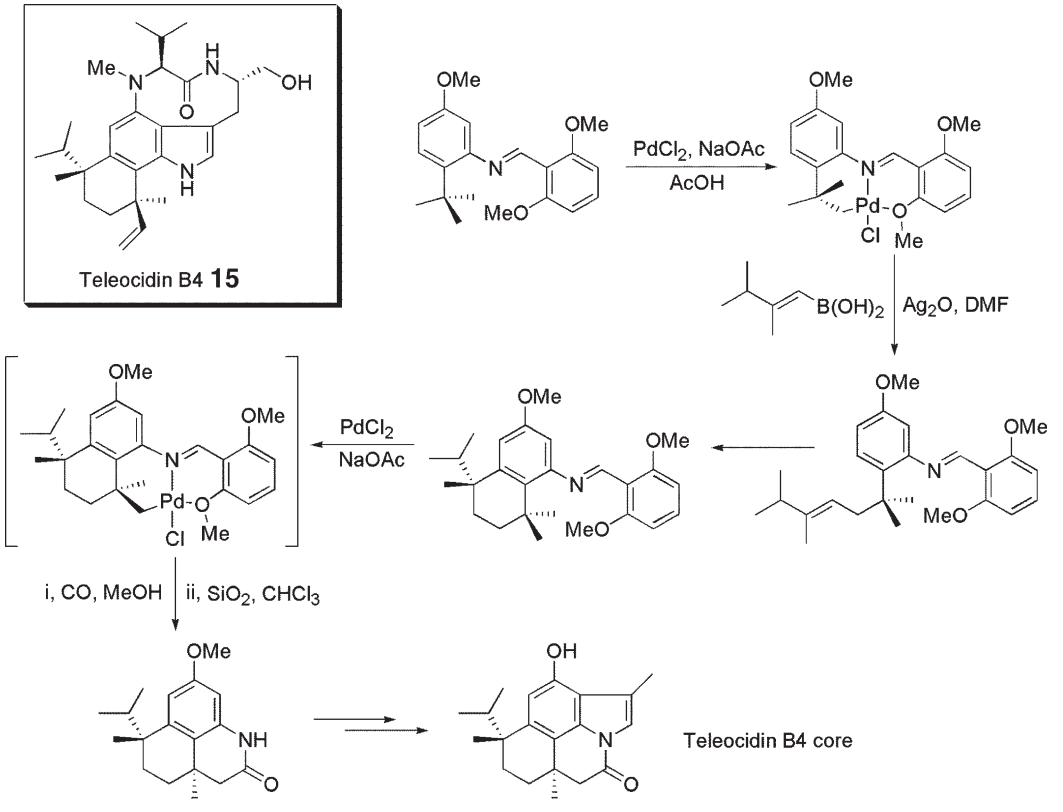


R = H, C(Ph)=CHSiMe$_3$

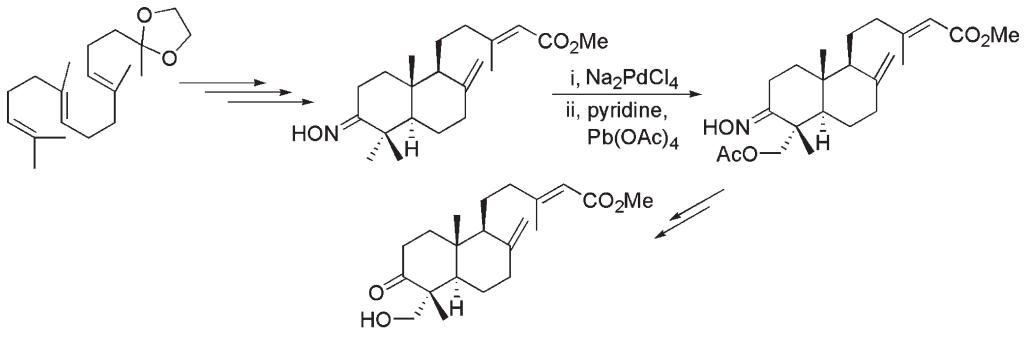
14

The teleocidin B4 core **15** is synthesized from the Shiff base of 2-*tert*-butyl-5-methoxyaniline, as shown in Scheme 16.[161] The key sequence of this synthesis consists of two C–H bond functionalizations, alkenylation and oxidative carbonylation of two methyl groups, via palladacycle formations.

The natural diterpenoid rostratone **16** is synthesized from ethylene ketal as shown in Scheme 17.[162] In this synthesis, the Pd-mediated remote acetoxylation is achieved by C–H bond activation by Na_2PdCl_4 giving palladacycle dimers followed by treatment with pyridine and lead tetraacetate.



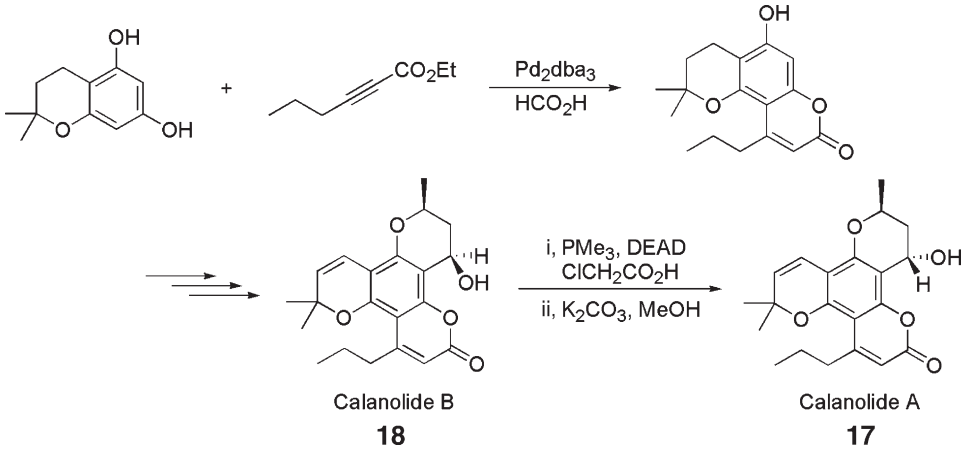
Scheme 16



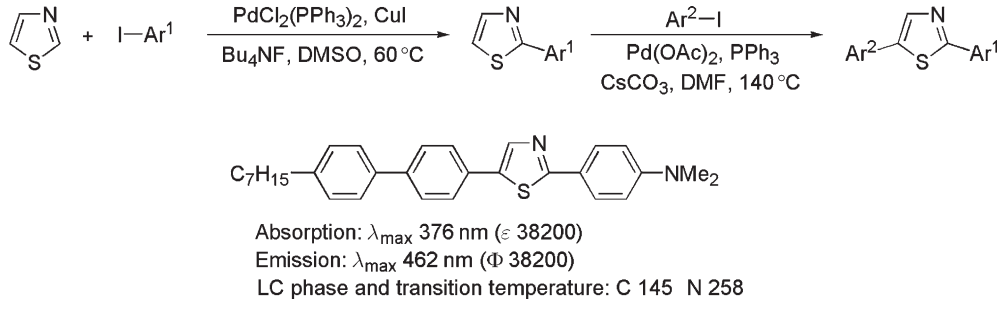
Scheme 17

Hydroarylation of alkynoates with phenols is applied to the synthesis of calanolides A **17** and B **18**, which are active against AZT-resistant strains of HIV-1.[163] The key step is the palladium-catalyzed coumarin formation reaction, as shown in Scheme 18.

Scheme 19 shows that arylation of sp^2 C–H bonds with aryl iodides can be applied to the synthesis of light-emitting and liquid crystalline molecules.[164] The Pd-catalyzed tandem C–H coupling reactions of thiazole with aryl iodides give the differently substituted 2,5-diarylthiazoles, which would be a highly potential single-layer EL method with polarized light emission.



Scheme 18

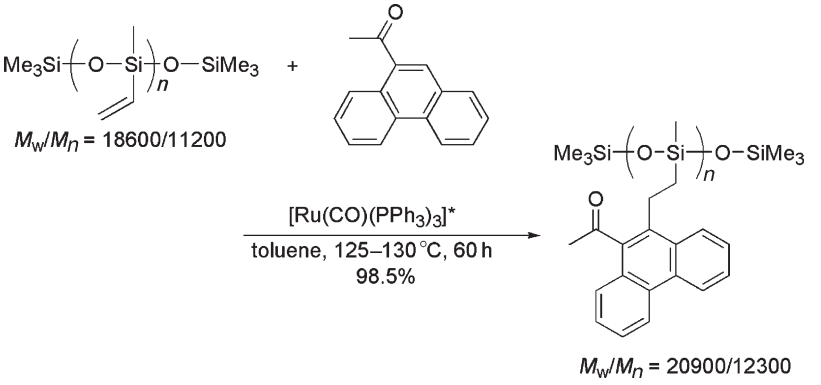


Scheme 19

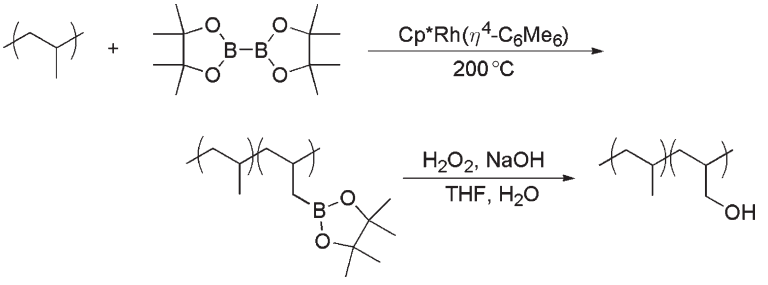
The rhodium-catalyzed borylation of alkanes is applied to regiospecific functionalization of polyolefines.[165,165a] The reaction of polypropylenes (atactic, isotactic, and syndiotactic) with B_2pin_2 in the presence of $Cp^*Rh(\eta^4\text{-}C_6Me_6)$ catalyst at 200 °C affords the borylated polymers, which are treated with basic hydrogen peroxide in a mixture of THF and H_2O to oxidize the boronate esters to the corresponding alcohols (Scheme 20). The hydroxylated polymers contain 0.2–1.5% hydroxymethyl side-chains.

Hydroarylation of alkenes is applied to achieve step-growth co-polymerization of aromatic ketones and α,ω-dienes such as 3,3,6,6-tetramethyl-3,6-disila-1,7-octadiene and 1,3-divinyltetramethyldisiloxane. Co-polymerization of acetophenone and 3,3,6,6-tetramethyl-3,6-disila-1,7-octadiene is catalyzed by Ru species which has been previously activated by treatment with styrene, and a significantly high molecular weight co-polymer, co-poly(3,3,6,6-tetramethyl-3,6-disila-1,8-octanylene/2-acetyl-1,3-phenylene), is obtained (Scheme 21).[166]

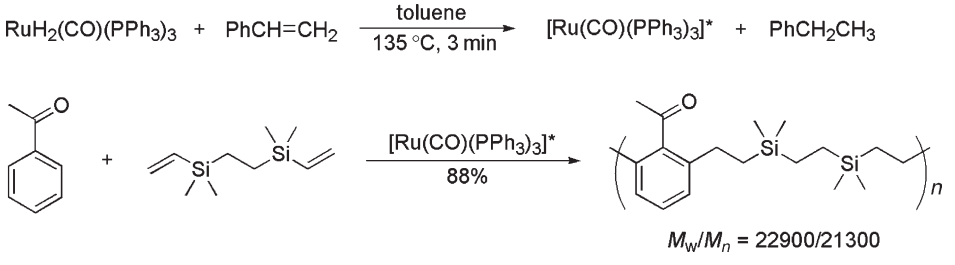
This ruthenium-catalyzed step-growth polymerization is also applied to substituted acetophenones, 4-acetylstyrene, benzophenone, 4-benzoylpyridine, and bis(5′-acetyl-2′-thienyl)benzenes.[167,167a–c] Co-polymerization of acetophenone and 1,4-bis[(trimethylsilyl)ethynyl]benzene gives a linear cross-conjugated co-polymer, while a similar reaction of 4-[(trimethylsilyl)ethynyl]acetophenone yields hyperbranched materials.[168] Chemical modification of poly(vinylmethylsiloxane) or α,ω-bis(trimethylsilyloxy)co-poly(dimethylsiloxyane/vinylmethylsiloxane) (99 : 1) is achieved by ruthenium-catalyzed hydroarylation with aromatic ketones (Equation (115)).[169,169a]



(115)



Scheme 20



Scheme 21

10.05.8 Conclusion

This chapter illustrates that synthetic reactions via C–H bond activation became popular in the past 10 years and are noted as one of the active fields in organic synthesis. The development of new catalytic systems will improve the selectivity and the scope of the reactions, and open up new reactions.

The synthetic methods via C–H bond activation have significant advantages over the method so far in use:

(i) The synthesis via C–H bond activation does not need halogenated or functionalized substrates that are essential for the conventional methods. This process provides an environment-friendly synthesis that is recognized to account for major parts in organic synthesis in future.
(ii) The synthetic process via C–H bond activation reduces the total steps of synthesis. This process is also applicable to a direct functionalization of hydrocarbons that are the main feedstocks for the chemical industry from oil and natural gas.

Recently there have been several studies on synthetic reactions via aromatic C–H bond activation. However, there are limitations that still need to be solved. The following points should be considered.

(i) simple arenes,
(ii) mild reaction conditions, and
(iii) simple catalytic systems.

Moreover, sp^3 C–H bond activation is one of the most significant subjects because aliphatic hydrocarbons including methane exist abundantly in nature.

A large number of synthetic reactions via C–H bond activation have been reported in the last 10 years. In near future, applications to natural products and functional materials will be the next research targets, together with the development of new synthetic reactions.

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10.06
C–C Bond Formation (Part 1) by Addition Reactions: through Carbometallation Mediated by Group 4–7 Metals

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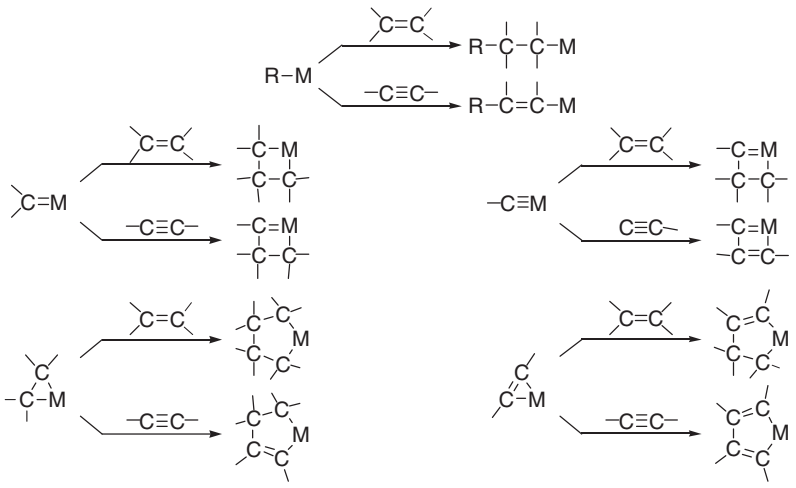
10.06.1 Introduction

The term "carbometallation" was most probably coined only about a quarter of a century ago.[1] However, the history of those reactions that can be classified as carbometallation reactions is much older. If one includes not only the Ziegler–Natta-type organometallic alkene polymerization reactions[2] but also various types of organometallic conjugate addition reactions,[3] carbometallation collectively is easily more than a century old. In its broadest definition, carbometallation may be defined as a process of addition of a carbon–metal bond to a carbon–carbon multiple bond. As such, it may represent either a starting material–product relationship irrespective of mechanistic details or an actual mechanistic "microstep" of carbon–metal bond addition to a carbon–carbon metal multiple bond irrespective of the structure of the product eventually formed.

In most cases, the carbon–carbon multiple bond-containing substrates are ordinary alkenes and alkynes, as shown in Scheme 1, but they may be allenes, conjugated dienes, enynes, and diynes as well as their higher homologs. Organometallic reagents in many cases contain a C–M singe bond, that is, R–M, where M is a metal-containing group, and R represents a variety of carbon groups including alkyl, aryl, alkenyl, and alkynyl. It is very important, however, to note that they may not only contain C═M and C≡M bonds but also be represented by metallacycles of various types. Carbometallation reactions of these C═M and C≡M bond-containing organometals and metallacycles have emerged over the past few decades as synthetically useful processes including olefin metathesis (for recent reviews,



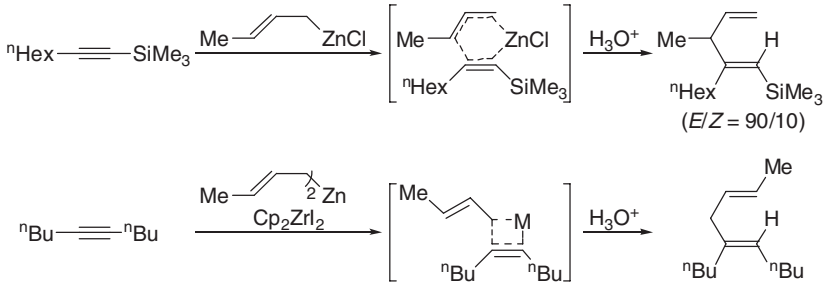
Scheme 1 Some representative patterns of the carbometallation reactions.

see Refs: 4, 4a, and 4b) and various cyclization reactions of alkenes and alkynes.[5,5a] Several fundamental processes representing a wide variety of these reactions are also shown in Scheme 1. Many similar additional patterns are also conceivable.

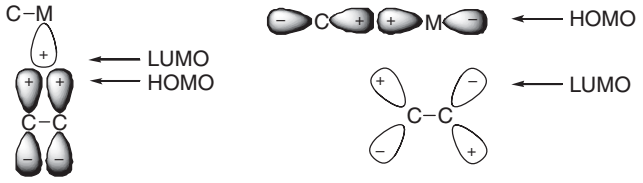
What are shown in Scheme 1 represent only those processes that are loosely termed four-centered processes. With conjugated dienes and related substrates as well as with allyl- and propargylmetals, six-centered processes have also been widely observed. Here again, these loosely termed processes, that is, four-centered and six-centered processes, may or may not imply actual mechanistic details and so on. For example, two seemingly similar allylzincation reactions display regioselectivity patterns that are diametrically opposed to each other[6] (Scheme 2). Although it is tempting to speculate that the uncatalyzed reaction of the alkynylsilane might involve a six-centered process, whereas the Zr-catalyzed reaction likely proceeds by a four-centered process, merely on the basis of the observed starting material–product relationship, nothing mechanistic has actually been firmly established.

It has become increasingly clear that carbometallation reactions are mechanistically diverse. Although most of the synthetically interesting carbometallation reactions of organotransition metals appear to involve concerted four-centered processes in which the presence or ready availability of a low-lying metal-empty orbital is critically important (Scheme 3), many other processes including radical and polar processes are also known.

As clearly indicated in Scheme 1, carbometallation converts an organometal into another organometal. If the organometallic product is sufficiently less reactive than the starting organometal, the monocarbometallation product can be obtained in high yield. Otherwise, oligomerization and polymerization of the starting alkenes or alkynes may be dominant. From the synthetic viewpoint, the value of monocarbometallation and that of oligo- and polycarbometallation are fundamentally different. The latter may be useful for the synthesis of oligomeric and polymeric compounds of material chemical interest, but they may not be useful for the synthesis of fine chemicals of biological and medicinal interest, unless the degree of polymerization, "pair"-, regio-, and stereoselectivities can be strictly controlled. In this chapter, attention is focused only on the stoichiometric and catalytic monocarbometallation processes



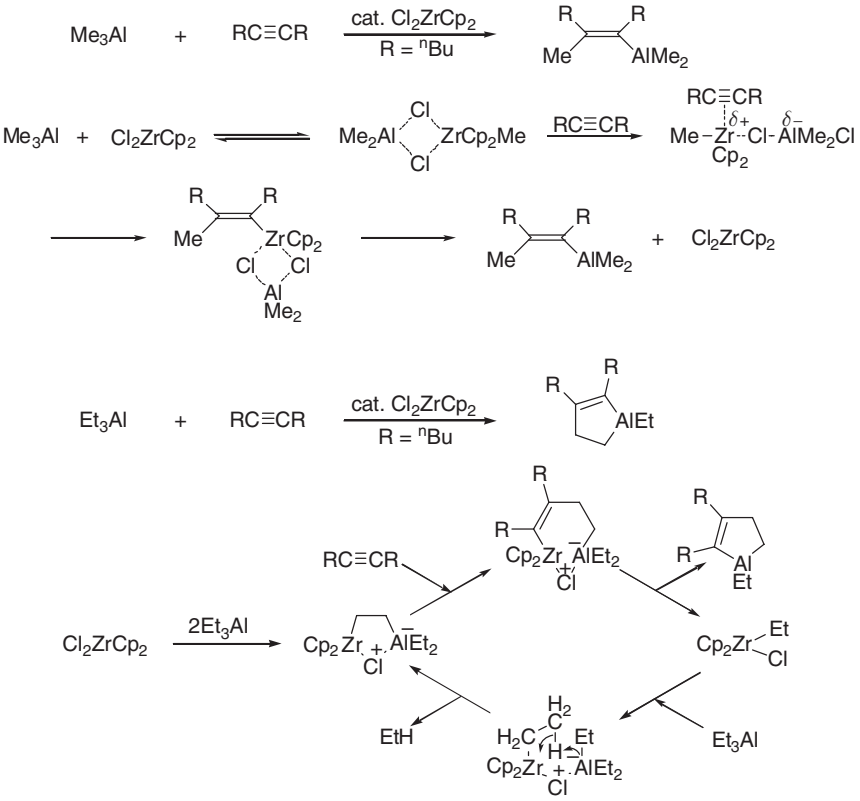
Scheme 2 Four- versus six-centered processes in allylmetallation.



Scheme 3 HOMO–LUMO interaction schemes for concerted four-centered carbometallation reactions.

and well-controlled oligomeric processes that group 4–7 transition metals undergo. This chapter excludes carbometallation reactions of C═M and C≡M-containing organometals, as they are discussed elsewhere in this enyclopedia. Also excluded is the vast topic of organometallic conjugate addition which is not normally considered as a carbometallation reaction. So, this chapter is mainly concerned about both acyclic and cyclic monocarbometallation reactions of alkenes, alkynes, allenes as well as conjugated and isolated dienes, diynes, enynes, and their higher homologs with organometals containing C–M single bonds, including alkyl-, aryl-, alkenyl-, and alkynylmetals as well as three-membered and higher metallacycles containing two C–M single bonds.

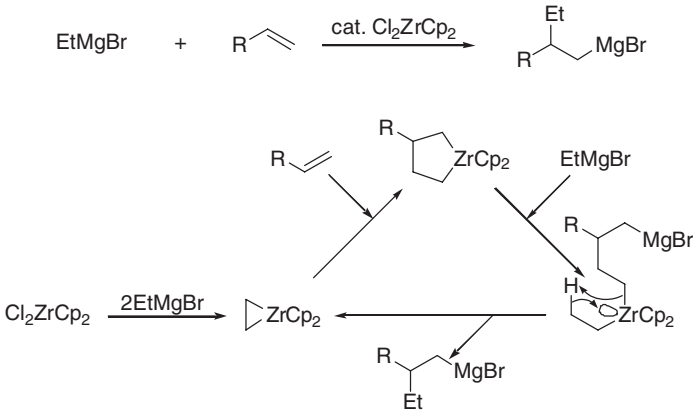
Over the past couple of decades, acyclic–cyclic dichotomy in carbometallation has emerged as a fundamentally important aspect, most probably penetrating through the entire field of concerted carbometallation reactions of organotransition metal complexes. For example, whereas the Zr-catalyzed carbometallation of alkynes with Me_3Al discovered in 1978[1] is considered to proceed via a four-centered acyclic methylzirconation,[7,8] the corresponding reaction of Et_3Al in non-polar solvents, which was also discovered in 1978,[1] has recently been shown to proceed via a complex cyclic or pseudocyclic process shown in Scheme 4.[9] Furthermore, a seemingly related Zr-catalyzed carbometallation of alkenes with EtMgX (X = halogen or Et) discovered in 1983 by Dzhemilev[10] was initially considered to be an acyclic process involving an addition of an ethyl–metal bond to the alkene. In 1991, a systematic investigation



Scheme 4 Acyclic and cyclic mechanisms for the Zr-catalyzed carboalumination of alkynes.

of the reaction of Et_2ZrCp_2 generated *in situ* from EtMgBr and Cl_2ZrCp_2 with alkenes unexpectedly led to the clarification of an intricate cyclic mechanism shown in Scheme 5[11] (for related articles, see Refs: 12, 12a, and 12b), which turned out to be closely related to the cyclic mechanism shown in Scheme 4. The Dzhemilev ethylmagnesation is an example of an acyclic monocarbometallation in terms of starting material–product relationship. Mechanistically, however, it is a cyclic carbometallation process. As alluded earlier, distinction between starting material–product relationship and mechanism must be made consciously and clearly in the use of acyclic and cyclic terminology. In a more chemical and scientific vein, β-agostic interaction leading to β-C–H activation and eventual β-H abstraction is clearly responsible for diversion to cyclic processes shown in both Schemes 4 and 5, even though there are other important processes leading to cyclic carbometallation reactions as well[13,13a–13g] (*vide infra*). In this context, it should be clearly reminded that closely related α-agostic interaction-induced α-H abstraction leads to the formation of metal–carbene and metal–carbyne complexes and their reactions including metathesis reactions.

Survey of the literature indicates that carbometallation involving group 4–7 transition metals excluding conjugate addition, alkene and/or alkyne metathesis, and their polymerization is currently dominated by that of Ti and Zr. In view of the widespread occurrence of alkene and/or alkyne metathesis reactions observed with other group 4–7 metals, especially with Cr, Mo, and W, there does not appear to be any reason why the scope of carbometallation with group 4–7 metals other than Ti and Zr should be limited. In this context, however, it might be useful to know approximate cost of these transition metals. The cost of representative group 4–7 metal chlorides in the most recent Strem Chemicals catalog (Strem catalog no. 20, 2004–2006, Strem Chemicals, Inc., Newburyport, MA, USA) are shown in Table 1. As such, only Mn, Ti, Zr, and possibly Cr and Nb may be generally viable candidates for synthetically useful metals in the stoichiometric carbometallation, even though catalysis could lead to practically attractive carbometallation reactions with any of these transition metals.



Scheme 5 Cyclic mechanism for the Zr-catalyzed ethylmagnesation of alkenes.

Table 1 Costs of representative group 4–7 metal chlorides

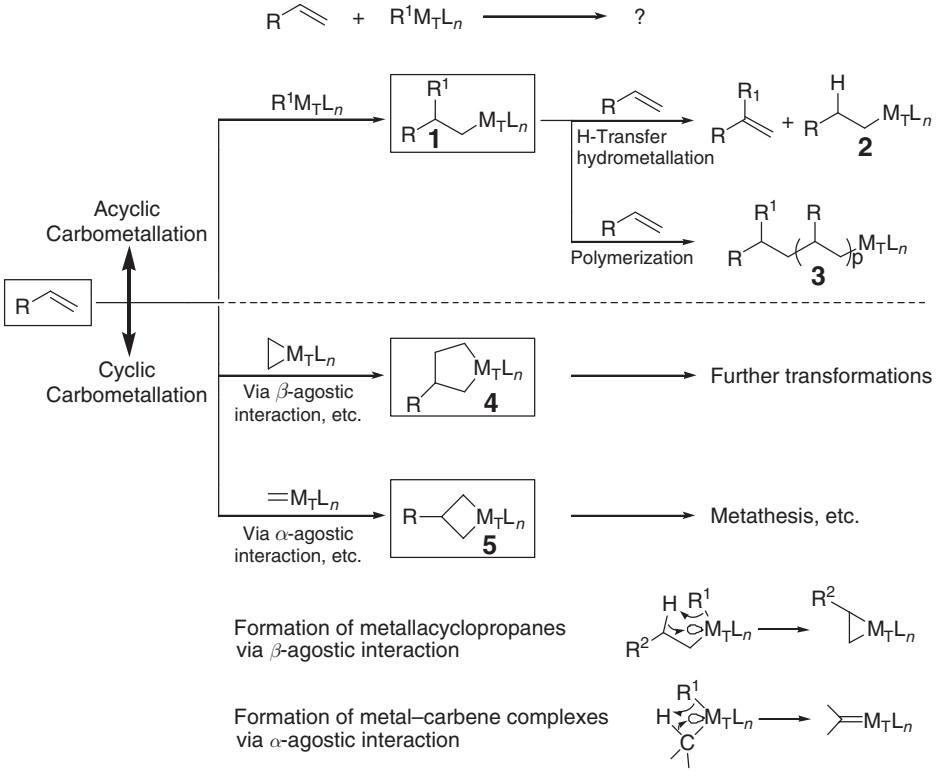
MCl_n	*Formula* wt.	*Purity* (%)	*Listed price*	*Price per mol*
$TiCl_4$	189.73	99.8	\$55/1 kg	\$9
$ZrCl_4$	233.03	99.5	\$38/250 g	\$35
$HfCl_4$	320.30	98	\$180/250 g	\$231
VCl_3	157.30	95	\$136/50 g	\$428
$NbCl_5$	270.17	99	\$94/250 g	\$102
$TaCl_5$	358.21	99.9	\$120/50 g	\$860
$CrCl_3$	158.35	99	\$157/250 g	\$99
$MoCl_3$	202.32	99.5	\$231/25 g	\$1,869
WCl_6	396.57	99.9	\$396/500 g	\$314
$MnCl_2$	125.85	97	\$99/2 kg	\$6
$ReCl_3$	363.47	99.9	\$143/5 g	\$10,395

10.06.2 Carbometallation Reactions of Group 4 Metals: Ti, Zr, and Hf

10.06.2.1 General Discussion

Although there does not appear to be any firm chemical or scientific reason, carbometallation reactions of the group 4 metals, especially Ti and Zr, have been widely known and extensively investigated. When metathesis reactions are excluded, as in this chapter, the great majority of the currently known carbometallation reactions of the group 4–7 metals are those of Ti and Zr. The carbometallation reactions involving Hf tend to resemble those of Zr. Generally speaking, however, carbometallation reactions involving Hf are more sluggish than the corresponding reactions of Zr. From a more practical viewpoint, Hf is several times as expensive as Zr, which, in turn, is several times as expensive as Ti. The current prices of MCl_4 ($\geq$98% pure), containing Ti, Zr, and Hf as M (Strem Chemical), are \$10/mol, \$35/mol, and \$230/mol, respectively. Probably for these reasons, relatively little is known about the carbometallation reactions of Hf. With the exception of W, the metals of the third transition series are the most expensive within a triad, and their stoichiometric carbometallation reactions appear to be accordingly less well investigated. Both Ti and Zr have very widely participated in various types of carbometallation reactions, even when their polymerization and metal–carbene reactions are excluded. Investigations over the last few decades have indicated that the two metals share some common features in many of their carbometallation reactions. At the same time, however, they also display significant differences; some of their most significant differences are briefly discussed below.

In principle, carbometallation of an alkene ($RCH{=}CH_2$) with a coordinatively unsaturated organotransition metal compound ($R^1M_TL_n$) can produce a monomeric carbometallation product **1** (Scheme 6). This reaction may not, however, stop at this stage. It can be accompanied by other processes of which (i) hydrogen-transfer hydrometallation to produce a potentially thermodynamically more favorable mixture of a 1,1-disubstituted alkene and a hydrometallation product **2** and (ii) polymerization to produce polyalkenes **3** are representative. The extents to which these side-reactions occur are functions of relative rates of various competing processes. For example, accumulation of the monomeric carbometallation product **1** can be favored in cases where the starting $R^1M_TL_n$ is more reactive toward alkenes than **1**. The organometal/alkene ratio is also an important parameter, since neither of the two side-reactions can proceed after all of the starting alkene has reacted.



Scheme 6 Unified scheme for carbometallation of alkenes with transition metal complexes.

The discussion presented above represents only a fraction of what can be observed in carbometallation of alkenes and alkynes with organometals. As shown in the bottom half of Scheme 6, metallacyclopropanes (or metallacyclopropenes) and metal–carbene (or metal–carbyne) complexes containing transition metals (M_T) can be generated via β- and α-agostic interactions, respectively. Once generated, they can then undergo cyclic carbometallation with alkenes to produce metallacyclopentanes **4** and metallacyclobutanes **5**, respectively. Although not shown in Scheme 6, there are various other routes to **4** and **5**, as discussed later in this chapter. In cases where both α- and β-agostic interactions are possible, the transformations proceeding via β-agostic interaction appear to be significantly more favorable than those proceeding via α-agostic interaction, although this point needs to be further clarified. In cases where β-agostic interaction cannot operate due to the absence of β-H atoms, for example, some transition metals, such as Ti, can still undergo α-H abstraction to produce the corresponding Ti=C complexes, whereas other metals, such as Zr, are much more reluctant to undergo α-H abstraction. This is indeed one of the notable differences between Ti and Zr or Hf.

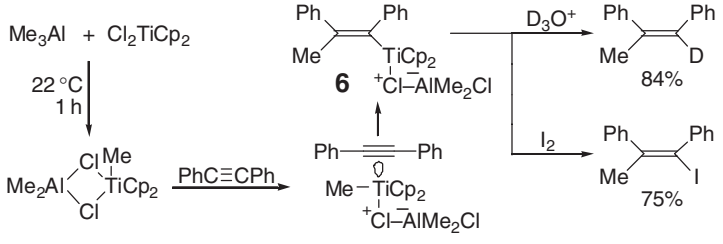
In general, Ti appears to display the widest range of reactivity among the three members of the Ti triad. The most common oxidation number for all three members is +4. Their complexes in which they exist in the +2 oxidation state have also been implicated in many cases. Furthermore, organotitanium complexes of the +3 oxidation states have been much more widely observed than the corresponding complexes of Zr and Hf.[14] The relatively ready accessibility of the +3 oxidative state along with the +4 and +2 oxidation states implies that Ti is more prone to one-electron transfer or radical processes than Zr or Hf, and this indeed has been the case. Undoubtedly, this is one of the main reasons for the versatile reactivity of Ti, which has led to a number of both favorable and unfavorable consequences relative to Zr or Hf.

10.06.2.2 Carbometallation Reactions of Organotitanium Compounds

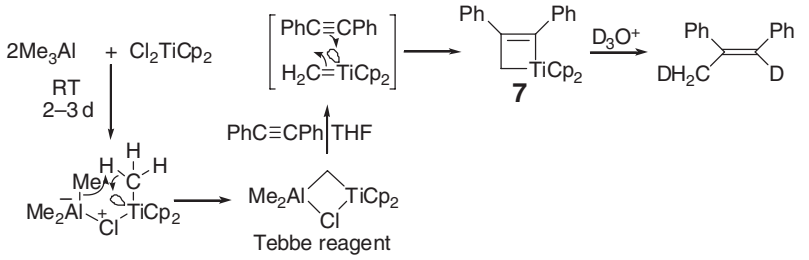
10.06.2.2.1 Controlled monocarbometallation

Although the Ziegler–Natta alkene polymerization via acyclic polycarbotitanation has been known since the 1950s,[2,15,15a,16] controlled acyclic monocarbotitanation producing the monocarbometallated compounds as discrete major product was probably reported first in 1978[17] (Scheme 7). The methyltitanation product **6** obtained in 84% yield was thought to have been formed via acyclic four-centered carbotitanation. Interestingly, Tebbe and Harlow[18] reported in 1980 a totally discrete reaction of the same three reactants, that is, Me_3Al, Cl_2TiCp_2, and PhC≡CPh, which produced a titanocyclobutene **7** via addition of the Tebbe reagent, reported in 1978,[19] to PhC≡CPh (Scheme 8). These two sets of results were confirmed to be true. The seemingly puzzling dichotomy was finally and fully clarified in 1997.[20] In the reaction shown in Scheme 7, in which all three reactants are mixed at the beginning of the reaction, a four-centered acyclic methyltitanation is the only process that is observable. In the reaction shown in Scheme 8, Me_3Al and Cl_2TiCp_2 are allowed to react in a 2 : 1 molar ratio for 2–3 days to produce the Tebbe reagent via α-agostic interaction-induced α-H abstraction.[21] The Tebbe reagent thus formed is then *in situ* converted into $H_2C{=}TiCp_2$ for reacting with PhC≡CPh to produce **7** in the presence of a base, such as THF or an amine. This reaction does not occur in the absence of a suitable base. Furthermore, a 1 : 1 mixture of the Tebbe reagent and Me_2AlCl slowly reacts with PhC≡CPh to produce the acyclic methyltitanation product in 86% yield. The structural and mechanistic details of all the results discussed above are shown in Scheme 9.[20]

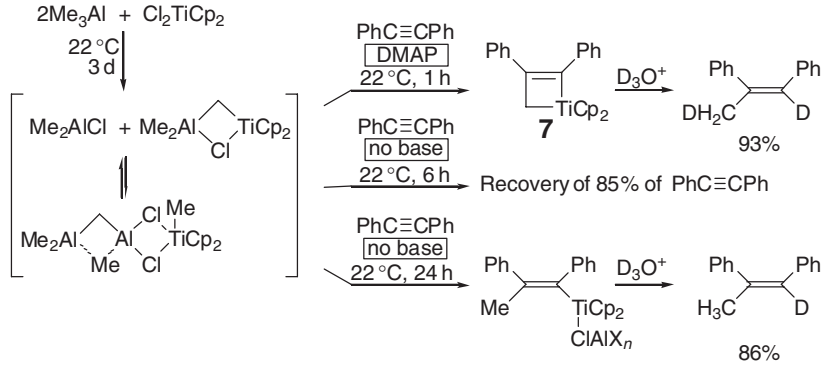
Although the results presented above are very intriguing and informative, the reactions of PhC≡CPh are hardly representative from the synthetic viewpoint. Thus, neither 5-decyne nor 1-octyne gives the expected methyltitanation product in good yields. The product from 5-decyne is 6-methyl-4,5-decadiene, obtained in 92% yield.[17] Evidently, the desired methyltitanation is followed by β-dehydrotitanation. The reaction of 1-octyne is not clean.



Scheme 7 Controlled monocarbotitanation of PhC≡CPh with Me_3Al and Cl_2TiCp_2.

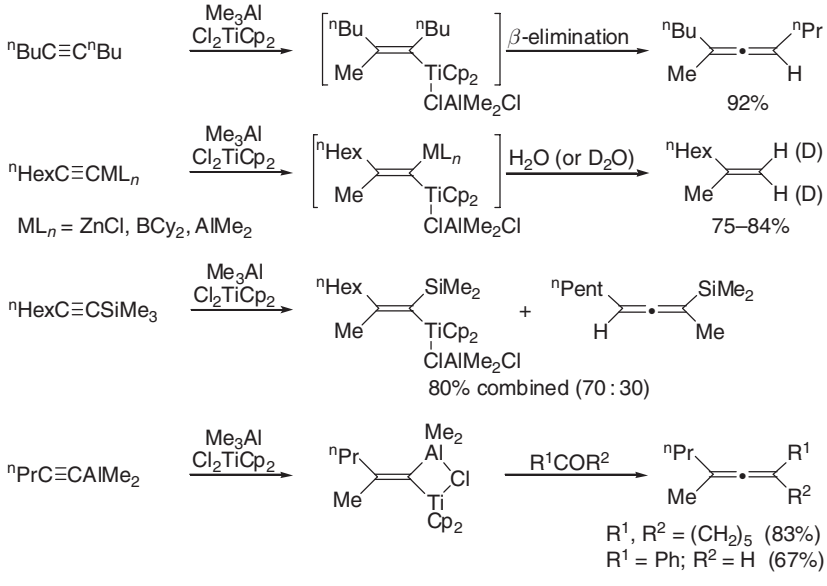


Scheme 8 Formation of the Tebbe reagent from Me_3Al and Cl_2TiCp_2 and its reaction with PhC≡CPh.

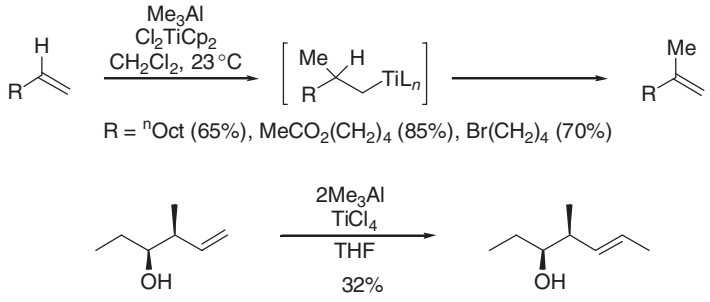


Scheme 9 Cyclic and acyclic dichotomy observed with the Tebbe reagent and PhC≡CPh.

Although not fully clarified, terminal metallation appears to be one of the side-reactions. On the other hand, terminally metallated alkynes containing Zn, B, Al, and Si undergo the desired methylmetallation in high yields. Although the reaction of $^nHexC{\equiv}CSiMe_3$ gives, after hydrolysis, a 70 : 30 mixture of 1- and 2-methylated products, the other cases are nearly 100% regioselective, placing Me β to the pre-existing metal.[17] 1,1-Aluminatitana-1-alkenes react with aldehydes and ketones to produce allenes in good yields;[22] these results are summarized in Scheme 10.



Scheme 10 Synthetic scope of methyltitanation of alkynes.

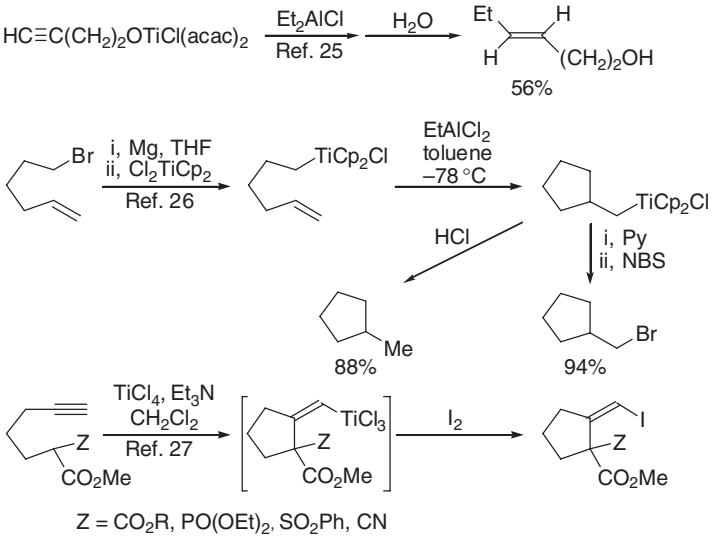


Scheme 11

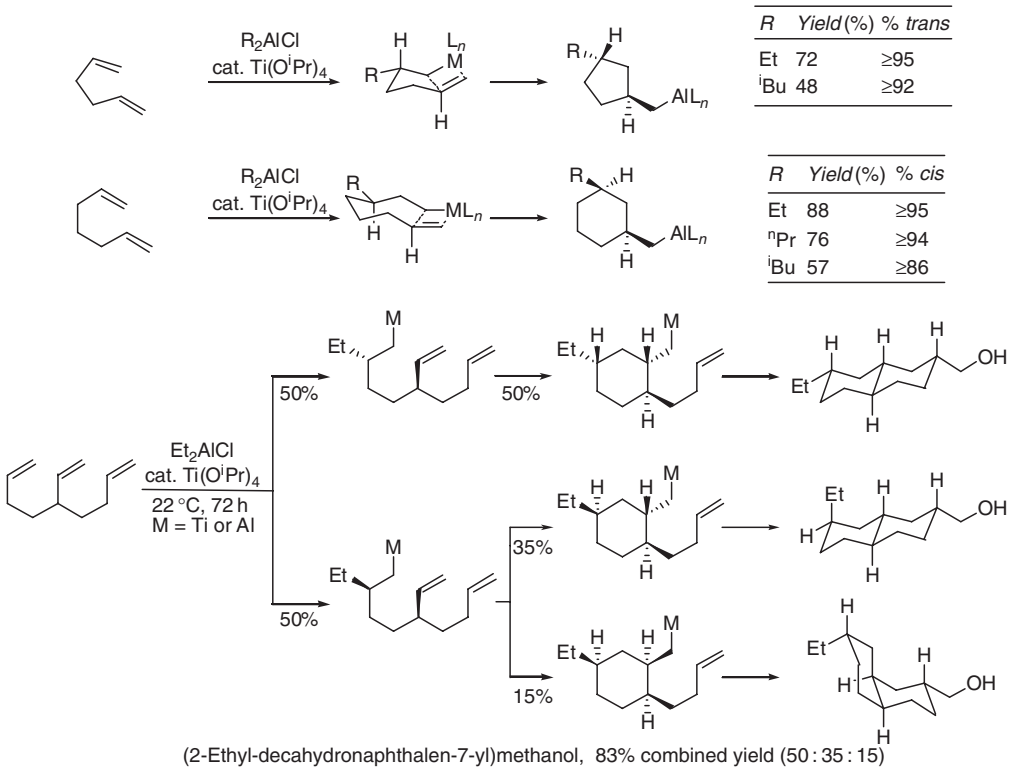
In addition to the formation of $H_2C{=}Ti$ derivatives via α-H abstraction, formation of alkenes via β-H abstraction has proved to be a widely observable side-reaction of carbotitanation. Thus, for example, the alkene version of the methyltitanation reaction shown in Schemes 7 and 10 was reported a year after the discovery of the original alkyne reaction, but only 2-methyl-1-alkenes were obtained in good yields[23] (Scheme 11). Evidently, the expected methyltitanation products were formed, but they must have undergone β-elimination to give the observed 2-methyl-1-alkenes under the reaction condition. Nonetheless, the reaction promises to be synthetically useful. The regiochemistry of the methyltitanation can be reversed through chelation in the cases of homoallyl alcohols[24] (Scheme 11).

The current scope of the controlled monocarbotitanation of alkenes and alkynes is still very limited at least in part due to competitive side-reactions arising via β- and α-agostic interactions, as alluded to Scheme 6. On the other hand, polymerization, also shown in Scheme 6, may be largely avoided or minimized in most cases. To overcome some of the difficulties mentioned above, cyclic version of monocarbotitanation have been explored,[25–27] as shown in Scheme 12. None of these reactions has as yet been widely used, but their further development might lead to synthetically useful methods.

Essentially all of the carbometallation reactions discussed in this section are stoichiometric in Ti. On the other hand, the reaction of 1,5-hexadiene and 1,6-heptadiene with R_2AlCl (where R is Et, ^{n}Pr, or ^{i}Bu, but not Me) in the presence of 2 mol% of $Ti(O^iPr)_4$ is a genuine example of Ti-catalyzed carbometallation reactions.[28] In this reaction, oligomerization is a potentially competitive side-reaction. Although the Ti-catalyzed reaction of 1,5-hexadiene or 1,6-heptadiene with Me_2AlCl did not produce the desired monomeric products in more than 5% yield, all of the starting dienes were consumed. It is likely that the products were oligomeric or even polymeric. One noteworthy feature of the reaction is that the cyclopentane-containing products are >90% *trans*, while their cyclohexane homologs are ≥86% *cis*. As suggested by the results shown in Scheme 13, the reaction promises to be of considerable synthetic potential.



Scheme 12 Examples of Ti-promoted cyclic monocarbometallation.



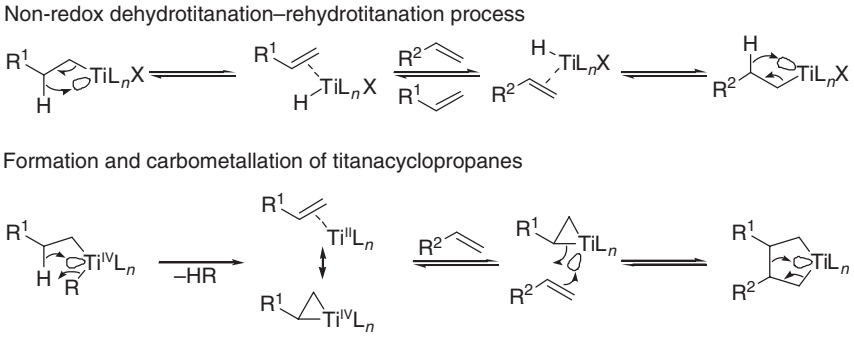
Scheme 13 Ti-Catalyzed acyclic–cyclic carbometallation tandem reactions of dienes and higher oligoenes.

10.06.2.2.2 Formation and carbometallation of titanacyclopropanes and titanacyclopropenes

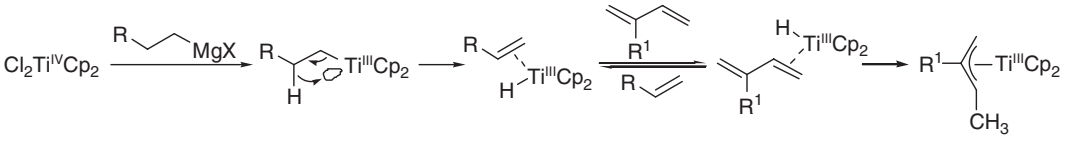
As discussed earlier in general terms (Scheme 6), coordinatively unsaturated alkyltransition metal complexes can participate in α- and β-agostic interactions. The former can lead to the formation of metal–carbene complexes that can, in turn, react with alkenes and alkynes to produce metallacyclobutanes **5** and metallacyclobutenes. Many of these species are known as organometallic intermediates in alkene and alkyne metathesis that are not discussed in this chapter. It was amply demonstrated in Section 10.06.2.2.1 that methyltitanium complexes lacking hydrogen atoms that are β to or more remote from Ti undergo a relatively slow α-agostic interaction-induced α-H abstraction to produce Ti-methylene complexes including the Tebbe reagent and a titanacyclobutene **7**. In cases where alkyltitaniums contain β-H atoms, β-H abstraction appears to be more facile than α-H abstraction and, most probably, any other processes involving abstraction of more remote H atoms in the absence of any overriding factors. As indicated in Scheme 6, there are at least two closely related but different consequences of β-H abstraction. One is a non-redox β-dehydrometallation that can lead to a hydrogen-transfer hydrometallation in the presence of an alkene or alkyne. Another is the formation of metallacyclopropanes and metallacyclopropenes. In as much as these species can also be represented as metal–alkene and metal–alkyne π-complexes, in which the oxidation number of the metal atom is lower by two than that in the original state, this latter process is often considered as a redox process in which the transition metal atom is two electron reduced. This, however, is a semantic issue. To avoid any further confusion, metallacyclopropanes and metal–alkene complexes may be best viewed as two limiting resonance structures of the same complexes differing in the metal oxidation number by two. Thus, these complexes may be represented interchangeably by either of the two (Scheme 14).

The processes shown in Scheme 14 are fundamentally very similar to the corresponding processes of alkylzirconocene derivatives discussed later in this chapter and mostly explored and developed before those of alkyltitanium derivatives. There are however some notable differences. As mentioned earlier, Ti can readily acquire the +3 oxidation state, leading to some processes that are not readily observable with Zr. Thus, for example, the reaction of conjugated dienes with $Cp_2Ti^{IV}Cl_2$ and alkyl Grignard reagents has yielded π-alkyl–Ti^{III} complexes[29] (Scheme 15), whereas the corresponding reaction of $Cp_2Zr^{IV}Cl_2$ typically gives diene–$ZrCp_2$ complex.[30]

Aside from the Ziegler–Natta polymerization, alkene and alkyne metathesis, and other reactions of Ti-methylene complexes, carbometallation reactions induced by alkyltitanium compounds have been dominated by those involving



Scheme 14 β-Hydrogen abstraction reactions of alkyltitanium compounds.



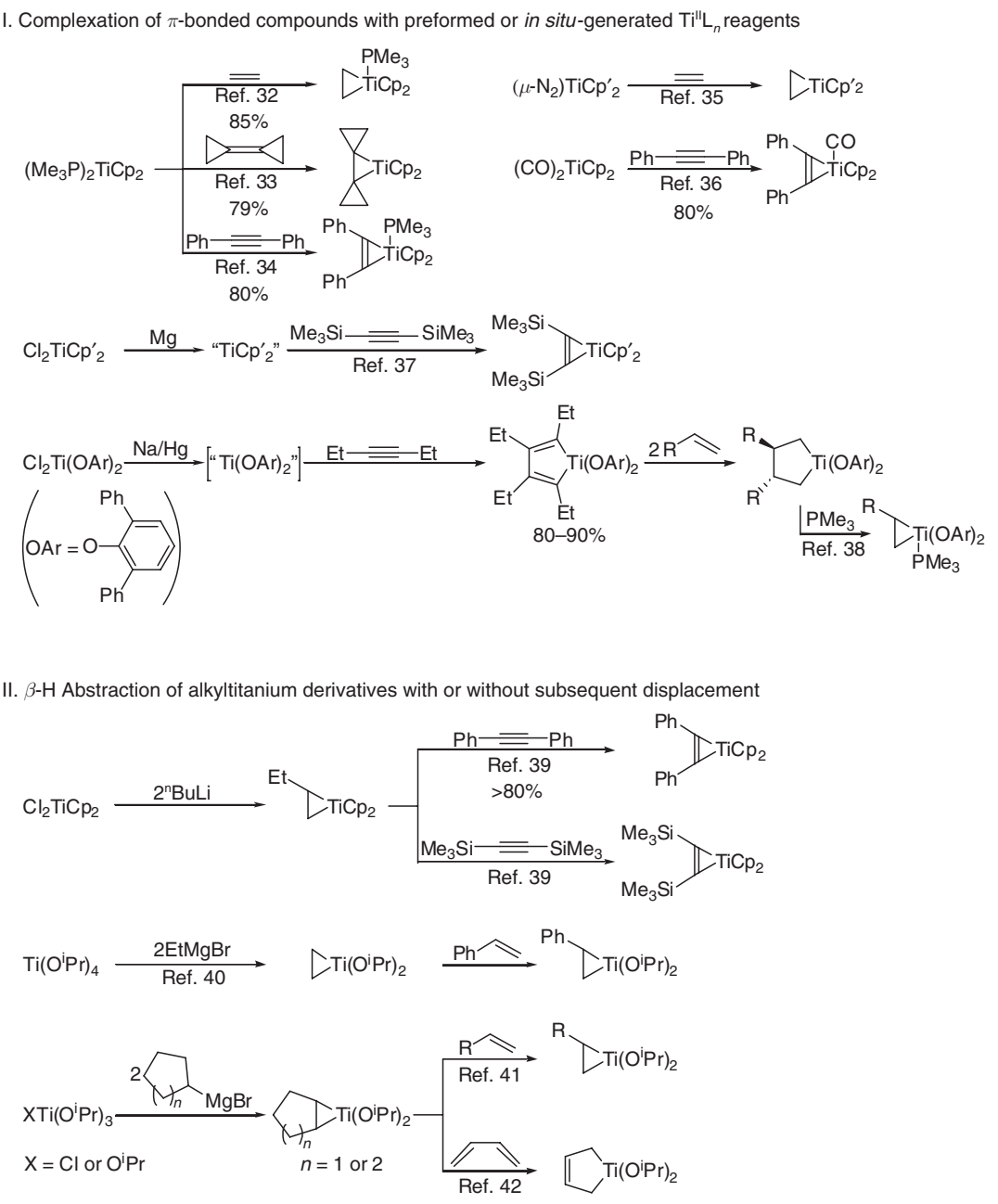
Scheme 15 Reaction of conjugated dienes with alkyl Grignard reagents and Cl_2TiCp_2.

titanacyclopropanes and titanocyclopropenes. This vast topic cannot be presented in detail in this chapter, and the readers are referred to recent reviews.[31] Here, only a brief overview which is supplemented with recent applications to natural products synthesis is presented below.

A number of methods have been developed for the synthesis of titanacyclopropanes and titanacyclopropenes as summarized in Scheme 16[32–42]. These three-membered titanacycles can react with various alkenes, alkynes, allenes, and conjugated dienes to produce five-membered titanacycles via cyclic carbotitanation, according to the generalized reaction patterns shown in Scheme 1. A large number of these reactions have been reported[31] mainly over the last couple of decades. It has also been demonstrated that titanacyclopropanes and titanacyclopropenes can react with various heteroatom analogs of the π-bonded compounds mentioned above including aldehydes, ketones, esters, amides, imines, CO, and CO_2. Since their reactions with heteroatom-containing π-bonded compounds may not be considered as carbometallation reactions, they are not discussed in this chapter. Even so, the amount of data on cyclic carbotitanation via three-membered titanacycles is enormous. Only some representative examples are shown primarily to indicate various known patterns of these reactions and their synthetic potentials. In this context, it is important to clearly note that controlling the "pair"-selectivity and regioselectivity of these reactions is a fundamentally difficult and largely pending issue to be overcome. In many cases, diastereo- and enantioselectivities are also critically important. Since Ti is rather inexpensive, catalysis may not be a serious issue, although desirable. However, catalysis in generally expensive chiral ligands would be a critical issue. To minimize complications and difficulties associated with various selectivity issues mentioned above, the use of tethered substrates has been considered, and many satisfactory results have been obtained. Except for the synthesis of organics of material chemical interest, most of organic compounds of biological and medicinal interest lack symmetry. Thus, for any synthetic methods to be generally applicable and useful, they must be able to accommodate those selectivity requirements mentioned above, and the examples shown below are carefully chosen with those selectivity features in mind.

The Ti-promoted coupling between an alkene or alkyne and another π-bonded compound, such as an alkene, a carbonyl compound, or an imine, may be classified as follows:

Carbometallative coupling	*Non-carbometallative coupling*
(i) Alkene–alkene	(iv) Alkene–carbonyl
(ii) Alkene–alkyne	(v) Alkyne–carbonyl
(iii) Alkyne–alkyne	(vi) Alkene–imine
	(vii) Alkyne–imine



Scheme 16 Some representative methods for the synthesis of titanacyclopropanes and titanacyclopropenes.

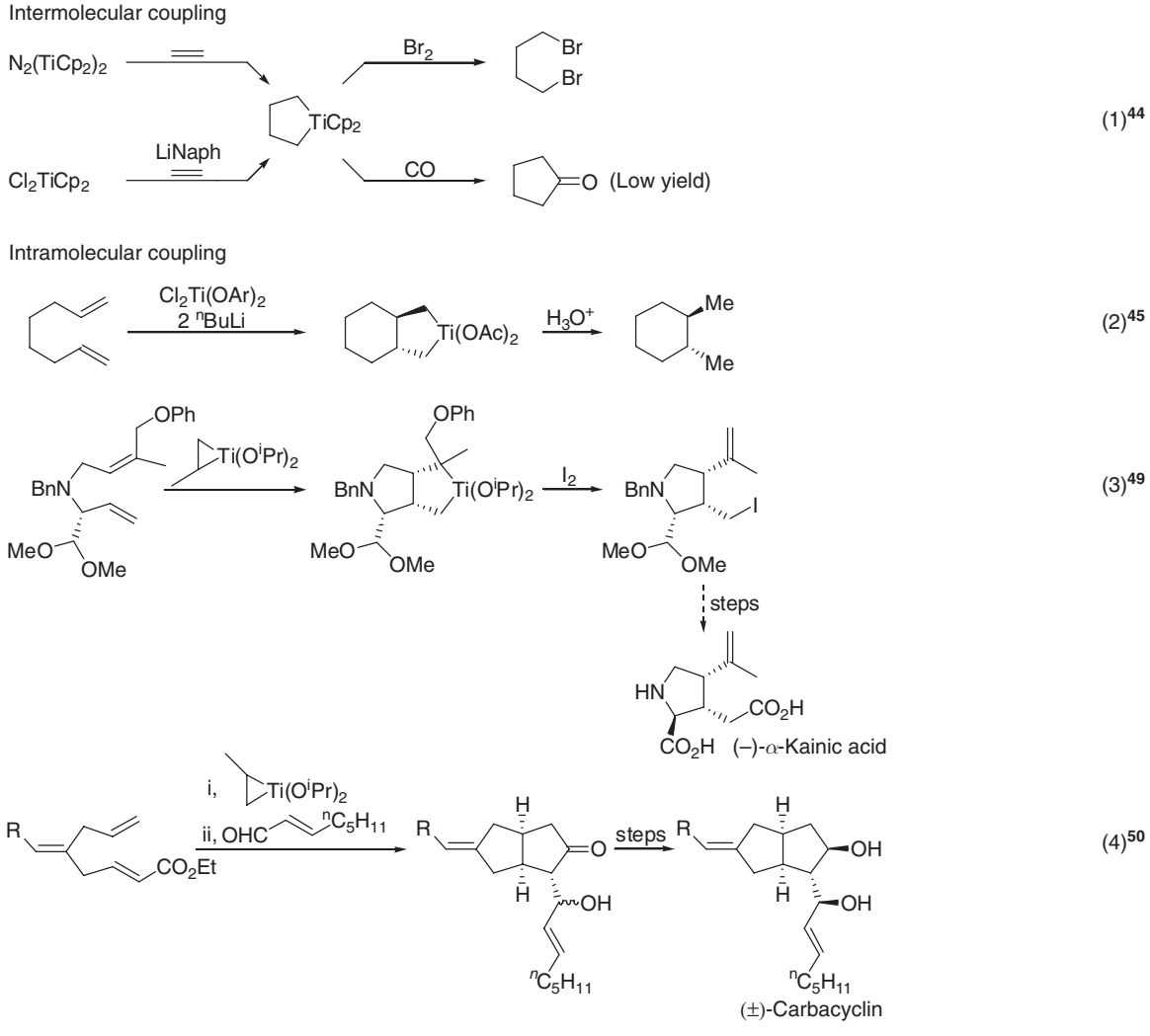
These coupling reactions may be either intermolecular or intramolecular. Allenes usually act as monoenes, and only one of the two C═C bonds participate in the reaction. On the other hand, conjugated and higher dienes can participate in Ti-promoted cyclic coupling processes as long as polymerization and other side-reactions seriously interfere with the cyclization processes. Various types of carbonyl compounds participate in related cyclic ring-expansion reactions in a manner similar to those of alkene reactions. Imines also react similarly. Carbon monoxide, on the other hand, undergoes one-atom insertion reactions with five-membered titanacycles rather than act as a two-atom π-bonded reagent for ring expansion of three-membered titanacycles. Although little, if

any, is known, isonitriles might be expected to react similarly. However, nitriles appear to act as heteroatom analogs of alkynes.[43]

10.06.2.2.2.(i) Alkene–alkene coupling

Formation of a titanacyclopentane via cyclic dimerization of ethylene was reported as early as 1976[44] (Scheme 17). In marked contrast with the corresponding Zr-promoted reactions discussed later in this chapter, the intramolecular version of the Ti-promoted alkene–alkene coupling reactions does not appear to have been well developed. Consequently, detailed aspects of "pair"-selectivity and regioselectivity still remain largely unknown.

Potentially troublesome factors, such as "pair"-selectivity and regioselectivity, can be avoided or minimized in cases where appropriately tethered dienes are used as the starting substrates. The *trans*-ring fusion observed in the formation of an 8-titanabicyclo[4.3.0]nonane derivative,[38c,45] shown in Equation (2) in Scheme 17, corresponds to that of the $ZrCp_2$-promoted reaction observed under thermodynamically equilibrating conditions.[46] It should be noted that the Zr-promoted reaction predominately yielded the *cis*-fused isomer under non-equilibrating conditions.[47,48] The synthetic utility of the Ti-promoted alkene–alkene coupling has been eloquently demonstrated in recent asymmetric syntheses of (−)-α-kainic acid[49] (Equation (3) in Scheme 17) and carbacyclin[50] (Equation (4) in Scheme 17).



Scheme 17 Ti-promoted alkene–alkene coupling.

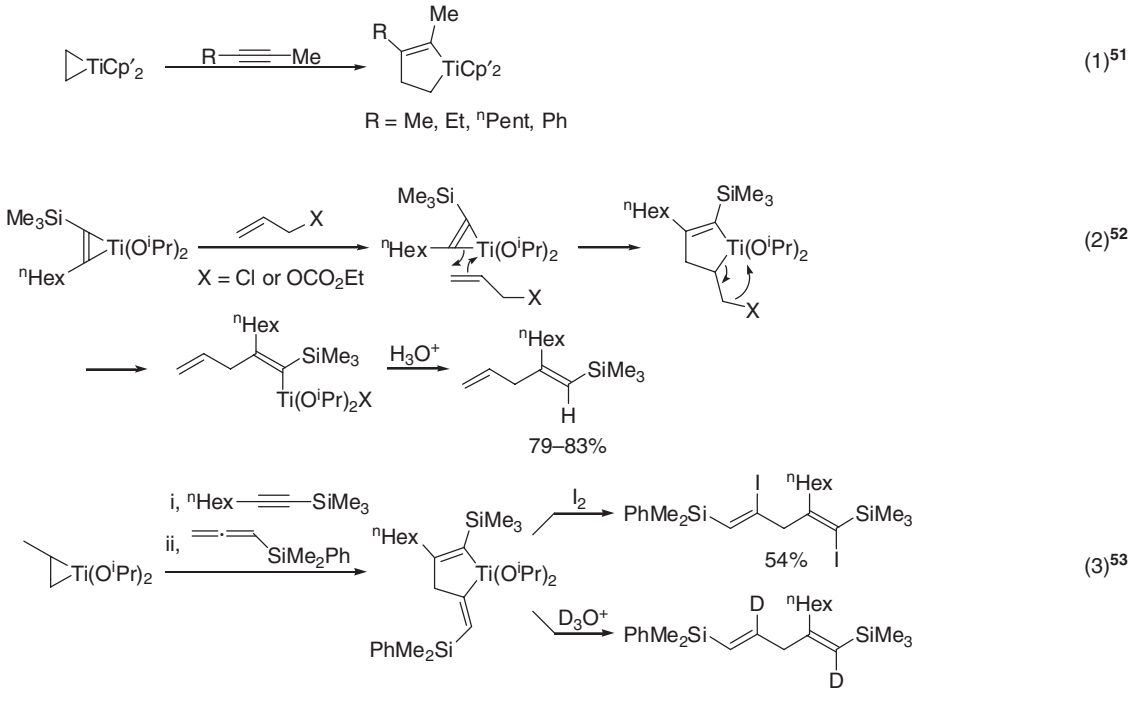
10.06.2.2.2.(ii) Alkyne–alkene coupling

Although a fair number of examples of the Ti-promoted intermolecular alkyne–alkene coupling reactions are known, those that display high "pair" selectivity and regioselectivity are still relatively limited. Some representative examples are shown in Scheme 18.[51–53,53a]

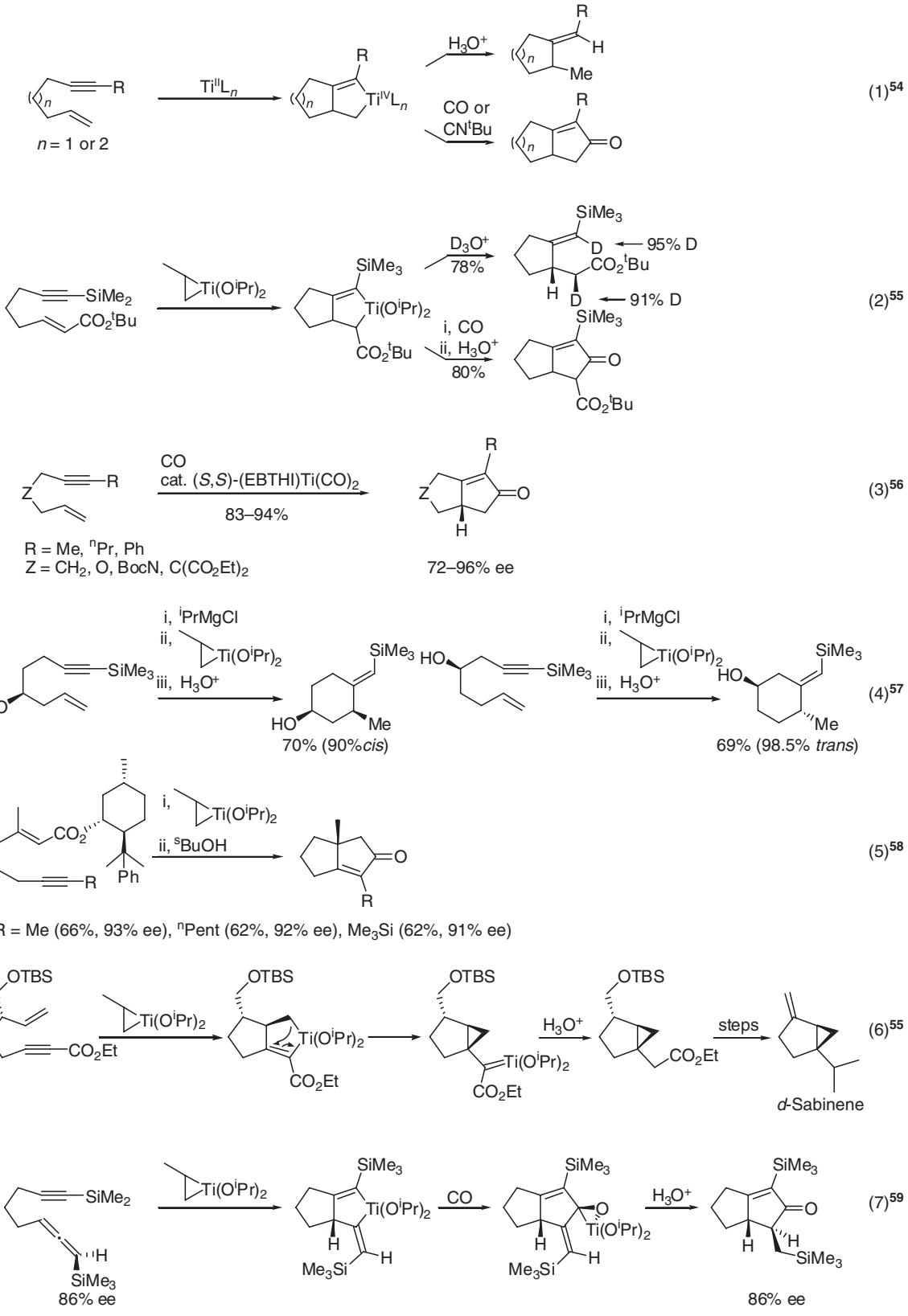
The intramolecular version of the Ti-promoted alkyne–alkene coupling has been extensively developed into a synthetically useful tool as indicated by the results shown in Scheme 19.[54–59] The great majority of these reactions are stoichiometric in Ti. Even though the formation of titacycles can only be stoichiometric, catalytic processes based on the enyne bicyclization may still be developed by combining it with some Ti-recycling processes, as shown in Equation (3)[56] of Scheme 19. This enantioselective reaction offers both high yields (83–94%) and a practical range of enantioselectivity (72–96% ee). It is also sensible to develop diastereoselective processes,[55,57,58] as many enyne precursors should be preparable as enantiomerically pure compounds without much difficulty. When alkynoic esters are used as the alkyne component of enynes, the expected titanabicycles undergo cyclopropanation, which has been exploited in an asymmetric synthesis of *d*-sabinene[55] (Equation (6) in Scheme 19). The Ti-promoted bicyclization of allenynes proceeds with retention of enantioselectivity[59] (Equation (7) in Scheme 19).[54–59]

The Ti-promoted enyne bicyclization appears to share a number of common features with the corresponding Zr-promoted reaction to be discussed later. However, the two reactions are also expected to be different in many other respects and hence complementary with each other. In a comparative study using both Ti and Zr, the bicyclization reactions of allyl propargyl ethers generally proceeded in higher yields with Cp_2ZrCl_2–Mg than with Cp_2TiCl_2–Mg. However, the Ti-promoted reaction was significantly more stereoselective.[54b] In another interesting comparison, the reaction of titanabicycles[60] and zirconabicycles[61] with PhCHO gave two different but isomeric products (Scheme 20).

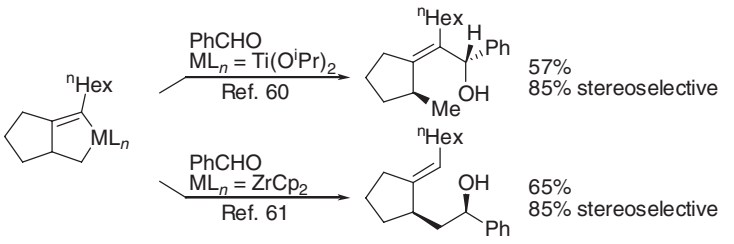
It has recently been reported that the titanacyclopropenes obtainable from various unsymmetrically substituted internal alkynes and $^{i}PrMgBr$–$Ti(O^{i}Pr)_4$ can react regioselectively with terminal alkynes to give titanacyclopentadienes with three different substituents in a prespecified manner[62] (Equation (1) in Scheme 21). This reaction has provided efficient and selective routes to conjugated dienes with three-to-five different substituents as well as benzenes and pyridienes with up to five different substituents, as shown in Scheme 21. 1,4-Diiodo-1,3-dienes can be selectively monomagnesiated. The dienylmagnesium product can then be subjected to intramolecular Heck reaction to give 2-methylphenols with three different additional substituents.[63] Moreover, the reaction of titanacyclopentadienes with propargyl bromide has been shown to give tetrasubstituted arenes in a fully regiocontrolled manner[64] (Equation (3)). This reaction has been modified for the synthesis of pentasubstituted arenes containing



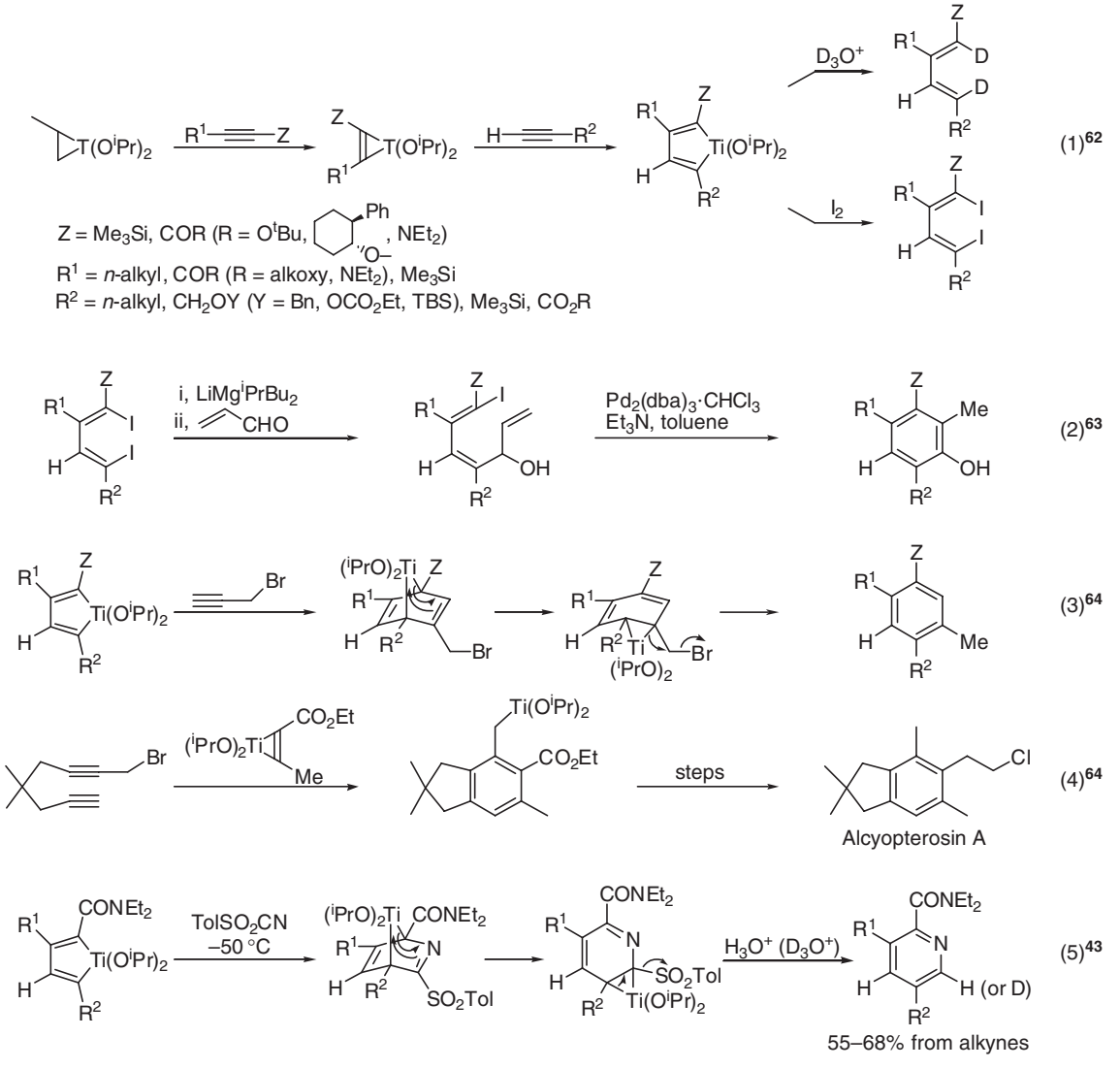
Scheme 18 Ti-promoted intermolecular alkyne–alkene coupling.



Scheme 19 Ti-promoted intramolecular alkyne–alkene coupling.



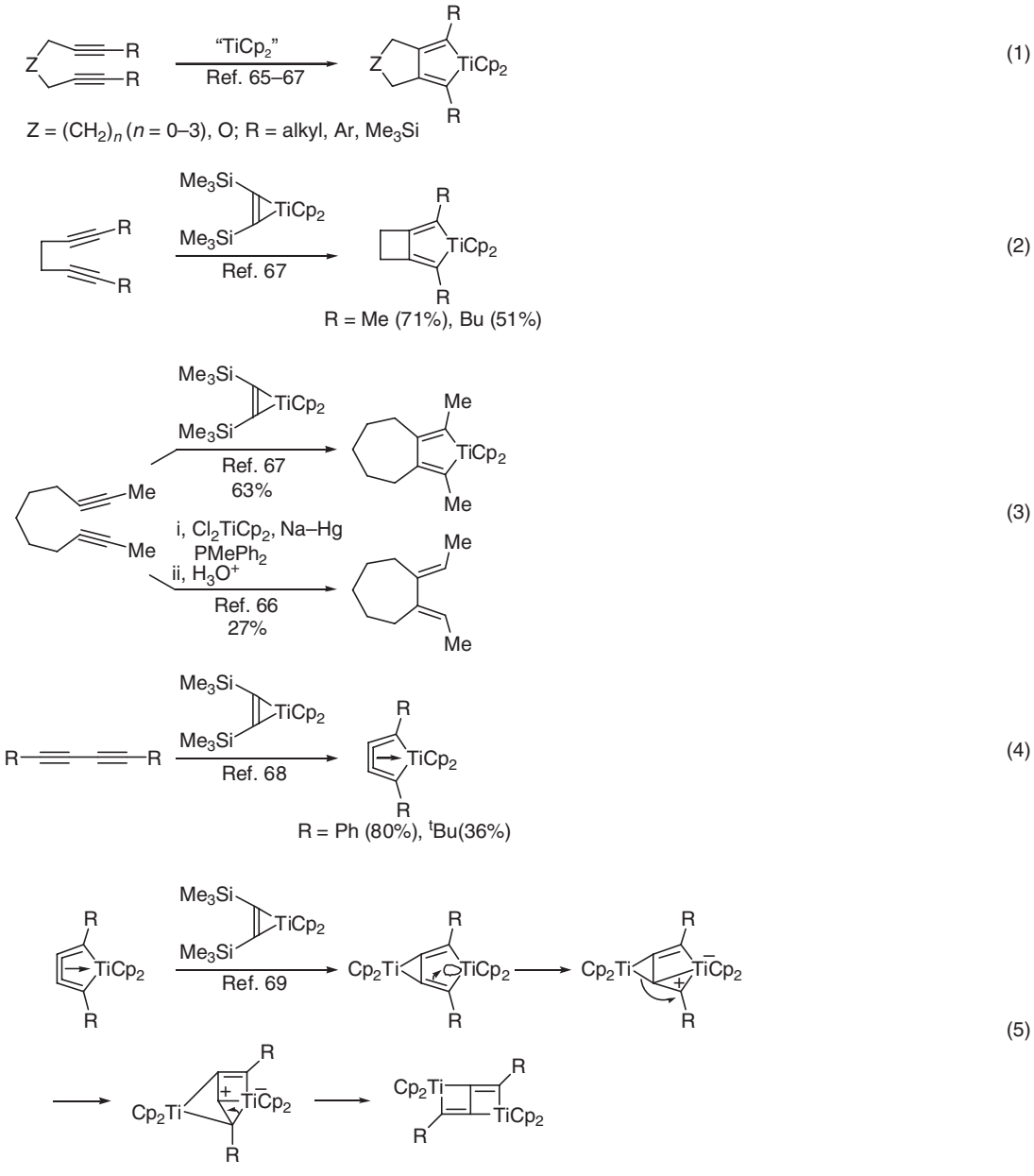
Scheme 20 Reactions of metallabicycles containing Ti or Zr with benzaldehyde.



Scheme 21 Ti-promoted alkyne–alkene coupling and its applications to the synthesis of conjugated dienes, arenes, and pyridines.

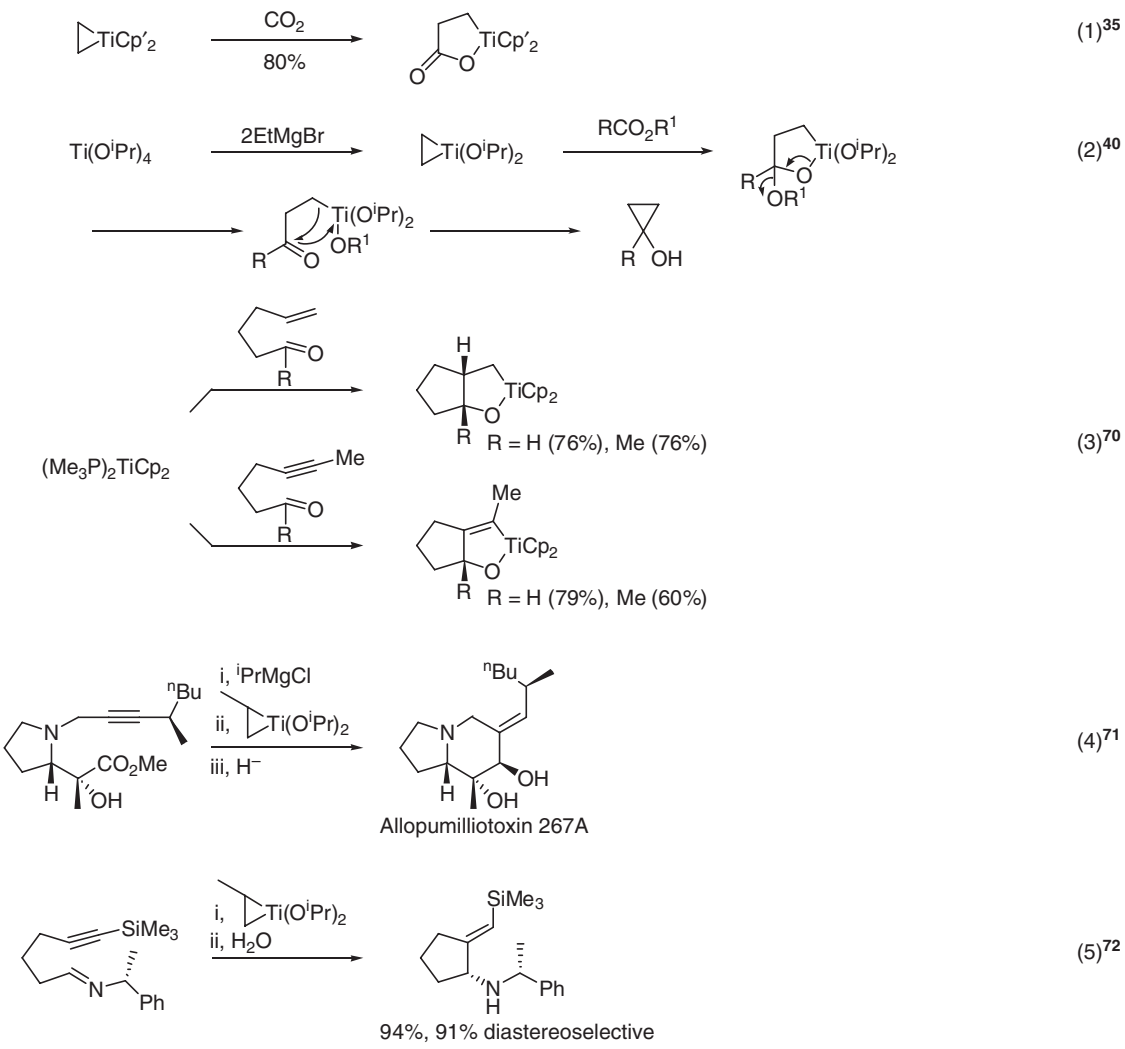
another ring fused to the benzene ring and applied to the synthesis of alcyopterosin A[64] (Equation (4)). The use of a nitrile as a third π-bonded reactant provides pyridines with control of regiochemistry[43] (Equation (5)).

The Ti-promoted intramolecular alkyne–alkyne coupling of tethered diynes was extensively developed earlier with "TiCp$_2$" derivatives as reagents[65,66] (Equation (1) of Scheme 22). Bicyclic titanacyclopentadienes fused to



Scheme 22 Ti-promoted bicyclization of diynes.

four-to-seven-membered rings have been prepared. For the synthesis of those containing four- or seven-membered rings, the use of $(Me_3SiC{\equiv}CSiMe_3)TiCp_2$ has been claimed to be advantageous[67] (Equations (2) and (3)). Although most of these earlier examples dealt with symmetrically substituted diynes, unsymmetrically substituted diynes would react similarly. At present, however, little is known about differentiation of the two Ti-bound alkenyl groups of the titanacyclopentadienes. The reaction of conjugated diynes with $(Me_3SiC{\equiv}CSiMe_3)TiCp_2$ gives titanacyclopentatrienes[68] (Equation (4) in Scheme 22). Addition of one extra equivalent of $(Me_3SiC{\equiv}CSiMe_3)TiCp_2$ to the 1 : 1 products gives a very intriguing bicyclo[2.2.0]hexadiene containing two Ti atoms[69] (Equation (5) in Scheme 22). Their formation may be readily explained in terms of a series of three 1,2-shift processes involving carbocationic species. Although no carbometallation may be involved, the following reactions are representative of the reactions of titanacyclopropanes and titanacyclopropenes with carbonyl compounds and imines (Scheme 23).[36,40,70–72]

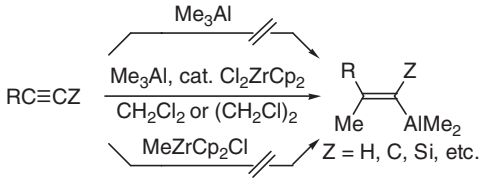


Scheme 23 Reactions of titanacyclopropanes and titanacyclopropenes with carbonyl compounds and imines.

10.06.2.3 Carbometallation Reactions of Organozirconium Compounds

10.06.2.3.1 Controlled monocarbometallation of alkynes with Me_3Al–$ZrCp_2Cl_2$

As discussed in Section 10.06.2.1, one of the crucial requirements for facile and concerted carbometallation is the presence or ready availability of a valence-shell empty metal orbital. This simple guiding principle indeed led to the discovery of a controlled single-stage carbotitanation of alkynes with Me_3Al and $TiCp_2Cl_2$ shown in Scheme 7,[17] but its synthetic scope was rather limited. In search for a superior reaction of wider synthetic scope, the other two members of the Ti triad, namely Zr and Hf, were examined. This led to the discovery of the Zr-catalyzed carboalumination of alkynes,[1] which has proved to be not only of wider synthetic scope with respect to the alkyne structure but also catalytic in Zr. Thus, the products are nearly exclusively alkenylalanes rather than alkenylzirconium derivatives. On the basis of the observed starting material–product relationship, this reaction has been called the Zr-catalyzed carboalumination, or more specifically Zr-catalyzed methylalumination, of alkynes. All of the available data, however, indicate: (i) *in situ* generation of a bimetallic species represented by $MeZrCp_2Cl$–$AlMe_2Cl$, (ii) its acyclic and four-centered methylzirconation to alkynes involving essentially 100% *syn*-addition of the Me–Zr bond, and (iii) back-transmetallation to give (*E*)-*β*-methylalkenylalanes,[7,8] as shown in Scheme 4. It is noteworthy that no carbometallation takes place in the absence of either Zr or Al (Scheme 24). Thus, the reaction is clearly bimetallic. It may be reasoned that the proposed bimetallic reactive species, that is, $MeZrCp_2Cl$–$AlMe_2Cl$, is more electrophilic and hence more reactive toward alkynes than the corresponding monometallic species, that is,



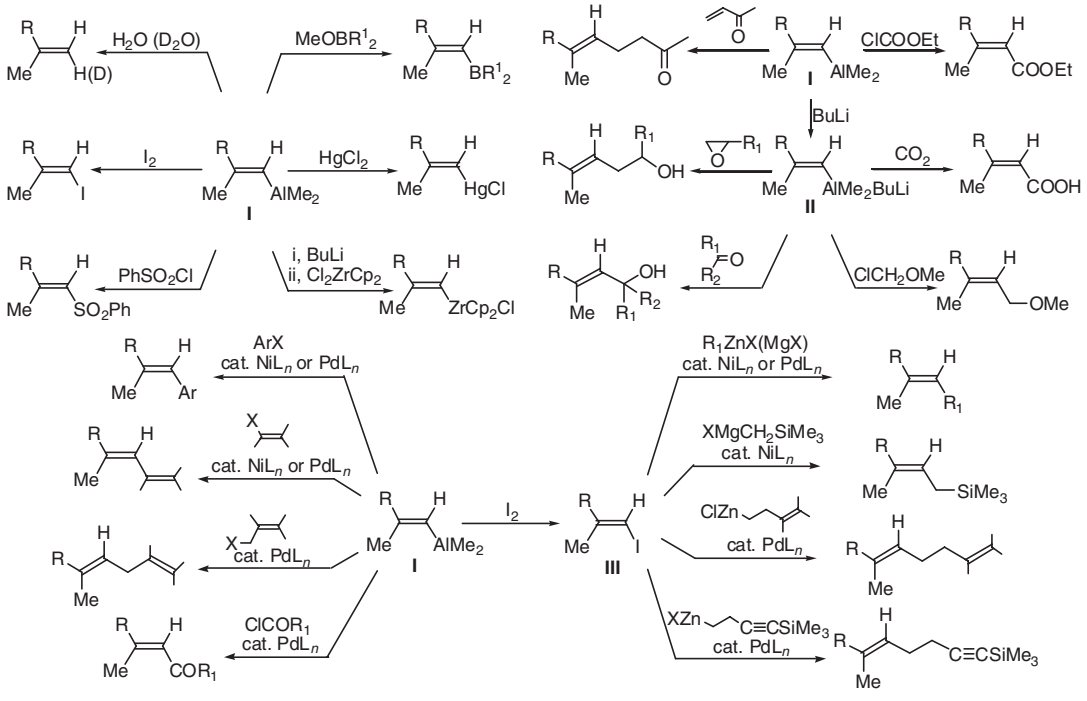
Scheme 24 Zr-catalyzed carboalumination of alkynes.

$MeZrCp_2Cl$, by virtue of the presence of the dipolar Cl^+–Al^- bond. Most likely, this reaction exemplifies a widely observable principle of activation of an electrophile by another electrophile to generate a "superelectrophilic" species that has been termed the "two-is-better-than-one" principle.[13c]

The Zr-catalyzed methylalumination of alkynes with Me_3Al–$ZrCp_2Cl_2$ has been shown to be stereo- and regioselective, generally high yielding, and broadly applicable. Thus, both terminal and internal alkynes containing various types of carbon groups as well as metal-centered groups of group 12–14 metals, such as Zn, B, Al, and Si, can be carbometallated in high yields. Some synthetically useful heterofunctional groups, such as amino, both unprotected and protected hydroxyl, and sulfur-containing groups can be accommodated.[73] On the other hand, carbonyl-containing groups, such as aldehydes, ketones, as well as carboxylic acids and their derivatives, cannot be readily tolerated, and such functional groups must be generated after the desired carbometallation. In general, the reaction involves essentially 100% *syn*-carbometallation. In the cases of methylalumination of terminal alkynes, the regioselectivity of approximately 95% has been observed. Moreover, the minor isomers are significantly less reactive in most of the subsequent reactions. So, organic products of >98% regioselectivity can be obtained in many cases after subsequent transformations.

(*E*)-β-Methyl-1-alkenylalanes generated by the Zr-catalyzed methylalumination of alkynes can be *in situ* converted into a wide variety of methyl-branched trisubstituted alkenes present in a wide variety of natural products of terpenoid and carotenoid origin as well as many other natural and unnatural compounds of biological and medicinal importance[13d–13g] (Scheme 25). In some cases of the Pd- or Ni-catalyzed cross-coupling, it is desirable or even mandatory to convert the alkenylalane products into the corresponding iodides or other related derivatives for the designed cross-coupling.

The synthetic utility of the Zr-catalyzed carboalumination of alkynes may be indicated by over 100 natural products including highly complex ones that have been synthesized by using this reaction[74–178] (Table 2).



Scheme 25 Conversion of (*E*)-2-methyl-l-alkenylalanes into various organic and organometallic alkenes.

Table 2 Applications of the Zr-catalyzed carboalumination of alkynes to the stereoselective syntheses of natural products

Year	*Name of natural product*	*Major author*	*References*
1978	Geraniol, ethyl geranate	Negishi, E.	74
1980	Monocyclofarnesol	Negishi, E.	75
1980	Mokupalide, dendrolasin	Negishi, E.	76
1980	Farnesol	Negishi, E.	77
1980	Brassinolide	Siddall, J. B.	78
1981	*a*-Farnesene	Negishi, E.	79
1983	Verrucarin J	Roush, W. R.	80
1983	Udoteatrial	Whitesell, J. K.	81
1984	Verrucarin J	Roush, W. R.	82
1984	Brassinolide, castasterone, dolicholide, dolichosterone	Mori, K.	83
1984	Verrucarin B	Roush, W. R.	84
1985	Zoapatanol	Cookson, R. C.	85
1985	Mycarose, *epi*-axenose	Roush, W. R.	86
1985	Aurodox, efrotomycin	Nicolaou, K. C.	87
1986	Lophotoxin	Tius, M. A.	88
1987	Methyl kolavenate	Tokoroyama, T.	89
1987	Milbemycin $ß_3$	Kocienski, P. J.	90
1988	Brassinolide	Mori, K.	91
1988	(+)-Sterpurene	Okamura, W. H.	92
1989	FK-506	Smith, A. B., III	93
1989	Lophotoxin, pukalide	Paterson, I.	94
1989	Ageline A	Tokoroyama, T.	95
1989	Lacrimin A	Kocienski, P.	96
1989	Milbemycin $ß_1$	Ley, S. V.	97
1990	Lacrimin A	Kocienski, P.	98
1990	Avermectin B_{1a}	Ley, S. V.	99
1990	FK-506	Ireland, R.	100
1991	Avermectin B_{1a}	Ley, S. V.	101
1991	Vitamin A	Negishi, E.	102
1991	Phytol	Takano, S.	103
1992	Aboa of theonellamide F	Hamada, Y.; Shioiri, T.	104
1992	Inhibitor of 2,3-oxidosqualene–lanoosterol cyclase	Oehlschlager, A. C.	105
1992	Milbemycin K	Takano, S.	106
1992	C(1)–C(14) tetraene unit of calyculin A	Barrett, A. G.	107
1993	1233A	Wovkulich, P. M.; Uskokovic, M. R.	108
1993	Forskolin	Welzel, P.	109
1993	Milbemycin E	Thomas, E. J.	110
1993	Callosobruchusic acid	Carpita, A.	111
1994	Suspensolide, anastrephin, epianastrephin	Oehlschlager, A. C.	112
1994	Inhibitors of 2,3-oxidosqualene-lanosterol cyclase	Oehlschlager, A. C.	113
1994	Manoalide	Kocienski, P.	114
1995	Curacin A	Gerwick, W. H.	115
1995	Curacin A	White, J. D.	116
1995	Vitamin A	de Lera, A. R.	117
1995	Pateamine A	Romo, D.	118
1996	Pateamine	Pattenden, G.	119
1996	Hygrolidin	Hashimoto, S.	120
1996	Phomactin D	Yamada, Y.	121
1996	CoQ_3, CoQ_4, CoQ_5, vitamin K_1, vitamin K_2	Lipshutz, B. H.	122
1997	Concanamycin A	Paterson, I.	123
1997	(−)-PI-091	Iwasawa, N.	124
1997	(+)-Curacin	White, J. D.	125
1997	(*3Z*)-α-Farnesene	Negishi, E.	126
1997	FK-506	Ireland, R.E.	127
1997	Freelingyne	Negishi, E.	128
1998	1233A	Langlois, Y	129
1998	(+)-Curacin A	Pattenden, G.	130
1998	Concanolide A	Toshima, K.	131

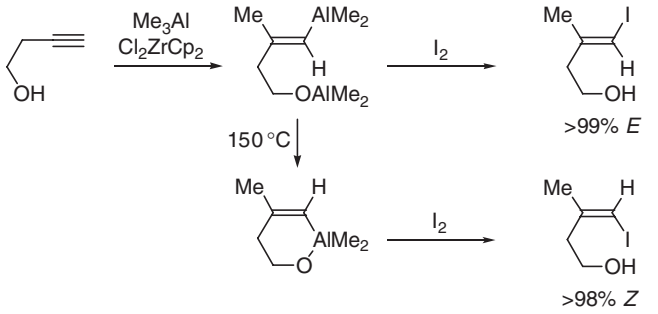
(*Continued*)

Table 2 (Continued)

Year	*Name of natural product*	*Major author*	*References*
1998	Concanoamycin A	Toshima, K.	132
1998	(−)-Pateamine A	Romo, D.	133
1998	Aurisides	Yamada, K.	134
1998	(+)-Calyculin A, (−)-calyculin B	Smith, A. B. III	135
1998	Okinonellin B	Romo, D.	136
1998	Menaquinone-3, CoQ_5	Lipshutz, B. H.	137
1999	Elenic acid	Hoye, R. C.	138
1999	(−)-Bafilomycin A	Roush, W. R.	139
1999	1233A	Ley, S. V.	140
1999	Amphidinolide B	Chakraborty, T. K.	141
1999	Epolactaene	Kobayashi, S.	142
1999	CoQ_6, CoQ_7, CoQ_8	Lipshutz, B. H.	143
1999	(+)-Calyculin A, (−)-calyculin B	Smith, A. B., III	144
2000	Pateamine	Pattenden, G.	145
2000	Phomactin D	Halcomb, R. L.	146
2000	CoQ_{10}	Negishi, E.	147
2000	Scyphostatin	Hoye, T. R.	148
2000	(*S*)-Methanophenazine, (*R*)-methanophenazine	Beifuss, U.	149
2000	Aplyronines	Marshall, J. A.	150
2000	Methanophenazine	Beifuss, U.	151
2001	Phomactin core	Rawal, V. H.	152
2001	Bafilomycin A_1	Hanessian, S.	153
2001	Concanamycin F	Toshima, K.	154
2001	Formamicin	Roush, W. R.	155
2001	(+)-Ratjadone	Bhatt, U.	156
2001	(+)-Calyculin A	Barrett, A. G.	157
2001	(*10R,11S*)-(+)-Juvenile hormones	Mori, K.	158
2001	Bis-deoxylophotoxin	Pattenden, G.	159
2001	β-Carotene, γ-carotene, vitamin A	Negishi, E.	160
2002	(−)-Bafilomycin A_1	Roush, W. R.	161
2002	Bafilomycin V_1	Marshall, J. A.	162
2002	Rhizoxin D	White, J. D.	163
2002	Meneaquinone-3, CoQ_3, CoQ_{10}	Negishi, E.	164
2002	Vicenistatin	Kakinuma, K.	165
2002	CoQ_{10}	Lipshutz, B. H.	166
2002	CoQ_{10}	Lipshutz, B. H.	167
2002	Callipeltosides, aurisides	Olivo, H. F.	168
2002	Manoalide	Kocienski, P.	169
2003	Carbazomadurin A	Knolker, H.	170
2003	Bafilomycin A_1	Prunte, J.	171
2003	(±)-Phomactin A	Pattenden, G.	172
2003	(±)-Phomactin A	Pattenden, G.	173
2003	(+)-Rottnestol, (+)-raspailol A, (+)-raspailol B	Rizzacasa, M. A.	174
2003	(*R*)-(−)-Elenic acid	Hoveyda, A. H.	175
2003	Epolactaene	Kobayashi, S.	176
2003	Rhizoxin D	Leahy, W	177
2004	Bafilomycin A_1	Lett, R.	178

Although the courses of the Zr-catalyzed methylalumination of alkynes are predictable on the basis of the generalization presented above, some unprecedented and/or abnormal features have also been observed, and some of them have proved to be synthetically useful, as briefly described below. The reaction of 1-metallo-4-halo-1-butynes with Me_3Al–$ZrCp_2Cl_2$ gives 1-metallo-2-methyl-1-cyclobutenes in good yields, and it has been shown to proceed via formation and ring expansion of cyclopropylcarbinylmetal derivatives[179,179a,179b] (Scheme 26). Another useful reaction is a nearly complete stereoisomerization of the methylalumination product obtained from 3-butyn-1-ol at 150 °C[126] (Scheme 27). Yet another noteworthy reaction is the Zr-catalyzed methylalumination run in the presence of methylaluminoxane (MAO) generated *in situ* by mere addition of water, which significantly accelerates the desired methylalumination.[180]

Scheme 26 Formation of 1-metallo-2-methyl-1-cyclobutenes by the reaction of 1-metallo-4-halo-1-butynes with Me_3Al–$ZrCp_2Cl_2$.

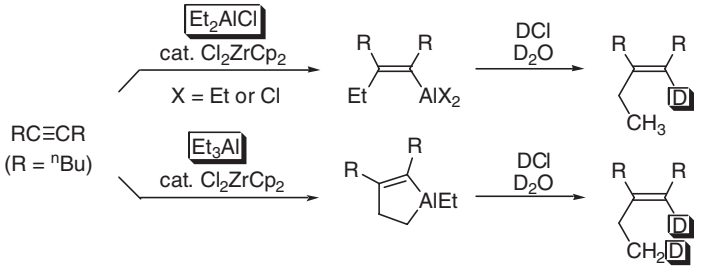


Scheme 27 Stereoisomerization of the methylalumination product derived from 3-butyn-1-ol.

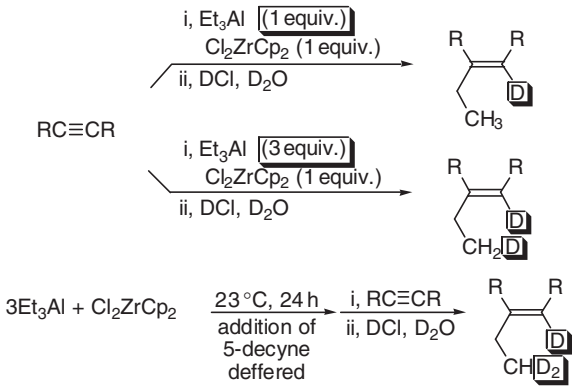
10.06.2.3.2 Other Zr-catalyzed monocarbometallation reaction of alkynes

Relatively little has been known about other Zr-catalyzed monocarbometallation reactions of alkynes. The reaction of internal alkynes, such as 5-decyne, with Et_3Al and a catalytic amount of $ZrCp_2Cl_2$ in non-polar solvents, such as hexanes, proceeds cleanly, but the product, upon deuterolysis, is converted into a dideuterated derivative. On the other hand, the corresponding reaction with Et_2AlCl–$ZrCp_2Cl_2$ gives a product that can only be monodeutereted[9] (Scheme 28). Furthermore, three sets of reactions using one full equivalent of $ZrCp_2Cl_2$ in each case led to three discrete but clean reactions[9] (Scheme 29). An intensive mechanistic investigation led to a most intriguing cyclic bimetallic mechanism shown in Scheme 4.[9]

In marked contrast with the reaction of Me_3Al–$ZrCp_2Cl_2$, the reaction of Et_3Al–$ZrCp_2Cl_2$ with 1-decyne is not highly regioselective, the regioisomeric ratio observed by using benzene as the solvent being essentially 1 : 1.[9] The observed low regioselectivity can be attributable to the cyclic carbozirconation which tends to be of low regioselectivity. With $^{i}Bu_3Al$–$ZrCp_2Cl_2$, the main course of the reaction is the hydrogen-transfer hydrometallation.[9] Clearly, further developmental work is necessary before the Zr-catalyzed ethyl- and higher alkylalumination of alkynes become as useful as the corresponding reaction of alkenes discussed later. The Zr-catalyzed benzyl- and allylalumination of alkynes[181] appears to proceed by acyclic mechanism, similar to that observed with methylalumination shown in Scheme 4. The allylalumination can proceed without allylic rearrangement, favoring a four-centered process over a six-centered process. Both benzyl- and allylalumination reactions appear to be synthetically useful. A Zr-promoted reaction of alkynes with Et_2Zn has also been developed.[182] At present, however, its synthetic scope and mechanistic details remain to be further investigated.



Scheme 28 Dichotomy in Zr-catalyzed ethylalumination of 5-decyne.

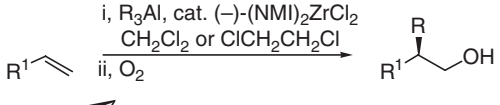


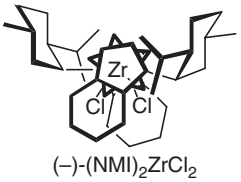
Scheme 29 Reaction of 5-decyne with Et_3Al and the stoichiometric amount of Cl_2ZrCp_2.

10.06.2.3.3 Zirconium-catalyzed asymmetric carboalumination of alkenes (ZACA reaction)

Shortly after the discovery of the Zr-catalyzed carboalumination of alkynes in 1978,[1] the corresponding reaction of Me_3Al with alkenes was examined, but no more than traces of the desired methylalumination products were obtained. The results were puzzling in the light of (i) the highly satisfactory alkyne methylalumination,[1] (ii) the subsequently reported Zr-catalyzed ethylmagnesation of alkenes,[10] and (iii) the Kaminsky modification[183] of the Ziegler–Natta-type alkene polymerization[2,16] with homogeneous zirconocene catalysts. These puzzles were unraveled over the following 15 years, and the initially encountered difficulties were finally overcome in 1995[184] and 1996.[185] The reaction of simple unactivated terminal alkenes with Me_3Al[184] as well as with ethyl- and higher alkylalanes[185] under the catalytic influence of bulky chiral indene-containing zirconium complexes, especially $Cl_2Zr(NMI)_2$[186], where NMI is 1-neomenthylindenyl, was shown to undergo the long-sought single-stage enantiofaceselective carboalumination in high yields (Scheme 30). With $Cl_2Zr(NMI)_2$ as a catalyst and CH_2Cl_2 or $ClCH_2CH_2Cl$ as a solvent, methylalumination proceeded typically in 70–90% ee, while the enantioselectivity in ethyl- and higher alkylalumination was as high as 90–95% ee. The alkyl groups in alkylalanes thus far employed successfully are primary alkyl groups represented by RCH_2CH_2 (R = a C group) in addition to Me and Et. At this time, it appears that they may not be β-branched isoalkyl groups, that is, $R^1R^2CHCH_2$ (R^1 and R^2 = C groups), or higher alkyl groups, that is, secondary and tertiary alkyl groups.

The Zr-catalyzed asymmetric carboalumination of alkenes, ZACA reaction hereafter, represents a prototypical example of enantioselective carbon–carbon bond-forming reactions of alkenes of one-point binding, namely, only one C=C bond as the binding site, requiring no other hetero- or carbofunctional groups, that are catalytic in chiral auxiliaries. In this context, it is instructive to compare this reaction with other currently widely used asymmetric reactions. Practically all widely used asymmetric C–C asymmetric reactions for the synthesis of methyl- and alkyl-substituted acyclic carbon frameworks are stoichiometric in chiral auxiliaries.[187] Alternatively, these compounds have often been prepared through the use of various catalytic enantioselective addition reactions of alkenes, represented by the Noyori reduction[188] and the Sharpless epoxidation.[189] These reactions, however, involve C–H or C–O bond-forming reactions often requiring geometrically defined (*E*)- or (*Z*)-alkenes. Furthermore, the two representative reactions mentioned above also critically require an allylic hydroxyl or a related heterofunctional group for achieving practically useful asymmetrical induction. Thus, these reactions require alkenes of two-point binding.





(–)-$(NMI)_2ZrCl_2$

	R = Me		*R* = Et	
R^1	*Yield* (%)	*ee* (%)	*Yield* (%)	*ee* (%)
^{n}Hex	88	72	64	92
^{i}Bu	92	74	77	90
$PhCH_2CH_2$	84	78	60	88
$HO(CH_2)_4$	79	75	90	91

Scheme 30 Zirconium-catalyzed enantioselective carboalumination of alkenes.

The relationship between the ZACA reaction and the Kaminsky version of the Ziegler–Natta-type alkene polymerization is intriguing. Although these two reactions must be fundamentally related, the following distinguishing features are to be clearly noted. First, one involves a single-stage methyl- or alkyalumination, the latter of which requires an alkyl group of the RCH_2CH_2 type, whereas the polymerization process must involve a series of isoalkylmetallation promoted by methylaluminoxane (MAO) and other related promoters. Second, steric control in both absolute and relative senses is of crucial importance in the single-state carbometallation. On the other hand, the absolute configuration appears to be practically unimportant in the alkene polymerization, although diastereoselectivity, that is, tacticity, is of paramount significance. Third, the single-stage carboalumination reaction can provide pure single products of well-defined structures, which can then be further converted into various chiral compounds including structurally defined oligomeric derivatives. On the other hand, the polymerization reactions invariably produce mixtures of compounds of various degrees of polymerization. Consequently, they are not well suited for the synthesis of oligomeric fine chemicals of well-defined and uniform structures.

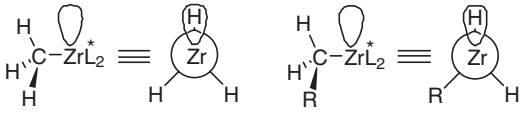
A couple of years before the discovery of the ZACA reaction, a seemingly related Zr-catalyzed asymmetric reaction of ethyl- and higher alkylmagnesium reagents with alkenes was reported.[190,190a] Evidently, this reaction involves a cyclic carbozirconation that will be discussed in the subsequent section, and it is a discrete reaction of fundamentally different synthetic scope. First, all of the reported examples exhibiting practically satisfactory enantioselectivity figures involve the use of allylically heterosubstituted alkenes.[190–192] Second, methylmagnesium derivatives lacking β-H atoms do not participate in this reaction. This is in accordance with the mechanistic notion that the reaction must involve the formation of zirconacyclopropanes via β-H abstraction and their subsequent cyclic carbozirconation of alkenes. Ethyl- and higher alkylmagnesium derivatives do participate in this reaction, but practically acceptable product yields have been observed mostly with ethylmagnesium derivatives[190,190a,191] except in cases where *N*-containing dienes were used as substrates.[192] Otherwise, the use of *n*-propyl- and *n*-butylmagnesium derivatives has led to disappointingly low yields of 35–40%.

One of the puzzling and practically important problems associated with the ZACA reaction is the unmistakably and significantly lower enantioselectivity range of mostly 70–80% ee observed in methylalumination,[184,194,195,195a] as compared with that for the corresponding ethyl- and higher alkylalumination (typically 85–95% ee).[185] It is possible that under the influence of chiral ligands, such as NMI, agnostic interaction involving α-CH bonds[193] can exert a secondary asymmetric induction effect with ethyl and higher alkyl groups but not with a methyl group, as shown in Scheme 31.

Although no further progress has thus far been made to elevate the enantioselectivity level of methylalumination beyond the 70–90% ee range, substantial progress has been made to apply the ZACA reaction to the synthesis of natural products and related chiral compounds. It is desirable to obtain chiral products of ≥98–99% ee and ≥98–99% de in high yields without the need for operationally cumbersome and potentially expensive optical resolution. With these practical goals in mind, two synthetic protocols have been developed. In cases where the target compounds contain two or more asymmetric carbon atoms, the methylalumination of 70–90% ee can often be satisfactory, thanks to statistical enantiomeric amplification arising from a combination of two or more asymmetric operations and/or fragments, as in the synthesis of 6,7-dehydrostipiamide.[196] Pursuing further the statistical amplification strategy, an unprecedentedly efficient, selective, and practical method for the synthesis of various deoxypolypropionates has been developed.[187,197,198] In addition to a deliberate exploitation of the statistical amplification strategy, recognition of three discrete protocols for the synthesis of Me-branched alcohols shown in Scheme 32 was critically important.

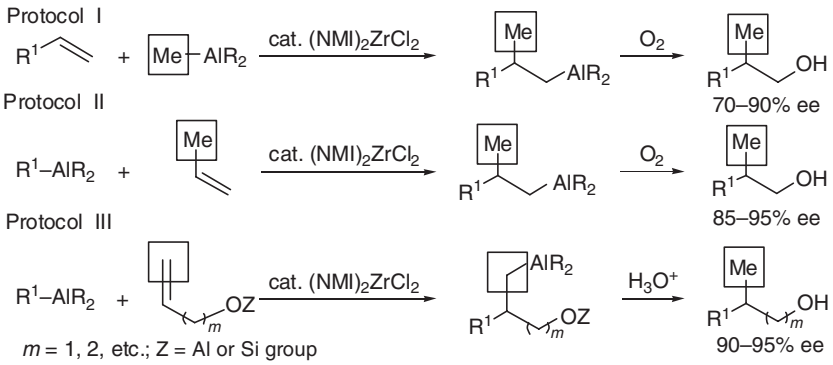
For the syntheses of a large number of deoxypolypropionates requiring α,ω-diheterofunctional intermediates, a couple of novel protocols, that are complementary with the conventional protocol using so-called Roche ester, have been developed (Scheme 33).[199,200] More recently, the combined use of the ZACA reaction and the lipase-catalyzed kinetic resolution via selective acetylation has been shown to be practically attractive for the synthesis of enantiomerically pure compounds that cannot be readily purified by ordinary chromatography or recrystallization[199,201] (Scheme 34).

The ZACA-based protocols have already been applied to a dozen or so natural products shown in Table 3.

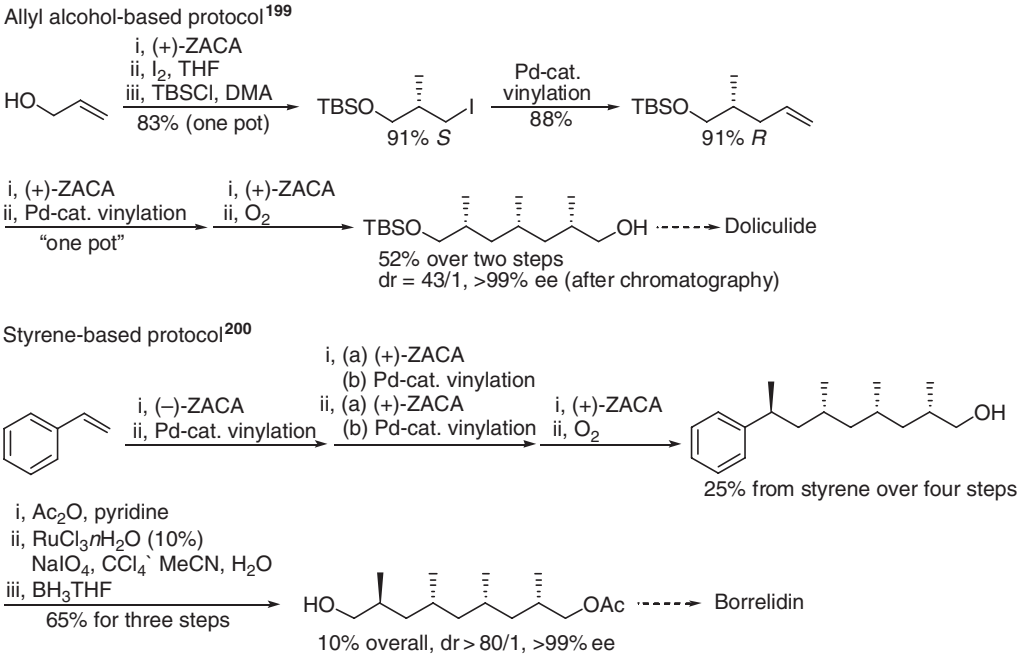


No asymmetric induction Asymmetric induction possible

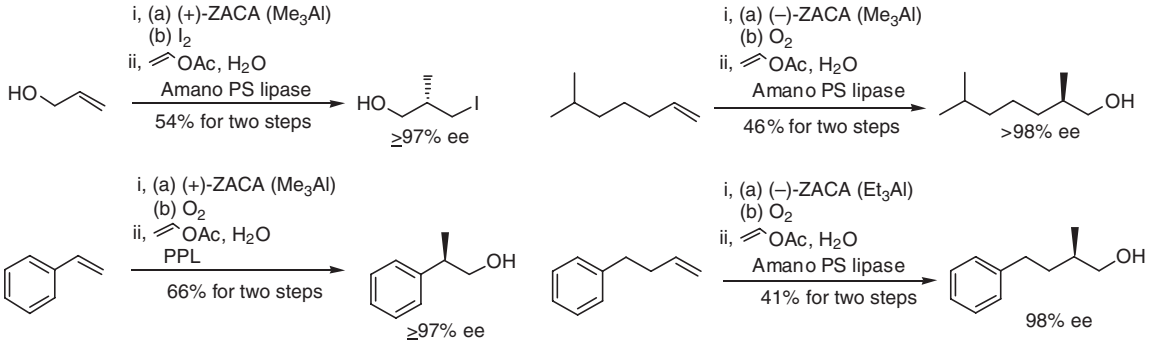
Scheme 31 Secondary asymmetric induction that can arise from α-agostic induction.



Scheme 32 Three discrete protocols of the synthesis of Me-branched alcohols via Zr-catalyzed asymmetric carboalumination.

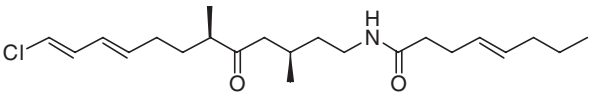
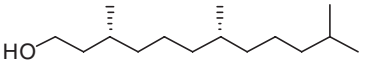
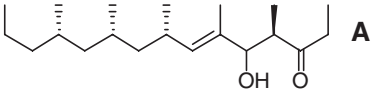
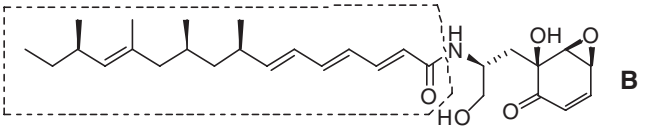
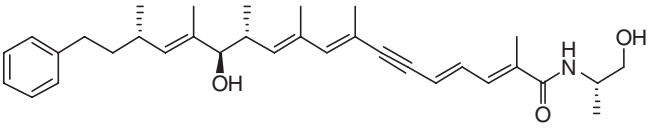
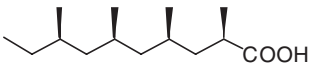
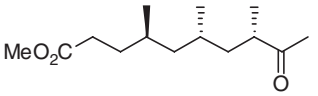
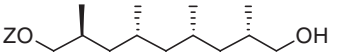
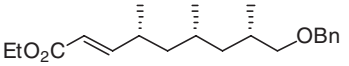
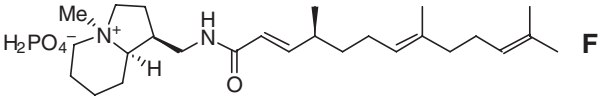
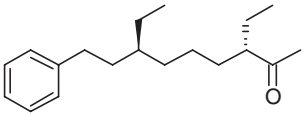


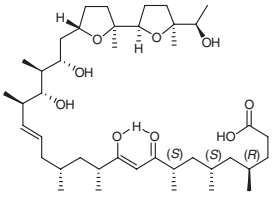
Scheme 33 Efficient ZACA reaction-based protocol for the synthesis of α,ω-diheterofunctional deoxypolypropionates.



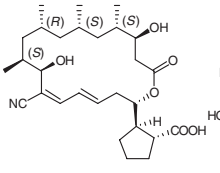
Scheme 34 ZACA–lipase-catalyzed kinetic resolution tandem protocol.

Table 3 Natural products synthesized via ZACA reaction

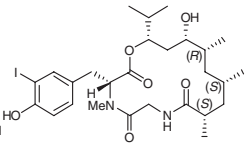
Natural product (*Year*)[Ref. No]	*Structure*
Pitiamide A (2000)[194]	
Vitamin E, vitamin K, phytol (2001)[195]	
Vitamin E (C_{15} side chain) (2002)[195a]	
Siphonarienal, siphonarienone, siphonarienolone (**A**) (2004)[197]	
Scyphostatin (**B**) (side chain) (2004)[198]	
6,7-Dehydrostipiamide (2004)[196]	
Preen gland wax of the graylag goose, *Anser anser* (2005)[199]	
Ionomycin (**C**) (C1–C10 fragment) (2005)[200]	
Borrelidin (**D**) (C3–C11 fragment) (2005)[200]	
Doliculide (**E**) (C1–C9 fragment) (2005)[199]	
Stellattamide A (**F**) (side chain)[201]	
(3*S*,7*S*)-Dianeackerone[201]	



C



D

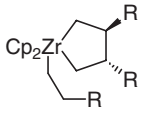


E

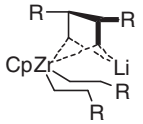
10.06.2.3.4 Cyclic carbometallation of organozirconium compounds

In the two preceding sections, the acyclic carbometallation reactions of organometals containing both Zr and Al with alkynes and alkenes were discussed. Unlike methyltitanium derivatives, methylzirconium derivatives do not appear to readily participate in α-agostic interaction leading to the formation of zirconium–carbene complexes. With methylzirconium derivatives lacking β-hydrogens, no β-H abstraction leading to the formation of three-membered zirconacycles is possible. However, cyclic carbozirconation reactions can be observed with ethyl- and higher alkylmetals, as shown in Schemes 4, 5, and 28. With organometals containing Zr and Al, both acyclic and cyclic carbometallation can be observable depending on the reaction parameters and conditions. It has become increasingly clear that the most readily observable mode of formation of three-membered organotransition metals is the β-agostic interaction-induced acid–base interaction of dialkylmetal complexes shown in Schemes 5 and 6. Since alkylaluminums in general are not sufficiently nucleophilic for dialkylation of $ZrCp_2Cl_2$, which has been by far the most widely used Zr compound, they must resort to an intricate monoalkylative but bimetallic β-H activation for generating cyclic organozirconium derivatives, as shown in Scheme 4.

In marked contrast, Grignard reagents can readily dialkylate $ZrCp_2Cl_2$. Dialkylzirconocenes thus formed have been shown to readily undergo cyclization to give three-membered zirconacycles, as exemplified in Scheme 5. Thus, the carbometallation chemistry of organometals containing Zr and Mg has been dominated by cyclic processes. Even in those cases that might appear to involve acyclic processes, such as the Dzhemilev ethylmagnesation,[10] they have been shown to proceed by cyclic processes, as shown in Scheme 5. As might be expected, the corresponding reactions of alkylmetals containing Li or other alkali metals proceed similarly under the stoichiometric conditions. There is however some notable differences between Mg and Li. Whereas their stoichiometric reactions tend to be very similar, alkyllithiums are much less capable of participating in Zr-catalyzed carbometallation reactions. For example, the Dzhemilev reaction cannot be carried out with ethyllithium. Interestingly, it has been found that the reaction of $ZrCp_2Cl_2$ with alkyllithiums, represented by $LiCH_2CH_2R$, can proceed beyond the formation of dialkylzirconocenes to produce $CpZr(CH_2CH_2R)_3$ and others, including **8** and **9**.[202] It is likely that the high nucleophilicity of alkyllithiums induces some reactions beyond dialkylation, thereby serving as catalyst poisons for Zr-catalyzed processes. The reaction of Et_2Zn with alkenes is also very interesting and instructive. In the presence of $ZrCp_2Cl_2$, Et_2Zn does not readily react with alkenes. When a 2 : 1 mixture of EtMgBr and $ZrCp_2Cl_2$ is used in place of $ZrCp_2Cl_2$, however, a smooth cyclic ethylzircation of alkenes takes place.[203] Evidently, Et_2Zn is incapable of converting $ZrCp_2Cl_2$ into (ethylene)zirconocene. Once generated by the action of 2 equiv. of EtMgBr, however, Et_2Zn is capable of sustaining a Zr-catalyzed ethylzincation that is similar to the Dzhemilev ethylmagnesation but cleaner and higher yielding. At this point, it is not clear if alkylzincs are also capable of undergoing Zr-catalyzed acyclic carbometallation similar to the Zr-catalyzed acyclic carboalumination (cf. Section 10.06.2.3.2). In summary, one of the crucial factors affecting the acyclic–cyclic dichotomy in the transition metal-catalyzed carbometallation among others is the intrinsic nucleophelicity of alkylmetals as a function of the metal countercations. The trends among four metals discussed above can be explained in terms of the relative basicities of alkylmetals containing them, that is, Li > Mg > Zn > Al.



8



9

As already indicated, the carbometallation reactions of zirconacyclopropanes and zirconacyclopropenes with alkenes and alkynes are in many ways similar to the corresponding reactions of titanacycles developed more recently. At the same time, however, there are a number of significant differences, as detailed in Section 10.06.2.2. At the present time, synthetically useful carbotitanation reactions are predominantly cyclic and stoichiometric in Ti and more so than the corresponding chemistry of Zr. It seems reasonable to state that Ti and Zr are complementary to each other more often than not. The cyclic carbozirconation may be either stoichiometric or catalytic. Frequently, the difference between the two is that the stoichiometric reactions lack one or more microsteps for completing catalytic cycles. Otherwise, they often share same stoichiometric microsteps. With this general notion in mind, many stoichiometric carbozirconation reactions have indeed been developed into Zr-catalyzed reactions, as discussed later.

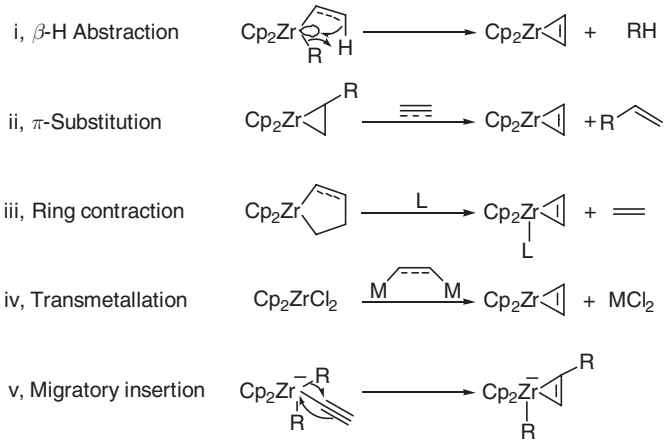
Since the topic of cyclic carbozirconation is so diverse and extensive, it cannot be discussed in detail in this chapter. So, the readers are referred to a number of recent reviews and chapters on this topic.[13,13b,13d–13g,204,204a,205] In this section, a very brief summary with emphasis on some previously unknown and unexpected reactions, which nevertheless promise to significantly broaden the scope of cyclic carbozirconation, is presented.

The topics of the cyclic carbozirconation may be divided as follows, and these topics will be discussed very briefly in the order indicated below:

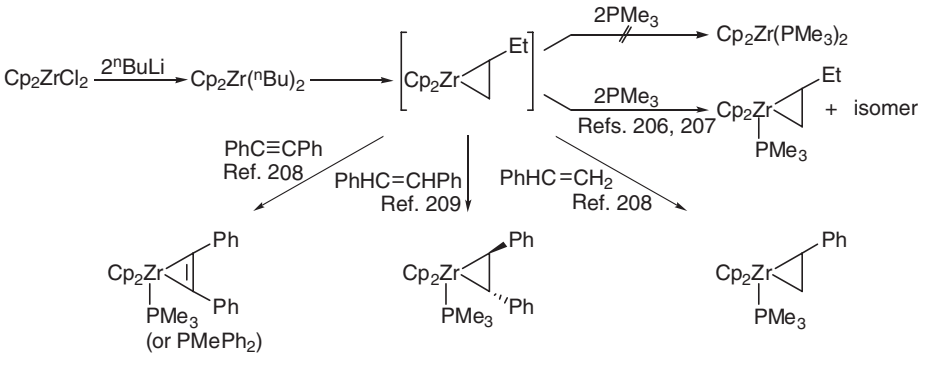
(i) formation and characterization of zirconacyclopropanes and zirconacyclopropenes;
(ii) stoichiometric cyclic carbozirconation reactions;
  (a) intramolecular cyclic carbozirconation of enynes, dienes, and diynes,
  (b) intermolecular cyclic carbozirconation,
(iii) catalytic carbozirconation proceeding via zirconacycles; and
(iv) other novel transformations of three- and five-membered zirconacycles.

10.06.2.3.4.(i) Formation and characterization of zirconacyclopropanes and zirconacyclopropenes

In addition to β-H abstraction of dialkylzirconocenes discussed earlier (Schemes 5 and 6), several other methods are also available for the preparation of three-membered zirconacycles as summarized in Scheme 35. From the viewpoint of cyclic carbozirconation reactions, especially those under Zr-catalyzed conditions, β-H abstraction, π-ligand substitution, and decarbometallative ring contraction are particularly important. As such, these three-membered zirconacycles are generally unstable, but they can be stabilized with phosphines, for example, PMe_3, and other bases, and are fully identified. Some of the well-identified examples are shown in Scheme 36.[206–209]



Scheme 35 Methods of generation of three-membered zirconacycles.



Scheme 36 Preparation of three-membered zirconacycles via (1-butene)zirconocene.

10.06.2.3.4.(ii) Stoichiometric cyclic carbozirconation reactions

10.06.2.3.4.(ii).(a) Intramolecular cyclic carbozirconation of enynes, dienes, and diynes

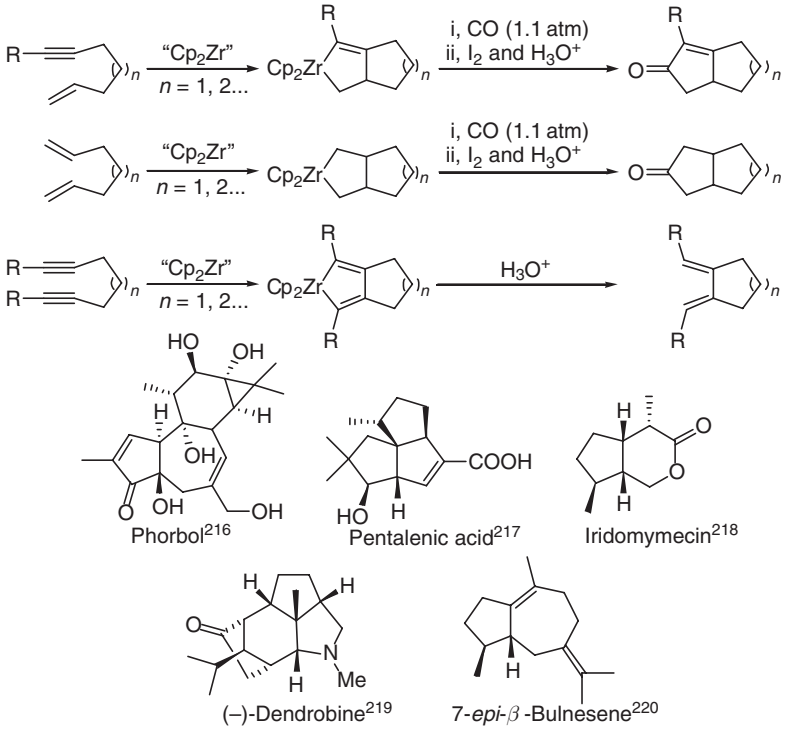
Carbometallative coupling of two π-bonded compounds as exemplified by the Pauson–Khand reaction[210] is a synthetically attractive process. In reality, however, some intricate issues including "pair-selectivity," regioselectivity, stereoselectivity must be well controlled for any such reaction to be synthetically useful, especially in the synthesis of unsymmetrically structured natural products and other molecules of biological and medicinal interest. With these concerns in mind, carbometallative bicyclization of tethered starting materials, that is, enynes,[204,206,211,212] dienes,[213,214,214a,214b] and diynes,[211,212,215,215a] was investigated. These reactions proved to be highly satisfactory, and have been profittably applied to the synthesis of complex natural products[216–220] (Scheme 37) and oligomers and polymers of materials chemical interest.[221] These reactions often compete with the Pauson–Khand[210] and other related reaction, some of which have been developed into catalytic processes. Although the Zr version still remains stoichiometric in Zr, it should be clearly noted that the stoichiometric generation of zirconabicycles has permitted many different subsequent reactions for the synthesis of a wide variety of organic compounds, as exemplified by the synthesis of phorbol.[216] The presence of heteroatoms in the starting compounds can lead to synthetically interesting variations, as shown in Scheme 38.[221–225,225a]

10.06.2.3.4.(ii).(b) Intermolecular cyclic carbozirconation

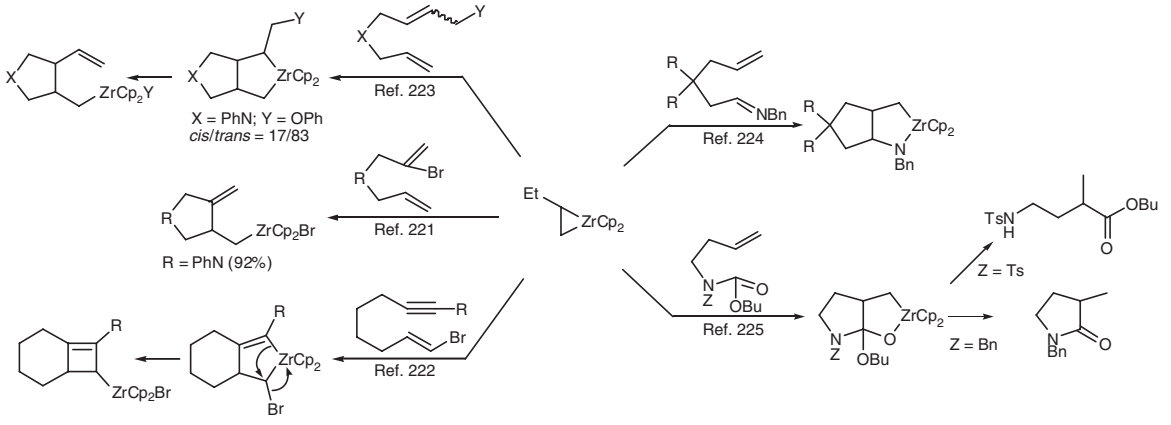
It is much more difficult to control the "pair-selectivity" and regioselectivity of the intermolecular cyclic carbozirconation. The fundamentally dynamic and reversible nature of most of the microsteps in these reactions is primarily responsible for the often capricious nature of these reactions. Nevertheless, considerable progress has been made recently. In particular, the use of (ethylene)zirconocene in place of (1-butene)zirconocene has been shown to provide convenient and selective procedures, as shown in Scheme 39.[13,13c,212,226,227] These procedures, however, are still not fully satisfactory, especially in terms of regioselectivity, and additional developmental works are desirable.

10.06.2.3.4.(iii) Catalytic carbozirconation proceeding via zirconacycles

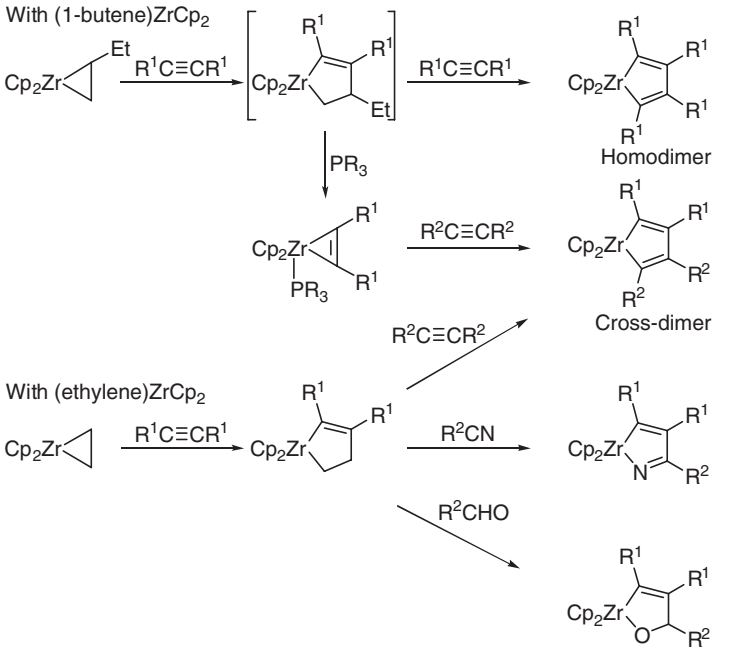
The Zr-catalyzed ethylalumination of alkynes under certain conditions[1,9] (Scheme 4) and ethylmagnesation of alkenes[10,11] (Scheme 5) represent some of the earliest examples of the catalytic carbozirconation proceeding via zirconacycles. In Scheme 5, the carbometallative ring expansion of (ethylene)zirconocene to produce a



Scheme 37 Zr-promoted bicyclization of enynes, dienes, and diynes. Some natural products synthesized by these reactions.



Scheme 38 Heteroatom variants of the Zr-promoted cyclization of dienes, enynes, and related compounds.



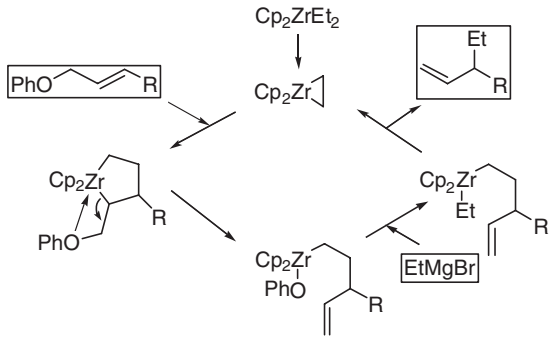
Scheme 39 "Pair-selective" preparation of five-membered zirconacycles via (1-butene)$ZrCp_2$ and (ethylene)$ZrCp_2$.

zirconacyclopentane derivative reacts further with EtMgBr to generate a dialkylzirconocene containing Mg via σ-bond metathesis for providing the missing link for completing a catalytic cycle.[11] In another example shown in Scheme 40,[228] the carbometallative ring expansion is followed by β-elimination, ethylation, and β-H abstraction for regeneration of (ethylene)zirconocene for completing a catalytic cycle. It should be noted that some of the Zr-catalyzed asymmetric ethylation reactions of allylic alcohols and related S and N derivatives[190–192] mentioned earlier are closely related to the reaction shown in Scheme 40.

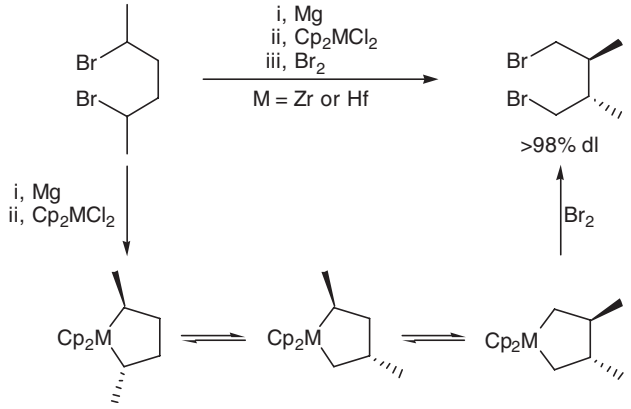
10.06.2.3.4.(iv) Other novel transformations of three- and five-membered zirconacycles

10.06.2.3.4.(iv).(a) Skeletal Rearrangement

Zirconacyclopentanes can readily undergo skeletal rearrangements, exemplified by those shown in Scheme 41. Although the process involving Zr reveals only the final zirconacycle, examination by NMR spectroscopy of the corresponding Hf reaction shows the formation and decay of the 2,5- and 2,4-dimethylhafnacyclopentanes.[229] All of the three hafnacycles as well as the zirconacyclic product are >98% dl.[229]



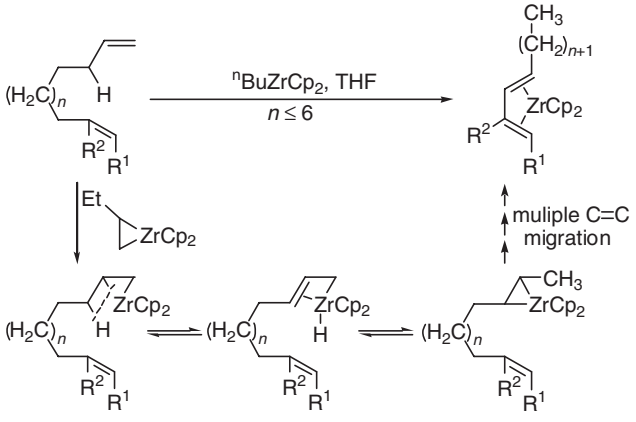
Scheme 40 Zr-catalyzed reaction of allyl ethers with EtMgBr to produce 3-ethyl-1-alkenes.



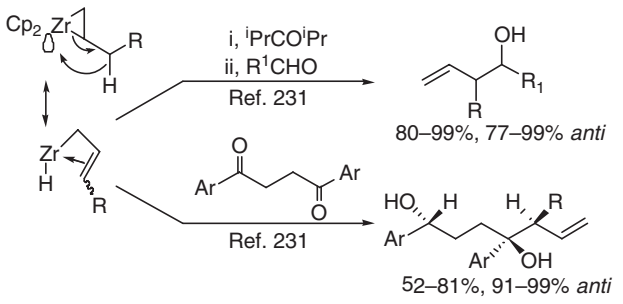
Scheme 41 Skeletal rearrangements of metallacyclopentanes containing Zr and Hf.

10.06.2.3.4.(iv).(b) Regioisomerization

The reaction of certain dienes with $^{n}Bu_2ZrCp_2$ was shown to undergo multipositional double bond migration to produce conjugated diene–zirconocene complexes, shown in Scheme 42.[230,230a] The available data indicate that the process involves a series of β-agostic interaction-induced allylic rearrangements, in which allylzirconocene hydrides must serve as intermediates along with (alkene)zirconocenes.[230] Recently, this reaction has been exploited as an ingeneous way of generating allylzirconocene derivatives used for allylation of carbonyl compounds[231,231a,231b] (Scheme 43).



Scheme 42 Regioisomerization of diene–zirconocene complexes.



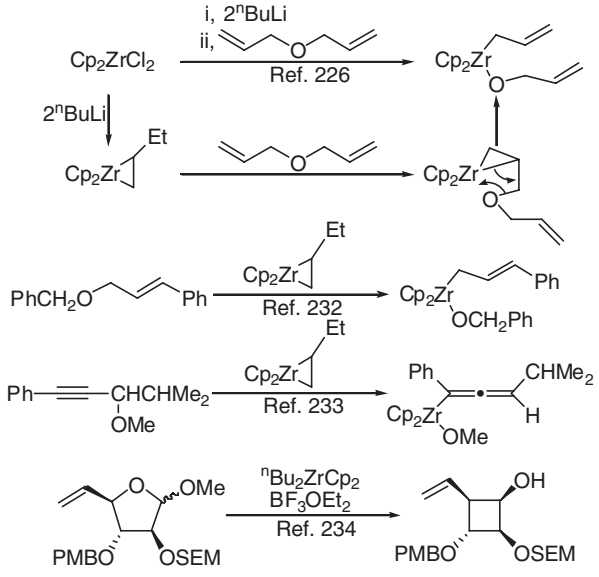
Scheme 43 *In situ* generation of allyl(hydrido)zirconocenes and their carbonyl reduction–allylation tandem processes.

10.06.2.3.4.(iv).(c) Oxidative addition of allyl and alkenyl electrophiles

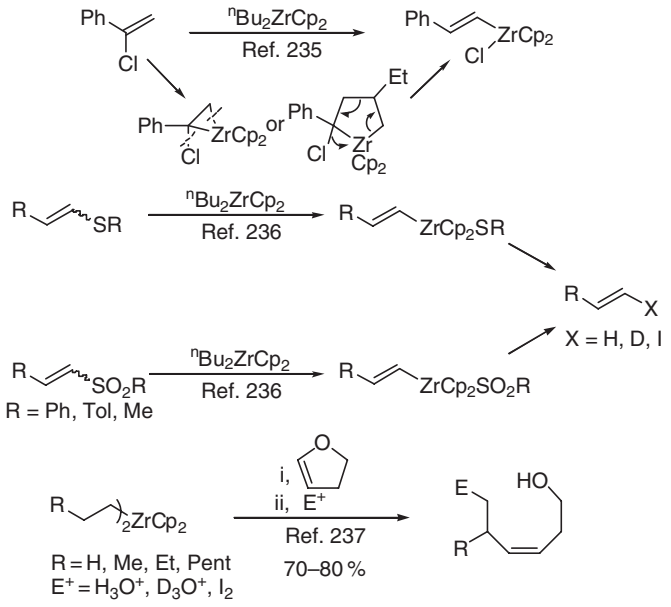
Failure to achieve the bicyclization of diallyl ether with $^{n}Bu_2ZrCp_2$ led to the unexpected discovery of the oxidative addition reaction,[226] shown in Scheme 44. This reaction has been extensively used for developing synthetically useful reactions, also shown in Scheme 44.[232–234,234a–234c] Another breakthrough on this topic was made with alkenyl chloride,[235] which led to more recent similar discoveries with alkenyl sulfides, sulfones, and ethers[236,236a,237] (Scheme 45).

10.06.2.3.4.(iv).(d) Stereoisomerization of alkenes

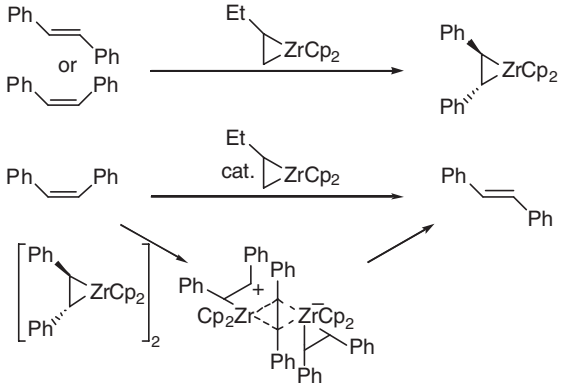
Most, if not all, of the reactions of low-valent $ZrCp_2$ were thought to proceed via concerted processes. However, an unexpected but facile (Z)-to-(E)-isomerization of stilbene in the presence of a catalytic amount of (1-butene)zirconocene led to an intriguing dipolar mechanism, shown in Scheme 46.[238] Rather surprisingly, the $ZrCp_2$-promoted diene bicyclization shown in Scheme 47 exclusively produced and maintained the *trans*-fused 2-zirconabicyclo[3.3.0]octane framework but slowly underwent stereoinversion at the Ph-bound carbon atom. It may be argued that organozirconocene derivatives can readily provide carbocationic species that are counterbalanced by proximal zirconate anions. This concept provides a plausible carbocation rearrangement path for a most unusual rearrangement process, shown in Scheme 48.[239]



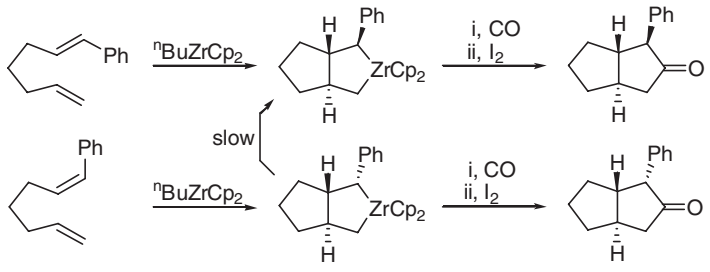
Scheme 44 Oxidative addition reactions of Cp_2Zr derivatives with allylic ethers.



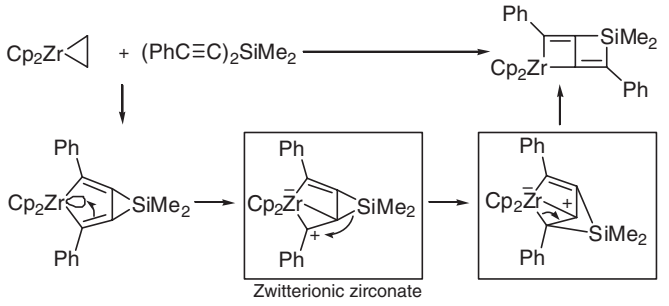
Scheme 45 Oxidative addition reactions of Cp_2Zr derivatives with alkenyl electrophiles.



Scheme 46 ''Cp_2Zr''-induced alkene stereoisomerization via partially non-concerted dipolar mechanism.



Scheme 47 Synthesis of *trans*-fused 2-phenylbicyclo[3.3.0]octan-3-ones.



Scheme 48 Skeletal rearrangement of zirconacycles via dipolar zirconates.

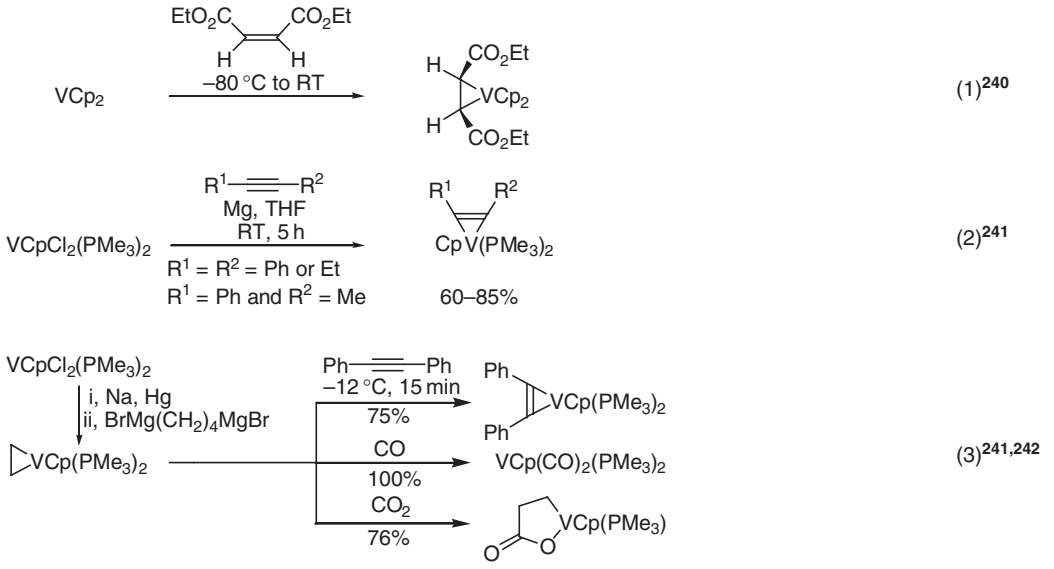
10.06.3 Carbometallation Reactions of Group 5–7 Metals

10.06.3.1 General Remarks about Carbometallation of Group 5–7 Metals

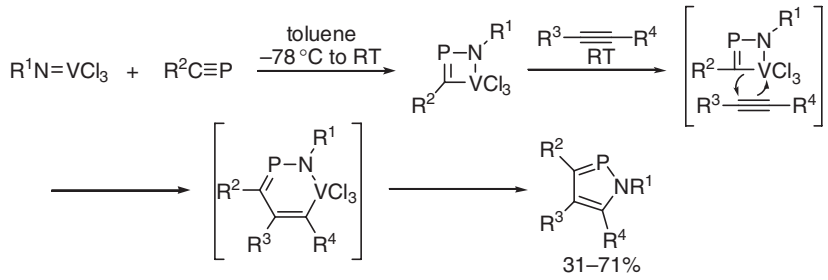
Relatively little is known about the carbometallation reactions of the group 5–7 metals other than their metathesis and polymerization reactions. Those that satisfy several important criteria, including (i) wide applicability, (ii) "pair-selectivity," (iii) high regio- and stereoselectivity, (iv) catalysis, and (v) overall economy, are fewer still. One of the limitations is the generally high costs of the group 5–7 elements relative to Ti and Zr with a notable and potentially significant exception of Mn (Table 1). This problem can, in principle, be overcome by using them catalytically. In fact, some expensive late transition metals, such as Ru, Rh, and Pd, have been shown to be very useful metals for catalylic carbometallation. There does not appear to be any fundamental and chemical reason rendering their carbometallation chemistry very limited. It may be predicted that many useful carbometallation reactions involving some of the group 5–7 metals would be discovered and developed through future explorations. Another apparent and striking fact is that the great majority of the currently known carbometallation reactions of group 5–7 metals are those cyclic carbometallation reactions proceeding via metallacyclopropanes and metallacyclopropenes. Very few controlled acyclic carbometallation of note have been developed, rendering the group 4 metals, especially Zr, rare and special among the group 4–7 metals.

10.06.3.2 Carbometallation of V

Some examples of the formation of three-membered vanadacycles containing VCp_2 and VCp moieties are known as shown in Scheme 49.[240–242] In these reactions, no carbometallation of these three-membered vanadacycles was



Scheme 49 Formation and reactions of vanadacyclopropanes and vanadacyclopropenes.



Scheme 50 1*H*-1,2-Azaphospholes via carbovanadation of alkynes with 1-aza-2-phospha-4-vanada-2-cyclobutanes.

observed, although CO_2 did participate in a three-to-five-membered ring expansion reaction. It is noteworthy that the formation of $(CH_2{=}CH_2)VCp(PMe_3)_2$ in Equation (3) must involve decarbometallative ring contraction, clearly indicating that five-membered vanacycles in these cases must be thermodynamically disfavored.

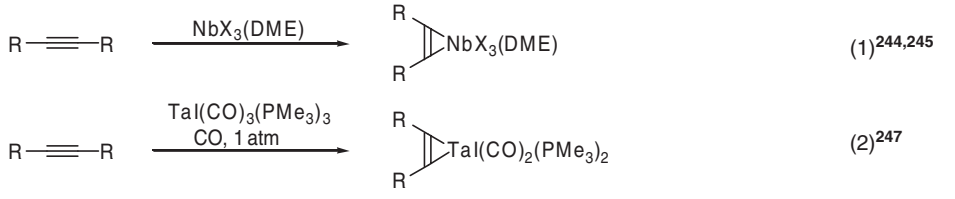
A potentially useful synthesis of 1*H*-1,2-azaphospholes by the reaction of alkynes with 1-aza-2-phospha-4-vanada-2-cyclobutenes generated from $R^1N{=}VCl_3$ and phosphaalkynes may be considered as an example of cyclic carbovanadation[243] (Scheme 50).

10.06.3.3 Carbometallation of Nb and Ta

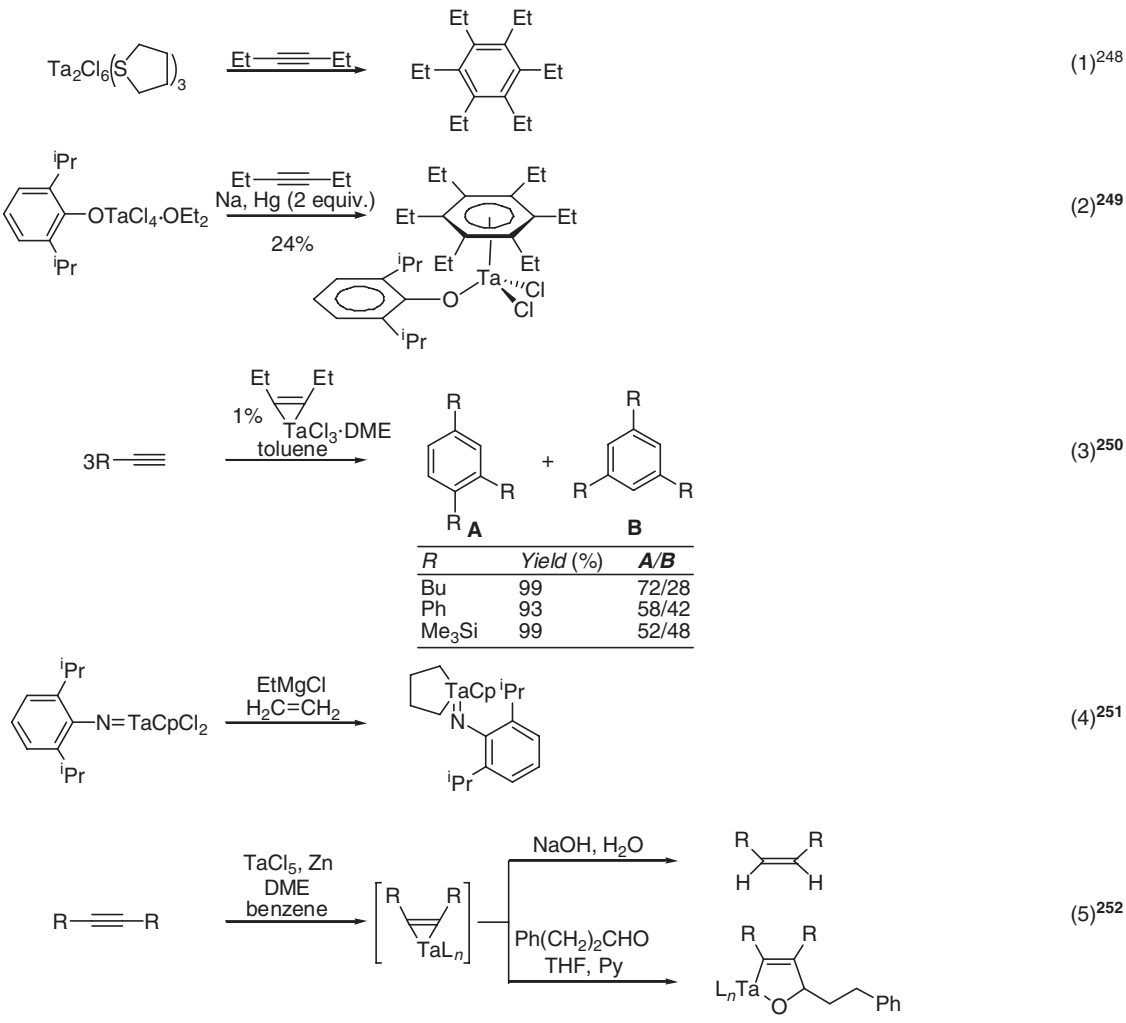
Despite the fact that Nb is significantly less expensive than V and Ta, relatively little appears to be known about its carbometallation. Formation of niobium–alkyne complexes by the reaction of alkyne with $NbX_3(DME)$ is known[244,245,245a,245b] (Scheme 51). Although polymerization of diynes with Nb salts including $NbX_3(DME)$, $NbCl_5$, $NbBr_5$, and $NbCl_5$–Ph_4Sn evidently proceeds via cyclotrimerization of diynes, which most probably involve cyclic carbometallation, details are not very clear.[246,246a] Related reactions of Ta and Mo complexes were also investigated in this study. Formation of tantallacyclopropenes by complexation of alkynes with Ta complexes has also been reported[247] (Scheme 51). In addition to the Ta-catalyzed polymerization of diynes mentioned above, Ta-catalyzed or -promoted cyclotrimerization reactions of alkynes to produce benzene derivatives,[248–250] a Ta-promoted ethylene dimerization,[251,251a] and a reaction of tantallacyclopropenes with aldehydes[252] are also known (Scheme 52). For these reactions to be of use in organic synthesis, several aspects mentioned in Section 10.06.3.1 must be further investigated. Nevertheless, the ability of Ta to participate in cyclic carbometallation appears to be well established.

10.06.3.4 Carbometallation Reactions of Group 6 Metals: Cr, Mo, and W

The currently known carbometallation chemistry of the group 6 metals is dominated by the reactions of metal–carbene and metal–carbyne complexes with alkenes and alkynes leading to the formation of four-membered metallacycles, shown in Scheme 1. Many different fates of such species have been reported, and the readers are referred to reviews discussing these reactions.[253] An especially noteworthy reaction of this class is the Dötz reaction,[254] which is stoichiometric in Cr in essentially all cases. Beyond the formation of the four-membered metallacycles via carbometallation, metathesis and other processes that may not involve carbometallation appear to dominate. It is, however, of interest to note that metallacyclobutadienes containing group 6 metals can undergo the second carbometallation with alkynes to produce metallabenzenes, as shown in Scheme 53.[255] As the observed conversion of metallacyclobutadienes to metallabenzenes can also proceed via a Diels–Alder-like

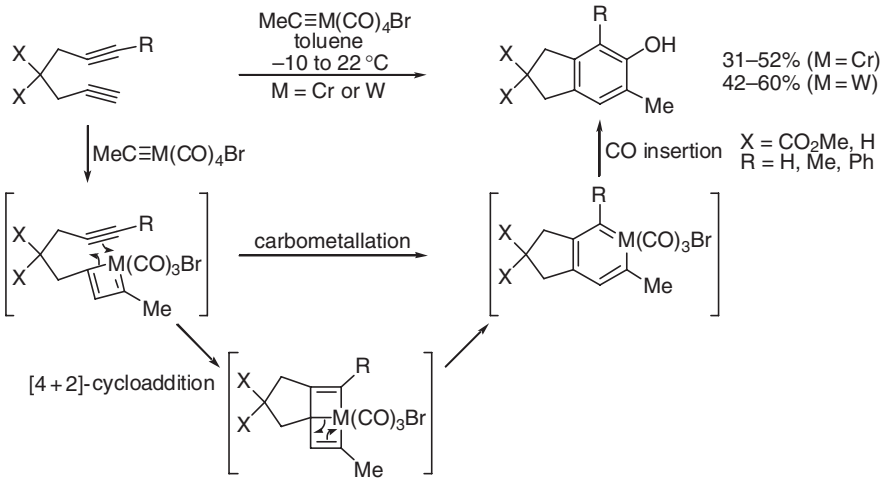


Scheme 51 Formation of niobium–alkyne and tantalum–alkyne complexes.

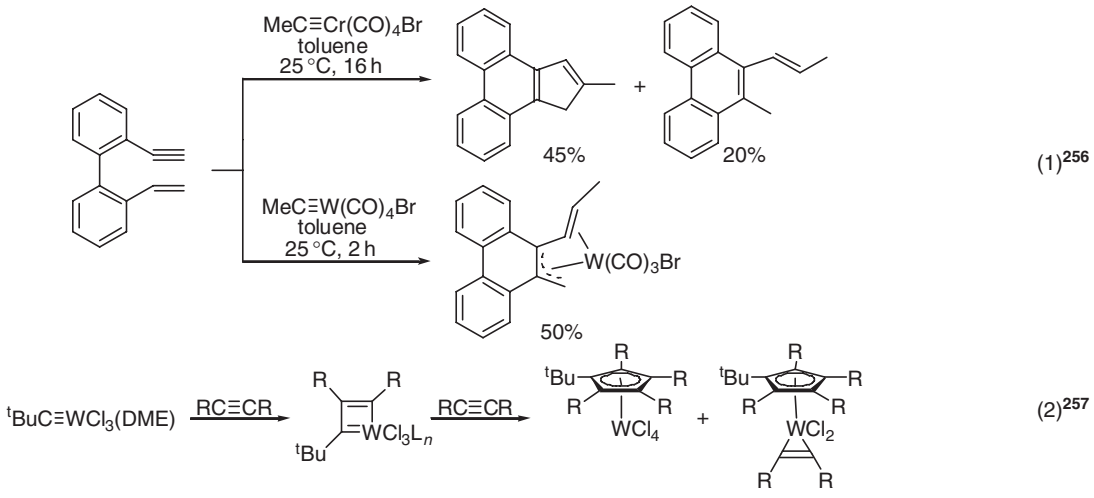


R	*Yield* (%)	***A*/*B***
Bu	99	72/28
Ph	93	58/42
Me_3Si	99	52/48

Scheme 52 Cyclic carbometallation and related reactions of organotantalum derivatives.



Scheme 53 Bicyclization of diynes with group 6 metal–carbyne complexes.



Scheme 54 Cyclization of alkynes with metal–carbyne complexes containing Cr or W.

[4 + 2]-cycloaddition, the exact course of the reaction does not appear to have been fully established. Nevertheless, it is presented here as a possible carbometallation process.

In addition to the reaction shown in Scheme 53, some other related reactions that are thought to proceed via cyclic carbometallation have also been reported (Scheme 54). In the cyclization reaction of 2-ethenyl-2′-ethynylbiphenyl, both Cr and W carbyne complexes must undergo the same cyclic carbometallation as that shown in Scheme 53 to give the corresponding metallacyclohexadiene intermediates, but the final products obtained were different.[256] Some tungsten–carbyne complexes have been shown to undergo a stepwise [2 + 2 + 2]-cyclization via formal cyclic carbometallation that can be followed by reductive elimination to produce cyclopentadiene–tungsten complexes.[257]

Although mechanistic details are unclear, both triallylchromium(III) and tetraallylchromium(II) were shown to react with 2-butyne in THF to give the same overall mixture of products containing 1,2,3,4-tetramethylbenzene, pentamethylbenzene, and hexamethylbenzene in 1971.[258] Possible intermediacy of chromacyclopentadienes was suggested in this report. More recently, an Mo-promoted [2 + 2 + 2]-cyclization of alkynes was reported.[259] The use of 35 mol% of $Mo(CO)_6$ leading to the formation of benzenes in up to 49% yields does not persuasively indicate that the reaction is catalytic in Mo. Unlike the reactions shown in Schemes 53 and 54, this reaction is believed to proceed via molybdenacyclopentadienes and molybdenacycloheptatrienes, the latter of which must undergo demetallative aromatization. A couple of other W-promoted reactions that appear to share common mechanistic features are also known (Scheme 55).[260,261]

Molybdenum-promoted cyclodimerization of cyclooctatetraene[262] and its cocyclization with alkynes[263,263a] also appear to proceed via three- and five-membered molybdenacycles followed by further cyclization reactions that may or may not involve promotion by Mo (Scheme 56).

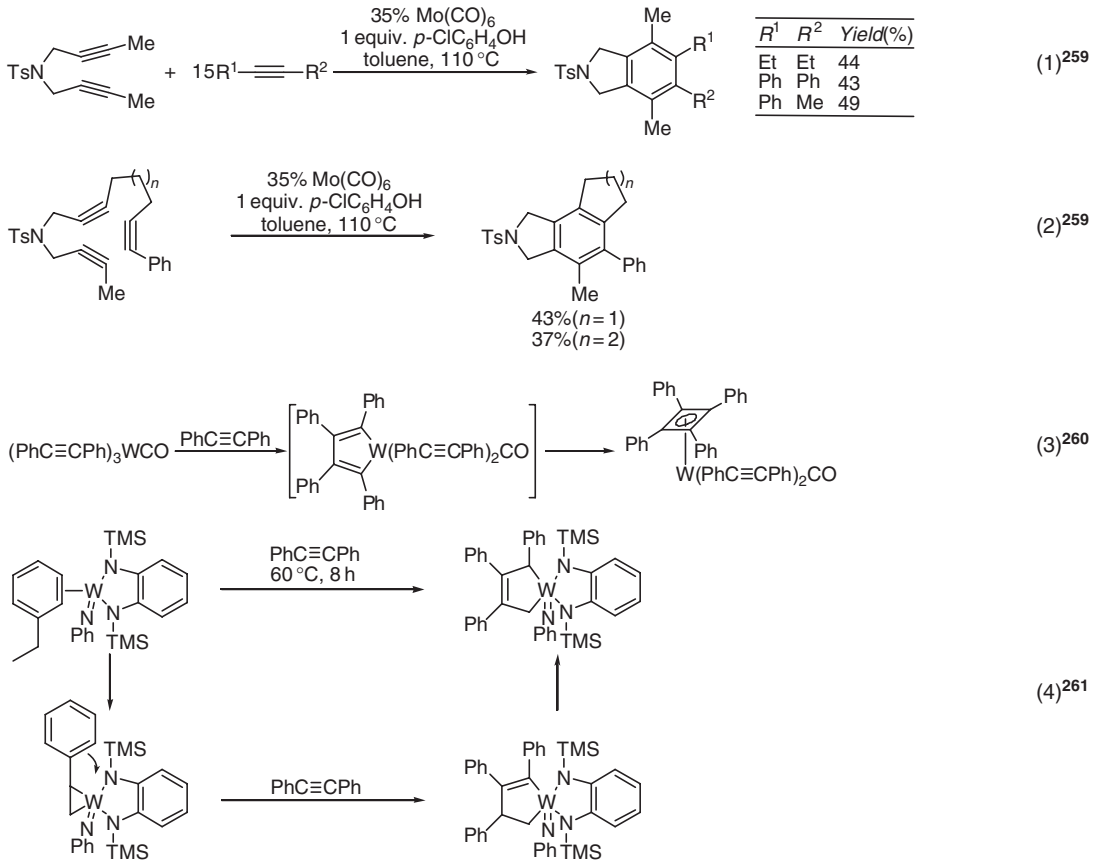
All of the reactions discussed above are cyclic carbometallation reactions of metallacycles. Very recently, an interesting Cr-catalyzed carboalumination of propargyl derivatives producing allenes via a carbometallation–elimination sequence has been studied.[264] This reaction provides an asymmetric synthesis of chiral allenes (Scheme 57).

10.06.3.5 Carbometallation Reactions of Group 7 Metals: Mn, Tc, and Re

Not surprisingly, little, if any, appears to be known about the carbometallation reactions of Tc. What is somewhat surprising is that similarly little appears to be known about the carbometallation of Re. Its high cost (cf. Table 1) might be one of the reasons for the apparent paucity of its carbometallation chemistry. So, the discussion in this section is limited to the carbometallation of Mn.

10.06.3.5.1 Stoichiometric carbomanganation with well-defined organomanganese compounds

The stoichiometric carbometallation with well-defined organomanganese compounds has thus far been limited to those of organomanganesecarbonyl compounds. One of the apparently common characteristics among them is their strong tendency to exist as coordinatively saturated 18-electron species. As such, they must be rather inert toward alkynes and alkenes (cf. Scheme 3). Dissociation of one of the CO's or some other ligands would facilitate their

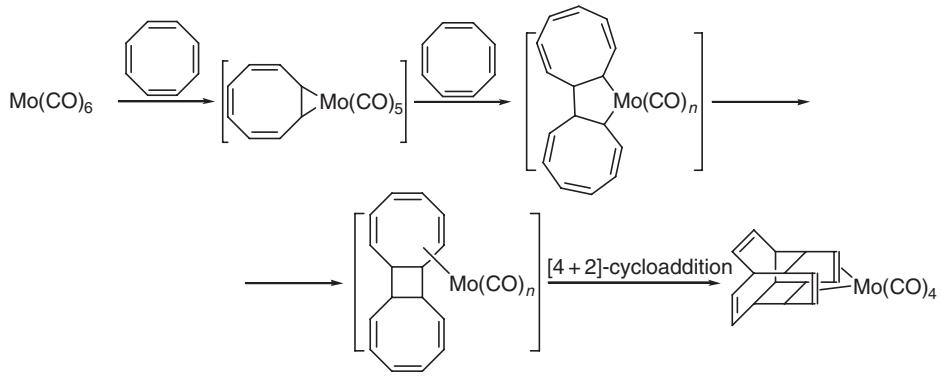


Scheme 55 Cyclization of alkynes and alkenes via three-, five-, and seven-membered metallacycles containing Mo or W.

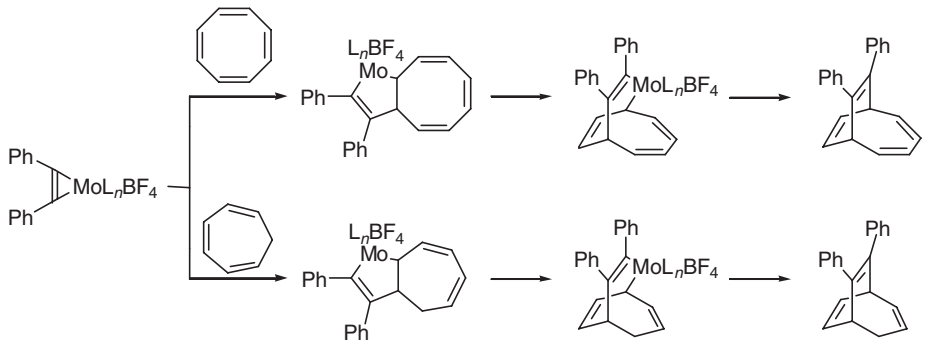
carbometallation. Photochemical dissociation of CO is well known for activation of metal–carbonyl complexes containing the group 6 metals,[253,254] but this method has not yet been extensively applied to the development of carbometallation reactions of organomanganese compounds. Alternatively, coordinatively unsaturated 16-electron organomanganese derivatives can also be generated via migratory insertion of CO. A 16-electron acylmanganese derivative thus generated can now undergo addition of the acyl–Mn bond to alkynes and alkenes to produce γ-oxoorganylmanganese derivatives that have been shown to exist as chelated five-membered manganacycles[265,265a,265b] (Scheme 58). This acylmanganation reaction is accelerated under high pressures of 2–10 kbar, suggesting that the addition of the acyl–Mn bond to alkynes and alkenes for converting two molecules into one must be the rate-determining step. Despite the requirement for high pressures, this reaction has been extensively investigated and developed into a potentially useful synthetic reaction.[265,265a,265b] A more recent report on the corresponding reactions of *C*-glycosylmanganese complexes is also promosing[266] (Scheme 59).

The acylmanganation of alkynes[265,265a,265b] has recently been applied to the development of Mn-mediated cyclization and bicyclization reactions of enynes[267] and diynes[268] (Scheme 60). The photochemically induced cyclization shown in Equation (1) can selectively produce either methylenecyclopentane derivatives in ether or bicyclo[3.1.0]hexane derivatives in MeCN in modest yields. Bicyclization of diynes, on the other hand, has been induced by treatment of the acylmanganated intermediates with Me_3NO.[268] Upon protonolysis, bicyclo[3.3.0]oct-1,4-dien-3-ol derivatives can be obtained in 52–90% yields from the acylmanganated intermediates (Equation (2)).

Carbomanganation of alkynes without incorporation of CO has recently been reported by using manganatricyclic reagents in which the imidazole moiety must serve as a ligand that can be temporarily dissociated under thermal conditions[269] (Scheme 61). The product yields are satisfactory (72–82%), but little or no regioselectivity has been observed. Nonetheless, the use of imidazoles as ligand that can be thermally dissociated for activation of organomanganese species for carbomanganation may prove to be important.

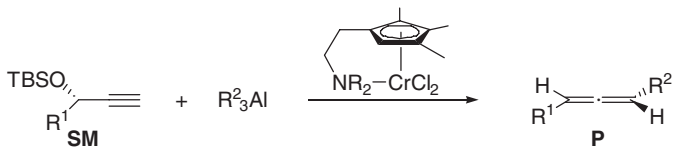


(1)[262]



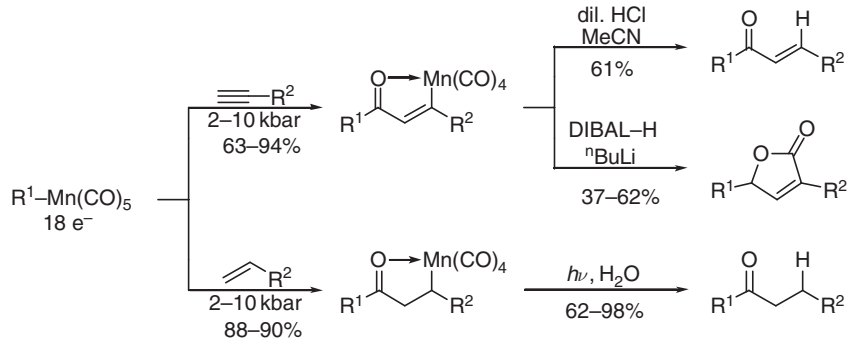
(2)[263]

Scheme 56 Mo-promoted cyclization of cyclooctatetraene and its co-cyclization with alkynes.



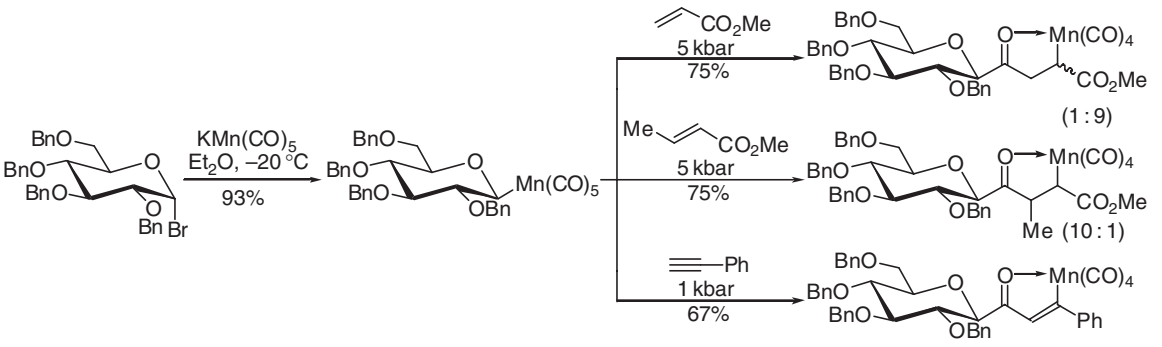
R^1	R^2	*Yield* (%)	*ee* (%) *of* ***SM***/*ee* (%) *of* ***P***
$TBSO(CH_2)_4$	Me	83	86/88
$TBSO(CH_2)_4$	Et	82	85/90
$TBSO(CH_2)_4$	^{i}Bu	79	82/90

Scheme 57 Cr-catalyzed synthesis of chiral allenes via carboalumination–elimination of chiral propargyl derivatives.

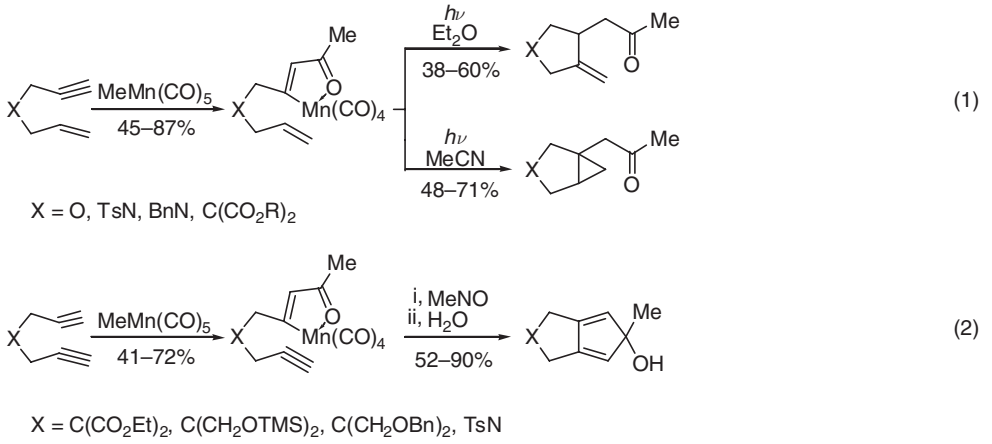


R^1 = Me, $PhCH_2$, $MeCH{=}CH_2$, etc; R^2 = CO_2Me, SO_2Ph, Ph, etc

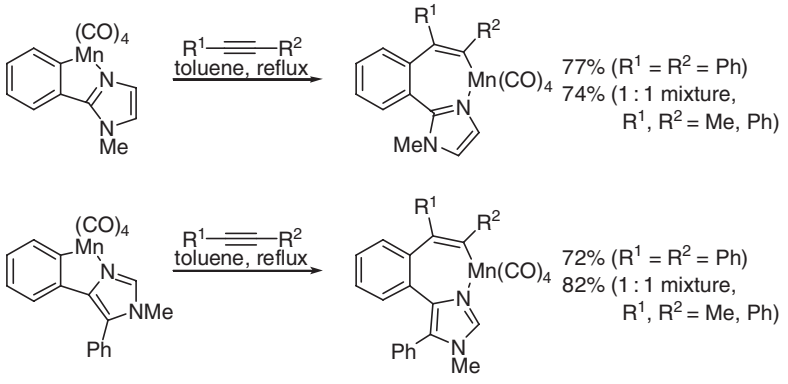
Scheme 58 Acylmanganation of alkynes and alkenes.



Scheme 59 Acylmanganation of *C*-glycosyl–mangnese complexes with alkynes and alkenes.



Scheme 60 Acylmanganation of enynes and diynes followed by cyclization induced by light or MeNO.

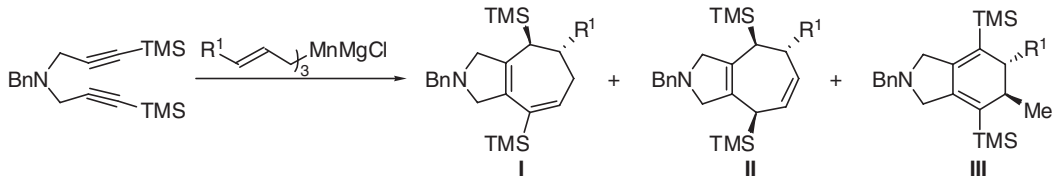


Scheme 61 Carbomanganation of alkynes without the incorporation of CO.

Although mechanistic details are unclear, a very interesting Mn-induced bicyclization of diynes shown in Scheme 62 has been reported.[270] Unfortunately, this reaction gives mixtures of three isomeric products.

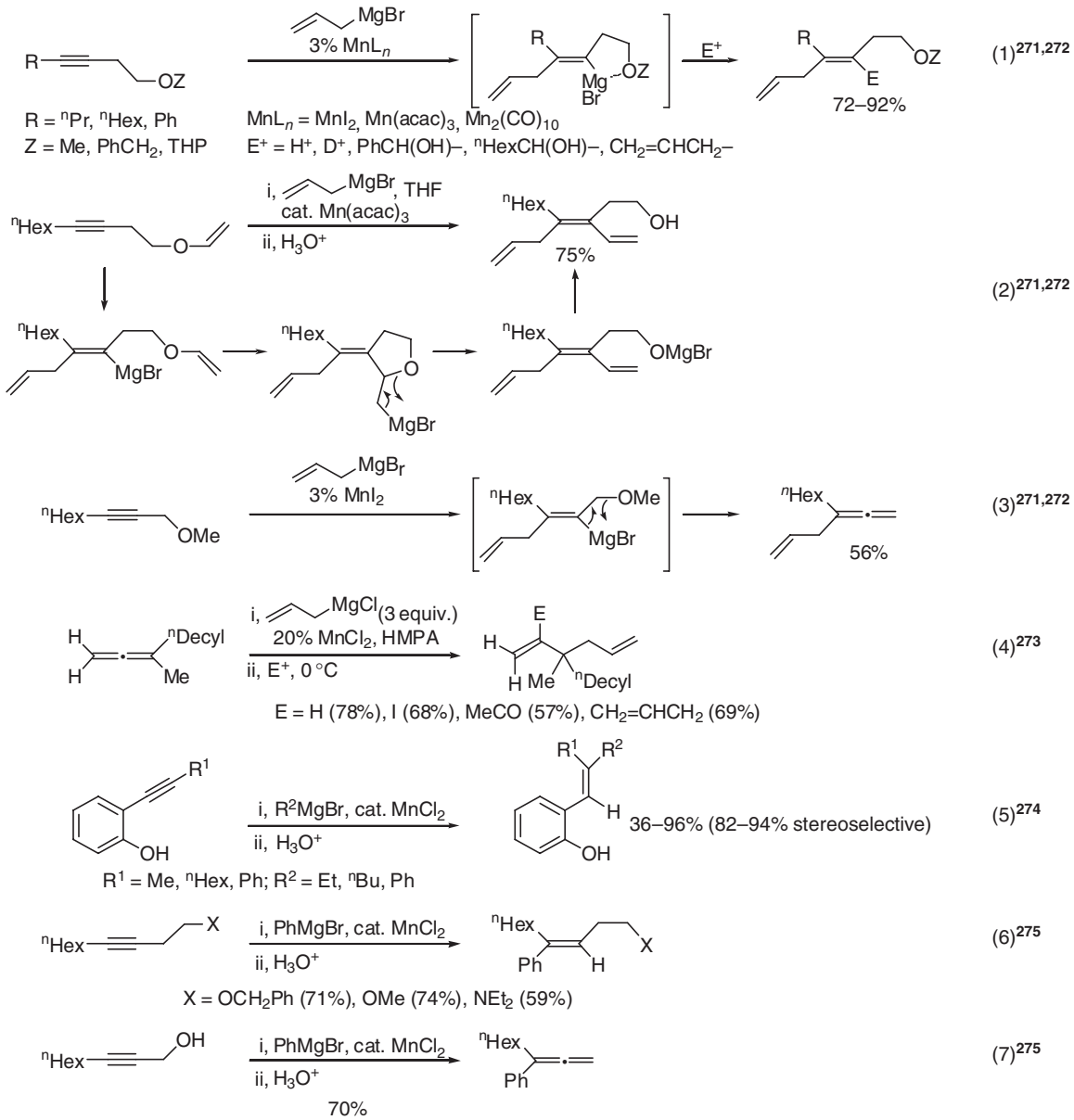
10.06.3.5.2 Mn-catalyzed carbometallation

All of the reactions discussed in the preceding section are stoichiometric in Mn. Over the past decade, however, Mn-catalyzed carbomagnesation reactions of potential synthetic utility have been developed by Oshima, as summarized in Scheme 63.[271–275] Attempts to use $PdCl_2(MeCN)_2$, $NiCl(PPh_3)_2$, $CrCl_3$, and $RuCl_3$ were unsuccessful, and



R^1	*I* (%)	*II* (%)	*III* (%)
H	20	25	25
Me	10	10	38
^{n}Decyl	15	15	36

Scheme 62 Mn-induced bicyclization of diynes.



Scheme 63 Mn-catalyzed allylmagnesation, alkylmagnesation, and phenylmagnesation of homopropargyl and propargyl alcohol derivatives as well as allenes.

ordinary alkynes without proximal heterofunctional groups do not readily participate in these reactions. Some of the reactions shown in Scheme 63 may also be carried out stoichiometrically with preformed organomanganese reagents, such as $(CH_2{=}CHCH_2)_3MnMgCl$ and $(CH_2{=}CHCH_2)_4Mn(MgCl)_2$.[272]

10.06.4 Conclusion

Controlled single-stage carbometallation reactions of alkenes and alkynes with group 4–7 metals are discussed with emphasis on regio-, stereo-, and chemoselectivity including clarification and understanding of factors governing these synthetically important aspects.

At present, the area covered in this chapter is overwhelmingly dominated by group 4 metals, especially Ti and Zr. Although some examples of carbometallation reactions that are catalytic in Ti are known (Scheme 13), the great majority of the currently known carbometallation reactions with Ti are stoichiometric processes involving titanacycles. These cyclic carbotitanation reactions have been extensively developed over the last decade, and they collectively provide many synthetically useful reactions and procedures. The ready availability of Ti and its complexes used in these reactions would justify the stoichiometric use of Ti in these and other reactions. Surprisingly, little is known about Ti-catalyzed controlled carbometallation reactions producing monomers and well-defined dimers and oligomers of use for the synthesis of fine chemicals. In view of the vast area of the Ziegler–Natta alkene polymerization which is catalytic in Ti, one may be tempted to predict that a number of Ti-catalyzed single-stage carbometallation reactions would be discovered and developed in the future.

By far, the most extensively investigated, developed, and used are those carbometallation reactions involving Zr. Some of the representative examples of this class include:

(i) Zr-catalyzed single-stage carboalumination of alkynes discovered and developed since 1978 that has been applied to the synthesis of more than 100 complex natural products,
(ii) Zr-catalyzed asymmetric carboalumination of alkenes (ZACA reaction) discovered and developed since 1995, which promises to be widely used, and
(iii) stoichiometric and catalytic carbozirconation of three-membered zirconacycles, which has been most extensively investigated among the topics discussed in this chapter.

As indicated above, both stoichiometric and catalytic carbozirconation processes have been discovered and developed. Zirconium is also capable of undergoing either acyclic or cyclic carbozirconation depending most critically on the metal countercations of organometals and solvents among other factors. It has also become increasingly apparent that the synthetic significance of Zr in the area of controlled, single-stage carbometallation of high stereo-, regio-, and chemoselectivity is attributable to its propensity to undergo facile orbital–orbital interaction-controlled concerted processes that are not seriously complicated by competitive polar and radical processes. In a more practical vein, its relatively low cost (Table 1) is a non-scientific but significant factor. Furthermore, the major significance of β-agostic interaction involving Zr overshadowing its α-agostic interaction has thus far made the formation of zirconium–carbene complexes and their subsequent metathesis processes rather insignificant. Although Hf is capable of undergoing many reactions that Zr undergoes, it suffers from a generally lower reactivity and a significantly higher cost.

At present, the carbometallation reactions of group 5–7 metals excluding their polymerization and metathesis reactions are of limited scope and significance. With the notable exception of Mn, which is one of the least expensive transition metals (Table 1), group 5–7 metals are considerably more expensive than Ti and Zr, although the use of the stoichiometric quantities of Nb and Cr may be acceptable in some cases. The generally high propensity of group 5–7 metals to participate in metal–carbene complex formation and subsequent metathesis reactions must be one chemical reason for the current paucity of their carbometallation reactions covered in this chapter. Even so, however, group 5–7 metals must be capable of undergoing controlled carbometallation reactions similar to those of Ti and Zr, when various parameters and reaction conditions are appropriately chosen and optimized. In this vein, some recently discovered carbometallation reactions involving Cr, such as Cr-catalyzed stereospecific chiral allene synthesis (Scheme 57), and Mn, such as Mn-catalyzed carbomagnesation (Scheme 63), are noteworthy and promising.

Various fundamentally significant factors governing carbometallation of group 4–7 metals, including (i) degree of polymerization, that is, single-stage processes versus oligomerization and polymerization, (ii) acyclic versus cyclic,

(iii) concerted versus polar ionic and radical, (iv) α-agostic versus β-agostic, and (v) regio-, stereo-, and chemoselectivity, have now been reasonably well investigated and understood. It may therefore be safely predicted that future investigations will lead to a number of new and/or improved carbometallation reactions and procedures of group 4–7 metals.

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10.07 C–C Bond Formation (Part 1) by Addition Reactions: through Carbometallation Catalyzed by Group 8–11 Metals

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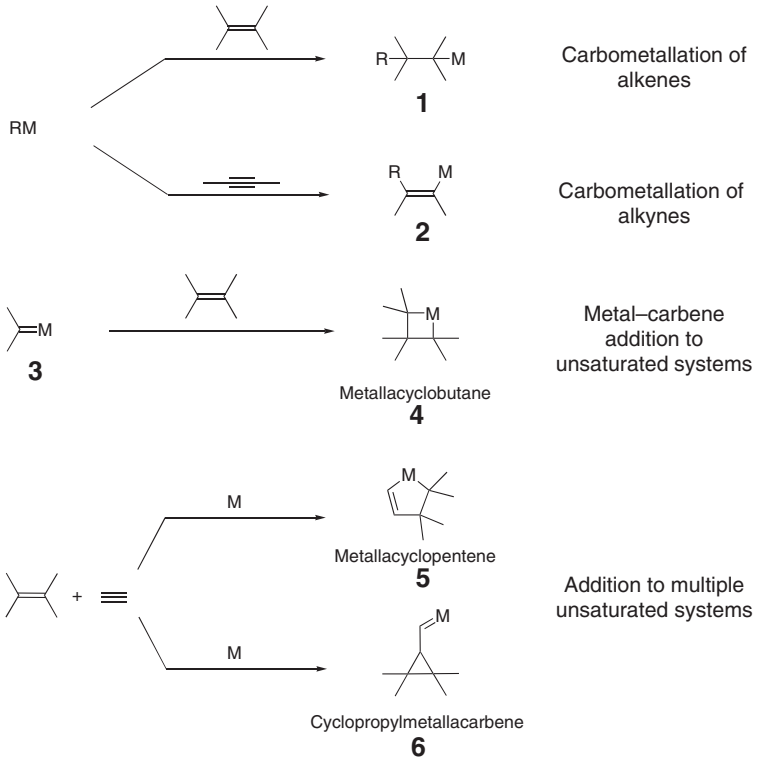
10.07.1 Introduction

This chapter is primarily devoted to the addition reactions of organometallics with alkenes and alkynes, for which the term carbometallation as coined by Negishi has been suggested and widely accepted.[1–3] More precisely, the focus is on catalyzed processes by group 8–11 metals, which represent a very vast body of different transformations. Nevertheless, these processes generally and schematically obey the simple equations of Scheme 1. Besides the simple addition to alkenes and alkynes, allenes and also heteroatom-substituted unsaturated components[4] such as enolates can be envisaged as partners. The reaction of a metal–carbene (carbyne) **3** with an alkene to form a metallacyclobutane (butene) **4** belongs also to this class of reactions. As an extension, the metal center can be the forum for an ene and an yne partner (or other unsaturated opponents) to undergo a chemical transformation such as a metallacyclopentene **5** formation, and as shown recently in skeletal rearrangement reactions, a cyclopropylmetallacarbene **6** formation. Naturally, the intramolecular versions of these processes offer intriguing potentialities in organic synthesis. All these aspects will be discussed in the aforementioned order.



Scheme 1

Transition metals have been widely investigated for applications in organic chemistry. A number of books report the applications and the recent developments of some metal catalysts from groups 8 to 11.[5–10]

10.07.2 Carbometallation of Unsaturated Partners

The intermolecular carbometallation reaction catalyzed by transition metals from groups 8 to 11 has been fully investigated during the last decade. Many examples have been reported in the literature concerning different metals in order to create C–C bonds. Overview of this powerful method will be given as exhaustively as possible and carbometallation reactions will be classified according to unsaturated systems.

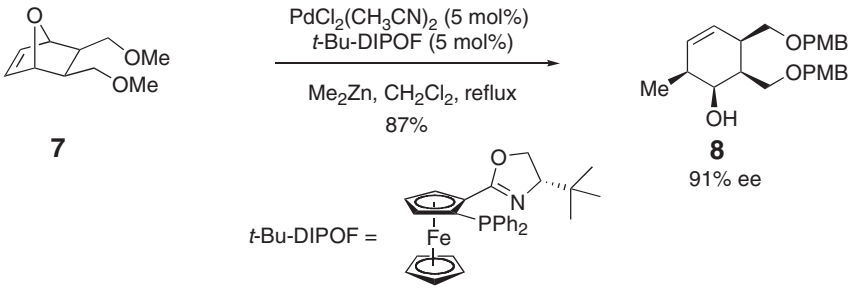
Such reactions involve the addition of organometallic reagent to unsaturated systems like alkynes, alkenes, allenes, or related structures in order to create a new C–C bond and C–M bond at the same time. The C–M bond can then be functionalized by an electrophile to generate a wide range of products.

In this chapter, only additions to unactivated systems are reported and conjugate addition considerations, cross-coupling reactions, and cross-metathesis are covered in Chapters 10.08, 11.01, 11.02, 11.08, 11.09, and 11.10.

10.07.2.1 Alkenes

The alkene functionality is one of the key units of organic reactivity. Addition of an organometallic species to an alkene has been well described, but in many cases, catalysis is required.[11–13]

Many research groups have studied the regio- and stereoselective ring-opening reactions of the oxabicyclic alkenes for the synthesis of cycloalkenols, mainly in an enantioselective fashion with a chiral ligand around the metal center (Scheme 2).[14] This transformation is catalyzed by a nickel,[15–17] palladium,[18,19] rhodium,[20–22] copper,[23,24] or iron[25] catalyst by using organometallic reagents such as an organoaluminum,[26] organozinc,[27] organoboron,[28] and a Grignard reagent.[25] The *syn*- or the *anti*-ring opening is reported, depending on additives. Most of the reported results show a *syn*-stereoselectivity in agreement with a carbometallation mechanism. Copper(I) salts with a free phosphine allowed



Scheme 2

the reversal of the stereoselectivity in favor of *anti*-product (>98 : 2).[23] Two mechanistic pathways are postulated to explain those reactions and especially the C–O bond cleavage. It can be either carbometallation/β-oxygen elimination or oxidative addition/π-allylmetal formation. The second pathway could explain the *anti*-selectivity by equilibration of intermediate π-allyl complexes. At present, no study has clarified this point. The ring opening of [2.2.1]-oxabicyclic substrate **7** is optimal with a ferrocene-based ligand like *t*-Bu-DIPOF, affording the tetrasubstituted cyclohexene derivative **8** in 87% yield and 91% ee (Scheme 2).[29]

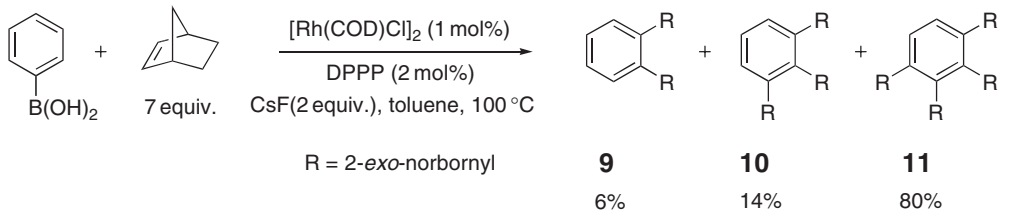
Miura reported a 1,4-shift of rhodium in the reaction of norbornene with arylboronic acids (Scheme 3) where rhodium moves from an alkyl sp^3-carbon to an aryl sp^2-carbon, and the arylrhodium species further reacts with another molecule of norbornene.[30] Polyalkylated phenyls are obtained in good yields. Cesium fluoride facilitates the transmetallation, generating the phenylrhodium complex which then coordinates to the *exo*-face of norbornene.

Alkylation of norbornene with acrylic acid derivatives occurs with ruthenium catalysts like $[RuCl_2(C_6H_6)]_2$/Zn in protic solvent.[31] (*E*)-*exo*-2-norbonylacrylates are obtained with high regio- and stereoselectivity in good yields.

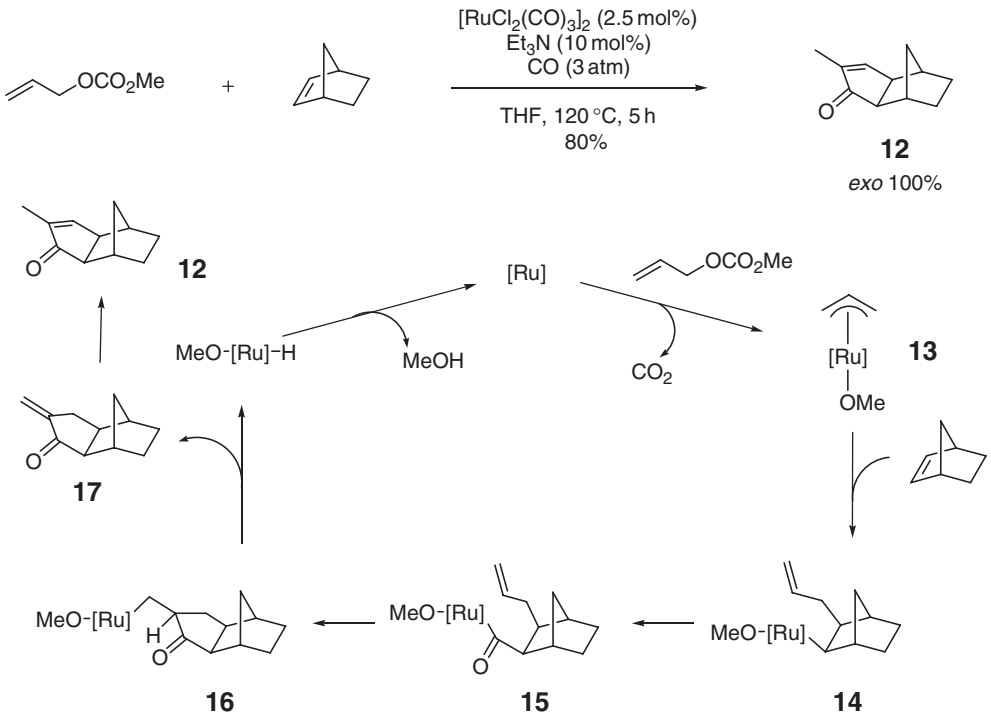
Allyl methylcarbonate reacts with norbornene following a ruthenium-catalyzed carbonylative cyclization under carbon monoxide pressure to give cyclopentenone derivatives **12** (Scheme 4).[32] Catalyst loading, amine and CO pressure have been optimized to give the cyclopentenone compound in 80% yield and a total control of the stereoselectivity (*exo* 100%). Aromatic or bidentate amines inhibit the reaction certainly by a too strong interaction with ruthenium. A plausible mechanism is proposed. Stereoselective *cis*-carboruthenation of norbornene with allylruthenium complex **13** followed by carbon monoxide insertion generates an acylruthenium intermediate **15**. Intramolecular carboruthenation and β-hydride elimination of **16** afford the *exo*-olefin **17**. Isomerization of the double bond under experimental conditions allows formation of the cyclopentenone derivative **12**.

In 2000, Nakamura reported the carbometallation of strained cycloalkenes such as cyclopropene acetal **18** with Grignard or organozinc reagents and an iron catalyst (Scheme 5).[27,33] This ternary catalytic system involves an iron salt, a chiral phosphine ligand, and a diamine. TMEDA slows down the reaction, but increases the enantioselectivity. Other bidentate phosphines have been investigated but BINAP and *p*-Tol-BINAP have shown the highest chiral induction. It should be noted that the organometallic intermediate can be used for further functionalization with an electrophile. Theoretical studies on the carbometallation of such cyclopropene derivatives have been reported in order to rationalize the selectivities and the reactivities of organometallic species in this reaction.[34,35]

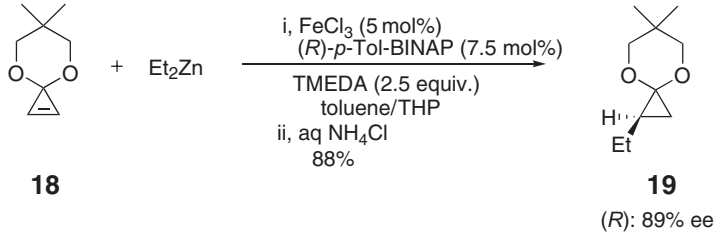
Intermolecular addition of activated methylenes to unsaturated systems has been investigated with silver,[36] silver/gold,[37,38] and palladium catalysts.[39] Thus, C–H addition of 2,4-pentandione to 1,3-cyclohexadiene occurs in THF at 0 °C with 5 mol% of palladium(II) catalyst without base. Josiphos ligand **20** is used as a chirality source to induce



Scheme 3



Scheme 4



Scheme 5

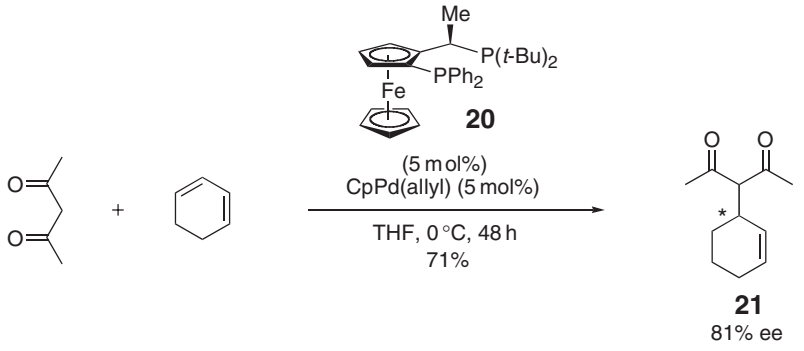
enantioselectivity of the addition (Scheme 6). Cyclohexene derivative **21** is obtained in good yield (71%) and good enantioselectivity (81% ee).

An electron-rich metal can deprotonate the dicarbonyl derivative, affording the hydridopalladium intermediate **23**, which can undergo a π-allyl **24** formation through diene insertion (which can be assimilated to a hydridopalladation of olefin) (Scheme 7). The attack of the enolate to the π-allyl species occurs with good enantioselectivity in the presence of the chiral ligand. The final product **21** is released and the palladium(0) complex **22** is regenerated.

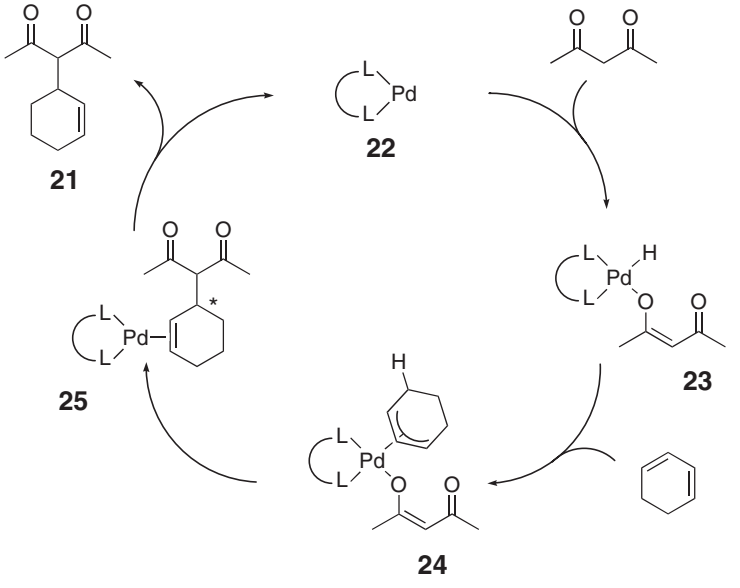
The intramolecular process has been proposed by Widenhoefer with palladium(II) catalysts.[40,41] Cyclization of alkenyl-1,3-dione **26** proceeds efficiently with commercially available palladium species in dioxane at room temperature (Scheme 8). Such mild conditions allow high tolerance vis-à-vis functionalities, and cyclic products are obtained in good yields. Cyclization, tolerated substitution at the terminal methyl group and at the active methylene. This protocol also allows the reaction of internal olefins with (*Z*)- or (*E*)-configuration to occur.

10.07.2.2 Alkynes

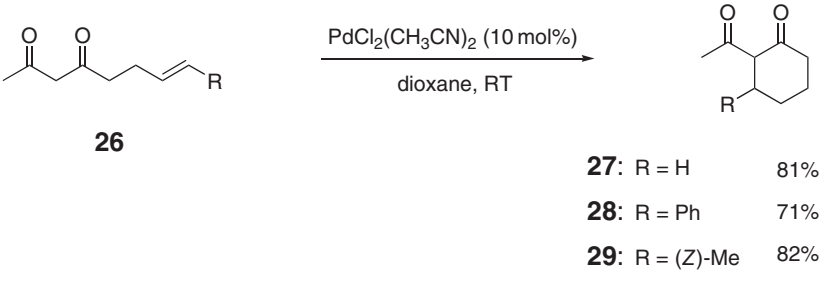
Because of their high reactivity and their low steric demand, alkynes are highly versatile partners. The resulting vinylmetal species are also important reactive entities. Accordingly, the intermolecular carbopalladation of alkynes has attracted the interest of organic chemists for years.[42–45]



Scheme 6



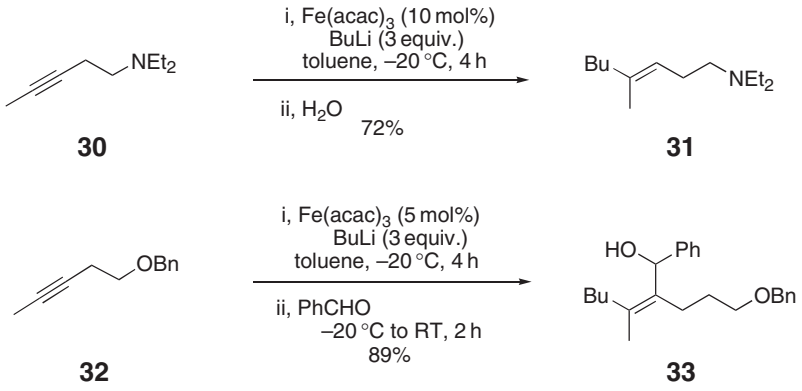
Scheme 7



Scheme 8

In this context, alkynes have been investigated under carbometallation conditions in order to generate tri- or tetrasubstituted alkenes with very good stereochemical control.[46] For the unactivated triple bonds, the major issue is the regioselectivity of the reaction.

Organolithium reagents[47] instead of organoaluminum derivatives[48,49] have been used for the carbometallation of unactivated alkynes under iron catalysis (Scheme 9). Thus, variously substituted alkynes **30** and **32**, bearing a tertiary



Scheme 9

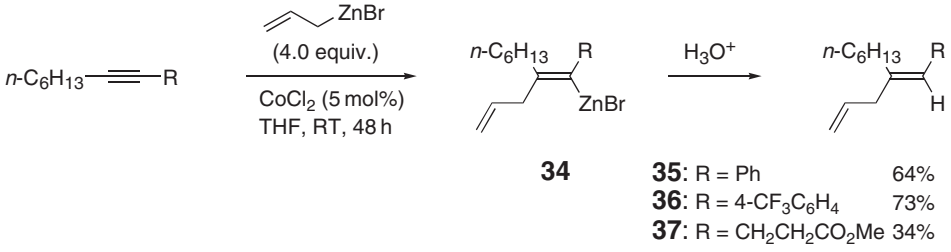
amine or an ethereal function, respectively, were easily converted into the corresponding olefins (**31** and **33**, respectively) in good to excellent yields. Different iron species have been tested in various solvents and $Fe(acac)_3$ gives the best results in toluene, mainly for solubility reasons. It is believed that the reaction involves a vinyllithium species as intermediate. This hypothesis is substantiated by the fact that the quenching of the reaction is possible with electrophiles such as chlorosilane or aldehydes, leading to the tetrasubstituted olefins.

Recently, Oshima has reported a cobalt-catalyzed allylzincation of internal alkyne derivatives (Scheme 10).[50] Optimization of the reaction leads to utilization of cobalt(II) chloride in THF at room temperature. No traces of regio- and stereoisomers are obtained. The resulting alkenylzinc species **34** can be trapped with a large number of electrophiles in order to generate stereoselectively the tri- and tetrasubstituted alkenes **35–37**.

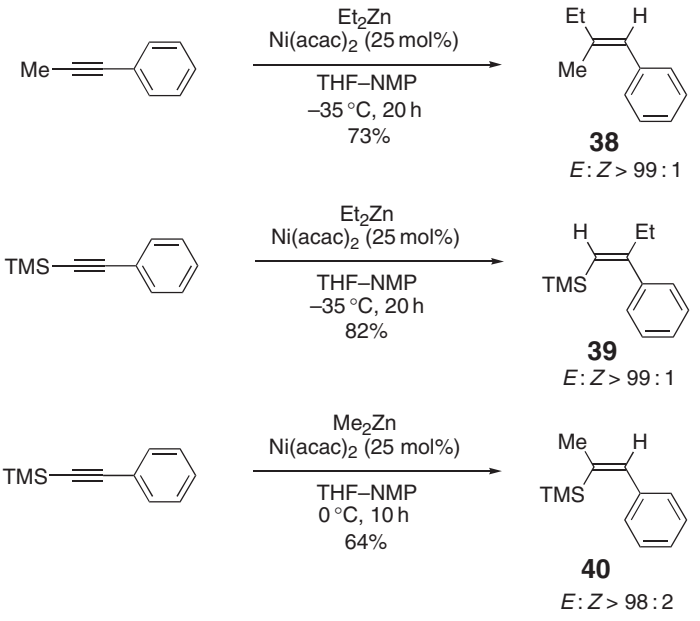
Trost reported the synthesis of 1,4-dienes with ruthenium catalysis through regioselective carbometallation of alkynes with alkenes.[51] Di- and trisubstituted olefins can also be obtained with arylboronic acids through an intermolecular process under rhodium,[30,52–55] nickel,[56] and palladium catalysis.[57] Recently, Larock has reported an efficient palladium-catalyzed route for the preparation of tetrasubstituted olefins.[58,59]

Regio- and stereoselective carbometallation is of special interest from the synthetic point of view. Nickel-catalyzed addition has been reported[60] and some examples with different dialkylzinc and diarylzinc species have been disclosed (Scheme 11).[61] The addition to substituted phenylacetylenes exhibits a *syn*-stereoselectivity (>99%) and a high regioselectivity. When methylphenylacetylene reacts with dimethylzinc, only (*Z*)-isomer **38** is obtained in good yield. Under the same conditions and with the same efficiency and stereoselectivity, the reaction of trimethylsilylphenylacetylene affords the (*Z*)-isomer **39** with diethylzinc and (*E*)-isomer **40** with dimethylzinc. Heteroaromatic acetylene compounds show similar reactivity and regioselectivity. The zinc reagent is transmetallated to $Ni(acac)_2$ and generates an alkylnickel complex coordinated to the triple bond. Carbonickelation takes place to form the alkenylnickel species, which is quenched by various electrophiles to functionalize the C–M bond. The regioselectivity of the carbometallation can be explained by steric and electronic considerations.

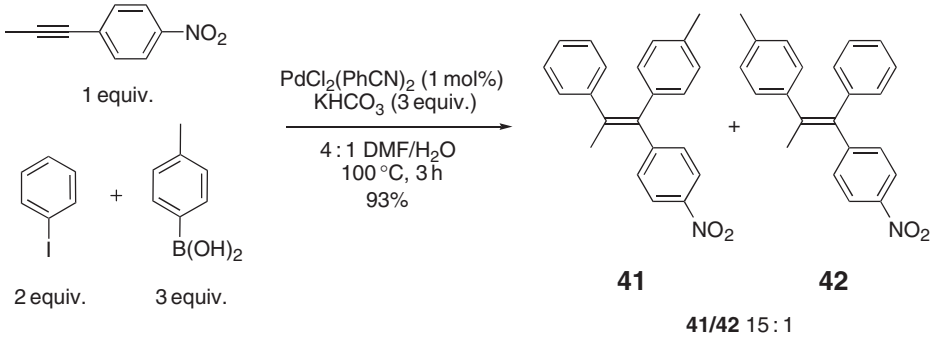
The regioselectivity of palladium-catalyzed additions of organoboronic acids to unsymmetrical alkynes is strongly dependent on steric and electronic effects (Scheme 12).[62] Multi-component reaction has been reported for the synthesis of tetrasubstituted alkenes.[58] The aryl group from an aryl iodide is generally added to the less hindered



Scheme 10



Scheme 11

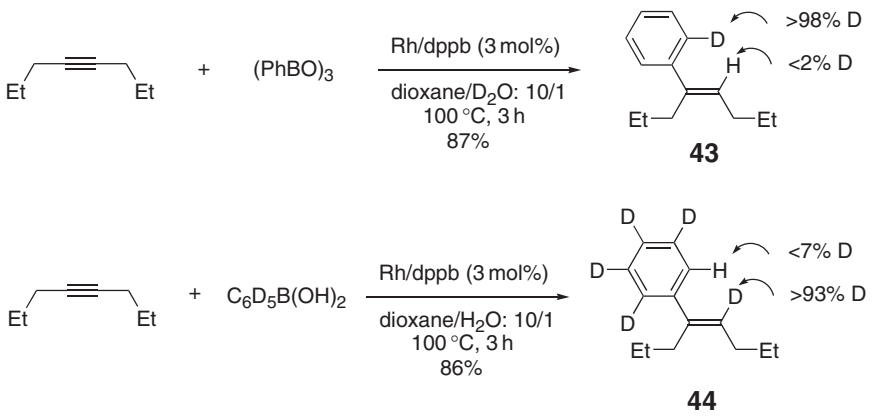


Scheme 12

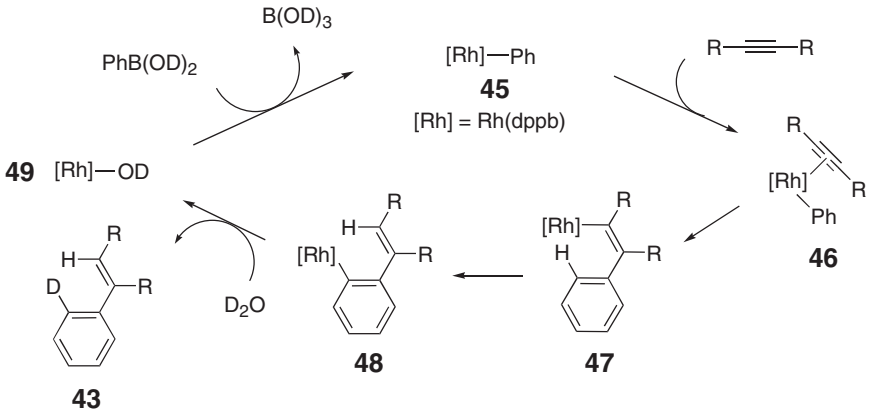
side of the internal alkyne, while the aryl group from an arylboronic acid prefers the opposite side. Electronic effects also play an important role. The aryl group from the boronic acid preferentially adds to the electron-poor end of the alkyne. The two regioisomers **41** and **42** are obtained in 93% yield.

The rhodium-catalyzed arylation of alkynes with arylboronic acids proceeds in aqueous medium to afford the corresponding styrene derivatives in good yield and high regioselectivity.[54] The reaction conducted in deuterium oxide medium yielded a deuteriated compound **43** that was surprisingly labeled on the aryl ring at the *ortho*-position (Scheme 13). On the contrary, the utilization of (D_5)-phenylboronic acid showed a deuterium transfer from the aromatic ring to the vinylic carbon leading to the formation of deuterated vinyl compound **44**. To explain this deuterium incorporation, a mechanism is proposed that involves a 1,4-shift of the rhodium atom from the vinylic carbon to the aryl ring.

The coordination of the alkyne to the rhodium catalyst allows the carborhodation of the triple bond to afford the vinylrhodium intermediate **47** (Scheme 14). The rearrangement of this organometallic compound into the 2-(alkenyl)phenylrhodium intermediate **48** is evidenced by one deuterium incorporation resulting from the deuteriolysis of the Rh–C bond. The addition of the phenylrhodium intermediate **45** must occur before its hydrolysis with water. The 2-(alkenyl)phenylrhodium intermediate **45**, generated by the phenylrhodation of an alkyne followed by



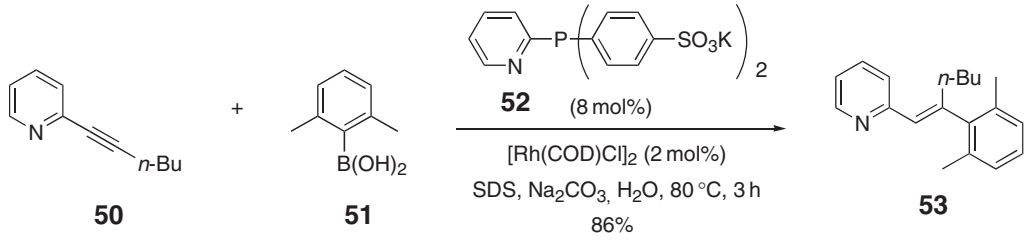
Scheme 13



Scheme 14

1,4-rearrangement, must undergo the hydrolysis rather than an additional insertion of alkyne. After the deuteriolysis, the hydroxyrhodium derivative **49** is liberated and the reaction with phenylboronic acid allows the regeneration of **45**.

The regioselective rhodium- and palladium-catalyzed[63] addition of an arylboronic acid can proceed in aqueous medium using the water-soluble ligand **52** (Scheme 15).[55] The presence of the pyridyl nitrogen atom on the acetylenic partner **50** has a dramatic effect on the regioselectivity of the carbometallation. A single regioisomer **53** is obtained in good yield. Chelation of the arylrhodium species with the triple bond and the nitrogen atom can explain the directed metallation only for the arylalkynes bearing a nitrogen atom at the *ortho*-position. Due to aqueous conditions, the (hydroxo)rhodium(I) complex exists as an active species that can be regenerated after hydrolysis of the sp^2-carbon–rhodium bond. The same directed carbometallation is observed in the reaction of Grignard reagents with alkynyl(2-pyridyl)silanes under a palladium catalysis.[64]



Scheme 15

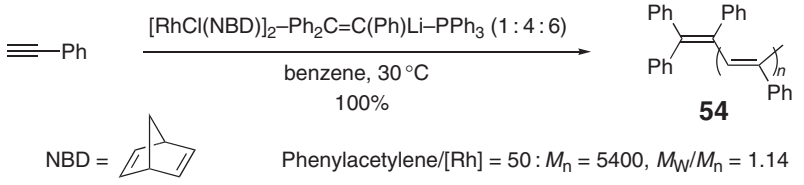
Recently, a rhodium-catalyzed tandem cyclization has been reported with an arylboronic ester bearing a pendant Michael-type acceptor olefin and acetylenic[65] or olefinic[66] derivatives. This transformation proceeds in a water-containing medium as solvent and proton source. This catalyst system is optimized with electron-rich and bulky ligands to stabilize the rhodium intermediate and decrease the protonolysis of boron derivatives in a protic solvent.

In the course of investigation into new C–C bond formation processes, Hiyama has developed an efficient nickel-catalyzed arylcyanation of alkynes.[67] The addition reaction of an aryl–CN bond to alkyne affords aryl-substituted alkene nitrile in good yield. Good regioselectivity is reported in the case of unsymmetrical alkynes with two sterically different substituents.

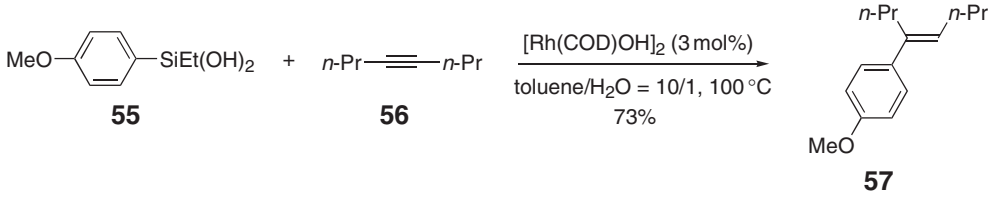
Some transition metal catalysts induce the living polymerization of various acetylenic compounds.[68,69] Such polymerizations of phenylacetylene catalyzed by rhodium complexes are used in conjunction with a quantitative initiation and introduction of functional groups at the initiating chain end (Scheme 16).[70] The catalyst is prepared from an $[RhCl(nbd)]_2/Ph_2C{=}C(Ph)Li/PPh_3$ mixture and proceeds smoothly to give quantitatively the polymer **54** with a low polydispersity ratio.

Silanediols can be used in the carbometallation of alkynes with a rhodium catalyst.[71] The reaction takes place in toluene and water mixture efficiently, while yields are lower in the absence of water (Scheme 17). The symmetrical alkynes with alkyl or aryl substituents undergo clean transformation. Under these conditions, the phenylacetylene carbometallation results in polymerization, and the disubstituted alkynes with electron-withdrawing groups such as methyl phenyl propiolate afford a complex mixture of undefined products. Alkenyl silanediols can be used for this reaction, and the corresponding dienes are obtained in good yields. No regioselectivity is reported concerning the unsymmetrical alkynes. Under the same conditions, an aryltributyltin does not react with 4-octyne.[72] This suggests that the hydroxy group of the silanediol plays an important role in the reaction, especially in protonation process. In fact, the addition of a proton source like triethyl silanol or diisopropyl silanediol to the reaction system yields the alkene product in 48% yield. The best result was obtained with the addition of 1 equiv. of phenol to give the alkene product in 72% yield.

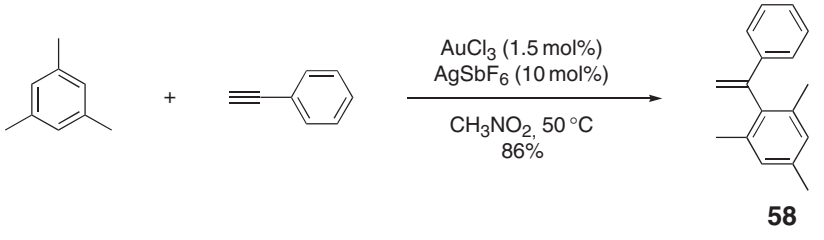
Gold catalysts are employed in the arylation of aryl-substituted terminal alkynes (Scheme 18).[73] Two different mechanisms are postulated. The first step can be the auration of the arene by gold(III) chloride, generating an arylgold



Scheme 16



Scheme 17



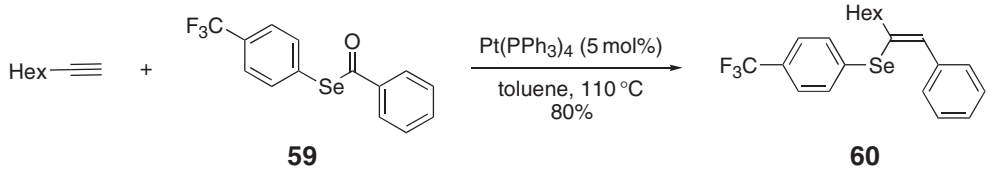
Scheme 18

intermediate.[74–77] But the reaction can also occur through a simple electrophilic activation of triple bond with metal (see Section 10.07.4.1 for more gold chemistry[78]).

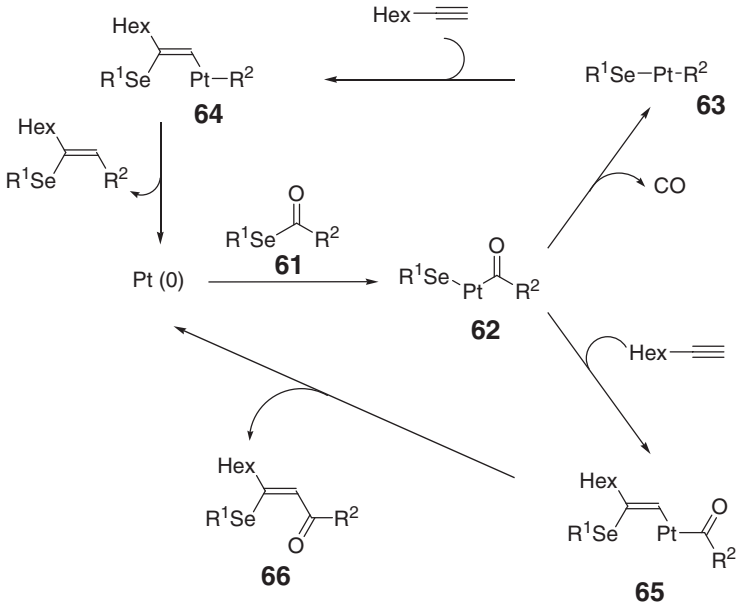
The palladium-catalyzed C–Se bond formation[79–81] and the platinum-catalyzed carboselenation of alkynes with selenoesters[82] have been reported in analogy with the thiolate chemistry.[83,84] An electron-withdrawing or electron-donating group on the aromatic residue leads to the formation of the desired carboselenation product with acceptable yields. Functionalities like benzyl, hydroxyl, or nitrile group are tolerant with the reaction conditions. This method provides a new access to the functionalized vinylselenide **60**,[82] molecules of interest as key intermediate (Scheme 19).[85]

The arylselenation is also reported under CO atmosphere during the carboselenation reaction.[82] A mechanism is proposed to explain the platinum catalysis (Scheme 20). The oxidative addition of platinum(0) into the Se–C bond of **61** affords the platinum(II) complex **62**, which can evolve through two different pathways. The decarbonylative pathway affords the R^1Se–Pt–R^2 complex **63** that can undergo insertion of the alkyne to form the corresponding vinylplatinum **64** with high stereo- and regioselectivity. The reductive elimination forms the C–C bond and regenerates the platinum(0) complex for another catalytic cycle. If the insertion of the alkyne into the Se–Pt bond takes place prior to decarbonylation, the resulting vinylacylplatinum **65** affords the α,β-unsaturated carbonyl compound **66** after reductive elimination.

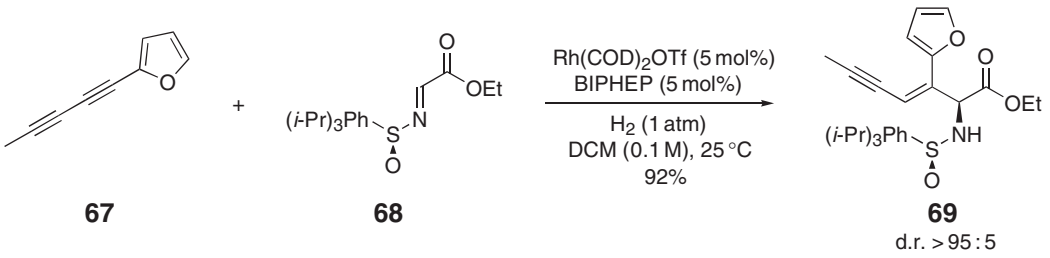
The hydrogen-mediated reductive coupling of conjugated alkynes with (*N*-sulfinyl)iminoacetate derivatives has been reported with regard to unnatural α-amino acid synthesis.[86] The same type of reaction has been applied to 1,3-diynes and carbonyl compounds to afford the corresponding allylic alcohol derivatives.[87] The 1,3-diyne **67** reacts with the electrophilic imine **68** and a rhodium catalyst under hydrogen to afford the α-amino acid ester **69** in high yield as a single regio- and stereoisomer (Scheme 21). No over-reduction has been observed. Sulfur substituents have an



Scheme 19



Scheme 20



Scheme 21

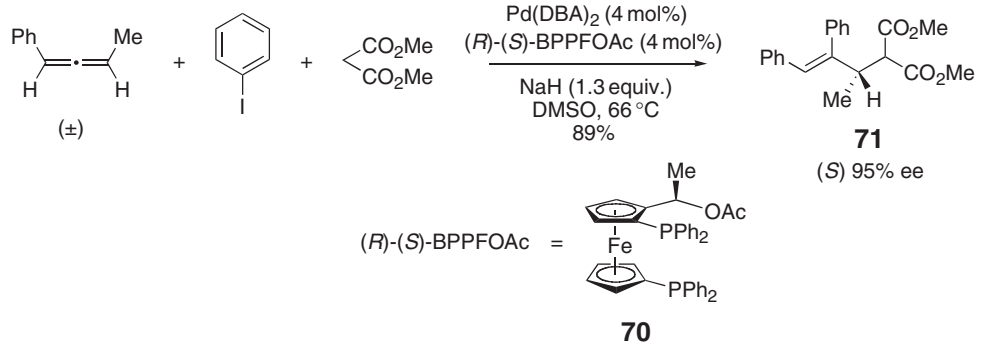
important role for reactivity and stereoselectivity. For example, a *tert*-butyl substituent inhibits the reaction, but 2,4,6-triisopropylphenyl group allows the transformation to occur, giving the product in 80–95% yield. An isotopic labeling experiment corroborates the catalytic mechanism involving an oxidative addition of the alkyne and the imine moieties followed by the hydrogenolysis of the thus-formed carborhodacycle intermediate.

10.07.2.3 Allenes

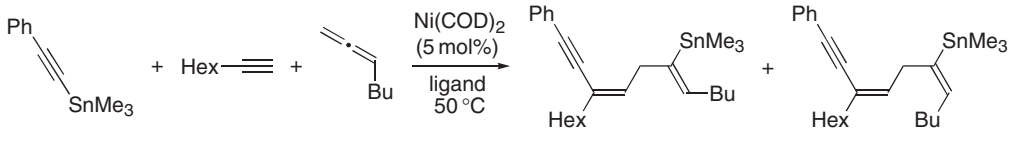
The carbopalladation of allenes has been investigated in an enantioselective manner with some chiral phosphine ligands.[88] Optimization of the ligand structure has been carried out. On the other hand, enantiopure allenes have also been studied with achiral ligand to demonstrate the complete enantiospecificity of this sequence. The Ph–Pd–I intermediate, generated from the phenyl iodide and a palladium(0) complex, reacts via carbopalladation of the allene to provide a π-allylpalladium complex (Scheme 22). The nucleophilic substitution with a malonate anion affords the corresponding functionalized olefin **71** in good yield (89%) and excellent enantioselectivity (95% ee). There is no kinetic resolution during the reaction because the starting allene was recovered as a racemic mixture. Phosphine ligands such as **70** promote the nucleophilic allylic substitution with high enantioselectivity through a sterically favorable π-allylpalladium intermediate bearing the chiral ligand.

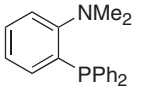
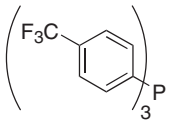
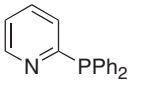
Vinyl- or arylboronic acids also react with allenes, affording 1,3-dienes or styrene derivatives, respectively.[89] This palladium-catalyzed addition proceeds with good regioselectivity and high stereoselectivity in favor of the formation of (*E*)-trisubstituted isomer.

The syntheses of functionalized alkenes by a transition metal-catalyzed carbostannylation of alkynes and dienes have shown high efficiency.[90] Tandem carbometallations of alkynes and allenes with alkynylstannanes are reported to involve sequential insertions of two C–C unsaturated bonds into an Sn–C bond (Scheme 23).[91] The phosphine ligands play an important role in this transformation to control the stereoselectivity. The use of [2-(dimethylamino)-phenyl]diphenylphosphane (pn) **74** affords the (*Z*)-isomer **72**, while the use of tris[*p*-(trifluoromethyl)phenyl]phosphane (ttpp) **75** and 2-(diphenylphosphanyl)pyridine (dpp) **76** leads to the formation of the (*E*)-isomer **73**. In each case, stereoselectivity is high. Moderate to good yields are observed depending mainly on the nature of alkynes and tin substitution.



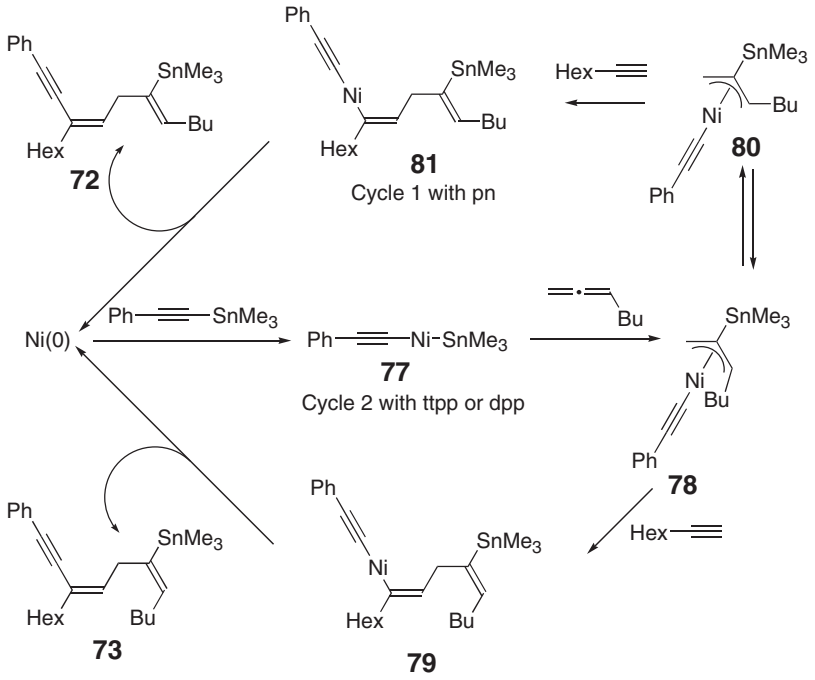
Scheme 22



Ligand		*Condition*	*Yield* (%)	**72 : 73**
	**74**	A : pn 5 mol% in BuO_2	56	98 : 2
	**75**	B : ttpp 10 mol% in toluene	73	4 : 96
	**76**	C : dpp 5 mol% in THF	55	1 : >99

Scheme 23

Two catalytic cycles are proposed to explain the difference in selectivity. In both cases, catalytic cycle is initiated by the oxidative addition of an alkynylstannane to nickel(0) species, leading to the formation of alkynylnickel(II) complex **77** (Scheme 24).[92] Then, an allene is inserted into the nickel(II) complex in a manner which avoids steric repulsion with the butyl group to afford the *anti*-π-allyl complex **80**. The carbometallation of the terminal alkyne can take place at the non-substituted allylic carbon of the corresponding *syn*-π-allyl complex **78**. The stereoselectivity is determined by the relative rate of the two possible insertion modes which depend on the ligand used. A bidentate

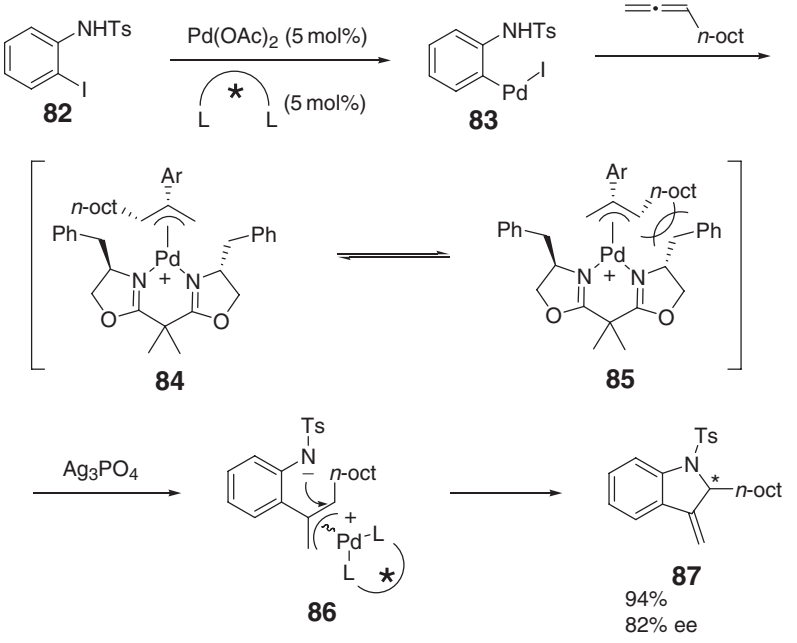


Scheme 24

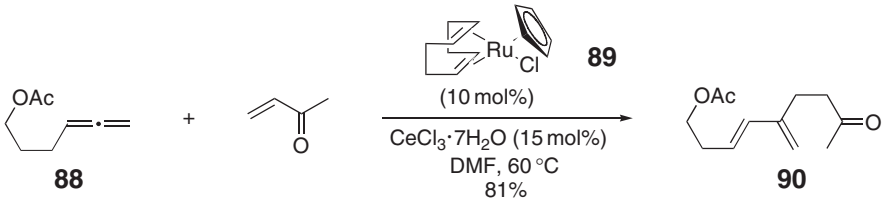
coordination with the nitrogen atom of the ligands **74** and **76** as well as the steric interaction generated by dimethylamino group is crucial to invert the stereoselectivity. Both catalytic cycles are completed by reductive elimination of vinylnickel intermediates **79** and **81**, affording the corresponding dienyne compounds and regenerating nickel(0) catalyst. The same type of transformation has been applied to the synthesis of trisubstituted vinylstannanes.[93]

The enantioselective palladium-catalyzed heteroannulation of allenes has been reported for the synthesis of heteroaromatic compounds.[94] The oxidative addition of palladium(0) to *o*-iodotosylaniline **82** affords the arylpalladium(II) intermediate **83** (Scheme 25). Then, the carbopalladation of an allenyl derivative generates π-allylpalladium complexes **84** and **85** in equilibrium. The interconversion occurs rapidly in terminal π-allylpalladium complexes leading to enantiodiscrimination in the subsequent step. Steric interaction between the benzyl group of the ligand and the terminal alkyl group generates preferences for one diastereoisomer. Intramolecular nucleophilic substitution on the π-allylpalladium **86** under basic conditions allows the ring closure to occur, leading to the formation of the bicyclic compound **87** in high yield and good enantioselectivity. The asymmetric induction is optimum in the presence of a silver salt in DMF due to the precipitation of AgI, resulting in the formation of a palladium–bisoxazoline complex without any nucleophile, which provides time for interconversion.

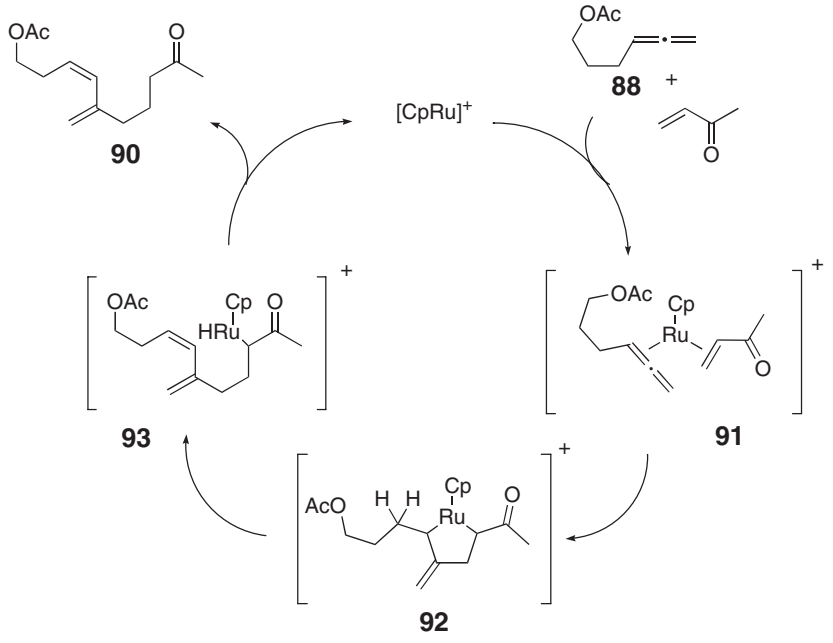
1,3-Dienes such as **90** can be accessed by a multi-component reaction under ruthenium catalysis involving an allene **88** and an enone (methyl vinyl ketone in this case), with cerium(III) chloride as an additive in DMF (Scheme 26).[95,96] With an allene concentration of 0.25 M, yields are moderate to good. Different ruthenium catalysts and additives were tested in order to optimize this reaction. CpRu(COD)Cl **89** and $CpRu(MeCN)_3PF_6$ appeared to be more versatile ones. The mono-, di-, tri-, and tetrasubstituted allenes have been investigated with methyl vinyl



Scheme 25



Scheme 26



Scheme 27

ketone as a partner. Other substituted olefins did not give an efficient reaction, leading to the formation of a complex mixture or no reaction.

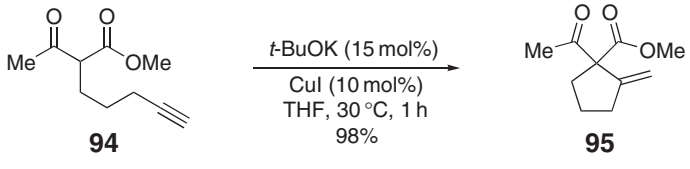
When polysubstituted allenes are used, the regioselectivity is determined by steric and electronic factors induced by the functionalities. 1,3-Dienes bearing different functional groups are used in Diels–Alder reactions, opening a rapid access to structurally complex molecules. The postulated mechanism involves a chelation of ruthenium to both the allene and the alkene molecules, leading to the formation of a ruthenacyclopentane **92** (Scheme 27). β-Hydrogen elimination triggers ring opening to generate the alkylruthenium intermediate **93**. The reductive elimination affords the 1,3-diene **90** and regenerates the catalyst.

Carbometallation of allenes with alkenylruthenium complexes has been reported in a stoichiometric process for the preparation of 2-alkenylallylruthenium complexes.[97] Such types of organometallic species have not been well explored, and could give rise to new applications in transition metal catalysis.

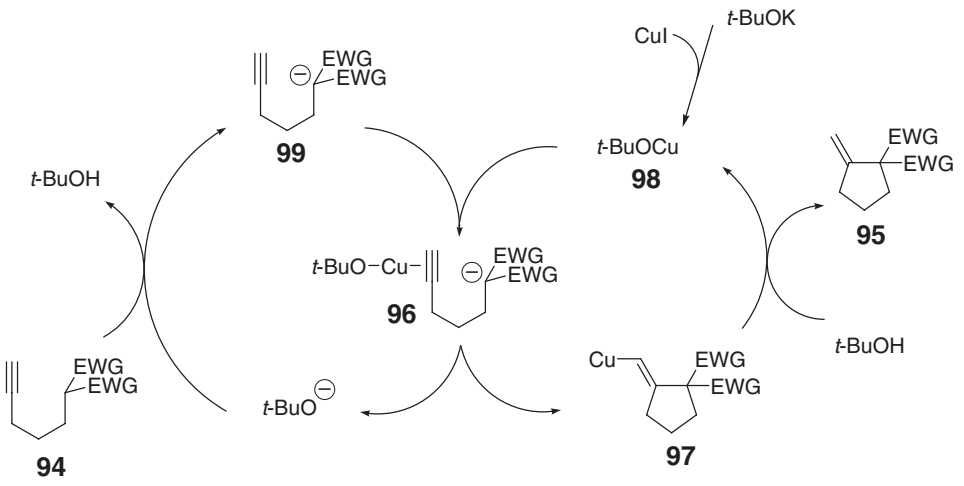
10.07.2.4 Conia-ene

The Conia-ene reaction is a thermal cyclization of an alkyl ketone with an alkyne to give the corresponding α-vinylated ketone.[98] The catalytic version of this reaction has been reported to generalize the process to more functionalized substrates.[99] The intramolecular carbocupration of alkyne **94** has been investigated under basic conditions in the presence of a catalytic amount of copper iodide (Scheme 28).[100] The cyclic product **95** is obtained in high yield.

Potassium *tert*-butoxide reacts with copper iodide to generate a copper *tert*-butoxide species **98** (Scheme 29). Activation of the alkyne **94** by this copper catalyst (intermediate **96**) allows the enolate attack to afford the cyclic



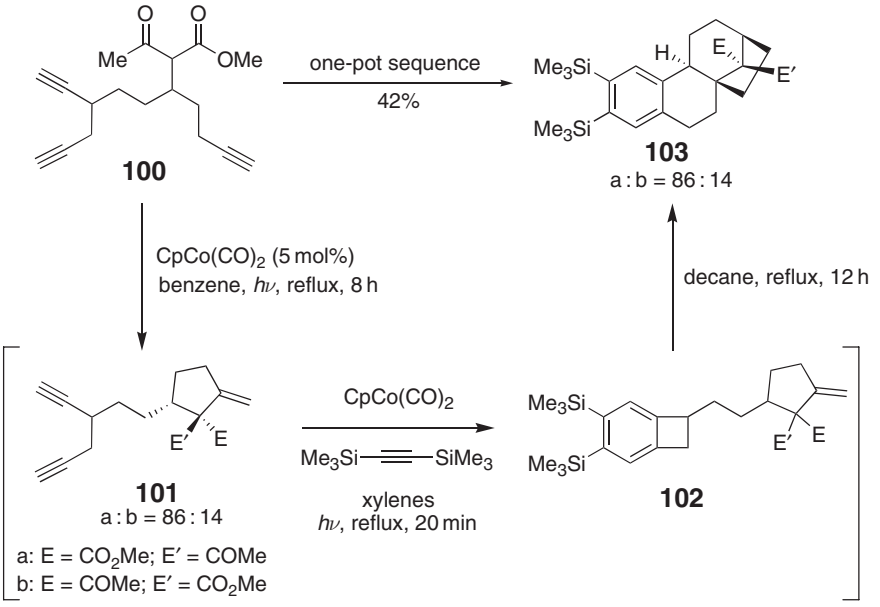
Scheme 28



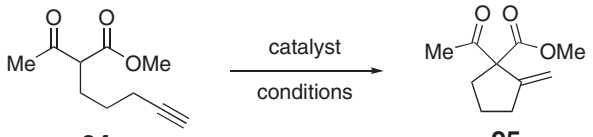
Scheme 29

vinylcopper **97**. Protonation by *tert*-butanol leads to the formation of the desired compound **95** and regeneration of the base and the copper catalyst. This catalytic process can be applied to disubstituted alkynes. However, the same reaction needs a stoichiometric amount of copper and base to afford the trisubstituted cyclic olefin in very good yields.

Other experimental conditions have been examined to avoid the use of strongly basic conditions (Scheme 30). The cobalt-catalyzed cyclization of stabilized ε-acetylenic carbanions has been studied and applied to cascade reactions in total synthesis.[101–104] This cascade process involves a Conia-ene, a [2 + 2 + 2]-, and a [4 + 2]-reaction, starting from the acyclic triyne **100** to afford the polycyclic compound **103** in good yield (42%) as a mixture of two diasteroisomers (86 : 14). Six sequential C–C bond formations are achieved in the same pot with a total regio- and stereoselectivity and good diastereoselectivity. Cobalt-catalyzed Conia-ene reaction is conducted in benzene under irradiation. The [2 + 2 + 2]-cycloaddition between the resulting cyclopentane derivative **101** and bistrimethylsilylacetylene (BTMSA) affords the corresponding benzocyclobutane **102**. The reaction mixture is then heated in refluxing decane



Scheme 30



94 **95**

Entry	*Catalyst*	*Conditions*	*Yield* (%)	*References*
1	20 mol% $Ni(PPh_3)_4$, 50 mol% $Yb(OTf)_3$	Dioxane, 50 °C,15 h	0	105
2	10 mol% $Ni(acac)_2$, 20 mol% $Yb(OTf)_3$	Dioxane, 50 °C,12 h	83	106
3	10 mol% AgOTf	DCE, RT, 18 h	50	106
4	10 mol% AgOTf, 10 mol% PPh_3	DCE, RT, 18 h	0	106
5	10 mol% $AuCl_3$	DCE, RT, 30 min	30	106
6	10 mol% $AuCl(PPh_3)$	DCE, RT, 60 °C, 6 h	0	106
7	10 mol% $AuOTf(PPh_3)$	DCE, RT, 15 min	95	106
8	1 mol% $[(PPh_3Au)_3O]BF_4$, 5 mol% TfOH	DCE, RT, 15 min	95	106

Scheme 31

to yield two diastereoisomers of the tetracyclic compound **103**. The proposed mechanism for the cobalt-catalyzed Conia-ene reaction involves the formation of a cobaltacyclopentene intermediate arising from the alkyne and an enol form of 1,3-dicarbonyl moiety. This type of mechanism is discussed further in Section 10.07.4.1.

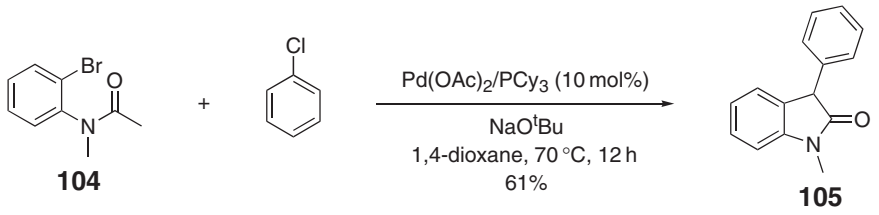
More recently, nickel,[105] silver,[106] and gold[106] catalysts have been investigated for Conia-ene reactions (Scheme 31). Under nickel catalysis conditions, Yang described the ineffectiveness of tetrakis(triphenylphosphine)-nickel(0) in dioxane with ytterbium(III) triflate as a co-catalyst even at 50 °C (entry 1). In contrast, the $Ni(acac)_2$/$Yb(OTf)_3$ system catalyzes the cyclization of the keto ester **94** to the cyclic product **95** in good yield (entry 2). Toste has shown that silver(I) triflate catalyzes the cyclization of the keto ester **94** in average yield (entry 3), while an addition of triphenylphosphine completely inhibits the reaction (entry 4). Gold(III) chloride quickly converts the starting material **94**, but only a small amount of the desired cyclic compound **95** is isolated (entry 5). Neutral gold(I) complex is inactive (entry 6), but cationic gold(I) complex promotes the rapid and efficient formation of the desired adduct **95** in very high yield (entry 7). The *in situ* protonation of $[(PPh_3Au)_3O]BF_4$ with triflic acid generates a cationic gold complex, which is very active for the cyclization reaction. The mechanism of this transformation seems to be highly metal dependent, and a number of mechanistic hypotheses have been proposed to explain the observed regio- and stereoselectivity.

10.07.2.5 Arylation of Carbonyl Compounds

The α-arylation of carbonyl compounds (sometimes in enantioselective version) such as ketones,[107–113] amides,[114,115] lactones,[116] azlactones,[117] malonates,[118] piperidinones,[119,120] cyanoesters,[121,122] nitriles,[123,124] sulfones,[125] trimethylsilyl enolates,[126] nitroalkanes,[127,128] esters,[129,130] amino acids,[131] or acids[132] has been reported using palladium catalysis. The asymmetric vinylation of ketone enolates has been developed with palladium complexes bearing electron-rich chiral monodentate ligands.[133]

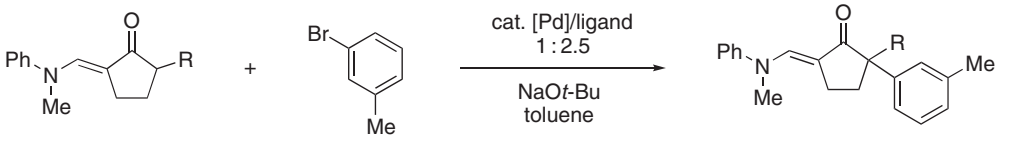
Hartwig has reported an intramolecular/intermolecular process affording the 3-aryloxindoles **105** (Scheme 32).[115] The intermolecular arylation of acetanilide derivative **104** is slower than the intramolecular arylation to form the oxindole. Thus, the overall transformation starts with cyclization followed by intermolecular arylation of indole. In order to slow down the intermolecular process and speed up the intramolecular reaction, chloroarene and bromine-substituted acetanilide precursors are used according to their respective reactivity with palladium(0) in the oxidative addition process.

The asymmetric arylation of ketone enolates represents an attractive method for the preparation of optically active carbonyl compounds with a stereogenic quaternary center at the α-position to the carbonyl group. Such types of compounds are important intermediates for natural product synthesis. Replacement of BINAP by **109** provides

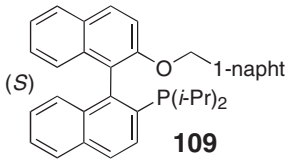


104 105

Scheme 32



106 107 108

Ligand	*R = Me*	*R = n-Pr*	*R = n-Pent*
(*S*)-BINAP	$Pd_2(DBA)_3$ (2.5 mol%) 100 °C 70% 80% ee (*S*)	$Pd_2(DBA)_3$ (2.5 mol%) 100 °C 74% 91% ee (*S*)	$Pd(OAc)_2$ (10 mol%) 100 °C 75% 93% ee (*S*)
 **109**	$Pd_2(DBA)_3$ (2 mol%) RT 85% 94% ee (*R*)	$Pd_2(DBA)_3$ (2 mol%) RT 85% 88% ee (*R*)	$Pd_2(DBA)_3$ (2 mol%) RT 86% 91% ee (*R*)

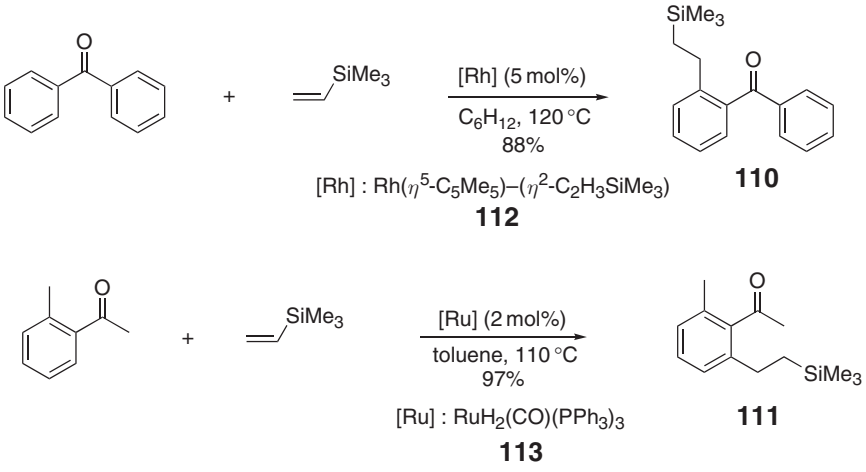
Scheme 33

significant improvement in the catalytic system (Scheme 33).[134] The reactions can proceed at room temperature with lower catalyst loadings. α-Arylation of enamino ketone **106** with *m*-bromotoluene **107** gives the desired compound **108** in high yield and high enantioselectivity. The size of the substituent has a critical effect on the enantioselectivity using (*S*)-BINAP as ligand. Thus, the largest substituent gives the highest enantiomeric excess. Enantioselectivity up to 80% ee and yield up to 70% are obtained. The monodentate ligand **109** and steric factors do not affect enantioselectivity, and even the methyl-substituted compound **106** (R = Me) gives high enantioselectivity (95% ee) under milder conditions.

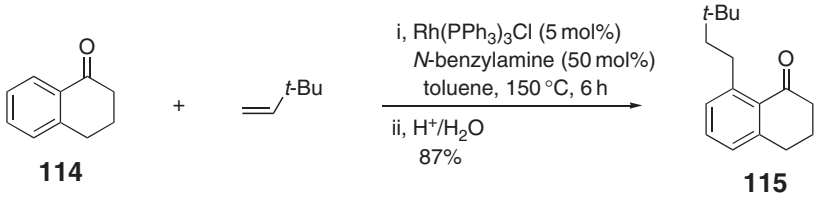
The ruthenium-, rhodium-, and palladium-catalyzed C–C bond formations involving C–H activation have been reviewed from the reaction types and mechanistic point of view.[135–138] The activation of aromatic carbonyl compounds by transition metal catalyst undergoes *ortho*-alkylation through the carbometallation of unsaturated partner. This method offers an elegant way to activate C–H bond as a nucleophilic partner. The rhodium catalyst **112** has been used for the alkylation of benzophenone by vinyltrimethylsilane, affording the monoalkylated product **110** in 88% yield (Scheme 34).[139] The formation of the dialkylated product is also observed in some cases. The ruthenium catalyst **113** has shown efficiency for such alkylation reactions, and *o*-methylacetophenone is transformed to the *ortho*-disubstituted acetophenone **111** in 97% yield without over-alkylation at the methyl substituent.

The postulated mechanism involves a directing effect of the carbonyl group to the metal center, ideally positioning this metal for insertion into the *ortho*-C–H bond. The resulting ruthenium hydride undergoes hydridometallation of the olefin followed by reductive elimination to give the new C–C bond.

A ketimine can also be alkylated by the same process.[140] *In situ* generation of a ketimine from the aromatic ketone **114** and benzylamine provides an efficient catalytic process with Wilkinson catalyst (Scheme 35). The alkylated aromatic ketone **115** is obtained in good yield. Better reactivity and selectivity are obtained with ketimine



Scheme 34



Scheme 35

intermediates than with ketones. The deuterium-labeling experiment for mechanistic studies has confirmed high selectivity for *ortho*-alkylation.

Intramolecular process with rhodium catalyst has been described for the syntheses of indane, dihydroindoles, dihydrofurans, tetralins, and other polycyclic compounds.[141] Wilkinson catalyst is efficient for the cyclization of aromatic ketimines and aldimines containing alkenyl groups tethered to the *meta*-position of the imine-directing group.

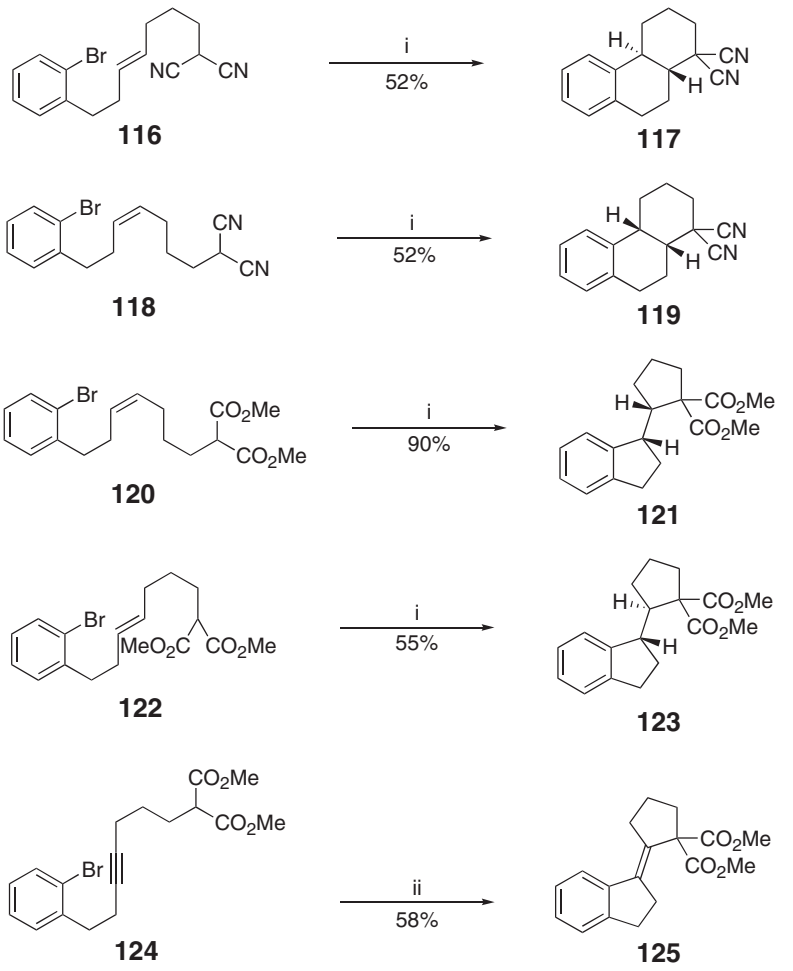
Cyclization process of arene–yne substrates has been reported with platinum(IV) catalyst ($PtCl_4$), resulting in C–H activation and functionalization.[142] This hydroarylation gives 6-*endo*-products in high yields with good tolerance to different functional groups like amine, ester, and ether. This method provides a rapid access to interesting molecules such as coumarins, chromenes, or dihydroquinolines.

10.07.2.6 Intramolecular Carbopalladation

Palladium-catalyzed cyclization of alkenes and alkynes were reported by Balme and co-workers.[143,144] Intramolecular carbopalladation occurs to give polycyclic compounds. It has been shown that the nucleophile type has a large influence on the cyclization process. Both 5-*exo*- and 6-*endo*-cyclization are observed for substrates with nitrile (**116** and **118**) and ester (**120**, **122**, and **124**) substituents, respectively (Scheme 36). When a mixed nucleophile (CN and CO_2Me) is used, a mixture of 5-*exo* and 6-*endo* products is obtained. The chemoselectivity is controlled by the size of the nucleophile used. The stereochemistry of the initial double bond plays an important role on the stereoselectivity of the cyclization. (*Z*)-olefins (**118** and **120**) and (*E*)-olefins (**116** and **124**) afford *cis*- (**119** and **121**) and *trans*-cyclization products (**117** and **123**), respectively.

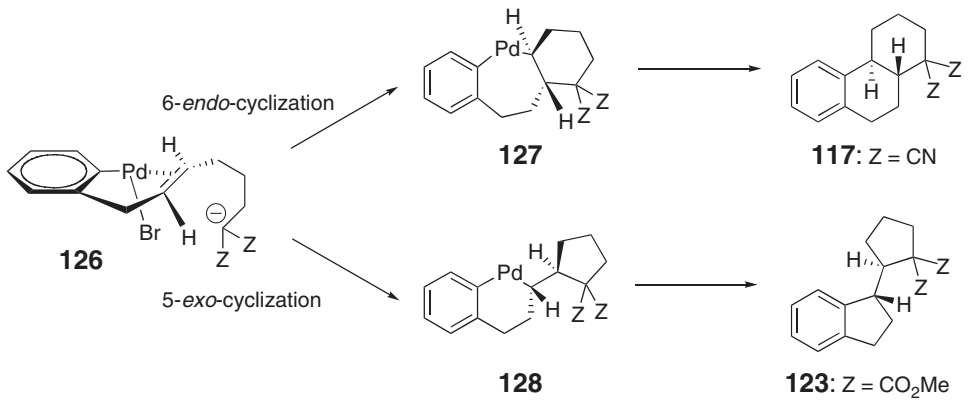
The cyclization of acetylenic homolog **124** leads to the selective formation of cyclopentylideneindane **125**, and in this case, the nucleophile size does not affect the reaction.

The oxidative addition of palladium(0) to aryl bromide generates the arylpalladium(II) intermediate **126** (Scheme 37). The electrophilic activation of the double bond by palladium facilitates the nucleophilic attack, resulting in cyclization.

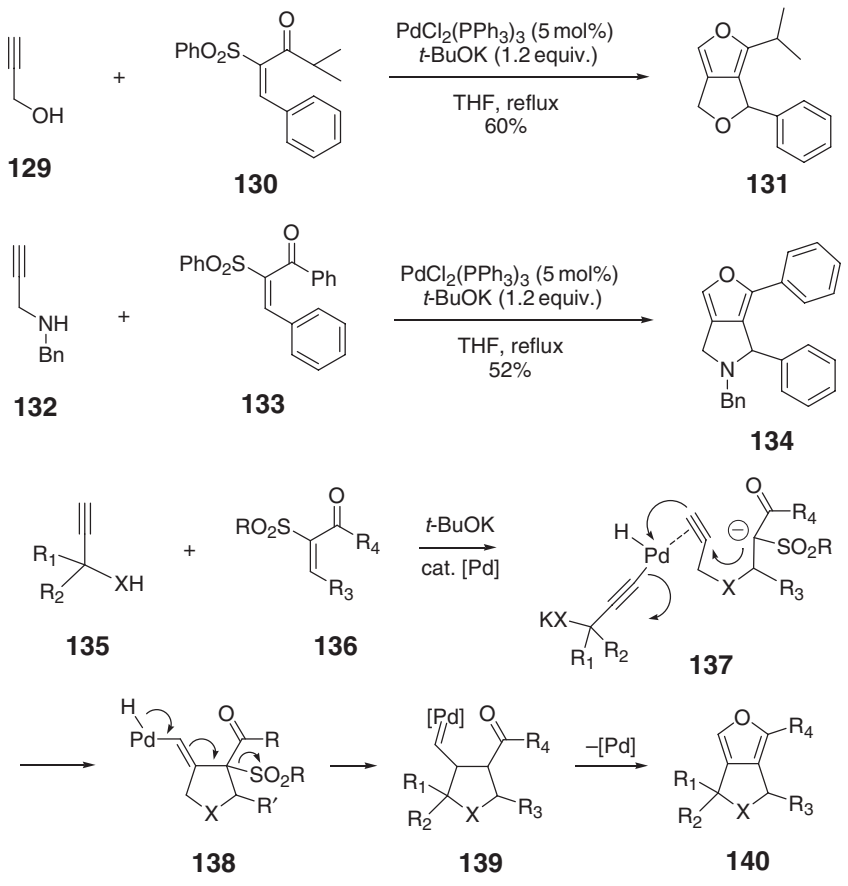


i, $Pd(OAc)_2$ (5 mol%), dppe (10 mol%), 1-heptene (10 mol%), 18-C-6 (20 mol%), *t*-BuOK, NMP, 50 °C; ii, $Pd(OAc)_2$ (5 mol%), dppe (10 mol%), 1-heptene (10 mol%), 18-C-6 (20 mol%), *t*-BuOK, DMSO, 90 °C.

Scheme 36



Scheme 37



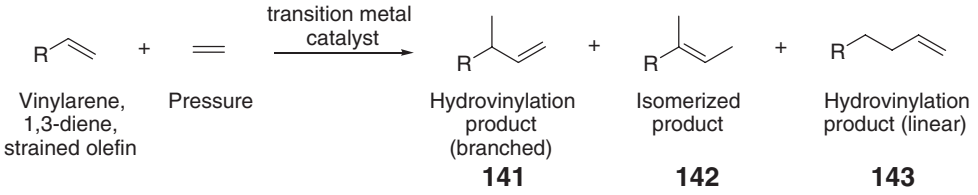
Scheme 38

The two different cyclization modes are in competition, depending on the bulkiness of the nucleophile. 6-*endo*-Cyclization gives the seven-membered ring palladacycle **127**, while the 5-*exo*-cyclization affords the six-membered ring palladacycle **128**. The evolution through reductive elimination yields the two tricyclic compounds **127** and **128** as a single stereoisomer. This stereoselectivity is explained by the concomitant stereocontrol of the two newly formed adjacent carbon centers, since the nucleophile and the organopalladium moieties react in an *anti*-fashion across the unsaturated linkage.

An elegant synthesis of furo[3,4-*c*]-heterocyclic (furans and pyrroles) compounds has been reported by Balme (Scheme 38).[145] The overall reaction is an intriguing interplay of inter- and intramolecular events. After a Michael addition involving an alkoxide or an amide, the resulting anion cyclizes in a 5-*exo*-*dig*-fashion, which is attributed to a palladium complexation of the triple bond. The palladium species involved is a σ-alkynyl–hydride species generated through insertion of the metal into the C–H bond of the terminal acetylene **135**, which reacts with the Michael addition product to form the intermediate **137**. The cyclization of this intermediate **137** gives the vinylpalladium–hydride intermediate **138**. Then, the abstraction of hydrogen from **138** by base triggers the formation of a palladium carbene species **139** through the loss of a sulfinate anion, which undergoes cyclization with the carbonyl moiety to give the fused bicyclic furan **140**. Thus, the anions of propargyl alcohol **129** and benzylpropargylamine **132** also trigger the bicyclization process, involving α,β-unsaturated ketosulfones as Michael acceptor to afford interesting heterobicyclic compounds **131** and **134**.

10.07.2.7 Hydrovinylation

The transition metal-catalyzed hydrovinylation has been reviewed by RajanBabu who focused mainly on asymmetric reactions, affording chiral compounds.[146] The vinylarenes are the most investigated substrates for the hydrovinylation reaction due to the high appeal of the final products in medicinal or polymer chemistry fields.[147]



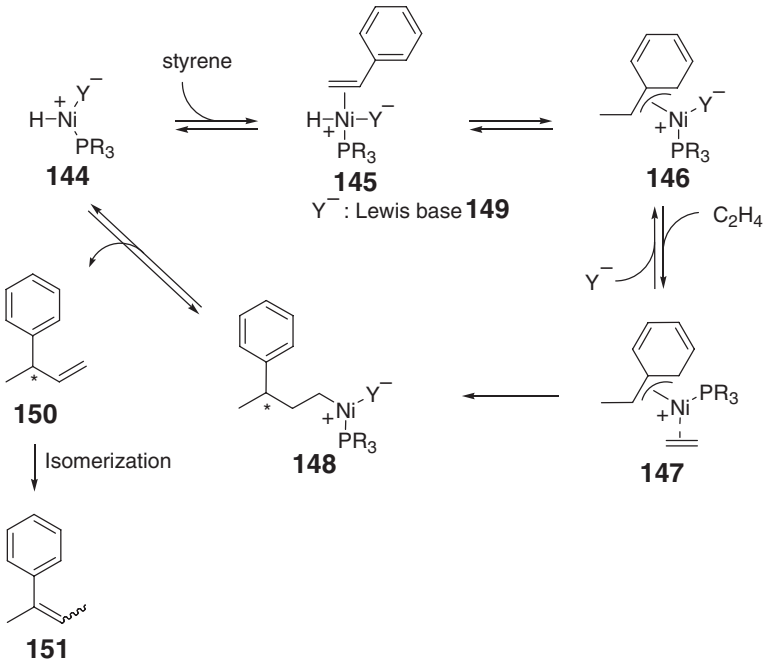
Scheme 39

The palladium-catalyzed hydrovinylation does not seem to be very useful due to the regioselectivity in favor of the linear compound **143** and the formation of a substantial amount of isomerized product **142** (Scheme 39).[148,149] Phosphines of basic nature can improve the selective formation of the desired branched product **141** by limiting the isomerization under the experimental conditions.[150]

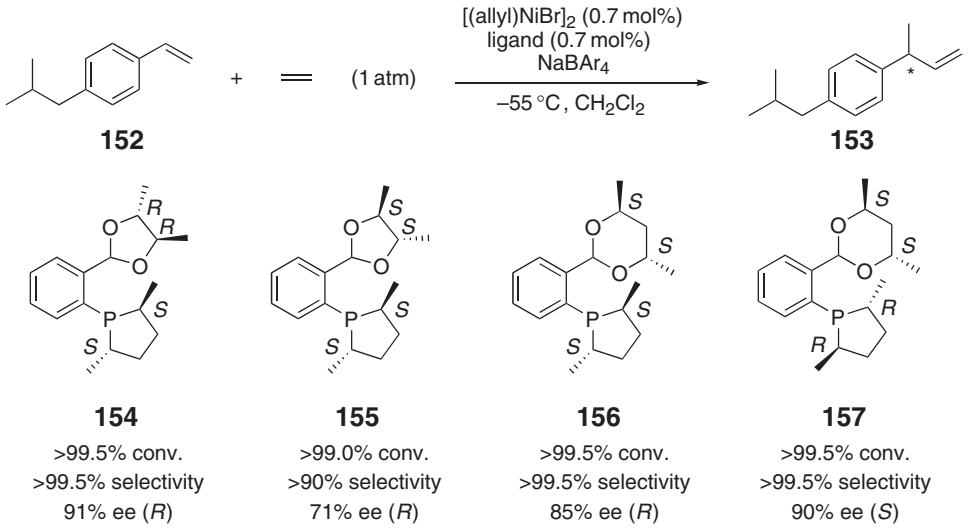
The palladium-catalyzed asymmetric hydrovinylation does not seem to be very attractive for the reasons mentioned above, but some nice examples have been reported using a chiral menthylphosphinite[151] as ligand where the importance of counterion is also mentioned. More recently, monodentate chiral *spiro*-phosphoramidite and phosphite ligands have been used under mild conditions in asymmetric hydrovinylation.[152] Dicationic palladium(II) and platinum(II) complexes have been investigated for the catalytic coupling of ethylene and substituted olefins.[153] This reaction gives either hydrovinylation or cyclopropanation product depending on the ligand and the metal used. DFT calculations and NMR studies have been performed to explain the enantioselectivity of asymmetric hydrovinylation catalyzed by phosphoramidite/nickel complexes.[154]

Only few examples of ruthenium-catalyzed hydrovinylation have been reported from the 1970s.[155,156] More recently, a ruthenium–hydride complex has been used as an efficient catalyst for the hydrovinylation of functionally and structurally different alkenes.[157,158] The catalyst is generated *in situ* from $(PCy_3)_2(CO)RuHCl$ and $HBF_4{\cdot}OEt_2$. Vinylarenes, dienes, and internal alkenes were found to give the hydrovinylation products in good yields. Isomerization was observed in the case of phenyl-substituted internal alkenes due to the requirement of higher reaction temperatures.

The proposed mechanism of the hydrovinylation is supported by available evidences, but so far no study has established clearly all the reaction intermediates. RajanBabu has proposed a mechanism of nickel-catalyzed hydrovinylation, which seems to be one of the most efficient processes, involving a cationic nickel hydride species **144** complexed with a weakly coordinated counterion (Scheme 40). The active catalyst species can be generated through



Scheme 40



Scheme 41

the first ethylene insertion into the Ni pre-catalyst and the subsequent β-hydride elimination. Insertion of the styrene into the Ni–H bond affords the benzylic complex **146** stabilized by η^3-coordination. The substitution of the Lewis base **149** by ethylene followed by insertion generates a cationic alkyl–Ni complex **148**. This intermediate evolves through β-hydride elimination to give the final product **150** and regenerate the active catalyst **144**. The counterion plays an important role in the efficiency of this reaction. In some cases, the desired compound **150** suffers from isomerization of the double bond to the corresponding styrene derivative **151**.

Some experimental evidences are in agreement with this proposed mechanism. For example, coordinating solvents like diethyl ether show a deactivating effect certainly due to competition with a Lewis base (**149**). For the same reason, poor reactivity has been observed for the substrates carrying heteroatoms when an aluminum-based Lewis acid is used. Less efficient hydrovinylation of electron-deficient vinylarenes can be explained by their weaker coordination to the nickel hydride **144**, hence metal hydride addition to form key intermediate **146**. Isomerization of the final product can be catalyzed by metal hydride through sequential addition/elimination, affording the more stable compound. Finally, chelating phosphines inhibit the hydrovinylation reaction.

The nickel-catalyzed asymmetric hydrovinylation of norbornene has been reported and results show a strong dependence of the enantioselectivity on the nature of ligand and counterion.[159] Reaction of the styrene derivative **152** is catalyzed by the Ni complexes of sugar-based phosphonite ligands[160] or dialkylphospholane ligands possessing a chiral hemiacetal pendant group (Scheme 41).[161] The best enantioselectivity (91%) is obtained by a combination of (*R,R*)-dimethyldioxolane and (*S,S*)-dimethylphospholane (ligand **154**). The modification of the chirality of the dioxolane moiety (ligand **155**) leads to a decrease in selectivity (10% of the product is isomerized) and enantioselectivity (71% ee). The ligands bearing a dioxane side chain seem to be very efficient for the product selectivity. The chiral centers at the phospholane moiety control the absolute configuration of the product **153**, but the product selectivity is not affected. Thus, the diastereomeric ligands **156** and **157** give the same excellent yields, although there is some difference in enantioselectivity. This catalyst has been applied to a three-step synthesis of (*R*)-(−)-α-curcumene, an important constituent of essential oils.[162]

10.07.3 Additions of Metallocarbenoids to Unsaturated Partners

These reactions are covered in other chapters of Volume 11 (Chapters 11.06 and 11.07). This part deals only with examples which are in connection with other sections of this chapter. Additions of metallocarbenoids to unsaturated partners have been extensively studied. Most of the initial studies have involved the transition metal-catalyzed decomposition of α-carbonyl diazo compounds.[163,164] Three main reaction modes of metallocarbenoids derived from α-carbonyl diazo precursor are (i) addition to an unsaturated C–C bond (olefin or alkyne), (ii) C–H insertion, and (iii) formation of an ylid (carbonyl or onium).[165] These reactions have been applied to the total synthesis of natural

products,[166] for instance, the assembly of tigliane ring[167] and pseudolaric acids.[168] These reactions have also been the source of fruitful and enantioselective cascade processes.[169]

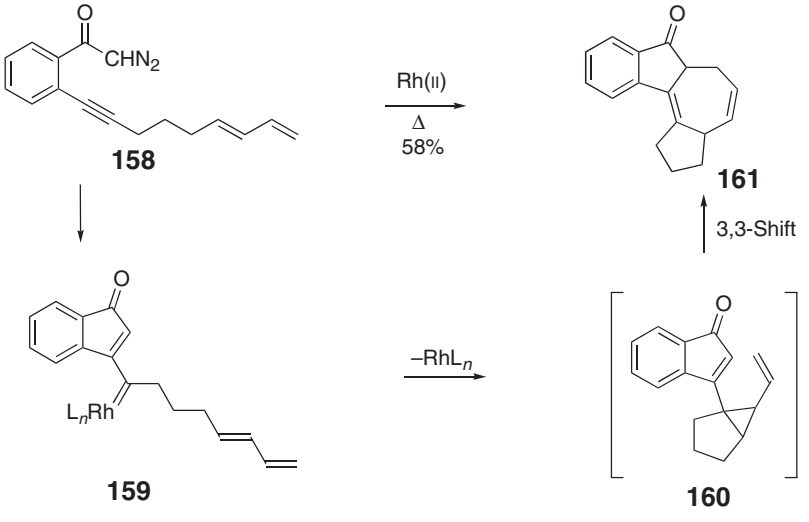
C–H insertions as well as formations of ylids are not mechanistically based on a carbometallation process, and these two facets of reactivity are not covered. However, the addition of a rhodium carbenoid to an unsaturated bond gives a three-membered ring adjacent to a carbonyl moiety, which is a rich functionality for further functionalization.[166] Inter- and intramolecular processes, as well as their asymmetric versions, have been reported.[170] With an alkyne acceptor, the addition of a carbenoid leads to the formation of a cyclopropene derivative. In an intramolecular context, the fused cyclopropene moiety is unstable and undergoes ring opening to generate an allylrhodium–carbenoid species that can then undergo cyclopropanation or cyclopropenation, C–H insertion, and ylide formation.[171] One of such processes is illustrated for the efficient transformation of **158** to **161** (Scheme 42).[172] In this case, the vinylcyclopropane intermediate **160**, resulting from the intramolecular addition of the carbene **159** to the diene moiety, undergoes a Cope rearrangement to produce **161**. This protocol has been widely utilized[171,172] and reviewed.[163]

Based on his previous work on the catalytic double addition of diazo compounds to alkynes[173] using $Cp^*RuCl(COD)$,[174] Dixneuf has developed an efficient one-step synthesis of alkenyl bicyclo[3.1.0]-hexane derivatives of type **163** from enyne precursors **162** (Scheme 43).[175] The catalytic cycle starts with the formation of an Ru=CHR species. It then adds to an alkyne to form ruthenacyclobutene **166**, which evolves into vinylcarbene **167**. [2 + 2]-Cycloaddition of **167** gives ruthenacyclobutane **168**. The novelty in this transformation is the subsequent reductive elimination to give **170** without leading to the formation of diene **169**. This can be attributed to the steric hindrance of the C_5Me_5–Ru group.

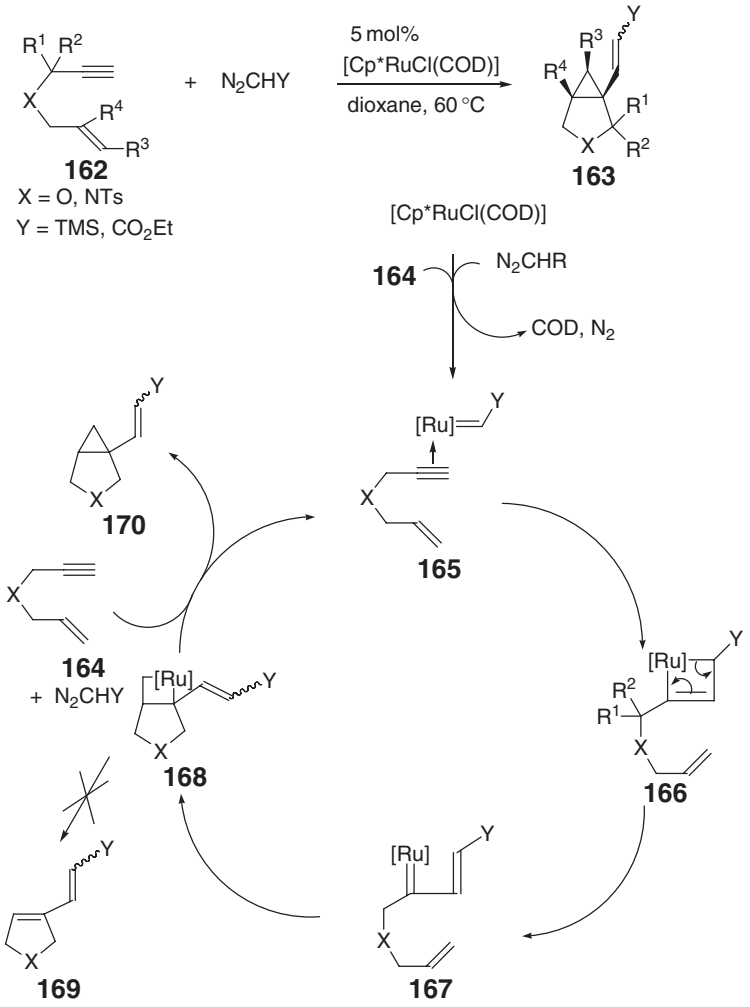
This catalytic tandem carbene addition–bicyclization of enynes has been very recently applied to the synthesis of fluorinated bicyclo[*n*.0.1]-amino esters.[176]

Allylic carbene species can also be generated from the intermolecular addition of TMS–diazomethane to an alkyne component in the presence of $Ni(COD)_2$ as a catalyst. If a diene moiety is also present, as in 1,6-enyne system **171** ($R^1 = R^2 = H$), the reaction of the nickel carbenoid with this partner gives the fused 5,7-bicyclic system **172** ($R^1 = R^2 = H$) in fair yields (Scheme 44). Several mechanistic scenarios are possible from the generic precursor **173**, including a metathesis-type sequence to generate a nickelacyclobutane **175**, followed by reductive elimination and Cope rearrangement, or rearrangement to a nickelacyclooctadiene intermediate **177** and reductive elimination. Another route, involving Ni(0) preliminary oxidative addition, was also proposed. Further studies will probably elucidate the mechanism of this [4 + 2 + 1]-cycloaddition of a diazoalkane, diene, and alkyne.[177] Other pathways to generate carbenoid species from an alkyne are discussed below.

Recently, Ohe and Uemura reported a novel approach to the catalytic cyclopropanation of alkenes via 2-furyl[178,179] or 2-pyrrolyl carbenoids[180] that originate from the intramolecular nucleophilic attack of a carbonyl oxygen or an imine nitrogen (ene–yne–ketone and ene–yne–imine precursor, respectively) on a π-alkyne complex or a cationic σ-vinyl complex. Initially, the group 6 complexes like $Cr(CO)_5$ were used. Soon it was found that a series of late transition



Scheme 42



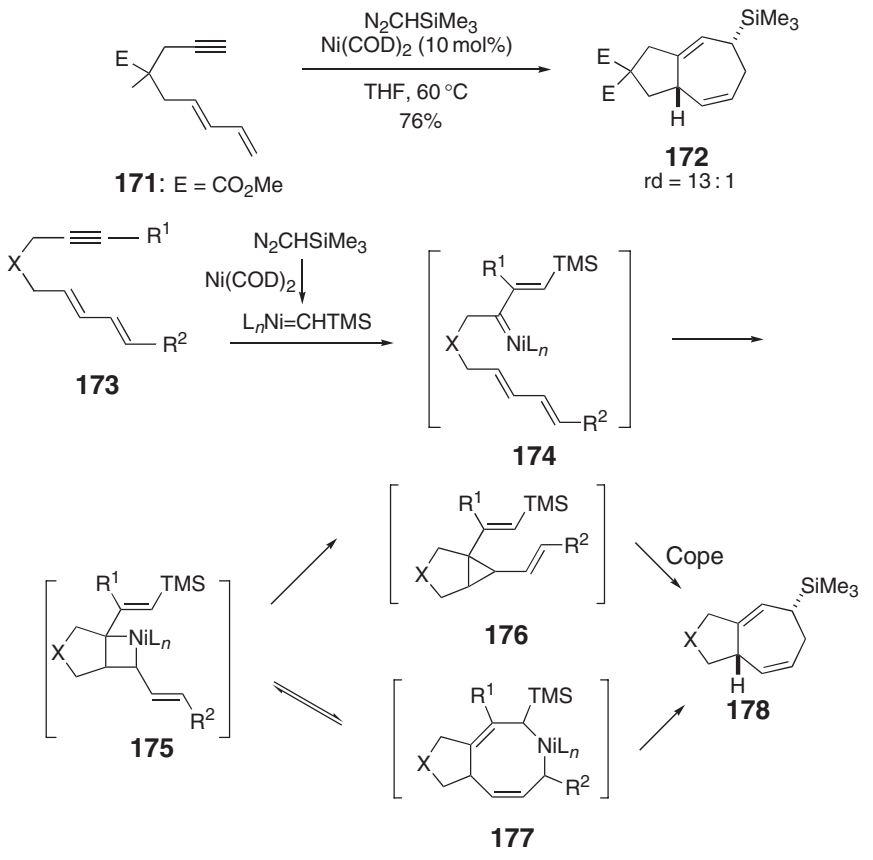
Scheme 43

metal compounds such as $[RuCl_2(CO)_3]_2$, $[RhCl(COD)]_2$, $[Rh(OAc)]_2$, $PdCl_2$, and $PtCl_2$ could also catalyze the inter- or intramolecular cyclopropanation, as shown in Scheme 45. The similar alkyne activation taking place in an enyne system is dealt with later on.

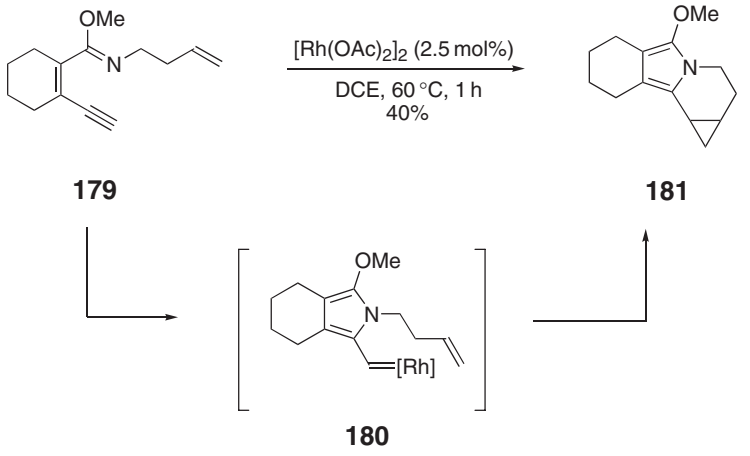
10.07.4 Carbometallation of Polyunsaturated Partners

10.07.4.1 Enynes

Polyunsaturated partners and in priority 1,*n*-enyne systems naturally constitute an interesting field of investigation with high synthetic potential in the context of transition metal-catalyzed C–C bond formation and notably carbocyclizations.[181] It is therefore no surprise that this special array of unsaturated partners has witnessed tremendous attention for two decades after the seminal report by Trost and Lautens in 1985.[182] It is also worth noting that most transition metals of groups 8–11 have exhibited exquisite reactivity toward the enyne system. The reaction modes of 1,*n*-enynes in the presence of transition metals can be classified into four main pathways (Scheme 46). The simultaneous complexation of both unsaturated bonds (path a) leads preferentially to the formation of the metallacycle **183**. Though almost all the transition metal complexes could react to generate such intermediates, their post reactivity can be quite different. Alternatively, the presence of a functional group at the allylic position leads to the formation of a π-allyl complex **184** (path b), which could further react with the triple bond moiety. On the other hand,

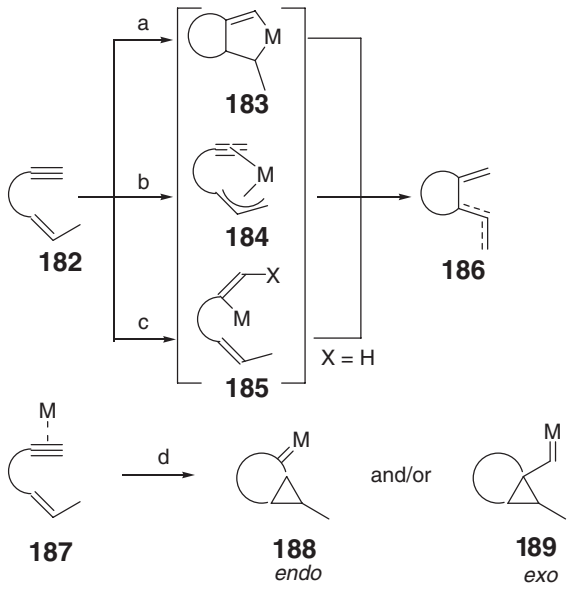


Scheme 44

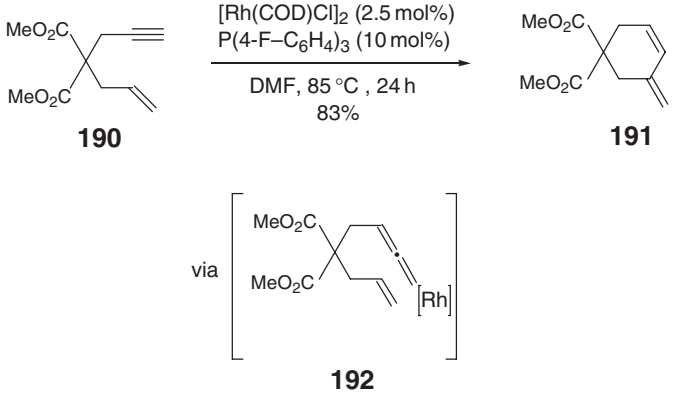


Scheme 45

the formation of a vinyl intermediate, in most cases via hydrometallation (X = H) of the alkyne moiety, forms the corresponding vinylmetal **185** (path c), which is reactive enough to undergo the carbometallation of the olefin moiety. A fourth pathway (d) has been recently conceptualized.[183] In the presence of some cationic metal complexes (mostly platinum(II), gold(I) or (III)),[184] the π-complexation of the alkyne moiety to the metal triggers the formation of a cyclopropylmetallacarbene intermediate in an *endo*- or *exo*-mode.



Scheme 46



Scheme 47

These different reaction modes are now presented. As most of this chemistry has been extensively reviewed from a synthetic[99] and a mechanistic point of view,[185,186] focus here is particularly on enantioselective versions of these reactions and the processes transiting through the path d mechanism since this is a rather new and rapidly growing field of research.

It should also be mentioned that very recently, a new cycloisomerization of enynes has been shown to proceed via a rhodium–vinylidene complex,[187] which, after [2 + 2]-cycloaddition and ring opening of a rhodacyclobutane, furnishes versatile cyclic dienes (Scheme 47).[188] Not only does this constitute a fifth mechanistic pathway, but it also opens new opportunites for C–C bond constructions.

10.07.4.1.1 Metallacyclopentene pathway

Chelation of the alkene and the alkyne moieties to a metal species generally results in the formation of a metallacyclopentene that can undergo three kinds of transformations.

The first transformation is the electrophilic cleavage of the carbon–metal bonds, which allows the functionalization of the substrate. This is more frequently observed with the group 4 metals (Ti, Zr, see Chapter 10.06). Carbonylation

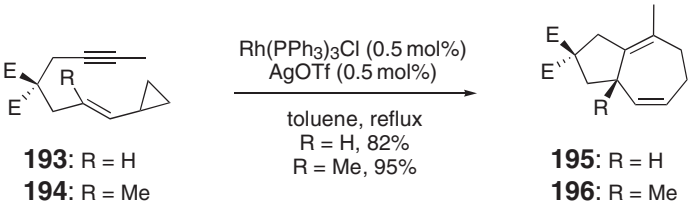
belongs to this class of reactions and can give Pauson–Khand-type adducts[189] upon using mainly cobalt, but also nickel, iron, ruthenium, and rhodium complexes. This chemistry is covered in Chapter 11.12.

The second transformation – reductive elimination of metallacyclopentene – occurs with the metal complexes that are not able to undergo a β-elimination and leads to the formation of bicyclic systems[190] or rearranged compounds, generally dienes resulting from the opening of the cyclobutene ring.[191] In some cases, the insertion of an unsaturated partner such as an alkene[192] or an alkyne takes place giving formal [2 + 2 + 2]-adducts.[193–195] These processes will be covered in Chapter 10.13 devoted to higher-order cycloadditions.

As invented by Wender,[196,197] a variant of the second transformation can take place if the alkene partner is substituted by a participating group such as a strained cyclopropyl or a cyclobutanone (in the case of a 1,6-diene).[198] The whole process, which mainly relies on the use of rhodium or ruthenium complexes,[199] results in the formal [5 + 2]- or [6 + 2]-cycloadditions, and provides a new method for the preparation of seven- or eight-membered rings. Intermolecular reactions[200–202] as well as multi-component versions[203] have been reported. Very recently, the catalysis of Ni/*N*-heterocyclic carbenes as ligands has been shown to provide cyclopentanes or cycloheptenes from cyclopropylenynes depending upon reaction conditions (Scheme 48).[204] More developments on higher-order cycloadditions will also be found in Chapter 10.13.

The third transformation, by far the most encountered process, is the β-hydride elimination which is the major and the fastest process in many cases (Scheme 49). The β-elimination is usually followed by the reductive elimination to give the cycloadduct and regenerate the active metal species. Depending on the regioselectivity of the elimination (H_a or H_b), two dienes, 1,3- and/or 1,4-diene, can be obtained. The products of the latter case formally correspond to Alder-ene adducts (see Chapter 10.12).

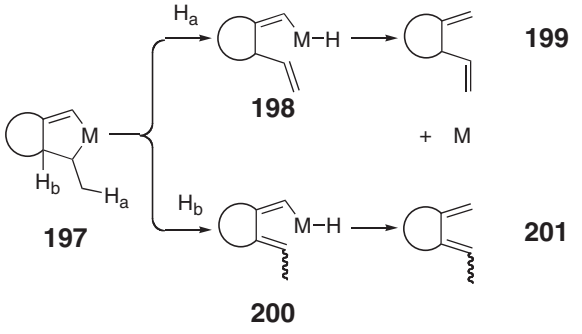
The β-elimination requires a vacant coordination site on the metal and a *cis*-relationship between the carbon–metal and carbon–hydrogen bonds, which have to be aligned to optimize the orbital overlap. While the C–H_a bond energy is higher than C–H_b, the alignment for the insertion of the metal into the C–H_a bond is good. On the contrary, the geometry for the β-hydrogen elimination of C–H_b bond is not ideal (dihedral angle is different from 0), but is compensated by a weaker bond strength due to its allylic nature. Four metals are mainly used for this transformation: palladium, ruthenium, cobalt, and rhodium.[205] However, it has been reported that iridium,[193,206] an early transition metal (titanium),[207] and, very recently, iron,[208] are able to catalyze the cycloisomerizations of enynes and dienynes. For almost two decades, the contribution of the Trost group in this field has been very important, and a plethora of articles compiling the factors governing the palladium-mediated cycloisomerizations of 1,*n*-enynes[209,210] and the applications to natural product syntheses have been published.[211,212]



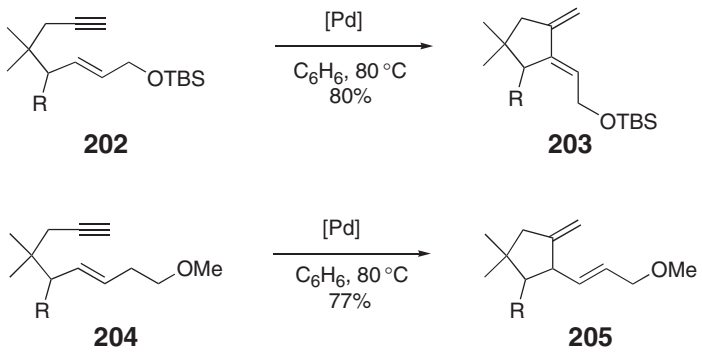
193: R = H
194: R = Me

195: R = H
196: R = Me

Scheme 48



Scheme 49



[Pd] = $[(o\text{-Tol})_3P]_2Pd(OAc)_2$; R = OPMB

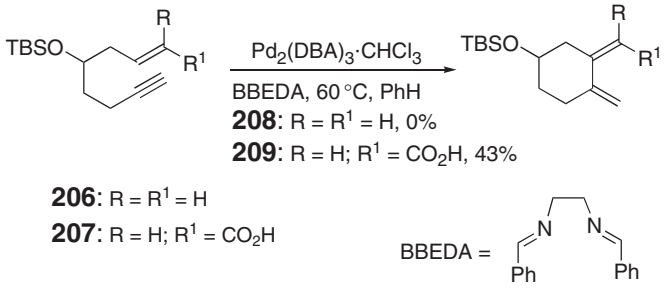
Scheme 50

Pioneering studies of Trost and his co-workers have explored all the parameters of this reaction. An interesting piece of work has, for instance, shown that the presence of an ether or a silyl ether in a substrate also exerts a profound effect on the regioselectivity of the cyclization. Thus, a silyl ether group at the allylic position (**202**) furnishes the corresponding 1,3-diene **203**, whereas an ether group at the homoallylic position gives exclusively the 1,4-diene **205** (Scheme 50).[210]

The formation of a six-membered ring is also feasible but is more limited, and the reaction is found to be more sensitive to the reaction conditions (Scheme 51). The difficulty for forming cyclohexanes is ascribed to the poorer ability of 1,7-enynes to function as bidentate ligands. This problem can be partially circumvented by introducing an alkene moiety (**206** vs. **207**) or a substituent that can coordinate to the metal, such as a free carboxylic acid,[213] although in this case, the actual mechanism involves hydropalladation as the first step (see Section 10.07.4.1.3.(i).).

Trost has also developed an efficient Ru(II)-catalyzed cycloisomerization of 1,6- and 1,7-enynes that leads to the formation of five- and six-membered rings. Cationic ruthenium(II) catalyst, $CpRu(CH_3CN)_3PF_6$, has proved to be better than CpRu(COD)Cl. The cycloisomerization presumably proceeds through the formation of a ruthenacyclopentene, involving alkynes, which bear either electron-donating or -withdrawing substitutents and di- or trisubstituted alkenes.[214] The ruthenium catalysis is found to be complementary to the palladium-catalyzed hydropalladation–carbometallation process in the sense that only 1,4-dienes are obtained via the ruthenium route, while the palladium catalysis yields both dienes. This is rationalized by a highly unfavorable β-elimination from the ruthenacyclopentene. Based on this rationale, the ruthenium-catalyzed cycloisomerization of 1,6- or 1,7-enynes bearing a TBS ether at the internal allylic position has emerged as an efficient way to prepare five- or six-membered rings with a configurationally defined silyl enol ether.[215] Very recently, in the total synthesis of (+)-allocyathin B2, the ruthenium- and the palladium-catalyzed reactions of 1,7-enynes have been compared in terms of stereoselectivity.[216]

Achieving efficient enantioselective cycloisomerizations of enyne systems has been a long-standing goal, and several break throughs have been made.[217] Mikami[218] has reported a highly enantioselective cyclization of a 1,6-enyne, which leads to the construction of an enantioenriched quaternary chiral center. Indeed, by using 5 mol% of $Pd(OCOCF_3)_2$ and



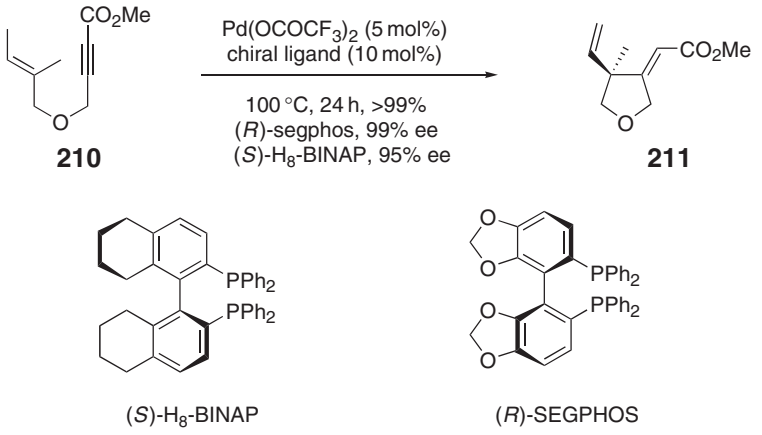
Scheme 51

10 mol% of a chiral ligand such as (*S*)-H_8-BINAP or (*R*)-SEGPHOS in thoroughly degassed benzene at 100 °C, the cyclization of the enyne **210** provided quantitatively the cycloadduct **211** with ee up to 99% (Scheme 52).

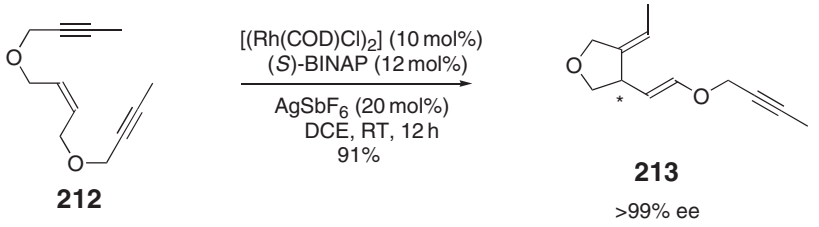
Zhang's group has reported highly enantioselective cycloisomerization processes catalyzed by rhodium(I) chiral complexes (Scheme 53). For instance, (*S*)-BINAP gives excellent asymmetric induction in the reaction of enediyne **212** to furnish the quasi-enantiopure Alder-ene product **213**.[219]

Recently, Mikami has also obtained high ee's for the cycloisomerization of related 1,6-enynes,[220] using Rh(I) catalysts with tropos (chirally flexible) BIPHEP ligands. This chemistry can be applied for an approach to the synthesis of kainic acids[221] and the formal synthesis of (+)-pilocarpine **216**,[222] which demonstrates the synthetic utility of this method for constructing functionalized γ-lactones (Scheme 54).

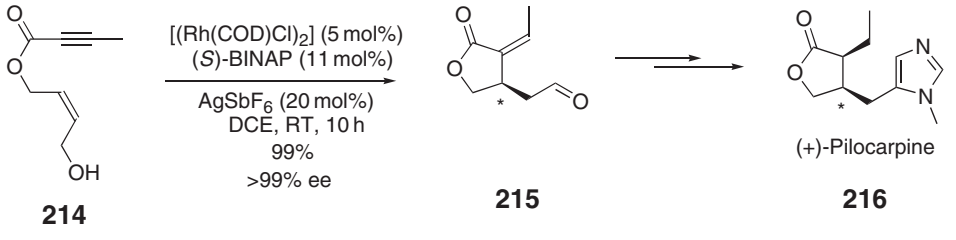
An interesting variation of metallacycle formation has been found and developed by Montgomery for the intramolecular nickel-catalyzed coupling of an alkyne with an enone in the presence or absence of a main group organometallic reagent.[223–225] This reaction has opened an easy access to variously functionalized (poly)carbocycles. This reaction includes the formation of a metallacycle via oxidative cyclization, possibly existing as the carbon-bound **218** or oxygen-bound tautomer **219** (Scheme 55), which would be followed by transmetallation and a reductive elimination.



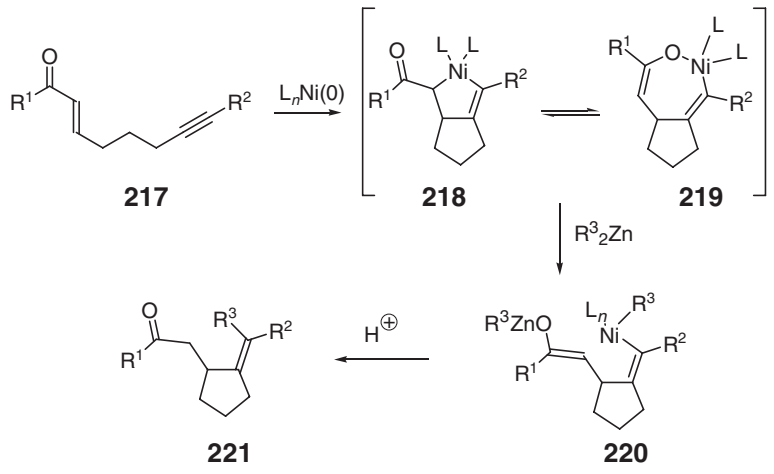
Scheme 52



Scheme 53



Scheme 54

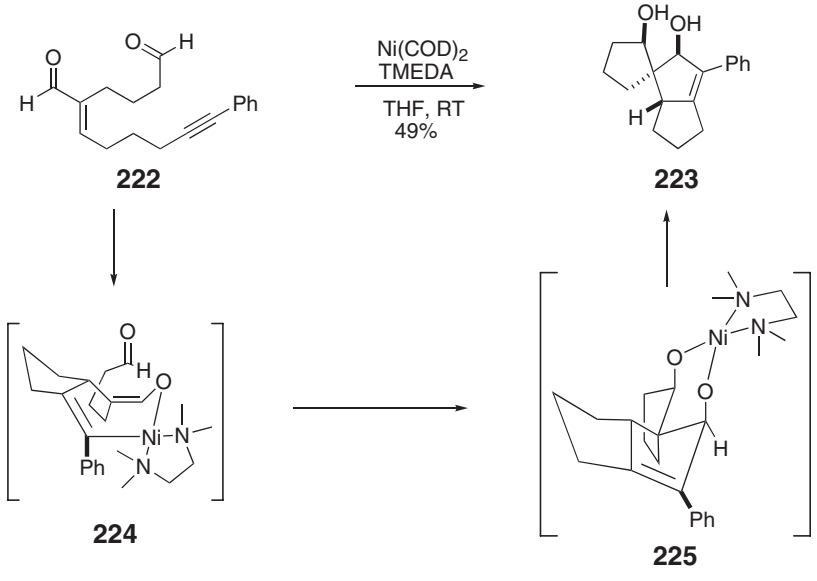


Scheme 55

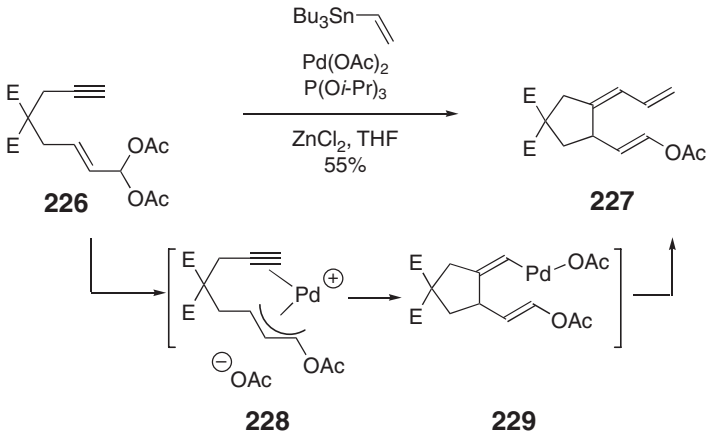
In order to gain more insight into this proposed mechanism, Montgomery and co-workers tried to isolate the intermediate metallacycle. This effort has also led to the development of a new [2 + 2 + 2]-reaction.[226] It has been found that the presence of bipyridine (bpy) or tetramethylethylenediamine (TMEDA) makes the isolation of the desired metallacycles possible, and these metallacycles are characterized by X-ray analysis (Scheme 56).[227] Besides important mechanistic implications for enyne isomerizations or intramolecular [4 + 2]-cycloadditions,[228] the TMEDA-stabilized seven-membered nickel enolates **224** have been further trapped in aldol reactions, opening an access to complex polycyclic compounds and notably triquinanes. Thus, up to three rings can be generated in the intramolecular version of the reaction, for example, spirocycle **223** was obtained in 49% yield as a single diastereomer from dialdehyde **222** (Scheme 56).[229]

10.07.4.1.2 The π-allyl pathway

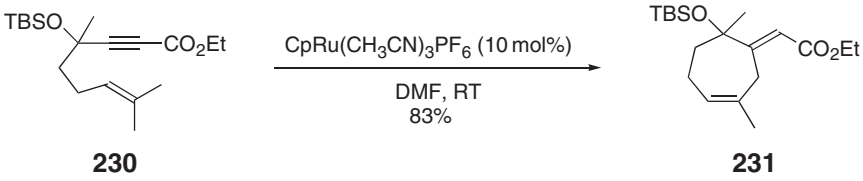
π-Allylic transition metal complexes in organometallic catalysis have found many applications for alkylation reactions[230] as well as cyclizations.[231] Dienes and polyenes have been extensively involved in this type of reactions (Section 10.07.4.2). Nevertheless, enynes can be involved in synthetic sequences.



Scheme 56



Scheme 57



Scheme 58

In the presence of *in situ*-generated palladium(0) species, an electrophilic π-allyl complex **228** is formed, which is readily engaged in an intramolecular carbometallation (Scheme 57). The resulting vinylpalladium species then undergoes a Stille-type cross-coupling to provide a triene.[232]

Trost has shown some mechanistic dichotomy in the ruthenium(II)-catalyzed enyne cycloisomerization.[233] Thus, as mentioned above, the cyloisomerization of enynes proceeds well for the formation of five- or six-membered ring for a variety of precursors. In sharp contrast, in the case of 1,6-enynoates with a quaternary propargylic position, a seven-membered ring is produced in good yield (Scheme 58).

It has been postulated that these cycloheptenes must be formed via a π-allylruthenium intermediate (Scheme 59). The cyclization is initiated by activation of the allylic C–H bond to form the π-allylruthenium **234**. The 7-*exo-dig* carboruthenation of the alkynoate **234** produces the hydrido–ruthenium enolate **235**. Equilibration of **235** followed by reductive elimination gives the corresponding cycloheptenes **237** and regenerates the cationic ruthenium complex.

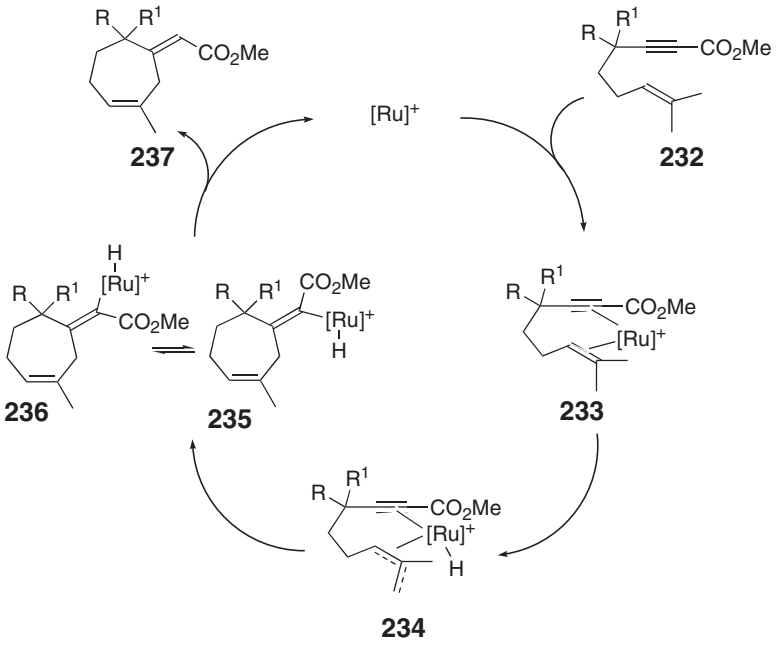
Nickel(0) catalysis has been utilized for a three-component coupling between an allylic electrophile, and alkyne, and $AlMe_3$ or $ZnMe_2$. This reaction takes place though the insertion of a π-nickel(II) intermediate into the alkyne, which is followed by transmetallation with the organometallic reagent. The process could be accomplished in an intramolecular fashion involving 1,6-enynes with an activating allylic group.[234,235]

Zhang[236] has also reported a Pd(0)-catalyzed cyclization–arylation cascade of 1,6-enynes that proceeds via the formation of a π-allylpalladium intermediate and the subsequent Suzuki coupling, yielding adducts with stereo-defined exocyclic double bonds (Scheme 60).

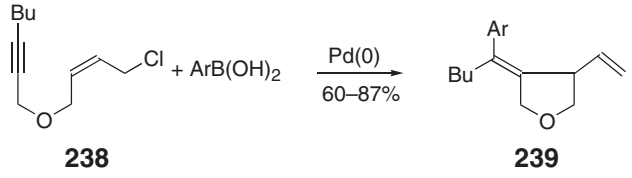
10.07.4.1.3 The vinylmetal pathway

The third pathway for the cycloisomerization of 1,*n*-enynes is the transformation that involves a vinylmetal intermediate (Scheme 61).

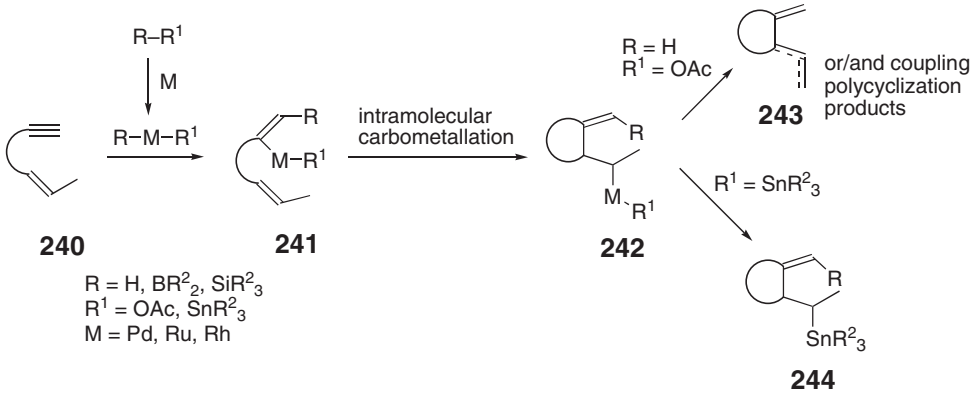
The addition of an R–M moiety to the triple bond gives the corresponding vinylmetal intermediate **241**, which is activated enough to react with the alkene moiety. Depending upon the nature of the R^1 group, several options are open. In the case of an initial hydridometallation by a metal hydride, which is most often formed *in situ* through the oxidative addition to acetic acid ($R–R^1 = H–OAc$), the resulting cyclization product **243** will liberate its metal component by



Scheme 59



Scheme 60



Scheme 61

β-elimination-coupling or polycyclization reactions. Palladium and ruthenium are the most frequently used metals for such transformations. On the other hand, palladium-catalyzed hydrosilylative or bismetallative cyclizations of enynes that presumably proceed via an initial heterometallation of the alkyne moiety have also been developed.

The vinylmetals are also efficiently prepared by oxidative addition of a metal to a Csp^2–halogen bond. However, the Heck and related reactions and their wide applications in organic synthesis, especially cascades,[237–240] are not

presented in this chapter, since this is covered elsewhere (Chapter 11.11). It is also worth noting that Barluenga has reported the first intramolecular carbometallation of lithiated double bonds catalyzed by CuCN to afford dihydropyrrole or indole derivatives.[241]

From a mechanistic point of view, if R is a carbon fragment, the overall transformation **240** → **242** corresponds to a double carbometallation. This powerful approach has been developed, for instance, by using an arylboronic partner in the initial step.

Next, the cycloisomerization of 1,*n*-enynes involving a vinylmetal species originating from the hydro-, hetero-, or carbometallation of the acetylene moiety in the first step is summarized.

10.07.4.1.3.(i) Hydrometallation

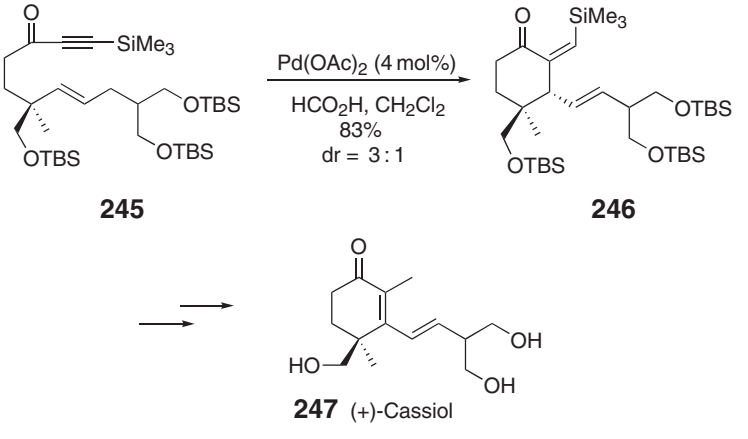
This reaction is now well understood, including its stereochemical features.[209,242] It should be noted that six-membered rings can be formed besides five-membered rings through this pathway, and their formation is facile with the catalytic system Pd(II)–Pd(IV). All of these set the stage for numerous synthetic applications, such as cycloisomerization [4 + 2] tandem processes,[243] and the enantioselective approach to the total synthesis of potent antiulcerogenic cassiol **247** (Scheme 62).[244]

New methods for the efficient preparation of heterocycles, especially nitrogen heterocycles, are important, because these compounds provide a key motif for a myriad of biologically relevant molecules. Due to the mildness of most reaction conditions, transition metal catalysis provides a very versatile synthetic protocol.[245] Along this line, Yamamoto[246] has devised a palladium-catalyzed cyclization of an alkyne and an imine to provide the functionalized 3-alkenylindole **249**. A palladium hydride is generated[247] by reaction of Pd(0) with AcOH which would originate from the reaction sequence illustrated in Scheme 63.[248] This palladium species would undergo hydropalladation of the acetylene moiety and the subsequent carbopalladation of the imine followed by β-elimination and double bond migration to give the indole **249**.

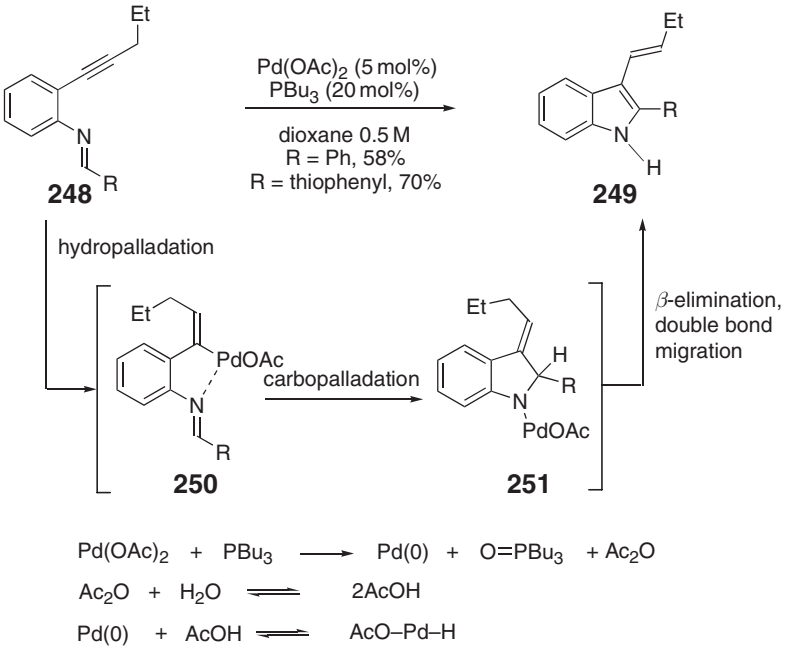
Ruthenium hydride catalysts can also initiate a variety of cycloisomerizations of 1,5- and 1,6-enynes as well as dienes, as exemplified by the $RuClH(CO)(PPh_3)_3$-catalyzed reactions shown in Scheme 64.[249]

Mori has also reported a synthesis of carbapenam skeletons by using $RuH_2(CO)(PPh_3)_3$-catalyzed cyclization, although in this case the reaction may proceed via C–H activation instead of hydroruthenation.[250] The pre-catalyst $RuCl(COD)C_5Me_5$ in the presence of acetic acid or ethanol would generate a ruthenium hydride by decoordination of the COD ligand, which catalyzes the selective one-step cycloisomerization of allyl propargyl ethers into 3,4-dialkylidenetetrahydrofurans in quite good yields.[251] Mori has invoked the same mechanism as the previous examples, that is, hydrometallation of the triple bond to generate the corresponding vinylruthenium, carbametallation of the alkene, and then β-elimination.

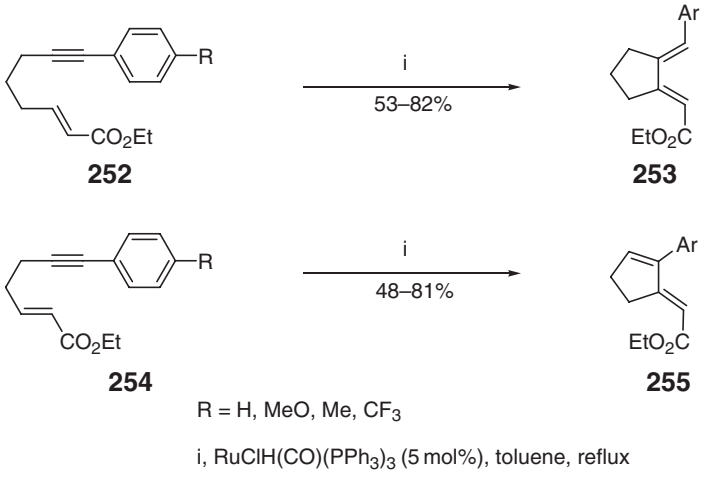
Asymmetric induction for the cycloisomerization of enynes that generate a 1,4-diene was explored by Trost who used an optically active acid such as *S*(−)-binaphthoic acid as a catalytic chirality-inducing agent. However, the asymmetric induction was modest (33% ee).[252] By using chiral diphosphines, Trost was able to improve the enantioselectivity up to 71% ee.[253] A major breakthrough was made by Ito,[254] who introduced more efficient bidentate ligands: the (*S*,*S*)-(*R*,*R*)-TRAP ligands, that is, (*R*,*R*)-2,2″-bis[(*S*)-1-(diarylphosphinyl)ethyl]-1,1″-biferrocenes (Scheme 65). While the



Scheme 62



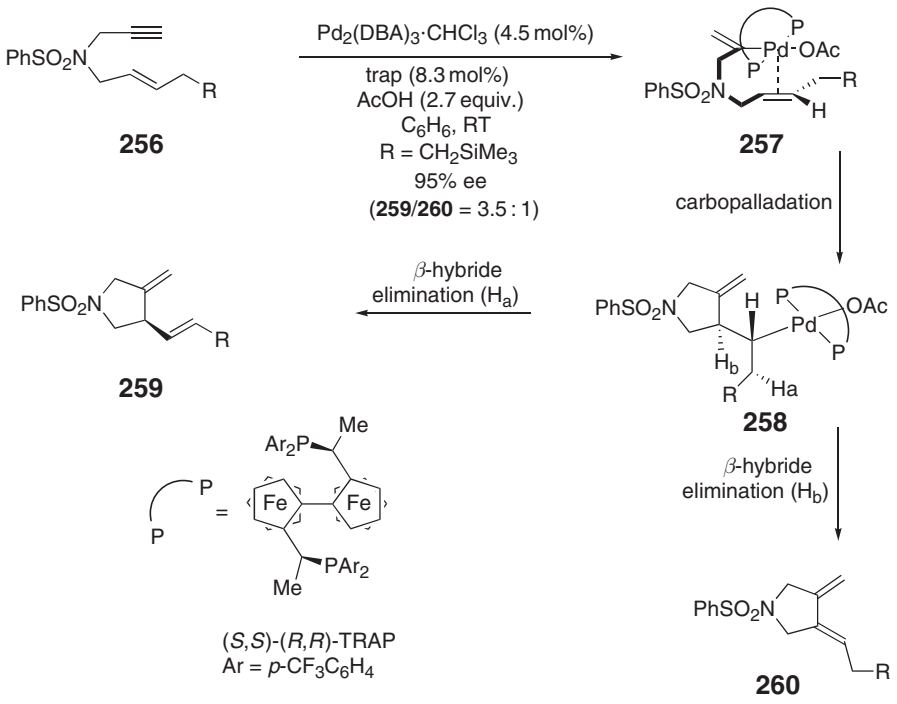
Scheme 63



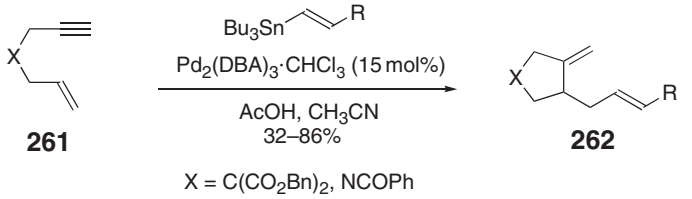
Scheme 64

trap ligands reduce the rate of cyclization, these ligands can still achieve smooth conversion and minimize side-reactions. The TRAP ligands also prolong the lifetime of the catalyst. It has been also shown that increasing the electron-withdrawing ability of the P–aryl substituents gives higher enantioselectivities (up to 95%) and reactivities. Other ligands such as CHIRAPHOS, DIOP, and BINAP exhibit much poorer reactivities and selectivities. Switching the alkene configuratiom from (*E*) to (*Z*) resulted in the reversal of stereoselectivity. Finally, the regioselective formation of 1,4-dienes can be rationalized by an easier β-elimination of H_a over H_b in the proposed palladium(II) intermediate.

As mentioned above, the formation of six-membered rings is rendered easy in these reactions. Mikami has exploited this for a highly enantioselective formation of quinoline derivatives bearing a stereogenic quaternary center using cationic BINAP–Pd(II) complexes.[255] Even more intriguing is the enantioselective (ee's up to 76%) formation of six-membered rings from 1,6-enynes by water-originated hydride addition based on palladium catalysis.[256]



Scheme 65



Scheme 66

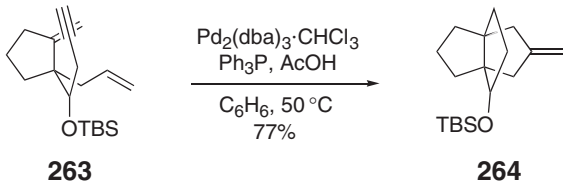
When an adequate reagent is present, β-elimination can be totally or partially inhibited and the σ-alkylpalladium complex, generated through the carbometallation, can be intercepted for further transformations. Particularly, it can undergo *in situ* Stille-type cross-coupling with vinyltin reagents to give cyclized products **262** bearing allyl appendages (Scheme 66). In this case, in order to prevent the formation of the β-elimination products, the reaction needs to be carried out in the absence of ligands.[257]

Few other examples of such reaction sequences have been described to date. Oh has reported the palladium-catalyzed reductive cyclizations of 1,6-enynes in the presence of formic acid or triethylsilane via an alkylpalladium intermediate and its application to organic synthesis.[258,259] Palladium complexes also catalyze the conversion of a range of enynes to cyclic δ,γ-unsaturated carboxylic acids in the presence of CO.[260]

Iterative trapping of the alkylpalladium species with tethered olefins is also possible, which allows tandem cycloisomerizations and zipper reactions to take place. Thus, depending upon the juxtaposition of the unsaturated bonds, Trost achieved highly atom-economical syntheses of triquinanes, propellanes (**264**) from the ynediene **263**, and polyspiranes (Scheme 67).[261]

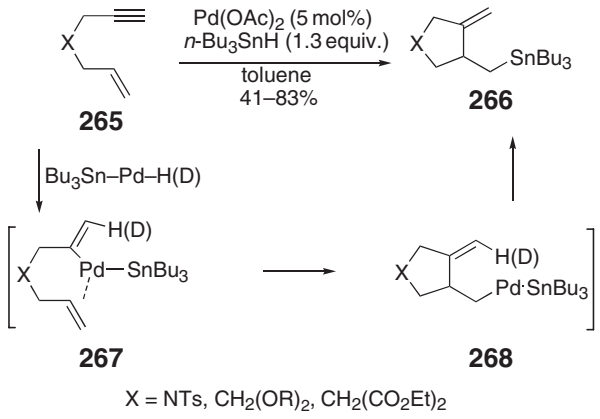
10.07.4.1.3.(ii) Hydrostannylation

The palladium-catalyzed hydrostannylative cyclization of enynes is dealt with first, since mechanistically it is closely related to hydrometallation. Lautens[262] reported the formation of homoallyl stannanes through the reaction of 1,6-enynes with tributyltin hydride in the presence of a catalytic amount of $Pd(OAc)_2$.[263] The active catalytic species is



263 **264**

Scheme 67



265 **266** **267** **268**

Scheme 68

generated by reduction of Pd(II) to Pd(0) with Bu_3SnH, which then oxidatively inserts into the Sn–H bond of another hydride. The reaction is believed to proceed via a hydropalladation of the acetylenic moiety to generate the vinylpalladium. Then, the carbopalladation of the alkene via a 5-*exo-trig*-process followed by a reductive elimination gives the cyclized compound and regenerates Pd(0) species (Scheme 68).

10.07.4.1.3.(iii) Hydrosilylation and related reactions

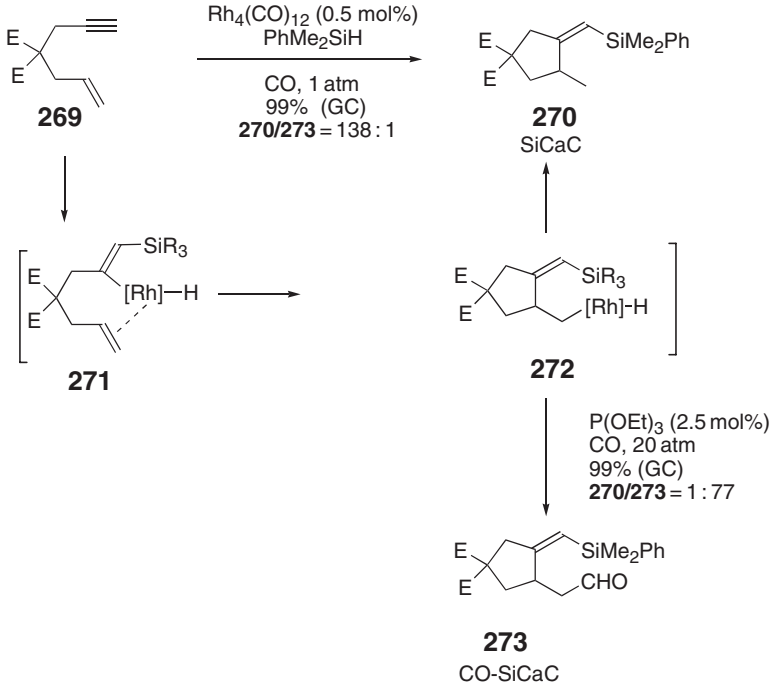
These transformations take advantage of the knowledge obtained from well-established intermolecular reactions (metal-catalyzed hydrosilylation, borostannylation, etc.) and operate in a way that functionalizes both ends of the two unsaturated partners (enyne in this section) in the same manner as in the parent intermolecular reaction.[264,265]

The pioneering works by Tamao and Ito, who reported the first example of nickel-catalyzed silylcarbocyclization (SiCaC) of 1,7-diynes,[266] and Ojima, who has initially used rhodium and rhodium–cobalt cluster catalysis for enynes,[267] have been the source of intense developments, such as silylcarbobicyclization (SiCaB)[268] with diynes, silylcyclocarbonylation (SiCCa),[269] and silylcarbotricyclization (SiCaT).[270] Thus, the reaction of a 1,6-enyne with a variety of hydrosilanes catalyzed by $Rh(acac)(CO)_2$, $Rh_4(CO)_{12}$, or Rh_2–$Co_2(CO)_{12}$ under ambient CO atmosphere or N_2 give the SiCaC product, 2-methyl–1-silymethylidene–2-cyclopentane **270**, while in the presence of phosphite ligand and by increasing the pressure of CO atmosphere, the carbonylative silylcarbocyclization (CO–SiCaC) takes place affording aldehyde **273** (Scheme 69).[271]

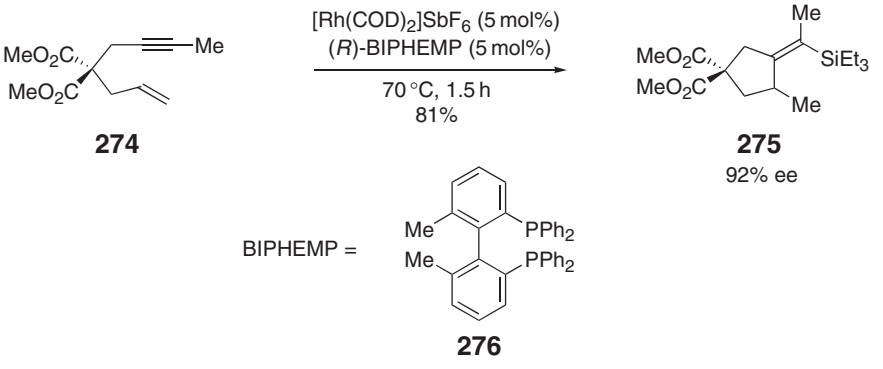
Very recently, Wiedenhoefer[272] has devised the first asymmetric 1,6-enyne hydrosilylation/cyclization tandem process using a rhodium(I) catalyst with (*R*)-**276** as chiral ligand where rhodium–BINAP complexes were not effective (Scheme 70). More developments on this reaction are covered in Chapter 11.13.

The borostannylation of an enyne has also been reported by Tanaka to proceed in a high yield (Scheme 71).[273] The mechanism of this cyclization has not been investigated in detail, but the insertion of the alkyne takes place preferentially into the Pd–B bond over the Pd–Sn bond. Then, the addition of the vinylpalladium **279** to the alkene moiety followed by reductive elimination furnished the cycloadduct **278**. However, Tanaka does not exclude a palladacycle intermediate. Similarly, a borylsilylative carbocyclization has also been reported by Tanaka.[274]

Finally, it has been shown that various enynes are able to react with $Me_3SiSnBu_3$ in the presence of $Pd_2(dba)_3·CHCl_3$ or $Pd(OH)_2$ on charcoal to afford cyclized products **283** bearing a vinylsilane moiety and a



Scheme 69



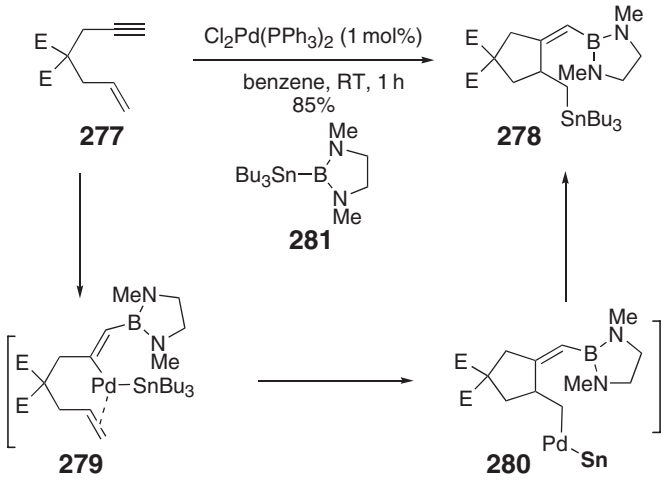
Scheme 70

homoallyltin moiety in good yields (Scheme 72).[275] Bicyclic heterocycles are produced stereospecifically from the corresponding enynes. Recently, other catalytic systems have been shown to promote the reaction, and the resulting homoallylstannane–vinylsilanes can undergo a destannylative cyclopropanation.[275–277] The suggested mechanism is totally similar to the one proposed for the borylstannylation.

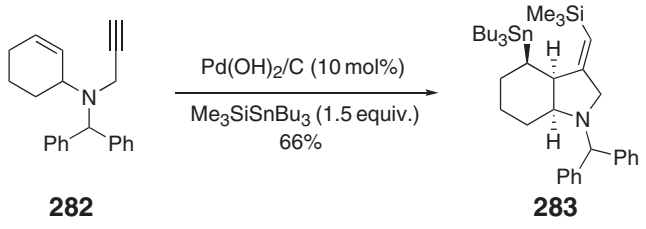
Based on a *trans*-acetoxypalladation of the triple bond,[278,279] Lu has developed a highly enantioselective (up to 87% ee) synthesis of γ-butyrolactones with Pd(II) catalysis (Scheme 73).[280] Following the initial *trans*-acetoxypalladation, a plausible mechanism for this sequence involves an intramolecular carbopalladation of the pendant olefin, and deacetoxypalladation instead of the common β-hydride elimination in the final step.

10.07.4.1.3.(iv) Carbometallation

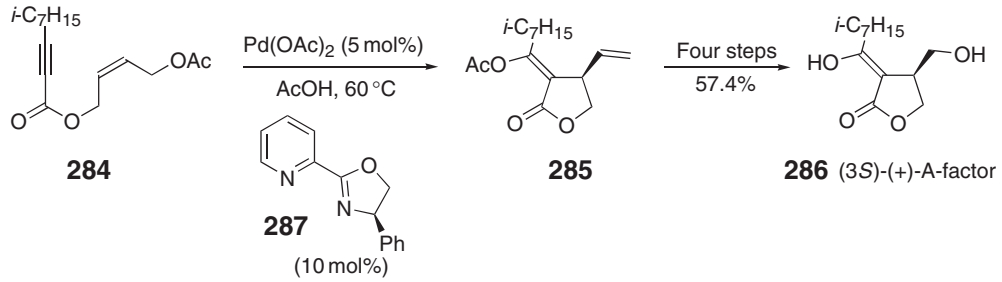
Very recently, Murakami has published an Rh(I)-catalyzed cyclization of 1,6-enynes triggered by addition of arylboronic acids (Scheme 74).[281] Initial carborhodation of the alkyne moiety is followed by insertion into the alkene moiety. β-Alkoxy elimination provides the final product **289** in good yield and regenerates the catalyst species.



Scheme 71



Scheme 72

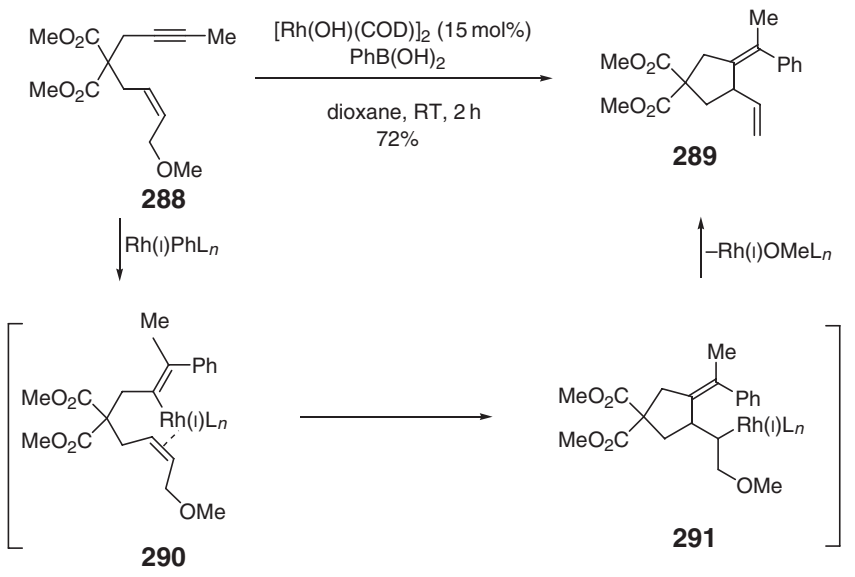


Scheme 73

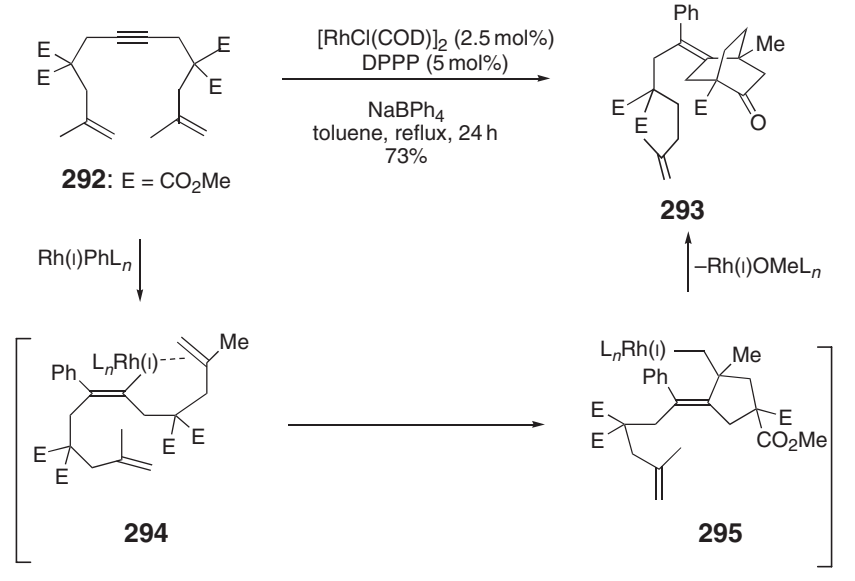
Using sodium tetraphenylborate under anhydrous conditions and $[RhCl(COD)]_2$ as a catalyst, a cascade reaction of dienyne **292** has been carried out, which ends by acylation of the alkylrhodium intermediate and the subsequent Rh^I–OMe formation, to afford bicyclo[2.2.1]-heptan-2-one **293** in good yield (Scheme 75).[282]

10.07.4.1.4 Skeletal rearrangements of enynes

The skeletal rearrangements are cycloisomerization processes which involve carbon–carbon bond cleavage. These reactions have witnessed a tremendous development in the last decade, and this chemistry has been recently reviewed.[283] This section will be devoted to π-Lewis acid-catalyzed processes and will not deal, for instance, with genuine enyne metathesis processes involving carbene complex-catalyzed processes pioneered by Katz[284] and intensely used nowadays with Ru-based catalysts.[285] By the catalysis of π-Lewis acids, all these reactions generally start with a metal-promoted electrophilic activation of the alkyne moiety, a process well known for organoplatinum



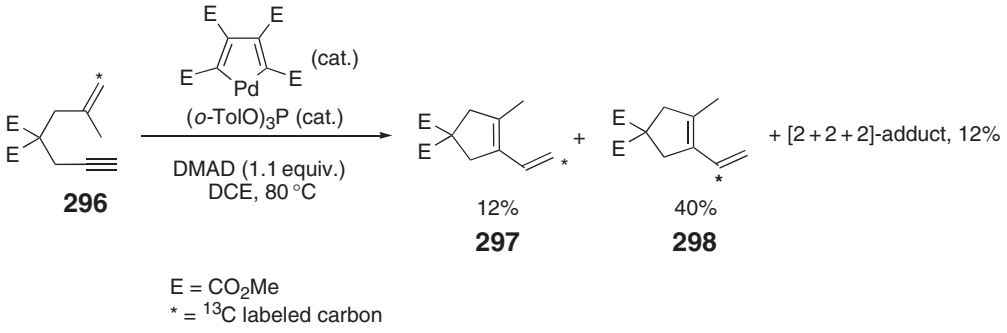
Scheme 74



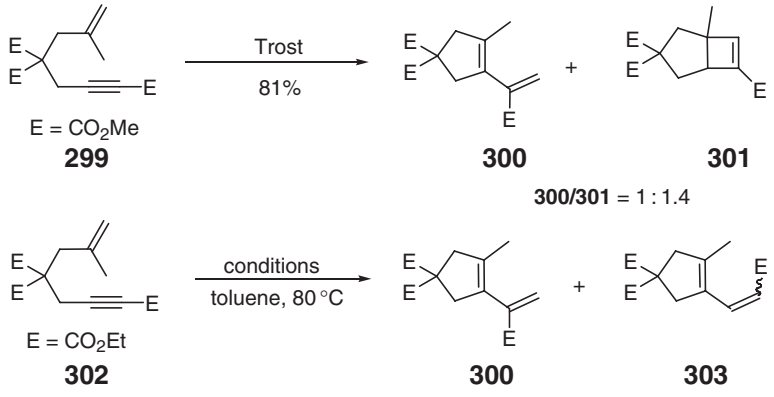
Scheme 75

complexes.[286] One of the first reports of skeletal rearrangements of an enyne partner was given by Trost in 1988,[287] which used a special, relatively electrophilic, palladium catalyst, tetracarbomethoxypalladacyclopentadiene (TCPC), in the presence of tri-*o*-toylphosphite, a catalyst rarely met later on (Scheme 76). Further studies by Trost and co-workers confirmed a metathesis-type reactivity of various enyne partners,[191,288] but the presence of a dienic isomer[287] (**297** vs. **298**) in some cases suggests that these reactions are mechanistically distinct from metal carbene-mediated pathways (see Scheme 76 as an example).

It is also worth noting that platinum(II) complexes can trigger the skeletal rearrangement.[191] In 1994, Murai and co-workers found a highly selective skeletal reorganization of 1,6- and 1,7-enynes using $[RuCl_2(CO)_3]_2$ under 1 atm of carbon monoxide.[289] Studying the same enyne **299** as that of Trost,[287] a different transformation was observed (Scheme 77). Interestingly, Murai also reported that other metal halides such as $[RhCl(CO)_2]$, $ReCl(CO)_5$,



Scheme 76



Entry	*Conditions*	*Yield* (%)	**300/303**	*References*
1	$[RuCl_2(CO)_3]_2$, CO, 3 h	90	6 : 94	289
2	$PtCl_2$, 9 h	98	1 : 3.2	296
3	$[IrCl(CO)_3]_n$, 5 h	80	1 : 9	206

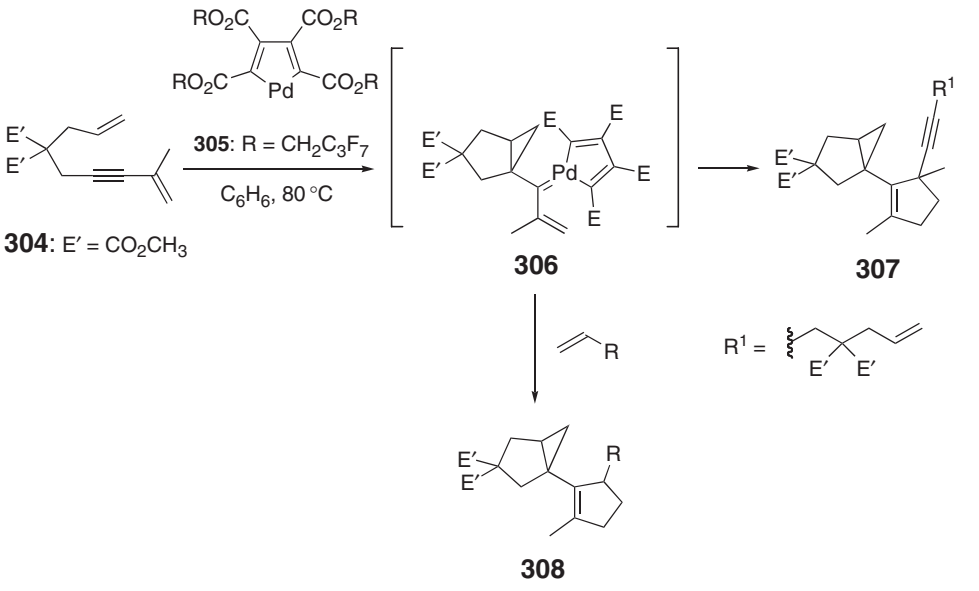
Scheme 77

$[IrCl(CO)_2]_n$, $PtCl_2$, and $AuCl_3$ were able to promote a similar skeletal reorganization. Murai also proposed three alternative mechanisms for the first step of the reaction that accounts for the observed reaction modes: (i) formation of a classical ruthenacyclopentene via oxidative cyclization; (ii) a vinylruthenium complex via chororuthenation;[290] and (iii) a slipped, polarized η^1-alkyne–ruthenium complex bearing a positive charge at the β-position via rearrangement of an η^2-alkyne–ruthenium complex, based on Dixneuf's findings.[291]

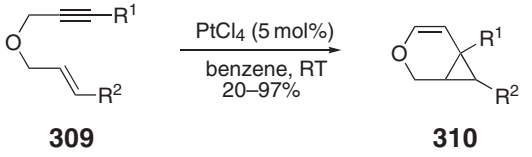
Further work by Trost established the involvement of metallacarbenoid species.[292,293] A dimer product **307**, incorporating a cyclopropyl group, was observed in the reaction of **304** in the presence of the highly electron-deficient palladole catalyst **305** (Scheme 78). This transformation is the signature of an intermediate of type **306**. This chemistry could be rendered useful by playing with other unsaturated bonds as the carbene acceptor, and a variety of polycyclic adducts such as **308** could be synthesized.

Shortly after Trost's works, two investigations demonstrated the high reactivity of platinum halide salts for this type of reactions. Blum reported a $PtCl_4$-catalyzed rearrangement of allyl propargyl ethers to 3-oxabicyclo[4.1.0]-heptenes (Scheme 79).[294] This series of reactions also represented the premiere entry into the versatile formation of cyclopropyl products based on skeletal rearrangements of enynes.[295] This intriguing aspect is discussed further.

Murai[296] introduced platinum dichloride as one of the most versatile catalysts for the promotion of various skeletal rearrangements, a finding soon confirmed by a myriad of follow-up papers describing new uses of this metal halide

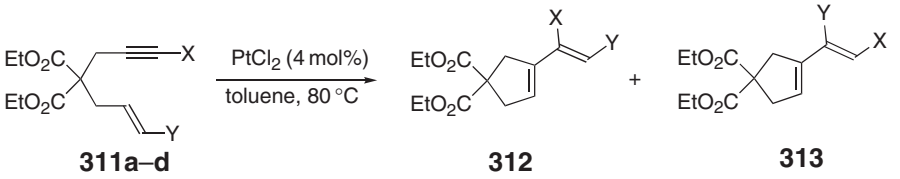


Scheme 78



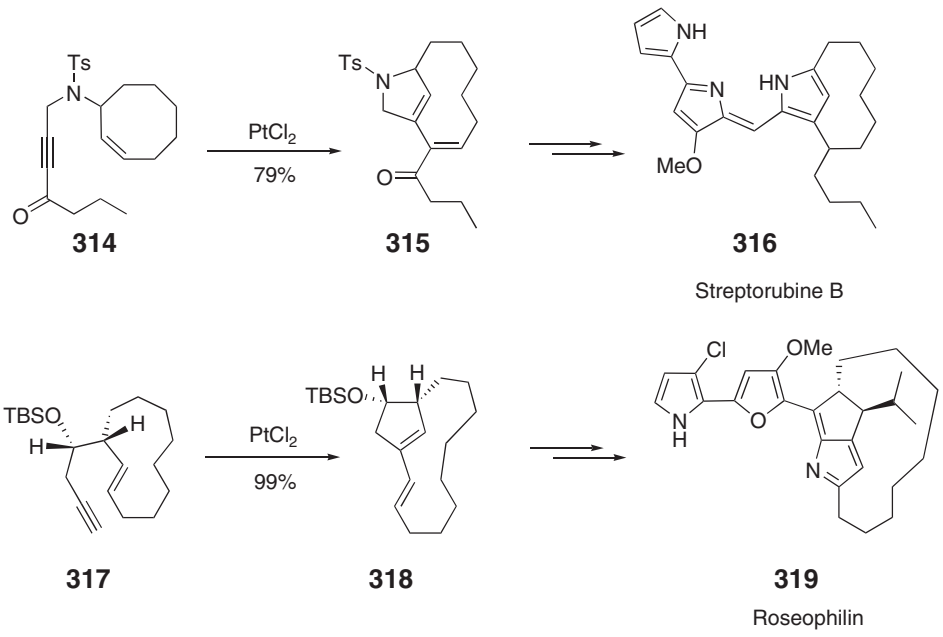
Scheme 79

complex.[297,298] There, it was shown that 1,6- or 1,7-enynes could be very efficiently transformed into vinylcyclopentenes or hexenes. As illustrated in Schemes 77 and 80, the anomalous metathesis product (by comparison with the expected product resulting from a carbene complex-catalyzed process) is observed in some cases. Recently, it was also shown that Ir(I)[206] (see Scheme 77) and Ga(III) could also trigger the skeletal reorganization of enynes to 1-vinylcycloalkenes in a stereospecific manner.[299]



a: X = H, Y = Ph	66%	–
b: X = Ph, Y = H	70%	4%
c: X = H, Y = D	3%	83%
d: X = CO_2Et, Y = H	–	80%

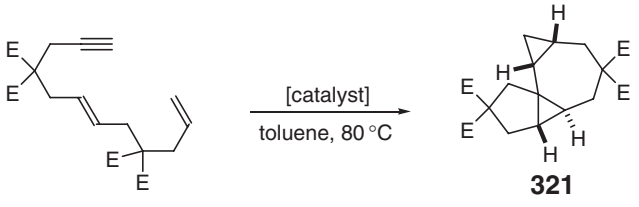
Scheme 80



Scheme 81

These studies paved the way for numerous synthetic applications, in particular total syntheses. Thus, the "low-tech" $PtCl_2$, $PtCl_4$, or $PtBr_4$ systems, as named by Fürstner, proved superior and more reliable compared to Trost's $TCPC^{TFE}$ system[288] for the reactions of the cyclooctene substrate as shown in Scheme 81.[300] These reactions, which could be run in a multi-gram scale, proved useful, for instance, for the formal total synthesis of streptorubine B. Similarly, a formal total synthesis of roseophilin was devised, based on a nearly quantitative transformation of an enyne moiety into a bicyclic diene system (Scheme 81).[301]

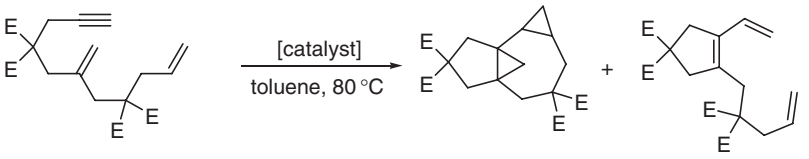
Numerous studies aimed at the understanding of the mechanism of these processes rapidly appeared. In this context, Murai examined the behavior of acyclic linear dienyne systems in order to trap any carbenoid intermediate by a pendant olefin (Scheme 82).[302] A remarkable tetracyclic assembly took place and gave the unprecedented tetracyclo[6.4.0.0]-undecane derivatives as single diastereomer, such as **321** in Scheme 82. This transformation proved to be relatively general as shown by the variation of the starting materials. The reaction can be catalyzed by different organometallic complexes of the group 8–10 elements (ruthenium, rhodium, iridium, and platinum). Formally, this reaction involves two cyclopropanations as if both carbon atoms of the alkyne moiety have acted as carbenes, which results in the formation of four carbon–carbon bonds.



320: E = CO_2Et

$[RuCl_2(CO)_3]_2$	84%
$PtCl_2$	75%
$[Rh(OCOCF_3)_2]_2$	72%
$[IrCl(CO)_3]_n$	54%

Scheme 82



322: E = CO_2Et		**323**	**324**
	$[RuCl_2(CO)_3]_2$	0%	75%
	$PtCl_2$	0%	90%
	$[Rh(OCOCF_3)_2]_2$	51%	34%

Scheme 83

An interesting finding was made by changing of the connectivity (1,1 instead of 1,2) of the central olefin moiety of the substrate, that is, the usual diene product **324** from the skeletal rearrangement was observed in this case (Scheme 83). The fact that by using rhodium instead of platinum or ruthenium, the reactivity pattern is totally different also suggests all the subtlety and complexity of the mechanism of these transformations.[302]

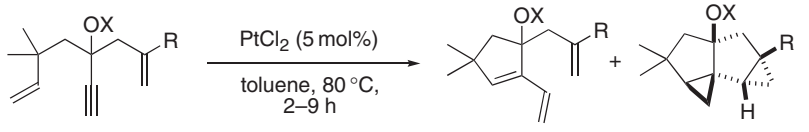
More recently, the bis-cyclopropanation of dienyne **325** has also been investigated by Fensterbank, Malacria, and Marco-Contelles to construct highly strained cyclopropyl-substituted diquinane frameworks **327** in a completely diastereoselective manner (Scheme 84).[303] It is noteworthy that the formal metathesis product was also observed in these reactions, albeit as a minor product, and that a simple introduction of a methyl group to one of the two ene moieties substantially affects the reaction.

Diver has recently reported new entries for the assembly of tetracyclic compounds.[304] Interestingly, ruthenium catalysts for metathesis have also yielded tricyclic products by incorporating a cyclopropane from dienynes, a process reminiscent of Dixneuf's work (see above).

Cationic gold-based catalysts have proved to be even more effective promoters of various reactions resulting from an initial electrophilic activation.[305] These gold catalysts also promote the formation of tetracyclic compounds **329a–329c** as single diastereomer from acyclic substrates **328a–328c** at low temperature (Scheme 85). In one case, the minor metathesis diene **330** was isolated. Tetracyclic products **329a** and **329b** resemble the natural product myliol and related tetracyclic sesquiterpenes, although the juncture of the dimethylcyclopropane unit has the opposite configuration to that of the natural products.

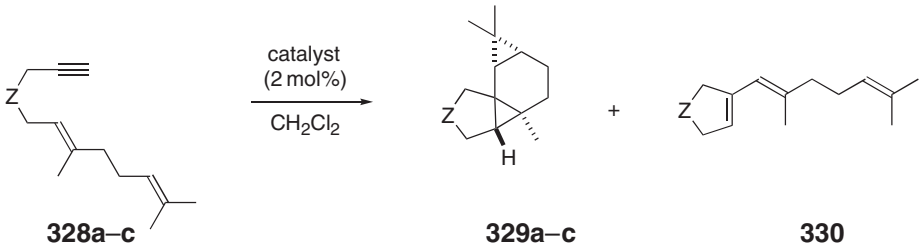
Two sets of findings gave additional insight into the mechanism of these transformations. Thus, Echavarren reported that 1,6-enynes can be converted into 1,4-dienes with a variety of metal halides (Pt(II), Pd(II), Ru(II), Ru(III) and Au(III)) if the ene moiety is a part of an allylsilane (stannane) subunit of the substrate (Scheme 86).[306,307] Usually, $PtCl_2$ gives the best results.

When the TMS group is absent and if the reaction is carried out in methanol, a platinum(II)-catalyzed alkoxycyclization takes place (Scheme 87).[308] This cyclization catalyzed by Pt(II) was found to be mechanistically similar to the carbohydroxypalladation reported by Genêt.[309,310] This process has intrinsic importance in organic synthesis since it allows the simultaneous and generally stereoselective formation of a C–O and a C–C bond to occur from an enyne system. This reaction has been applied for the synthesis of a key intermediate of podophyllotoxin.[311]



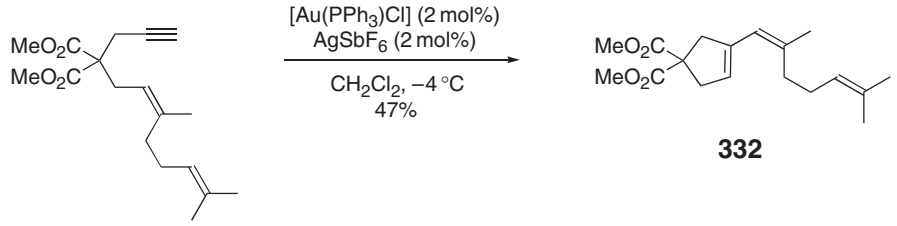
325	**326**	**327**
R = H; X = H	7%	48%
R = H; X = $SiMe_2CH_2Br$	5%	61%
R = H; X = Me		68%
R = Me; X = Me		34%

Scheme 84



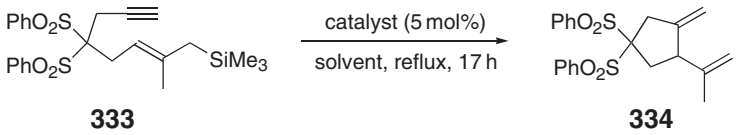
328a–c **329a–c** **330**

Compound	*Catalyst*	*T* (°C)	*t* (min)	*Yield* (%) **329**	**330**
328a: Z = $C(CO_2Me)_2$	$[Au(PPh_3)Cl]/AgBF_4$	–30	20	78	7
328a: Z = $C(CO_2Me)_2$	$[Au(PPh_3)Me]$/TFA	23	240	63	–
328b: Z = $C(SO_2Ph)_2$	$[Au(PPh_3)Cl]/AgSbF_6$	–4	20	49	–
328c: Z = NTs	$[Au(PPh_3)Cl]/AgSbF_6$	0	15	89	–



331 **332**

Scheme 85



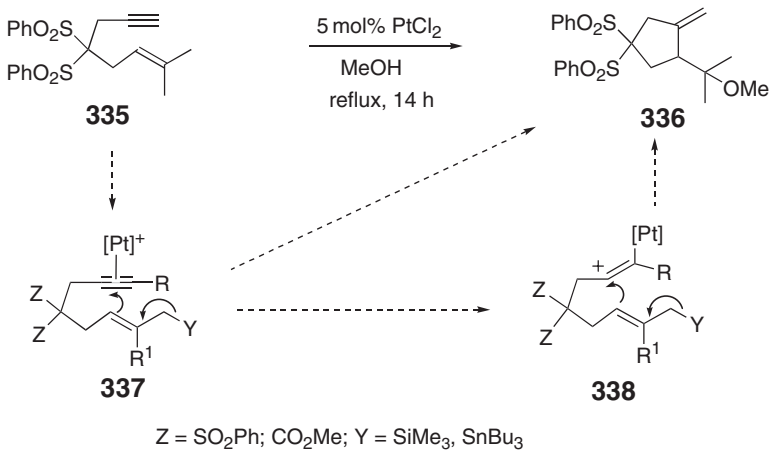
333 **334**

$CpRuCl(PPh_3)_2$, $NaPF_6$(10 mol%), MeOH	92%
$RuCl_3$, MeOH	53%
$PdCl_2$, MeOH	47%
$Pd(MeCN)_4(BF_4)_2$, MeOH	82%
$PtCl_2$, acetone	94%

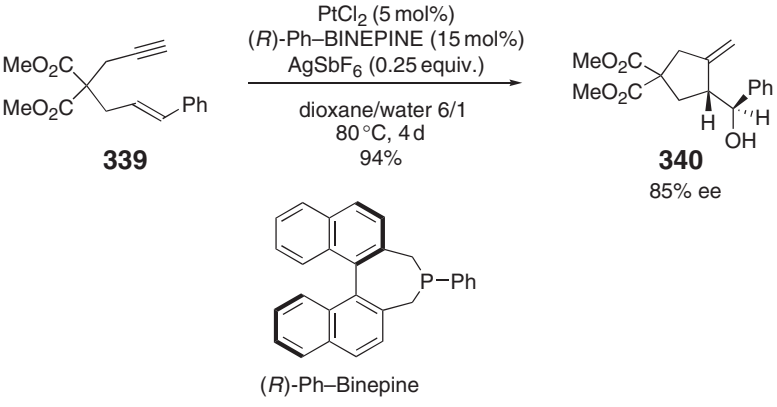
Scheme 86

This reaction has lent itself to the development of its asymmetric version (Scheme 88). The trick here is to remove the choride ligands from the coordination sphere of the platinum–chiral ligand complex. This makes the metal center more electrophilic, thus reactive reactions can be run at lower temperature. Interestingly, the best ligand was found to be the atropisomeric monophosphine (*R*)-Ph–BINEPINE.[312] Enantiomeric excess up to 85% was observed. Very recently, enantioselectivity up to 94% ee has been achieved using $[(AuCl)_2$(Tol-BINAP)] as pre-catalyst for the reaction of another enyne.[313]

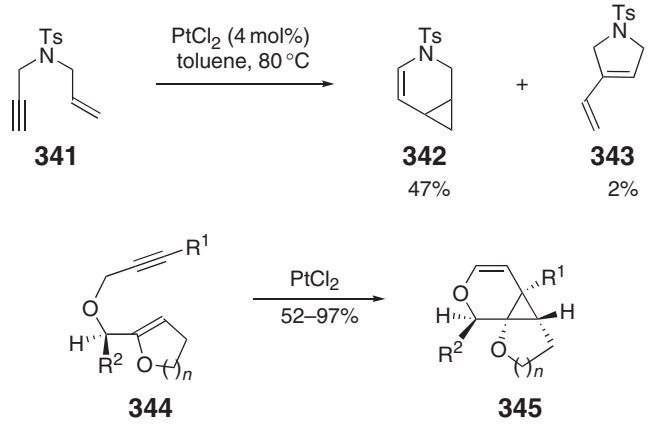
As first disclosed by Blum,[294] cyclopropyl products can also be formed if a heteroatom (nitrogen or oxygen) is present at the propargylic position. The observed heteroatom effect has been rationalized, as shown below. This



Scheme 87

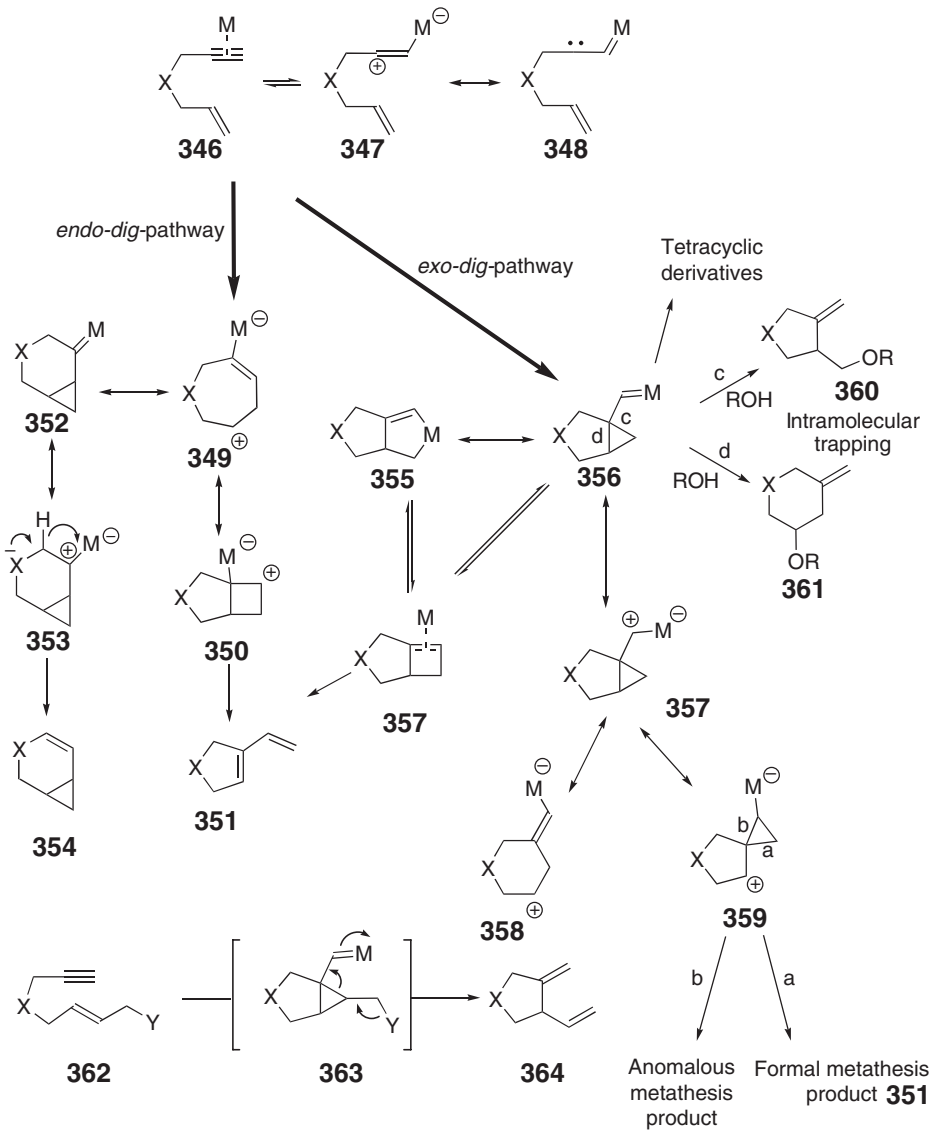


Scheme 88



Scheme 89

heteroatom effect is applicable to a simple enyne such as **341** to give bicyclo[4.1.0]-heptenes such as **342** (Scheme 89) as well as other interesting substrates, including polycyclic compounds,[314,315] and judiciously functionalized substrates such as **345**.[316] Recently, an asymmetric catalysis of a cationic iridium catalyst to give enantiomerically enriched 3-azabicyclo[4.1.0]-heptenes has been published.[317]



Scheme 90

A rationale for the heteroatom effect has recently been provided for the reaction of 1,6-enynes based on detailed mechanistic studies,[318,314] especially DFT calculations performed by several groups (Scheme 90).[183,319–321] From what has been disclosed so far, an interplay of cationic and carbenoid species is obvious in these processes. Nowadays, there is a good consensus to adopt the involvement of cyclopropyl metallacarbene intermediates.

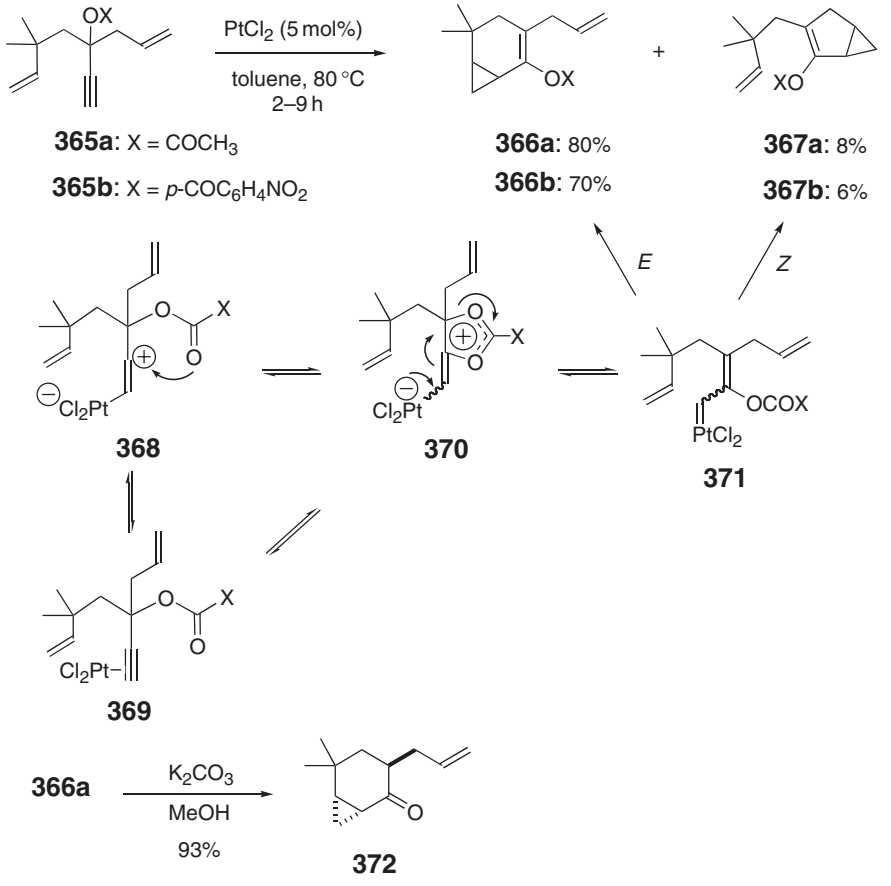
Electrophilic activation of the alkyne moiety of enyne **346** by the metal triggers the nucleophilic attack of pendant olefin in an *exo*-**355** or *endo*-mode **349**. The involvement of the previously invoked slipped, polarized η^1-platinum complex **347** is not supported by DFT and it is proposed, instead, that the triple bond is η^2-coordinated. It is also consistent with the fact that alkynes coordinated to Pt(II) or related metal centers are known to be highly electrophilic.[322] DFT calculations also support a direct formation of **356** and **352** in a single step, and also indicate that when X is CH_2, the *exo*-mode is kinetically favored over the *endo*-mode which gives the more stable metallacarbene. Nucleophilic opening of this intermediate through pathways c and d with a hydroxylated nucleophile gives five- and six-membered rings **360** and **361**. Similarly, α-silyl- or α-stannyl-substituted cyclopropyl carbenes such as **363** can reopen to form 1,4-dienes **364**. A closer look at intermediates **357**, **358**, and **359** shows that they are resonance forms of the "non-classical" homoallyl–cyclopropylmethyl–cyclobutyl carbocation. This finds its relevance to rationalize the mixture of classical and anomalous metathesis products.[318]

When X is O, the *endo*-mode becomes the kinetic and the thermodynamic pathway. The resulting metallacarbenoid is then ideally suited for a 1,2-hydride shift **353**, which installs an endocyclic double bond.

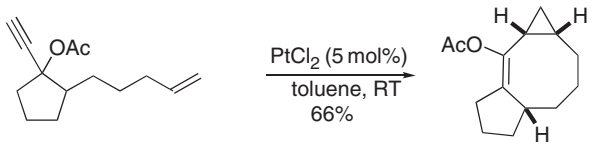
Extensions of the electrophilic activation of the alkyne moiety as well as an alkene moiety have been developed and applied. The applications include various reactions, for instance, Friedel–Crafts type alkylations,[323] anchimeric assistance of heteroatomic moiety generally followed by rearrangements (see below),[324] implementation of more sophisticated functional groups such as ynamides[325,326] and allenynes, which are discussed below.

Other types of nucleophiles can also react with the electrophically activated triple bond. An *O*-acyl group has been shown to be an excellent participating group. Interestingly, this process, which is reminiscent of the well-known palladium(II)–mediated 1,3-migration of allylic acetates[327] represents a highly efficient means for the formation of allylic metallacarbenoid species subsequent to a 1,2-migration of a carboxylate group. As rationalized first by Rautenstrauch in 1984,[328,329] this isomerization initially served for the synthesis of cyclopentenones from 1,4-enyne systems bearing an acetate group at the 3-position. Access to bicyclic cyclopropyl compounds was also very useful. Nevertheless, this process had remained dormant for almost two decades, until it was evidenced with simple $PtCl_2$ on dienynes, as in Scheme 91.[303]

Thus, when an acetate is present at the propargylic position **365**, a completely different reaction was observed giving a mixture of bicyclic products **366** and **367**. This should be directly compared with the reaction of dienynes **325** (Scheme 84). π-Electrophilic complexation of the Pt catalyst to form the alkyne–$PtCl_2$ complex **369**, which can be in equilibrium with zwitterionic complex **368**, triggers a 1,2-*O*-acyl migration to give oxonium ion complex **370**. Charge readjustment leads to the formation of platinacarbene intermediate **371** which mainly undergoes cyclization to give the six-membered ring **367**. An alternative mechanism would be the previously mentioned *endo-trig*-pathway, followed by the acetate migration. Methanolysis furnishes cyclic cyclopropyl ketone **372**. This process has been the source of numerous recent reports. Uemura developed an intermolecular version of the process using $PtCl_2$ and mainly $[RuCl_2(CO)_3]_2$ as catalyst.[330]



Scheme 91



373 **374**

Scheme 92

This reaction has also opened a rapid access to various polycyclic compounds, as illustrated by the transformation of a mixture of diastereomers **373** into tricyclic compound **374** as a single diastereomer, through a completely stereoconvergent process (Scheme 92). Interesting entries into the syntheses of carane family natural products have also been disclosed by Fürstner with $AuCl_3$[331] and by Marco-Contelles with $PtCl_2$.[332]

In the reaction of disubstituted alkynes, 1,3-migration of the acetate takes place to give allenyl esters that can be versatile substrates, especially for [3,3]-Cope rearrangements.[333] 1,5-Enynes have proved to be versatile substrates for the preparation of perfumery agents such as sabinol[334] and sabina ketone.[335] Transannular systems undergo similar reactions.[336]

There is an interesting issue associated with the transfer of chirality in these transformations. Using highly reactive gold complexes and highly enantioenriched 1,4-enyne-3-acetates, Toste revisited the Rautenstrauch isomerization and confirmed that the reaction leading to the formation of 2-cyclopentenones proceeded with a high degree of chirality transfer. This suggests that C–C bond formation is taking place before the scission of the stereogenic C–O bond.[337]

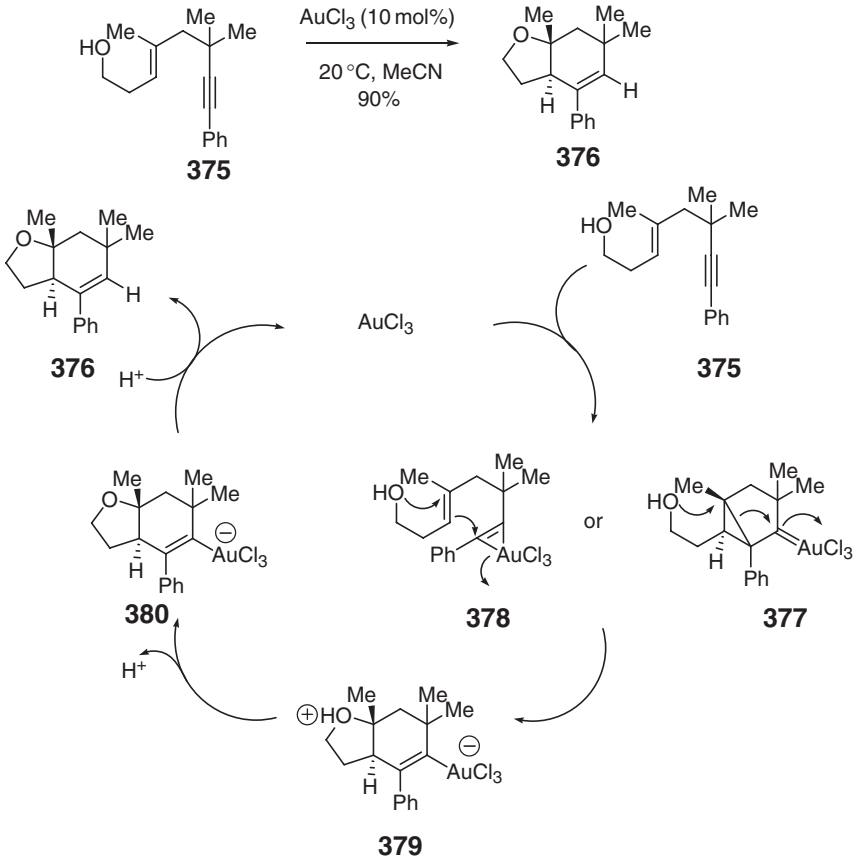
1,5-Enyne systems have also been the source of important contributions, especially involving gold(I) or gold(III) complexes.[338] Kozmin[339] has reported a gold-catalyzed assembly of heterobicyclic systems like **376**, which consists of a double cyclization of simple 1,5-enynes of type **375** tethered with either oxygen or nitrogen-based nucleophiles (Scheme 93). The diastereospecific course of the reaction is rationalized by either a concerted process via an η^2-gold complex **378** or via a stepwise mechanism involving a nucleophilic opening of the cyclopropyl gold–carbene intermediate **377**, followed by a 5-*endo-dig*-process. Proton transfer from the resulting intermediate **380** completes the construction of the bicyclic framework.

An electron-enriched 1,3-diene moiety as in the substrate **381** can act as a nucleophile toward an activated alkyne moiety (Scheme 94). Iwasawa[340] has reported an elegant synthesis of a diquinane framework **382**, which is catalyzed by various metals and the rhenium(I) complex appears to be the best catalyst among the metal complexes examined. Minor product **384** presumably is formed through an insertion of a carbenoid species into the neighboring activated benzylic C–H bond. The same carbenoid species can undergo a 1,2-H shift to give the major product **383**.

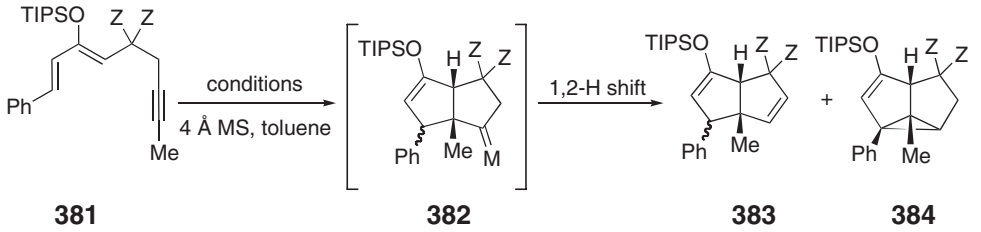
Uemura's group has developed an efficient method for the one-step synthesis of fused polycyclic compounds through an intramolecular cyclization of a propargyl alcohol moiety onto a pendant olefin moiety of enyne substrates **385** to give the tetracyclic compounds **386** as with high *syn*-selectivity (Scheme 95).[341] An intriguing aspect of this reaction is that the catalyst is a mixture of a ruthenium and a platinum complex, each acting separately and selectively. The thiolate-bridged diruthenium complex first promotes propargylic substitution via allenylidene complex **387**. Then an ene reaction follows to give a 1,5-enyne system **388**, which cyclizes in the presence of $PtCl_2$ to afford **386** in a 5-*endo-dig*-manner.

10.07.4.2 Dienes and Polyenes

Interestingly, the transition metal cycloisomerization of 1,6-dienes was discovered before that of enynes. The first report by Malone in 1971[342] was for the reaction of diallyl ether catalyzed by hydrated rhodium trichloride in the presence of a small amount of allyl alcohol. In 1984, Grigg disclosed the feasibility of the rhodium- and palladium-catalyzed cycloisomerization of 1,6-, 1,7- and 1,8-dienes to cyclopentenes and methylenecyclopentenes.[343] Very recently, this reaction has witnessed renewed interest. A variety of metal complexes have been shown to catalyze this process, including Ni,[344] Pd,[345] Ru,[346,347] and also metathesis catalysts.[348] In the case of metathesis catalysts, the nature of the diene substrates dictates the fate of the reaction, that is, metathesis or cycloisomerization.[349] Mechanistic studies by RajanBabu, Wiedenhoffer,[350,351] and Lloyd-Jones[352] have given deeper insight and support for the intervention of a metallacyclopentane intermediate. Most of these studies have been comprehensively reviewed by Lloyd-Jones.[186] From a synthetic point of view, some promising results on the asymmetric cycloisomerization of dienes deserve attention. Diallyl malonate and diallyl tosylamide are certainly the most frequently used



Scheme 93

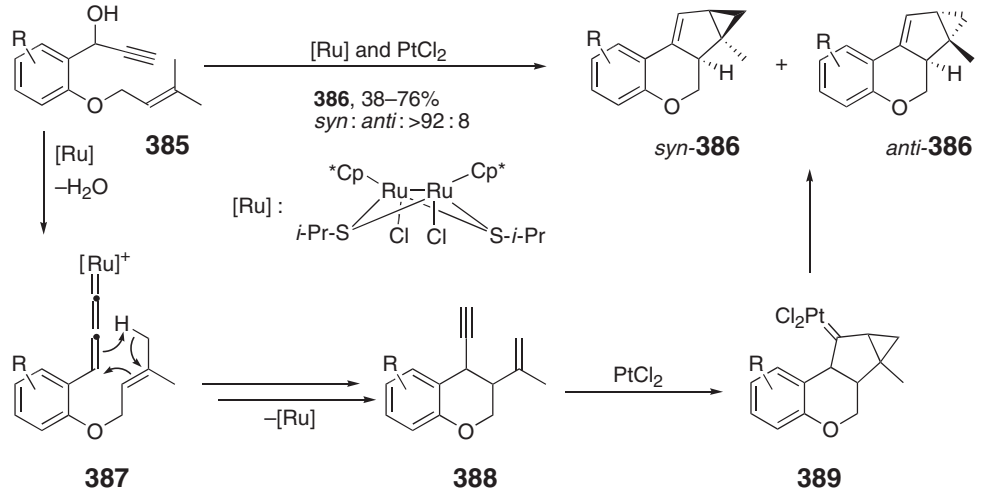


381 **382** **383** **384**

Conditions	*t* (h)	*Yield* (**383** + **384**) (%)	**383** ($\alpha:\beta$) : **384**
$[W(CO)_6]$ (10 mol%), $h\nu$	4	88	86(9 : 1) : 14
$[PtCl_2]$ (10 mol%), 70 °C	48	67	59(1.3 : 1) : 41
$[AuBr_3]$ (10 mol%), RT	24	79	65(7.7 : 1) : 35
$[ReCl(CO)_5]$ (10 mol%), $h\nu$	3	98	91(12.5 : 1) : 9
$[ReCl(CO)_5]$ (0.5 mol%), $h\nu$	16	92	86(4.2 : 1) : 14

Z = CO_2Me, TIPS = triisopropylsilyl, MS = molecular sieves.

Scheme 94



Scheme 95

test substrates for these studies. Pioneering work by Heumann[353,354] showed that a cationic palladium catalyst made from $(CH_3CN)_2PdCl_2$ and $AgBF_4$, in the presence of chiral *N,N*-ligands like sparteine, gave the cyclization products with ee's up to 60% but with low conversion and regioselectivity.

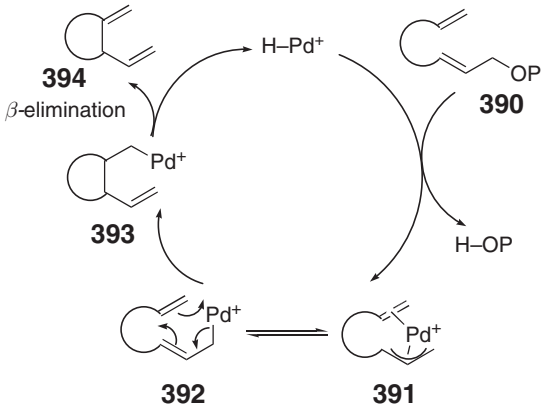
Very recently, Leitner has reported cationic nickel(II) catalyst systems for the cycloisomerization of diethyl diallyl malonate that shows high activities and regioselectivities for the formation of diethyl 3-methylene-4-methylcyclopentane-1,1-dicarboxylate with ee values up to 80% when using Wilke's azaphospholene ligand.[355]

Another approach is based on the palladium-catalyzed intramolecular carbocyclization of the allylic acetate moiety with the alkene moiety (Scheme 96). After the formation of a π-allylpalladium complex, with the first double bond the intramolecular carbometallation of the second double bond occurs to form a new C–C bond. The fate of the resulting alkylpalladium complex **393** depends on the possiblity of β-elimination. If β-elimination is possible, it generates a metallated hydride and furnishes the cycloadduct **394**. This cyclization could be viewed as a pallada–ene reaction, in which palladium replaces the hydrogen atom of the allylic moiety.[231]

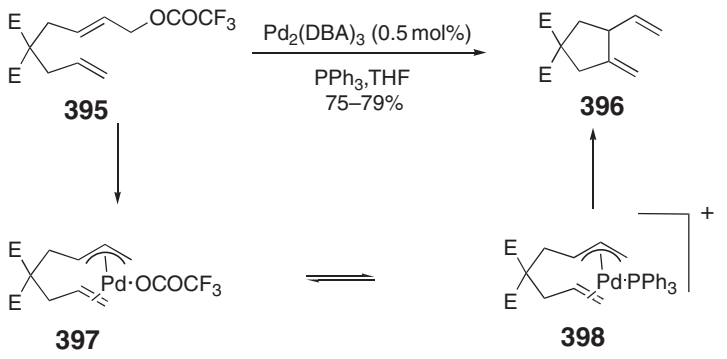
Echavarren has studied the carbometallation step of the olefin moiety and showed that the reaction proceeds through a cationic complex such as **398** (Scheme 97).[356]

Thus, after the formation of the π-allyl complex **397** from the corresponding allyl trifluoroacetate, an exchange of ligand with triphenylphosphine generates **398**. The formation of the phosphine–Pd complex **398** appears to be the key to successful cyclization, because the complex **397** failed to cyclize.

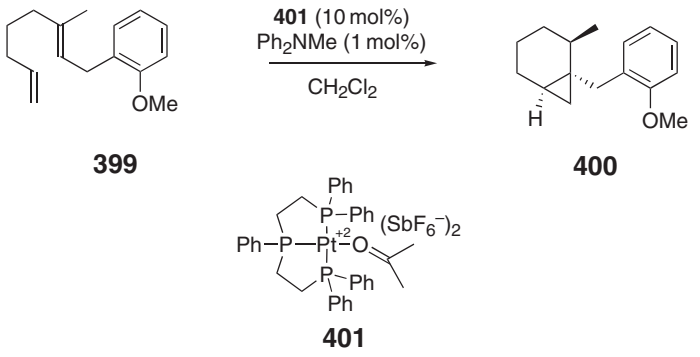
An asymmetric version of such a cyclization has been developed, but the yield and the enantioselectivity are moderate.[357] It is worth noting that these reactions can be performed in aqueous medium.[358]



Scheme 96



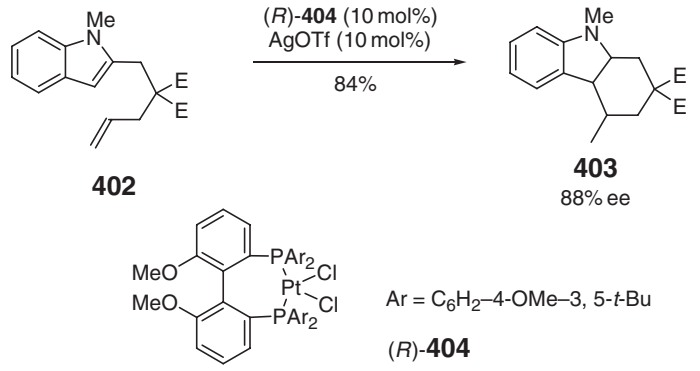
Scheme 97



Scheme 98

In connection to the discussion on skeletal rearrangement (Section 10.07.4.1.4) and based on Vitagliano's results on the dimerization of olefins,[359] Gagné[360] has studied the cycloisomerization of 1,6-dienes using a particular electrophilic pincer-ligated platinum(II) dication as the catalyst (Scheme 98).[361] In a rather atypical manner, cyclopropanation takes place to form the terpene-like bicyclo[4.1.0]-product. The proposed mechanism for this reaction is consistent with a cycloisomerization process which proceeds via carbocation, intermediates which are generated because of the inhibition of β-hydride elimination. The corresponding cyclohexene product can be obtained by using another pincer ligand.[360]

A closely related dicationic platinum complex has been shown to transform efficiently β-citronellene into *cis*-thujane in a highly diastereoselective manner, which mimics terpene biosynthesis.[362] Also, using platinum(II) catalysis, Widenhoefer has reported an intramolecular alkylation of indoles with unactivated olefins, which can be carried out in an enantioselective fashion (Scheme 99).[363]



Scheme 99

Widenhoefer has also disclosed an interesting extension consisting of hydrosilylative cyclization of a diene catalyzed by palladium. High enantioselectivity (up to 95% ee) was achieved by using palladium catalysts with C_1-symmetric pyridine–oxazoline ligands[351,364] and recent mechanistic studies have confirmed the involvement of an intramolecular carbometallation step.[365]

10.07.4.3 Polyenes

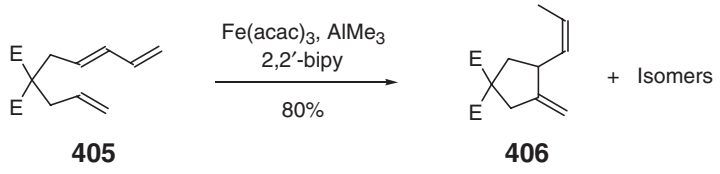
Takacs has reported the cyclization of ω-enedienes catalyzed by an iron(0) complex that is generated *in situ* through the reduction of iron(III) tris(acetylacetonate) with triethylaluminum in the presence of a ligand such as 2,2′-bipyridine or bisoxazoline (Scheme 100). The 1,4-diene cycloadducts are obtained in very good yields.[366]

The complexation of the two π-systems to Fe(0) species, followed by the oxidative cyclization, furnishes the iron(II) complex **408**. After β-hydride elimination, the reductive elimination affords the cycloadduct **406** (Scheme 101).

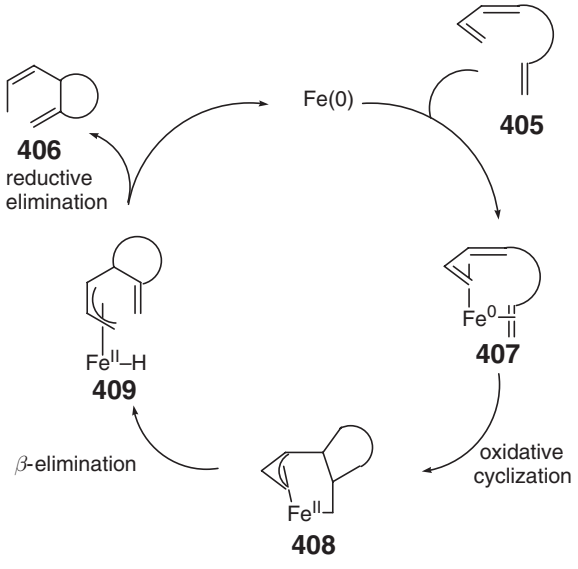
The effects of the allylic substituent, the alkene geometry, and the diene substitution as well as the influence of resident stereogenic centers incorporated in the tether connecting the 1,3-diene and the alkene subunits were totally investigated. This process has been applied to the reactions of more elaborated systems including heterocyclic structures,[367] and the total synthesis of (−)-gibboside.[368]

The palladium complexes are the catalysts of choice for the cycloisomerization of the bisdienes,[369] which lead to the formation of either five- or six-membered enedienes with *trans*-stereorechemistry for the vicinal substituents in the newly formed ring in high yields (Scheme 102).[370]

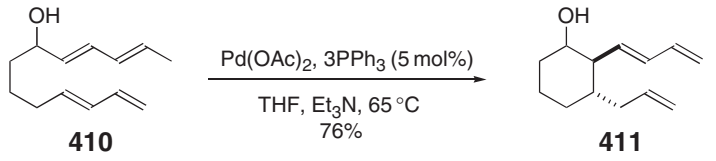
Labeling studies showed that the hydrogen is not transferred intramolecularly, that is, deprotonation rather than β-elimination takes place.[370] Recently, through the screening of five catalyst precursors and thirteen ligands, Takacs has optimized the formation of *N*-hydroxyphthalimide.[371]



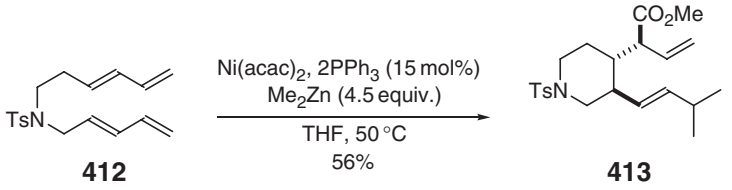
Scheme 100



Scheme 101



Scheme 102



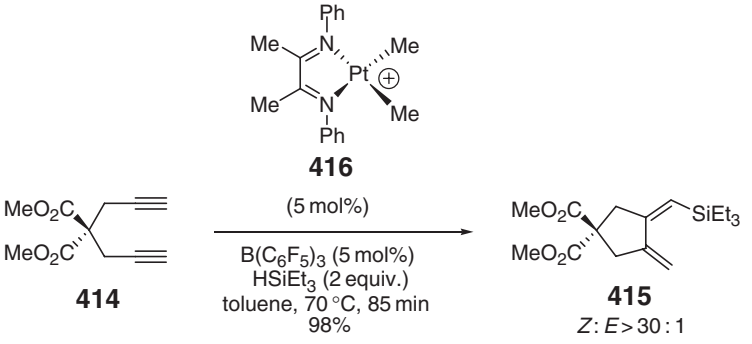
Scheme 103

Inspired by the well-established nickel-catalyzed co-oligomerization of 1,3-dienes with CO_2, which proceeds via bis-π-allyl intermediate, Mori has developed a powerful intramolecular version of this process (Scheme 103). After insertion of CO_2 into the bis-π-allyl complex, a transmetallation with an organozinc reagent takes place to generate the Ni(0) catalyst. Highly functionalized carbo- and heterocyclic compounds with complete stereocontrol can[372] be synthesized by this method.

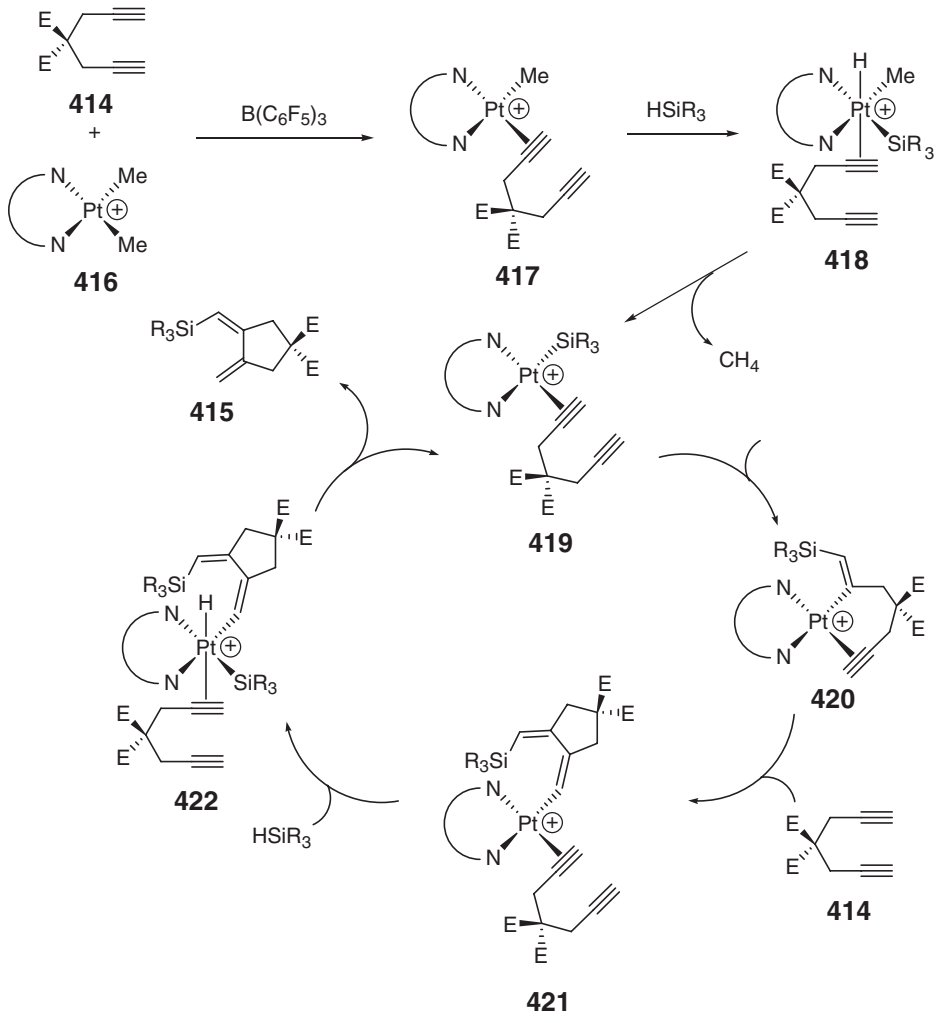
10.07.4.4 Diynes

Platinum-[373] and rhodium-catalyzed[374] carbocyclization/hydrosilylation of 1,6- and 1,7-diynes have been investigated by Widenhoefer. In the case of platinum, this process is catalyzed by a cationic complex **416** with a diimine as ligand (Scheme 104). This reaction proceeds in the presence of tri(pentafluorophenyl)borane and 2 equiv. of triethylsilane as reducing agent in toluene to give the silylated 1,2-dialkylidene cyclopentane **415** in good yield and moderate to high stereoselectivity in favor of the (*Z*)-isomer. A number of experiments show high functionality tolerance like amide, ester, sulfone, silyl ether, and ketone. Substitution of one of the alkynyl groups plays against the efficiency of the reaction. However, the reaction of substrates with an electron-deficient internal triple bond affords the desired products in moderate yield.

The proposed mechanism starts with a methyl group abstraction on platinum complex **416** with the borane reagent in the presence of diyne **414** (Scheme 105). The square-planar cationic diyne–platinum(II) complex **417** is converted to the octahedral platinum(IV) hydride intermediate **418** through oxidative addition of the hydrosilane. This complex decomposes rapidly with methane release to form another tetracoordinated platinum(II) species **419**, followed by platinasilylation of the triple bond. The resulting vinylplatinum **420** undergoes an intramolecular carboplatination to



Scheme 104

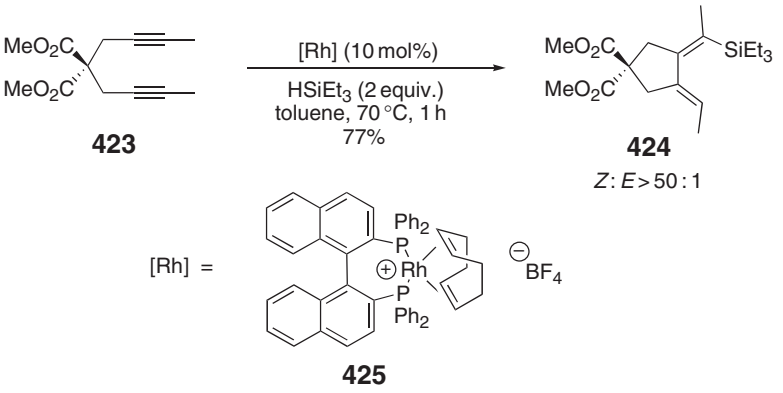


Scheme 105

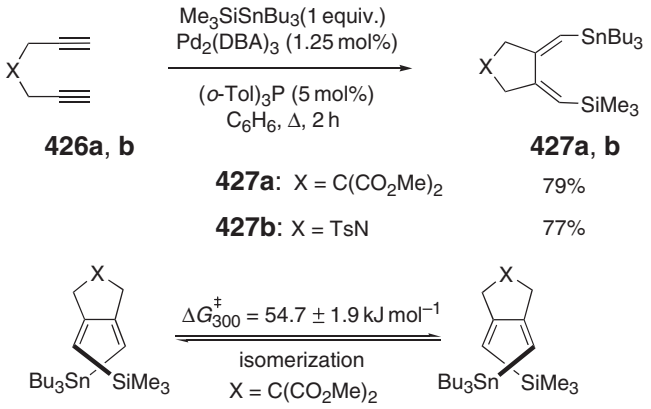
the other triple bond. Coordination of another diyne molecule to the platinum, followed by oxidative addition of another hydrosilane, generates the platinum(IV) intermediate **422**, which is readily decomposed via reductive elimination to release the cyclization product **415** and regenerate the catalyst.

The rhodium-catalyzed cyclization/hydrosilylation of internal diyne proceeds efficiently with high stereoselectivity (Scheme 106). However, terminal diynes show low reactivity to rhodium cationic complexes. Tolerance of functionalities seems to be equivalent between the rhodium and platinum catalysts. The bulkiness of the hydrosilane used is very important for the regioselectivity of the rhodium-catalyzed cyclization/hydrosilylation. For example, less-hindered dimethylethylsilane gives disilylated diene without cyclization (resulting in the double hydrosilylation of the two alkynes), and *t*-butyldimethylsilane leads to the formation of cyclotrimerization compound.

RajanBabu developed an original method for the bis-functionalization/cyclization of 1,6-diynes leading to the formation of asymmetrical internal 1,3-dienes.[375] Trialkylsilyltributyltin and 1,6-diyne react under palladium catalysis following a sequential reaction involving cyclization, stannylation, and silylation (Scheme 107). Bis-alkylidene cyclopentane **427a** and pyrrolidine **427b** derivatives were obtained in good yields. *Z,Z*-stereochemistry of substituted 1,3-dienes should impose a non-planar structure by steric demand of the silyl and stannyl groups. The system thus formed is a very interesting example of helical chirality.[376] The activation energy of the enantiomerization has been determined and the surprisingly low value ($\Delta G = 52$–$57\ \text{kJ mol}^{-1}$ at 300 K) is attributed to angular properties of exocyclic bonds. The bulkiness of Si and Sn substituents does not affect the rapid equilibration between the two helical forms at room temperature.



Scheme 106



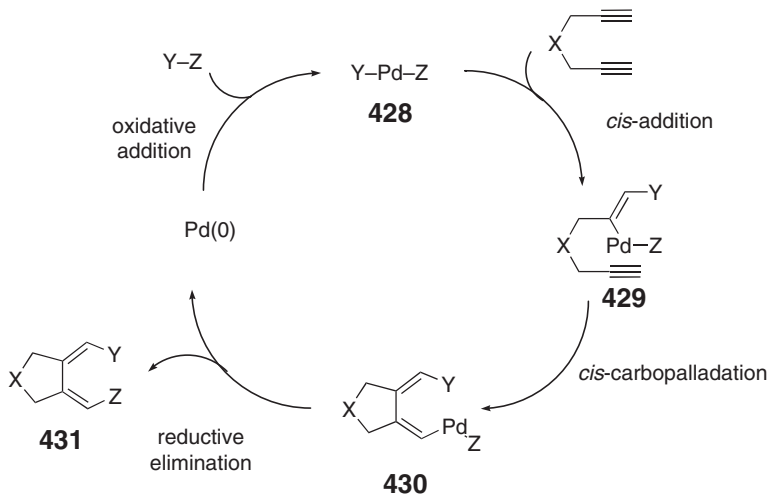
Scheme 107

Insertion of palladium into the Si–Sn bond generates intermediate **428** that undergoes *cis*-addition on the triple bond (Scheme 108). The resulting vinylpalladium **429** ensures the carbopalladation of the second triple bond followed by reductive elimination with retention of stereochemistry.[376]

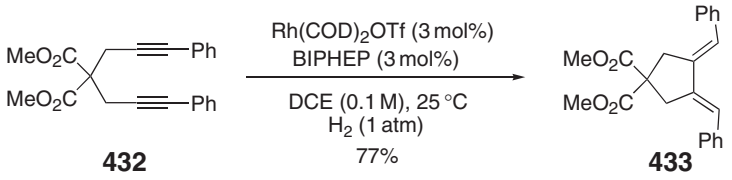
The same type of bis-functionalization has been reported for the palladium-catalyzed borylstannylative carbocyclization of 1,6-, 1,5-, 1,7-diynes, bis-propargylamine, and ether.[377] It should be noted that even 1,2-dialkylidene cyclobutane can be obtained in reasonable yield. Ito has proposed the related silaborative reaction involving nickel(0) catalysis.[378] This reaction has been performed in an intra- and intermolecular fashion. The intramolecular reaction allows the formation of cyclic dienes and the intermolecular process proceeds through a dimerization of alkynes to give acyclic dienes.

1,2-Dialkylidene cyclopentanes can be obtained via a rhodium-catalyzed reductive cyclization of diynes in the presence of molecular hydrogen, which is termed "C–C bond-forming hydrogenation" (Scheme 109).[379] This carbocyclization of 1,6-diynes involves a cationic rhodium(I) pre-catalyst. At ambient temperature under 1 atm of molecular hydrogen as terminal reducing agent, cyclic dienes **433** are obtained in good to excellent yields as single stereoisomer. Different ligands have been tested, and best results were obtained with BIPHEP and *rac*-BINAP. Reaction of unsubstituted alkynes provides cyclization products in poor yields. Pre-organization by Thorpe–Ingold effect does not seem to be necessary for an efficient cyclization process.

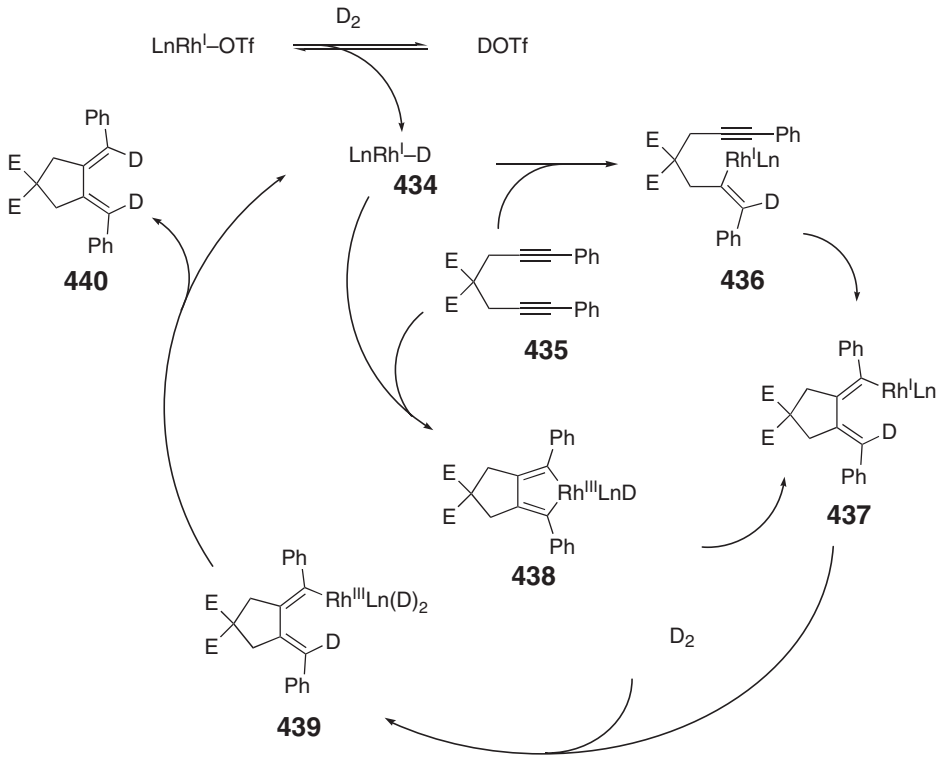
In order to probe the mechanism, this transformation was conducted under molecular deuterium atmosphere with cationic rhodium(I) complex (Scheme 110). The final compound **440** showed the incorporation of two deuterium atoms in each double bond. This is in agreement with a heterolytic activation of D_2. Two different pathways are proposed. The first one involves the formation of a rhodacycle **438** followed by reductive elimination. The second one consists of a deuteriorhodation/carborhodation sequence, affording the same intermediate **437**. A vinylrhodium



Scheme 108



Scheme 109



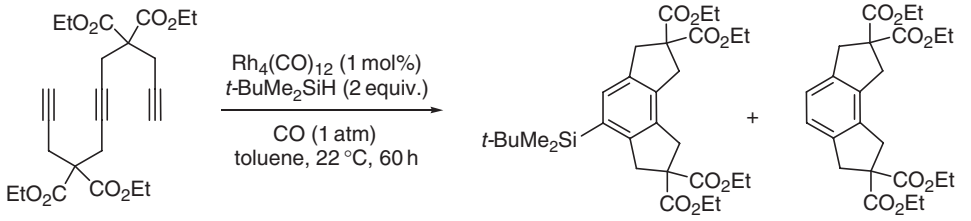
Scheme 110

species reacts with D_2 followed by reductive elimination, affording dideuterated compound and regenerating catalytic rhodium species **434**.

Extensively developed by Ojima and co-workers, SiCaT and carbonylative silylcarbocyclization (CO-SiCaC) represent a rapid entry into polycyclic molecules of interest.[271] For instance, the rhodium-catalyzed intramolecular SiCaT of triyne **441** afforded tricyclic compound **442** in high yield, accompanied by a small amount of cycloadduct **443** (Scheme 111).[270]

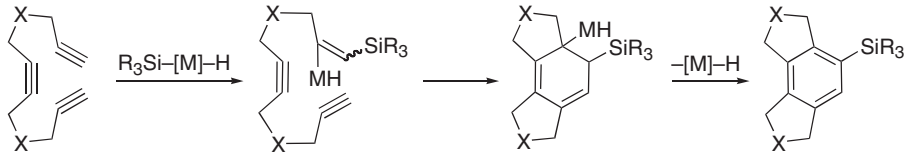
It is worth noting that product **443** was not obtained without silicon assistance, which means that the reaction is in fact initiated by an Si–[Rh] species (Scheme 112). Fused tricyclic benzenes such as **443** are formed exclusively using an exactly stoichiometric amount of silane. On the other hand, 2 equiv. of silane preferably lead to the formation of silylated benzenes such as **447** through a hydrosilylation–carbocyclization–β-hydride elimination cascade process.

Ruthenium(II)-catalyzed cycloadditions of diynes with bicycloalkenes illustrate the synthetic importance of ruthenacyclopentatrienes as biscarbenoid intermediates.[380] Reaction of 1,6-diyne **448** and biscyclic alkene **449** with ruthenium catalyst afforded a mixture of biscyclopropanation product **450** and cyclotrimerization product **451** (Scheme 113).



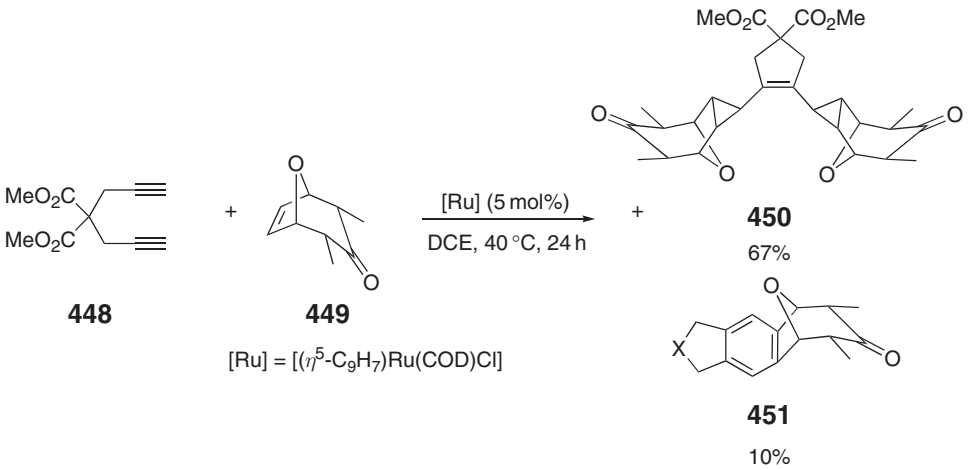
441 **442** 93% **443** 7%

Scheme 111



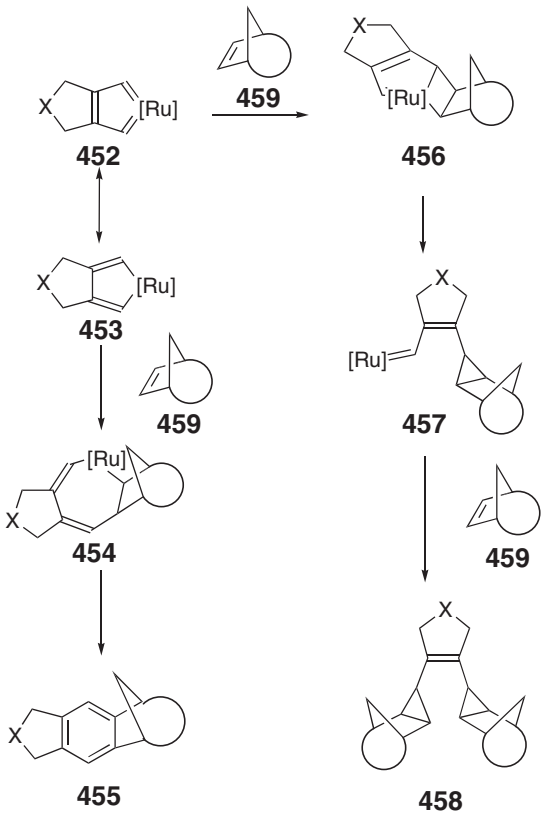
444 **445** **446** **447**

Scheme 112



448 **449** **450** 67% **451** 10%

Scheme 113



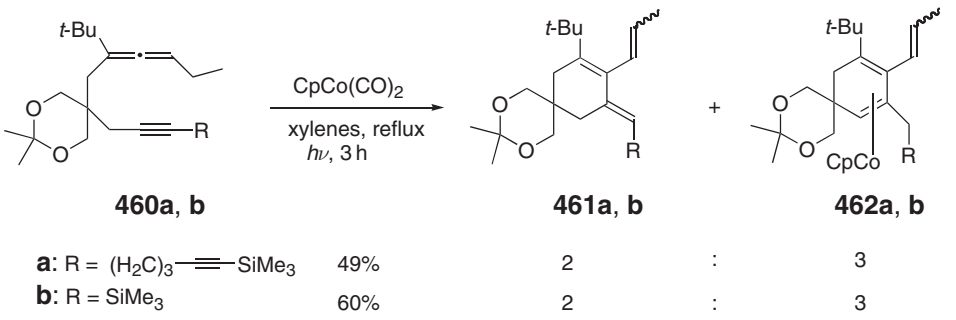
Scheme 114

From the mechanistic point of view, the observed competitive reactions can be explained by considering two different pathways (Scheme 114). The intermediacy of ruthenacyclopentadiene **453** or biscarbenoid **452**, formed from the reaction of a diyne and a ruthenium(II) complex, is postulated in the proposed mechanism. Cyclopropanation of the alkene starts with the formation of ruthenacyclobutane **456**, which leads to the generation of the vinylcarbene **457**. Then, the second cyclopropanation occurs to afford the biscyclopropyl product **458**. Insertion of the alkene **459** into the ruthenacyclopentadiene **453** affords the ruthenacycloheptadiene **454**. The subsequent reductive elimination gives the cyclotrimerization product **455**. The selectivity toward the bis-cyclopropyl product **458** is improved with an increasing order of haptotropic flexibility of the cyclopentadienyl-type ligand.

Hydrative cyclization of diynes with ruthenium catalyst has been reported for the synthesis of sulfolenes or enones in aqueous medium.[381] Reactions of unsymmetrical 1,6-diynes have been investigated, and some substrates are found to exhibit a directing effect of the ketone moiety in a pendant group.

10.07.4.5 Allenynes

Allenynes are highly appealing substrates for organometallic catalysis, because of their high level of unsaturation.[382] Reactions of allenynes have been mainly applied to two types of reactions: Pauson–Khand [2 + 2 + 1]-reaction, and Alder-ene reaction that gives cross-conjugated trienes. These two reactions are reviewed in Chapters 11.12 and 10.12, respectively. During their study on the cobalt-catalyzed [2 + 2 + 2]-reaction of allenynes, Malacria and Aubert discovered the first example of metal-mediated Alder-ene reaction with $CpCo(CO)_2$ (Scheme 115).[383] When the allenyne **460a** was exposed to a stoichiometric amount of (η^5-cyclopentadienyl)cobalt dicarbonyl [$CpCo(CO)_2$] under irradiation in refluxing xylenes for 3 h, a 2 : 3 mixture of the adduct **461a** and the (η^4-cyclohexadiene)cobalt complex **462a** was obtained in 49% yield. Adducts **461a** and **462a** consisted of a 7 : 3 mixture of (*E*)- and (*Z*)-isomers. No traces of [2 + 2 + 2]-cycloadducts were observed, which means that the silylated triple bond in the substituent R was not

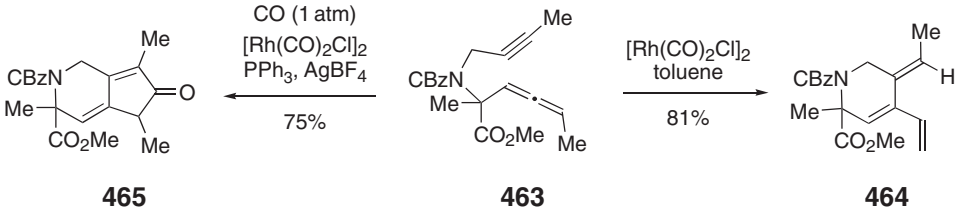


Scheme 115

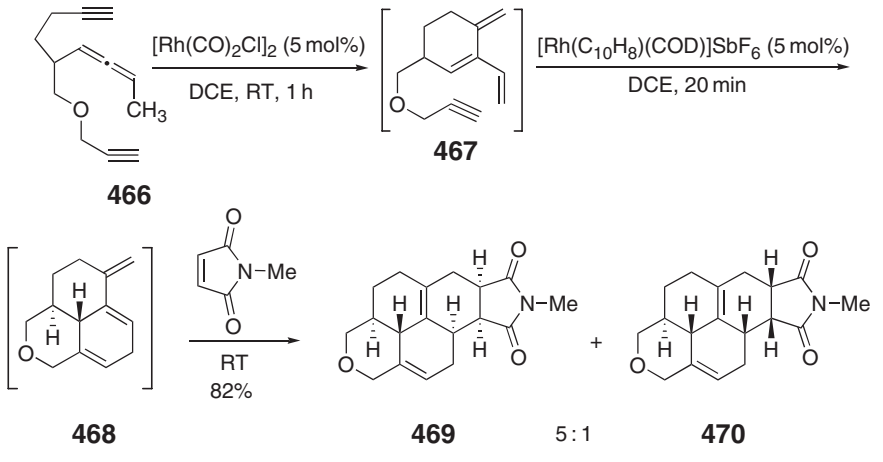
involved in the overall process. Similarly, exposure of the allenyne **460b** to $CpCo(CO)_2$ under the same conditions led to the formation of **461b** and **462b** in 60% yield.

Currently, these reactions are typically conducted with Rh(I) or Ir catalysts.[384,385] The Pauson–Khand-type reaction of allenynes has also witnessed important developments,[386,387] especially in its applications to natural products synthesis.[388] Brummond's group has been very productive in both areas. Duality in the reaction of allenynes is shown below. In the context of diversity-oriented synthesis, simply changing the reaction conditions gives versatile heterocycles in high yields (Scheme 116).[389]

Acyclic allenynes can be efficiently converted into tetracyclic compounds via consecutive rhodium-catalyzed Alder-ene, rhodium-catalyzed intramolecular Diels–Alder cycloaddition, and Diels–Alder cycloaddition of the resulting diene with an external nucleophile (Scheme 117).[390] For example, the Rh-catalyzed Alder-ene reaction transformed the alkynyl allene **466** to the triene–yne **467** using rhodium biscarbonyl chloride dimer as a catalyst. Conversion of **467** to the triene **468** was achieved using either $[Rh(dppe)Cl]_2$, in the presence of $AgSbF_6$, or $[Rh(C_{10}H_8)(COD)]SbF_6$. Exposure of the triene **468** to an external dienophile gave the desired *N*-methylsuccinimide tetracyclic products in good yield. This one-pot procedure is highly chemoselective for the Alder-ene reaction, and



Scheme 116



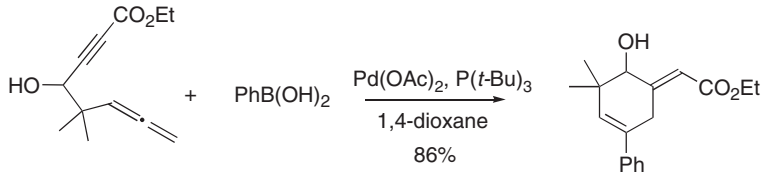
Scheme 117

the first intramolecular Diels–Alder reaction provides a single isomer. Although not diastereoselective, the second intermolecular Diels–Alder reaction is highly regioselective when unsymmetrical dienophiles are employed. The trapping of the cycloadduct **468** with methyl vinyl ketone regioselectively furnished the corresponding tetracyclic product in 75% yield **468** as a 1 : 1 mixture of diastereomers. Better diastereoselectivity (up to 5 : 1) was obtained when using symmetrical cyclic dienophiles such as *N*-methyl maleimide (Scheme 117).

Alacaide has fixed the allene and the yne moieties as pendant arms in a β-lactam skeleton and carried out the Pauson–Khand-type reaction as well as an unprecedented tandem allene-cyclization/intramolecular Heck reaction.[391] Oh has shown that 6-allen-1-ynes exhibit different modes of cyclization with palladium or rhodium catalysts.[392] Thus, after the initial hydropalladation of the alkyne moiety, the vinylmetal species adds to the central carbon of the allene moiety to form a six-membered ring to give an allylmetal species, which has several possibilities for further transformations, depending on reaction conditions. In contrast, the Rh(I)-catalyzed reaction gives a five-membered ring product. A Pd(0)-catalyzed reductive cyclization of 5-allen-1-ynes in the presence of formic acid, yielding five-membered ring products, has also been reported.[393] In these reactions, hydropalladation always takes place first with the allene moiety. This inspired Oh to develop a palladium-catalyzed carbocyclization of 5-allen-1-ynes based on the initial addition of organoboronic acids to the allene moiety (Scheme 118).[394]

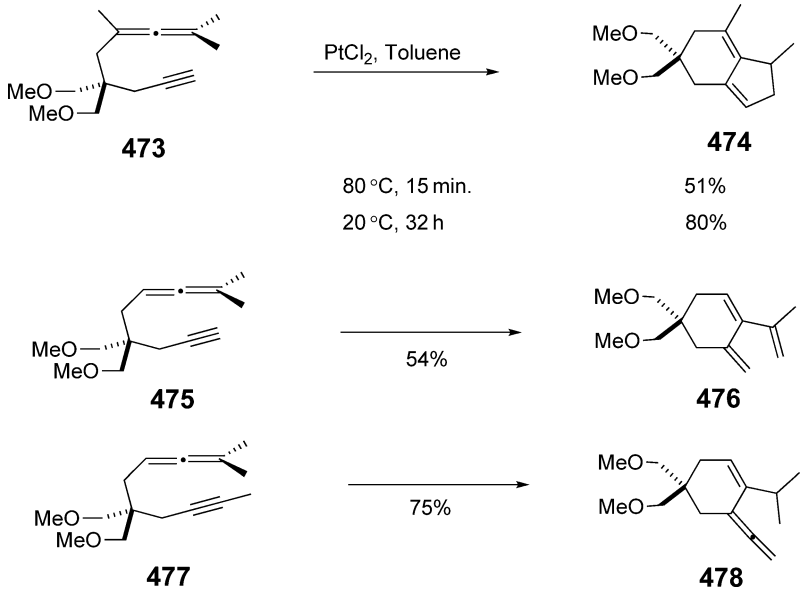
Following up the reactions presented in Section 10.07.4.4 (reactivity of **426a** and **426b**), RajanBabu has shown that trialkylsilyltrialkylstannane reagents undergo efficient and selective Pd-catalyzed additions to 1,2-dien-7-ynes and 1,2-dien-8-ynes to give stannylidene cycloalkanes bearing a vinylsilane moiety.[395] Along the same line, Shibata has disclosed a chemo- and regioselective intramolecular hydrosilylative carbocylization of allenynes.[396]

Catalysis of platinum dichloride has provided an intriguing panel of reactions of allenynes just by subtle modifications in the substitution pattern (Scheme 119). Thus, while the reaction of the allenyne **473** gives the previously unknown hydrindene product **474**, the reaction of allenyne **475** that does not have a methyl group at the internal



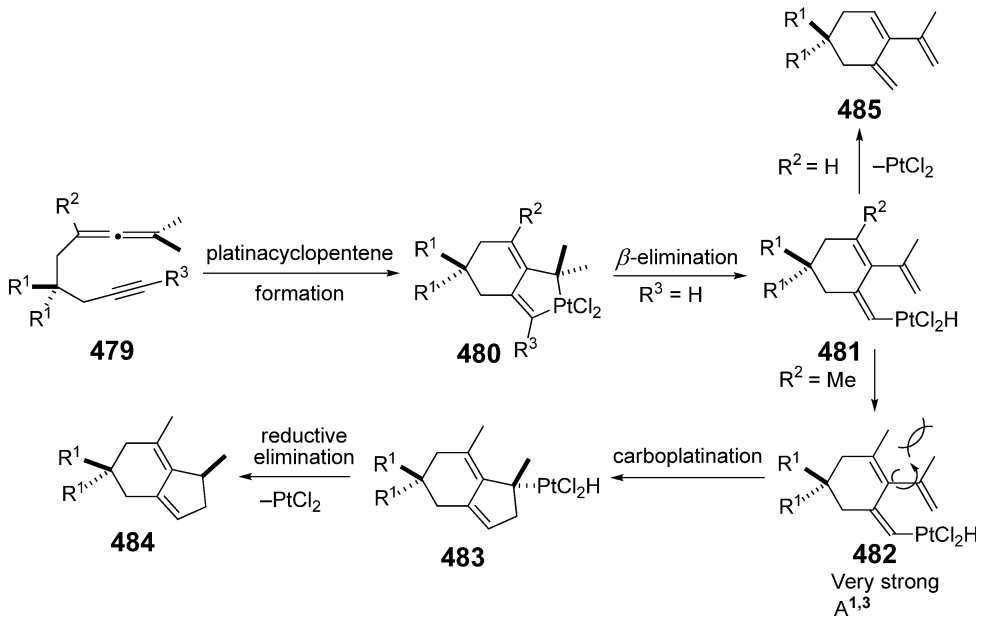
471 **472**

Scheme 118



473 **474** **475** **476** **477** **478**

Scheme 119



Scheme 120

position of the allene moiety gives the classical Alder-ene product **476**. Introduction of a methyl group in the alkyne moiety as in **477** leads to the formation of an unprecedented type of product, vinylallene **478**.

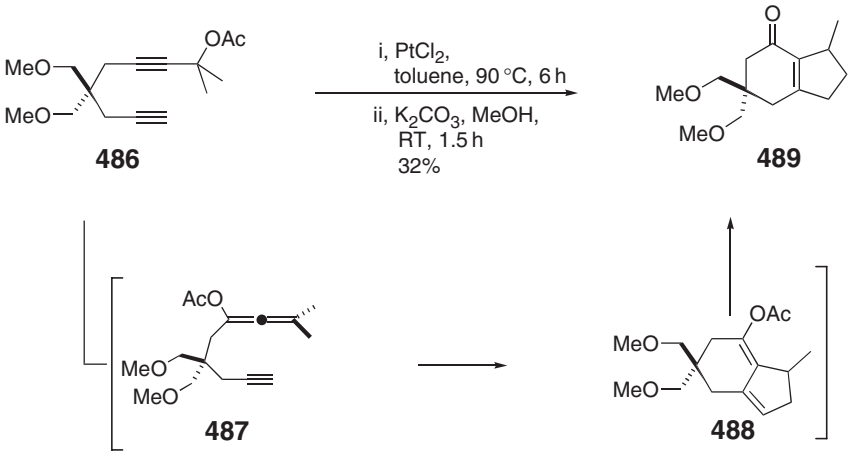
As shown in Scheme 120, the regioselective formation of platinacyclopentene intermediate **480** is followed by β-elimination to give platinahydride **481**. When R^2 is H, reductive elimination provides Alder-ene adduct **485**. However, when R^2 is Me, β-elimination generates an unconjugated diene intermediate **482** because of a strong 1,3-allylic strain between the two methyl groups. This would set the resulting methallyl group in a good position for an unprecedented 5-*endo*-*trig*-carboplatination to give intermediate **483**. A related 5-*endo*-*trig*-carbocupration of a vinylcopper species has already been invoked.[397] An alternative pathway would include an intramolecular hydroplatination. Final reductive elimination would then deliver product **484**. The unprecedented reaction of **477** ($R^3 = Me$) should be directly compared with the work of Brummond[384] in which a cyclohexyltriene is exclusively formed from the corresponding malonate using $[Rh(CO)_2Cl]_2$ as the catalyst. In contrast with Brummond's case, the elimination involves allylic hydrogens and not the hydrogen of the *gem*-dimethyl groups. Such distinct pathways exhibited by rhodium and platinum catalysts might be attributed to the substantial difference in the geometries of the intermediate metallacyclopentene complexes.

Allenynes are clearly appealing substrates for organometallic catalysis. One problem though might reside in the tedious synthesis of these substrates. In order to alleviate this issue, Malacria *et al.* have quite recently reported the dual catalysis of $PtCl_2$ (Scheme 121). The first catalytic step is a 1,3-migration of the propargylic acetate group of **486**, which generates the allenyl ester intermediate **487**.[398] The intermediate **487** then undergoes the previously described cycloisomerization process giving rise to a dienyl ester **488** that can be cleanly hydrolyzed to the bicyclic conjugated enone **489**. This reaction sequence represents an interesting case of concurrent tandem catalysis.[399]

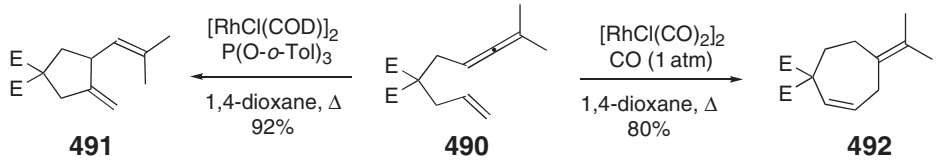
10.07.4.6 Allenenes

Allenenes have been much less involved in transition metal-mediated cyclizations than the allenyne counterparts. Nevertheless, interesting synthetic reactions have been developed mainly through the use of Rh(I) catalysis. Itoh has reported two distinct reactions of the same substrates, which depend on the nature of the catalyst (Scheme 122).[400] While *exo*-methylenecyclopentane product **491** presumably arises from a rhodacylopentene intermediate through *exo*-cyclization, the formation of *exo*-methylenecycloheptene **492** strongly suggests the intermediacy of an allylic C–H bond cleavage and formation of a π-allyl–Rh intermediate, prior or subsequent to *endo*-cyclization.

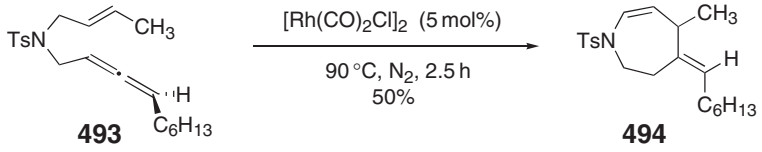
Using the same rhodium catalyst, Brummond has also observed the formation of seven-membered ring products and applied to interesting syntheses of azepines and oxepines (Scheme 123).[401]



Scheme 121



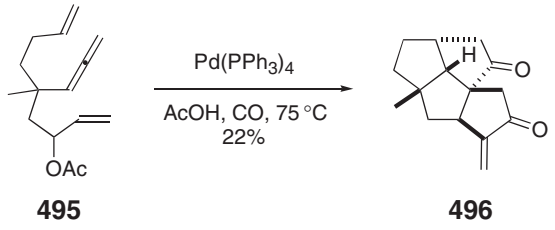
Scheme 122



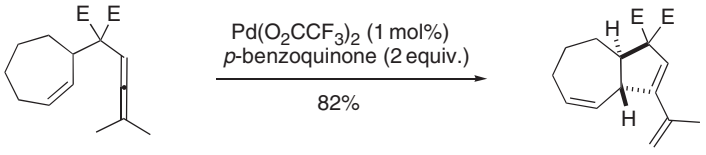
Scheme 123

An allene moiety can serve as a nucleophile vis-à-vis a π-allylpalladium species generated from an allylic acetate moiety in substrates such as **495** (Scheme 124). The cyclization involving these two moieties generates another π-allyl intermediate, and the stage is set for the subsequent carbonylative cascade process as demonstrated by the transformation of **495** to **496**.[402]

Based on a similar approach, Bäckvall[403] established the stereochemical course of such reactions and developed efficient routes to bicyclo[4.3.0]-nonadiene and bicyclo[5.3.0]-decadiene systems. Bäckvall[404] has also reported a $Pd(O_2CCF_3)_2$-catalyzed oxidative carbocyclization of allenenes (Scheme 125). The process is efficient even with catalyst loading as low as 1 mol%, although if requires *p*-benzoquinone as the stoichiometric oxidant, which represents the first example of a C–C bond formation using a catalytic amount of Pd(II). Bicyclic adducts have been obtained in



Scheme 124



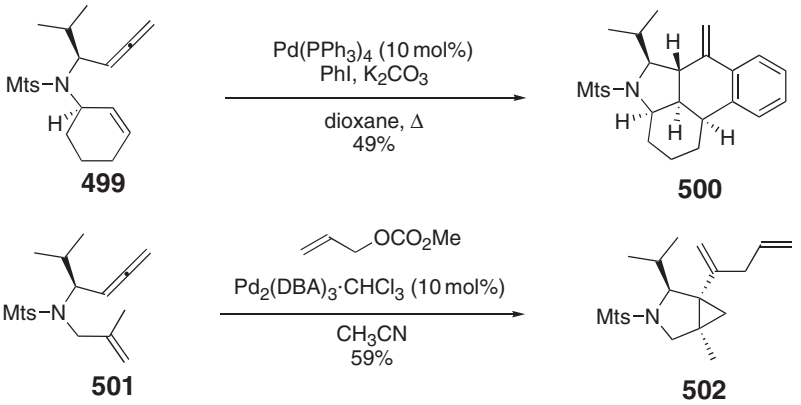
497 498

Scheme 125

good yields as shown for the synthesis of **498** from **497**. Two mechanisms can operate in these transformations, depending on the mode of the π-allyl intermediate formation which involves either the allene or the alkene functionality. This chemistry can also be extended to allene dienes.[405]

Similar to the reactions of allenynes,[394] allenenes have been shown by Tanaka to undergo a stereoselective cyclization to form pyrrolidines, which is triggered by the initial addition of an arylmetal to the allene moiety (Scheme 126).[406,407] The resulting π-allyl metal species then undergoes 5-*exo*-cyclization followed by β-elimination. If β-elimination is impeded, then carbometallation to the aromatic ring takes place to give a polycyclic product, as exemplified by the formation of **500** as a single diastereomer.[406] A more peculiar example is the formation of 3-azabicyclo[3.1.0]-hexanes such as **502**[407] in the presence of allyl carbonate.[408] The mechanism of the formation of the cyclopropane ring has not been elucidated, but it might be attributable to a Pd–carbene intermediate or to the 3-*exo-trig*-cyclization of an alkylpalladium species.

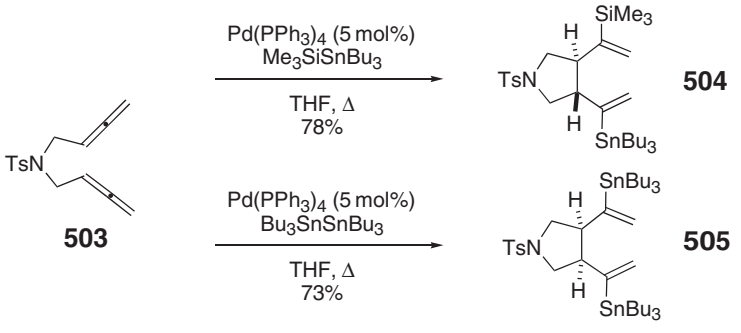
Kang has studied the Pd(0)-catalyzed silastannylation and distannylation of bis-allenes such as **503** (Scheme 127). While both processes work nicely with a complete diastereoselectivity, the relative configuration of **504** is not the



499 500 501 502

Mts: 2,4,6-trimethylphenylsulfonyl

Scheme 126



503 504 505

Scheme 127

same as that of **505**. The larger steric hindrance of the trimethylsilyl groups appears to favor the *trans*-cyclization mode.[409]

Very recently, Ma has reported a rhodium-catalyzed route to 18,19-norsteroid skeletons from bis-allenes, involving a cyclometallation–carbometallation–reductive elimination–Diels–Alder reaction cascade process.[410]

10.07.5 Concluding Remarks

The C–C bond formation by addition reactions through carbometallation has witnessed intense development over the last decade, especially processes catalyzed by group 8–11 metals. Inter-and intramolecular events, as well as sequences mixing both, can now be safely programmed to provide valuable substrates including carbo- and heterocycles. In that context, the use of judiciously designed polyunsaturated precursors has given remarkable results, and applications in the total synthesis of various natural products have been worked out. Thanks to an ever-growing arsenal of organometallic complexes and sophisticated ligands, asymmetric catalysis has already proved to be viable for the preparation of highly enantioenriched products. New opportunities are also now open with the development of skeletal rearrangement reactions that are catalyzed by electrophilic metal salts.

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10.08
C–C Bond Formation through Conjugate Addition of C–M to C═C–C═O and C═C–NO_2

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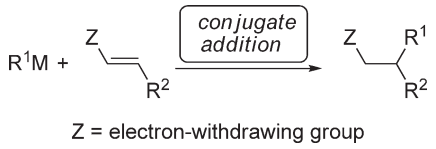
10.08.1 Introduction

Conjugate addition (1,4-addition) of carbon nucleophiles to α,β-unsaturated compounds is one of the most important carbon–carbon bond-forming reactions in synthetic organic chemistry. Notably, a broad range of donors and acceptors can be employed in this versatile reaction; the nucleophiles can be organometallic reagents, Michael donors, and some carbanions. The acceptors can be α,β-unsaturated aldehydes, ketones, esters, and nitroalkenes (Scheme 1). In recent years, the design of new chiral ligands and catalysts has led to the realization of the asymmetric 1,4-conjugate additions of dialkylzinc reagents as well as arylboronic acids with excellent levels of stereocontrol. Several review articles have dealt with various aspects of the reaction, such as the reactivity, the stereochemistry, and the reaction mechanism, although the mechanistic aspects are still somewhat controversial.[1–3] This chapter summarizes some of the most recent developments (from 1993 to 2004) in the 1,4-conjugate addition reaction employing different



Scheme 1

organometallic reagents; special attention is paid to the reactivities and enantioselectivities. Michael reaction of active methylene compounds is not included in this chapter.

10.08.2 Enantioselective Conjugate Additions

10.08.2.1 Organolithium Nucleophiles[2,3]

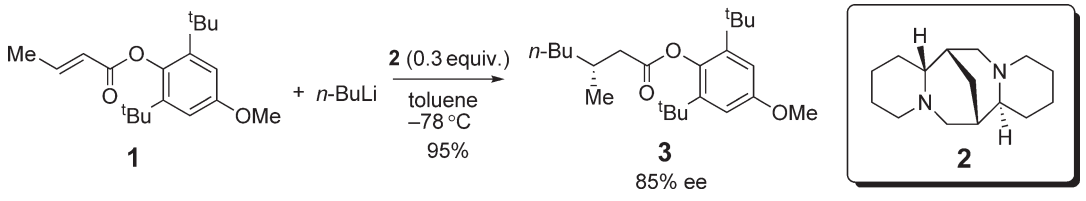
Organolithium compounds are highly reactive and have been used in a variety of organic transformations. A major problem in the development of catalytic asymmetric conjugate additions of organolithium reagents to α,β-unsaturated carbonyl compounds is that the high reactivity of RLi may cause both low chemoselectivity (1,2- vs. 1,4-addition) and low enantioselectivity.

The use of external chiral ligands, which can convert the oligomeric organolithium reagents to more reactive monomeric chiral organolithium species, has been proved to realize the asymmetric conjugate addition of organolithium reagents with satisfactory enantioselectivity. For example, the 1,4-addition of *n*-BuLi to 2,6-di-*tert*-butyl-4-methoxyphenyl (BHA) ester **1**, which contains a large steric ester moiety to ensure the 1,4-addition, gives (*R*)-**3** with 99% ee in the presence of stoichiometric amount of (−)-sparteine. Reducing the quantity of sparteine to 0.3 equiv. still yields **3** in 85% ee (Scheme 2).[4,4a] Tomioka and co-workers have successfully applied chiral diether **4,** which can also bind to organolithium to form a chiral nucleophile, to both stoichiometric and catalytic addition reaction of acyclic and cyclic unsaturated BHA esters.[4,4a,5]

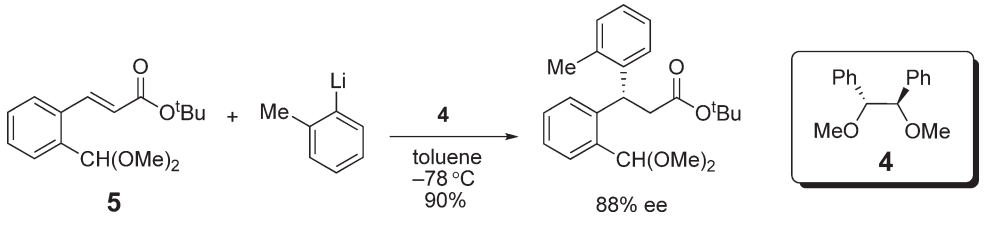
Xu and co-workers performed similar transformations on α,β-unsaturated *tert*-butyl esters **5** with aryllithium reagents. The use of functionalized substrates and aryllithiums is the key feature of this study (Scheme 3).[6]

Asymmetric conjugate addition of lithium amides to alkenoates has been one of the most powerful methods for the synthesis of chiral 3-aminoalkanoates. High stereochemical controls have been achieved by using either chiral acceptors as *N*-enoyl derivatives of oxazolidinones (Scheme 4),[7,7a–8] chiral lithium amides (Schemes 5 and 6),[9–12] or chiral catalysts.[13,14]

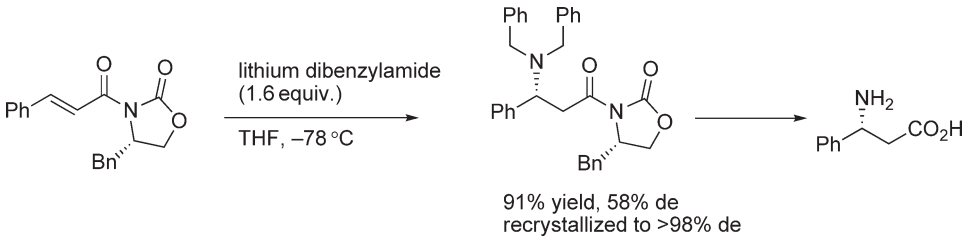
Tomioka and co-workers first described the conjugate addition of lithium *N*-benzyltrimethylsilylamide to enoates catalyzed by external chiral ligand **4** to produce β-amino esters in high enantioselectivities (up to 99% ee) and high yields (Scheme 7).[13] However, this method relies on the use of *N*-benzy-*N*-trimethylsilylamine as a nitrogen source which requires subsequent removal of the benzyl group. Another nitrogen nucleophile allylamine containing easily removable allyl group has also been developed for the asymmetric addition to alkenoates (Scheme 8).[14]



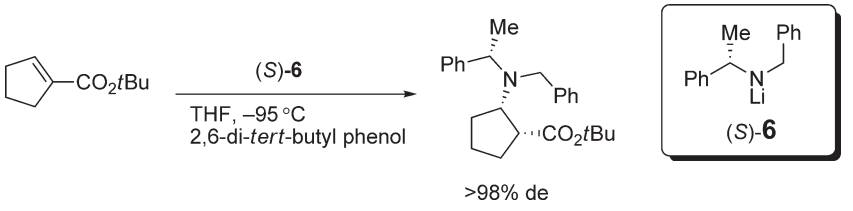
Scheme 2



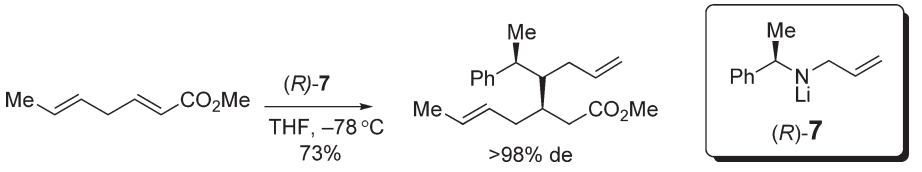
Scheme 3



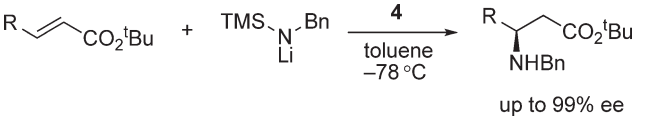
Scheme 4



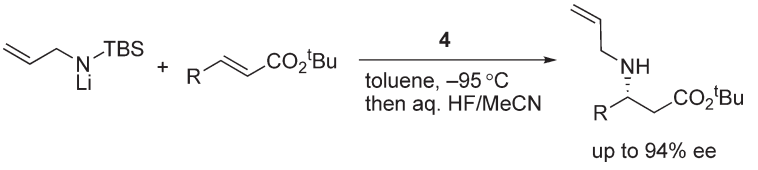
Scheme 5



Scheme 6



Scheme 7



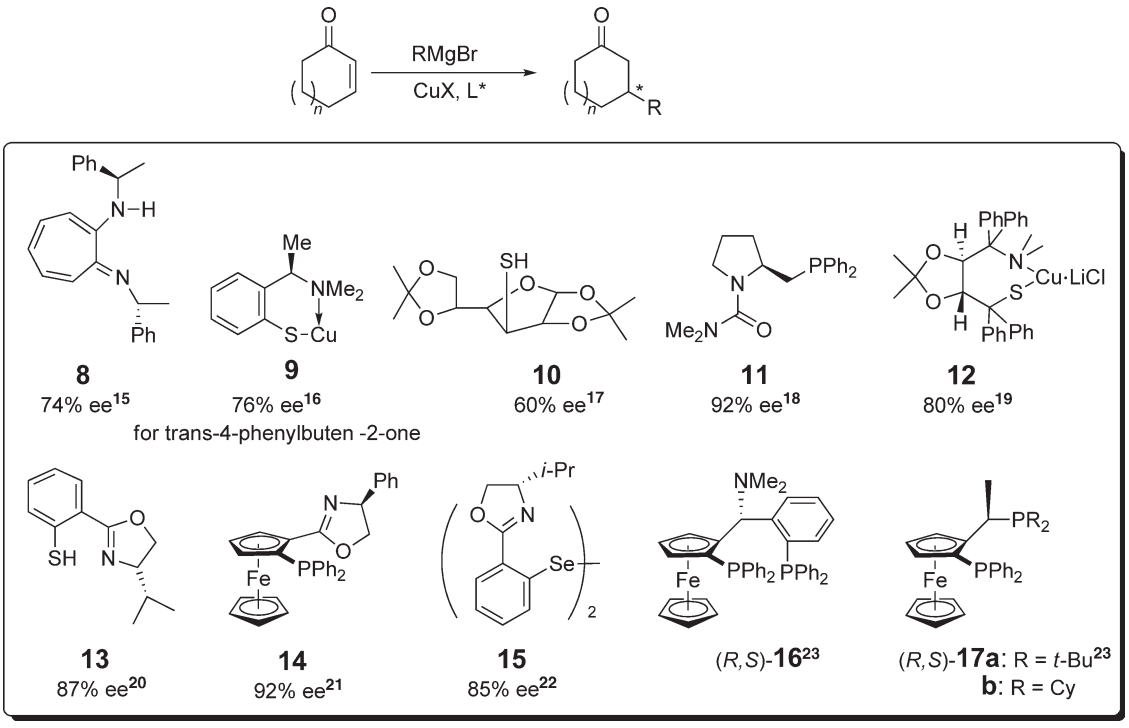
Scheme 8

10.08.2.2 Organomagnesium Nucleophiles

Though Grignard reagents are one of the most frequently employed organometallic reagents in organic reactions, considerable difficulties have been experienced in attempts to reach high stereoselectivities in the asymmetric 1,4-conjugate addition reaction due to the high reactivity of Grignard reagents and the fast, uncatalyzed 1,2-addition reaction.

In 1988, Lippard and co-workers reported the first enantioselective conjugate addition of Grignard reagent to 2-cyclohexenone using catalytic amounts of copper-amide **8** complex.[15,15a] Subsequently various ligands (e.g., **9**–**15**) were developed. Most of them combined P, S, or Se with N or O donor atoms in their structures to facilitate the selective coordination to Cu and Mg species, yet the enantioselectivities rarely reached 90% (Scheme 9).[15,15a–22]

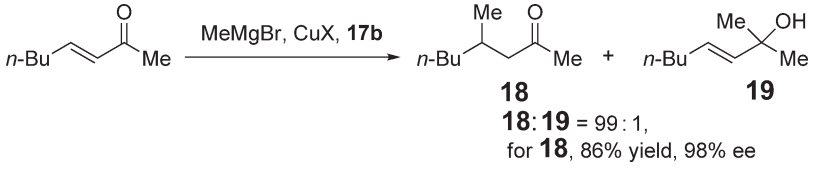
Recently, Feringa and co-workers realized the asymmetric conjugate additions of Grignard reagents to cyclic enones with enantioselectivities up to 96%.[23] The high stereocontrol was achieved by using CuCl or CuBr·SMe$_2$ as metal source, with ferrocenyl diphosphines as chiral ligands. Ligand **16** was found to be the best for the 1,4-addition of cyclohexenone (96% ee), while **17a** was superior for cyclopentenone to provide the 1,4-adduct with 99% regioselectivity and 92% ee. Compound **17a** also led to higher level of enantioselectivity (82% ee) for lactone substrate.



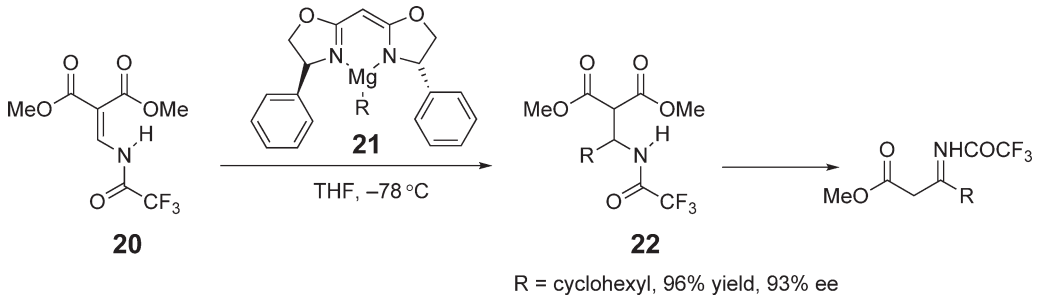
Scheme 9

In the presence of 5 mol% $CuBr{\cdot}SMe_2$ and 6 mol% **17b**, acyclic aliphatic enones can also react with Grignard reagents to provide β-substituted linear ketones in high yields (62–91%), good regioselectivities (>94 : 6), and excellent enantioselectivities (90–98%) (Scheme 10).[24]

It should be emphasized that the diastereoselective conjugate addition of organomagnesium nucleophiles to α,β-unsaturated acid derivatives attached to a chiral auxiliary is also a well-known methodology in asymmetric synthesis. One example presented by Sibi *et al.* for the preparation of β-amino esters is shown in Scheme 11.[25] The reaction of enamidomalonate **20** with Grignard reagents in the presence of a phenyloxazole compound **21** gives the target product **22** with good ee.



Scheme 10



Scheme 11

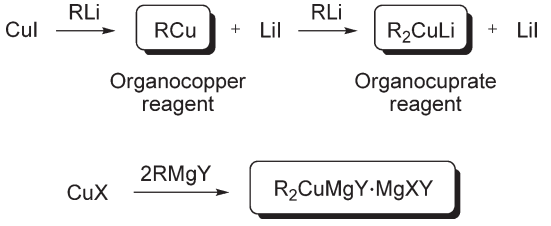
10.08.2.3 Organocopper Nucleophiles

The diastereoselective and enantioselective conjugate additions involving organocuprates have been previously reviewed with emphasis on the synthetic utility, structural properties, and mechanism.[1–3,26a,27] Organocopper compounds RCu and cuprates R_2CuLi are usually prepared by the transmetallation of organolithium or Grignard reagents with copper(I) salts (Scheme 12). The enantioselective conjugate additions of organocuprates have been realized in two ways: one used chiral non-transferable ligand and the other involved external chiral ligands.

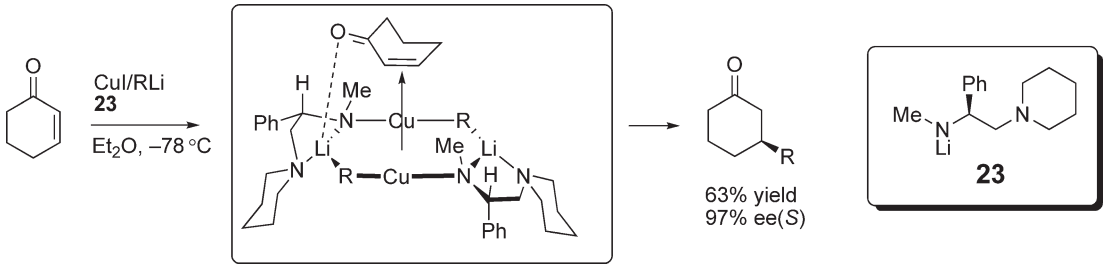
10.08.2.3.1 Organocuprates with chiral non-transferable ligand

In 1994, lithium amide **23** was used in the conjugate addition of 2-cyclohexenone to afford optically active adduct with up to 97% ee (Scheme 13).[28–29] A dimeric structure was proposed as the intermediate, where the phenyl group in **23** blocked the bottom face and the cyclohexenone substrate approached from the upper face.

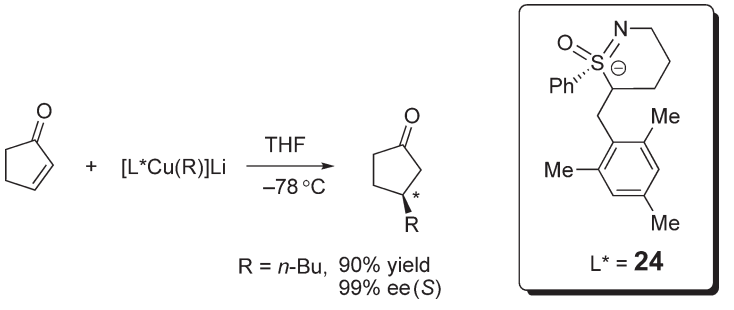
Recently, the use of chiral carbanionic ligands as non-transferable ligands has received attention. Gais and Boßhammer have successfully applied cyclic α-sulfonimidoyl carbanion **24** in the conjugate addition of alkylcuprates to cycloalkenones (Scheme 14).[30]



Scheme 12



Scheme 13



Scheme 14

10.08.2.3.2 Organocuprates with external chiral ligands

Unlike the non-transferable ligands, external ligands can be utilized in substoichiometric amounts in enantioselective conjugate addition. Tomioka and co-workers studied the addition of lithium organocuprate to chalcone in the presence of stoichiometric chiral amidophosphine **25** with ee up to 90% (Scheme 15).[31] The reaction of cycloalkenone with **26** also worked well to give the adduct with up to 95% ee (Scheme 15).[32] ^{13}C NMR studies showed that the carbonyl oxygen and phosphorus atoms of the ligand selectively coordinated to lithium and copper of the organocopper species.[32–33c] However, the catalytic version of the reaction with lithium cyanocuprate was unsuccessful.

It is noteworthy that different donor solvents may give opposite enantiomers since the geometry is changed around the copper complex and thus the aggregation of the cuprate reagent is influenced. Dambacher and Bergdahl studied the solvent-dependent reaction pathways for the conjugate addition of Li[BuCuI] to *N*-crotonyl-2-oxazolidinone **27**, and obtained 96% de of (*S*)-product in THF and 88% de of (*R*)-diastereomer in Et_2O with the same catalyst system (Scheme 16).[34]

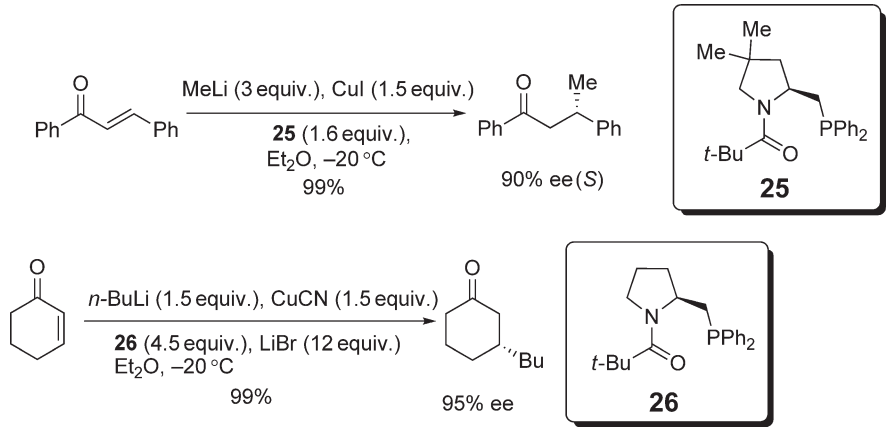
10.08.2.4 Organozinc Nucleophiles

In recent years, the asymmetric 1,4-conjugate addition using organozinc nucleophiles has been developed into one of the most successful areas of synthetic chemistry.[3,26,35,35a] Compared with other organometallic reagents, dialkylzinc reagents have some distinct advantages. They show low reactivity in uncatalyzed 1,4-addition reaction, but effective catalysis may be achieved through the use of various ligands and transition metal complexes. They also show high tolerance for functional groups both in the substrate and in the zinc reagent.

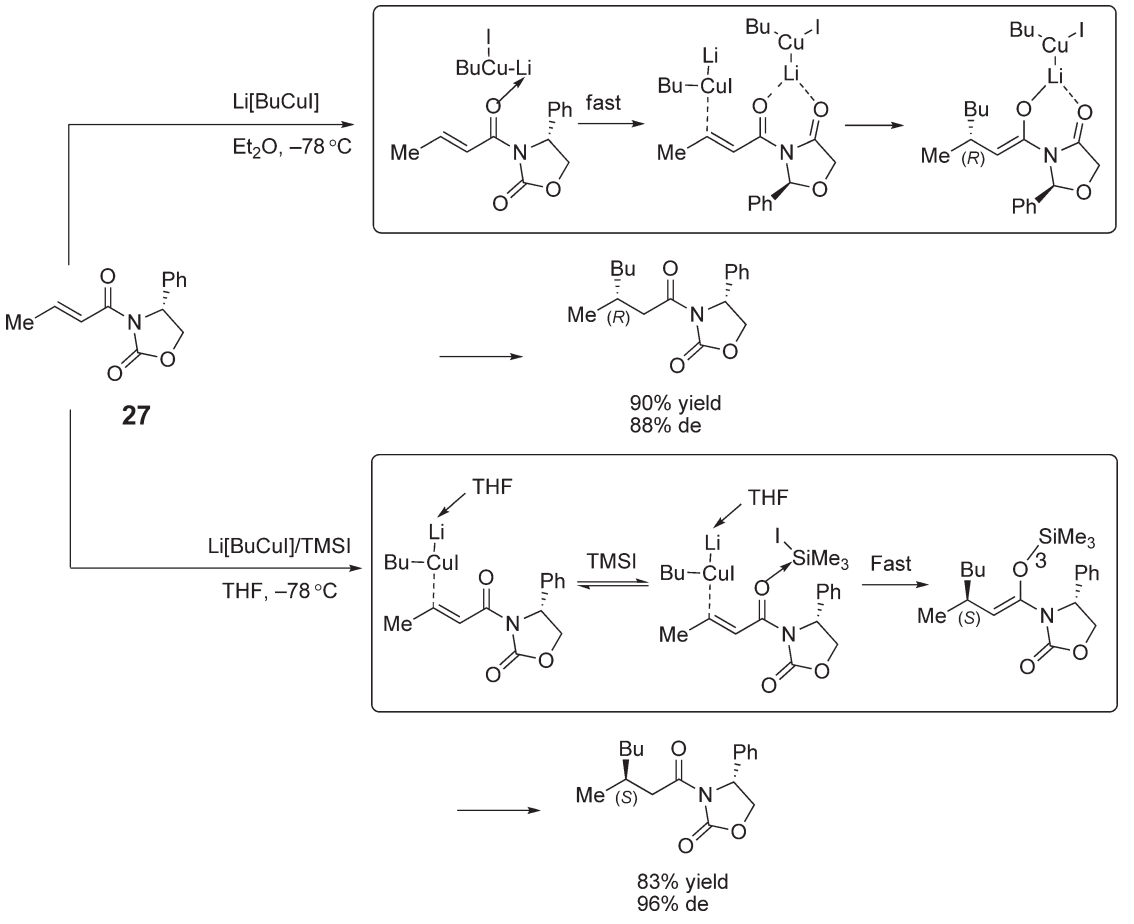
In 1993, Alexakis *et al.* reported the first copper-catalyzed asymmetric conjugate addition of diethylzinc to 2-cyclohexenone using phosphorous ligand **28** (32% ee).[36] An important breakthrough was achieved by Feringa *et al.* with chiral phosphoramidite (*S,R,R*)-**29** (Figure 1), which showed excellent selectivity (over 98% ee) for the addition of 2-cyclohexenone.[37] Since then, efficient protocols for the conversion of both cyclic and acyclic enones, as well as lactones and nitroalkenes, have been developed featuring excellent stereocontrol.

10.08.2.4.1 Detailed mechanism

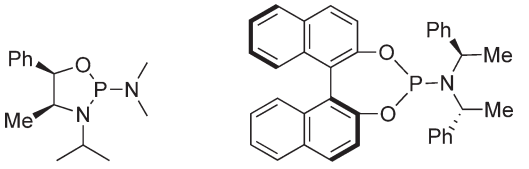
Feringa *et al.* proposed a pathway for the catalytic 1,4-addition (Scheme 17).[37] Starting from either Cu(I) complex or Cu(II) complex (which was reduced *in situ* to give the corresponding Cu(I) complex), subsequent alkyl transfer from zinc to copper gave L_2CuR and RZnX. Complexation of RZnX with carbonyl group and formation of the π-complex between L_2CuR and enone gave complex **30**. This step was followed by alkyl transfer, and the resulting zinc enolate **31** afforded β-substituted cycloalkanone upon protonation. The enolate **31** could be trapped with other electrophiles in tandem procedure, which might be a useful strategy for total synthesis. This proposed mechanism was confirmed by Schrader and co-workers.[38]



Scheme 15



Scheme 16



28 (*S*,*R*,*R*)-**29**

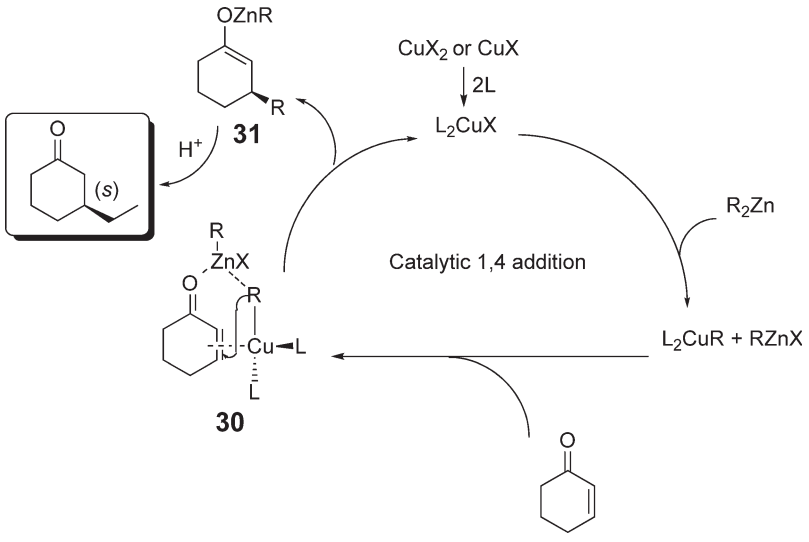
Figure 1

10.08.2.4.2 Addition to α,β-unsaturated ketones

A remarkable number of chiral phosphorus ligands (phosphoramidites, phosphites, and phosphines with modular structures) have been introduced into the copper-catalyzed conjugate addition of R_2Zn reagents, and high enantioselectivities (>90%) are now possible for all three different classes of substrates: 2-cyclohexenones and larger ring enones, 2-cyclopentenones, and acyclic enones.

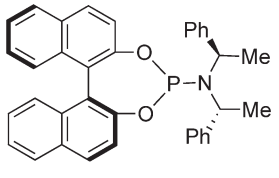
10.08.2.4.2.(i) 2-cyclohexenones and larger rings

With chiral phosphoramidite (*S*,*R*,*R*)-**29**, 3-ethylcyclohexanone, 3-ethylcycloheptanone, and 3-ethylcyclooctanone were obtained with >97% ee's.[37,39] (*R*,*R*,*R*)-**32** also showed excellent enantioselectivity in the addition of Et_2Zn to both 2-cyclohexenone (93% ee) and larger ring enone as 2-cyclopenta-decen-1-one (95% ee).[40]

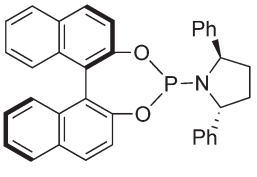


Scheme 17

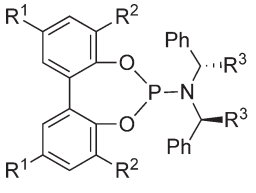
Alexakis *et al.* used a series of new phosphoramidites **33** and **34** with *ortho*-substituted biphenol backbone in copper-catalyzed 1,4-addition of diethylzinc to a wide range of substrates. Enantioselectivities up to >99.5% were obtained for 2-cyclohexenone.[41–43] Ojima and co-workers designed monophosphoramidite ligand (*S*,*R*,*R*)-**35** possessing chiral 6,6′-dimethylbiphenol moiety;[44] Zhou and co-workers reported (*R*,*R*,*R*)-**36** containing chiral *spiro*-biindane structure.[45] The fine-tuning capability of these ligands played a significant role in achieving high enantioselectivity in the asymmetric conjugate addition of diethylzinc to cycloalkenones (Figure 2).



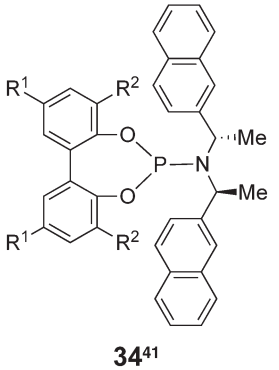
(*S*,*R*,*R*)-**29**[37,39]
For cyclohexenone, 98% ee (*R*)
For cycloheptenone, 98% ee
For cyclooctenone, 97% ee



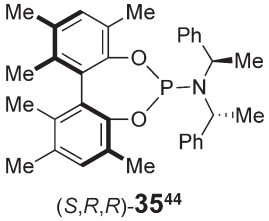
(*R*,*R*,*R*)-**32**[40]
For cyclohexenone, 93% ee (*R*)



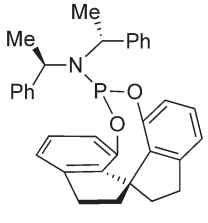
33a: R^3 = Me, for cyclohexenone, 99% ee[42]
33b: R^3 = Et, for cyclohexenone, 96% ee



34[41]
For cyclohexenone, >99.5% ee
For cycloheptenone, 98% ee



(*S*,*R*,*R*)-**35**[44]
For cyclohexenone, 99% ee (*S*)
For cycloheptenone, 98% ee (*S*)

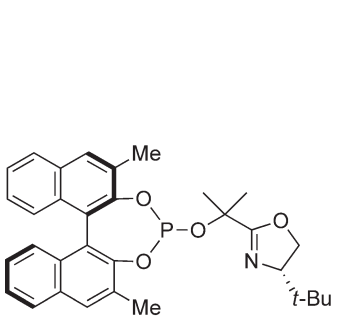


(*R*,*R*,*R*)-**36**[45]
For cyclohexenone, 98% ee

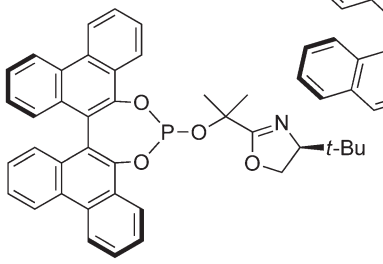
Figure 2

Some phosphates based on 1,1′-bi-2-naphthal (or 2,2′-dihydroxy-1,1′-binaphthyl; BINOL) with various bridging units have been proved to afford high enantioselectivity for the copper-catalyzed conjugate addition (Figure 3). For example, Pfaltz and Escher introduced phosphites **37** and **38** with chiral oxazoline units; **37** gave enantioselectivities as high as 90% for 2-cyclohexenone and **38** gave 94% ee for cycloheptenone.[46] Reetz *et al.* developed diphosphonites **39** with achiral ferrocene backbone; enantioselectivities of up to 99% were observed in the conjugate addition of Et_2Zn to enones.[47] Chan and co-workers achieved good enantioselectivities in the 1,4-additions of diethylzinc to 2-cyclohexenone (ee up to 90% and 98%, respectively) by using chiral BINOL-bridged phosphites **40** and **41**.[48,48a–48d] Alexakis *et al.* found TADDOL-based phosphate **42** to be very selective for the asymmetric 1,4-additon of 2-cyclohexenone (96% ee).[49] Good enantioselectivity was also observed with chiral phosphite **43** for the addition of large ring cyclic enones (87% ee for 2-cyclopenta-decen-1-one, the precursor of muscone).[49a]

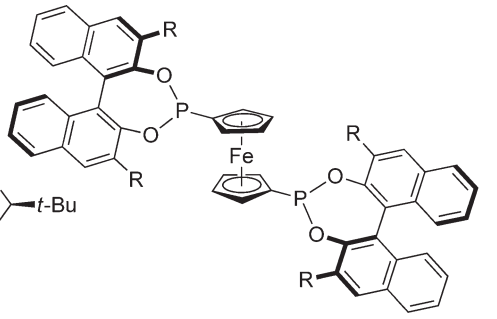
A number of chiral phosphine ligands has also been reported (Figure 4). Zhang and co-workers described binaphthalene phosphine **44** with a pyridine moiety to afford the addition product with up to 92% ee.[50,50a] With chiral bisphosphine **45**, Imamoto *et al.* got only moderate enantioselectivity for the addition of cyclohexenone,



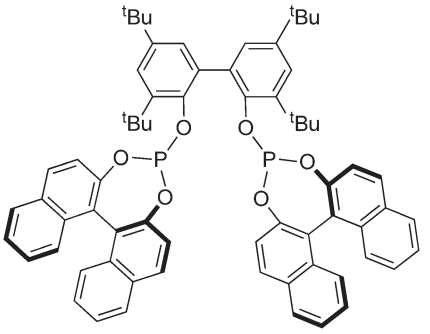
37[46]
For cyclohexenone, 90% ee



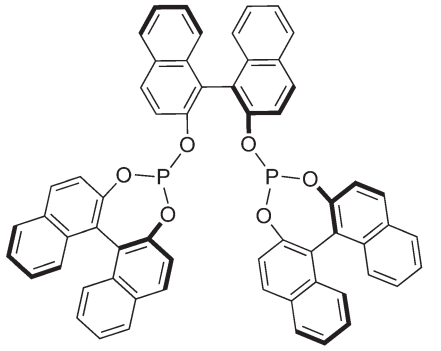
38[46]
For cycloheptenone 94% ee



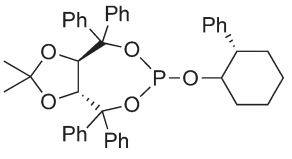
39a: R = H, for cyclohexenone, 96% ee,[47] for cycloheptenone, 93% ee
39b: R = Me, for cyclohexenone, 99% ee(*R*)



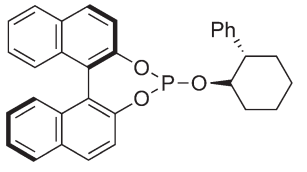
40[48,48a–48d]
For cyclopentenone, 89% ee(*S*)
For cyclohexenone, 90% ee(*S*)



(*S*,*R*,*S*)-**41**[48,48a–48d]
For cyclopentenone, 93% ee
For cyclohexenone, 98% ee



42[49,49a]
For cyclohexenone, 96% ee(*S*)



43[49,49a]
For 2-cyclopenta-decen-1-one, 87% ee

Figure 3

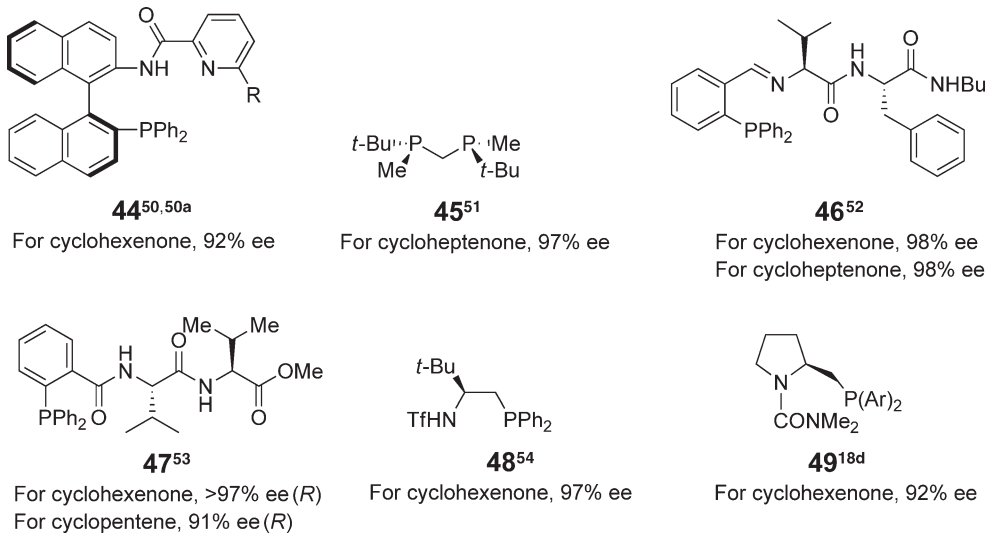


Figure 4

whereas excellent ee was obtained for cycloheptenone substrate (97% ee).[51] Modular peptide-based phosphine ligand **46**, which was introduced by Hoveyda and co-workers, provided excellent stereocontrol (up to 98% ee) in the 1,4-addition to six- and seven-member cyclic enones.[52] Breit and Laungani developed another peptidyl phosphane ligand **47**, and obtained higher than 97% ee.[53] Over 90% ee was also obtained with ligands **48**[54] and **49**[18b].

A summary of other chiral ligands with corresponding enantioselectivities in the copper-catalyzed 1,4-addition of dialkylzinc to cyclic enones is shown in Figure 5.[55–58]

10.08.2.4.2.(ii) 2-Cyclopentenone substrate

Optically active cyclopentanes are useful structural units for many natural products such as steroids, terpenoids, and prostaglandins, but the development of highly enantioselective catalytic 1,4-addition reactions to 2-cyclopentenones has proved to be a challenging goal. Besides the very low stereoselectivities, a major problem with this substrate is the

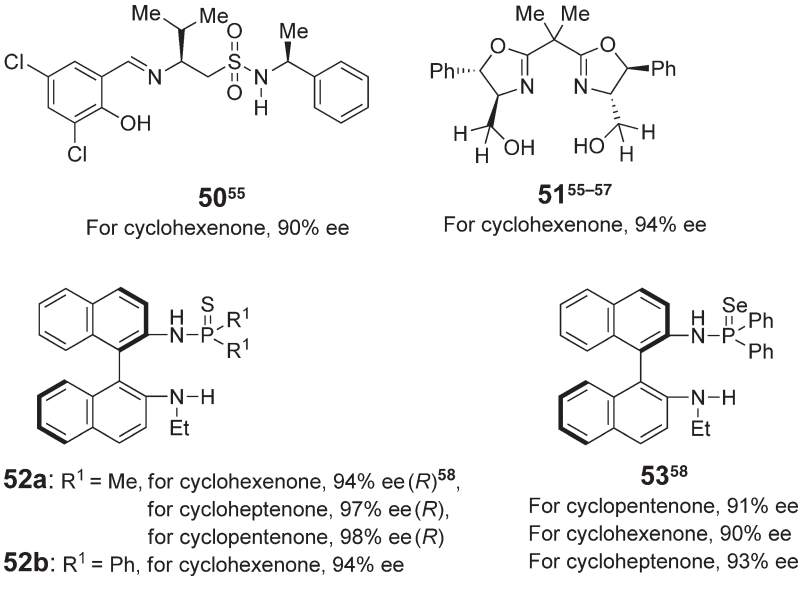


Figure 5

low chemical yields (due to the oligomerization of zinc enolate) and the high volatility of the addition products. Several examples of high enantioselectivities (up to 97% ee) by using chiral phosphorus ligands have been reported (Scheme 18).

The first catalytic 1,4-addition of diethylzinc to 2-cyclopentenone with over 90% ee was described by Pfaltz and Escher, who used phosphite **54** with biaryl groups at the 3,3′-positions of the BINOL backbone.[46] Chan and co-workers achieved high enantioselectivity in the same reaction (up to 94% ee) by using chiral copper diphosphite catalyst (*R,R,R*)-**41**.[48,48a–48d] Hoveyda and co-workers used ligand **46** to realize excellent enantiocontrol (97% ee) in the 1,4-additions of 2-cyclopentenones,[52] which may be used in the practical asymmetric synthesis of some substituted cyclopentanes (including prostaglandins).

10.08.2.4.2.(iii) Acyclic enones

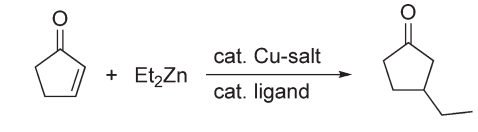
Aryl-substituted enones such as chalcone and benzalacetone have been used as model substrates in the study of asymmetric 1,4-addition of acyclic enones. Many chiral ligands have been found to afford good enantioselectivities (Scheme 19). Typical results are summarized in Table 1.[46,50,58–66]

In 1999, Zhang and co-workers provided the first ligand that gave >90% ee for both cyclic and acyclic enones in the copper-catalyzed 1,4-additions.[50,50a] For acyclic chalcone and benzalacetone adducts, 96% ee and 90% ee were obtained respectively, with the pyridine–phosphine **44**. Later, Hu and co-workers designed and synthesized a series of pyridine–phosphite ligands **58** with similar backbone, which gave up to 97% ee for the enantioselective 1,4-conjugate addition of acyclic enones.[62] Ligands **59** derived from (*S*)-H_8-NOBIN (NOBIN = 2-amino-2′-hydroxy-1,1′-binaphthyl) also provided comparable results with their parent ligands **58**. Ligand **59a** afforded up to 98% ee for *trans*-4-aryl-3-buten-2-ones, whereas **59b** was very efficient for various *para*-chalcones (up to 97% ee).[62a] Recently, they developed another chiral ligand **60** with biphenyl structure for the conjugate addition of *para*-substituted chalcones, and in most cases over 95% ee was obtained.[62b]

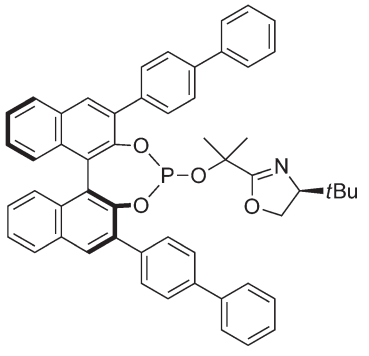
Chiral binaphthylthiophosphoramide **52b** and binaphthylselenophosphoramide **53** have been developed by Shi and co-workers, and high enantioselectivity (up to 97%) has been achieved in the asymmetric conjugate addition of acyclic enones under the optimized conditions.[58]

10.08.2.4.3 Addition to α,β-unsaturated esters and amides

Unsaturated lactone can be viewed as the oxygen heterocyclic analog of 2-cyclohexenone. The copper-catalyzed 1,4-additions of lactones have been realized in high enantioselectivity with dialkylzinc as nucleophile (Scheme 20). Reetz and co-workers achieved 87% conversion and 88% ee using ferrocene-derived chiral diphosphonate ligand **39b**.[47] Employing diphosphite **40**, Chan and co-workers achieved 92% ee for the six-membered lactone and 56% ee for the five-membered lactone.[48a] Further ligand modification provided a more effective ligand (*S,R,S*)-**41**, which gave up to 98% ee in the addition of diethylzinc to 5,6-hydro-2H-pyran-2-one.[48d,67]



Ligand	*ee* (%)
40	89[48b]
(*R,R,R*)-**41**	93[48d]
46	97[52]
54	94[46]



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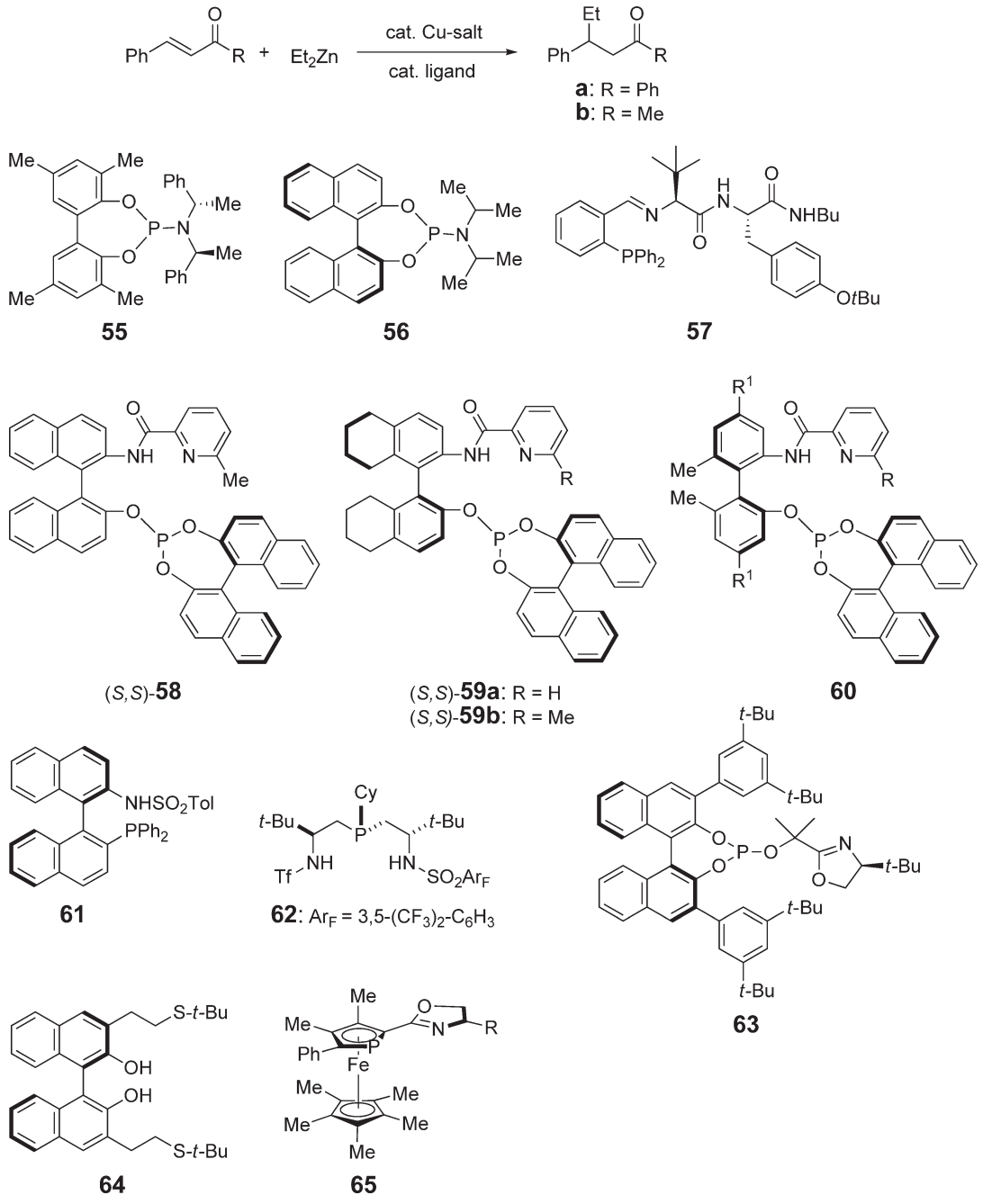
Scheme 18



Scheme 19

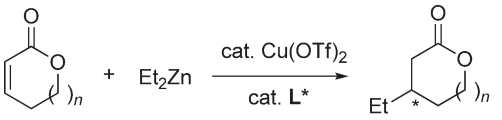
Simple acyclic α,β-unsaturated esters are not reactive in the conjugate addition of dialkylzincs. In contrast, nitro-substituted unsaturated esters[68] and malonates[69] are applicable for this reaction. Using peptide-based chiral phosphine **66**, Hird and Hoveyda realized the Cu-catalyzed conjugate addition of Et_2Zn to *N*-acyloxazolidinones with excellent enantioselectivity (Scheme 21).[70]

Feringa and co-workers applied chiral phosphoramidite ligand (*S*,*R*,*R*)-**67** in the conjugate addition of dimethylzinc to acyclic unsaturated malonates **68** and obtained up to 98% ee (Scheme 22).[71]

Carreira and co-workers demonstrated the asymmetric conjugate addition reaction of Meldrum's acid-derived acceptors (Scheme 23).[72] The adducts were obtained in good enantioselectivities (up to 94% ee).

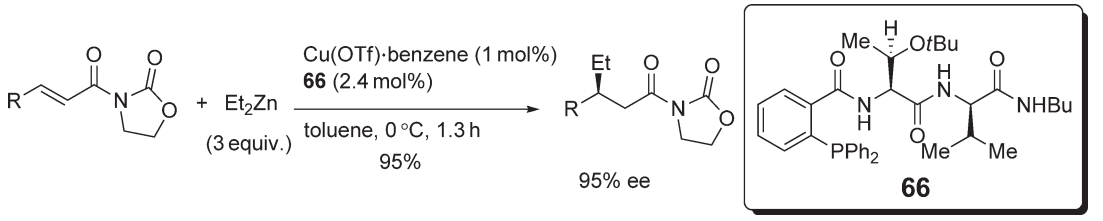
Table 1 Enantioselective conjugate addition to acyclic enones

Ligand	*ee (%) of* ***a***	*ee (%) of* ***b***	*Ligand*	*ee (%) of* ***a***	*ee (%) of* ***b***
(*R*,*S*,*S*)-**29**		93(*S*)[59]	**59**	94[62a]	92[62a]
44	96(*S*)[50]	90(*S*)[50]	**60**	>95[62b]	
52b	97(*S*)[58]		**61**		99[63]
53	96(*S*)[58]		**62**		94[64]
55		93(*S*)[59]	**63**		87(*S*)[46]
56	89(*S*)[60]		**64**	96[65]	
57		93[61]	**65**	87[66]	81[66]
58	97[62]				

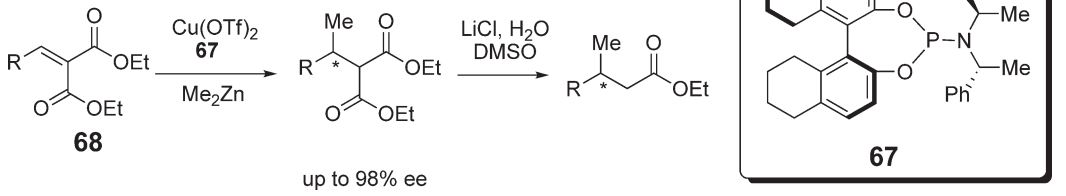


Ligand	*ee*(%)
39b	88
25	92
41	98

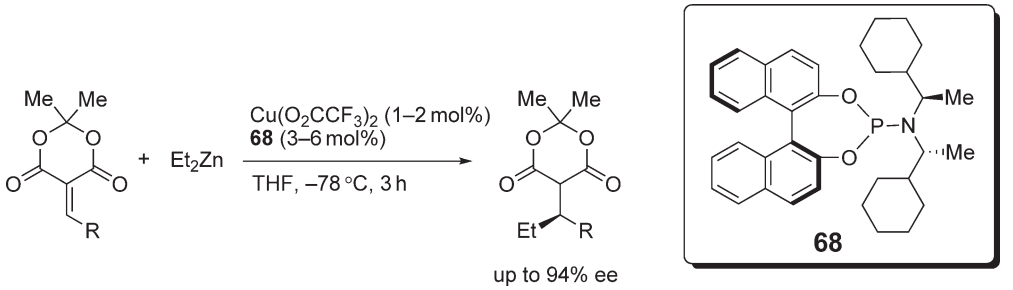
Scheme 20



Scheme 21



Scheme 22



Scheme 23

In the case of α,β-unsaturated lactams, the stereoselective introduction of a carbon–carbon bond in the β-position of a lactam is mostly based on the use of stoichiometric amounts of chiral auxiliaries[73,73a,73b] or reagents.[74,74a] Recently, Feringa and co-workers reported an excellent enantioselective conjugate addition of α,β-unsaturated lactams bearing appropriate protecting–activating groups on the nitrogen (Scheme 24).[75] With (*R*,*S*,*S*)-**29** as the chiral ligand, optically active β-ethyl substituted lactams were obtained in 95% ee and complete conversion in 2 h.

10.08.2.4.4 Addition to nitroolefins

Nitroolefins are good Michael acceptors and their reactivity toward diethylzinc is different depending on the presence or absence of Lewis acids. Since the nitro group can be further transformed to a variety of useful *N*-containing functionalities,[76,76a] the asymmetric 1,4-additions of nitroolefins may provide an easily accessible pathway to highly versatile optically active synthons.

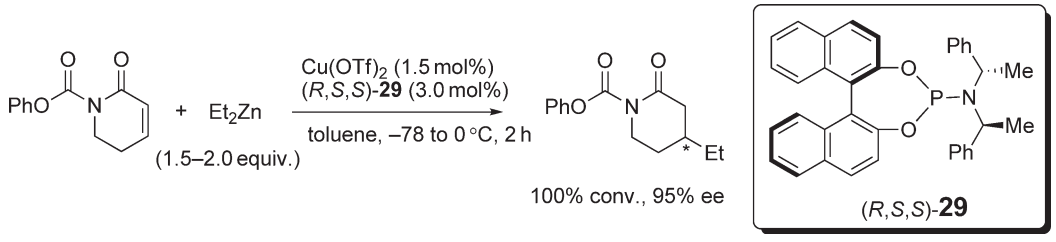
A catalytic version of this transformation utilizing Cu(II) complex and Feringa's ligand (*R*,*S*,*S*)-**29** (Figure 6) was reported by Sewald and Wendisch with moderate ee's (up to 86% ee).[77] Later, Alexakis and Benhaim tried various chiral trivalent phosphorus ligands in the conjugate addition of nitroolefins.[78] They found that TADDOL-based phosphonite **69** gave the highest ee's for arylnitroalkenes (up to 86% ee), whereas phosphoramidite (*R*,*S*,*S*)-**29** was the best ligand for alkylnitroalkenes (up to 94% ee).

The enantioselective conjugate addition of dialkylzinc to nitroalkenes using other phosphoramidite,[79,79a–83a] sulfonamide,[84] and binaphthol-based thioether ligands[65] has also been studied in the past few years. Particularly noteworthy are the efficient chiral monodentate phosphoramidite ligands (*S*,*R*,*R*)-**29** and (*S*,*S*)-**55** developed by Feringa *et al.* and Alexakis *et al.*, respectively, for this reaction. (*S*,*R*,*R*)-**29** provided excellent enantioselectivities (up to 98% ee) for acyclic nitroalkenes (Scheme 25).[80] It also worked well for other nitroolefin substrates such as 3-nitrocoumarin **70**[68] and methyl 3-nitropropenoate **71**[85].

Alexakis *et al.* showed that under optimized experimental conditions, the enantioselectivity of the Cu-catalyzed conjugate addition of dialkylzinc to cyclic nitroolefin was improved to 95% with both (*S*,*S*)-**55** and (*R*,*S*,*S*)-**29**.[79,79a] Biphenol-based phosphoramidite ligand (*S*,*S*)-**55** also provided acyclic nitroalkenes adducts with 95–96% ee.[42]

Ojima and co-workers found that chiral monodentate phosphoramidite (*S*,*R*,*R*)-**35** was highly effective for the enantioselective conjugate addition of diethylzinc to acyclic nitroalkenes (up to 99% ee).[86]

Hoveyda and co-workers presented the asymmetric addition of alkylzincs to small-, medium-, and large-ring nitroolefins with chiral peptide-based phosphines **57** as catalyst.[87] The enantioselectivities were typically >90%. Ligand **57** also worked well in the asymmetric addition of dialkylzinc to acyclic disubstituted nitroalkenes (up to 95% ee; Scheme 26).[88]



Scheme 24

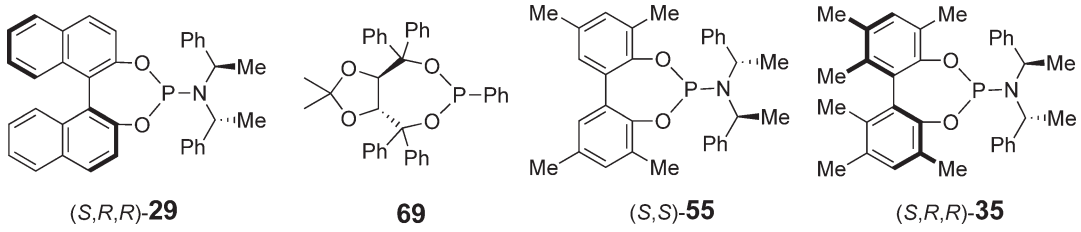
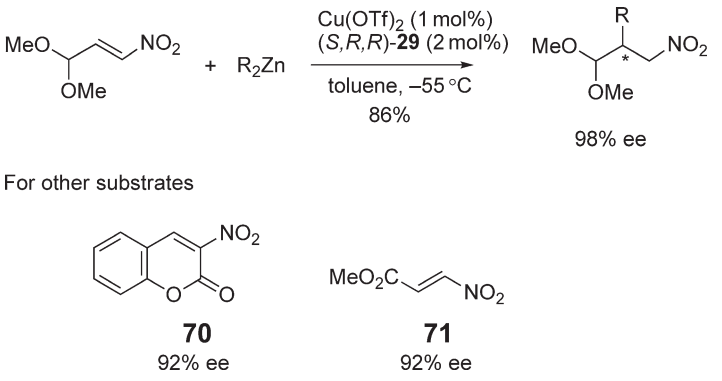
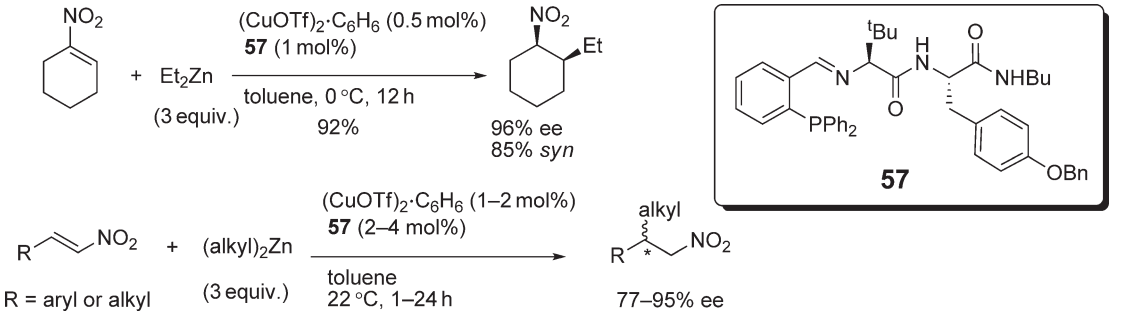


Figure 6



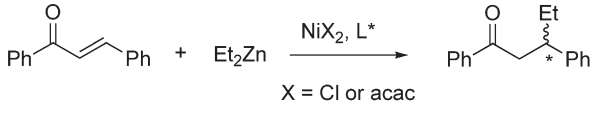
Scheme 25

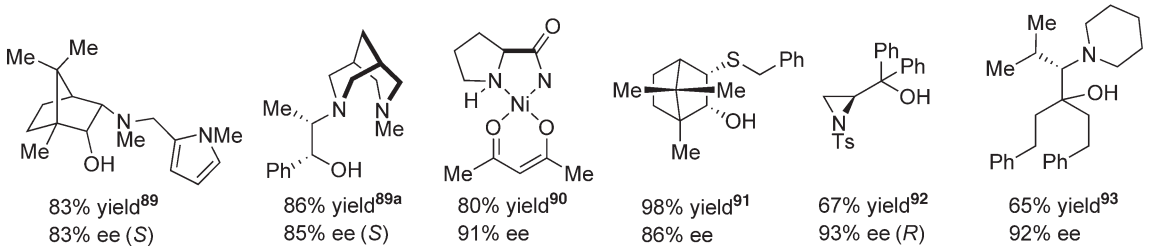


Scheme 26

10.08.2.4.5 Nickel-catalyzed conjugate addition to acyclic enones

The general binding mode of cyclic enone to copper is through the π-bonded olefin while that to nickel is through the carbonyl oxygen. The latter bonding mode is less favorable for the delivery of the alkyl group in a stereocontrolled manner in conjugate additions. In the case of acyclic enone substrates, both the carbonyl oxygen and the olefin π-bond can bind to nickel catalyst to provide high enantioselectivity in the conjugate addition. Scheme 27[89,89a–93] summarizes various amine-based chiral ligands and their enantioselectivities in the Ni(II) catalyzed addition of diethylzinc to chalcones.





Scheme 27

10.08.2.5 Organoboron Nucleophiles[94,95]

The first example of asymmetric rhodium-catalyzed 1,4-addition of organoboron reagents to enones was described in 1998 by Hayashi and Miyaura. Significant progress has been made in the past few years. This asymmetric addition reaction can be carried out in aqueous solvent for a broad range of substrates, such as α,β-unsaturated ketones, esters, amides, phosphonates, nitroalkenes. The enantioselectivity is always very high (in most cases over 90% ee). This asymmetric transformation provides the best method for the enantioselective introduction of aryl and alkenyl groups to the β-position of these electron-deficient olefins.

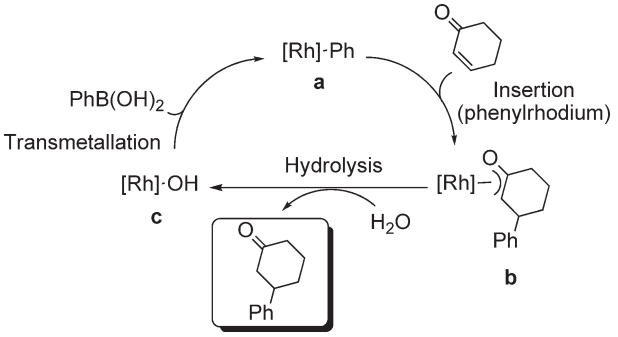
10.08.2.5.1 Detailed mechanism

Hayashi *et al.* proposed a catalytic cycle for the rhodium-catalyzed 1,4-addition of phenylboronic acid to 2-cyclohexenone (Scheme 28), which was confirmed by NMR spectroscopic studies.[96] The reaction presumably involved three intermediates, phenylrhodium **a**, oxa-π-allylrhodium **b**, and hydroxorhodium **c** complexes. Complex **a** reacted with 2-cyclohexenone to give **b** by insertion of the carbon–carbon double bond of enone into the phenyl–rhodium bond followed by isomerization into the thermodynamically more stable complex. Complex **b** was converted to **c** upon addition of water, liberating the phenylation product. Transmetallation of the phenyl group from phenylboronic acid to rhodium took place in the presence of triphenylphosphine to regenerate **a**.

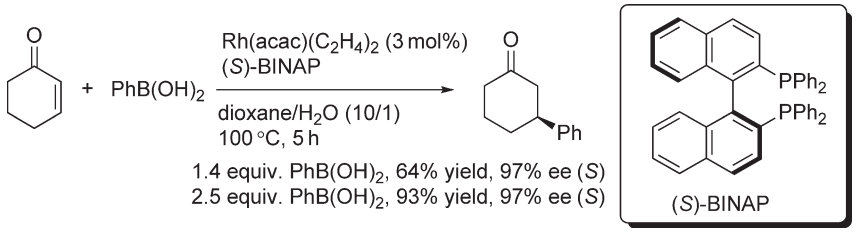
10.08.2.5.2 Addition to α,β-unsaturated ketones

In 1997, Miyaura and co-workers reported the nonasymmetric version of 1,4-addition of aryl- and alkenylboronic acids to α,β-unsaturated ketones using rhodium–phosphine complex as the catalyst.[97] Later, Hayashi and Miyaura realized the asymmetric 1,4-addition with high catalytic activity and enantioselectivity.[98] In the presence of (*S*)-BINAP, the reaction of 2-cyclohexenone with 2.5 equiv. of phenylboronic acid gave (*S*)-3-phenylcyclohexanone with 97% ee (BINAP = 2,2′-bis (diphenylphosphino)-1,1′-binaphthyl; Scheme 29).[99]

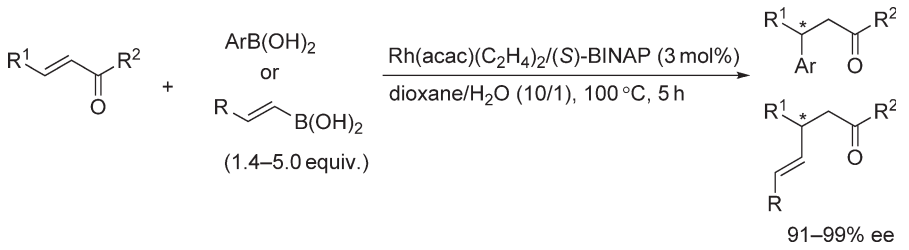
A broad substrate scope for the rhodium-catalyzed asymmetric 1,4-addition has been observed.[98] Both arylboronic acids with either electron-donating or electron-withdrawing aryl substituents and alkenylboronic acids can be introduced into acyclic or cyclic enones with high enantioselectivities (Scheme 30).



Scheme 28



Scheme 29



Scheme 30

Tomioka and co-workers reported that amidomonophosphine **26** was a good supporting ligand for the asymmetric addition to cyclic enones (Figure 7).[100,100a] Notably, Reetz applied 1,1′-binaphthol-based diphosphonites **72–74** for the asymmetric conjugate addition.[101] Even at 0.3 mol% of rhodium catalyst no significant loss of enantioselectivity was observed. The variation of achiral backbone (from ethylene bridge to butylene bridge) of ligand **72** affected the absolute configuration of the product.[101] Michelet and Genet utilized water-soluble ligand **75** for the phenylation of 2-cyclohexenone.[102] With ethylene glycol as solvent and in the presence of sodium carbonate, asymmetric 1,4-addition proceeded smoothly in high yields and enantioselectivity (98% ee). The catalyst level can be lowered to 0.005 mol% with acceptable enantioselectivity (88% ee).[102] Chan and co-workers recently reported the applicability of atropisomeric dipyridyldiphosphine ligand (*S*)-P-Phos **76** in the asymmetric 1,4-addition (P-Phos = 2,2′,-6,6′,-tetramethoxy-4,4′-bis(diphenylphosphino)-3,3′-bipyridine).[103] Excellent yields and ee's were obtained for cyclic enones.

Higher than 98% ee and exceedingly high reaction rates have been reached in the rhodium-catalyzed arylboronic acid addition to enones using Feringa's monodentate phosphoramidite ligand **77** (Scheme 31).[104] Temperature-dependent studies showed that monodentate phosphoramidites formed stable metal complexes and induced high enantioselectivities even at high temperatures in polar solvents.[104] Recently, Miyaura and co-workers showed that the addition of a base, such as KOH or Et_3N, significantly accelerated the rate of asymmetric 1,4 addition to enones.[105] They applied Feringa's monodentate phosphoramidite ligands (derived from (*R*)-BINOL and alkylamines) to this asymmetric transformation with excellent enantioselectivity (up to 99% ee).

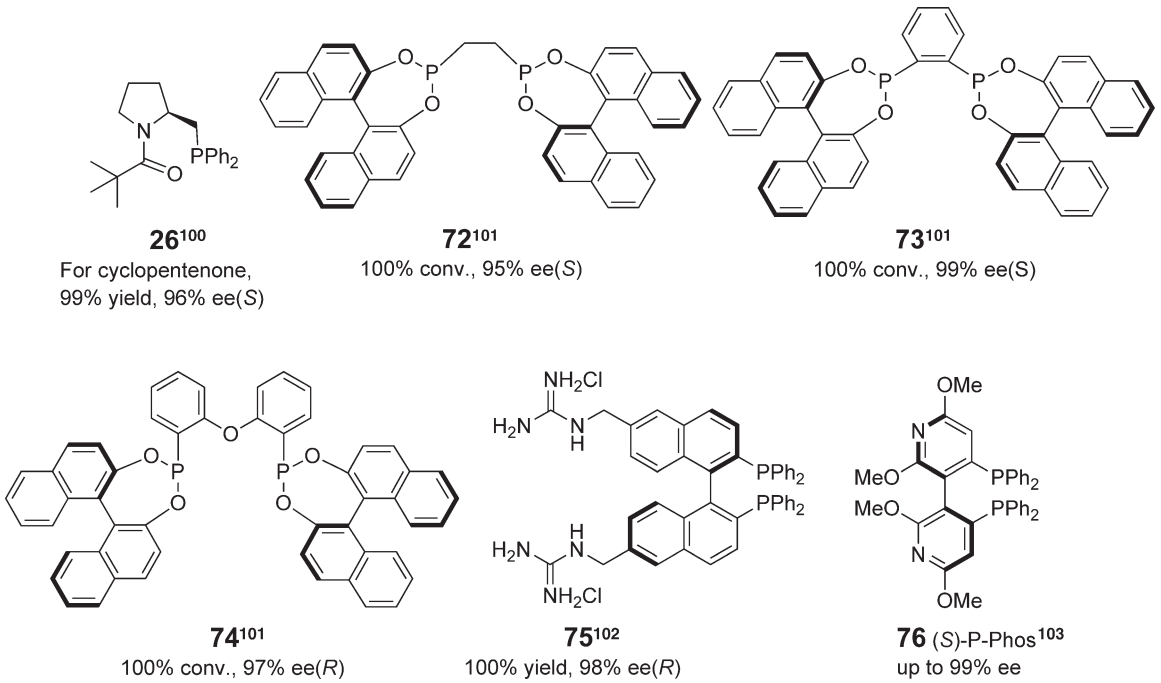
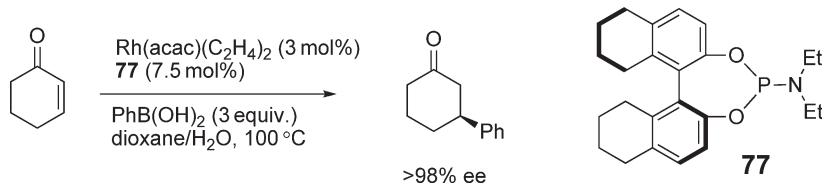


Figure 7



Scheme 31

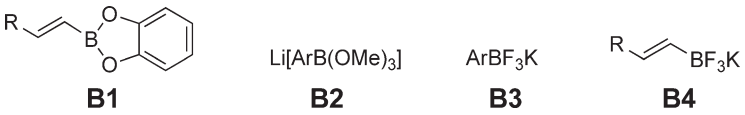
In addition to aryl boronic acids, other borane sources are effective in the asymmetric addition of activated olefins, for example, alkenylcatecholboranes **B1**,[106] lithium trimethyl arylborates **B2**,[107] potassium organotrifluoroborates **B3** and **B4** (Scheme 32).[108,108a] Compounds **B3** and **B4** were shown by Darses and Genet to progress the asymmetric 1,4-addition when using cationic rhodium catalysts generated from $[Rh(COD)_2][PF_6]$ (COD = 1,5-cyclooctadiene) and some chiral bisphosphines as (*R*)-BINAP (98% ee), (*R*)-(*S*)-Josiphos (99% ee), and (*R*)-MeO-Biphep (98% ee; MeO-Biphep = (6,6′-dimethoxy-1,1′-biphenyl-2,2′-diyl) bis(diphenylphosphine); Scheme 33).[108,108a] Recently, Feringa and co-workers also demonstrated that chiral phosphoramidite **77** catalyzed the arylation of cyclohexenone with $ArBF_3K$ to give 3-arylcyclohexanone with excellent enantioselectivities (up to 99% ee).[109]

10.08.2.5.3 Addition to α,β-unsaturated esters and amides

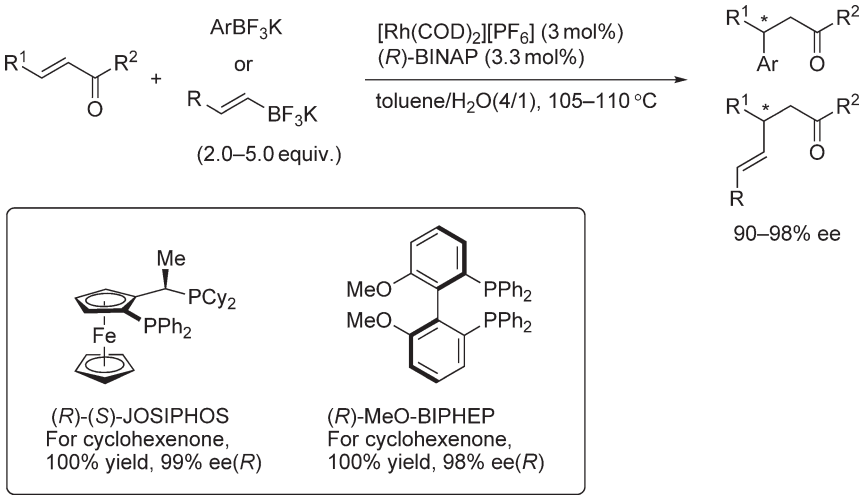
Various substituted phenyl and 2-naphthyl groups were introduced to the β-position of isopropyl ester **78** with enantioselectivities ranging from 93% to 97% ee in high yields in the reactions with lithium arylborates (Scheme 34).[110]

The reaction of cyclic α,β-unsaturated esters also proceeds with high enantioselectivity (97–98% ee) and yields (Scheme 35).[110] Similar results for the asymmetric 1,4-addition to α,β-unsaturated esters have been independently reported by Miyaura and co-workers.[111]

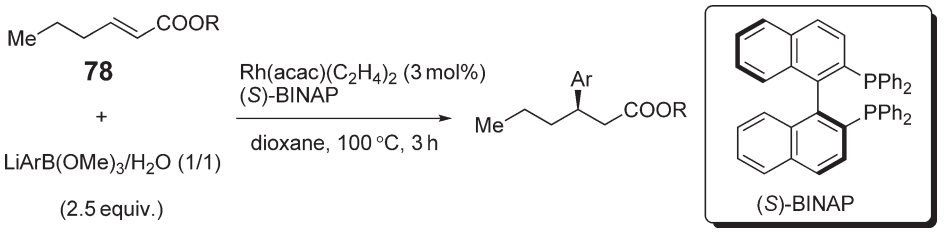
In 2001, Miyaura and Sakuma reported the asymmetric addition of arylboronic acids to α,β-unsaturated amides in the presence of the $Rh(acac)(C_2H_4)_2$/(*S*)-BINAP catalyst (acac = acetylacetonate; Scheme 36).[112] The



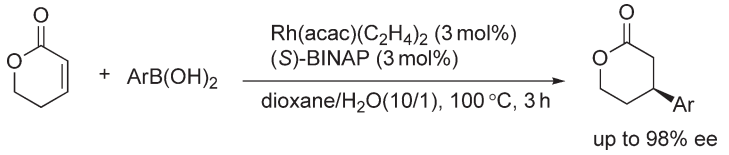
Scheme 32



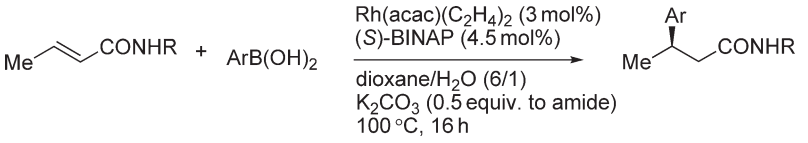
Scheme 33



Scheme 34



Scheme 35

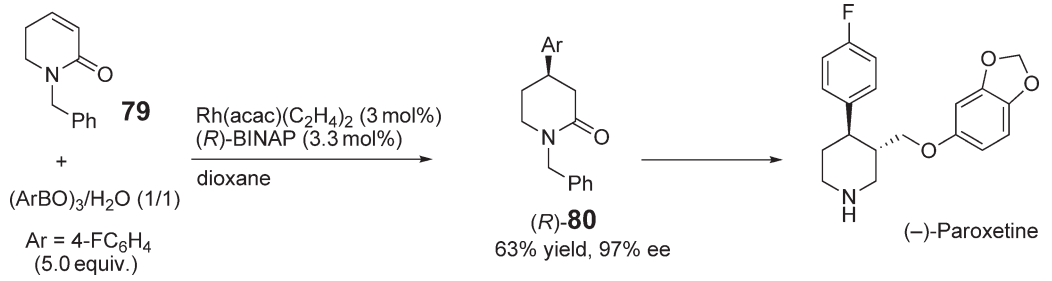


Scheme 36

enantioselectivity was comparable to the addition of the corresponding esters and the presence of an aqueous base such as potassium carbonate significantly improved the chemical yield of the adducts.

The reaction of lactam **79** with 4-fluorophenylboroxine and 1 equiv. (with respect to boron) of water in the presence of Rh(acac)$(C_2H_4)_2$/(*R*)-BINAP afforded 63% yield and 97% ee of (*R*)-**80,** a precursor to (−)-paroxetine (Scheme 37).[113] This route offered a better synthetic strategy than the reaction carried out under usual reaction conditions.

Other interesting electron-deficient olefin substrates for the asymmetric conjugate addition include α-acetamidoacrylic ester **S1**,[101] dimethyl itaconate **S2**,[114] α,β-unsaturated sulfones **S3**,[115] and alkenylphosphonate **S4**[116] (Figure 8).



Scheme 37

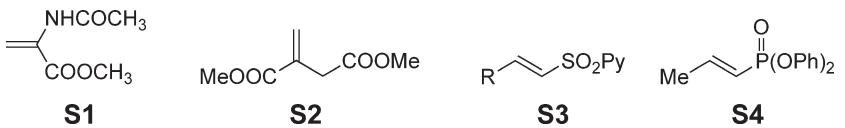


Figure 8 Other electron-deficient olefin substrates.

10.08.2.5.4 Addition to nitroolefins

Nitroalkenes are good candidates for the rhodium-catalyzed asymmetric 1,4-addition of organoboronic acids. Hayashi *et al.* reported that the reaction of 1-nitrocyclohexene with phenylboronic acid in the presence of rhodium/(*S*)-BINAP catalyst gave 99% ee of 2-phenyl-1-nitrocyclohexane (Scheme 38).[117]

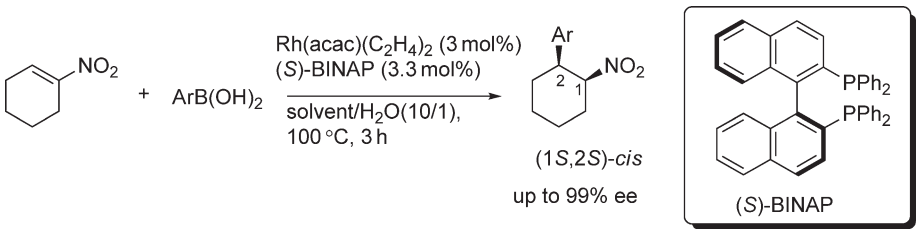
Feringa and co-workers applied monophosphoramidite ligand **81** in the addition of phenylboronic acid to nitroalkene and got moderate enantioselectivity (Scheme 39).[118]

Alkynyl boronates have long been known to be good achiral reagents in conjugate addition to enones.[119,120] Chong *et al.* performed the first examples of enantioselective conjugate additions of alkynyl groups to enones using alkynyl boronates **82** as chiral nucleophiles (Scheme 40).[121] Good ee's of the 3-alkynyl enones were obtained.

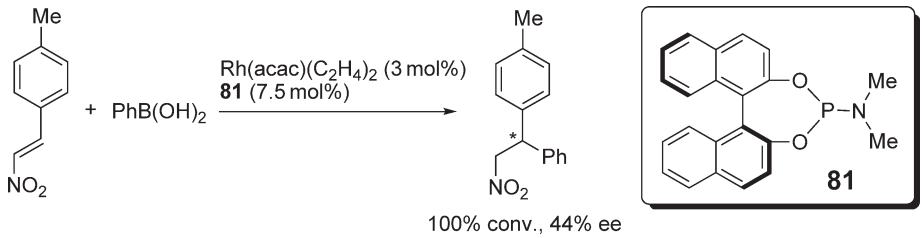
10.08.2.5.5 New trends in the asymmetric 1,4-addition of organoboron reagents

10.08.2.5.5.(i) Diene ligands

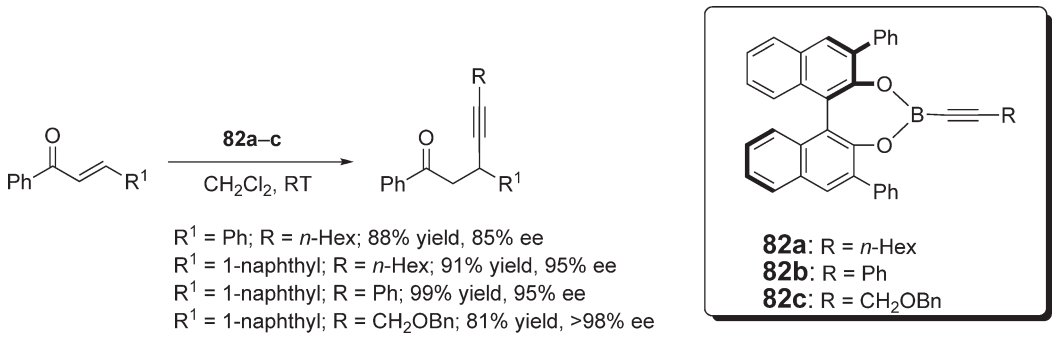
Recently considerable attention has been given to chiral η^2-bonded olefin "spectator" ligands for the asymmetric conjugate addition.[122] Hayashi and Carreira independently reported that new chiral diene ligands **83**,[123] **84**,[124] and **85**[125] showed high enantioselectivities in Rh(I)-catalyzed conjugate addition of arylboronic acids to enones (Scheme 41).



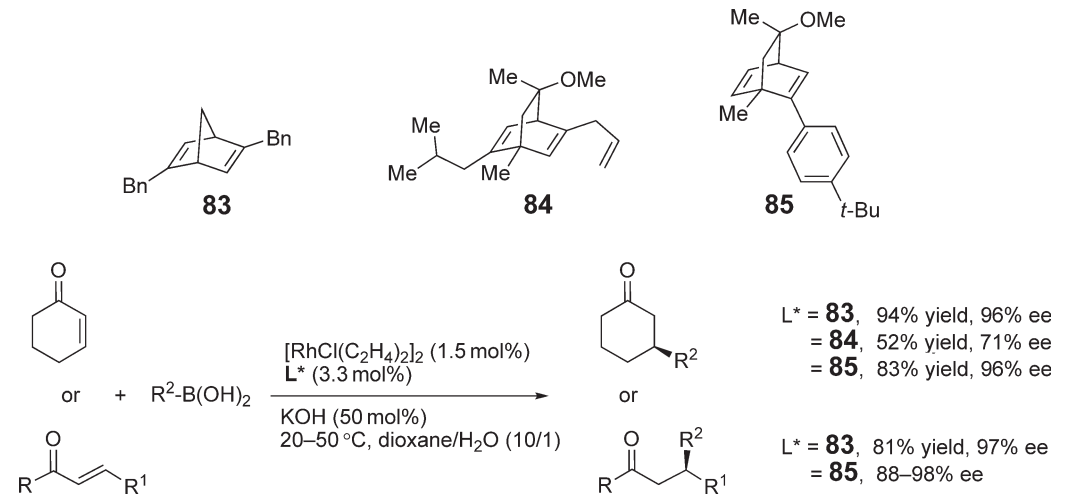
Scheme 38



Scheme 39



Scheme 40



Scheme 41

10.08.2.5.5.(ii) Palladium-catalyzed asymmetric 1,4-addition of organoboron reagents

Rhodium(I) complexes are excellent catalysts for the 1,4-addition of aryl- or 1-alkenylboron, -silicon, and -tin compounds to α,β-unsaturated carbonyl compounds. In contrast, there are few reports on the palladium(II) complex-catalyzed 1,4-addition to enones[126,126a] for the easy formation of *C*-bound enolate, which will result in β-hydride elimination product of Heck reaction. Previously, Cacchi *et al.* described the palladium(II)-catalyzed Michael addition of ArHgCl or $SnAr_4$ to enones in acidic water.[127] Recently, Miyaura and co-workers reported the 1,4-addition of arylboronic acids and boroxines to α,β-unsaturated carbonyl compounds. A cationic palladium(II) complex $[Pd(dppe)(PhCN)_2](SbF_6)_2$ was found to be an excellent catalyst for this reaction (dppe = 1,2-bis(diphenylphosphine)ethane; Scheme 42).[128]

10.08.2.6 Organoaluminum Nucleophiles

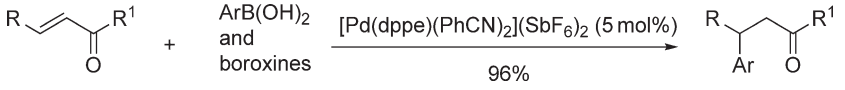
Organoaluminum reagents are inexpensive and readily available in large quantities. However, only a few examples of conjugate additions using trialkylaluminum nucleophiles have been reported.

When trimethylaluminum reacted with 3-methyl-cyclohexa-2,5-dienone in the presence of chiral oxazoline ligands **86**, the conjugate addition proceeded efficiently at the less-substituted double bond with up to 68% ee (Scheme 43).[129,129a] The two *ortho*-substituents on the phenyl ring of ligands **86** were considered to be important for selectivity.

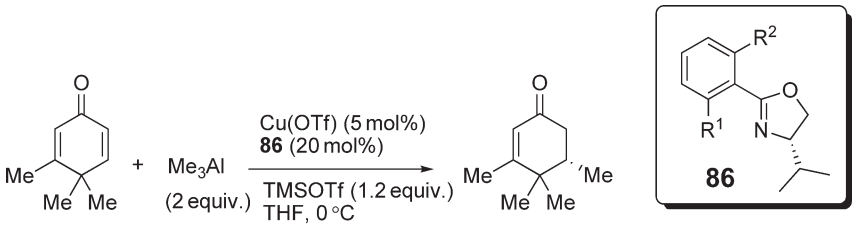
Woodward and co-workers utilized $[Cu(MeCN)_4]BF_4$ and (*S*)-BINOL-derived thiourethane ligand **87** in the addition reaction of trimethylaluminum to acyclic enones. Both yields and enantioselectivities were moderate (Scheme 44).[130]

Dieguez *et al.* reported that phosphine–phosphite ligand **88** (Figure 9) gave 62% ee in the reaction of triethylaluminum with 2-cyclohexenone.[131]

Recently Chan and co-workers synthesized diphosphite ligands **89** and **40**; both of them showed excellent enantioselectivities in the copper-catalyzed conjugate addition of organoaluminum to cyclic enones. (Ligand **89** afforded 3-methylcyclohexanone in 96% ee[132] and ligand **40** afforded 3-ethylcyclopentanone in 94% ee.[133]) Binaphthol-derived thioether **90** also catalyzed the 1,4-addition of $AlMe_3$ to linear aliphatic enones to give 80–93% ee for most substrates.[134]

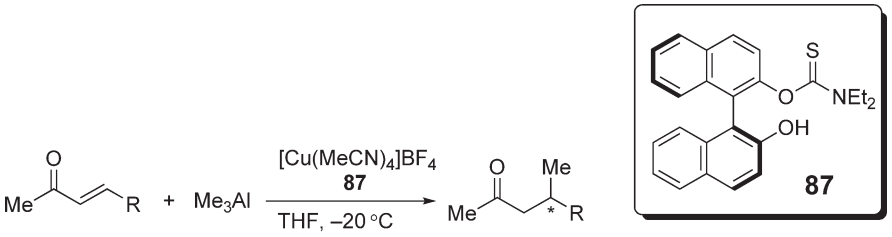


Scheme 42



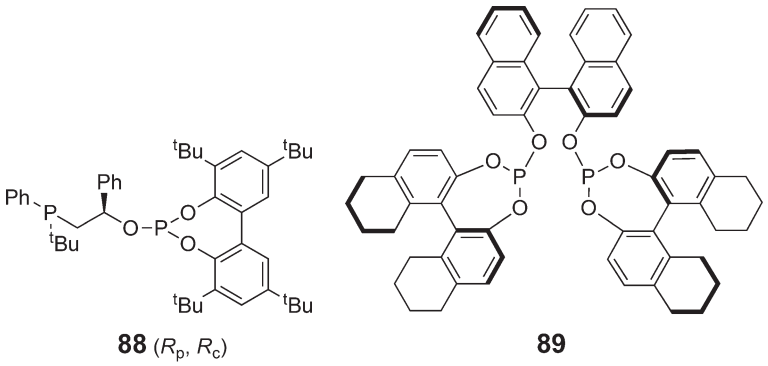
86a: R^1 = SMe; R^2 = H; 39% yield, 63% ee
86b: R^1 = OMe; R^2 = OMe; 88% yield, 68%ee

Scheme 43

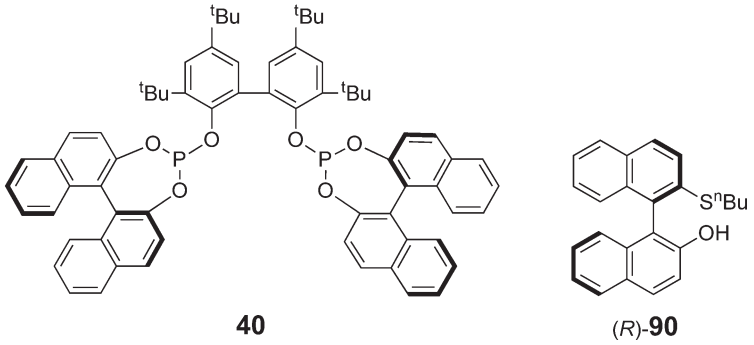


87a: R = n-C_5H_{11}, 47% yield, 51% ee
87b: R = n-C_3H_7, 51% yield, 46% ee

Scheme 44

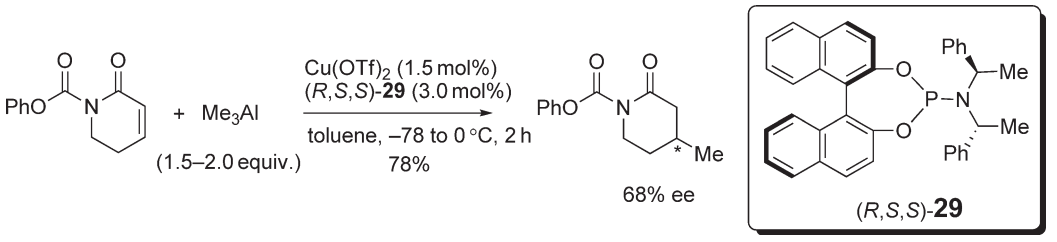


88 (R_p, R_c) **89**

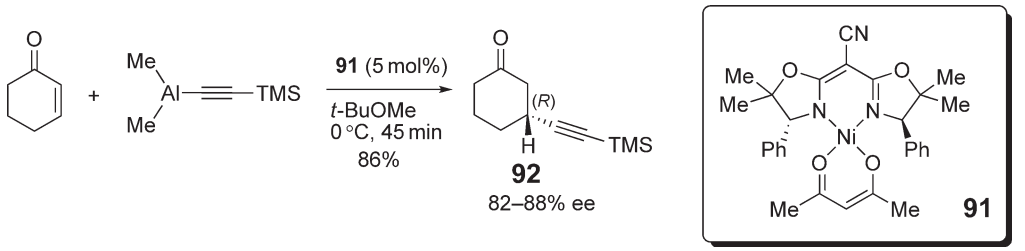


40 (*R*)-**90**

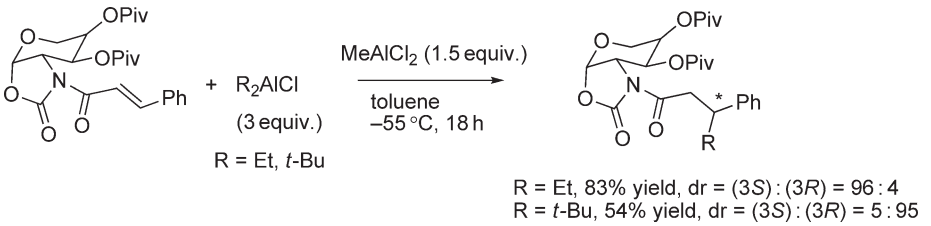
Figure 9



Scheme 45



Scheme 46



Scheme 47

Feringa and co-workers found that Cu(OTf)$_2$-**29** can catalyze the addition of Me_3Al to lactam to give corresponding methyl addition product with moderate enantioselectivity (68% ee; Scheme 45).[75]

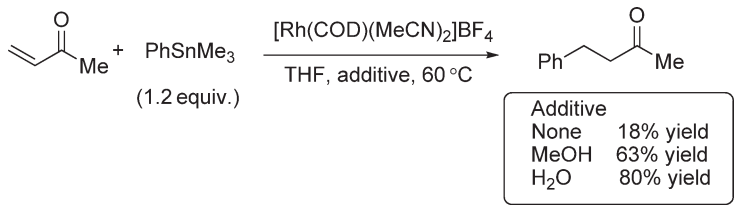
The conjugate addition of alkynyl moiety to acyclic α,β-unsaturated ketones has previously been accessed by organoaluminum acetylides in the presence of Ni(I) catalyst, which was generated *in situ* by the reduction of Ni(acac)$_2$ with equivalent diisobutylaluminum hydride (DIBAL-H).[135,135a] Later, using a catalytic amount of chiral bisoxazoline-Ni complex **91,** Corey and Kwak accomplished the first catalytic asymmetric addition of dimethylaluminum TMS-acetylide to 2-cyclohexenone in good yield and high ee (TMS = tetramethylsilyl group; Scheme 46).[136]

The asymmetric synthesis of β-branched carboxylic acid derivatives was accomplished by conjugate addition of mixed organoaluminum reagents to optically active Arabinose-derived α,β-unsaturated *N*-acyloxazolidinones (Scheme 47). Efficient stereocontrol was achieved using different optically active bicyclic oxazolidinones, yielding (*R*)- or (*S*)-configured β-branched carboxylic acid derivatives.[136a]

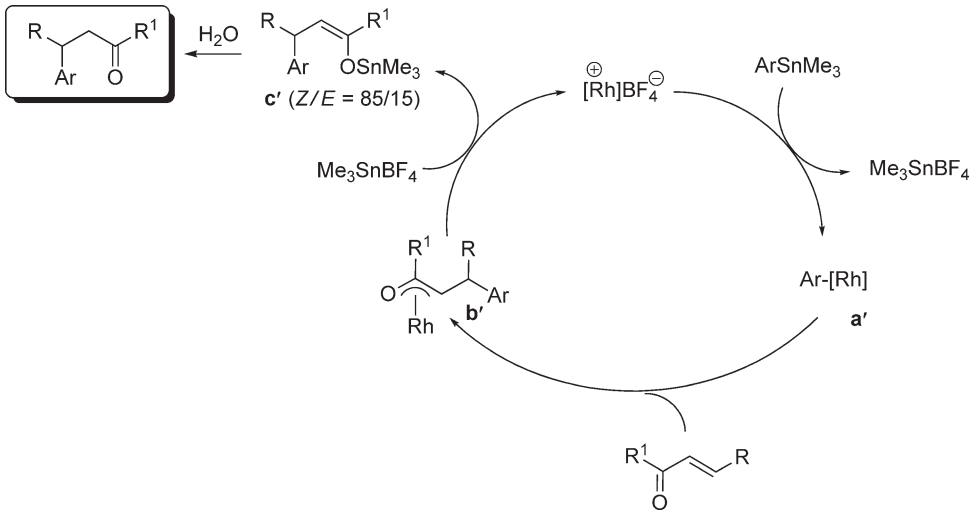
10.08.2.7 Organotin Nucleophiles

The application of organostannanes in rhodium-catalyzed 1,4-addition reactions was first studied by Oi and co-workers.[137,137a] The treatment of enones or enolates with a slight excess of aryltrimethylstannane and catalytic amounts of [Rh(COD)(MeCN)$_2$]BF$_4$ generates the conjugate addition products in good yields. The use of protic additives enhanced the yield of the reaction (Scheme 48).[138]

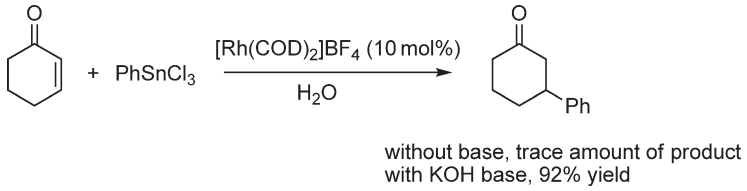
This catalytic reaction was believed to proceed analogously to those with phenylboronic acids (Scheme 49).[137,137a] Transmetallation of the arylstannane with the cationic rhodium complex generated the rhodium aryl species **a′** and trimethyltin tetrafluoroborate. Conjugate addition generated rhodium enolate **b′**, which subsequently reacted with



Scheme 48



Scheme 49



Scheme 50

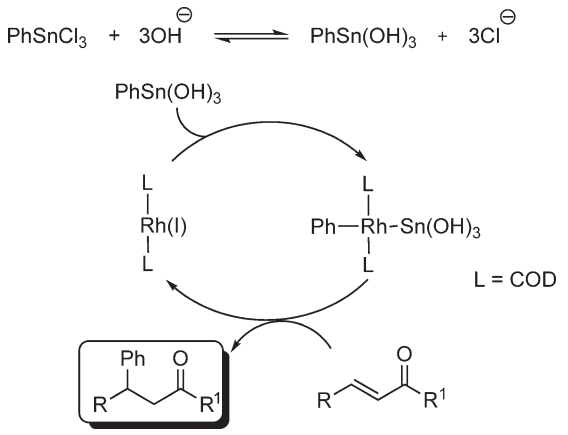
trimethyltin tetrafluoroborate to regenerate the cationic rhodium catalyst and liberated the tin enolate **c′**. The addition of protic additives resulted in the rapid hydrolysis of the enolate **c′** to provide the desired addition products.

Recently, Li and co-workers also reported the Rh-catalyzed arylstannane addition to enones in water under reflux.[139] The addition of KOH helps the reaction to proceed smoothly (Scheme 50). A tentative mechanism was proposed for the Rh-catalyzed conjugated addition of phenyltin trichloride under basic conditions (Scheme 51). Later, this kind of reaction was found to work even in water at 50 °C.[140]

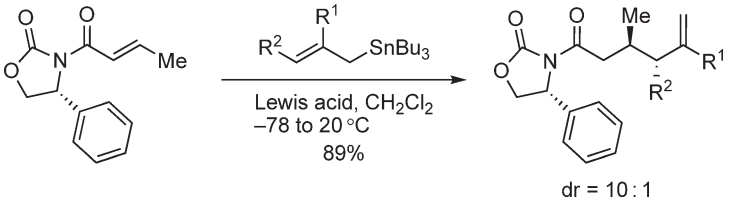
Although there are some examples of diastereoselective addition of allylic stannanes to substituted 1,3-oxazolidinones (Scheme 52),[141] these reactions have still not been applied to asymmetric synthesis.

10.08.2.8 Organosilicon Nucleophiles

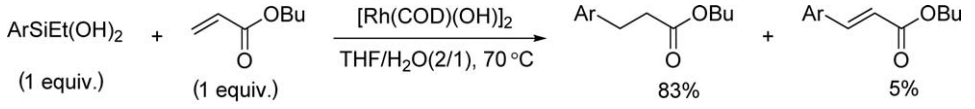
In 2001, Mori *et al.* found that [Rh(OH)(COD)]$_2$ catalyzed the coupling of various acrylates and acrylamides with aryl silanediols, and the reaction could be controlled to give predominantly 1,4-addition products (Scheme 53).[142,142a,142b]



Scheme 51



Scheme 52



Scheme 53

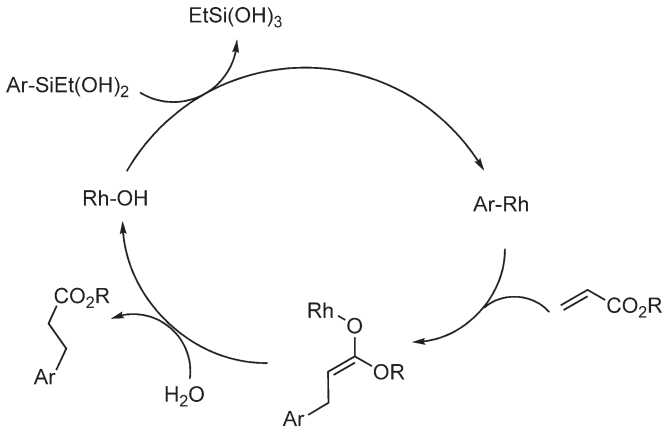
The proposed mechanism (Scheme 54) indicated that transmetallation of the aryl silanediol to the rhodium hydroxide catalyst followed by 1,4-addition and hydrolysis of the *O*-bound enolate generated the addition product and regenerated the Rh–OH catalyst.

Li and co-workers also reported a highly efficient conjugate addition reaction with arylsilanes as nucleophilic reagents. The reaction of 2-cyclohexenone with 4 equiv. of either diphenyldichlorosilane or phenylmethyldichlorosilane in water generated the conjugate addition product in 97% and 95% yields, respectively (Scheme 55).[143] An excess of sodium fluoride additive was important in this reaction.

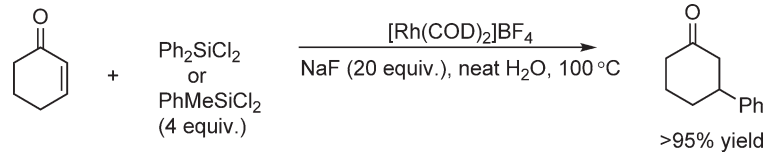
Organotrialkoxysilanes ($ArSi(OR)_3$) were used as organometallic reagents without fluoride additives (Scheme 56).[144,144a] $ArSi(OR)_3$ was easy to use because of its higher air and moisture stability. Oi and co-workers believed that hydrolysis of the trialkoxysilanes to generate silanetriols was likely occurring prior to transmetallation of the cationic rhodium complex.

The scope of arylsilane nucleophiles has been extended to poly(phenylmethylsiloxane), which is used industrially as a highly thermoresistant silicone oil (Scheme 57).[142]

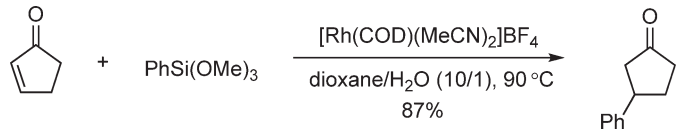
Although the use of organosilicon compounds for the rhodium-catalyzed 1,4-addition has been studied, only a few reports have appeared on the asymmetric version of this reaction. In 2003, Oi *et al.* described a highly enantioselective 1,4-addition of aryl- and alkenyltrialkoxysilanes to α,β-unsaturated ketones in the presence of $[Rh(COD)(MeCN)_2]BF_4$ and (*S*)-BINAP (Scheme 58).[145] The enantioselectivities were as high as those using the corresponding boronic acids, though the chemical yields were a little lower.



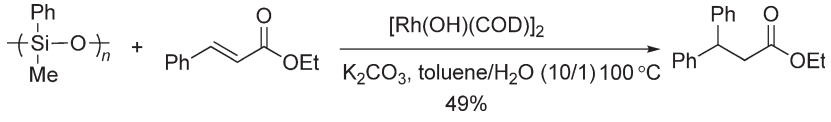
Scheme 54



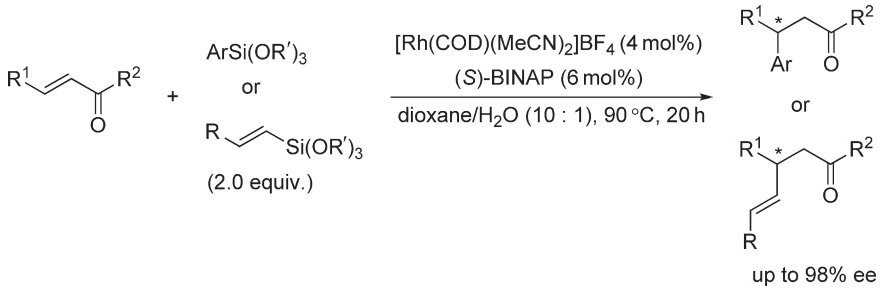
Scheme 55



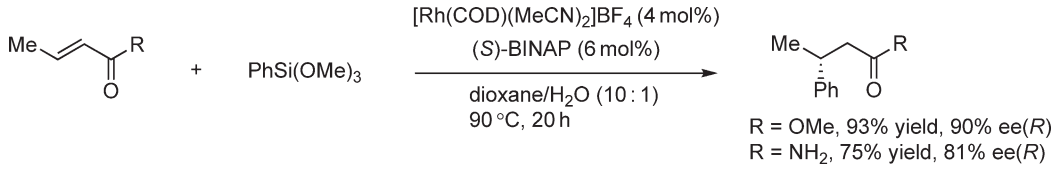
Scheme 56



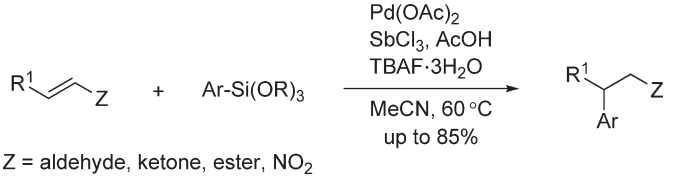
Scheme 57



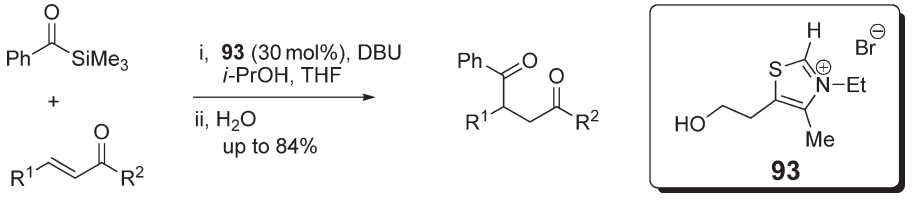
Scheme 58



Scheme 59



Scheme 60



Scheme 61

This kind of asymmetric addition was also applicable for α,β-unsaturated ester and amide, which gave the corresponding β-phenylation products with good selectivity (Scheme 59).

Besides rhodium catalysts, palladium complex also can catalyze the addition of aryltrialkoxysilanes to α,β-unsaturated carbonyl compounds (ketones, aldehydes) and nitroalkenes (Scheme 60).[146] The addition of equimolar amounts of $SbCl_3$ and tetrabutylammonium fluoride (TBAF) was necessary for this reaction to proceed smoothly. The arylpalladium complex, generated by the transmetallation from a putative hypercoordinate silicon compound, was considered to be the catalytically active species.

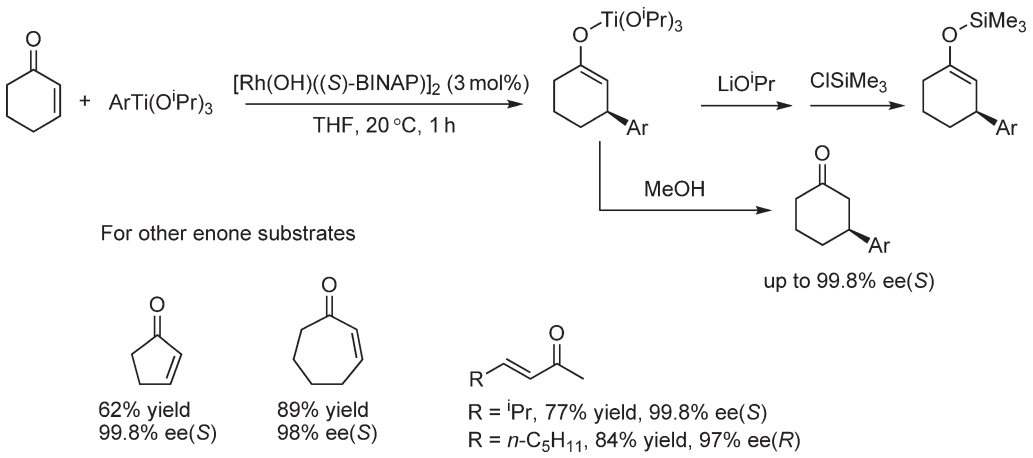
Recently, a thiazolium-catalyzed conjugate addition of acylsilanes to unsaturated esters and ketones was reported (Scheme 61).[147]

10.08.2.9 Organotitanium Nucleophiles

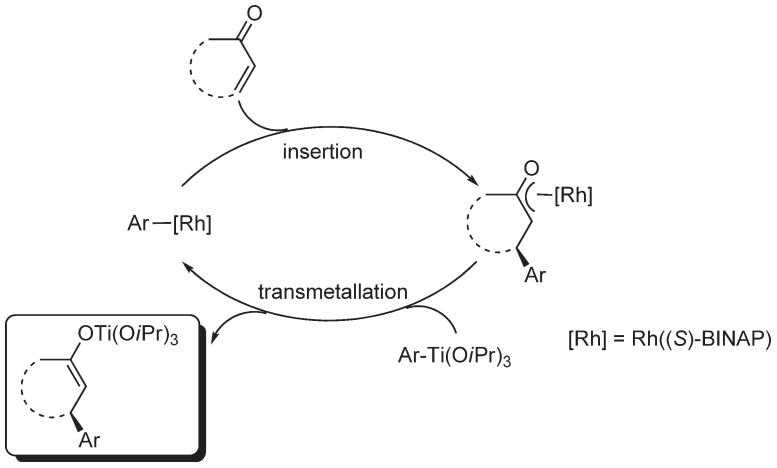
Hayashi found that the addition of ArTi(O*i*Pr)$_3$ to 2-cyclohexenone was completed within 1 h in the presence of 3 mol% [Rh(OH)((*S*)-BINAP)]$_2$ to give the titanium enolates in high yield and excellent enantioselectivity.[148] The titanium enolates were further converted into either silyl enol ether or 3-arylcyclohexanone. Other cyclic and linear enones were also good substrates for this asymmetric addition, affording the corresponding phenylation products with over 97% ee (Scheme 62). NMR studies revealed that this catalytic cycle involved a transmetallation of aryl group from titanium to rhodium of the (oxa-π-allyl) rhodium intermediate, giving the arylrhodium species and the titanium enolate (Scheme 63).

10.08.2.10 Organobismuth Nucleophiles

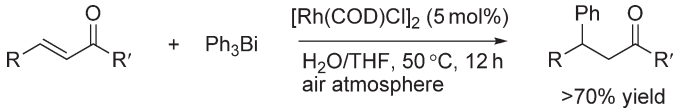
When a variety of β-substituted enones and acrylates were treated with Ph_3Bi in the presence of catalytic amount of neutral [Rh(COD)Cl]$_2$ or cationic [Rh(COD)$_2$]BF$_4$, 1,4-addition products were obtained in greater than 70% yield (Scheme 64).[139,149] Substrates without β-substituent resulted in significantly lower yields, whereas substrates bearing a hydroxyl group reacted smoothly and did not require protection and deprotection steps.



Scheme 62



Scheme 63

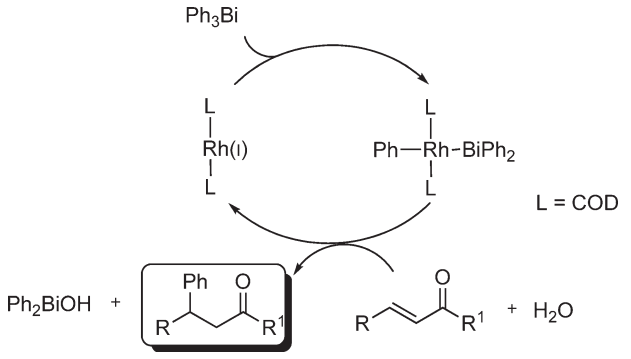


Scheme 64

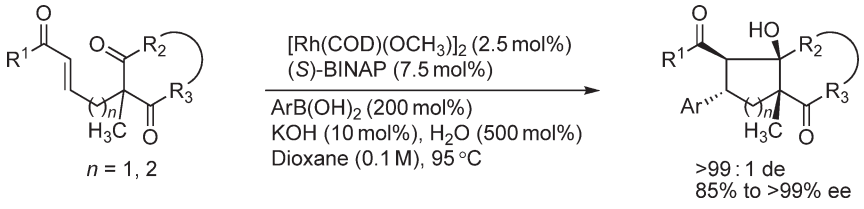
Scheme 65 outlined a proposed mechanism in which rhodium served as catalyst for the conjugate addition, and the C–Bi bond was proposed to be oxidatively added to the Rh complex.

10.08.3 Applications in Organic Synthesis

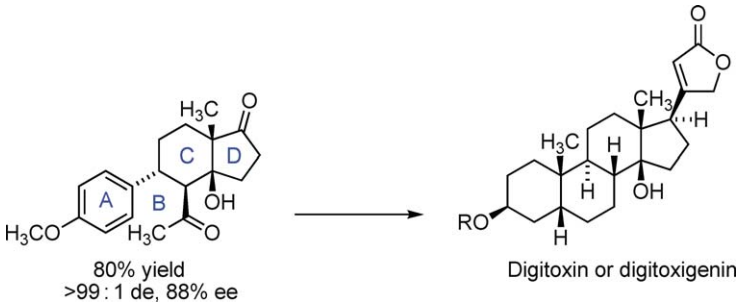
Recently, Krische and co-workers developed an effective protocol for the catalytic desymmetrization and parallel kinetic resolution of enone–diones via tandem conjugate addition–aldol cyclization (Scheme 66).[150] This transformation, involving enantioselective rhodium-catalyzed conjugate addition methodology, enabled the formation of two C–C bonds and four contiguous stereogenic centers from simple precursors with high diastereo- and enantiocontrol.



Scheme 65



Scheme 66



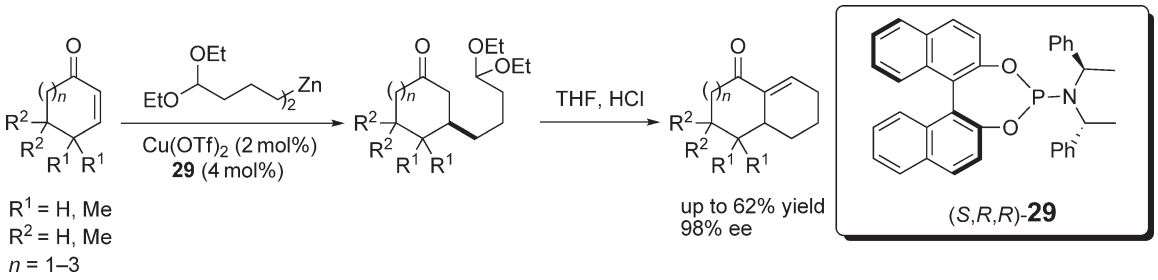
Scheme 67

Application of this tandem conjugate addition–aldol cyclization methodology may lead to the concise synthesis of digitoxin (Scheme 67) and related cardiac steroids.

Feringa and co-workers described the tandem addition–aldol cyclization protocol leading to the formation of 6,6-, 6,7-, and 6,8-annulated bicyclic systems (Scheme 68).[39] Using Cu(II)-**29** as catalyst and functionalized organozinc reagents as nucleophiles, the conjugate addition reaction followed by aldol cyclization can offer highly enantioselective annulation products (up to 98% ee). This method can be used in the synthesis of carbocyclic compounds, such as steroids, terpenes, and other natural products.

10.08.4 Conclusion

During the past 10 years, great progress has been made in enantioselective conjugate addition methodologies. Numerous nucleophiles can now be used in this reaction with good stereochemical control. In particular, rhodium-catalyzed organoboron addition and copper-catalyzed organozinc addition have showed sufficiently high activities



Scheme 68

and selectivities for practical organic synthesis. Although this review shows comprehensive applications of various nucleophiles in asymmetric conjugate addition, this area is far from being exhausted. This type of reaction is believed to have a great synthetic value of various diversified compounds by proper combination of different organometallic reagents, newly designed chiral ligands, and various types of α,β-unsaturated substrates.

Acknowledgment

The authors thank the Hong Kong Research Grants Council (project number PolyU 5001/03P), the University Grants Committee Areas of Excellence Scheme in Hong Kong (AoE P/10-01), and the Hong Kong Polytechnic University ASD Fund for financial support. G. Lu also wants to thank the Humboldt Foundation for the award of a fellowship.

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10.09
C–C Bond Formation through Addition of C–M to C═O, C═N, and C≡N Bonds

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10.09.1 Introduction

Carbon–carbon bond formation using addition reactions of organometallics to carbonyl and related compounds is among the most fundamental and useful processes in organic synthesis. This chapter covers these very important research areas focusing on the use of group III to group XI transition metals, and is divided into several sections according to addition of the corresponding organometallic compound (C–M) to C═O, C═N, and C≡N bonds. The discussed transformations include nucleophilic addition of C–M to C–X multiple bonds as well as migratory insertion of C–X multiple bonds into C–M. Many of these reactions are mechanistically clear, whereas in some cases the precise structure of organometallic intermediates or catalytically active species has not been proved. Simple activation of C–X multiple bonds (electrophiles) by transition metal Lewis acids and insertion of carbon monoxide into C–M as well as addition of C–M to C–C multiple bonds, including conjugate addition to activated alkenes or alkynes, are not discussed.

This chapter covers publications between 1993 and 2005, since works in this field have been summarized in COMC (1982) and COMC (1995) until 1992. Cross-references to these previous editions and other leading book references or reviews have been included as much as possible.

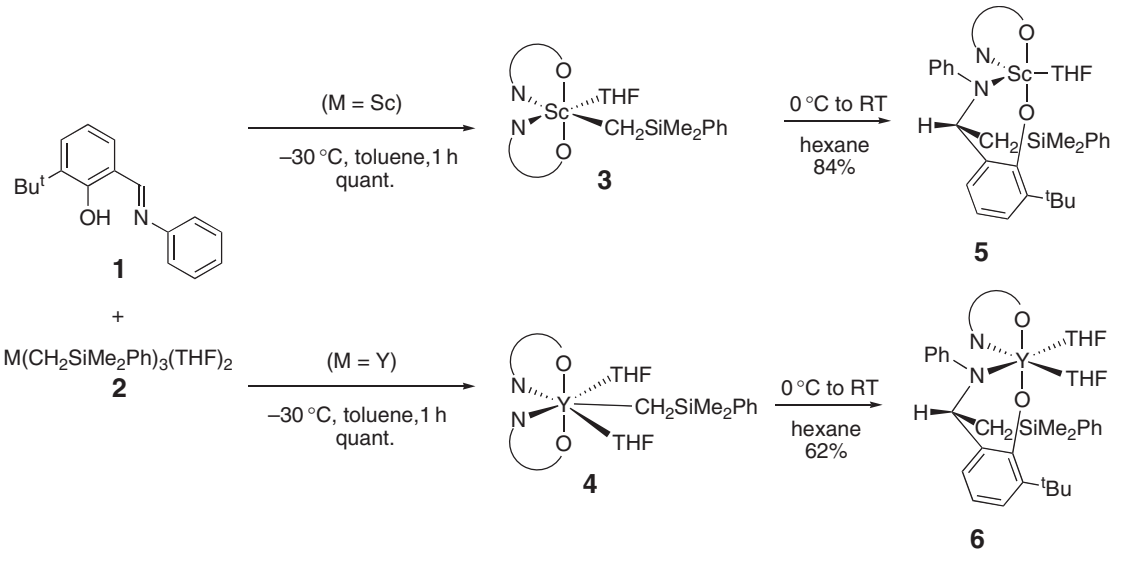
10.09.2 Group III Metals

10.09.2.1 Scandium and Yttrium

Although many complexes of Sc and Y can be seen in the literature, these complexes have been mostly used as Lewis acids in organic synthesis. There are a few examples where addition reactions of organometal species to C═O double bond, C═N double bond, and C≡N triple bond were used in preparation of metal complex.

10.09.2.1.1 Addition to C═N

As for yttrium, insertion reactions of metal–carbon bond-containing species into carbon–heteroatom unsaturated bonds have been introduced for the formation of the metal complex; the modes of the reaction are similar to those seen in main group metal chemistry, that is, the anionic carbon bound to metal attacks the cationic carbon electrophile. In most cases, bent metallocene or Cp-amido ligand are used.[1,1a] One example of a non-cyclopentadienyl ligand is illustrated in Scheme 1.[2] This chemistry takes advantage of a salicylaldiminato ligand framework, the structure of the complexes determined by X-ray crystallography. Complexes **3** and **4** are formed by combination of ligand **1** and metal complexes **2** in quantitative yields. Although **3** and **4** are not stable at temperatures higher than



Scheme 1

0 °C, an intramolecular insertion of a C═N double bond to a carbon–scandium bond occurs to afford covalent N–M (M = Sc, Y) bonds.

10.09.2.1.2 Addition to C≡N

(Cyclopentadienylamine)scandium(2,3-dimethyl-1,3-butadiene) **7** was synthesized in good yield, as shown in Scheme 2. Complex **7** reacted with benzonitrile to form a μ^2-imido complex **8**, the structure of which was characterized by single crystal X-ray diffraction. This product **8** was proposed to be formed by nitrile insertion followed by an attack of another diene methylene group on the carbon atom of the imido intermediate.[3] An unsaturated metal imido species was formed, which easily dimerized to produce **8**. However, the yield of **8** was not reported.

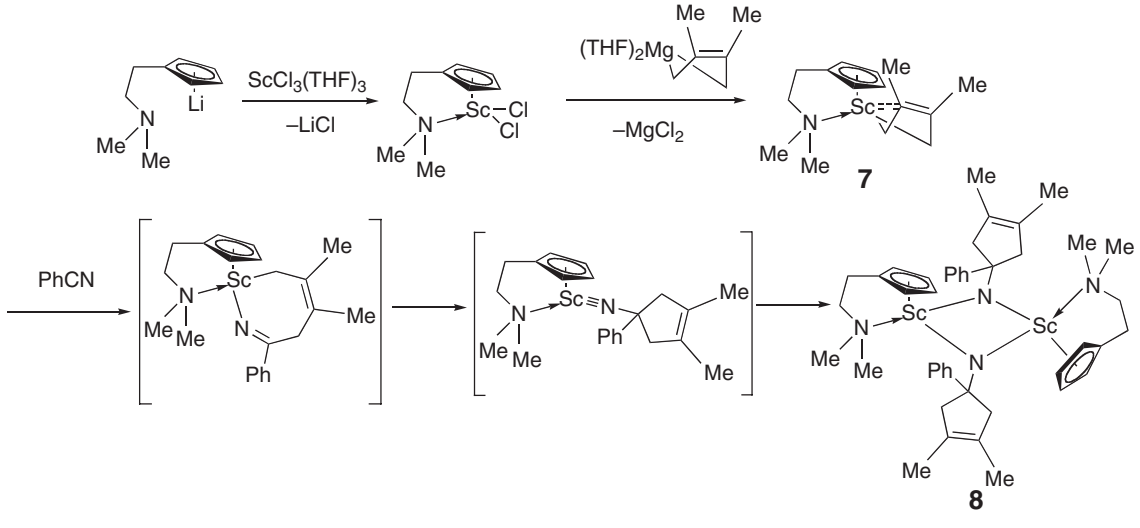
10.09.2.2 Cerium

Organocerium chemistry was pioneered by Imamoto and co-workers who reported the first organocerium compounds and their usefulness.[4] Since then, research in this area has grown rapidly and organocerium reagents have been utilized extensively in a wide range of organic chemistry. The difference between organocerium reagents and other organometallic species like Grignard reagents or organolithium compounds is their basicity, oxidation potential, and nucleophilicity. Nucleophilic addition of Grignard reagents or organolithium compounds to carbon–heteroatom unsaturated functionalities like ketones, imines, and nitriles sometimes encounter problems such as concomitant enolization and reduction. These side-reactions are attributed to their high basicity, oxidation potental, and lower nucleophilicity. In contrast, organocerium reagents facilitate nucleophilic additions without such problems to give the desired adducts, generally in high yields. Some reviews of organocerium chemistry, which cover the literature up to 1998, were reported previously.[5,5a–5c] Here we concentrate on the somewhat newer chemistry of organocerium and compile its early applications to assemblies of complex molecules.

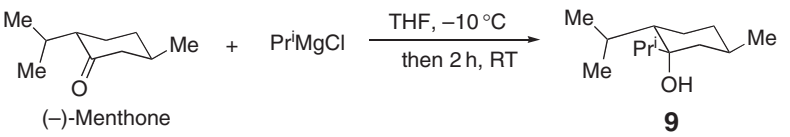
10.09.2.2.1 Addition to C═O

Addition of organocerium compounds to menthone was reported in 2000 (Scheme 3).[6] The use of organocerium compounds instead of organomagnesium reagents or organolithium compounds resulted in an enhancement of the yields of **9** in almost all cases examined.

Highly stereoselective titanium-mediated addition of organocerium reagents to β-keto amides **10** was reported (Equation (1)).[7] Although a stoichiometric amount of $TiCl_4$ and excess organocerium reagents are necessary, diastereoselectivities are generally high.

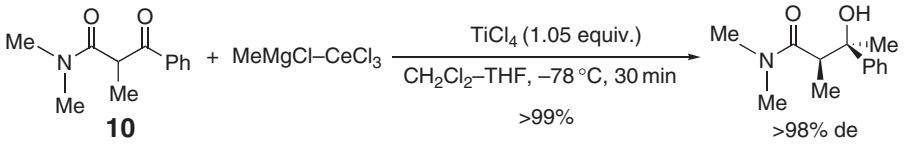


Scheme 2



$CeCl_3$	*Yield* (%)
Without $CeCl_3$	38
With $CeCl_3$	81

Scheme 3



(1)

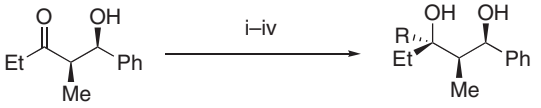
The same authors also reported the stereoselective addition of organocerium reagents to 1,3-ketoalcohol **11** involving titanium alkoxide intermediates (Scheme 4).[8]

Cerium(III) chloride could mediate high-yielding additions of *N*-benzyl-α,*N*-dilithio methanesulfonamide **12** to aldehydes and ketones of biologically importance (Scheme 5).[9] Excess amount of $CeCl_3$ (8.2 equiv.) afforded the adduct in excellent yield, while lower yield of the adduct was obtained in the absence of $CeCl_3$.

The use of vigorously dried anhydrous $CeCl_3$ in organocerium chemistry has been known to be important.[10] This was again recognized recently in the cerium-catalyzed Grignard addition reaction to ester **13**, where residual water from $CeCl_3$ affected the product ratio between desired tertiary alcohol **14** and undesired ketone product **15** (Scheme 6).[11] Residual water increased the basicity of organocerium reagents, which caused the enolization of the ketone product **15** to afford, after hydrolysis, the undesired ketone product **15**.

As emphasized above, the practical utility of organocerium compounds is to circumvent the problems which are faced with the corresponding Grignard and organolithium reagents because of their inability to react effectively with sterically demanding carbonyl compounds and carbon–heteroatom unsaturated bonds which have acidic α-protons. Some of the latest examples are shown below.

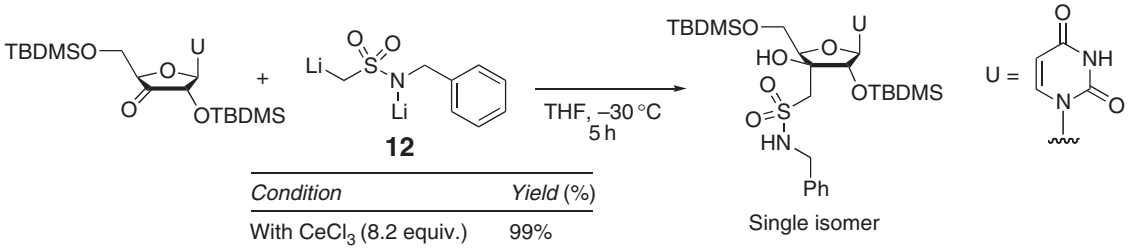
An ethynylcerium reagent was effectively utilized in the last step for the total synthesis of desogestrel **17**.[12] Desogestrel was isolated in 92% yield from the corresponding ketone **16**, bearing acidic α-protons (Equation (2)).



Nucleophile	*Yield* (%)	*dr*
PhMgCl–$CeCl_3$	80	>99 : <1
PhMgCl	0	

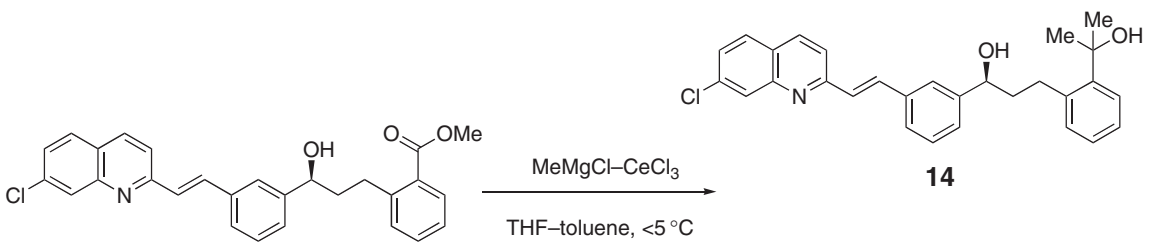
i, LiH (1.3 equiv.), THF, –30 °C; ii, $TiCl_4$(1.3 equiv.), CH_2Cl_2, –30 °C; iii, RMgX–$CeCl_3$ or RMgX, THF; iv, H_3O^+

Scheme 4



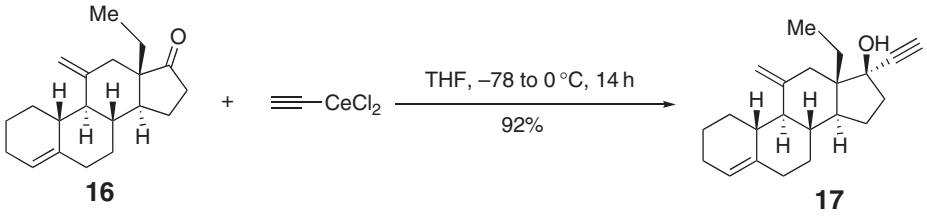
Condition	*Yield* (%)
With $CeCl_3$ (8.2 equiv.)	99%
Without $CeCl_3$	30%

Scheme 5



H_2O wt.%	%*Conversion*	%*Diol* **14**	%*Ketone* **15**
0.74	99.7	90.5	9.1
1.88	99.0	83.2	15.8
3.97	98.2	80.7	17.5

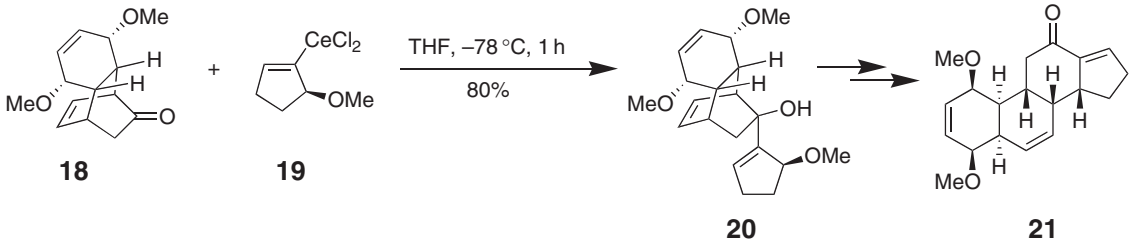
Scheme 6



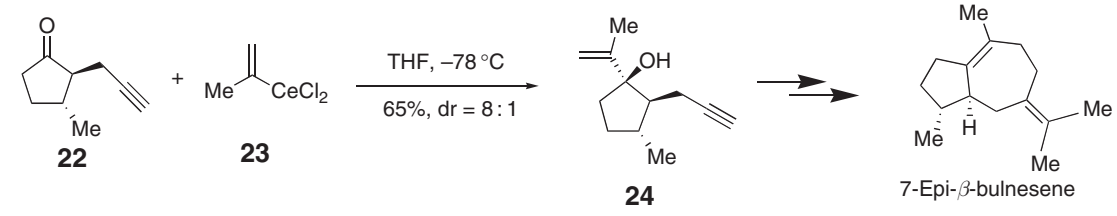
(2)

Cyclic vinylcerium reagent **19** reacted with ketone **18** to afford tertiary alcohol **20** in 80% yield in a completely diastereofacially selective manner (Scheme 7).[13] Compound **20** is an intermediate of steroid-like compound **21**.

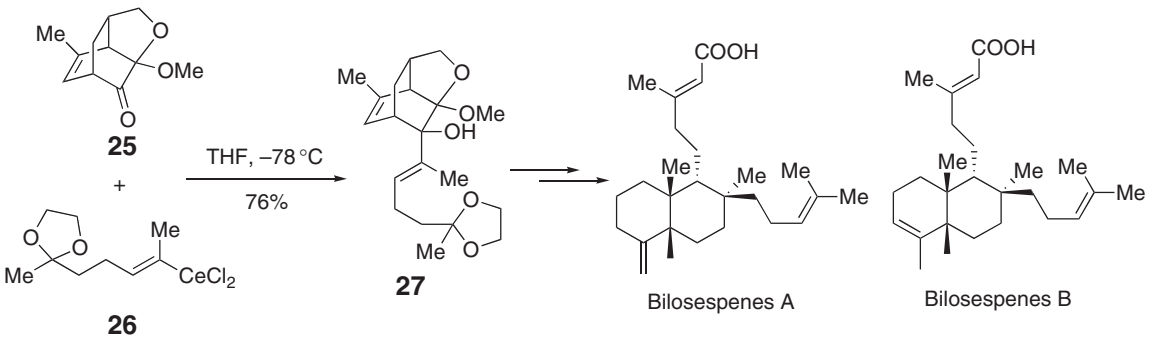
A short total synthesis of racemic 7-epi-β-bulnesene was achieved, in which vinyl cerium **23** was used for the introduction of a three-carbon unit to a ketone **22** to afford tertiary alcohol **24**, the substrate for the key intramolecular cyclization/Claisen rearrangement sequence (Scheme 8).[14]



Scheme 7



Scheme 8



Scheme 9

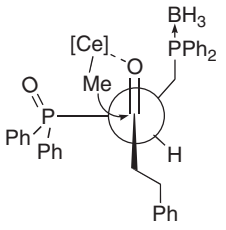
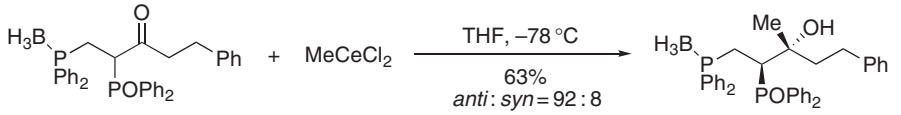


Figure 1 Proposed transition state model of methylation of **28**.

A similar but bulkier organocerium reagent **26** was applied to the total synthesis of bilosespenes A and B.[15] Upon reaction of **26** and ketone **25**, the target intermediate **27** was obtained in 76% yield as a single isomer (Scheme 9).

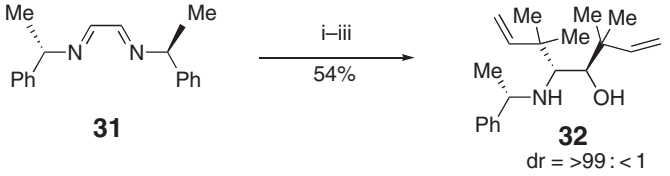
Addition of methylcerium reagent **29** to ketone **28**, bearing a stereogenic center at the α-positon, successfully occurred to give the tertiary alcohol **30** in an *anti*-stereofacial selective manner (Equation (3)).[16] This stereoselectivity is rationalized by conceiving an intramolecular transfer of methyl group from an $MeCeCl_2$ ketone complex (Figure 1).



28 **29** **30** (3)

10.09.2.2.2 Addition to C═N

Barbier-type organocerium reagents reacted with *N*,*N*-bis[(*S*)-1-phenylethyl]ethanediimine **31** to form 1,2-aminoalcohol **32** via hydrolysis of the initially formed iminoamine product by water released from $CeCl_3$ hydrate (Scheme 10).[17] Aminoalcohol **32** was produced as a sole product.



i, Zn (4 equiv.), Prenyl bromide (1.5 equiv.), $CeCl_3 \cdot 7H_2O$ (1 equiv.), THF, 25 °C, 0.5 h;
ii, $CeCl_3 \cdot 7H_2O$ (2 equiv.), 65 °C, 1 h; iii, prenyl bromide (1.5 equiv.), 25 °C, 1 h

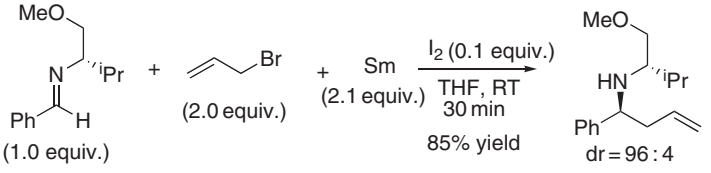
Scheme 10

10.09.2.3 Samarium

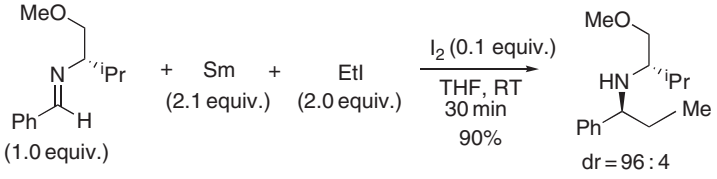
Among various samarium reagents, SmI_2 has been most widely used for many transformations in organic synthesis. Since many reviews on SmI_2 chemistry have been already published,[18,18a–18e] this chapter covers the organosamarium-induced reactions other than those of SmI_2.

10.09.2.3.1 Allylsamarium reagents

Applications of allylsamarium reagents in organic synthesis have been of great importance. These reagents are usually generated *in situ* by halogen–metal exchange using SmI_2 with allyl halides[19,19a,19b] or from allylic palladium with SmI_2.[20] Although SmI_2 is a mild, neutral, and soluble one-electron reductant, its difficulty in handling due to its sensitivity to moisture and oxygen is a drawback. Stable and cheap samarium metal as well as SmI_2 also have a strong reducing ability; it can be used with a catalytic amount of iodine (0.1 equiv. is the best) in Barbier-type allylations of imines, as shown in Equation (4). A diastereoselective version was reported using imines prepared from (*S*)-valinol.[21] Not only allyl halides but also alkyl halides were subjected to insertion of Sm under the same conditions to afford alkylsamarium reagents, which reacted with imines successfully (Equation (5)). Figure 2 shows one of the plausible reaction mechanisms, where Sm(III) species deposited in the reaction mixture during the short induction period works as a strong Lewis acid. Sm(III) species is chelated between oxygen and nitrogen, and consequently *Re* face attack was hindered by valinol-derived methyl groups.

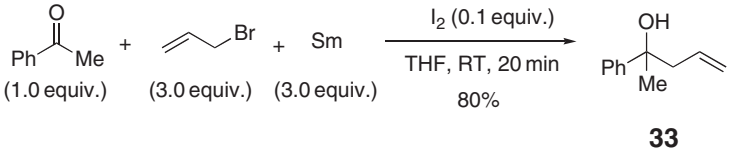


(4)



(5)

Samarium-mediated Barbier-type reactions of carbonyl compounds were reported in a similar reaction system (Equation (6)).[22] THF is the key solvent to obtain the product **33**. In MeOH, pinacol coupling-type reaction proceeded predominantly, while the reaction failed to produce any desired compound in CH_3CN.[23]



33

(6)

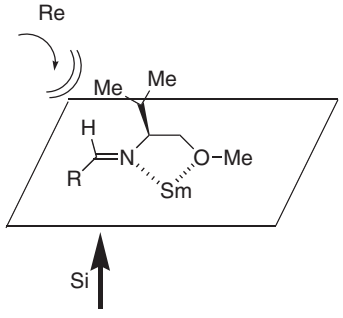
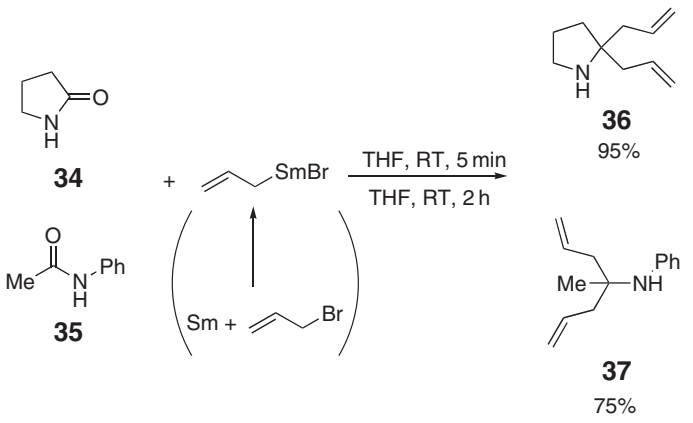
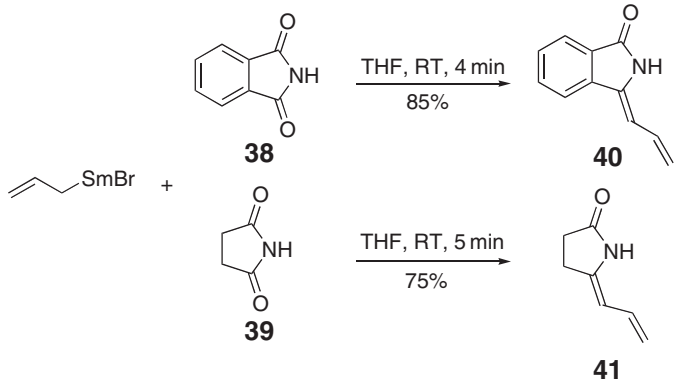


Figure 2 Plausible mechanism of Barbier-type allylation and alkylation with Sm and iodine (cat.).

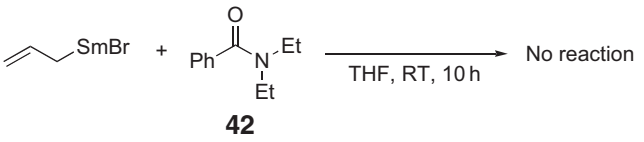


Scheme 11



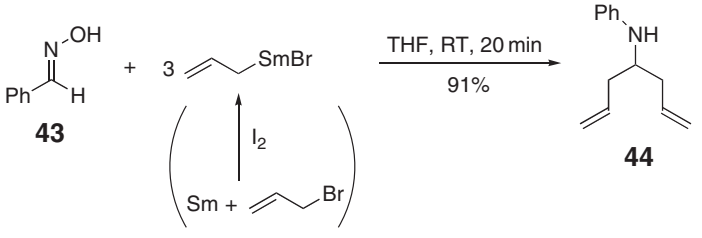
Scheme 12

When lactam **34** and acyclic amide **35** containing an N–H bond were treated with allylsamarium bromide, which was prepared from samarium metal and allylbromide in THF, geminal diallylation occurred to construct quaternary carbons of **36** and **37** in high yields (Scheme 11).[24] On the other hand, the reactions of *o*-phthalimide **38** and succinimide **39** reacted with allylsamarium bromide and did not form the diallylated compounds but gave conjugated diene compounds **40** and **41**, respectively, in good yields (Scheme 12). *N*-trisubstituted amide **42** failed to react with allylsamarium bromide (Equation (7)).

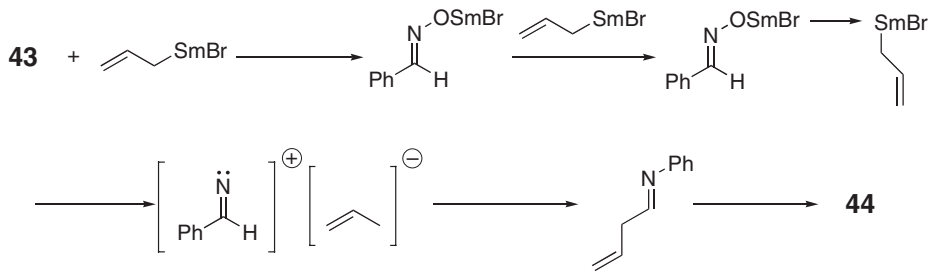


(7)

Oximes are also good substrates for allylsamarium bromide addition.[25] The Beckmann rearrangement product **44** was produced from oxime **43** in good yields when the ratio of allysamarium bromide to oximes was more than 3 : 1 (Equation (8)). This type of product was also obtained when the other allylic organometallic compounds were used. The reaction mechanism was proposed as shown in Scheme 13.

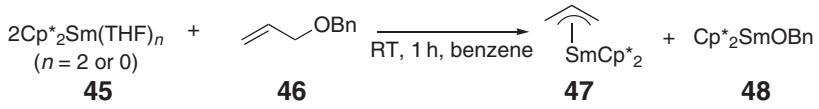


(8)



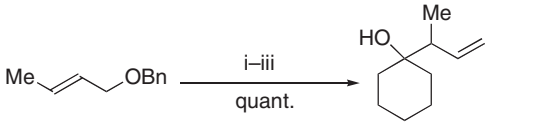
Scheme 13

In addtion to Sm metal, $Cp^*_2Sm(THF)_n$ ($n = 2$ or 0) can be a good starting material for allylsamarium generation. In the case of $Cp^*_2Sm(THF)_n$ ($n = 2$ or 0), allylic ethers are useful precursors since they are able to coordinate to the low-valent lanthanide metal via the internal oxygen. Samarium complexes **45** react with allyl benzyl ether **46** to produce allylsamarium complex **47** and benzyloxide **48** as illustrated in Equation (9).[26]



(9)

On the other hand, allyl chloride and $Cp^*_2Sm(THF)_n$ ($n = 2$ or 0) led to the formation of the corresponding allylsamarium species in low yield with Cp^*_2SmCl as byproduct.[27] It is known that $Cp^*_2Sm(THF)_2$ and allylic ethers afford a fluxional η^3-allyl complex in equilibrium with the η^1-allyl form caused by the coordination of THF, whereas the static η^3-allyl complex is formed from Cp^*_2Sm.[28] The reaction of allylsamarium thus generated with cyclohexanone took place at the most substituted terminus of the allylic moiety to give the branched homoallylic alcohol **49**, unlike the allylic lanthanides generated by transmetallation and halogen–metal exchange where the least branched homoallylic alcohol was obtained predominantly (Scheme 14). This allylsamarium reacted with prochiral ketones and aldehydes like acetophenone and pivalaldehyde to form homoallylic alcohols **50** and **51**, respectively, in good yields with high selectivity in favor of the *anti*-diastereoisomer (Schemes 15 and 16).



49
Only branched isomer

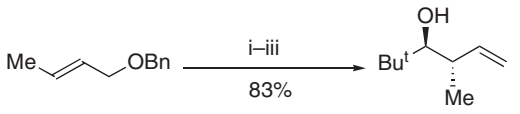
i, $Cp^*_2Sm(THF)_2$, toluene; ii, cyclohexanone; iii, H_3O^+

Scheme 14

50
anti : *syn* = 79 : 21

i, $Cp^*_2Sm(THF)_2$, toluene; ii, acetophenone; iii, H_3O^+

Scheme 15

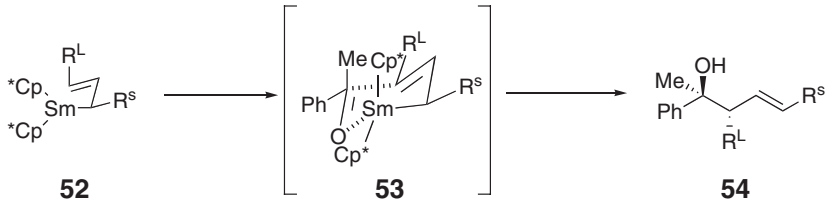


51

anti: *syn* = 96 : 4

i, $Cp^*_2Sm(THF)_2$, toluene; ii, pivalaldehyde; iii, H_3O^+

Scheme 16

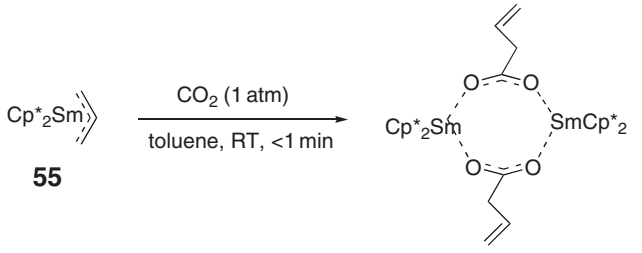


52 **53** **54**

Scheme 17

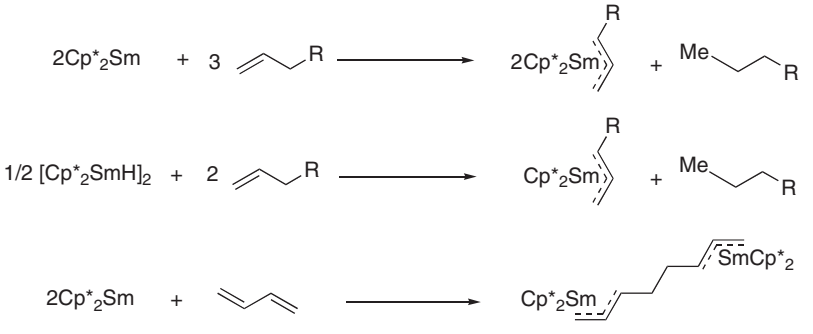
This regio- and stereochemistry in these reactions can be accounted for as shown in Scheme 17.[26] When coordinating electrophiles like ketones and aldehydes are used, the equilibrium between η^1- and η^3-allyl complexes shifts to η^1, resulting in the formation of the least substituted η^1-complex **52** preferentially. Carbon–carbon bond formation takes place via a six-membered ring transition state **53**, leading to the formation of the branched homoallylic alcohols **54** with *anti*-diastereoselectivity.

The fact that organosamarium allyl complexes of the type $Cp^*_2Sm(CH_2CH{=}CHR)$ can arise from the treatment of Cp^*_2Sm or $[Cp^*_2Sm(\mu\text{-}H)]_2$ with a variety of olefin and diene substrates makes samarium chemistry more intriguing.[29] The reaction modes are illustrated in Scheme 18. These allylsamarium complexes **55** react with CO_2 to afford the carboxylate products **56**, which participate in monometallic/bimetallic interconversions (Equation (10)). Carbon disulfide and O═C═S also insert into carbon–samarium bonds, which form only monometallic species.[29]



55 **56**

(10)



Scheme 18

10.09.2.3.2 Vinylsamarium reagents

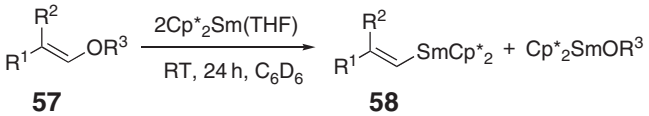
The reactions of carbonyl compounds with vinylsamariums are also efficient to provide allylic alcohols in one step. Vinylsamarium **58** can be synthesized from vinyl ethers and $Cp^*_2Sm(THF)_n$ ($n = 1$ or 2) in good yields (Table 1). The reaction of the vinylsamarium thus formed reacts with aldehydes and ketones to afford allylic alcohols, respectively (Scheme 19).[30]

Cp^*_3Sm **59** (it can be regarded as a vinylsamarium when a Cp^* coordinates Sm in an η^1-fashion) is an extremely crowded molecule, which displays high reactivity with substrates including CO, nitriles, isonitriles and isocyanates.[31] The reactions proceed according to Scheme 20.

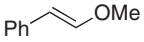
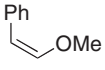
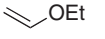
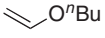
10.09.2.3.3 Samarium enolates

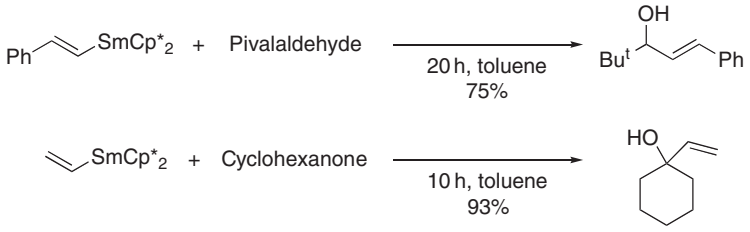
Samarium enolates **60** can be easily prepared by reduction of α-bromocarboxylic acid esters with SmI_2. These enolates mediated well-defined synthesis of star-shaped block co-polymers **61** (Scheme 21).[32,32a] SmI_3 also mediated the formation of samarium enolates. Phenacyl thiocyanate **62**[33] and α-haloketone **64**[34] are converted to samarium(III) enolate intermediates **63** and **65**, respectively, which undergo addition to benzaldehyde derivatives affording the corresponding α,β-unsaturated ketones as shown in Schemes 22 and 23.

Table 1 Reaction of alkyl vinyl ether 57 with $Cp^*_2Sm(THF)$

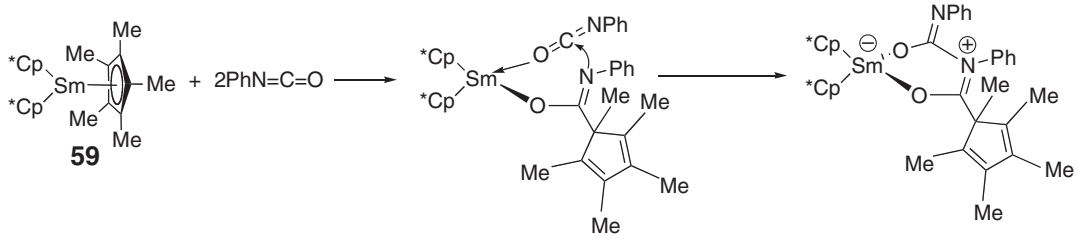


57 **58**

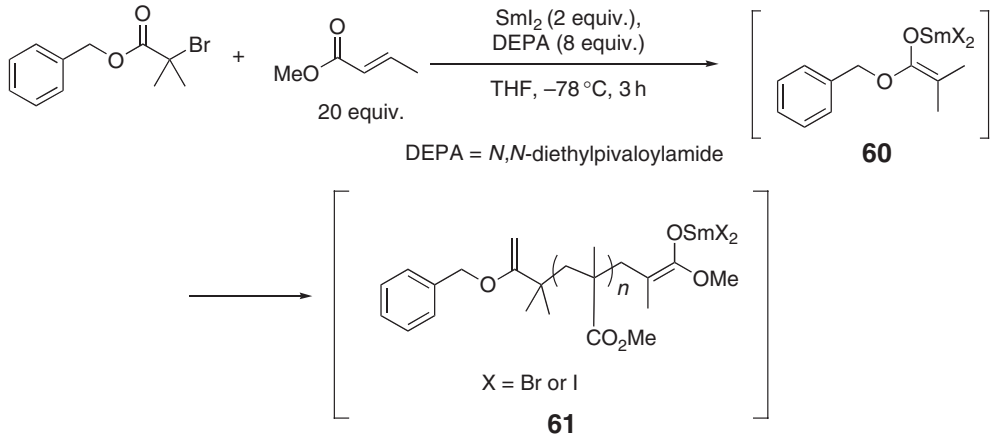
57	*Yield of* **58** (%)
	58
	30
	94
	67



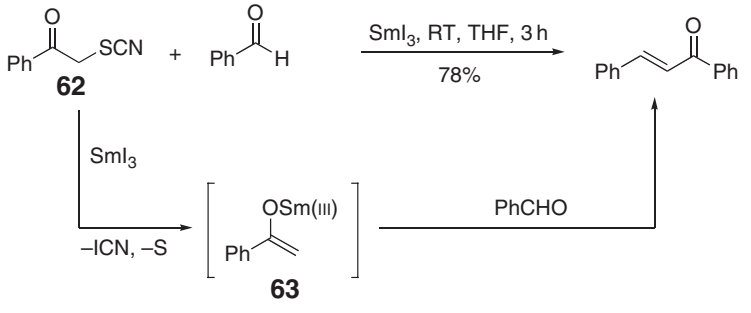
Scheme 19



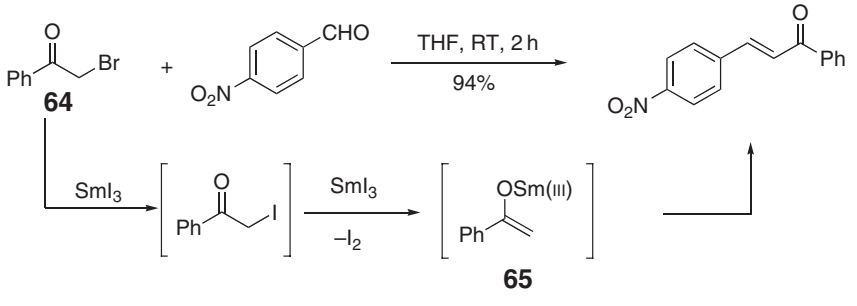
Scheme 20



Scheme 21



Scheme 22



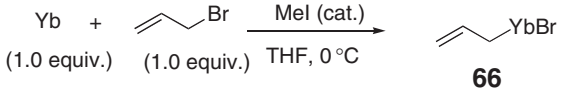
Scheme 23

10.09.2.4 Ytterbium

Organoytterbium chemistry has been developed in the last 20 years, although the development rate is much slower than the other lanthanides like samarium or cerium. Dianionic complexes that are produced from the reaction of ytterbium with diaryl ketones react with various kinds of electrophiles including carbon–heteroatom unsaturated bonds.[35] Phenylytterbium iodide, a Grignard-type reagent, is known to have reactivity toward carbon dioxide,[36] aldehydes, ketones,[37,37a] and carboxylic acid derivatives[38,38a] to form the corresponding adducts respectively.

10.09.2.4.1 Addition to C═O and C═N

In 2001, the preparation of allylytterbium bromide and the synthesis of homoallylic alcohols using allylytterbium bromide were reported.[39,39a] Ytterbium metal was found to be activated by a catalytic amount of MeI at 0 °C in THF to produce allylytterbium bromide **66** (Equation (11)). The allylation reaction of a wide range of aromatic aldehydes and ketones proceeded at ambient temperature or less in good to high yields (Table 2). Imines also reacted with allylytterbium bromide to afford homoallyl amines (Table 3).



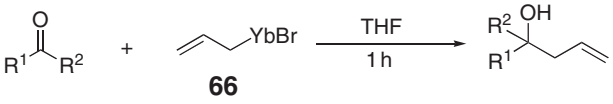
(11)

10.09.3 Group IV Metals

10.09.3.1 Titanium

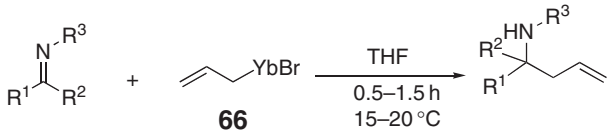
The chemistry of titanium has been reviewed in COMC (1982) and COMC (1995)[40,41] as well as in *Comprehensive Coordination Chemistry II*.[42] Since then, several contributions have covered the coordination chemistry of cyclopentadienyltitanium carboxylates and related complexes,[43] new titanium imido chemistry,[44] the use of titanium(IV) chloride[45] and isopropoxide[46] in stereoselective synthesis, the preparation and synthetic applications of 1,*n*-dicarbanionic titanium intermediates[47] and organotitanium complexes,[48,49] and titanium-catalyzed enantioselective

Table 2 Allylation of aldehydes and ketones with allylytterbium bromide



Aldehyde or ketone	*Temp.* (°C)	*Yield* (%)
$R^1 = Ph$; $R^2 = H$	25	75
$R^1 = p\text{-}MeC_6H_4$; $R^2 = H$	25	78
$R^1 = p\text{-}ClC_6H_4$; $R^2 = H$	25	80
$R^1 = p\text{-}BrC_6H_4$; $R^2 = H$	25	81
$R^1 = Ph$; $R^2 = Me$	15	88
$R^1 = p\text{-}MeC_6H_4$; $R^2 = Me$	15	82
$R^1 = p\text{-}ClC_6H_4$; $R^2 = Me$	15	83
$R^1 = p\text{-}BrC_6H_4$; $R^2 = Me$	15	86

Table 3 Allylation of imines with allylytterbium bromide



Imine	*Yield* (%)
$R^1 = 2\text{-thienyl}$; $R^2 = Me$; $R^3 = Ph$	55
$R^1 = 2\text{-furyl}$; $R^2 = H$; $R^3 = Ph$	75
$R^1 = p\text{-}ClC_6H_4$; $R^2 = H$; $R^3 = Ph$	82
$R^1 = p\text{-}MeOC_6H_4$; $R^2 = H$; $R^3 = Ph$	79
$R^1 = n\text{-}Bu$; $R^2 = H$; $R^3 = Ph$	52
$R^1 = Ph$; $R^2 = H$; $R^3 = n\text{-}Bu$	67
$R^1 = Ph$; $R^2 = H$; $R^3 = Ph$	81

additions of alkyl groups to aldehydes.[50] Most recent developments and applications of titanium complexes in organic synthesis have been reviewed until 2002.[51] The most recent review to date covers functionalized organotitanium reagents in organic synthesis.[52]

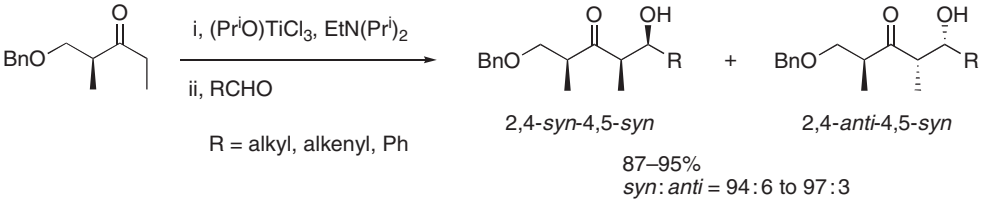
10.09.3.1.1 Addition to C═O

Very recently, Eisch and co-workers have developed new alkylidene–group IV metal complexes such as methylidene titanium dichloride **67**, readily accessible from titanium(IV) chloride and an excess of methyllithium at low temperature (Scheme 24).[53] The new methylenating agent **67** can easily convert benzophenone at low temperature into 1,1-diphenylethylene in quantitative yield.

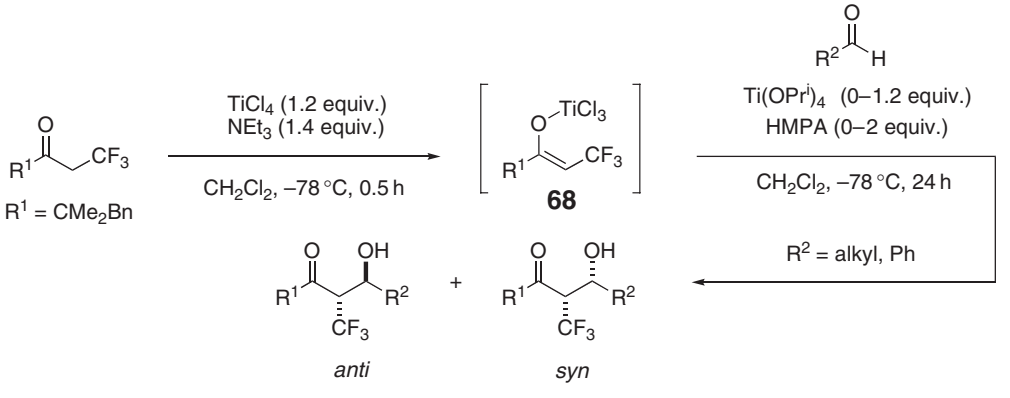
Titanium enolates[54] are widely used in aldol reactions and this research area has been reviewed until 2003.[55] Thus, examples described in this chapter cover the literature since 2003. Recently, Mikami and co-workers reported the direct generation of titanium enolate **68** of an α-trifluoromethyl ketone[56] for a high-yielding and *anti*-diastereoselective aldol reaction (Scheme 25).[57] The aldol reaction proceeded more smoothly if titanium(IV) isopropoxide was added as Lewis acid. On the other hand, low yield and moderate *syn*-selectivity were obtained if HMPA was used instead of the titanium(IV) Lewis acid.

Several other examples of *anti*-diastereoselective aldol reactions with titanium enolates and carbonyl electrophiles have been reported in the literature.[58–63]

A *syn*-diastereoselective aldol reaction based on titanium enolates from (*S*)-1-benzyloxy-2-methyl-3-pentanone was developed by Solsona *et al.* (Equation (12)).[64] The titanium enolate of this chiral ketone afforded the corresponding *syn–syn* aldol adducts in high yields and diastereomeric ratios with a broad range of aldehydes.



Scheme 24



Scheme 25

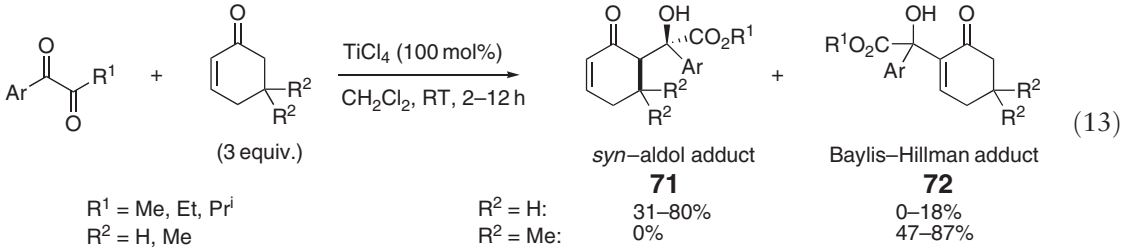
Various other examples of *syn*-diastereoselective[60–67] or non-selective aldol reactions of titanium enolates with carbonyl electrophiles have been described.[68]

Finally, several diastereoselective aldol reactions using titanium enolates and carbonyl electrophiles have also been applied to the total synthesis of natural products.[69–72]

Recent developments of aldol-type reactions with titanium enolates include the α- and β-C-glycosidation of glycals[73] and the diastereoselective addition to 2-acetoxytetrahydrofurans.[74] Mukaiyama and co-workers have developed a one-pot procedure for the preparation of unsymmetrical double aldols.[75]

Hayashi *et al.* have reported a novel Knoevenagel-type reaction with titanium enolate **70** derived from diketene **69** as the C_4 unit source (Scheme 26).[76] In contrast to the conventional Knoevenagel reaction (basic conditions), this transformation proceeds under mildly acidic conditions and provides higher yields and better $E:Z$ ratios.

A titanium(IV) chloride mediated Baylis–Hillman-type or aldol reaction between α-ketoesters and cyclohex-2-enones has been studied (Equation (13)).[77] The steric effect of the R^2 substituent is crucial for the reaction pathway since the aldol reaction only proceeds with the unsubstituted cyclohexenone (aldol adduct **71** with $R^2 = H$; to a small extent the Baylis–Hillman reaction occurs), whereas with the substituted substrate ($R^2 = Me$) gives exclusively the Baylis–Hillman adduct **72**.

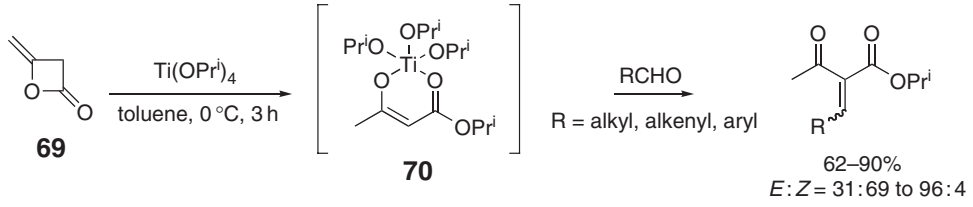


(13)

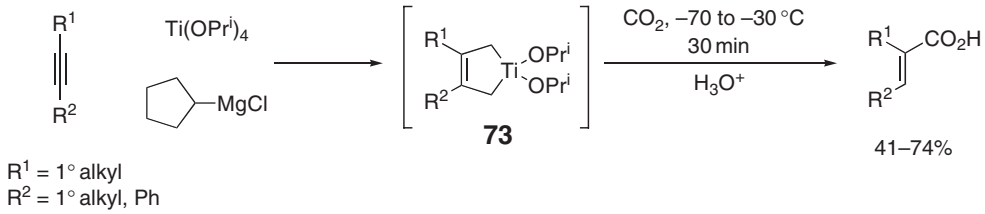
Recently, the conversion of alkenes or non-activated internal alkynes into the corresponding carboxylic acids and/or butenolides has been achieved through carboxylation of titanacycle intermediates of type **73** with carbon dioxide (Scheme 27).[78]

Additionally, it has been shown that novel benzylidene titanium complexes of type **74** react with polymer-bound carboxylic esters to form the corresponding enol ethers (Scheme 28).[79]

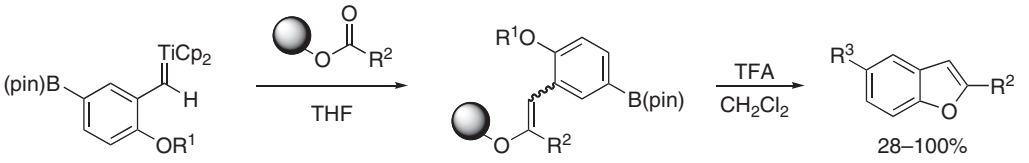
Titanium-mediated pinacol coupling reactions have been reviewed until 2000.[80,81] Since then, various intermolecular pinacol couplings have been reported with aldehydes,[82–97] ketones,[85–100] α-ketoesters,[85] and imines,[90] as well as asymmetric versions thereof.[101–104] Scheme 29 shows one example of an asymmetric pinacol coupling of aromatic aldehydes, promoted and catalyzed by the new chiral titanium complex (*S*)-**75**, that has been developed by Riant and co-workers.[101] Yields for pinacol products **76** are generally high. Under catalytic conditions, ee is moderate (up to 63%), while stoichiometric conditions allow to obtain up to 91% ee.



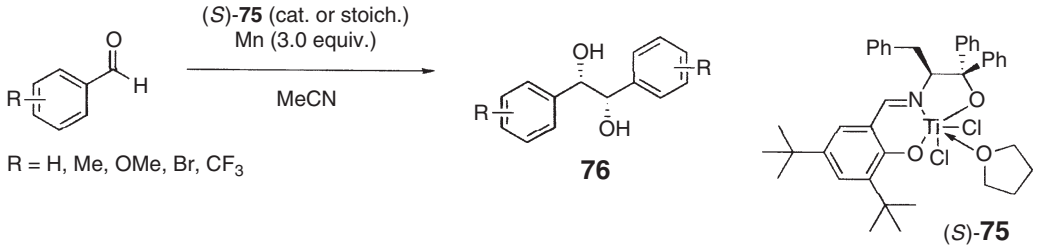
Scheme 26



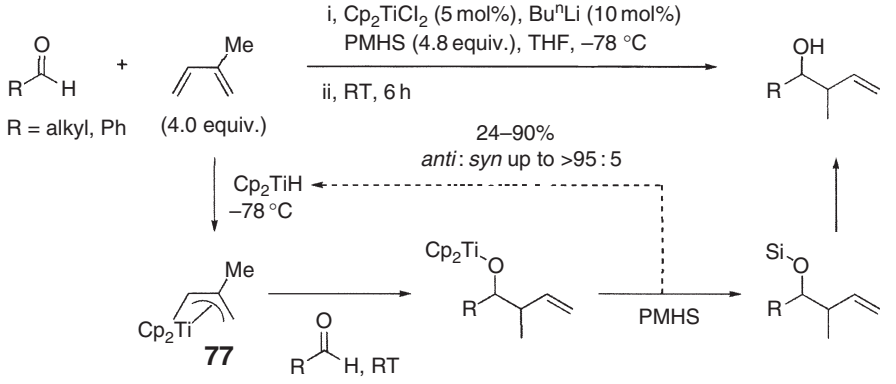
Scheme 27



Scheme 28



Scheme 29



Scheme 30

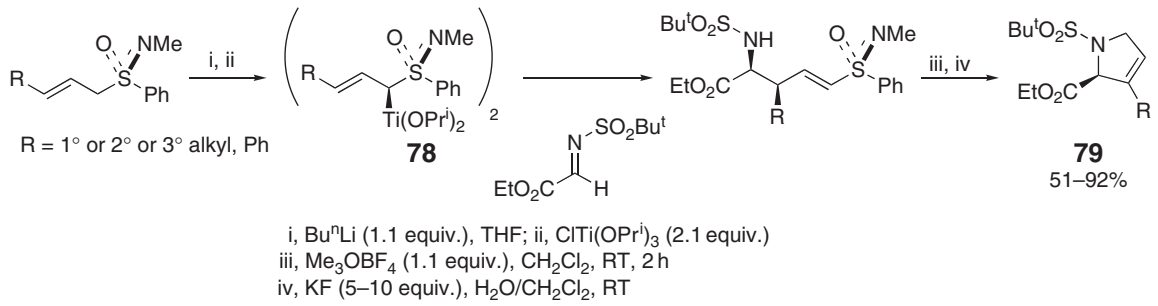
Some applications to the total synthesis of natural products have also been reported.[105,106]

Very recently, the first example of a catalytic allyltitanation reaction of aldehydes with dienes has been described (Scheme 30).[107]

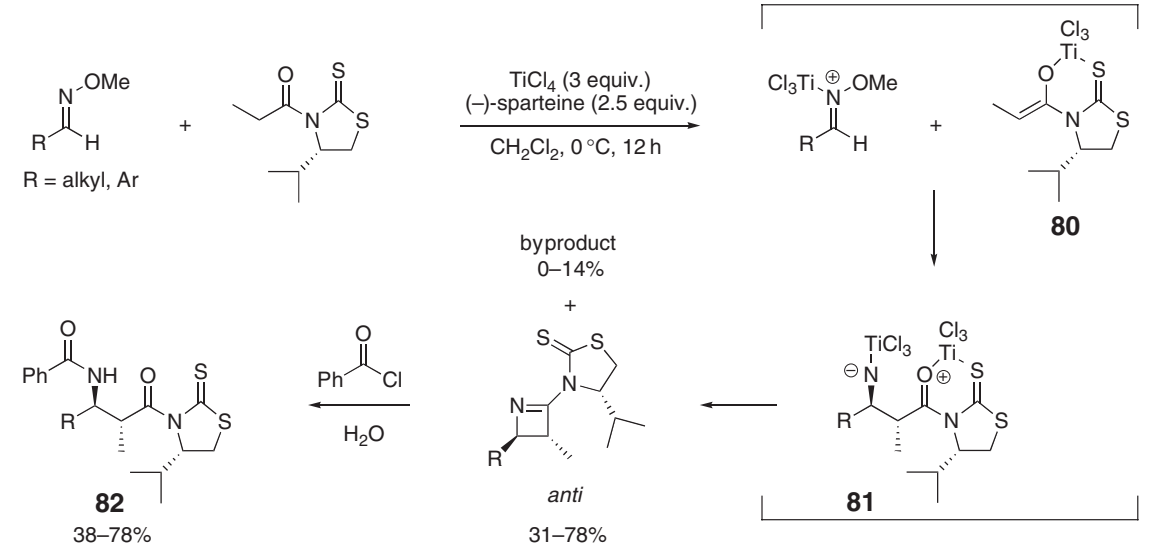
The authors prepared π-allyltitanium species **77** at low temperature from isoprene and *in situ*-generated Cp_2TiH (from Cp_2TiCl_2 and *n*-BuLi) before adding the corresponding aldehyde at room temperature. The Cp_2TiH complex can be regenerated from the titanium alkoxide intermediate by using stoichiometric amounts of poly(methylhydrosiloxane) (PMHS). It is worth noting that a more complicated diene such as myrcene is amenable to this transformation.

10.09.3.1.2 Addition to C═N

Gais and co-workers recently reported the preparation and use of chiral sulfoximine-substituted allyltitanium(IV) complexes of type **78** for the asymmetric synthesis of 3-substituted unsaturated proline derivatives **79** (Scheme 31).[108]



Scheme 31



Scheme 32

Titanium enolates of various carbonyl compounds play an increasingly important role in Mannich-type reactions with different electrophiles. Recently, Liotta and co-workers reported a novel diastereoselective addition of chlorotitanium enolate **80** of *N*-acylthiazolidinethione to various types of *O*-methyl oximes to afford the desired *anti*-azetines, precursors of α,β-disubstituted β-amino carbonyl derivatives **82** (Scheme 32).[109]

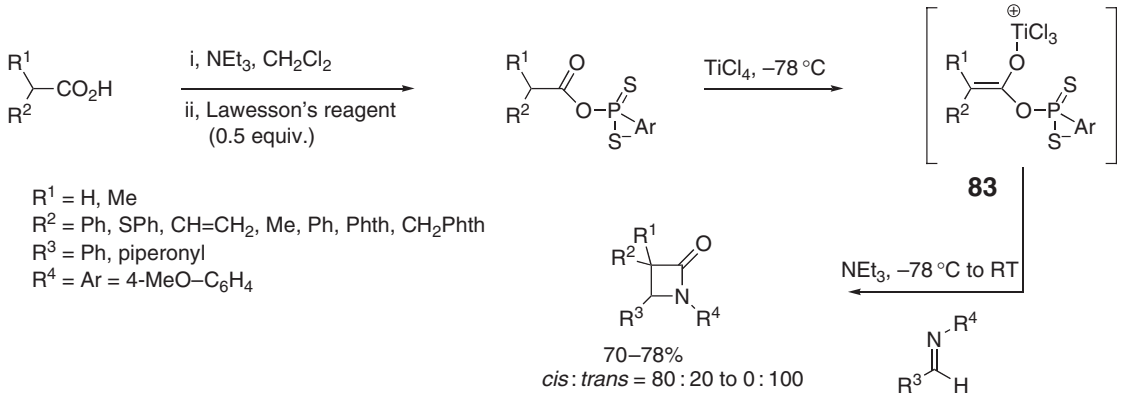
The initially formed titanium enolate **80** adds, in a diastereoselective fashion, to the electrophilic center of the activated oxime. The generated adduct **81** cyclizes chemoselectively to afford the desired *anti*-azetine, which is converted, with retention of configuration, to the corresponding β-amino carbonyl compounds **82** via *N*-acetylation followed by hydrolysis.

Very similar transformations have been reported by using titanium enolates of chiral thiazolidine-2-thiones or oxazolidine-2-ones in combination with various *in situ*-generated acyclic or cyclic *N*-acyliminium ions as electrophiles.[110–112]

Moreover, stereoselective titanium enolate additions to different *N*-sulfinyl imines[113,114] or *in situ*-prepared *N*-arylimines (three-component reaction) have been carried out to afford the corresponding sulfinyl amides or valuable β-amino acid precursors.[115]

A new and direct method for the synthesis a range of 2-azetidinones (β-lactams) has been developed by Sharma and Kanwar via condensation of titanium enolate **83** of various mixed anhydrides with different imines (Scheme 33).[116]

Based on a similar literature method,[116] stereoselective coupling reactions between various 3-acetoxy-4-alkyl-β-lactams and *in situ*-generated titanium enolates of cyclohexanone[117] or propiophenone derivatives[118] were developed, yielding the corresponding α,β-disubstituted β-lactams.



Scheme 33

10.09.3.1.3 Addition to C≡N

Nucleophilic additions of titanium nucleophiles to nitriles or isonitriles are relatively rare. Eisch *et al.* recently reported the formation of three-membered ring titanacycles of type **84** and their reactions with benzonitrile and carbon dioxide, respectively (Scheme 34).[119,120]

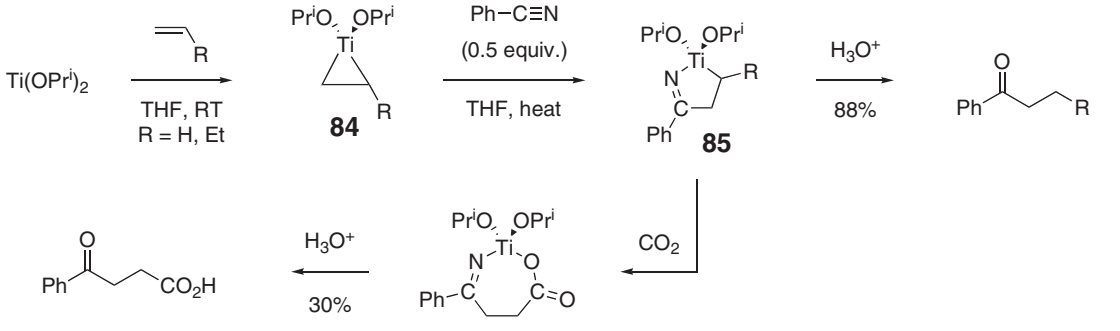
Titanium(II) isopropoxide, readily accessible through alkylative reduction of $Ti(OPr^i)_4$ with *n*-butyllithium or via coordination-induced reductive elimination of a dialkyltitanium(IV) species, undergoes epimetallation to form the three-membered ring titanacycle **84**. Benzonitrile inserts into a Ti–C bond of this titanacycle, providing access to the five-membered ring intermediate **85**, whose hydrolysis gives rise to the corresponding ketone. Alternatively, intermediate **85** was also transformed into 3-benzoylpropanoic acid, through carboxylation with carbon dioxide followed by hydrolysis.[120]

Finally, Odom and co-workers reported a titanium-catalyzed three-component coupling between primary amines, alkynes, and isonitriles for the preparation of α,β-unsaturated β-iminoamines in good yields (Scheme 35).[121] Beside the three-component coupling product, an *N,N*-disubstituted formamidine and an imine were also identified as minor byproducts.

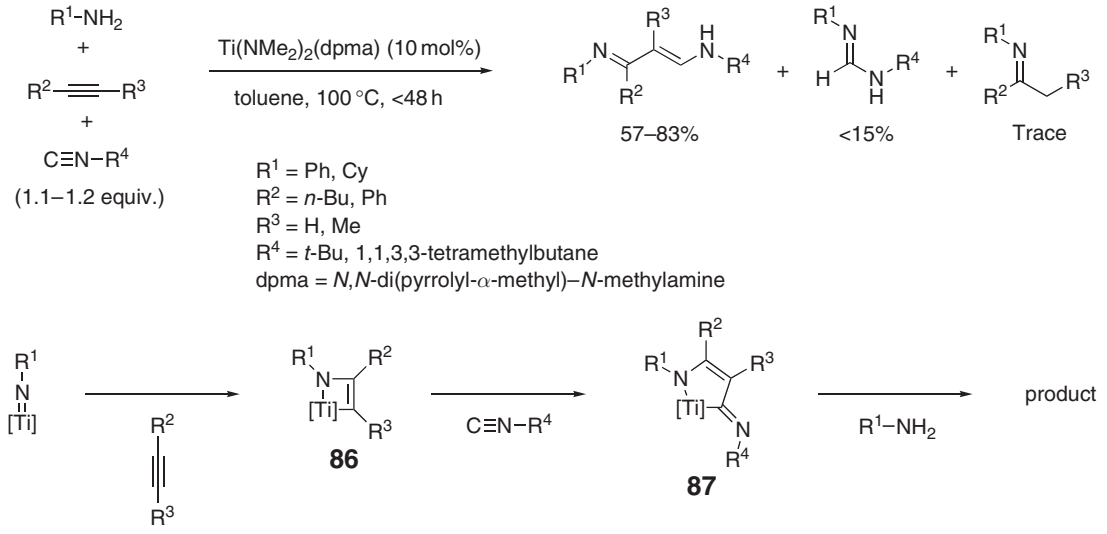
Based on the established mechanism for titanium-catalyzed hydroamination, the authors propose a reversible reaction between a titanium imide complex and the alkyne to form metalloazacyclobutene **86**, which in turn undergoes 1,1-insertion of the isonitrile into the Ti–C bond. The generated five-membered ring iminoacyl–amido complex **87** with the new C–C bond is protonated by the primary amine to afford the desired three-component coupling product, with regeneration of the catalytic imidotitanium species. Very recently, titanium-catalyzed carbon–carbon bond-forming reactions have been reviewed.[122]

10.09.3.2 Zirconium

The chemistry of zirconium has been reviewed in COMC (1982) and COMC (1995)[123,124] as well as in *Comprehensive Coordination Chemistry II*.[125] Various other reviews cover applications of zirconium alkoxides,[126] zirconium–phosphorous



Scheme 34



Scheme 35

reagents,[127] and zirconocene complexes in catalysis.[128] Most recent developments and applications of zirconium complexes in organic synthesis have been reviewed until 2002.[129,129a] Additionally, a review about functionalized organozirconium reagents in organic synthesis appeared very recently.[130]

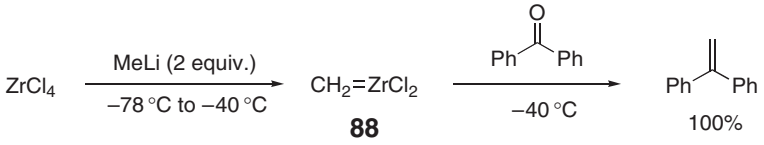
10.09.3.2.1 Addition to C═O and C═N

As mentioned above, Eisch and co-workers have synthesized new methylidene–group IV metal complexes, such as the methylidene zirconium complex **88** from zirconium(IV) chloride and 2 equiv. of methyllithium at low temperature (Scheme 36).[53] By using this reagent, benzophenone was easily converted at low temperature into the desired 1,1-disubstituted alkene in quantitative yield.

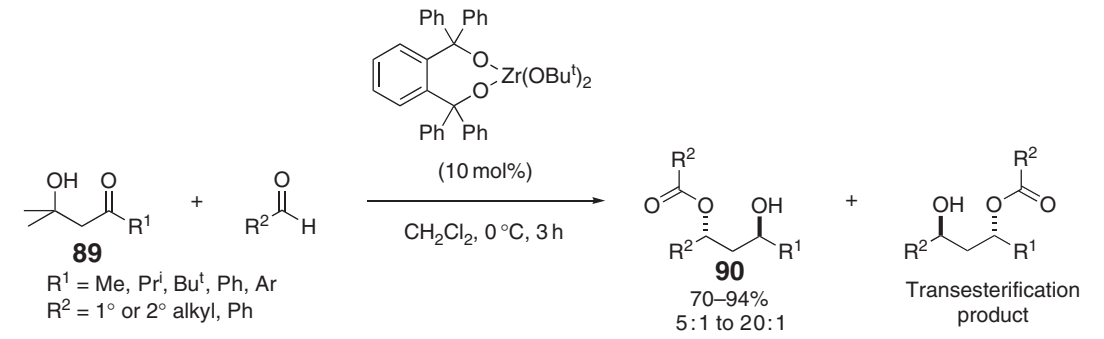
Various examples for the preparation of zirconium enolates[131] and their use in aldol-type reactions are described in the literature.[132] Among others,[133,134] Schneider *et al.* reported zirconium alkoxide-catalyzed aldol-Tishchenko reactions[135] of ketone aldols **89** as an efficient strategy for the preparation of differentiated 1,3-*anti*-diol monoesters **90** (Scheme 37).[136] The proposed reaction mechanism proceeds via a zirconium initiated retro-aldol reaction of the ketone aldol **89** with generation of a zirconium enolate, which in turn undergoes aldol reaction with the aldehyde to reversibly form a zirconium aldolate. This intermediate forms, with a second equivalent of the aldehyde, a hemiacetal zirconium alkoxide in which a selective intramolecular hydride transfer should occur. Since the transesterification has proved to be a slow process in most cases, excellent product ratios up to 20 : 1 can be obtained.

Whitby and Kasatkin reported the regiospecific formation of zirconium enolates through reaction of alkenylzirconocene chlorides (generated *in situ* from the corresponding terminal alkynes) with sulfonyloxiranes,[137] involving the sequential insertion (with loss of phenylsulfinate)/rearrangement. The regio-defined zirconium enolates add to various aliphatic or aromatic aldehydes in 54–68% yield with diastereoselectivities up to 74%.

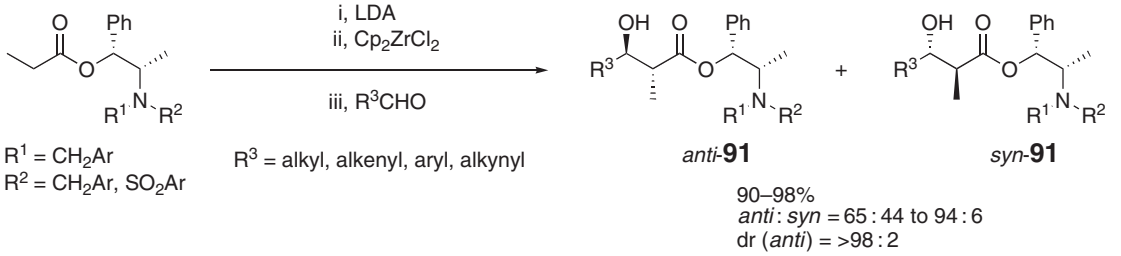
A highly diastereofacial *anti*-selective aldol reaction by using ester derivatives of norephedrine as a chiral auxiliary has been recently reported by Kurosu and Lorca (Scheme 38).[138] This practical and general method proceeds via initial (*E*)-selective substrate enolization and provides access to a broad range of optically active 2-alkyl-3-hydroxycarboxylic acid esters of type **91**.



Scheme 36



Scheme 37



Scheme 38

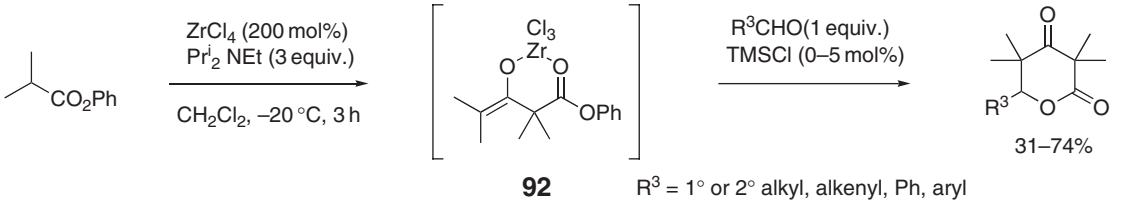
A similar method has been described by Badia and co-workers who used chiral amides derived from pseudoephedrine.[139] Moreover, a zirconium-mediated Claisen–aldol tandem reaction of an α,α-dialkylated ester with several aldehydes has been reported (Scheme 39).[140] After the initial Claisen condensation, zirconium enolate intermediate **92** reacts with various types of aldehydes through aldol-type reaction and subsequent lactonization, providing the corresponding pyran-2,4-diones.

Additionally, various zirconium-assisted aldol condensations between different types of zirconium enolates and aldehydes have been reported.[141–145]

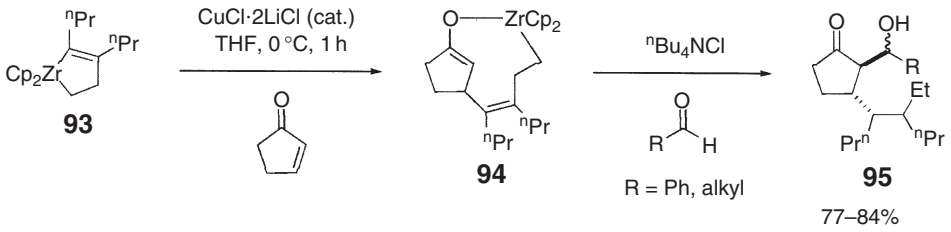
Finally, Lipshutz and co-workers developed catalytic copper(I)-assisted polyfunctionalizations of zirconacyclopentenes of type **93** by trapping the intermediary zirconium enolates **94** with an aldehyde to form the corresponding 2,3-disubstituted cyclopentanones **95** (Scheme 40).[146]

Recently, Oshima *et al.* developed the conversion of acid chlorides into the corresponding homoallylic alcohols catalyzed by *in situ*-prepared hydridozirconium allyl reagents (Scheme 41).[147,147a] The proposed mechanism suggests an initial hydride transfer from the zirconocene crotyl hydride species, in equlibrium with its Cp$_2$Zr(1-alkene),[147a] to the acid chloride with subsequent allylation to afford the corresponding homoallylic alcohols.

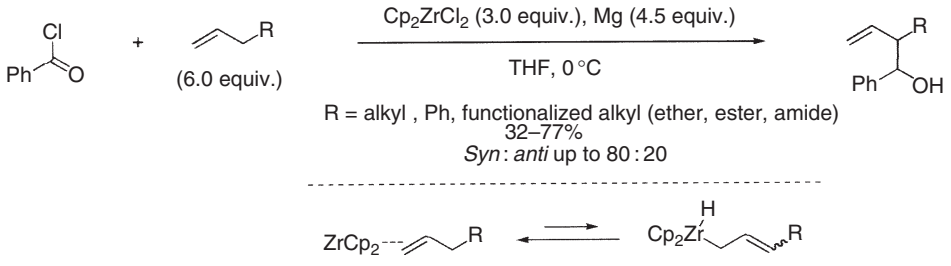
Zirconium enolates of various carbonyl compounds have also been investigated for Mannich-type reactions with different electrophiles. According to Shibasaki's method,[148] the coupling reaction between a 3-acetoxy-4-alkyl-β-lactam and the *in situ*-generated zirconium enolate **96** of a cyclohexanone derivative was realized as a key step during the total synthesis of an anitibiotic (Scheme 42).[117,149]



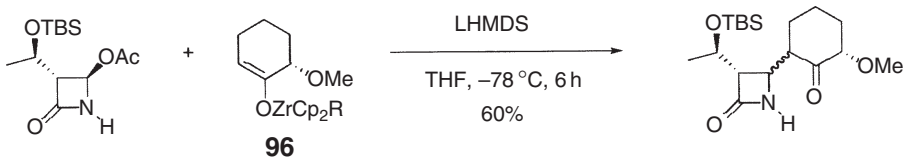
Scheme 39



Scheme 40



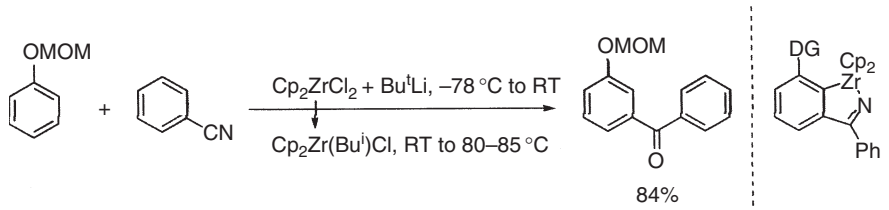
Scheme 41



Scheme 42

10.09.3.2.2 Addition to C≡N

Buchwald and co-workers reported a directed zirconium-mediated *meta*-acylation of various aromatic compounds, bearing a directing group, with different nitriles.[150] One representative example is shown in Equation (14).



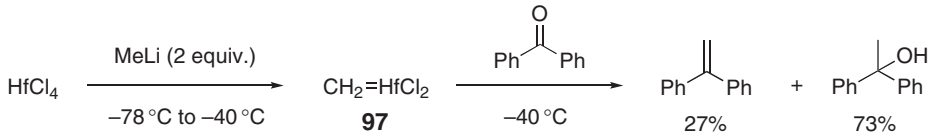
(14)

The *in situ*-generated $Cp_2Zr(Bu^i)Cl$ converts the arene into a zirconocene–benzyne complex which undergoes C–C bond formation with a nitrile to form an intermediary azazirconacycle (Equation (14)). The acidic hydrolysis of the latter species provides the corresponding 3-acyl-1-substituted benzene derivatives.

10.09.3.3 Hafnium

The organometallic chemistry of hafnium has been reviewed in COMC (1982) and COMC (1995)[123,124] as well as in *Comprehensive Coordination Chemistry II*.[125]

The chemistry of hafnium is mostly known for Lewis acid activation, even though transmetallation from tin or zinc to hafnium has been suggested in one case.[151]



Scheme 43

As mentioned already, new methylidene–group IV metal complexes have been prepared and were subsequently used in nucleophilic additions to carbonyl electrophiles (Scheme 43).[53] In contrast to titanium and zirconium, the reaction of methylidene hafnium dichloride **97** benzophenone stopped at the first stage (i.e., addition). The tertiary alcohol was obtained in 73% yield, while the corresponding alkene was formed only as minor product.

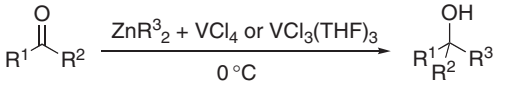
10.09.4 Group V Metals

10.09.4.1 Vanadium

The organometallic chemistry of vanadium has been surveyed in COMC (1982) and COMC (1995).[152,153] The chemical and biological importance of vanadium was reviewed in a dedicated edition of *Coordination Chemistry Reviews*.[154] Relevant synthetic aspects of vanadium chemistry have also been reviewed,[155–158] including early report by Hirao *et al*. on formation of ketones from organovanadium compounds and acid chlorides.[159]

10.09.4.1.1 Addition to C═O

Kataoka *et al*. showed that vanadium(III) or (IV) chloride, upon reaction with 1 equiv. of an alkylzinc reagent, generates an alkylvanadium species *in situ* which reacts with aldehydes or ketones at 0 °C to give the corresponding secondary or tertiary alcohols (Equation (15)).[160]

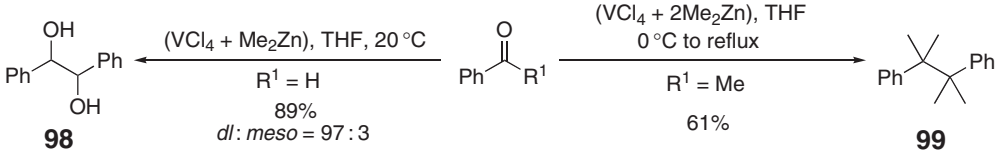


R^1 = Ar, vinyl, alkyl; R^2 = H, alkyl; R^3 = Me, Et

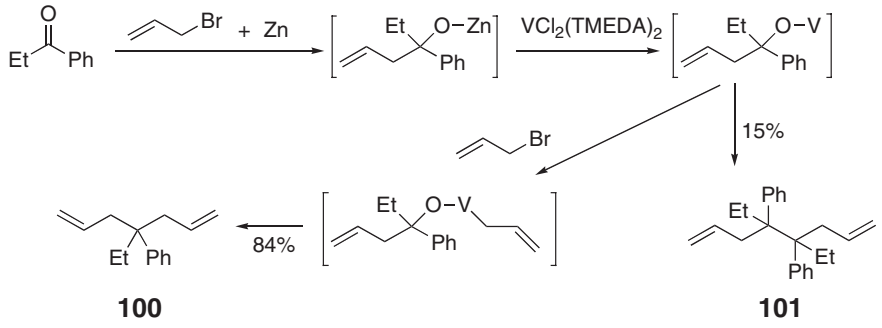
82–99% (15)

These authors also found that the same *in situ*-generated vanadium/zinc species at higher temperatures (20 °C) gave the pinacol coupling product of benzaldehyde **98** in 89% yield with a 97 : 3 ratio in favor of the *dl*-product (Scheme 44). Additionally, upon increasing the amount of alkylzinc reagent and heating at reflux in THF, the dialkylated coupling product **99** was obtained in 61% yield. Early reports of vanadium/zinc-mediated pinacol couplings include those by Konradi *et al*.,[161] Kraynack and Pederson,[162] and Hirao *et al*.[163]

Kataoka *et al*. have also published a number of related studies concerning vanadium-mediated allylation of carbonyl functionalities, including reactions similar to those shown in Scheme 44.[164–167] Scheme 45 outlines a reported mechanism where C–O cleavage results in diallylated product **100** and coupling product **101** akin to **99**.[166] Equation (16) shows the use of a mixed THF : HMPA solvent system (1 : 1 at 20 °C), which resulted in the successful formation of tertiary allylic alcohols **102**, obtained in good to high yields ($R^1 \neq H$) with *anti* : *syn* ratios up to 3.8 : 1. The best yields (97%) were obtained when propiophenone or acetophenone was reacted with allyl bromide in the presence of a vanadium complex, as shown in Equation (16).[166] A number of other groups can be accommodated for

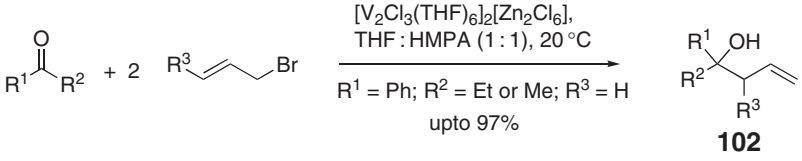


Scheme 44



Scheme 45

R^1 to R^3 with yields ranging from 20% to 90%. For the reaction of acetophenone, allyl bromide can be replaced with propargyl bromide, benzyl bromide, or an α-bromoester, affording the corresponding tertiary alcohols in 86%, 86%, and 66% yields, respectively.



(16)

10.09.4.1.2 Addition to C═N and C≡N

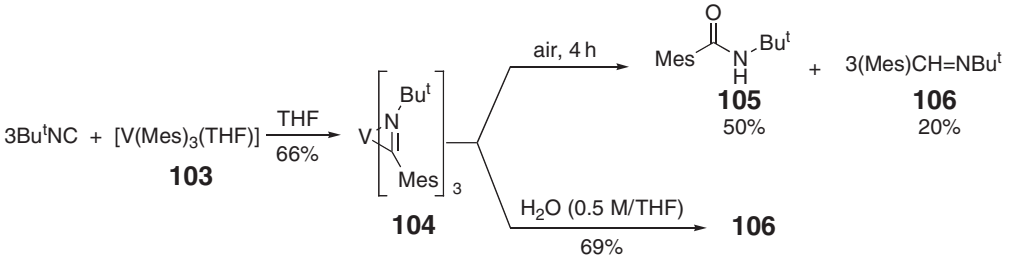
For group V metals, the literature describing reactions with imines, nitriles, and carbonyls is dominated by those where organometallic species are reacted but potential organic products are not necessarily isolated. In the case of vanadium, an isocyanide is bound to the metal in an η^2-fashion after intramolecular aryl transfer (Scheme 46). A series of reports described the addition of *t*-butyl isocyanide to trismesityl vanadium(III) **103**.[168–170] Subsequent reactions at the resulting η^2-mesitylimine **104** were performed, including hydrolysis in the presence (or absence) of oxygen, which gave a mixture of amide **105** and imine **106** (or only **106**) as isolated organic products.[168]

Addition of excess *t*-butyl isocyanide, CO_2, or CyNCO resulted in the formation of five-membered ring chelate compounds **107**, the metal-bound imino acid **108**, and the metal-bound imino amide **109**, respectively, as shown in Scheme 47.[170]

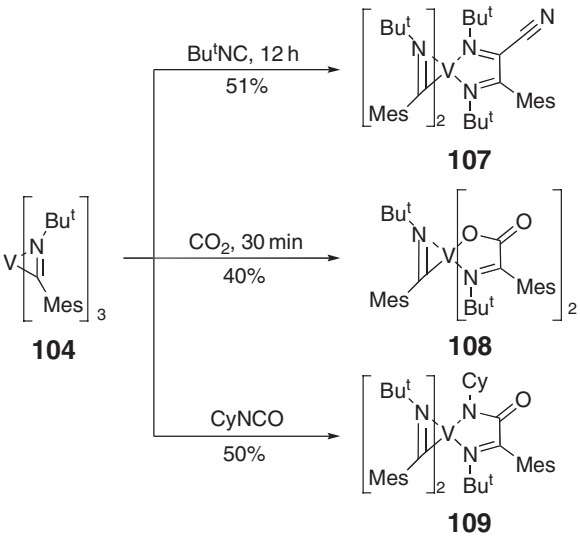
Vanadium NMR may provide potentially useful information about complex structure, which might provide one of the best tools employed for shedding light on these and related systems (^{51}V natural abundance 99.78%).[171]

10.09.4.2 Niobium

The chapters for niobium and tantalum in COMC (1982) and COMC (1995) provide an in-depth discussion concerning complexes of these metals as well as their applications to catalysis.[172,173] Alkylcyclopentadienyl complexes of niobium and tantalum have also been reviewed.[174] Similarly to vanadium (Section 10.09.4.1.2), the



Scheme 46

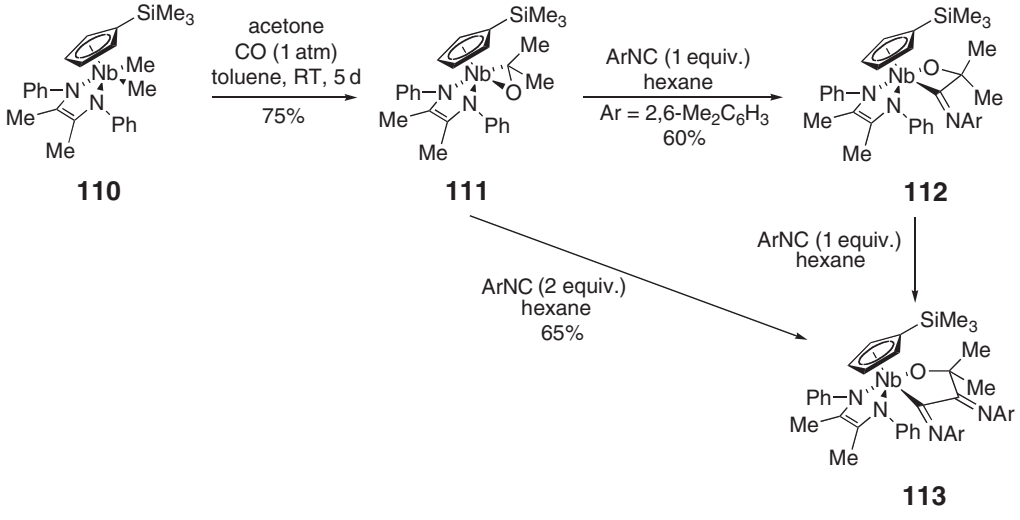


Scheme 47

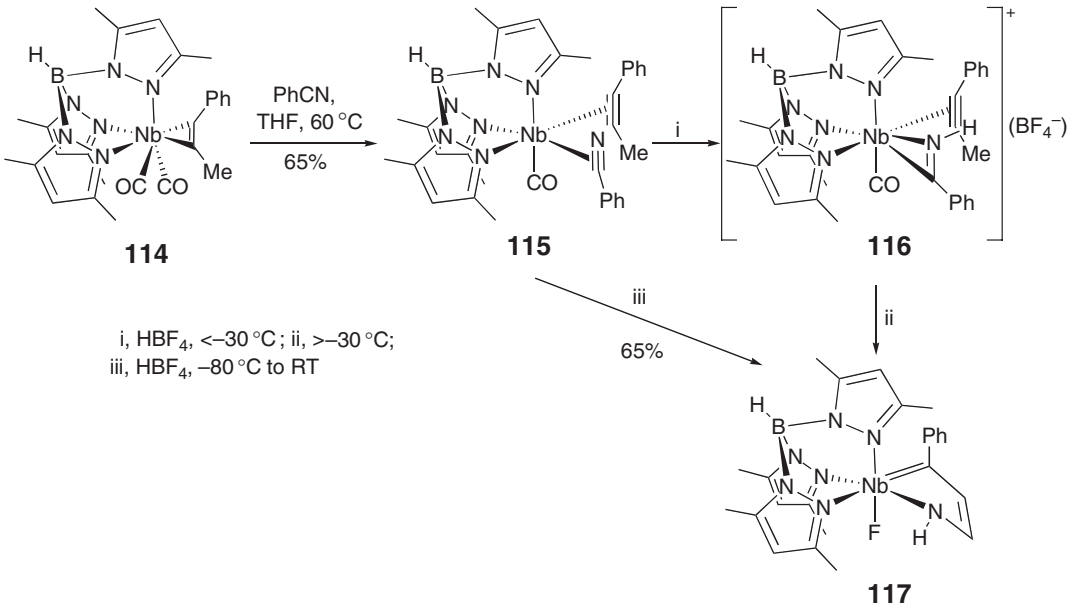
organometallic chemistry of niobium with imines, nitriles, carbonyls, and isocyanides is predominantly associated with η^2-attachment to the metal with subsequent reactions being performed on the resultant complexes. However, the full potential for the use of these complexes in organic synthesis has not yet been exploited. Only a few examples of reactions truly fit the scope of this chapter.

10.09.4.2.1 Addition to C≡N

Insertions of isocyanide into niobium–carbon bonds follow a path similar to that with vanadium, resulting in the formation of the η^2-iminoacyl complexes, which can then be involved in further chemistry.[175,176] The reaction of acetone with cyclopentadienyl complex **110** under a carbon monoxide atmosphere gives the η^2-acetone compound **111**. Complex **111** subsequently undergoes either stepwise insertion of two isocyanides via **112** or double insertion of the isocyanide to give complex **113** (Scheme 48).[177]



Scheme 48



Scheme 49

Carbon–carbon bonds can be generated between a nitrile carbon and an alkyne while they are coordinated to niobium.[178] Protonation of the η^2-nitrile of **115** gives intermediate **116** from which metallocycle **117** is generated (Scheme 49).

Although this investigation did not lead to the separation or identification of an organic product, the potential of niobium-mediated nitrile–alkyne coupling for future applications is of note, that is, it may be possible to form C–C bonds, affording nitrogen-containing products that might otherwise be difficult to synthesize.[178] More recently, Etienne and co-workers reported an alternative route to niobium scorpionate architectures bearing η^2-terminal alkynes, that is, **114**-type structures where CO is substituted with Cl, and the alkyne can be generalized as H–C_αC–R.[179]

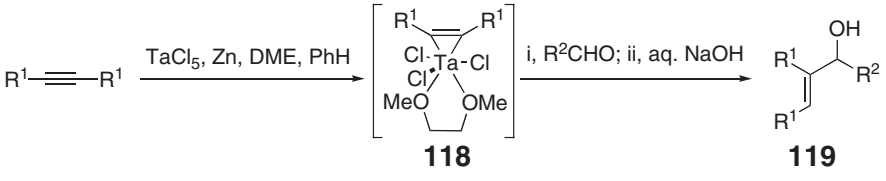
10.09.4.3 Tantalum

Tantalum and niobium are often studied in parallel, and references from Section 10.09.4.2.1 are relevant as well because of the concomitant nature of these reports.[172–174] Within the scope of Gómez's review, organotantalum species including η^2-ketones and isocyanides are well covered.[174]

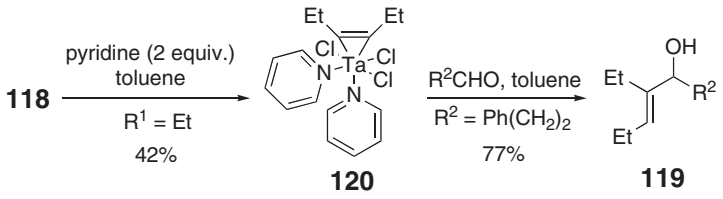
10.09.4.3.1 Addition to C═O

Tantalum(v) chloride can be used in the generation of η^2-alkyne complexes (general formula **118**) which have been shown to react with aldehydes to afford, after basic aqueous workup, allylic alcohols **119** (Scheme 50).[180]

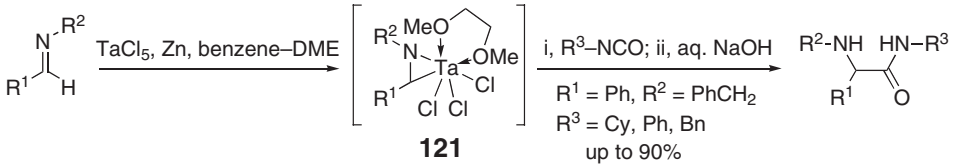
Recent work, focused on some mechanistic aspects of this reaction, revisited the fundamental allylic alcohol formation reaction.[181] Pyridine easily replaced DME of **118** to give bis(pyridine) complex **120** (Scheme 51).



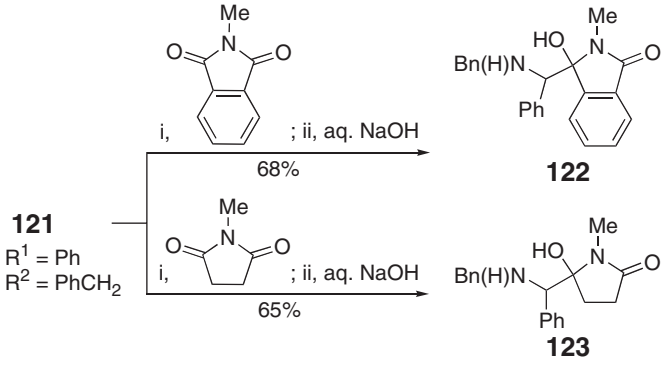
Scheme 50



Scheme 51



Scheme 52



Scheme 53

TMEDA and bipyridine also gave the corresponding complexes. Amoung those complexes, only **120** was found to react smoothly with 3-phenylpropanal to give **119** in good yield. When the aldehyde and the acetylene of Scheme 51 were replaced with acetone and dipentylacetylene, respectively, the corresponding allylic tertiary alcohol could be obtained in 83%.

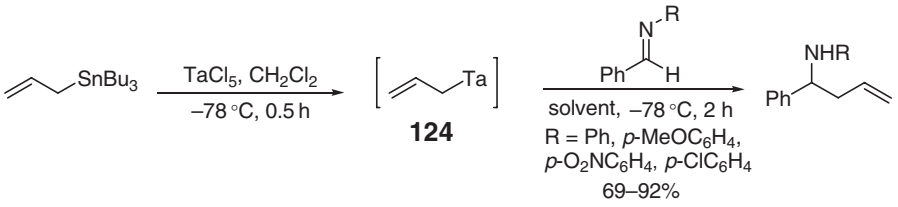
Imines can react with organotantalum species to form three-membered ring nitrogen-containing tantallacycles **121**.[182,183] Recently, tantallacycles **121** was shown to react with isocyanides to give α-amino amides (Scheme 52).[184,185] A cyclohexanone-derived aniline ketimine was also found to undergo the same reaction, giving the corresponding product in 48% yield.[184]

Isocyanates can be replaced with a phthalimide and a succinimide to give hemiaminals **122** and **123** in 68% and 65% yield, respectively (Scheme 53).[185]

10.09.4.3.2 Addition to C═N and C≡N

Allyltantalum-mediated allylation of aldimines was reported by Bhuyan *et al.* in 1993; these workers compared tantalum and bismuth organometallic reagents over a series of transformations. Up to 60% yield was obtained for tantalum-mediated allylation (benzylidene aniline as electrophile). Bismuth reagents offered better yields in the cases compared but, in all cases, a remarkable effect for the addition of Bu^n_4NBr was observed.[186]

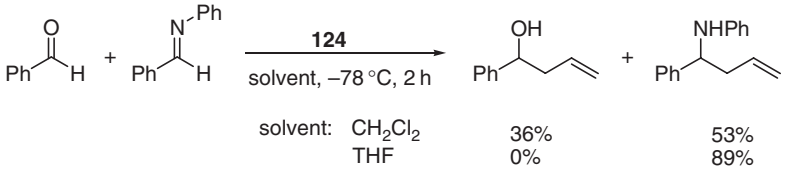
Allyltantalum reagent **124** can be generated by transmetallation of allyltributyltin with tantalum(V) pentachloride.[187] Shibata *et al.* focused on reactions of **124** with α,β-unsaturated ketones and found, in all cases, that 1,4-addition proceeded in good to excellent yields.[187] On the other hand, **124** was later shown to react more smoothly



Scheme 54

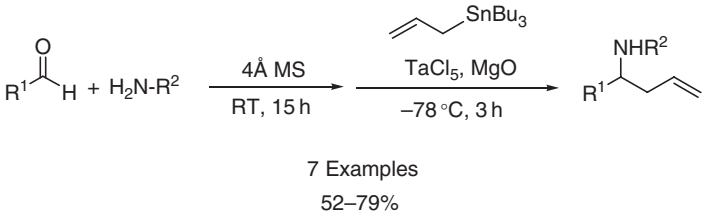
with imines to afford the corresponding amines in good yield (Scheme 54). *N*-aliphatic imines derived from benzaldehyde could also be accommodated at slightly higher temperatures.[188]

In competition experiments with benzaldehyde, allyltantalum reagent **124** was found to add selectively to an imine, when THF was employed as the solvent (Equation (17)).



(17)

These authors also found that the addition of excess MgO during the *in situ* preparation of allyltantalum species improved reaction outcomes, even allowing for the first example of allylation of imines derived from aliphatic amines and aliphatic aldehydes (prepared *in situ* at room temperature in the presence of molecular sieves) (Equation (18)). The selective addition to imines permitted three-component reactions.



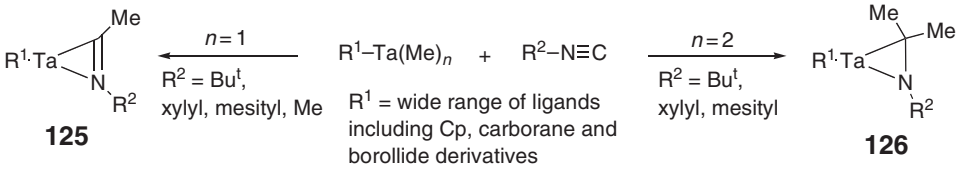
(18)

As seen in the vanadium chemistry (Schemes 46 and 47), activation of isocyanides is one of the key mechanisms in organotantalum chemistry. Scheme 55 generalizes the examples where organotantalum chemistry of isocyanides leads to the formation of products. Although these products remain coordinated to tantalum, these reactions provide insight into the potential for applications to organic synthesis.[175,189–202] Methyltantalum species allow formation of η^2-imines or three-membered ring metallacyclic amines if one or two methyl groups are transferred, resulting in the formation of compounds with general formula **125** or **126**.[203] Silyl transfer is also possible in these reactions.

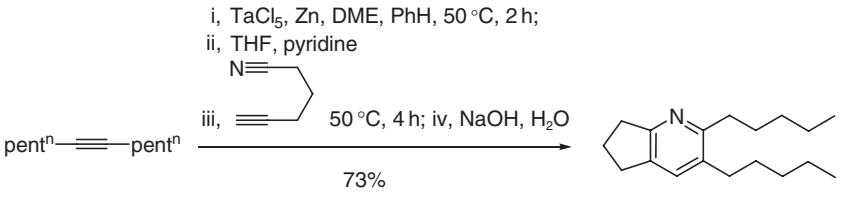
Although monodentate isocyanide–tantalum complexes are available by alternative routes,[204] the majority of studies are concerned with the resultant η^2-imines. Conversely, similar reactions with nitriles give monodentate imine moieties, which can undergo reactions while remaining attached to the metal.[195,203–209]

An intermolecular cyclotrimerization of an acetylenic nitrile was reported to proceed via the same alkyne–tantalum complex. The resultant pyridine derivative was obtained in 73% yield (Scheme 56).[210]

Pivalonitrile was also shown to be able to undergo a similar [2 + 2 + 2]-cyclotrimerization with a tantallacyclopentadiene derived from metallocyclization of 2 equiv. of $HC_\alpha CBu^t$. The resulting tantalum η^2-pyridine



Scheme 55



Scheme 56

complex was isolated in 76% yield, from which 2,4,6-tri-butylpyridine could be obtained in 34% yield after sublimation.[211]

Although group V organometallic species have not found wide-ranging applicability in reactions of imines, nitriles, and carbonyls, the examples given in this chapter demonstrate the potential of group V metals which may bloom over the coming years into mainstream organic synthesis.

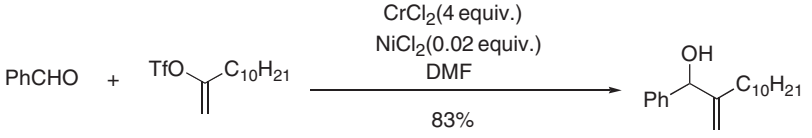
10.09.5 Group VI Metals

10.09.5.1 Chromium

Nucleophilic addition of organochromium compounds to carbonyls or imines has been well investigated.[212–214]

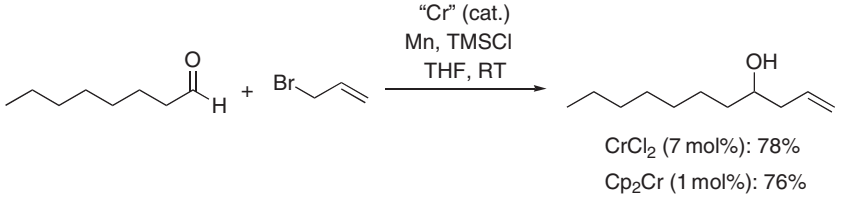
10.09.5.1.1 Addition to C═O

Nozaki–Hiyama–Kishi (NHK) reactions[215,216] are well known and often employed as a useful method for the synthesis of natural products by coupling of allyl, alkenyl, alkynyl, and aryl halides or triflates with aldehydes. The organochromium reagents are prepared from the corresponding halides or triflates and chromium(II) chloride, and are employed in polar aprotic solvents (THF, DMF, DMSO, etc.). Subsequently, it was found that nickel salts exhibited a significant catalytic effect on the formation of the C–Cr bond[217,218] (Equation (19)).



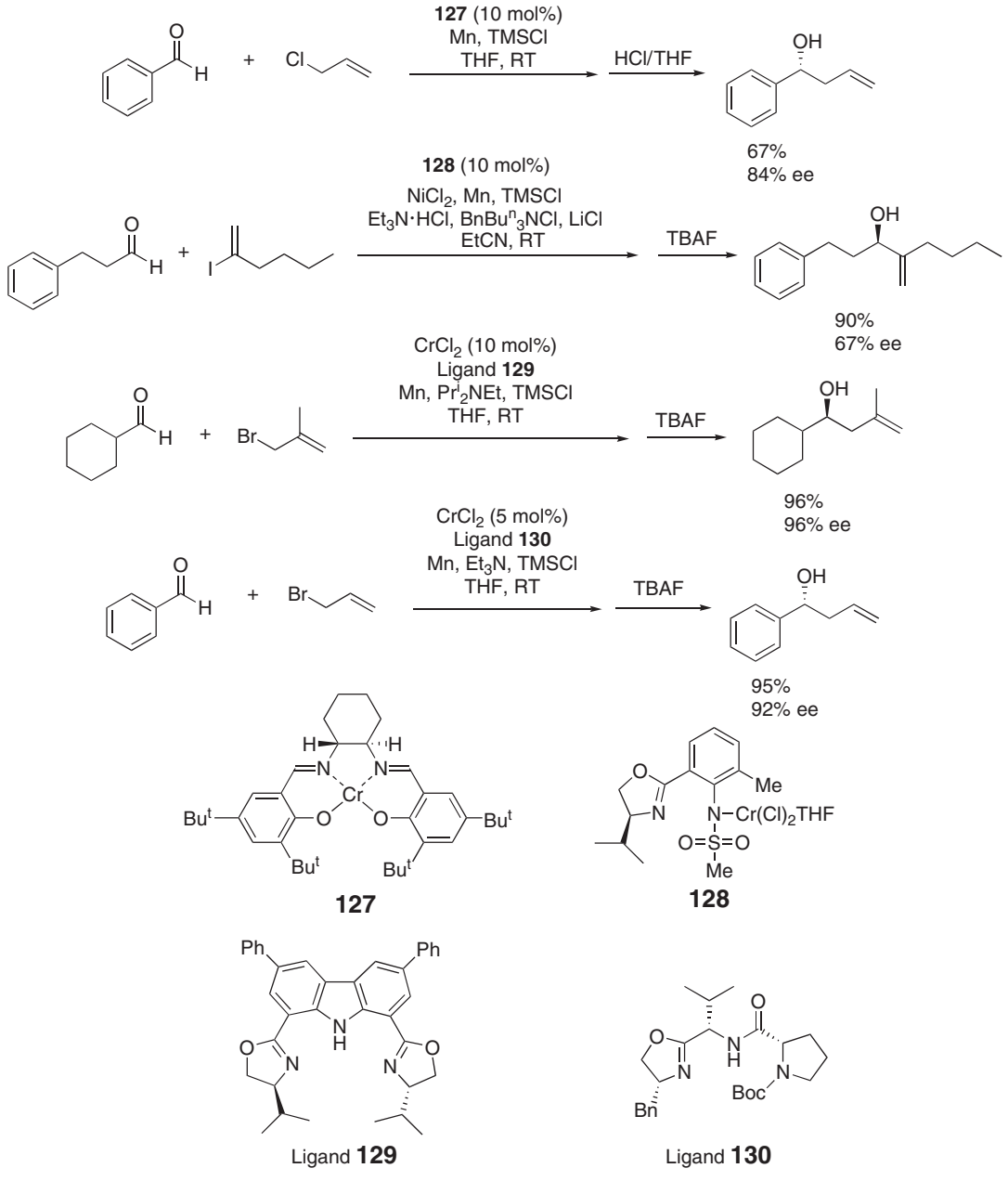
(19)

However, more than stoichiometric use of the chromium salt was problematic, and the toxicity of the salt makes this versatile process inadequate for large-scale synthesis. Truly catalytic use of chromium was achieved in 1996 by using Mn powder as a co-reductant (Equation (20)).[219,220] In another approach, electrochemical reduction of chromium for catalytic use was also examined.[221–223]



(20)

Recently, asymmetric NHK reactions have been investigated.[224,225] Among them, catalytic versions of this reaction have been successful: a Cr-chiral salen complex **127**,[226–228] a Cr-chiral sulfonylamide complex **128**,[229] a Cr-tridentate ligand **129** complex,[230,231] and a Cr-chiral oxazoline ligand **130** complex[232] were found to be effective to achieve good to high enantioselectivity (Scheme 57).

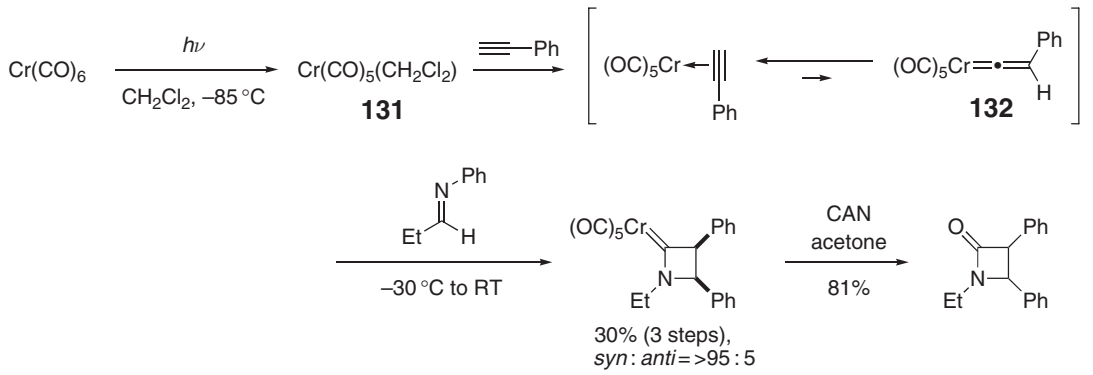


Scheme 57

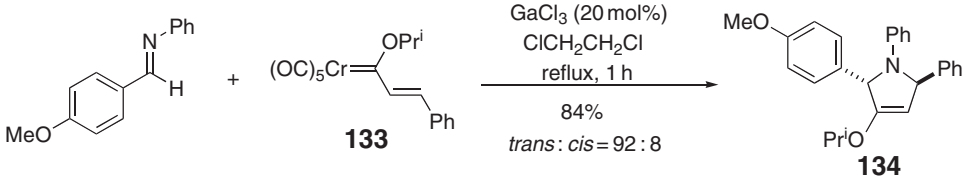
10.09.5.1.2 Addition to C═N

A chromium(0) pentacarbonyl–methylene chloride complex **131** was formed under irradiation, which reacted with an alkyne to form a vinylidene complex **132**. Complex **132** further reacted with an imine or a dialkylcarbodimide to afford β-lactams after decomplexation of chromium (Scheme 58).[233]

Chromium carbene complexes have also been known to react with imine equivalents to afford β-lactam derivatives[234]. Furthermore, [3 + 2]-cycloaddition of an alkenylchromium carbene **133** with imines proceeded to afford 3-pyrroline derivatives **134** in the presence of a Lewis acid catalyst (Equation (21)),[235] where $GaCl_3$ or $Sn(OTf)_2$ were efficient promoters. Alkenylcarbenes bearing chiral auxiliaries afforded the desired cycloadduct in optically pure form.[236]

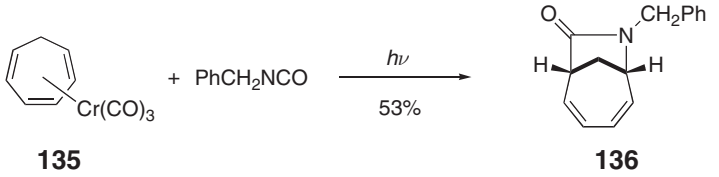


Scheme 58



(21)

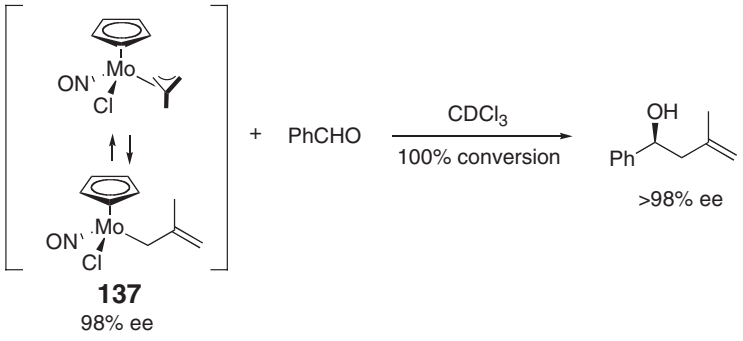
The [6 + 3]-cycloaddition between (cycloheptatriene)chromium(0) tricarbonyl **135** and isocyanate or ketene occurs under photo-irradiation conditions, for example, bicyclo[4.2.1]nonane-type adduct **136** was obtained in moderate yield (Equation (22)).[237,238]



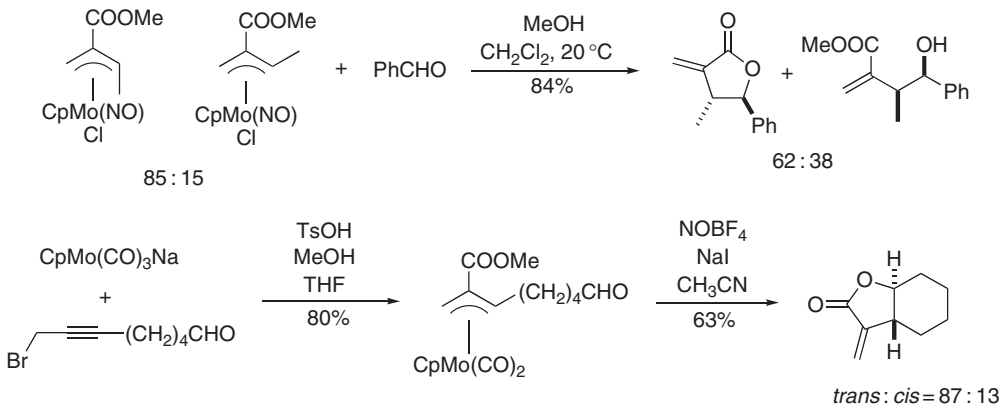
(22)

10.09.5.2 Molybdenum

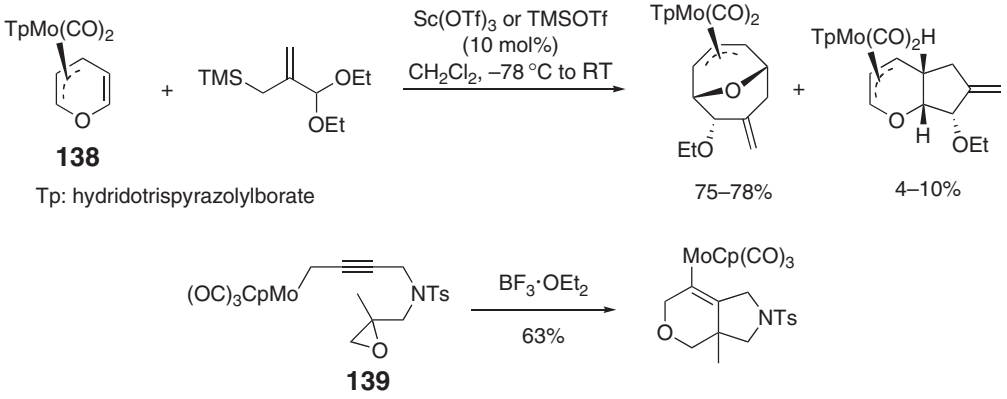
Nucleophilic addition of organomolybdenum complexes to carbonyl groups was well studied.[239] Among them, stereoselective allylation reactions were mainly investigated recently.[240] A π-allyl complex of cyclopentadienylmolybdenum can work as an allylating agent. The enantiomerically pure allylmolybdenum complex **137** was resolved and employed in the asymmetric allylation of aldehydes (Equation (23)).[241–245] This type of the complex is robust, air stable, and stereoselectivity in allylation is high. Reactivity of the complex depends on the ligands on molybdenum atom.



(23)



Scheme 59



Scheme 60

Allylation of aldehydes accompanying alkoxycarbonylation using cyclopentadienylmolybdenum complexes was also applied to butenolactone synthesis.[246,247] Intra- and intermolecular cyclization occurred after allylation of the aldehyde to give α-methylene butenolactone derivatives (Scheme 59).

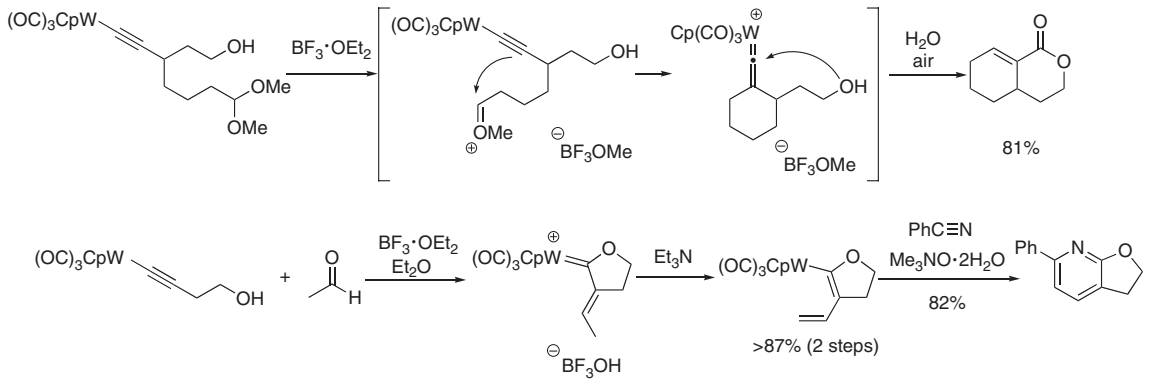
Modified allyl- or propargylmolybdenum complexes **138** and **139** reacted with aldehydes or their equivalents in the presence of a Lewis acid to give the corresponding bicyclic products (Scheme 60).[248,249]

10.09.5.3 Tungsten

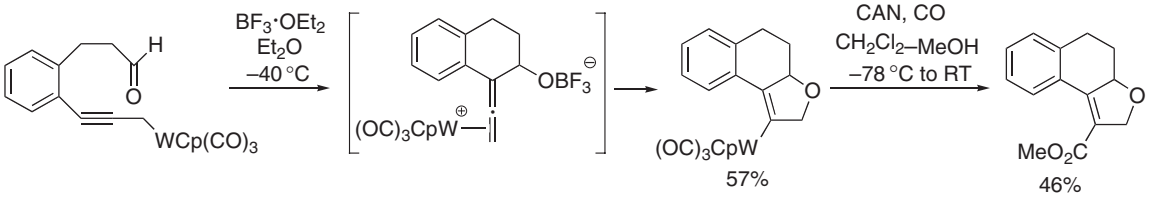
Tungsten carbonyl complexes containing α,β- or β,γ-unsaturated alkyl chain substituents facilitate nucleophilic addition to carbonyl compounds or their equivalents.[239,250] Alkynylcyclopentadienyltungsten complexes react with carbonyls or their equivalents in the presence of a Lewis acid such as $BF_3{\cdot}OEt_2$ to afford vinylidene tungsten species, which further react with nucleophilic moieties, affording oxa- or azacyclic compounds (Scheme 61).[251–254] Epoxides and aziridines also worked as carbonyl or imine equivalents.[249–256] In the presence of nitrile compounds, these tungsten species undergo further cyclization.[257]

Propargyltungsten complexes react with aldehydes in the presence of a Lewis acid to afford hydropyran derivatives (Scheme 62).[258,259] They also form allyltungsten species after alkoxycarbonylation, which can react with aldehydes to afford homoallylic alcohols through activation by ligand exchange on the tungsten metal (Scheme 63).[260,261] A pent-4-en-2-yn-1-yltungsten complex reacts with CO and an alcohol to afford pentadienyltungsten species, which react with aldehydes in the presence of a Lewis acid, followed by hydration to give 1,3-diol derivatives (Scheme 64).[262]

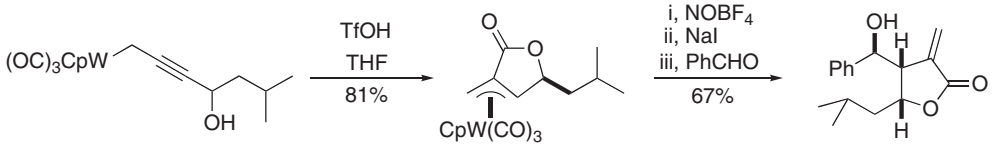
Tungsten(0) pentacarbonyl–methylene chloride complex and alkynes form vinylidene complexes by photo-irradiation, which react with an imine or a dialkylcarbodimide to afford β-lactams after decomplexation of the metal.[233]



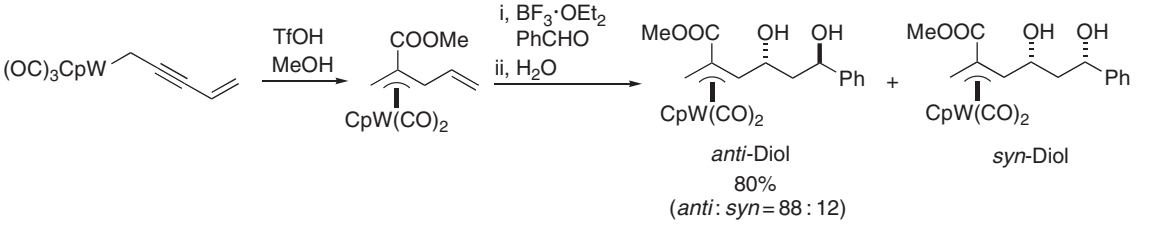
Scheme 61



Scheme 62



Scheme 63



Scheme 64

10.09.6 Group VII Metals

10.09.6.1 Manganese

The organometallic chemistry of manganese has been thoroughly reviewed in COMC (1982) and COMC (1995).[263,264] Other reviews cover some applications of organomanganese reagents in organic synthesis.[157,158] Reactions with isocyanides, similar to those of group V, have been reported where potentially useful organic moieties are generated although they remain attached to manganese after the reactions.[265–267] Additionally, *N*-heterocyclic carbene complexes of manganese can be generated via a coupling between an isocyanide and a homopropargylic

amine on the metal.[268] The coordinated bis-imines can undergo alkylation and subsequent rearrangement to give mixed amine–imine chelation compounds[269] or CO metallacycles.[270] Manganese cyclopentadienyl derivatives have been attached to gold surfaces via amide linkages.[271] Top *et al.* have shown how ketone derivatives of cyclopentadienylmanganese tricarbonyl reacts with diaromatic ketones to give alkenes after photolytic cleavage from the metal.[272–274] Cooper and co-workers demonstrated that η^6-benzene complexes of manganese, after two-electron reduction, underwent [2 + 2 + 2]- or [3 + 2]-cycloadditions and Vilsmeier–Haack–Arnold reactions.[275–277] Dimanganese decacarbonyl can be used as a radical initiator for the alkylation of hydrazones, derived from aldehydes, in good yields.[278,279]

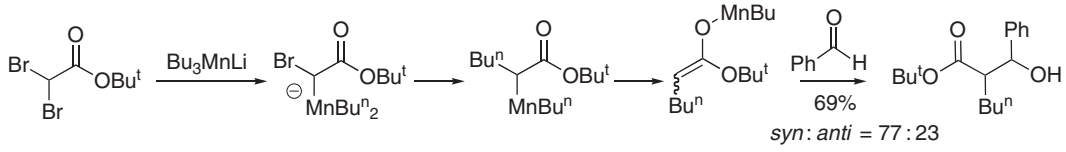
10.09.6.1.1 Addition to C═O

Organomanganese reagents can be used for the formation of ketones from acid chlorides with excellent functional group tolerance,[280–285] the corresponding ketones isolated in good yield. Gallo *et al.* have reported some heteronuclear Schiff base complexes of manganese and lithium where manganese carries a methyl or an aryl group and lithium is coordinated with an aldehyde as key species in the nucleophilic addition reaction affording secondary alcohols.[285,289–291] Acyl silanes were also shown to undergo stereoselective alkylation or allylation with organomanganese reagents to afford the corresponding alcohols in good yields, wherein the silyl group could be removed by treatment with TBAF/THF to give free secondary alcohols.[288] Allylmanganese reagents can be prepared from allylic alcohols or halides and readily allylate aromatic aldehydes resulting in the formation of the corresponding secondary allylic alcohols.[285–291] Ketones and alkyl aldehydes are not so amenable to this type of reaction as demonstrated by Li *et al.*[289] Nishikawa *et al.* described how an organomanganese compound could ring-open an allylic tetrahydropyran to give allylic secondary alcohols by a different mechanism.[292]

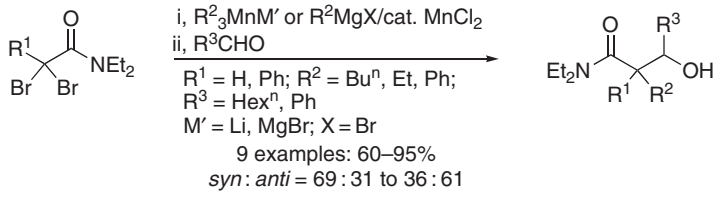
Alkylmanganese reagents were used in three-component, one-pot coupling reactions to afford α-substituted esters and amides.[293] The reported reactions, where benzaldehyde or *n*-hexanal is used as electrophile, are of particular relevance to this chapter, and examples are given in Schemes 65 and 66.

Aryl and ferrocenyl aldehydes (and their vinylogous counterparts) can be transformed into their α,β-unsaturated homologs **144**, that is, overall ethylene insertion (vinylogation) by reaction with a manganese Fischer carbene **140**.[294] Scheme 67 outlines the general procedure employed in these reactions. It should be noted that all intermediates were identified in each case and yields reported: 54–87% for **142**, 72–92% for **143**. When 1,1′-diformylferrocene was employed as the aldehyde, single and double addition products were obtained in high yields, respectively, depending on the ratio of carbene **140** to the aldehyde.[294] The utility of this procedure was also demonstrated by employing the isolated products as substrates in the subsequent reactions in some cases.

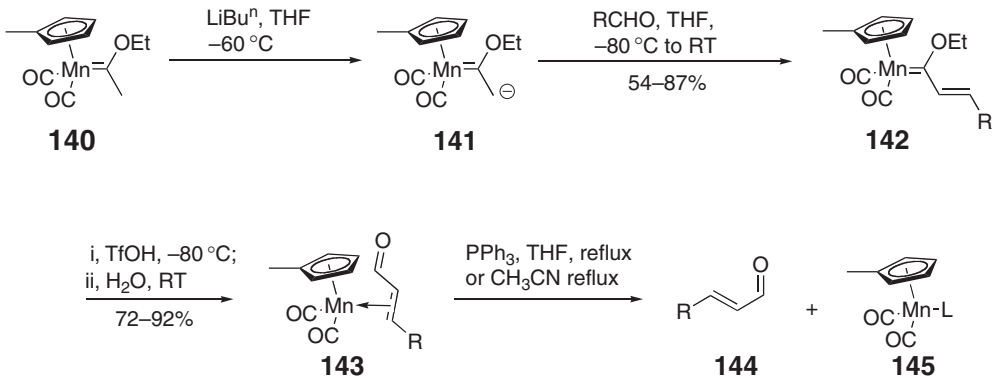
Organomanganese compounds as reagents for the formation of C–C bonds with carbonyl-containing compounds can be extremely useful for generating reactive carbon nucleophiles, particularly for reaction with aldehydes. Manganese chemistry associated with unsaturated nitrogen-containing bonds is still in its infancy. Thus, most of the cases in which organomanganese compounds have successfully reacted with imines or nitriles result in the formation of the corresponding manganese complexes, but the chemistry of the potential organic product has not



Scheme 65



Scheme 66



Scheme 67

received much attention. Nevertheless, a good number of publications suggest some advances made toward a truly efficient organic synthesis with organomanganese complexes.

10.09.6.2 Technetium

The scarceness of reports concerning organotechnetium was commented upon in COMC (1982) and COMC (1995).[295,296] Both chapters on this element cited the cost of technetium and precautions necessary for handling radioactive nuclei among as the major reasons for the sparsity of publications concerning its organometallic chemistry. As such, publications relevant to this chapter are unavailable. Although technetium-containing compounds are of significant interest as radiopharmaceuticals, the synthesis and applications of these compounds are beyond the scope of this chapter.[297–300] Readers should be referred to other chapters in COMC (1982) and COMC (1995) for detailed discussions of the organometallic chemistry of technetium,[295,296] which should provide a basis for designing useful organotechnetium-mediated organic syntheses.

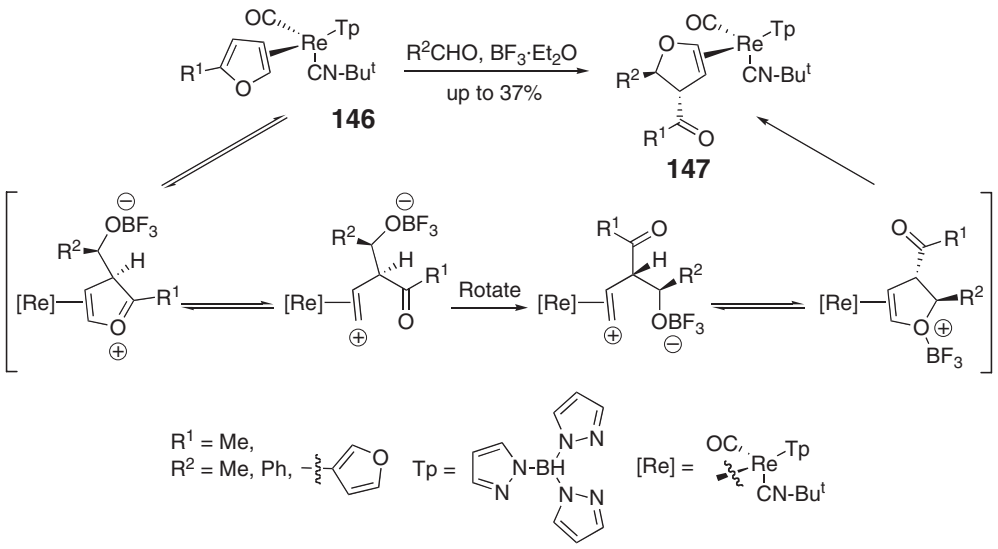
10.09.6.3 Rhenium

As discussed in COMC (1982) and COMC (1995), rhenium,[291,301] bearing the lowest atomic number among the group VII metals, offers investigators an opportunity to observe reaction intermediates which have very short lifetimes compared with their two higher atomic number congeners.[302] Some very interesting reactions on the metal, which provide a solid background to this chapter, are contained there. However, in only a few cases were organorhenium complexes shown to be involved in the reactions where the organic product was liberated from the metal or studied further. This chapter focuses on reactions where the principal bond-forming step is mediated by, or occurs in the presence of, an organorhenium species, and are of potential use to those interested in wider aspects of organometallic chemistry, but the potential organic product is not always liberated from the metal.

10.09.6.3.1 Addition to C═O

An interesting class of reactions includes the activation of furan derivatives by their hapto coordination to a rhenium centre. Harman and co-workers have made a number of contributions to this field,[303–305] with a particularly significant paper that appeared in 2003 (Scheme 68).[306] Harman and co-workers also reported on the activation of non-heteroaromatics, such as benzene and naphthalene.[307–309]

Compound **146** was converted to **147** (relative stereochemistry is shown in Scheme 68) by addition of a series of aldehydes, and other isomers were also obtained which were easily purified. But attempts to liberate a dihydrofuran from **147** were unsuccessful, which is believed to be due to decarbonylation by rhenium.[306] Alternative approaches can be envisaged, although the authors noted the difficulty in the preparation of the starting material as a serious barrier to this.[306]



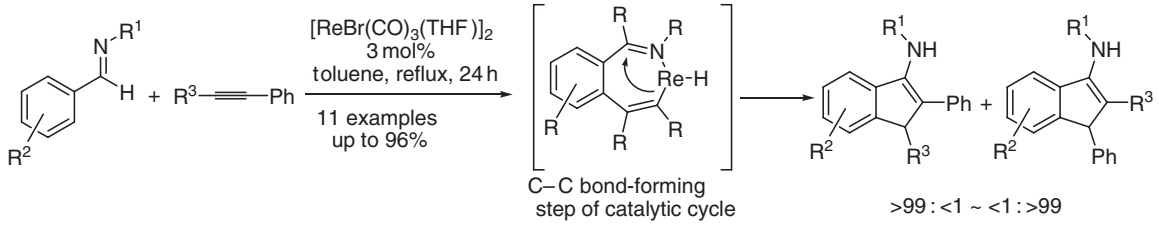
Scheme 68

10.09.6.3.2 Addition to C═N

N-bounded enolatorhenium complexes were identified as important intermediates in catalytic Michael and Knoevenangel reactions.[310] Treatment of a hydrido(dinitrogen)rhenium species with excess ethyl 2-cyanopropionate or alkyl cyanoacetates resulted in enolatorhenium complexes. Substrate scope was good, and the Michael or Knoevenangel products were obtained in 43–82%. A typical Michael reaction between acrylonitrile and ethyl cyanoacetate gave 77% yield of the corresponding Michael adduct with only 1 mol.% of rhenium. It is also worth noting that catalytic use of a base (e.g., Hünig's base) is not required. The requirement for nitrile coordination was demonstrated by the fact that the rhenium-catalyzed Knoevenangel reaction of malononitrile with benzaldehyde proceeds smoothly, whereas use of dimethyl malonate or pentane-2,4-dione in combination with benzaldehyde gave no desired product. Malononitrile's pK_a (11) lies between malonate and pentane-2,4-dione (13 and 9, respectively), thus ruling out relative acidity as the origin of the difference between nitrile- and carbonyl-containing substrates.

Rhenium-catalyzed [3 + 2]-cycloaddition reactions between imines and nitriles affording indene derivatives were reported by Kuninobu *et al.*; these authors demonstrated that only 3 mol.% of $[ReBr(CO)_3(THF)]_2$ allowed the transformation to proceed in high yield (Scheme 69).[311]

Depending on the nature of the substrates, selectivity could be completely reversed between the two isomeric products. For example, switching R^1 group between Bu^t and Ph gave high yields of the first and second product structures, respectively. The authors noted that the reaction did not proceed if the imine contained an *ortho*-MeO group at R^2 or if the imine was replaced with an aldehyde, oxime, or hydrazone. The catalytic cycle is initiated by C–H activation of the imine, that is, the formation of a five-membered metallocycle; alkyne insertion affords the intermediate drawn in Scheme 69. It is noteworthy that this is the first report of catalytic synthesis of indene derivatives via a C–H insertion mechanism (C–H activation, insertion, intramolecular addition).



Scheme 69

10.09.7 Group VIII Metals

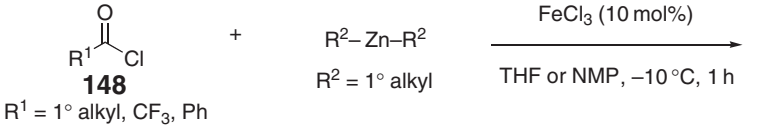
10.09.7.1 Iron

The chemistry of iron has been reviewed in COMC (1982) and COMC (1995)[312–314] as well as in *Comprehensive Coordination Chemistry II*.[315] More recent reviews cover iron-catalyzed transformations with samarium(II) iodide,[18d] the chemistry of tricarbonyliron–diene complexes,[316] and iron-catalyzed reactions in organic synthesis in general.[317]

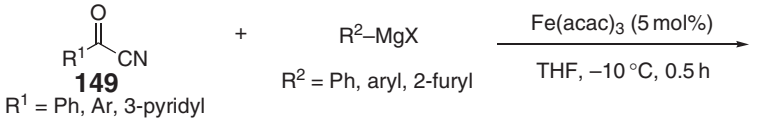
10.09.7.1.1 Addition to C═O

Iron-catalyzed cross-coupling reactions of various acyl chlorides[318–320] or thioesters[321] with Grignard reagents have been pioneered by Marchese *et al.* and other research groups.[322] These transformations provide general and convenient access to a wide range of ketones and have been further extended to the use of a supported iron(III) complex.[323]

Recent notable improvements by Knochel and co-workers include iron-catalyzed cross-coupling reactions of various acid chlorides **148** with dialkylzinc reagents (Equation (24))[324] as well as the iron-catalyzed arylation of aroyl cyanides **149** with Grignard reagents (Equation (25)).[325] In the first case Knochel's reaction conditions tolerate ester groups on the organozinc compounds, while in the latter case ester, aryl alkyl ether, cyano, and chloro functionalities on the aromatic moieties are compatibles with the reaction conditions.

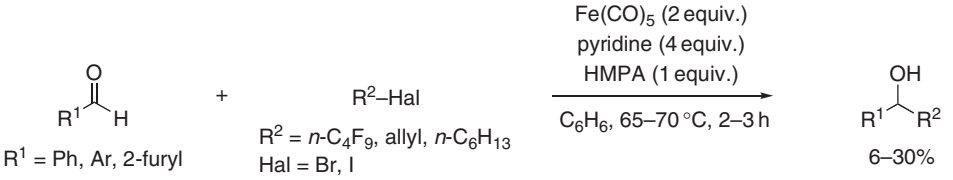


(24)



(25)

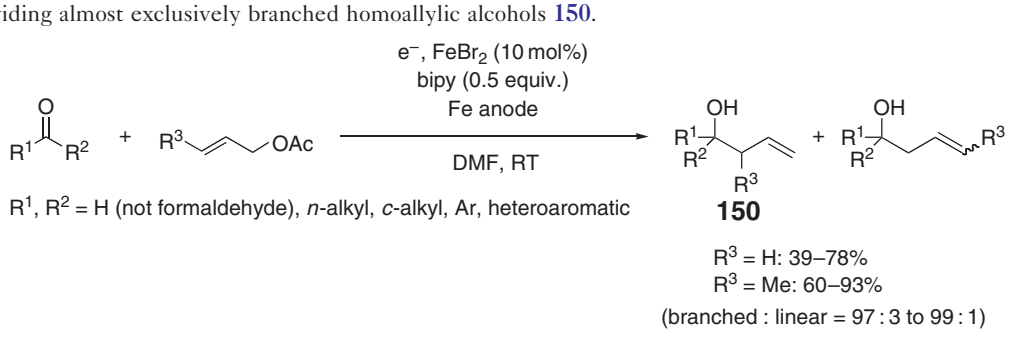
Recently, the iron-promoted Barbier-type addition of alkyl halides to aromatic aldehydes has been reported (Equation (26)).[326] According to the proposed mechanism, the initial step is the formation of an alkyl radical, which can be reduced to the corresponding carbanion. This carbanion nucleophile can react, while coordinated to the iron pentacarbonyl complex, with the corresponding aldehyde. This stoichiometric method is limited with respect to substrate scope and yield. The same authors have also developed the Reformatsky-type addition of α-halosubstituted carbonitriles to aldehydes and ketones in the presence of iron pentacarbonyl.[327]



(26)

Additionally, various intra- and intermolecular iron-catalyzed Barbier-type reactions of organosamarium compounds and carbonyl electrophiles have been reported by Molander and co-workers.[328–332]

Durandetti *et al.* have described iron-catalyzed electrochemical allylation of carbonyl compounds with allylic acetates (Equation (27)).[333] In the case of aldehydes, slow addition of the corresponding aldehyde is required in order to avoid pinacol formation. With crotyl acetate ($R^3 = Me$), the reaction proved to be highly regioselective, providing almost exclusively branched homoallylic alcohols **150**.



(27)

The same electrochemical process was also used for the coupling between aldehydes or ketones and activated alkyl halides such as α-chloroesters, -nitriles, and -ketones as well as α,α-dichloroesters.[334] Electroanalytical studies have shown initial electroreduction of Fe(II) to Fe(I) and subsequent formation of an iron organometallic intermediate (e.g., a π-allyliron complex in Equation (27)) before reaction with the corresponding carbonyl compounds.[335]

10.09.7.1.2 Addition to C═N

Iron-catalyzed cross-coupling reactions between aryl or alkenyl triflates and Grignard reagents, previously developed by Fürstner *et al*., have been extended by the same authors to the use of dichloroarenes for the selective iron-catalyzed cross-coupling with Grignard reagents (Scheme 70).[336] This monoalkylation of 2,4-dichloro-1,3-pyrimidine and 2,6-dichloro-1,4-pyrimidine tolerates both acetal and aryl alkyl ether functionalities in the Grignard reagents. The substitution reactions occurred selectively in the 4- and 2-positions respectively, furnishing the corresponding cross-coupling products **151** and **152** in up to 83% yield.

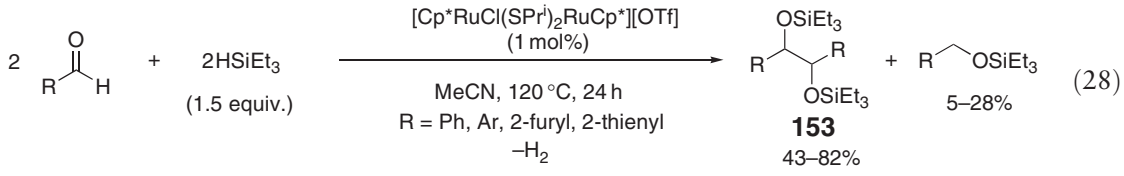
This methodology has been successfully extended to an approach toward the total synthesis of (*R*)-(+)-muscopyridine by the same research group.[337]

10.09.7.2 Ruthenium

The chemistry of ruthenium has been reviewed in COMC (1982) and COMC (1995)[338,339] as well as in *Comprehensive Coordination Chemistry II*.[340] More recent reviews summarize the synthesis, properties, and applications of diruthenium tetracarboxylates[341] as well as ruthenium catalysis in organic synthesis in general.[342] Most recent developments and applications of ruthenium complexes in organic synthesis have been reviewed up to 2004.[343]

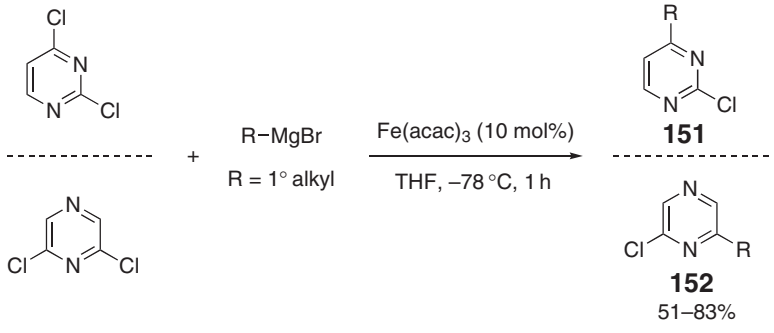
10.09.7.2.1 Addition to C═O and C═N

A pinacol-type silylative dimerization of various aromatic aldehydes promoted by a cationic thiolate-bridged diruthenium complex has been reported by Hidai and co-workers (Equation (28)).[344] 1,2-Diaryl-1,2-disiloxyethanes **153** were isolated as the major products along with the corresponding arylmethyl silyl ethers as minor products.

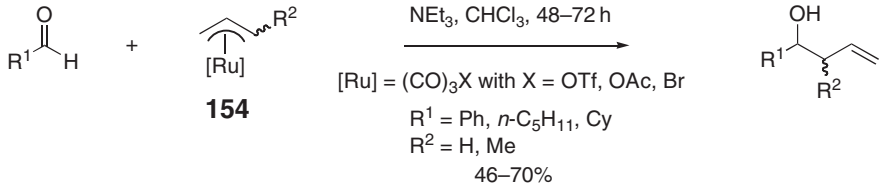


(28)

Kondo and Watanabe developed allylations of various types of aldehydes and oximes by using nucleophilic (π-allyl)ruthenium(II) complexes of type **154** bearing carbon monoxide ligands (Equation (29)).[345] These η^3-allylruthenium complexes **154** are ambiphilic reagents and the presence of the carbon monoxide ligands proved to be essential to achieve catalytic allylation reactions. Interestingly, these transformations occur with complete regioselectivity; only the more substituted allylic terminus adds to the aldehyde.



Scheme 70



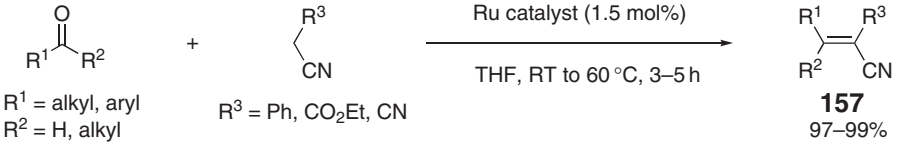
(29)

The formation as well as the reactivity of (π-allyl)ruthenium(II) complexes bearing phosphine ligands have been described in a series of articles.[346,346a–347] However, the main drawback in these cases is the use of non-catalytic amounts of ruthenium catalyst.

Based on Watanabe's intermolecular hydroacylation of olefins with aldehydes,[348] Kondo and Misudo developed the first ruthenium-catalyzed hydroacylation of 1,3-dienes with aldehydes (Scheme 71).[349] Usually, palladium-mediated hydroacylations of 1,3-dienes with aldehydes give tetrahydropyran and/or open-chain homoallylic alcohol derivatives.[350] However, in the present ruthenium-catalyzed transformations, the corresponding β,γ-unsaturated ketones were obtained exclusively.

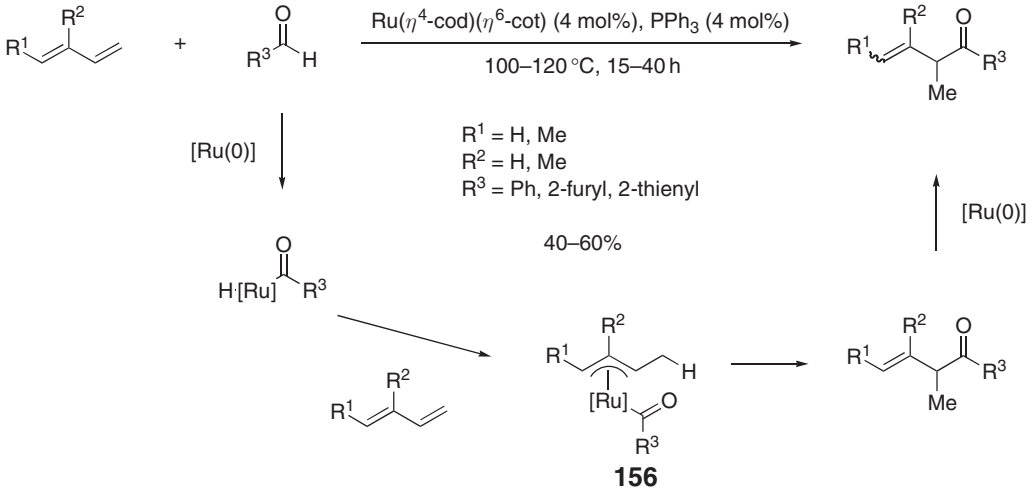
The most plausible mechanism proceeds through oxidative addition of the aldehyde to an active Ru(0) species to form (acyl)(hydrido)ruthenium(II) complex **155**. Insertion of the less-substituted double bond of the 1,3-diene into the Ru–H bond occurs to generate an (acyl)(η^3-allyl)ruthenium(II) intermediate of type **156**. Successive regioselective reductive eliminations between the acyl and the η^3-allyl ligands provide the desired product with regeneration of the active ruthenium(0) species.

Murahashi and co-workers developed an aldol-type condensation between various activated nitriles and aldehydes or ketones, catalyzed by cyclopentadienylruthenium enolate complexes (Equation (30)).[351,351a,351b]



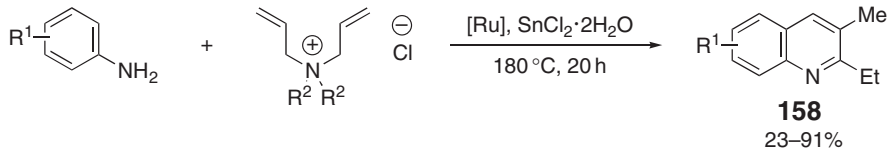
(30)

This aldol condensation is assumed to proceed via nucleophilic addition of a ruthenium enolate intermediate to the corresponding carbonyl compound, followed by protonation of the resultant alkoxide with the C–H acidic starting nitrile, hence regenerating the catalyst and releasing the aldol adduct, which can easily dehydrate to afford the desired α,β-unsaturated nitriles **157** in almost quantitative yields. Another example of this reaction type was reported by Lin and co-workers,[352] whereas an application to solid-phase synthesis with polymer-supported nitriles has been published only recently.[353]



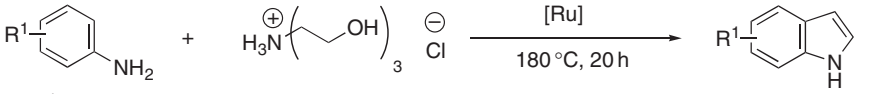
Scheme 71

The ruthenium-catalyzed one-step synthesis of quinoline[354] and indole[355,355a] derivatives **158** and **159** in aqueous medium starting from the corresponding anilines has been described (Equations (31) and (32)).



158
23–91%

(31)



R1 = alkyl

159
16–98%

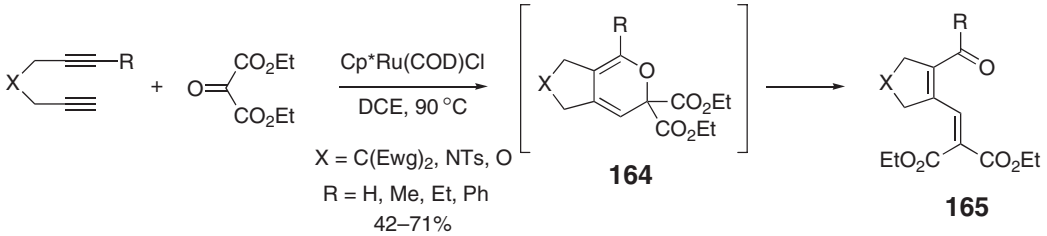
(32)

The proposed mechanisms are similar in both cases and involve in particular an (aryl)(hydrido)ruthenium intermediate in which the ruthenium is additionally coordinated by an *in situ*-generated *N*-phenylimine moiety tethered to the same Ru-bound aromatic ring. The C–C bond-forming step for the construction of the corresponding heterocyclic framework proceeds via insertion of the C═N double bond into the C–Ru bond with transfer of the (hydrido) ruthenium complex to the now phenylamine nitrogen. The desired heterocycles **158** and **159** were obtained after successive reductive elimination, deamination, and dehydrogenation.

Itoh and co-workers reported the ruthenium(II)-catalyzed [2 + 2 + 2]-cycloaddition of 1,6-diynes with isocyanates to afford the corresponding bicyclic pyridones **163** (Scheme 72).[356,357] For previously reported ruthenium-catalyzed [2 + 2 + 2]-cycloaddition of 1,6-diynes see Refs: 358 and 358a, and for theoretical calculations of the cyclocotrimerization of alkynes with isocyanates, isothiocyanates, and carbon disulfide see Refs: 359 and 359a.

The assumed mechanism proceeds via ruthenacyclopentadiene intermediates of type **160** or structure **161** as possible intermediates. Subsequently, the common bicyclic intermediate **162** is formed through insertion of the C═N double bond into the C–Ru bond, and reductive elimination of the ruthenium fragment gives rise to the desired bicyclic pyridones **163**.

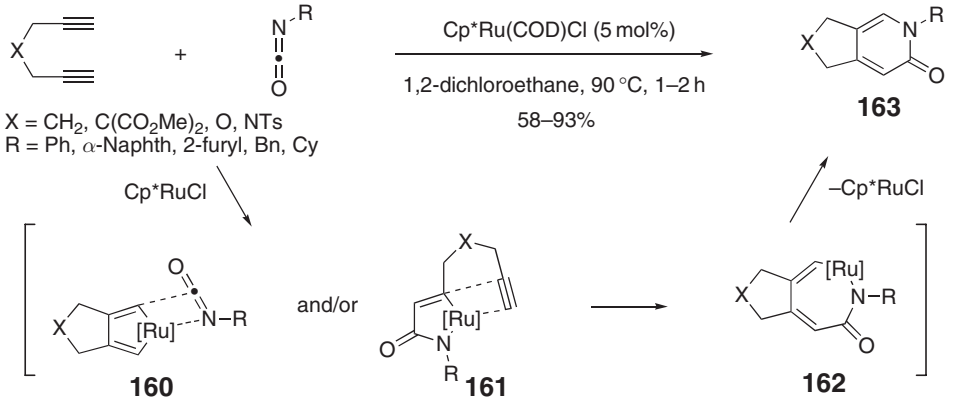
The same authors extended the [2 + 2 + 2]-cycloaddition methodology to the use of highly electron-deficient tricarbonyl compounds such as ketomalonates (Equation (33)).[360] In that particular case, the reaction does not stop at the initial stage of 2*H*-pyrans **164**. Instead, a thermally induced electrocyclic ring opening occurred to form the corresponding cyclopentenes **165** as final product.



164

165

(33)



160 **161** **162**

163

Scheme 72

A plausible mechanism for the cyclotrimerization includes initial oxidative cyclization between the less-hindered alkyne terminus and the ketone carbonyl group to form an oxaruthenacyclopentene intermediate. The insertion of the second alkyne terminus into the C–Ru bond, followed by reductive elimination, affords the *2H*-pyran compounds.

A ruthenium-catalyzed Grignard-type reaction of phenylacetylene with aldehydes via *sp*-carbon–hydrogen bond activation in water has been described by Li and Wei (Scheme 73).[361] The proposed mechanism suggests simultaneous activation of the C–H bond of phenylacetylene by the ruthenium catalyst and the aldehyde carbonyl by the indium(III) Lewis acid. The generated ruthenium intermediate can then undergo a Grignard-type addition to the activated C═O double bond, followed by subsequent hydrolysis to provide the desired propargylic alcohols of type **166**, and regenerate the catalytic ruthenium species.

Li and Wei have extended their Grignard-type methodology in water to the use of *in situ*-generated imines from the corresponding aldehydes and arylamines, thus furnishing the corresponding propargylamines in a three-component one-pot procedure.[362]

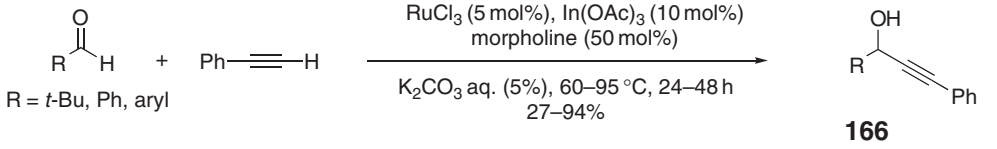
Recently, ruthenium-catalyzed tandem olefin migration/aldol-type or Mannich-type reactions have been developed with aldehydes or imines and allylic alcohols (Scheme 74).[363]

A tentative mechanism includes ruthenium-induced isomerization of the initial allylic alcohol via (hydrido)(π-allyl)ruthenium complex **167** to the corresponding Ru-bound enol **168**. This *in situ*-generated nucleophile complex can then add to aldehydes or imines under formation of the desired products.

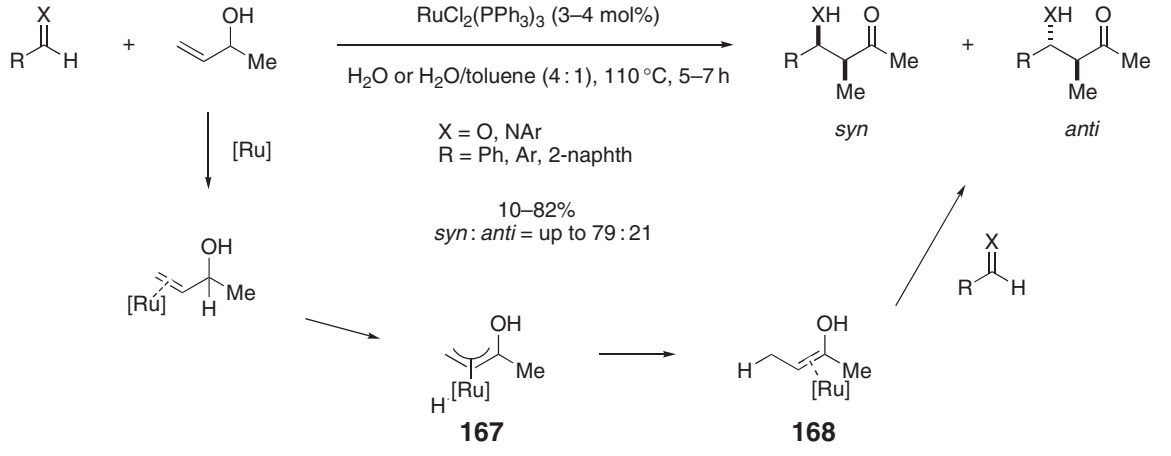
Che and co-workers developed a catalytic *cis*-selective aziridination of aromatic *N*-arylimines with ethyl diazoacetate catalyzed by a ruthenium(II) porphyrin complex (Scheme 75).[364] The corresponding pyrrolidines were isolated as minor byproducts.

It is assumed that the mechanism proceeds via activation of the imine by the ruthenium catalyst (structure **169**), followed by reaction with ethyl diazoacetate to generate a metal-bound ylide intermediate. Intramolecular ruthenium- assisted attack of the carbanion **170** onto the iminium ion provides the corresponding aziridine with moderate to high *cis*-selectivity. Imines bearing electron-donating groups (R^2) showed significant rate enhancement.

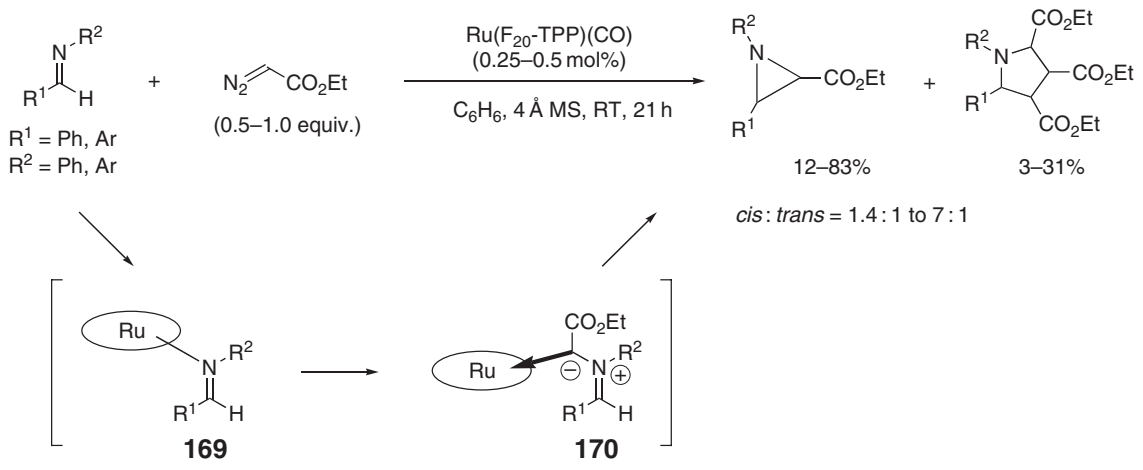
Finally, Shibasaki and co-workers reported the use of acetonitrile as a *C*-nucleophile by cooperative activation with a soft cationic ruthenium catalyst, DBU as base, and a sodium salt (Scheme 76).[365]



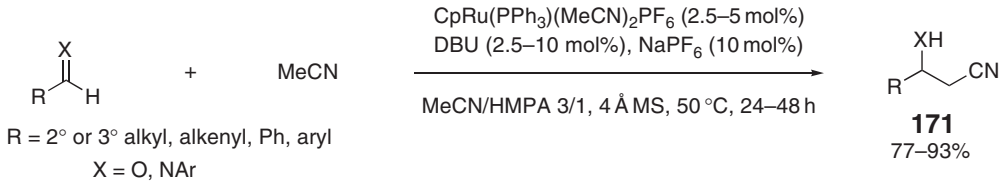
Scheme 73



Scheme 74



Scheme 75

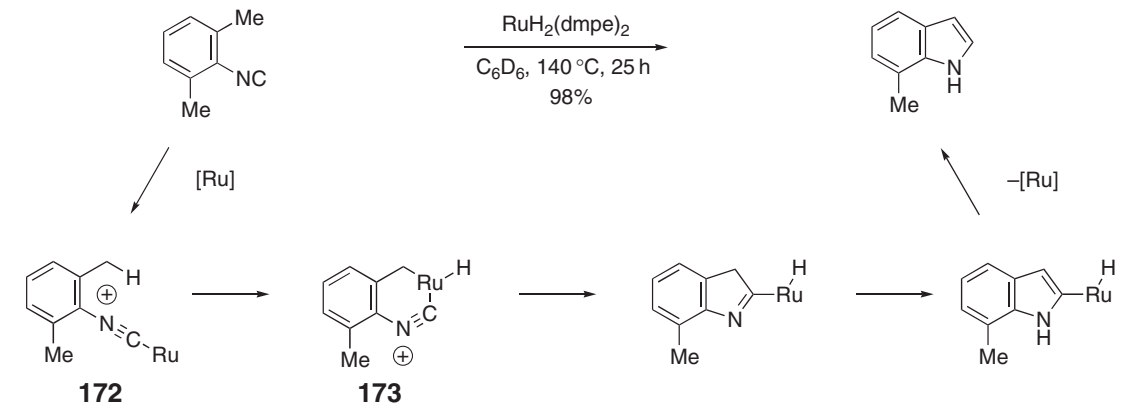


Scheme 76

The assumed mechanism includes the activation of acetonitrile by *N*-coordination to the metal center, followed by deprotonation with DBU. The generated carbanion, *N*-coordinated to the ruthenium atom, adds to the corresponding electrophile, while the presence of the sodium salt allows the regeneration of the ruthenium catalyst. Both various types of aldehydes as well as activated aromatic imines have been successfully employed as electrophiles, providing the corresponding adducts **171** in good to high yields.

10.09.7.2.2 Addition to C≡N

Jones and co-workers reported the ruthenium-catalyzed synthesis of indol derivatives in a single step starting from di-*o*,*o*′-substituted aromatic isonitriles; a representative example is shown in Scheme 77.[366,366a]

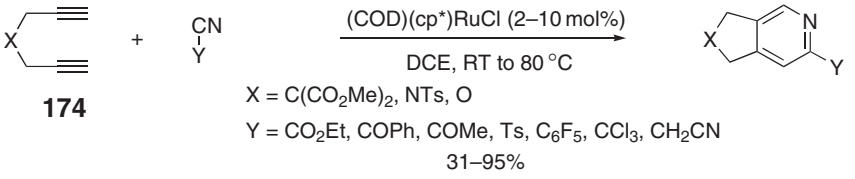


Scheme 77

This transformation proceeds through coordination of the isocyanide group to the ruthenium complex (structure **172**), followed by insertion of the *C*-bound ruthenium into the benzylic C–H bond (intermediate **173**). After ruthenium-mediated addition of the benzylic carbon to the isonitrile carbon and tautomerization, the desired product was obtained via elimination of the ruthenium complex.

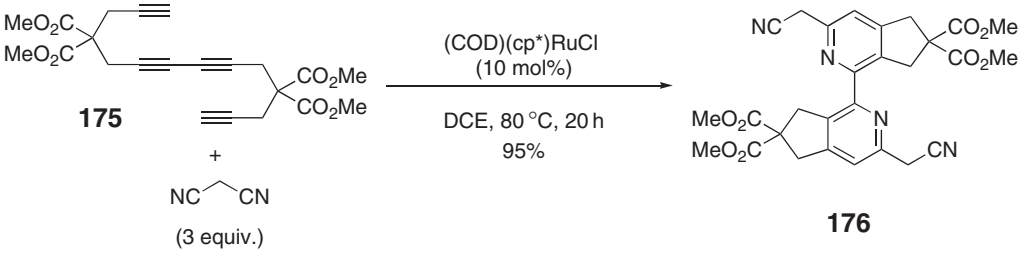
Cycloadditions on a ruthenium(II) complex between 2 equiv. of phenylacetylene and various types of isonitriles were described for the first time by Singleton.[367,367a] These transformations were shown to proceed through coordinatively unsaturated ruthenacycle intermediates to furnish the corresponding imino-2,5-diphenylcyclopentadiene complexes.

Based on this work, Itoh and co-workers developed ruthenium(II)-catalyzed [2 + 2 + 2]-cyclotrimerizations of 1,6-diynes **174** and electron-deficient nitriles (Equation (34)).[368,368a] These partially intramolecular cycloadditions proceed through ruthenacycle intermediates as well. The importance of using electronically activated nitriles is underlined by the fact that acetonitrile and benzonitrile gave only very low yields.



(34)

Additionally, the synthetic utility of this procedure was demonstrated by the efficient one-step synthesis of a 2,2′-bipyridine **176** starting from the corresponding tetrayne **175** and malodinitrile (Equation (35)).



(35)

Monoalkynes and acetonitrile also reacted in cyclo-co-trimerizations to afford the corresponding pyridines; however, almost stoichiometric amounts of the ruthenium(0) catalyst were required in that particular case.[369]

10.09.7.3 Osmium

The chemistry of osmium has been reviewed in COMC (1982) and COMC (1995)[339,370] as well as in *Comprehensive Coordination Chemistry II*.[340] A recent review covers the applications of diosmium tetracarboxylates.[341]

10.09.7.3.1 Addition to C═O

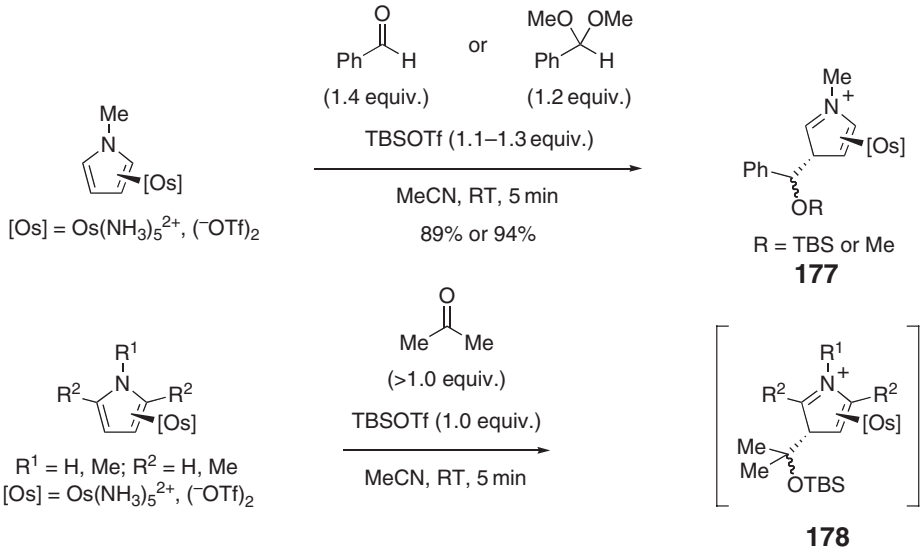
The β-electrophilic additions of pentaamineosmium(II) complexes bearing various 4,5-η^2-coordinated pyrroles to carbonyl compounds have been reported by Harman and co-workers (Scheme 78).[371] 1-Methylpyrrole complex, when reacted with benzaldehyde or its dimethylacetal in the presence of *t*-butyldimethylsilyl triflate (TBSOTf), afforded the corresponding aldol adduct **177** as a 1 : 1 ratio of diastereoisomers. Pyrrole, 1-methylpyrrole, or 2,5-dimethylpyrrole osmium complexes reacted with an excess of acetone in the presence of TBSOTf to give the *O*-silylated 3*H*-pyrrolium aldol adducts **178**, which may serve as intermediates for various other reactions.

Furthermore, an η^2-coordinated furan complex of pentaamineosmium(II) was shown to react, in the same way, with the dimethylacetal of benzaldehyde in the presence of a Lewis acid.[372]

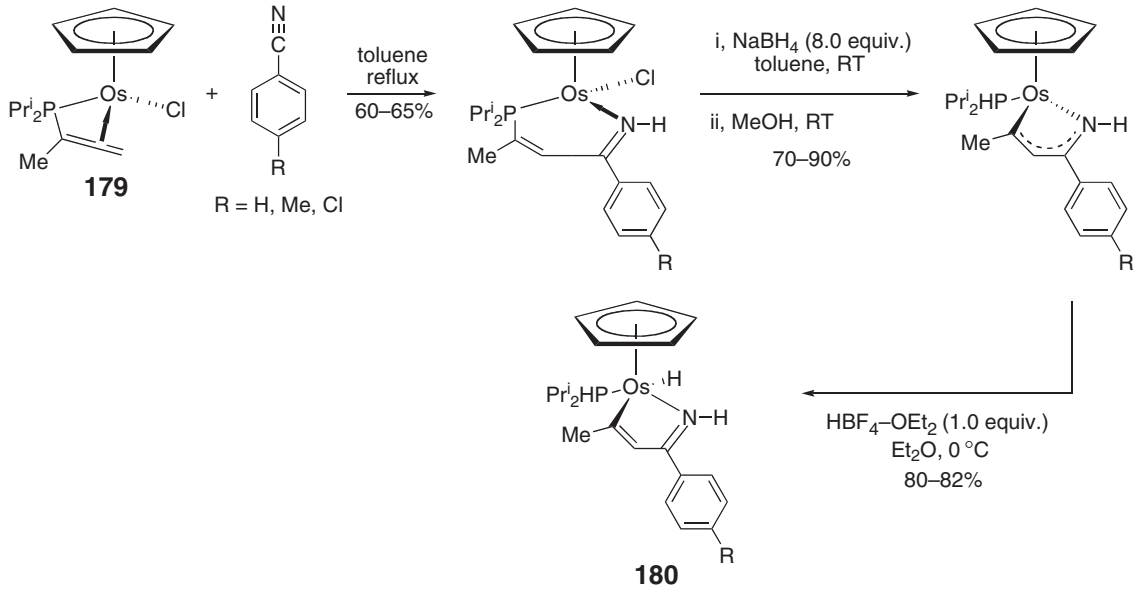
10.09.7.3.2 Addition to C≡N

Very recently, the formation of azabutadienylosmium complexes through transfer of the isopropenyl group of a phosphine ligand to benzonitriles on a Cp–Os metal complex has been reported (Scheme 79).[373]

The readily accessible diisopropyl(isopropenyl)phosphine complex **179** was shown to react with various benzonitriles through regiospecific sp^2–sp carbon–carbon couplings to form the corresponding iminophosphine complexes.



Scheme 78

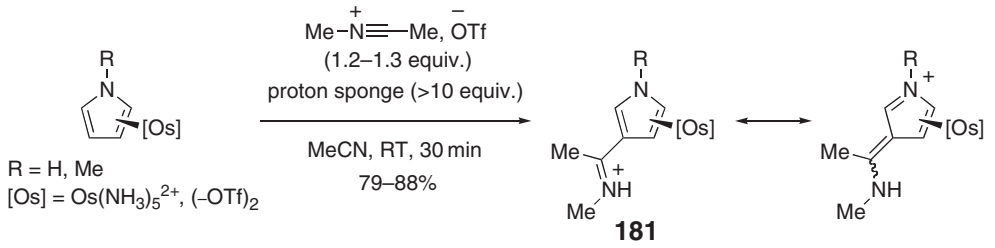


Scheme 79

The isopropenyl–benzonitrile units were then released from the phosphine group via cleavage of the P–C bond to afford osmapyrroles, whose metal centers were protonated to furnish the desired azabutadienylosmium(IV) hydride complexes **180**.

Pentaamineosmium(II) 4,5-η^2-coordinated pyrrole complexes have been reacted with methylacetonitrilium triflate in the presence of an excess of proton sponge to afford the corresponding iminium salt of 2-[1-(*N*-methylimino)ethyl]-pyrrole-Os complexes **181** (Scheme 80).[371]

Finally, various η^2-coordinated furan complexes of pentaamineosmium(II) were converted, in a similar way, to the corresponding iminium salt of 2-[1-(*N*-methylimino)ethyl]furan-Os complexes.[372]



Scheme 80

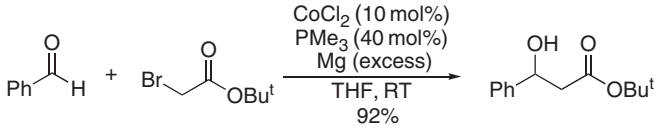
10.09.8 Group IX Metals

10.09.8.1 Cobalt

Stoichiometric, nucleophilic addition of alkylcobalt compounds to carbonyl compounds were reviewed in 1996.[374] This chapter focuses on recent progress in the reactions of cobalt enolates with carbonyls and cobalt-catalyzed coupling reactions.

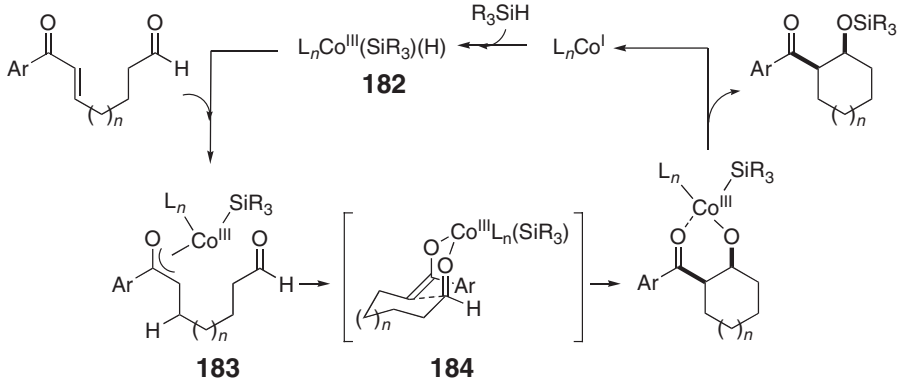
10.09.8.1.1 Addition to C═O

Activated halogen derivatives (α-halo esters, amides, ketones, and phosphonates) react with carbonyl compounds in the presence of a cobalt(0)–phosphine complex to give the corresponding alcohol derivatives.[375,375a–375c] The cobalt complexes are prepared *in situ* from $CoCl_2$, a phosphine, and Mg in THF. The amount of cobalt can be reduced to catalytic when a sufficient quantity of magnesium metal is present (Equation (36)). Monophosphines such as PMe_3 and PPh_3 afford better results than bidentate phosphines. Oxidative addition of activated halogen derivatives to cobalt(0) may give a nucleophilic organocobalt(II)–phosphine intermediate which then reacts with carbonyl compounds with high 1,2-addition selectivity.



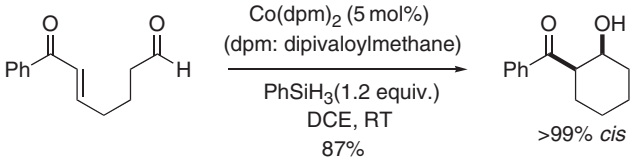
(36)

Although a cobalt-catalyzed intermolecular reductive aldol reaction (generation of cobalt enolates by hydrometallation of acrylic acid derivatives and subsequent reactions with carbonyl compounds) was first described in 1989, low diastereoselectivity has been problematic.[376] However, the intramolecular version of this process was found to show high diastereoselectivity (Equation (37)).[377,377a,378] A Co(I)–Co(III) catalytic cycle is suggested on the basis of deuterium-labeling studies and the chemistry of Co(II) complexes (Scheme 81). Cobalt(III) hydride **182**, which is



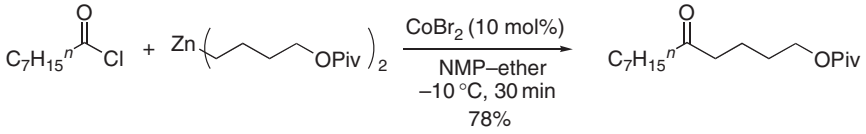
Scheme 81

generated by single electron transfer from Co(II) to hydrosilane or disproportionation of Co(II) followed by oxidative addition of hydrosilane to Co(I), undergoes hydrometallation of the enone moiety to form cobalt(III) enolate **183**, followed by intramolecular addition to the aldehyde moiety. The observed high *cis*-selectivity is explained by a Zimmermann–Traxler-type transition state **184**.



(37)

$CoBr_2$ is a very efficient catalyst for acylation of organozinc compounds with aliphatic and aromatic acid chlorides, oxalyl chloride, or trifluoroacetic anhydride to afford various functionalized ketones (Equation (38)).[324,379]



(38)

10.09.8.2 Rhodium

Nucleophilic additions of organorhodium species to C═O and CN multiple bonds constitute important classes of catalytic organic reactions and have experienced significant progress in the last decade.[380]

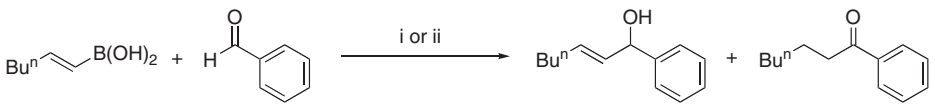
10.09.8.2.1 Addition to C═O

Rhodium complexes catalyze 1,2-addition of organotin, boron, and silicon compounds to aldehydes. Table 4 summarizes the reported methods for this process. Reactions of electron-rich organometallic reagents and electron-poor aldehydes tend to give high yields, and rhodium catalysts having bulky and electron-donating ligands generally provide high catalytic activity. In many cases, a base and water play important roles to achieve high catalyst turnover.

The mechanism of these reactions presumably consists of three key steps: (i) transmetallation of the organic group from an organometallic reagent to a rhodium catalyst, (ii) insertion of an aldehyde to the resulting carbon–rhodium bond, then (iii) hydrolysis of the generated rhodium alkoxide to afford an alcohol product along with regeneration of the catalyst. Hartwig and Krug reported that isolated arylrhodium(I) complexes such as **185** undergo insertion of aromatic aldehydes into the aryl–Rh bond to give rhodium alkoxides which result in formation of aryl ketones **186** under non-aqueous conditions or that of diarylmethanols **187** in aqueous THF (Scheme 82).[394] Effectiveness of bulky and electron-donating ligands can be ascribed to two factors: (i) formation of a coordinatively unsaturated organorhodium(I) intermediate to give sufficient Lewis acidity to aldehydes, and (ii) enhancement of nucleophilicity of the organorhodium intermediate.[386]

Selection of the reaction conditions brings about a complete reversal between 1,2- and 1,4-addition in the reaction of cinnamaldehyde (Scheme 83).[386]

Not only arylboronic acids but also 1-alkenylboronic acids or esters add to aldehydes to give the corresponding allylic alcohols (Equation (39)).[395] Isomerization of the allylic alcohols to saturated ketones occurs in less protic media and at higher temperatures.

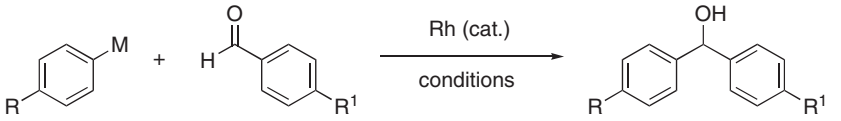


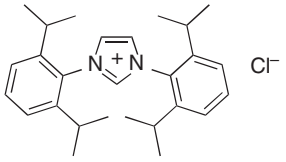
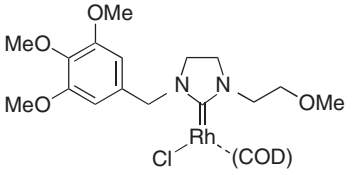
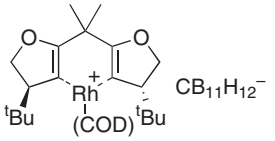
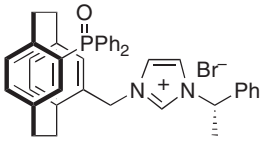
(39)

i, $[RhOH(COD)]_2$ (1.5 mol%), dppf(3 mol%), KOH, MeOH–H_2O, 25 °C, 16 h: 78% yield (94 : 6)

ii, $[RhCl(COD)]_2$ (1.5 mol%), dppf(3 mol%), KOH, DME–H_2O, 80 °C, 16 h: 80% yield (0 : 100)

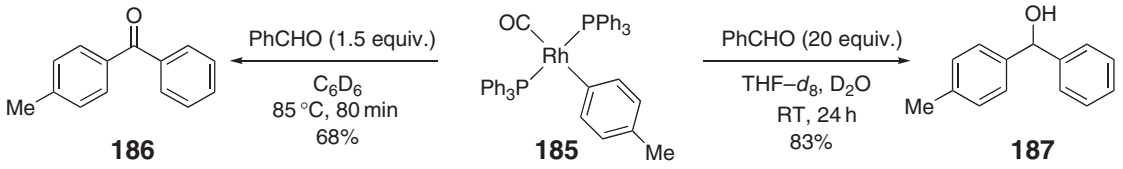
Table 4 Addition to aldehydes



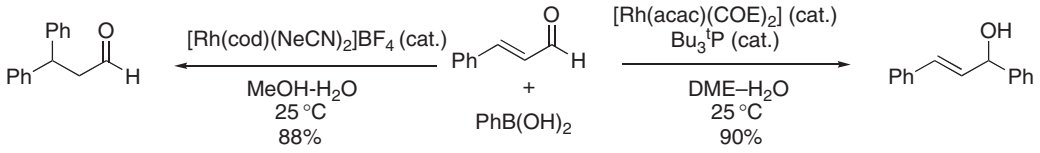
M	*Catalyst*	*Conditions*	*R*	R^1	*Yield (%)*	*References*
$SnMe_3$	$[Rh(COD)(MeCN)_2]BF_4$	THF, 60 °C, 5 h	H	H	85	381,381a
$SnMe_3$	$[Rh(COD)_2]BF_4$	H_2O, 110 °C, 12 h	H	H	82	382
$SnCl_3$	$[Rh(COD)_2]BF_4$	KOH, H_2O, 100 °C	H	H	71	383
$SnXPh_2$	$[Rh(COD)_2]BF_4$	H_2O, 100 °C			0 (X: Cl)	
			H	H	31 (X: OH) 43 (X: Bu)	384
$B(OH)_2$	$[Rh(acac)(CO)_2]$, dppf	DME, H_2O, 80 °C, 16 h	H	H	92	385
$B(OH)_2$	$[Rh(acac)(CO)_2]$, PBu^t_3	DME, H_2O, 25 °C, 16 h	H	MeO	99	386
$B(OH)_2$	$RhCl_3 \cdot 3H_2O$	DME, H_2O, 80 °C, 0.2 h				
			H	H	95	387
$B(OH)_2$		KOBu^t, DME, H_2O, 80 °C, 0.4 h	H	OMe	96	388,388a
$B(OH)_2$		DME (anhydrous), 80 °C	OMe	CF_3	86	389
$B(OH)_2$	$[Rh(OAc)_2]_2$, NaOMe	DME, H_2O, 60 °C				
			H	Cl	84 (29% ee)	390
$BF_4^-K^+$	$[Rh(acac)(CO)_2]$, dppf	DME, H_2O, 80 °C, 16 h	H	H	99	391
BCl_2	$[Rh(COD)_2]BF_4$	KOH, H_2O, 100 °C	H	H	75	384
$SiMeF_2$	$[Rh(COD)(MeCN)_2]BF_4$	KF, THF, 60 °C, 20 h	H	H	95	384
$SiEt(OH)_2$	$[Rh(OH)(COD)]_2$	THF, 70 °C, 24 h	H	H	53	392
$Si(OEt)_3$	$[Rh(OH)(COD)]_2$, COD, NaOH	Dioxane, H_2O, 90 °C, 16 h	H	H	79	393

Addition of arylboronic acids to aldehydes using recoverable, water-soluble rhodium catalysts has also been reported.[396]

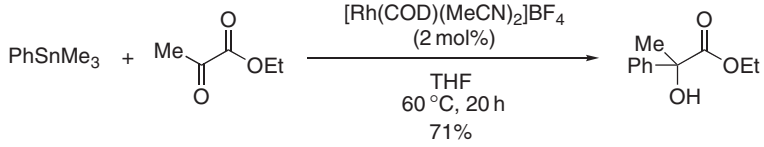
The reaction does not tolerate simple ketones, but reactions of activated ketones, α-diketones, or α-keto esters with arylstannes[381a] and intramolecular reactions[395] are possible (Equations (40) and (41)).



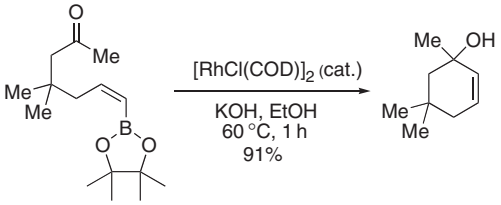
Scheme 82



Scheme 83

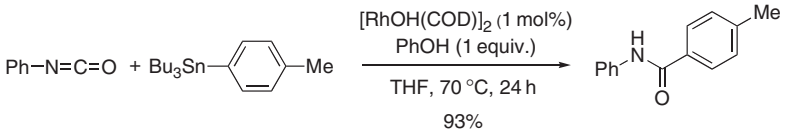


(40)



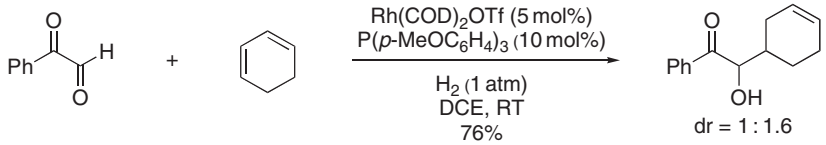
(41)

Arystannanes add to isocyanates in the presence of a rhodium catalyst to afford amides (Equation (42)), where phenol as an additive is essential to obtain a high yield.[397]

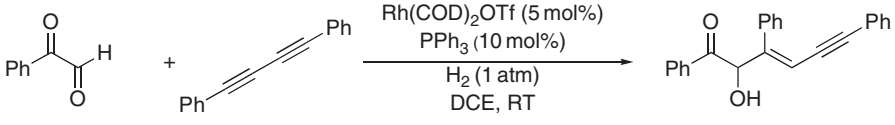


(42)

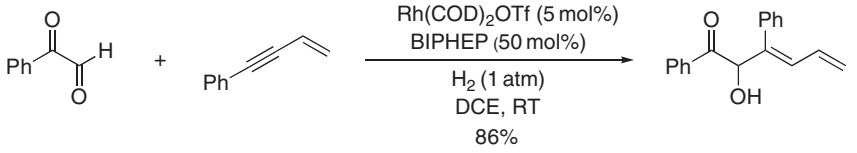
Rhodium-catalyzed reductive coupling of 1,3-dienes, 1,3-diynes, or 1,3-enynes and glyoxals, and (*N*-sulfinyl)iminoacetates under a hydrogen atmosphere has been disclosed recently (Equations (43)–(47)).[398,398a–398e]



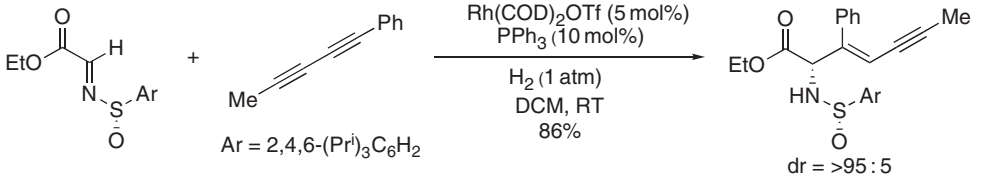
(43)



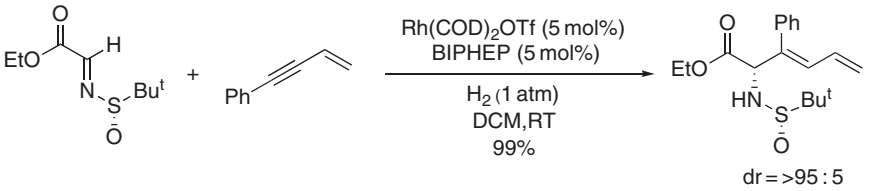
(44)



(45)

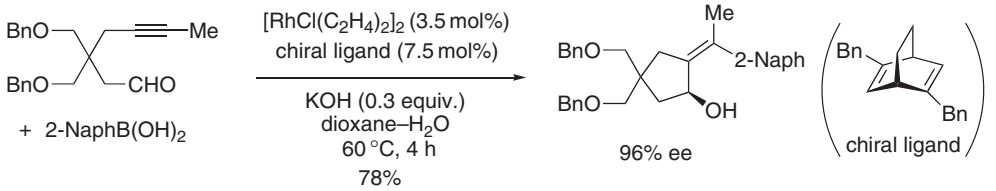


(46)



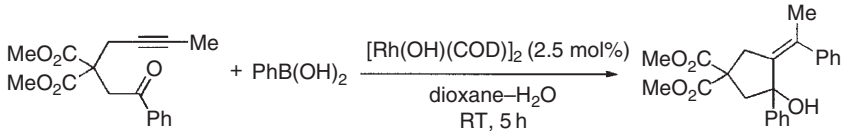
(47)

Arylative cyclization of alkynals with arylboronic acids is catalyzed by rhodium–diene complexes and even proceeds enantioselectively in the presence of a chiral diene (Equation (48)).[399]

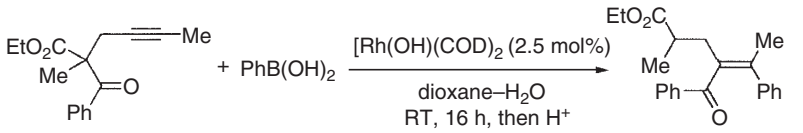


(48)

Simiraly, alkynones undergo arylative cyclization with arylboronic acids in the presence of a rhodium catalyst (Equation (49)).[400] When acetylenic β-keto esters are employed as shown in Equation (50), arylative cyclization (formation of cyclobutanols) and subsequent, facile acid-catalyzed bond cleavage take place to give δ-keto esters.[401] Ring expansions of cyclic β-keto esters are also possible according to this reaction.

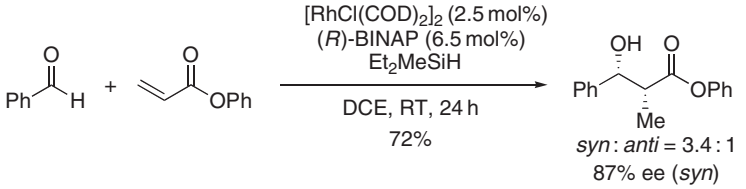


(49)



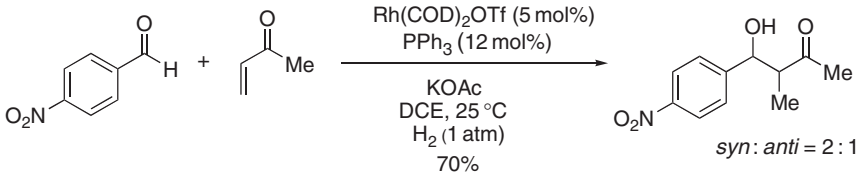
(50)

A number of rhodium-catalyzed reductive aldol reactions using silanes have been reported since the first report by Revis.[402,402a–402d] Enantioselecive versions have recently been achieved by Morken and co-workers (Equation (51)).[402b,402c]

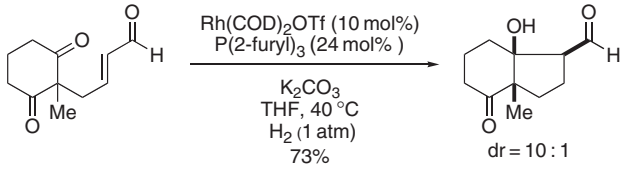


(51)

Krische and co-workers have revealed efficient reductive generation of rhodium enolates under hydrogenation conditions.[403,403a–403d] Both inter- and intramolecular reductive aldol reactions proceed smoothly and stereoselectively, although intermolecular reactions generally show low diastereoselectivity (Equations (52) and (53)).

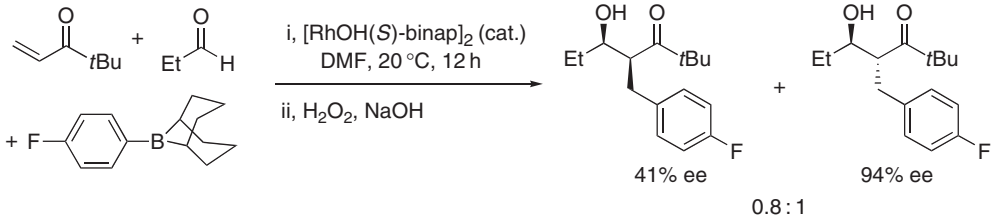


(52)

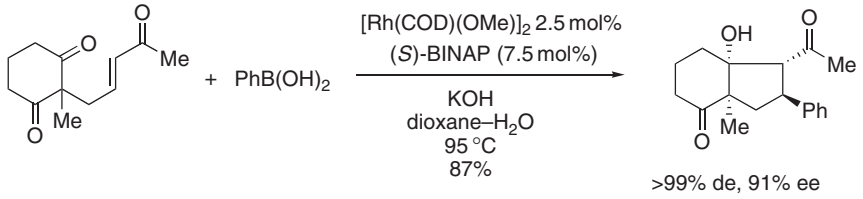


(53)

Alkylative aldol reactions with aryl- or vinylboron reagents are also catalyzed by rhodium complexes.[404,404a,404b] Equations (54) and (55) show examples of enantioselective reactions.

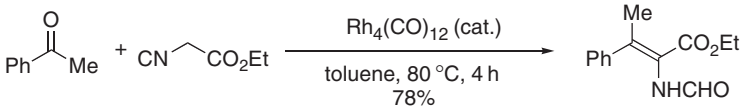


(54)

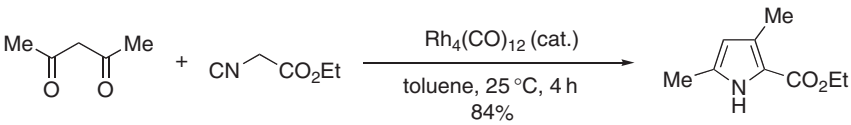


(55)

Low-valent rhodium complexes are efficient catalysts for addition of isocyanoacetates to ketones or 1,3-dicarbonyl compounds (Equations (56) and (57)).[405] The formation of isocyanoalkylrhodium species via α-C–H activation of isocyanoacetates followed by insertion of carbonyl compounds is proposed.

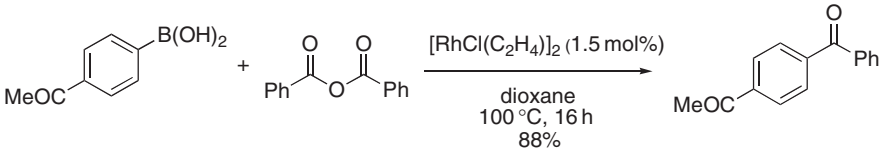


(56)



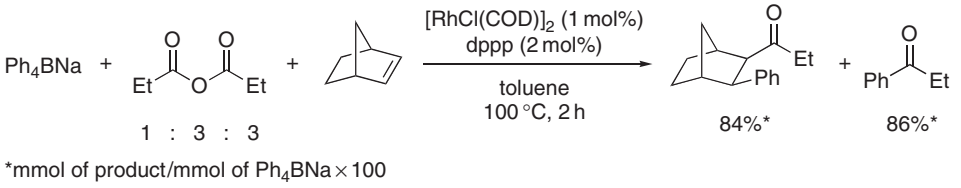
(57)

Reactions of aryl- and styrylboronic acids with acid anhydrides are catalyzed by rhodium complexes to give ketones (Equation (58)).[406]



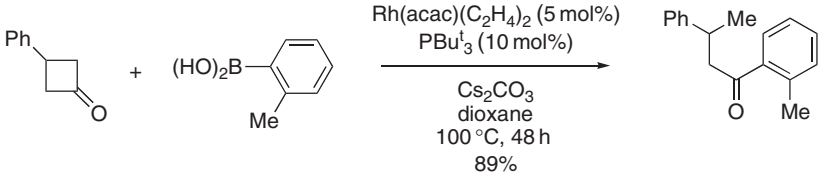
(58)

Sodium tetraphenylborate can be used for this transformation.[407] In addition, three-component coupling products are obtained in the presence of norbornene (Equation (59)).



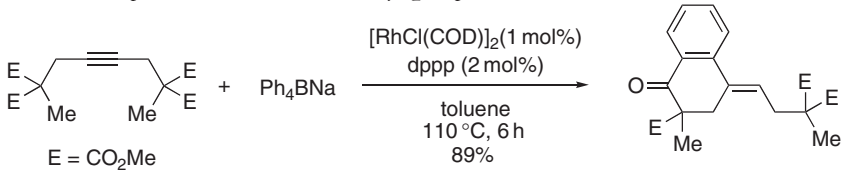
(59)

Cyclobutanones react with arylboronic acids to afford butyrophenones (Equation (60)).[408] Addition of arylrhodium species to the carbonyl group followed by β-carbon elimination is proposed.

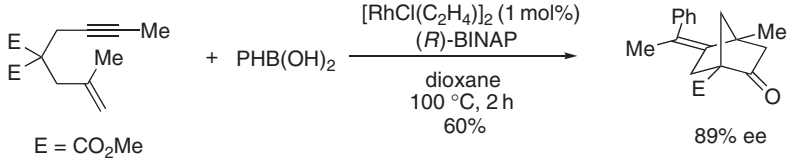


(60)

Acetylenic esters react with arylboron reagents in the presence of rhodium diphosphine catalyst to give cyclic ketones.[409] Equation (61) shows an example which may involve *ortho*-metallation and ketone formation. A catalytic, enantioselective reaction was also achieved (Equation (62)). These processes presumably involve unprecedented addition of organorhodium species to the ester carbonyl group.



(61)

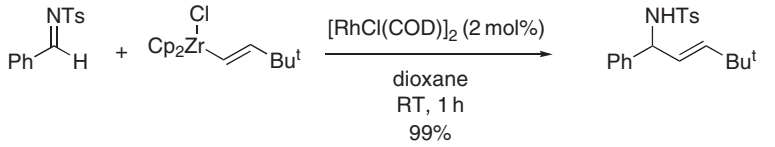


(62)

10.09.8.2.2 Addition to C═N

Rhodium complexes catalyze 1,2-addition of main group metal compounds to aldimines as well. Table 5 summarizes the reported methods. Electron-withdrawing substituents such as sulfonyl and acyl groups on the imino nitrogen atom are important to obtain sufficiently high reactivity. Asymmetric synthesis (diastereoselective and enantioselective) has also been accomplished.

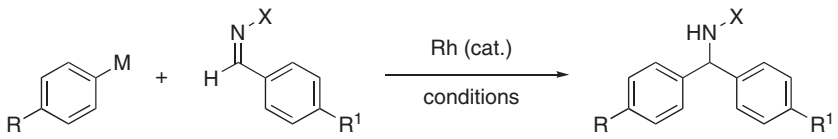
Alkenylzirconium reagents generated from alkynes and the Schwartz reagent react with aldimines under mild conditions in the presence of $[RhCl(COD)]_2$ to give homoallylic amine derivatives (Equation (63)).[418]

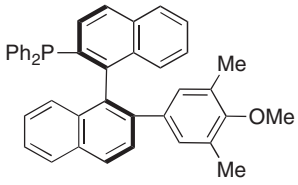
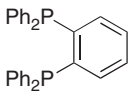
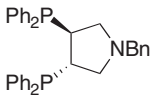


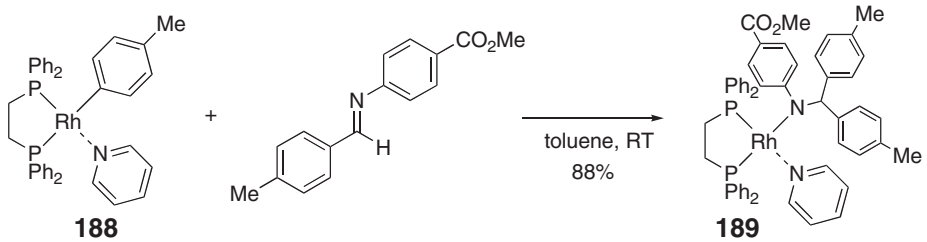
(63)

The mechanism of these reactions may be analogous to that with aldehydes. Arylrhodium(I) complex **188** was shown to undergo insertion of electron-poor aldimines to give amide complex **189**, possible intermediates of the catalytic reaction (Equation (64)).[419]

Table 5 Addition to aldimines



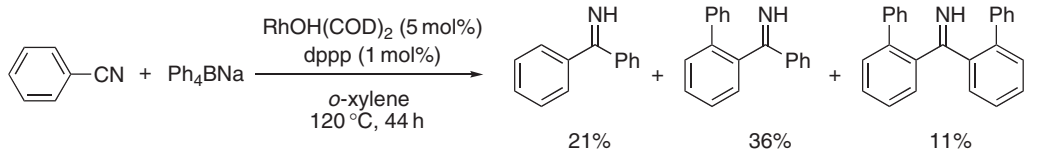
M	*Catalyst*	*Conditions*	*X*	*R*	R^1	*Yield* (%)	*References*
$SnMe_3$	$[Rh(COD)(MeCN)_2]BF_4$	THF, 60 °C, 5 h	Ts	H	H	85	410
			$PO(OEt)_2$	H	H	84	
			Bz	H	H	48	
			Boc	H	H	74	
			Bu, Bn, Ph	H	H	<10	
$SnMe_3$	$[RhCl(COD)]_2$	H_2O, 35 °C, sonication	Ts	H	H	81	411
$PbMe_3$	$[RhCl(COD)]_2$	H_2O, 35 °C, sonication		*o*-Cl	H	76 (34% de)	411
$SnMe_3$	$[Rh(acac)(C_2H_4)_2]$ 	LiF, dioxane, 110 °C, 12 h	Nos	H	CF_3	90 (96% ee)	412,412a
$BPh_3^-Na^+$	$[Rh(COD)(MeCN)_2]BF_4$, dppb	dioxane, 90 °C, 3 h	SO_2Ph	H	H	99	413
$B(OH)_2$	$[Rh(COD)(MeCN)_2]BF_4$, dppb	Dioxane, 90 °C, 16 h	SO_2Ph	H	H	99	414
$(PhBO)_3$	$[RhCl(C_2H_4)_2]_2$, KOH 	Dioxane, H_2O, 60 °C, 6 h	Ts	H	CF_3	97 (95% ee)	415
$B(OH)_2$	$Rh(acac)(COE)_2$ 	Dioxane, 70 °C, 6 h		H	Me	96 (94% de)	416
$B(OH)_2$	$Rh(acac)(COE)_2$ 	Et_3N, 3 Å, MS, dioxane, 70 °C, 24 h	$POPh_2$	Cl	H	97 (94% ee)	411
$B(OH)_2$	$[Rh(COD)(MeCN)_2]BF_4$	Et_3N, dioxane, H_2O, RT, 6 h		H	CF_3	94 (93% de)	417



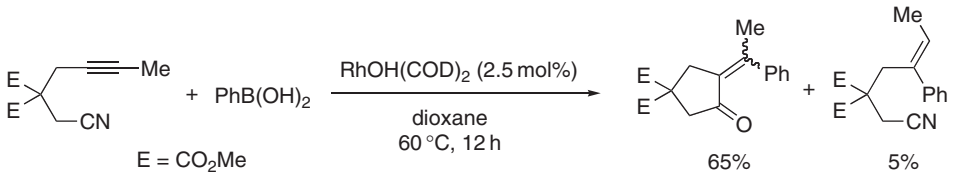
(64)

10.09.8.2.3 Addition to C≡N

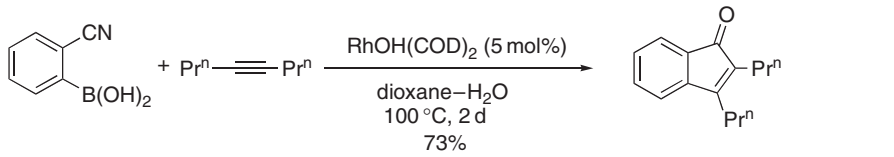
Recently, addition of organorhodium species to nitriles has been reported.[420,420a,420b] Intermolecular reaction of benzonitrile with phenylborate (accompanied with *ortho*-arylation) (Equation (65)), arylative cyclization of acetylenic nitriles (Equation (66)), and cyclization of 2-cyanophenylboronic acid with alkynes or strained alkenes (Equation (67)) are proposed to proceed via this process.



(65)

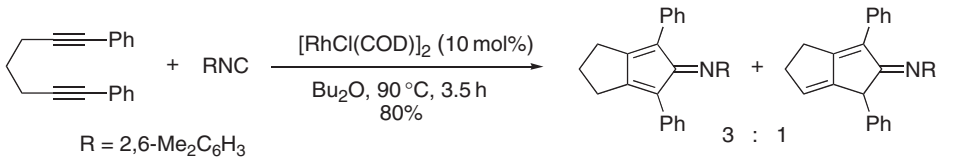


(66)



(67)

Rhodium-catalyzed reactions of diynes and an isonitrile give rise to iminocyclopentadienes (Equation (68)).[421] Portionwise addition of the isonitrile (5×0.2 equiv.) was found to increase the yield. The reaction may proceed through formation of metallacyclopentadienes followed by insertion of an isonitrile molecule.



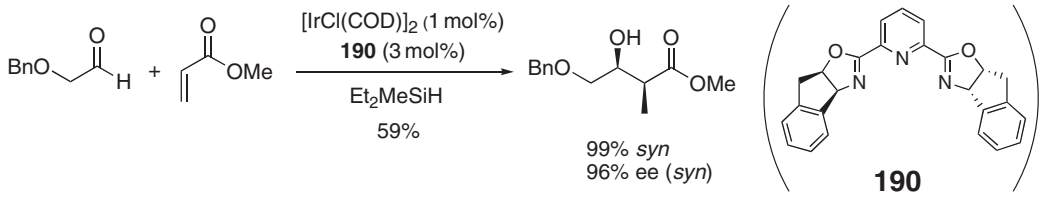
(68)

10.09.8.3 Iridium

Although addition of organoiridium compounds to carbonyls and CN multiple bonds has been little investigated in comparison with those of organorhodium compounds, several characteristic reactions have been disclosed recently.

10.09.8.3.1 Addition to C═O

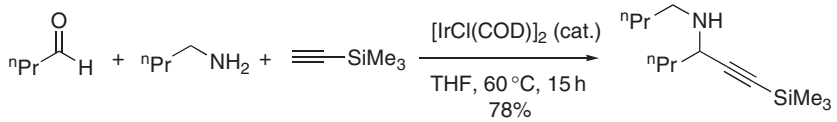
The first iridium-catalyzed reductive aldol reaction was reported in 2001.[422] Methyl acrylate reacts with certain aldehydes and diethylmethylsilane with high enantio- and diastereoselectivies (Equation (69)).



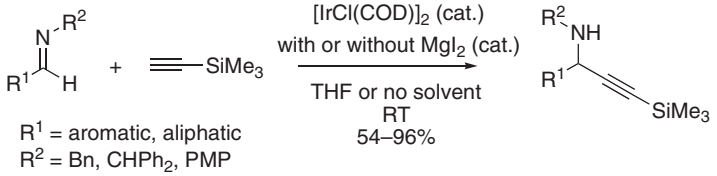
(69)

10.09.8.3.2 Addition to C═N

Formation of propargylic amines by an iridium-catalyzed three-component reaction of an aldehyde, a primary amine, and trimethylsilylacetylene (Equation (70))[423,423a] or a two-component reaction of imines and trimethylsilylacetylene (Equation (71))[424,424a] were recently described. Those reactions are presumably initiated by the oxidative addition of the Ir(I) complex to the terminal C–H bond of the alkyne. Significant acceleration was observed by addition of a catalytic amount of MgI_2.[424a] Interestingly, other terminal alkynes such as 1-octyne undergo a different type of three-component reaction with aldehydes and primary amines.[423]



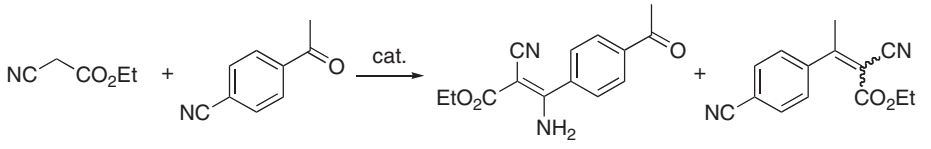
(70)



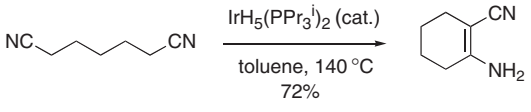
(71)

10.09.8.3.3 Addition to C≡N

Iridium hydride complexes effectively catalyze addition of nitriles or 1,3-dicarbonyl compounds (pronucleophiles) to the C≡N triple bonds of nitriles to afford enamines.[425,425a] Highly chemoselective activation of both the α-C–H bonds and the C≡N triple bonds of nitriles has been observed (Equation (72)). To activate simple alkane dinitriles, $IrH_5(P^iPr_3)_2$ has proved to be more effective (Equation (73)). The reaction likely proceeds through oxidative addition of the α-C–H bonds of pronucleophiles to iridium followed by selective insertion of the CN triple bonds to the Ir–C bond.



(72)



(73)

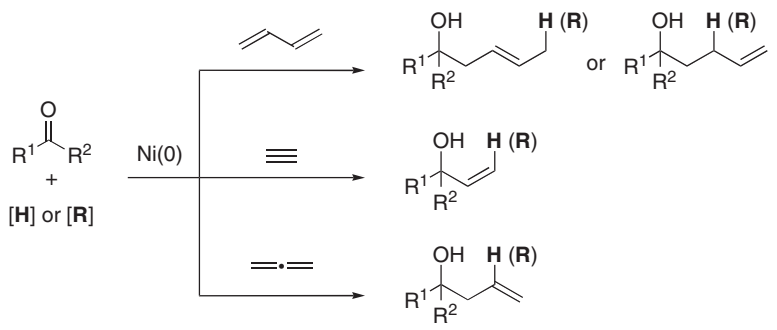
10.09.9 Group X Metals

10.09.9.1 Nickel

10.09.9.1.1 Addition to C═O

Nickel(0)-catalyzed reductive and alkylative additions of unsaturated carbon–carbon compounds (dienes, alkynes, and allenes) to carbonyl compounds have greatly advanced in the last decade (Scheme 84).[426] Extended studies have been made by groups of Mori,[427,427a–427i] Tamaru,[428,428a–428e] Montgomery,[429,429a–429i] Jamison,[430,430a–430f] and others.[431] Table 6 shows the classification of the modes of reactions. Although similar sets of the conditions were reported for these transformations, the reaction outcomes are dependent on combination of ligands and reagents.

For example, a dienyl aldehyde reductively cyclizes in the presence of an Ni(0)/PPh_3 complex and triethylsilane to give homoallylic cyclopropentanol with high regio- and stereoselectivities, while bishomoallylic cyclopropentanol is obtained as major product under the conditions using stoichiometric Ni(0)–diene complexes (Scheme 85).

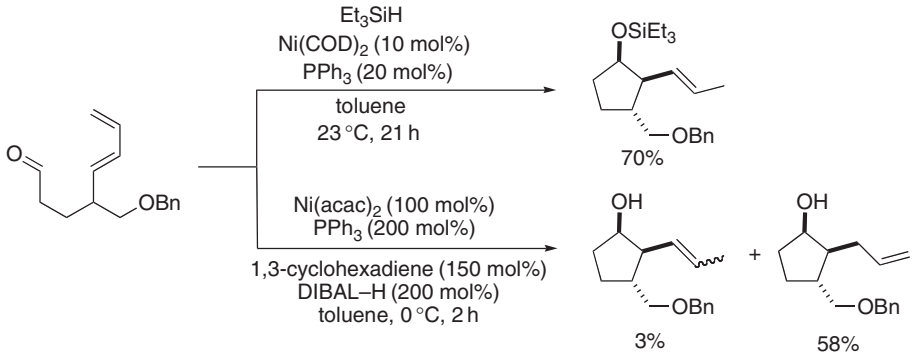


[**H**]: Reducting agents, [**R**]: alkylating agents

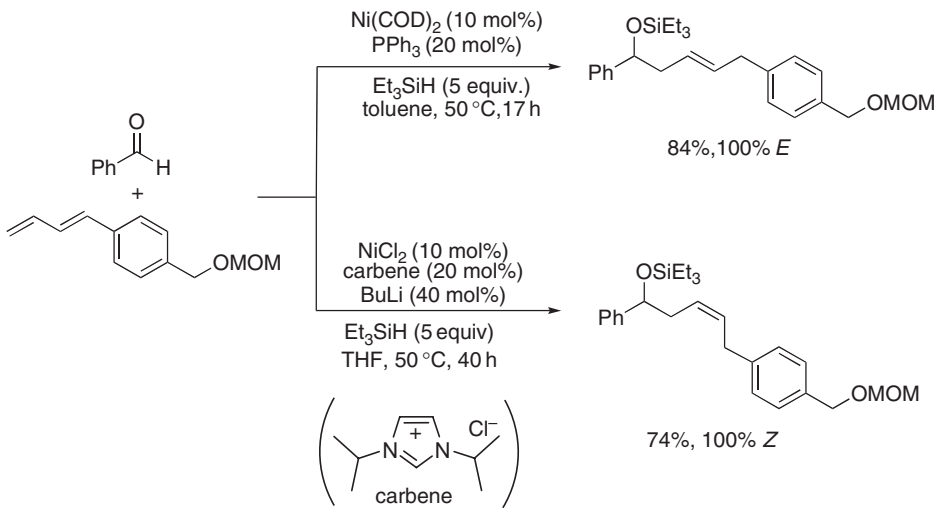
Scheme 84

Table 6 Classification of coupling reactions of carbonyl compounds

Mode of reaction	*Reagents*	*References*
Diene, intramolecular, reductive	Only Ni(0)	427,427a,427c,427e–427g
	Si–H	427,427b,427c,427g
	Al–^{i}Bu	427f,427g,427i
Diene, intramolecular, alkylative	Zn–Me	427f
	Al–Me	427f
Diene, intermolecular, reductive	Si–H	427d,427h,427i
	B–Et	428,428a,428d
	Zn–Et	428a,431
Diene, intermolecular, alkylative	Zn–R (R = Me or Ph)	428b,428e
	B–R (R = Me or Ph)	428b,428e
Alkyne, intramolecular, reductive	Si–H	429a,429c
	Zn–Et	429
	B–Et	429f,430b,430e
Alkyne, intermolecular, alkylative	Zn–R	429,429d–429f
	B–Et	430,430a,430c,430d
Alkyne, intermolecular, alkylative	Si–H	429g
	Zn–R	429h,429b
Allene, intramolecular, alkylative	Zn–R	429h,429i,431a
Allene, intermolecular, reductive	Si–H	430f



Scheme 85

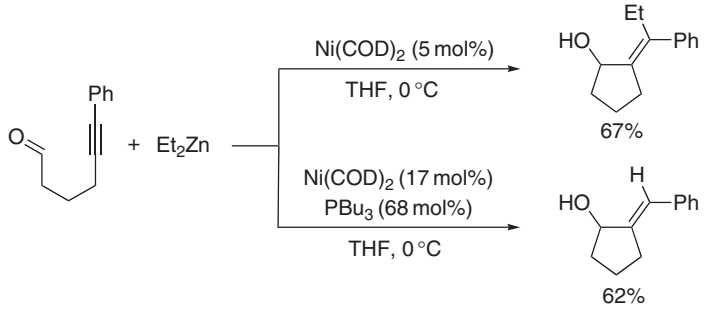


Scheme 86

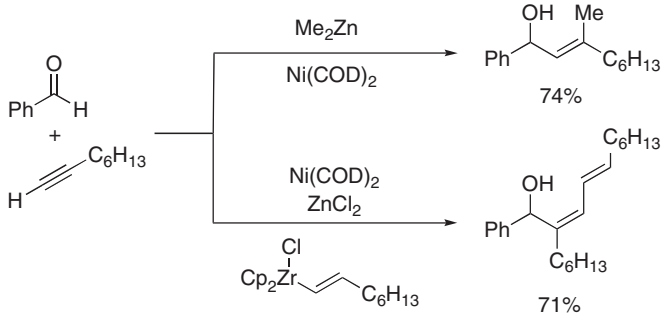
Meanwhile, the olefinic geometry is completely controlled by selection of suitable ligands (PPh_3 vs. heterocyclic carbene) and nickel sources (Scheme 86).

$Ni(COD)_2$ alone catalyzes intramolecular alkylative cyclization of an alkynal with diethylzinc, while $Ni(COD)_2/PBu_3$ catalyzes reductive cyclization with the same zinc reagent (Scheme 87).

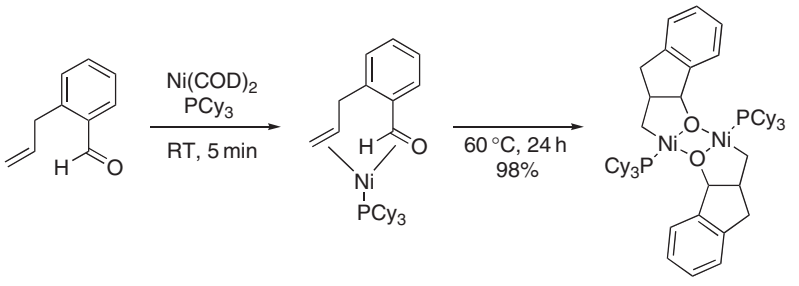
The opposite regioselectivity is observed in intermolecular alkylative coupling of terminal alkynes and aldehydes with diethylzinc and with alkenylzirconium/$ZnCl_2$ (Scheme 88).



Scheme 87



Scheme 88



191 **192**

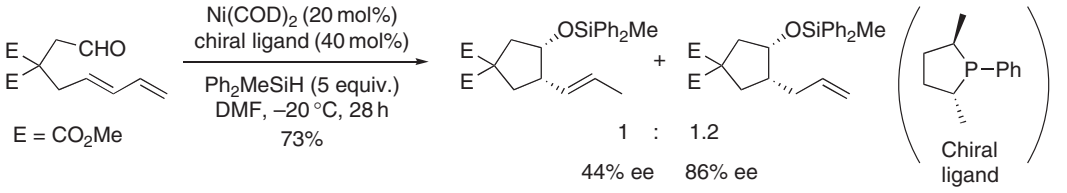
Scheme 89

In some cases, direct, uncatalyzed 1,2-addition of diethylzinc to aldehydes becomes a significant problem. Triethylsilane for intramolecular reactions or triethylborane for intermolecular reactions is often helpful to address this issue.

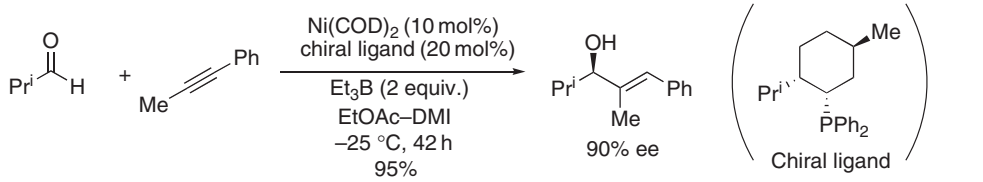
Two essentially different mechanisms, (i) oxidative cyclization of two π-components (formation of metallacycle) and (ii) oxidative addition of reducing or alkylating agents followed by insertion of π-components, can operate in these three-component reactions.[426] However, the aforementioned phenomena such as the reversal of regiochemistry and the crossover from reductive to alkylative manifolds remain unsolved.

In relation to the above mechanisms, direct observation of oxidative cyclizations of nickel–enal complexes such as **191** with $Ni(COD)_2/R_3P$ (1 equiv.) (R = Cy or Ph) to nickelacycles **192** was reported (Scheme 89).[432]

Enantioselective catalysts have been developed for cyclization of dienyl aldehydes and coupling of aldehydes with alkynes (Equations (74) and (75)). For reactions with dienes see Refs: 433 and 433a, and for reactions with alkynes see Refs: 433b–433e. Chiral monodentate phosphines have proved to be effective.

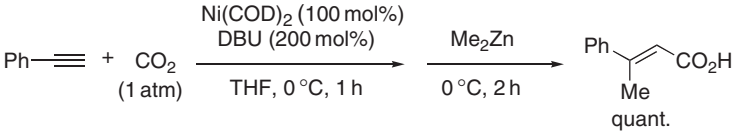


(74)

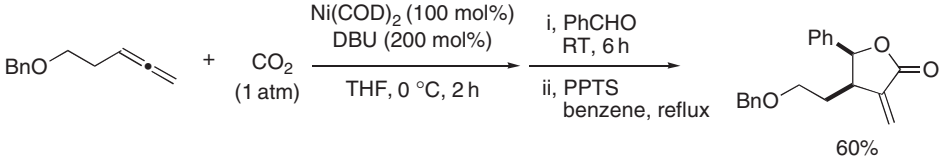


(75)

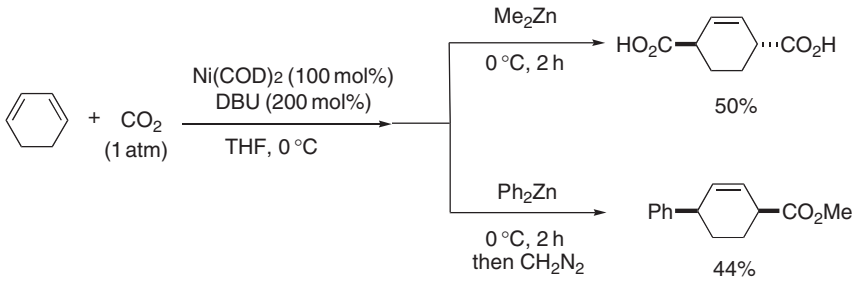
Carbon dioxide instead of aldehydes can be involved in Ni(0)-promoted reductive coupling reactions (Equations (76) and (77); Scheme 90).[434,434a–434c] A stoichiometric amount of $Ni(COD)_2$/DBU reacts with CO_2 and dienes, alkynes, or allenes to afford a metallacycle intermediate. This metallacycle reacts with organozinc compounds or aldehydes in one-pot to give carboxylic acid derivatives. As shown in Scheme 90, double carboxylation occurs in the presence of dimethylzinc, where the stereochemical outcome is opposite to that of the reaction with diphenylzinc.



(76)

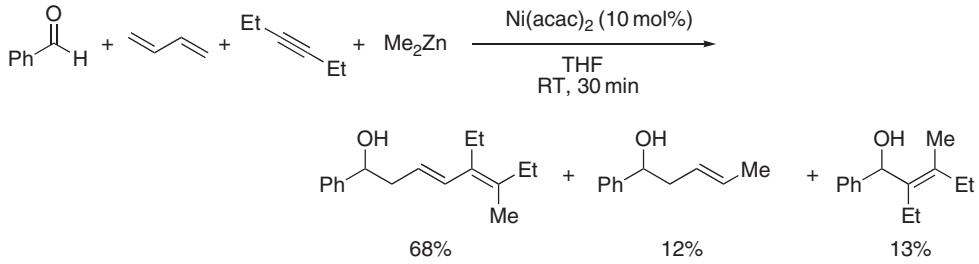


(77)



Scheme 90

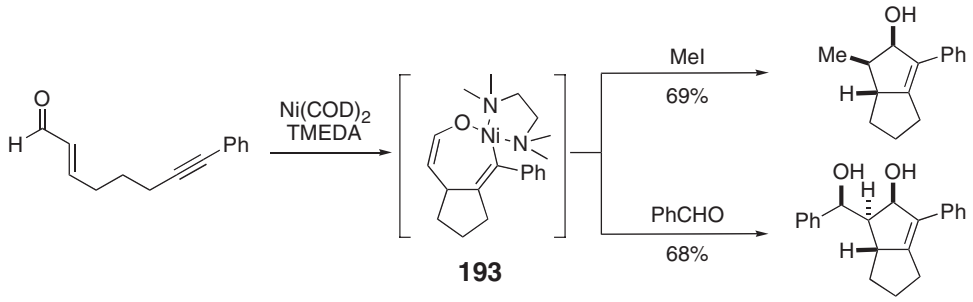
Recently, four-component coupling reactions of aldehydes, alkynes, dienes, and dimethylzinc catalyzed by a nickel complex have been reported (Equation (78)).[435] Similarly, 1,ω-dienynes react with carbonyl compounds and dimethylzinc in the presence of an Ni catalyst to afford the corresponding cyclized products.



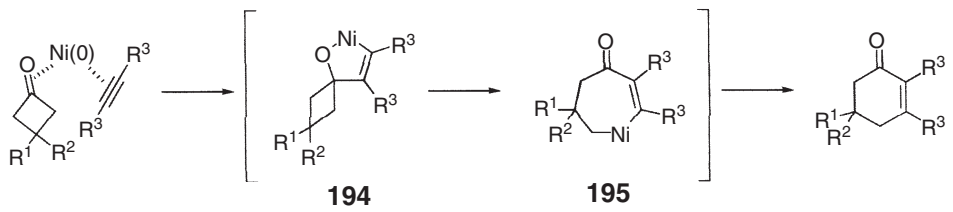
(78)

Alkynyl enals cyclize on treatment with a stoichiometric amount of Ni(COD)$_2$/TMEDA complex to give nickel enolates such as **193**.[436,436a] These metallacycles react with electrophiles including methyl iodide and benzaldehyde to yield cyclopentenol derivatives (Scheme 91).

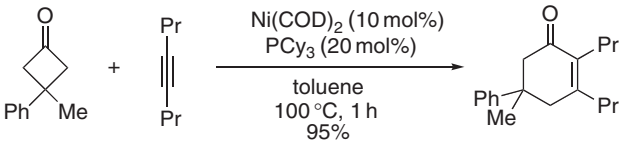
A nickel(0) complex catalyzes insertion of alkynes into cyclobutanones (Equation (79)).[437] Formation of metallacycle **194** via oxidative cyclization of an alkyne with the carbonyl group of a cyclobutanone followed by β-carbon elimination (formation of metallacycle **195**) and reductive elimination are postulated for the mechanism (Scheme 92).



Scheme 91

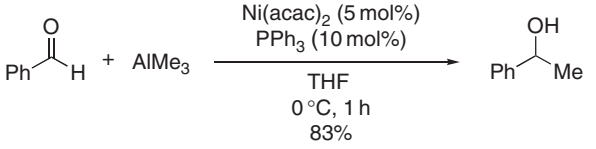


Scheme 92



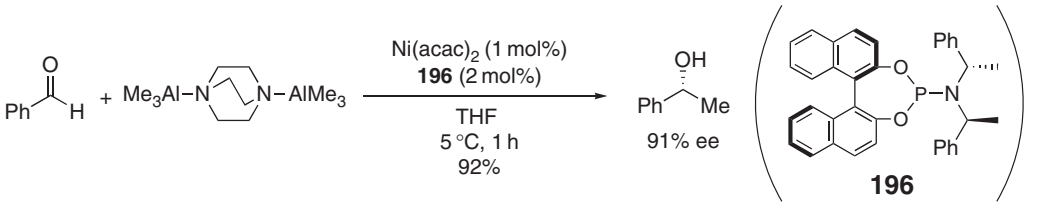
(79)

Methylation of aldehydes with trimethylaluminum is catalyzed by nickel complexes (Equation (80)).[438] Phosphine or phosphite ligands considerably accelerate the reactions.



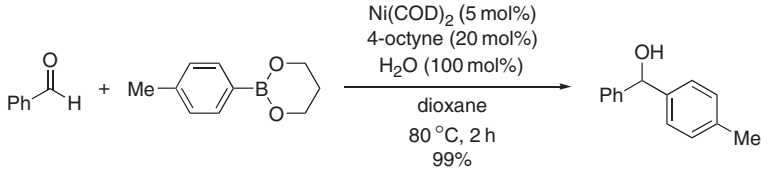
(80)

Woodward and co-workers recently achieved catalytic enantioselective alkylation of aldehydes with $(R_3Al)_2$·DABCO complexes or R_3Al (R = Me or Et) in the presence of Ni(acac)$_2$/Feringa's ligand **196** (Equation (81)).[439]



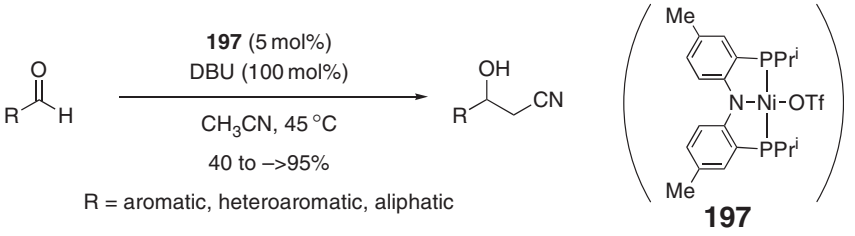
(81)

Aryl- or styrylboronates add to aldehydes in the presence of Ni(COD)$_2$/4-octyne/water (Equation (82)).[440] Interestingly, the alkyne and water are indispensable to attain high catalytic activity, though their roles are not yet clear. Glutaraldehyde can be used since the reaction tolerates water.



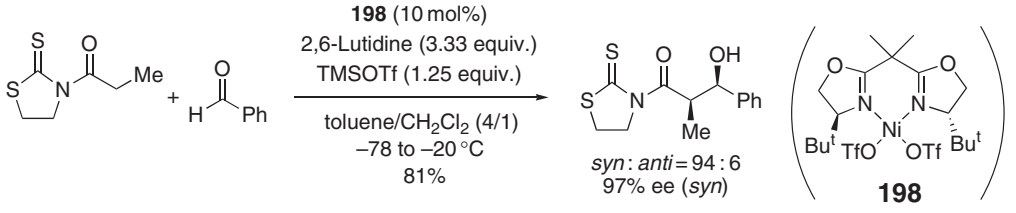
(82)

Nickel(II) complex **197** bearing a diarylamido-based PNP ligand is an efficient catalyst for addition of acetonitrile to aldehydes. The reaction proceeds at 45 °C in acetonitrile as solvent in the co-presence of 1 equiv. of DBU (Equation (83)).[441]

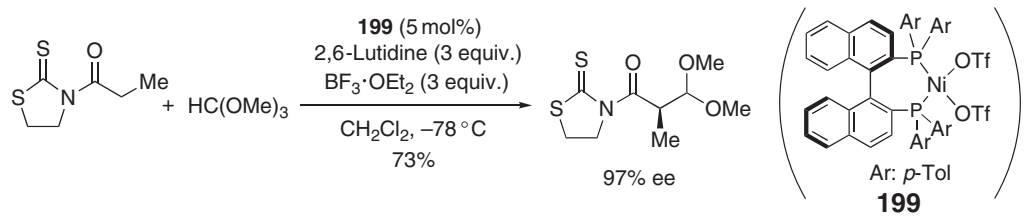


(83)

Evans *et al.* reported enantioselective addition of achiral *N*-acylthiazolidine thiones to C═O electrophiles catalyzed by chiral nickel complexes **198** and **199** (Equations (84) and (85)).[442,442a] *In situ* generation of chiral nickel enolates in the presence of a base is proposed.



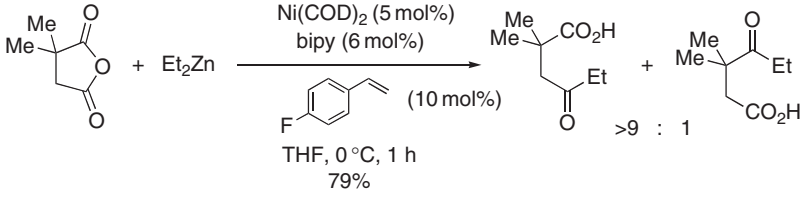
(84)



(85)

Electrochemical formation of allylnickel species and their addition to aldehydes were reported.[443,443a] Allylnickel(I) species generated via one-electron reduction of η^3-allylnickel(II) intermediates are considered as active nucleophilic species.

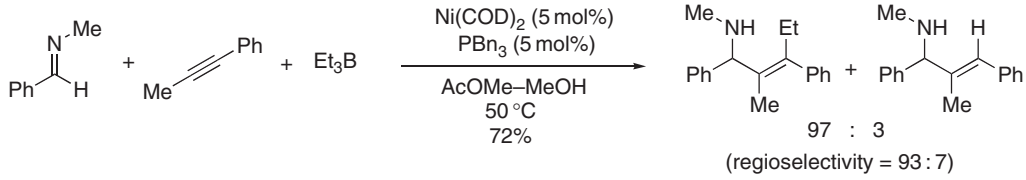
Cross-coupling of succinic and glutaric anhydrides with organozinc reagents is catalyzed by low-valent nickel complexes.[444,444a] Regioselective alkylation of an unsymmetrical succinic anhydride (Equation (86)) and a profound effect of electron-deficient styrene derivatives on the reaction rate suggest a mechanism involving oxidative addition of a cyclic anhydride into the nickel complex followed by transmetallation. Use of a chiral phosphino–oxazoline ligand allows enantioselective desymmetrization of glutaric anhydride.



(86)

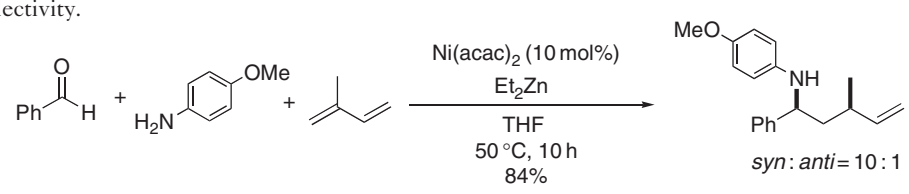
10.09.9.1.2 Addition to C═N

Jamison and Patel reported the reaction of imines with alkynes and organoboron reagents catalyzed by a nickel complex (Equation (87)).[445] Interestingly, triethylborane serves as alkylating agent in this case. Aryl- and alkenylboronic acids can be utilized as well. Although the selectivities are still moderate, enantioselective reactions are possible by using a chiral monophosphine as ligand.



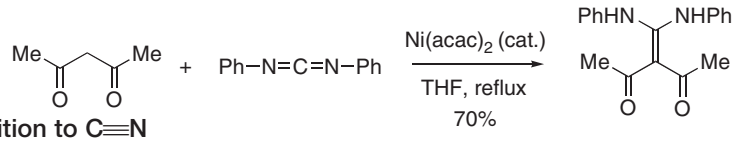
(87)

More recently, Tamaru and co-workers reported nickel-catalyzed reductive coupling of dienes with *in situ*-generated aldimines from aldehydes and amines (Equation (88)).[446,446a] The reaction exhibits high regio- and diastereoselectivity.



(88)

Nickel(II) acetylacetonate catalyzes the addition of acetylacetone or ethyl acetoacetate to carbodiimides (Equation (89)).[447] The acetylacetonate ligand of $Ni(acac)_2$ may react with a carbodiimide to give a nickel complex having a 3-substituted acetylacetonate, which is then protonated by another acetylacetone to afford an adduct and $Ni(acac)_2$.



(89)

10.09.9.1.3 Addition to C≡N

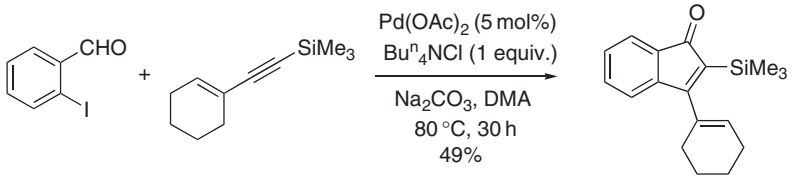
Diynes react with nitriles and aldehydes in the presence of a nickel(0) complex to give pyridines and dienones, respectively (Scheme 93).[448,448a,448b]

10.09.9.2 Palladium

Addition of organopalladium species (aryl-, vinyl-, allylpalladium and palladium enolates) to C═O and CN multiple bonds has enjoyed wide applications as the key step of various catalytic processes.

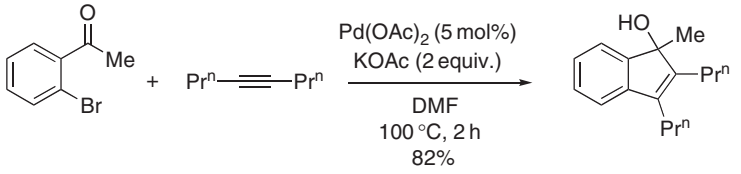
10.09.9.2.1 Addition to C═O and C═N

Although Heck and co-workers first reported the palladium-catalyzed formation of 3,4-diphenyl-1-indenone from *o*-iodobenzaldehyde and diphenylacetylene,[449] extended studies on this reaction were carried out by Larock *et al.*[450] Various types of internal alkynes reacted with *o*-iodo- or *o*-bromobenzaldehyde under conditions using $Pd(OAc)_2$, NaOAc or Na_2CO_3, Bu^n_4NCl in DMF or DMA. When unsymmetrical alkynes containing hindered groups such as trimethylsilyl are used, 1-indenones with those groups at the 2-position are obtained with high regioselectivity (Equation (90)).

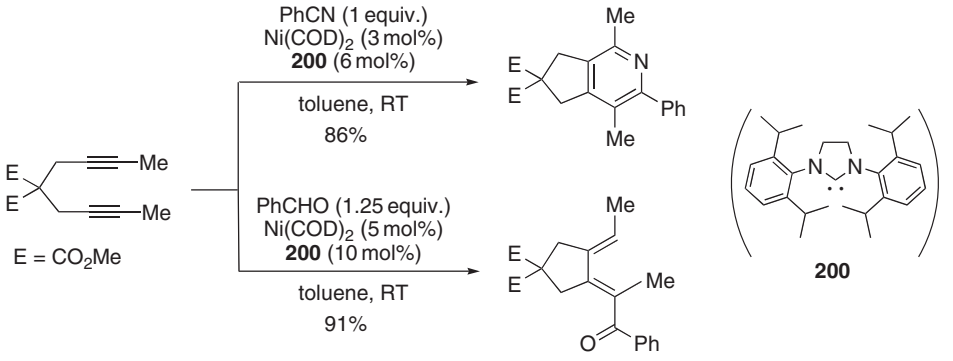


(90)

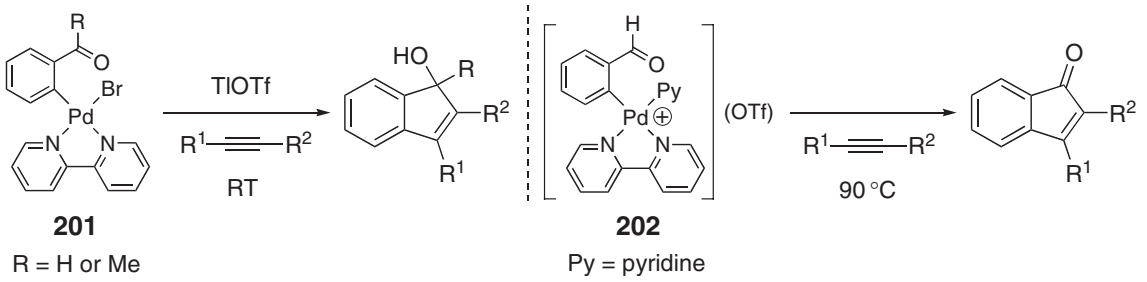
On the other hand, Yamamoto and co-workers found that indenols were obtained from *o*-bromoaryl ketones and internal alkynes in the presence of a palladium catalyst (Equation (91)).[451] They suggested a mechanism consisting of oxidative addition of the aryl halide to Pd(0), insertion of the internal alkyne, and intramolecular nucleophilic addition of the resulting vinylpalladium species to the carbonyl group. Even *o*-bromobenzaldehyde gave the indenol derivatives at lower temperature (60 °C) under the conditions using ethanol as an additive.[452] A possible inclusion of the transfer hydrogenation of indenones with ethanol was excluded by the observation of exclusive deuterium incorporation at the 1-position of the indenol in the reaction of deuterated *o*-bromobenzaldehyde (Equation (92)).



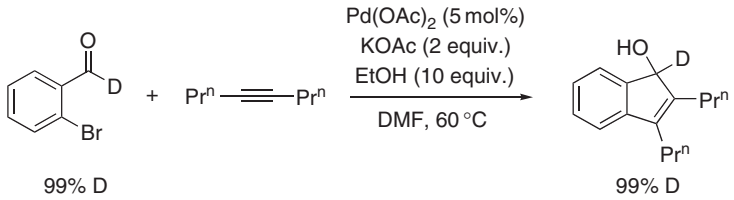
(91)



Scheme 93



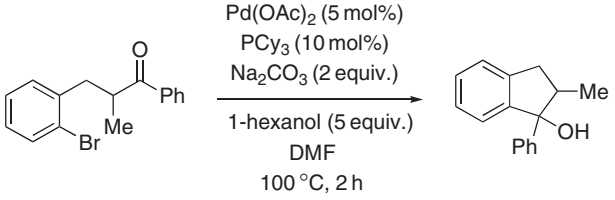
Scheme 94



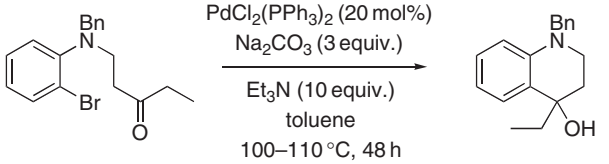
(92)

The reaction of 2-formyl- and 2-acetylarylpalladium(II) bromide complexes **201** with internal alkynes and TlOTf affords indenols at room temperature, whereas cationic 2-formylarylpalladium(II) pyridine complexes **202** do not react with alkynes at room temperature but afford indenones at 90 °C (Scheme 94).[453]

The nucleophilic addition of *in situ*-generated organopalladium species to C═O bonds can be further extended to the intramolecular addition of aryl halides to ketones.[454,454a–454c] Various types of *o*-halophenyl ketones cyclize under the conditions using $Pd(OAc)_2/PCy_3/Na_2CO_3$(KOAc)/1-hexanol in DMF (Equation (93))[454] or $PdCl_2(PPh_3)_2/Cs_2CO_3/Et_3N$ in toluene (Equation (94)).[454a,454b] The importance of 1-hexanol or triethylamine in the system may be attributed to their facilitation of the reduction of Pd(II) species to the Pd(0) catalyst species.

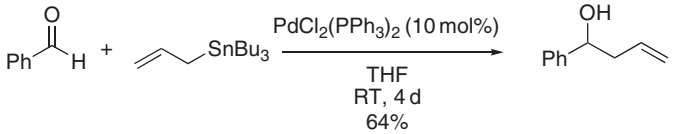


(93)



(94)

Formation of a bis-allylated product of 4-nitrobenzoyl chloride by the reaction with allyltrimethyltin in the presence of a benzylpalladium(II) complex was observed by Stille and co-workers in 1983.[455] Trost and King also reported allylation of aldehydes by allyltin reagents in 1990.[456] However, the precise mechanism was unclear until the extended studies were performed by Yamamoto and co-workers since 1995.[457,457a–457j] Aldehydes and imines react with allyltin reagents in the presence of a palladium catalyst (Equations (95) and (96)), and imines are chemoselectively allylated in the presence of aldehydes (Equation (97)).[457,457a,457b] Mechanistic studies using NMR spectroscopy proved that bis-π-allylpalladium complex **203** is a key nucleophilic intermediate (Figure 3).



(95)

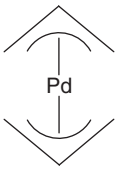
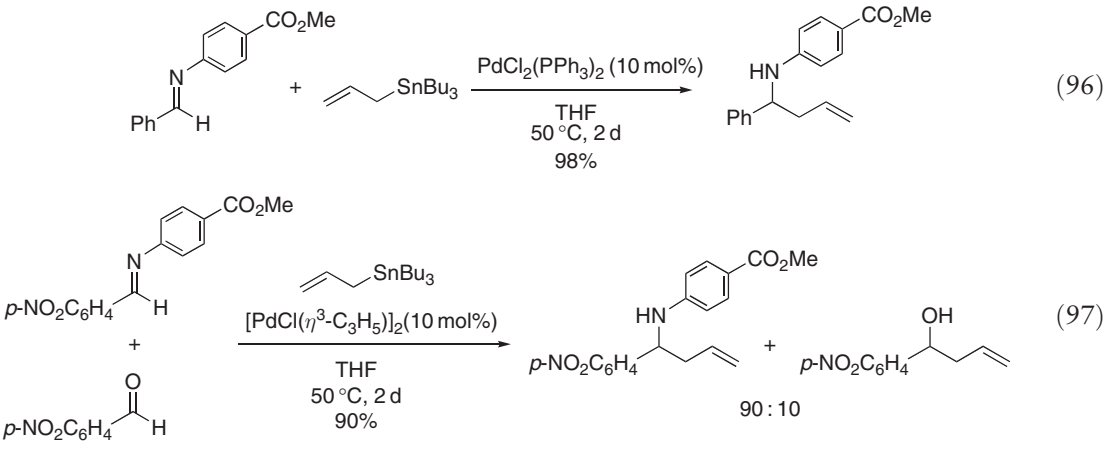
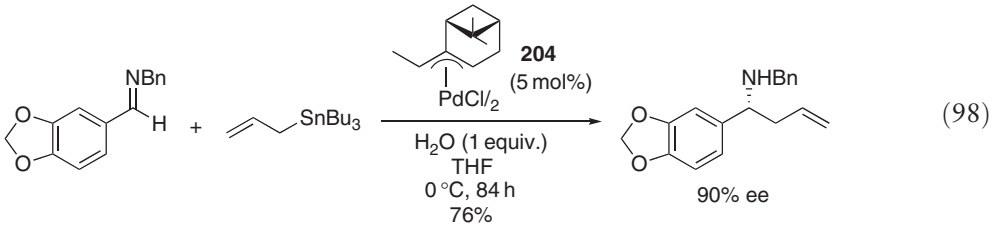


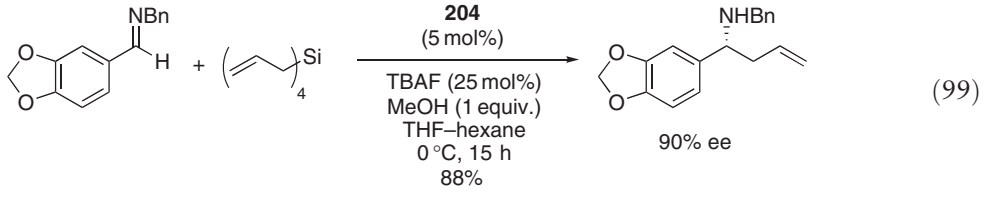
Figure 3 Bis-π-allylpalladium intermediate.



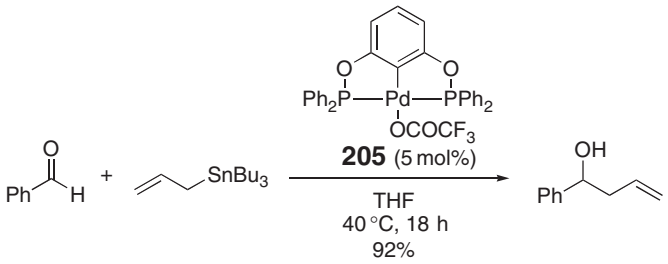
Accordingly, chiral π-allylpalladium complex **204** was found to catalyze enantioselective allylation of imines with good to high selectivity (Equation (98)).[457c,457e,457g,457i]



Allylsilanes serve as allylating agents in the presence of fluoride anions.[457d,457h] Notably, a tetraallylsilane/TBAF/MeOH system achieves shorter reaction time and higher yields and enantioselectivities compared to the procedure using allyltributyltin or allyltrimethylsilane (Equation (99)).[457h]

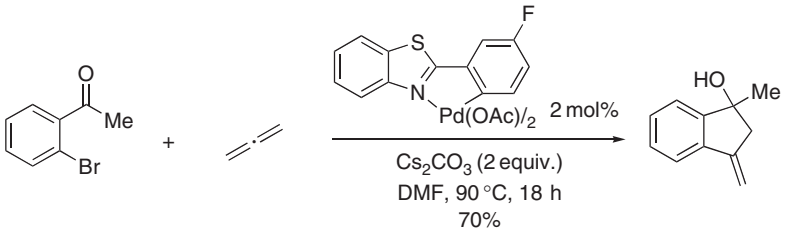


Related experimental and theoretical studies have been performed by the group of Szabó.[458,458a–458j] They revealed that palladium pincer complexes such as **205** show high catalytic activities (Equation (100)).[458d,g,i] Mono-η^1-allyl palladium pincer complexes are proposed to be active intermediates.

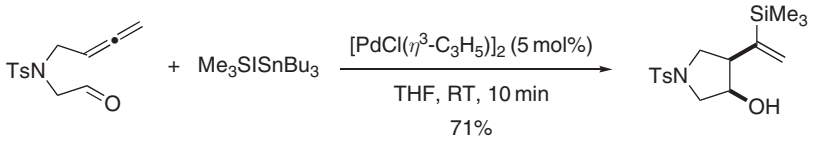


(100)

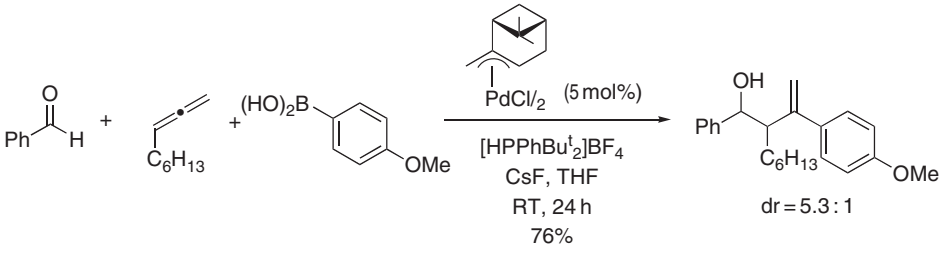
Arylative or silylative cyclizations of allenyl aldehydes or ketones have been reported (Equations (101) and (102)).[459,459a] The intermolecular process, that is, three-component coupling reaction of aldehydes, allenes, and arylboronic acids, is catalyzed by palladium as well (Equation (103)).[460,460a] These reactions are proposed to proceed through nucleophilic attack of the allylpalladium intermediates to the carbonyl groups.



(101)

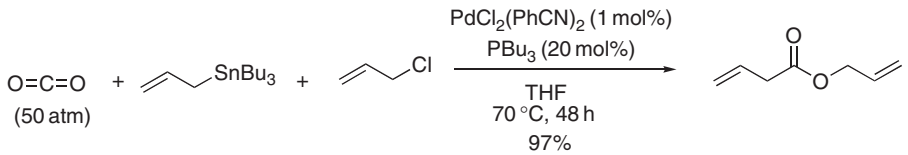


(102)

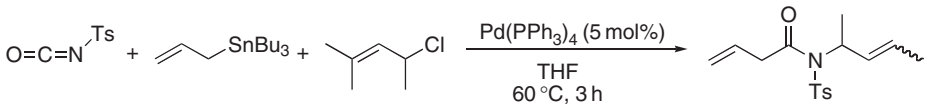


(103)

Palladium complexes effectively catalyze the three-component coupling reactions of CO_2[461] or isocyanates,[462,462a] allyltributyltin, and allyl chloride to afford allyl 3-butenoate or *N*-tosyl-*N*-allyl-3-butenamides, respectively (Equations (104) and (105)).



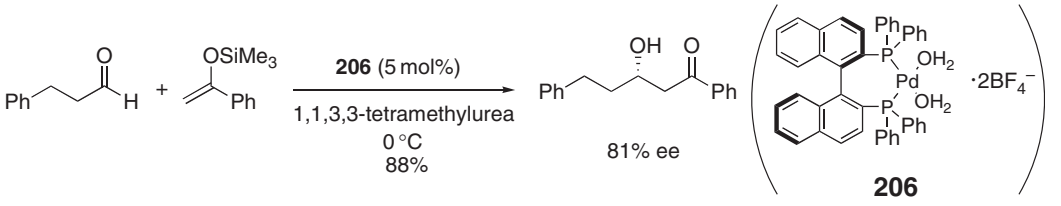
(104)



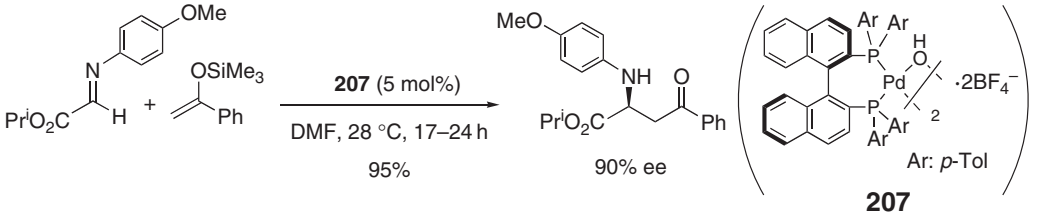
(105)

Preparation of palladium enolates and their reactions (β-hydride elimination to enones, migratory insertion to C–C multiple bonds, reductive coupling with allyl or aryl groups, etc.) have been reported. However, the nucleophilic addition of palladium enolates to C═O and C═N bonds has been little investigated.[463]

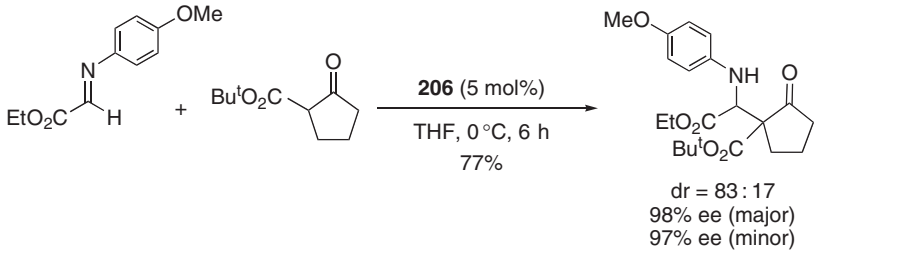
Sodeoka and co-workers have reported enantioselective aldol and Mannich reactions (Equations (106) and (107)).[464,464a–464e] Involvement of palladium enolates was confirmed by ^{1}H NMR and ESI-MS spectrometry. β-Keto esters (pronucleophiles) directly add to imines with high selectivity without preformation of silicon enolates (Equation (108)).



(106)

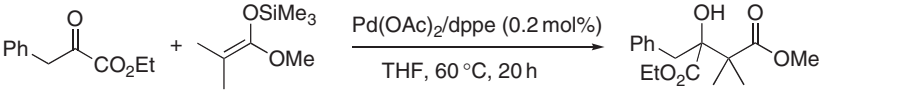


(107)



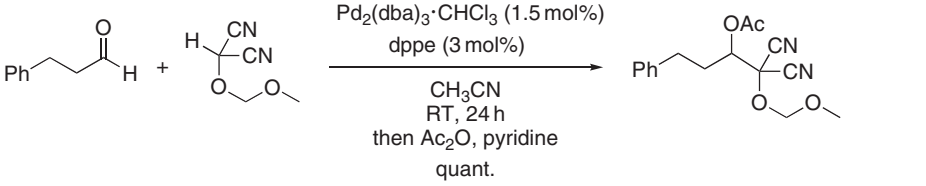
(108)

Addition of ketene silyl acetals to aldehydes and ketones is also mediated by achiral palladium(II) acetate–diphosphine complexes (Equation (109)).[465,465a] Although the precise mechanism is still unclear, high catalytic activity may be ascribed to the intermediacy of palladium enolates.



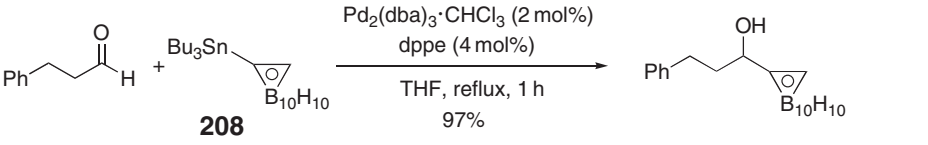
(109)

In relation to palladium enolates, Yamamoto and co-workers reported palladium-catalyzed addition of malononitrile derivatives to imines or aldehydes (Equation (110)).[466,466a] Oxidative addition of the C–H bond of the malononitrile to Pd(0) followed by insertion of an electrophile is proposed.



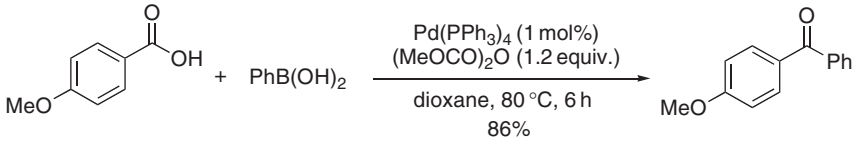
(110)

Addition of 1-carboranyltributyltin **208** to aldehydes is catalyzed by palladium(0) (Equation (111)).[467] Addition of simple organotin compounds has not been reported.



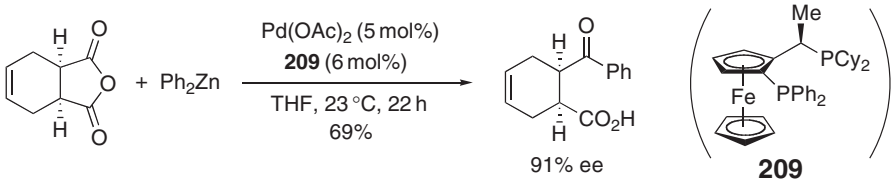
(111)

Palladium complexes catalyze the formation of ketones from carboxylic acid derivatives and organometallic reagents. (From acid chlorides, see a review;[158] from thioesters, see Refs: 468, 468a–468b; and from aryl trifluoroacetates, see Ref: 468c.) Oxidative addition of acid derivatives to a palladium catalyst followed by transmetallation of an organometallic reagent and reductive elimination are generally accepted as the mechanism. Recently, direct synthesis of aryl ketones from carboxylic acids and arylboronic acids was reported.[469,469a–469d] In the presence of dimethyl dicarbonate and a Pd catalyst, carboxylic acids and arylboronic acids are directly converted to aryl ketones in high yield (Equation (112)).[469c]



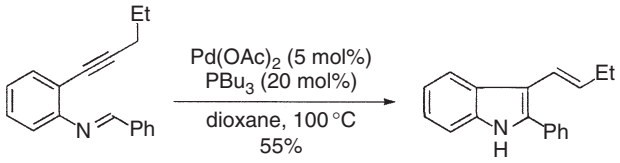
(112)

Enantioselective desymmetrization of *meso*-succinic anhydrides with diphenylzinc is catalyzed by $Pd(OAc)_2$/chiral diphosphine **209** (Equation (113)).[470]



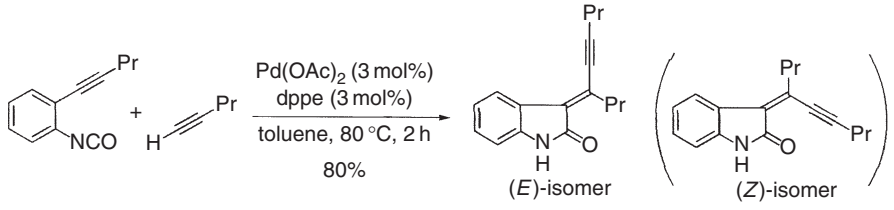
(113)

Cyclization of 2-(1-alkynyl)-*N*-alkylidene anilines is catalyzed by palladium to give indoles (Equation (114)).[471] Two mechanisms are proposed: the regioselective insersion of an H–Pd–OAc species to the alkyne moiety (formation of a vinylpalladium species) followed by (i) carbopalladation of the imine moiety and β-hydride elimination or (ii) oxidative addition to the imino C–H bond and reductive coupling.



(114)

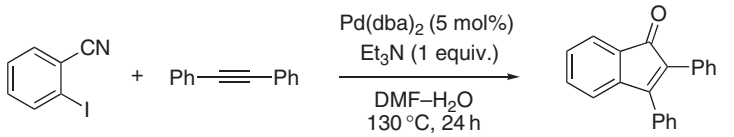
A related cyclization of 2-(alkynyl)phenylisocyanates with terminal alkynes to oxindoles was also reported by the same group (Equation (115)).[472] (*E*)-*exo*-olefinic oxoindoles are selectively obtained. It was proposed that a palladium acetylide generated by the C–H activation of terminal alkynes regioselectively inserts to the alkyne moiety and the resulting vinylpalladium intermediate adds to the C═O part of the isocyanate to give a (*Z*)-oxindole. This (*Z*)-isomer is isomerized to the (*E*)-isomer under the reaction conditions through catalysis of the phosphine.



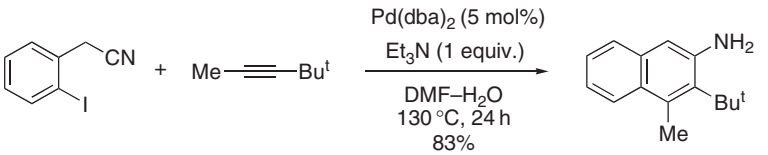
(115)

10.09.9.2.2 Addition to C≡N

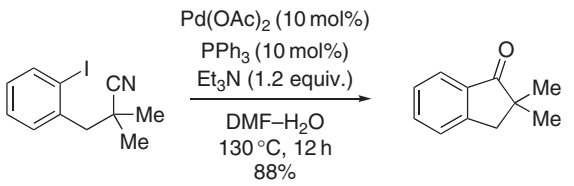
Larock *et al.* reported the palladium-catalyzed reactions of alkynes and nitriles with 2-iodophenyl group (Equations (116)–(118)).[473,473a–473c] Ketones and naphthylamines are obtained presumably through the formation of vinylpalladium species followed by their addition to nitriles to afford palladium imine intermediates.



(116)

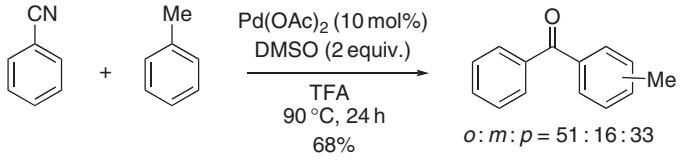


(117)



(118)

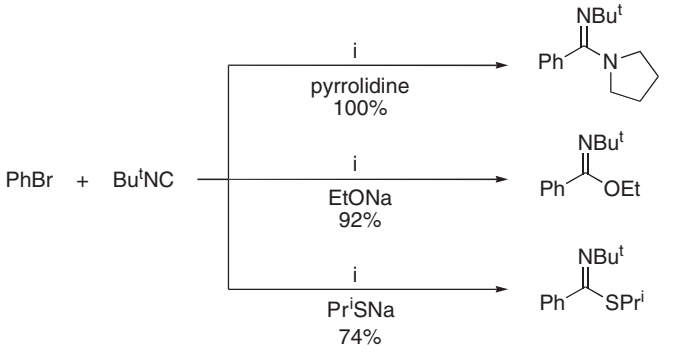
Recently, synthesis of aryl ketones by a combination of palladium-catalyzed C–H activation of arenes and intermolecular carbopalladation of nitriles has been reported (Equation (119)).[474]



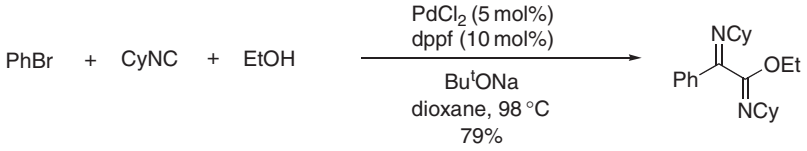
(119)

In 1977, Ito *et al.* reported that stoichiometric reactions of organopalladium species with isonitriles gave imino-acylpalladium complexes, which then afforded ketenimines on treatment with DBU.[475] It was later reported that palladium-catalyzed coupling reactions of aryl halides, isonitriles, and tin compounds[476] or alkylboron reagents[477] gave the corresponding imino compounds or ketones (after hydrolysis). More recently, heteroatom nucleophiles proved to serve as the third components instead of tin or boron reagents. Amines, alkoxides, and thiolalkoxides react with aryl or vinyl halides and isonitriles in the presence of a palladium catalyst to give amidines, imidates, and thioimidates, respectively (Scheme 95).[478,478a–478c] Intramolecular reactions of amines or alcohols possessing 2-bromophenyl group give cyclic amidines or imidates as well.

Interestingly, by using an alcohol (5.0 equiv.)/Bu^{t}ONa (1.2 equiv.) instead of an alkoxide (5.0 equiv.), double isonitrile insertion takes place to give α-iminoimidates (Equation (120)).[479]

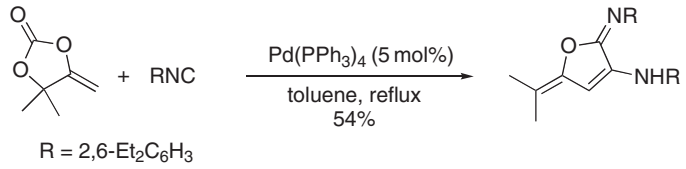


Scheme 95



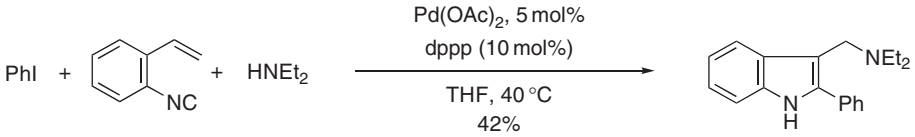
(120)

5,5-Dimethyl-4-methylene-1,3-dioxolan-2-one reacts with isonitriles in the presence of a palladium catalyst to afford iminofurans (Equation (121)).[480] Successive insertion of isonitriles to the carbon–palladium bond of π-allylpalladium intermediate is postulated.



(121)

The 2,3-substituted indols are formed via a palladium-catalyzed coupling reaction of aryl halide, *o*-alkenylphenyl isocyanide, and amine (Equation (122)).[481] Oxidative addition of an aryl halide, insertion of both the isonitrile and alkene moieties of *o*-alkenylphenyl isocyanide, and 1,3-hydrogen migration may form a π-allylpalladium species, which is then attacked by an amine to afford an indol.



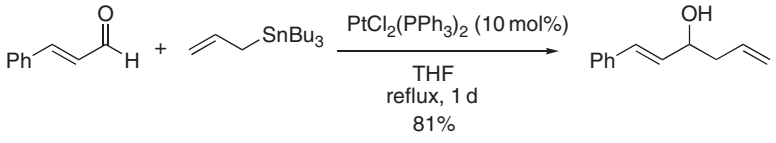
(122)

10.09.9.3 Platinum

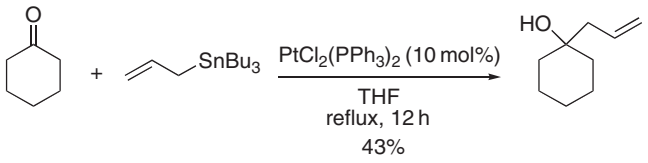
Nucleophilic addition of organoplatinum compounds to carbonyls and CN multiple bonds has been little investigated in comparison with those of organopalladium compounds.[482]

10.09.9.3.1 Addition to C═O

Platinum-catalyzed allylation of aldehydes with allyltin reagents was first reported in 1995.[457,457b,483,483a] Aromatic, aliphatic, α,β-unsaturated aldehydes and even cyclohexanone undergo allylation with allyltributyltins in the presence of $PtCl_2(PPh_3)_2$ in THF at room temperature or higher temperature (Equations (123) and (124)). Allylplatinum species are considered to be the active intermediates on the basis of related mechanistic studies on palladium catalysis.

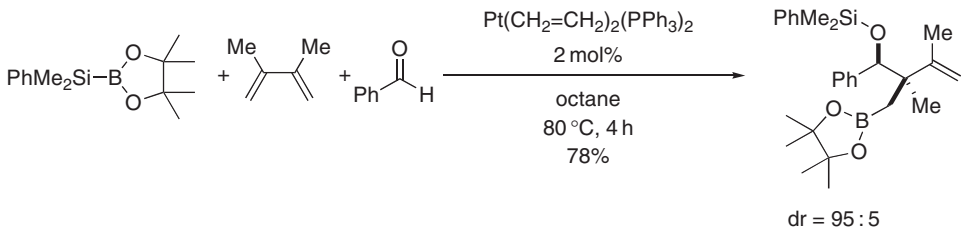


(123)



(124)

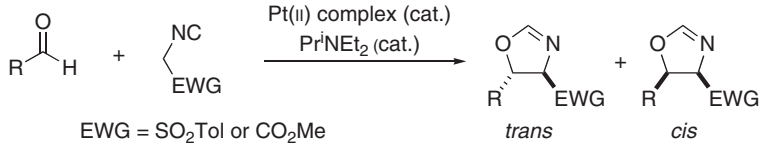
Allylplatinum intermediates generated in the course of silaboration of dienes readily react with aldehydes to give homoallylic alcohols (Equation (125)).[484] The observed high diastereoselectivity is explained by a chair-like cyclic transition state.



(125)

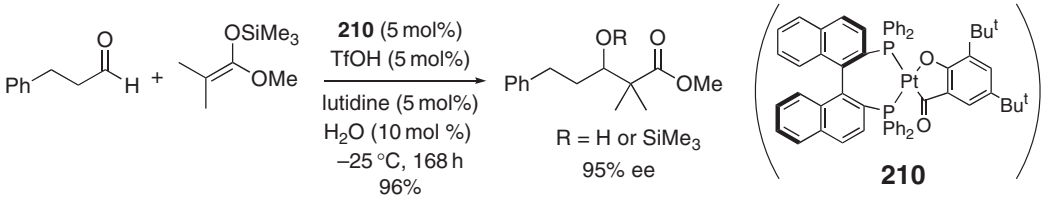
Platinum complexes effectively catalyze three-component coupling reactions of CO_2, allyltributyltin, and allyl chloride to afford allyl 3-butenoate as well as palladium complexes (see Equation (104)).[461]

Aldol reactions of isocyanides with aldehydes are catalyzed by cationic platinum complexes having P–C–P or N–C–N ligands in the presence of a catalytic amount of an amine base to give 2-oxazolines (Equation (126)).[485,485a,485b] Platinum-coordinated α-isocyano carbanions presumably serve as nucleophiles toward aldehydes. Low to moderate enantioselectivities were obtained by using chiral platinum complexes.[485,485a]



(126)

Chiral bis-phosphine acylplatinum complex **210** with a strong acid such as TfOH serves as an effective enantioselective catalyst for aldol-type reactions of aldehydes with ketene silyl acetals (Equation (127)).[486] The presence of water and oxygen in the catalyst preparation step is required to obtain the highly enantioselective catalyst. The intermediacy of a *C*-bound platinum enolate was suggested by IR and ^{31}P NMR spectroscopies.



(127)

10.09.10 Group XI Metals

10.09.10.1 Copper

Organocopper reagents have been widely used in organic chemistry since the first report of Gilman-type reagents because of their unique nature, which is not to be seen in Grignard reagents or lithium compounds.[487] Conjugate addition of organocopper reagents is the most important and characteristic process among various organocopper-mediated reactions. Grignard reagents and organolithium compounds react with α,β-unsaturated carbonyl compounds to give a mixture of 1,2- and 1,4-addition products, whereas organocopper reagents afford, in general, 1,4-addition products predominantly. In these reactions, it is proposed that Cu(III) is involved as the intermediate complex although the mechanism is still unclear. In addition to conjugate addition reactions, S_N2 substitution reactions of alkyl, alkenyl, and aryl carbons also make use of organocopper reagents. Many aspects of organocopper reagents were well reviewed.[488,488a]

The addition reactions of organocopper reagents to carbon–heteroatom unsaturated bonds, the topic of this chapter, have been mainly used when Grignard reagents or organolithium compounds would result in side-reactions such as additions to ester groups because of their higher nucleophilicities than organocopper reagents. This chapter covers recent examples of organocopper reagents and copper enolate-mediated catalytic asymmetric additions to aldehydes.

10.09.10.1.1 Stoichiometric use of copper

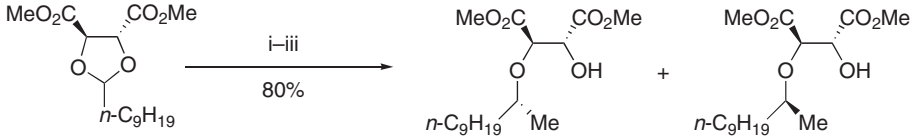
Ring-opening reactions of tartrate acetal **211** with cuprates and dialkyl boron bromides were conducted (Scheme 96).[489] The reaction proceeds stereoselectively in favor of the formation of **212**. Ester groups are tolerant to these reaction conditions.

β-Substituted (*N*-Boc)-β-aminoaldehydes **213** were reacted with organocopper reagents, and stereoselectivities were compared with those obtained when Grignard reagents and organolithium compounds were employed.[490] The *anti*-selectivity was substantially increased by using organocopper reagents, as shown in Scheme 97.

High stereoselectivity was also observed in the reaction of organocopper reagents **215** with the aldehyde moiety of (η^4-diene)$Fe(CO)_3$ complexes **214** (Scheme 98).[491]

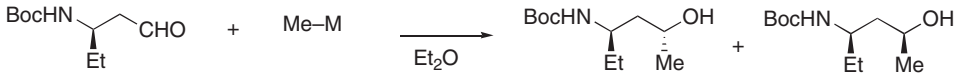
Highly functionalized organocopper reagents can be used as shown in the following schemes. In the total synthesis of (+)-laurencin, silylated enyne organocopper reagent **219** was used for an addition to aldehyde **218** (Scheme 99).[492] Although the selectivity was low, this copper chemistry serves for the facile assembly of a highly functionalized molecule in relatively few steps.

Propargylic dithioacetal **220** was reported to serve as an allene 1,3-zwitterion synthon (Scheme 100).[493,493a] The organocopper intermediate **222** generated by treatment of dithioacetal **220** with organocopper reagent **221** can react with a number of electrophiles. When an aldehyde was used as an electrophile, **222** afforded alcohol **223** leading to the formation of furan derivative **224** after cyclization by eliminating the sulfur moiety. An imine also reacted with **222** to produce pyrrole derivative **226** via an amine intermediate **225**.[494]



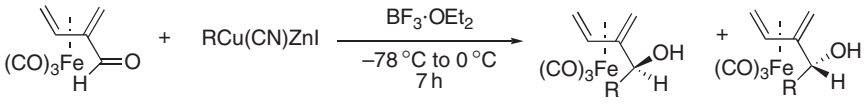
i, Me_2BBr, –78 °C; ii, –78 °C to 25 °C, then to –30 °C; iii, $Me_2Cu(CN)Li_2$

Scheme 96



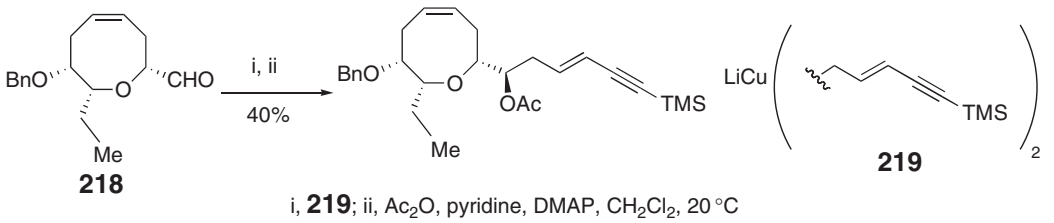
Me–M	*Temp.* (°C)	*Yield* (%)	*anti* : *syn*
MeLi	–80 °C to –20 °C	78	48 : 52
$Me_2CuLi{\cdot}LiI$	–90 °C	74	85 : 15

Scheme 97

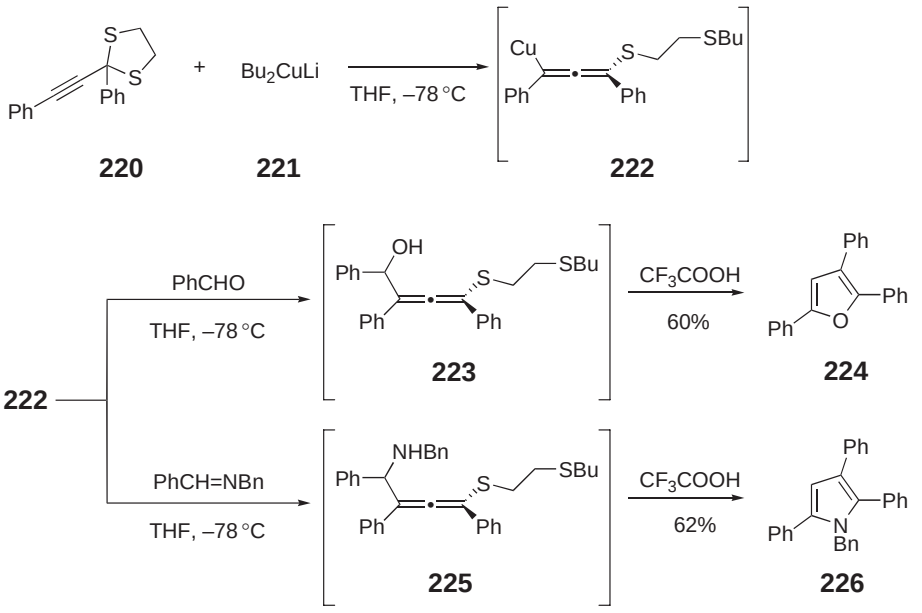


RCu(CN)ZnI	**216** : **217**	*Yield* (%)
R = $(CH_2)_3CN$	92 : 8	93
R = $(CH_2)_3CO_2Et$	90 : 10	76

Scheme 98



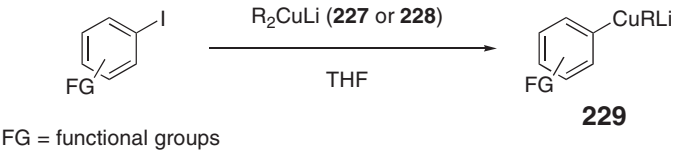
Scheme 99



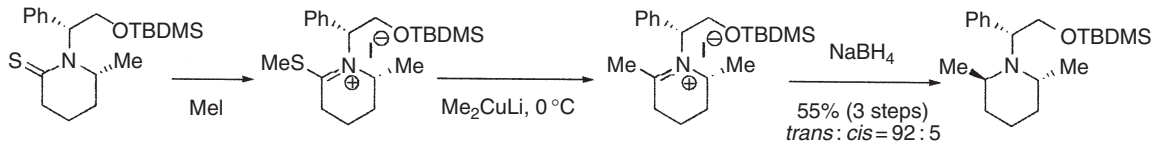
Scheme 100

In the chemistry of organometallic compounds, compatibility with reactive functional groups, especially electrophilic groups, is always a concern. Although organomagnesium compounds, which bear ester, nitrile, amino, or nitro groups, have been developed,[495] more sensitive groups like ketones and aldehydes are not compatible with carbon–magnesium bonds. In 2002, a preparation method for organocopper reagents which bear ketones or even aldehydes was disclosed by Knochel and Piazza[496] Sterically hindered lithium dialkylcuprates like lithium dineopentylcuprate ($neopent_2CuLi$, **227**) and $(PhMe_2CCH_2)_2CuLi$ **228** react with functionalized aromatic iodides to give copper reagents **229** (Scheme 101).

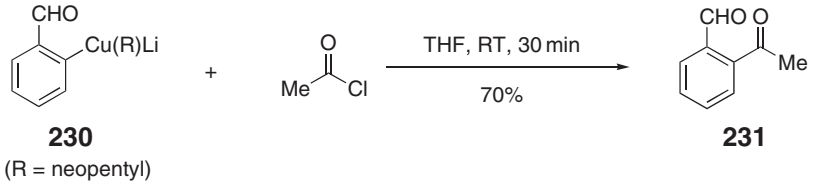
One example for the reaction of a **229**-type copper reagent is shown in Equation (128). Neopentyl-substituted organocopper reagent **230**, which bears aldehyde, is generated followed by treatment with acetyl chloride to provide coupling product **231** in 70% yield. Application of this method to the selective functionalization of polyhalogenated aromatics was also reported.[497]



Scheme 101

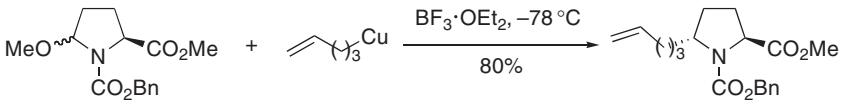


Scheme 102

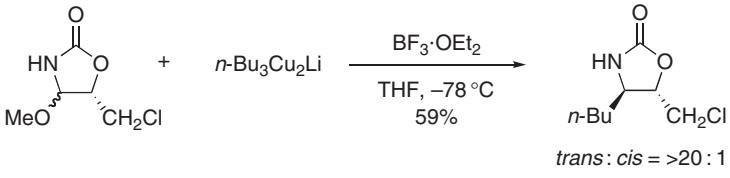


(128)

Addition of organocopper reagents to imine derivatives can readily afford functionalized amine derivatives. Three recent examples are shown below (Equations (129) and (130); Scheme 102).[498,498a,498b] In these cases, iminium ions are employed as an activated imine.



(129)

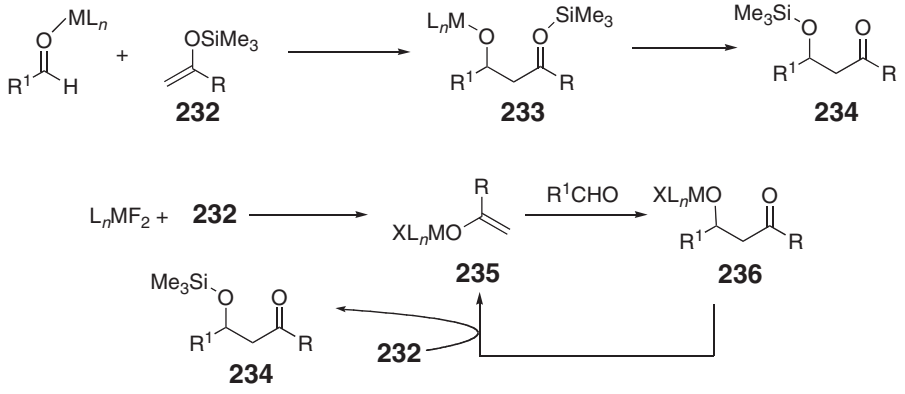


(130)

10.09.10.1.2 Catalytic use of copper

Though organocopper reagents such as Gilman-type or Lipshutz-type reagents have been widely used to date, there have been only a few reports concerning the catalytic use of a copper source.

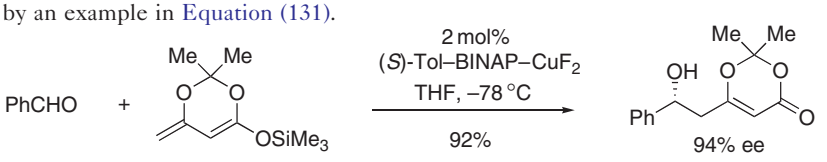
Carreira and Krüger reported facile transmetallation of silicon enolates to other soft metal enolates including Cu derivatives.[499] They reasoned that the use of soft metal fluoride complexes enabled silyl metal transmetallation with catalytic use of a soft metal source. The concept is illustrated in Scheme 103. Normal Lewis acid-catalyzed reactions of silicon enolates with aldehydes proceed via activation of aldehydes by carbonyl oxygen coordination to Lewis acids, as shown in the upper equation of Scheme 103. A key step for catalytic turnover is the desilyation of **233** by the



Scheme 103

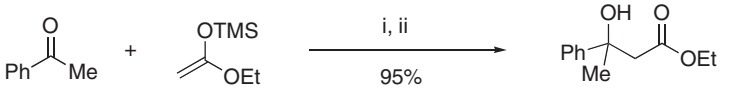
generated metal alcoholate. In contrast, soft metal fluorides generate metal enolates **235**, which react with aldehydes to produce metal alcoholate intermediate **236** (lower equation of Scheme 103). Metal alcoholate **236** leads to the formation of product **234** by exchange of metal with silicon, which regenerates metal enolate **235**.

Catalytic enantioselective dienolate additions to aldehydes were realized by Tol–BINAP–Cu(II) fluoride complexes as shown by an example in Equation (131).

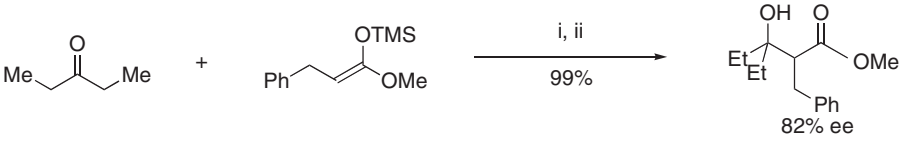


(131)

Shibasaki *et al.* also developed catalytic reactions of copper, some of which can be applied to catalytic asymmetric reactions. Catalytic aldol reactions of silicon enolates to ketones proceed using catalytic amounts of CuF (2.5 mol%) and a stoichiometric amount of $(EtO)_3SiF$ (120 mol%) (Scheme 104).[500] Enantioselective alkenylation catalyzed by a complex derived from CuF and a chiral diphosphine ligand **237** is shown in Scheme 105.[501] Catalytic cyanomethylation by using $TMSCH_2CN$ was also reported, as shown in Scheme 106.[502]

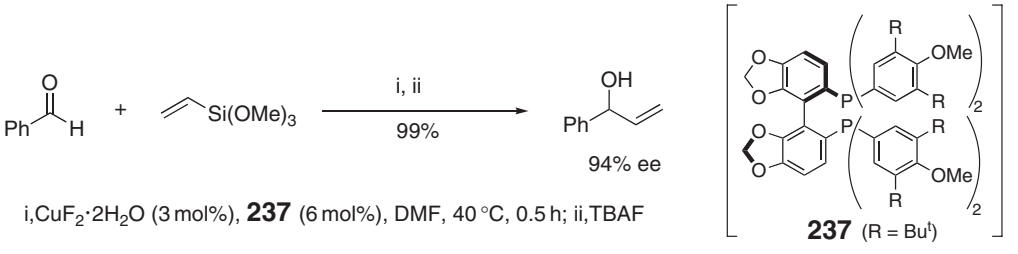


i, CuF·3PPh$_3$·2EtOH (2.5 mol%), $(EtO)_3SiF$ (120 mol%), 2 h, THF, RT; ii, 3HF·NEt$_3$



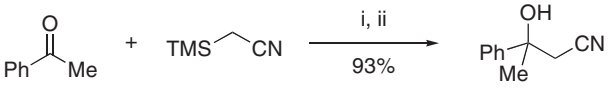
i, CuF·3PPh$_3$·2EtOH (2.5 mol%), (*S*)-*p*-Tol–BINAP (5 mol%), $(EtO)_3SiF$, THF, –20 °C, 24 h; ii, 3HF·NEt$_3$

Scheme 104



i,CuF_2·2H$_2$O (3 mol%), **237** (6 mol%), DMF, 40 °C, 0.5 h; ii,TBAF

Scheme 105



i, CuF·3PPh$_3$·2EtOH (2.5 mol%), $(EtO)_3SiF$ (120 mol%), 12 h, THF, RT; ii, 3HF·NEt$_3$

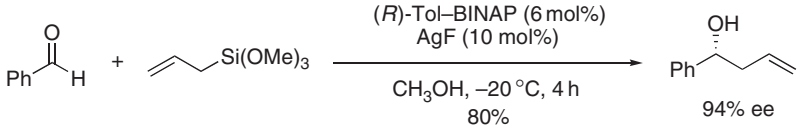
Scheme 106

10.09.10.2 Silver

The use of organosilver reagents in organic synthesis has not been well studied compared to organocopper compounds. Also, as a catalyst for the purpose of coupling, silver has not received much attention although very recently several silver-catalyzed reactions such as aza-Diels–Alder reactions,[503,503a,503b] asymmetric aldol reactions,[504,504a,504b] couplings,[505,505a,505b] cyclizations[506] and allylations[507,507b] have been reported.

10.09.10.2.1 Silver enolates

Some silver enolates were reported to be formed and used, although not for addition to carbon–heteroatom unsaturated bonds.[508,508a] Yamamoto *et al.* reported that chiral allylic silver species are generated from allylic trimethoxysilanes by *in situ* transmetallation and that addition of allylic silver species to aldehydes occurs in good yields with high enantioselectivities (Equation (132)).[509,509a] In this report, they confirmed that when crotyltrimethoxysilane was treated with a mixture of BINAP·AgF and DMF in CH_3OD, no peaks of the crotylsilane were observed in the ^{13}C NMR spectrum, that is, transmetallation from silicon to silver occurred.



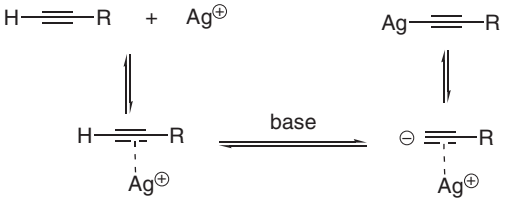
(132)

10.09.10.2.2 Silver acetylenides

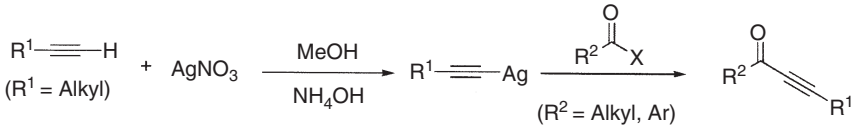
Silver belongs to the late transition metals and, like gold, favors coordination to C≡C triple bonds. A lot of silver-containing organometallic complexes, where silver–alkyne interactions assist the assembly of the complexes, are known. None of these complexes, however, was applied to efficient carbon–carbon bond formation in organic synthesis.

Silver acetylenide is an organosilver reagent that is relatively widely employed in organic synthesis because it can be generated under mild conditions by taking advantage of the strong affinity of silver to C≡C triple bonds.[510,510a] Moreover, their hydrolytic stability and wide functional group tolerance, which are not typical of analogous compounds of active metals, encourage synthetic organic chemists to use silver acetylenides. The mechanism for the silver–acetylene carbon bond formation is proposed as shown in Scheme 107.[511] A weak base such as NH_4OH works well for their formation in general.

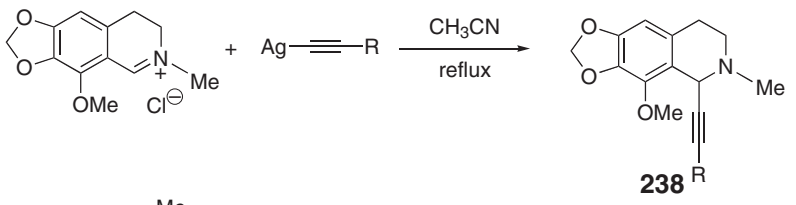
The preparation of acetylenic ketones from soluble silver acetylenides and acid chlorides was reported in 1956 (Scheme 108).[512] Analogously to that report, the reaction of silver acetylenides with acylpyridinium salts was reported to proceed effectively.[513] This chemistry was applied to the synthesis of cotarnine derivatives, as exemplified in Scheme 109.[514,514a]



Scheme 107



Scheme 108



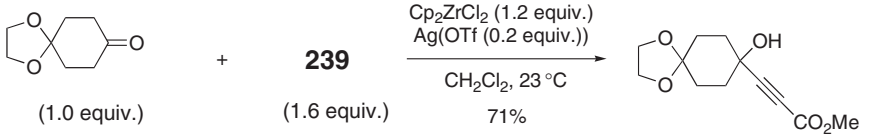
238a 238b 238c

238	*Yield* (%)
238a	66
238b	46
238c	75

Scheme 109

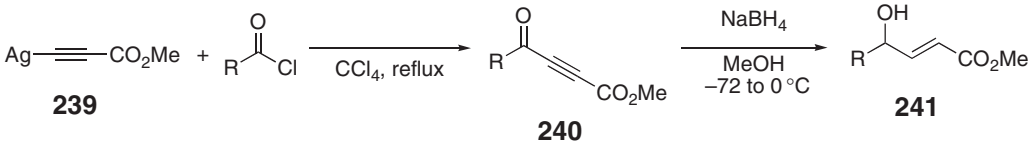
The γ-hydroxy-α,β-(*E*)-alkenoic esters were prepared readily from acid halides and silver acetylenides followed by $NaBH_4$ reduction (Table 7).[515]

Silver acetylenide **239** was found to react with aldehydes (Table 8) and the ketone in Equation (133) by using a stoichiometric amount of Cp_2ZrCl_2 and a catalytic amount of AgOTf at room temperature to afford the corresponding γ-hydroxy-α,β-acetylenic esters in high yields.[516]



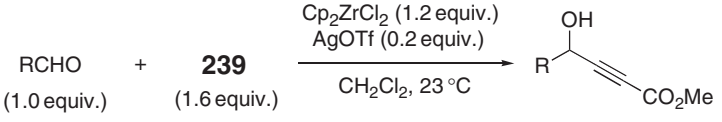
(133)

Table 7 Reaction of silver acetylenide **239** with acid chlorides



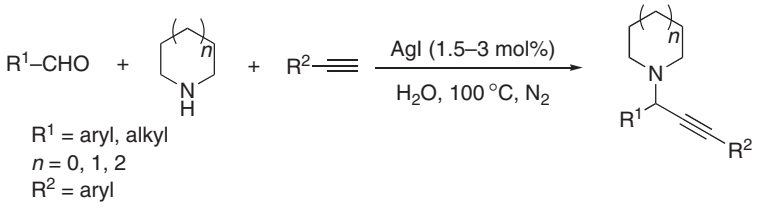
Acylhalide	*Time* (h)	*Yield of* **240** (%)	**241** (%)	*Yield* (%)
R = Me	3	50	R = Me	70
R = *c*-Hex	3	89	R = *c*-Hex	63
R = *t*-Bu	3	99	R = *t*-Bu	47
R = Ph	48	61	R = Ph	60

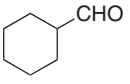
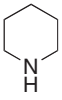
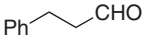
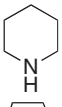
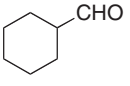
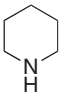
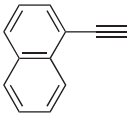
Table 8 Cp_2ZrCl_2/AgOTf-promoted alkynylation of aldehydes

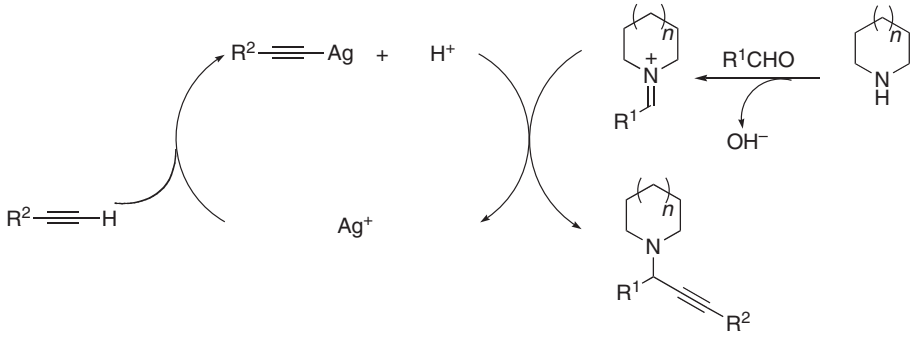


R	*Time* (h)	*Yield* (%)
Ph	10	84
CH_3	4	53
Cy	1	78

Table 9 Coupling of aldehydes, alkynes, and amines catalyzed by AgI in water



Aldehyde	*Amine*	*Alkyne*	*Yield* (%)
			96
			85
			95
			89



Scheme 110

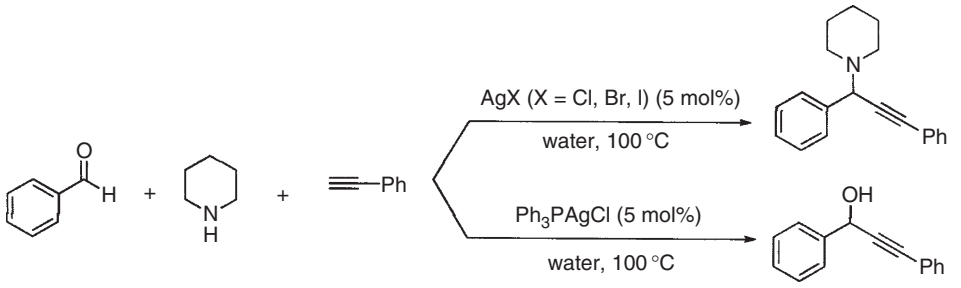
Catalytic coupling reaction of aldehydes, alkynes, and secondary amines promoted by less than 3 mol.% of Ag(I) salt was reported by Li *et al.*[517] In this reaction, pure water was used as solvent and AgI was found to be the best catalyst without need of any additives or co-catalysts (Table 9). The reaction mechanism has been proposed as shown in Scheme 110.

This system also worked well in ionic liquids.[518] Li *et al.* found silver–phosphine complexes to promote aldehyde–alkyne coupling in water. When triphenylphosphinesilver chloride was used as a catalyst in water, the only detected product was the aldehyde addition product instead of the adduct derived from imine (Scheme 111).[519]

Chan *et al.* reported a similar reaction, that is, Ag(I)-catalyzed alkynylation of α-imino esters (Table 10).[520] The β,γ-alkynyl α-amino acid derivatives were obtained in high yields.

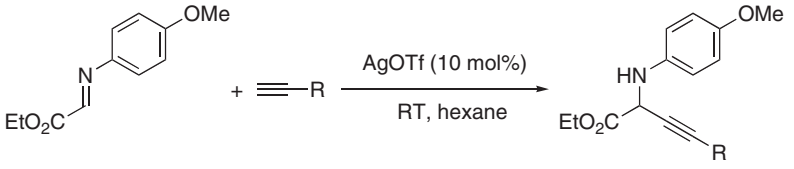
10.09.10.3 Gold

While main group metals and early transition metals are hard Lewis acids favoring coordination of carbonyl groups, gold, one of the late transition metals, is classified as a soft metal that activates π-electron systems like olefins and



Scheme 111

Table 10 AgOTf-catalyzed addition of terminal alkynes to α-imino ester



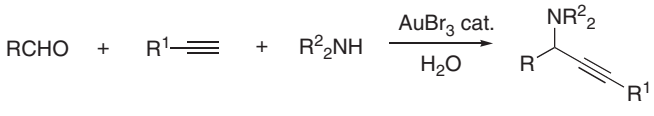
R	*Time* (h)	*Yield* (%)
Ph	0.5	93
$PhCH_2CH_2$	0.5	87
n-butyl	0.5	84
n-hexyl	0.5	91
$TMSCH_2$	1	79

C≡C triple bonds. Although there have been a number of organogold complexes reported, applications to organic synthesis have not been extensively explored. Recently some groups utilized gold complexes as catalysts in organic synthesis where C═C double bonds or C≡C triple bonds coordinate to the gold catalysts and are subsequently subjected to nucleophilic attacks to form C–Au bonds.[521] However, there is only one report where a tentative mechanism that organogold reagents attack carbon–heteroatom unsaturated bonds is proposed.[522]

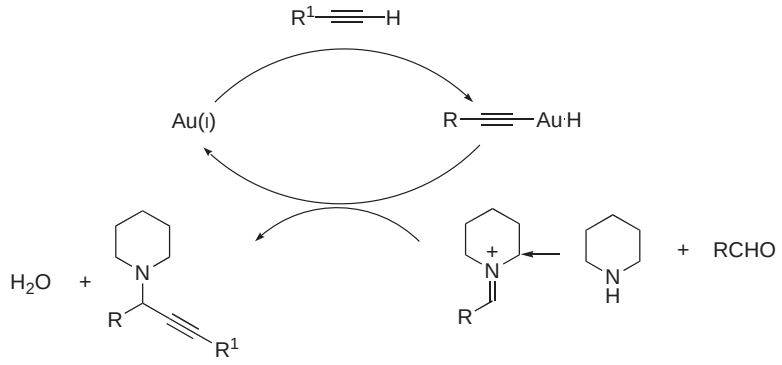
10.09.10.3.1 Addition to C═N

As shown in Table 11 and Scheme 112, a C–H bond of terminal alkynes is activated by an Au(I) species producing gold acetylenide intermediates, which react with immonium ions generated *in situ* from aldehydes and secondary amines to provide propargylamines in high yields. This reaction proceeds in water with 1 mol.% of Au(I) or Au(III)

Table 11 Coupling of aldehydes, alkynes, and amines catalyzed by gold in water



Aldehyde	*Amine*	*Yield* (%)
PhCHO	piperidine	>99
p-MeC_6H_4CHO	piperidine	87
PhCHO	$HN(allyl)_2$	95
$CH_3(CH_2)_9CHO$	piperidine	53



Scheme 112

catalyst (Au(III) species is reduced *in situ* by an alkyne molecule to generate Au(I) species which works as a real catalyst).

10.09.11 Conclusive Remarks

The last decade has witnessed many examples of C–C bond formations through addition of transition metal organometallics to C═O and CN multiple bonds, and the number of publications, dealing with this issue, is still growing. Although various elegant, catalytic reactions have been developed, most transformations still require the use of more than stoichiometric amounts of expensive and potentially toxic transition metal sources. Therefore, and from an environmental point of view, catalytic use of these transition metal complexes has been strongly desired. In this endeavor, ligands attached to transition metal complexes play a key role, and development of truly catalytic reactions using transition metal complexes will retain increasing attention. Importanly, continuous mechanistic studies might lead to conceptually new, catalytic reactions. Since C–C bond formation via addition of organometallic compounds to C═O and CN multiple bonds is highly important to construct (chiral) organic molecules, truly efficient catalysis including asymmetric versions thereof will further make an impact on organic synthesis in near future.

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10.10 Metal-catalyzed Reductive Carbocyclization (C═C, C≡C, C═O Bonds)

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10.10.1 Introduction and Scope

Beginning with the Fischer–Tropsch reaction (1922)[1,1a–1d] and alkene hydroformylation (1938),[2] catalytic methods for the reductive coupling of π-unsaturated reactants began to appear in the chemical literature nearly a century ago.[3,3a–3c] While these processes have long been applied to the industrial manufacture of commodity chemicals,[4] catalytic reductive C–C bond formation has only just begun to find traction in the context of fine chemical synthesis.[5] The recent renaissance in metal-catalyzed reductive coupling is linked to the broader availability of mild terminal reductants in particular silanes, which provide an alternative to elemental hydrogen. Indeed, the first examples of "non-hydrogen-mediated" metal-catalyzed reductive C–C bond formation, which involve the hydrosilylative dimerization of conjugated dienes,[6,6a–6f] appeared in 1969 – approximately 16 years after the first reported metal-catalyzed alkene hydrosilylation.[7,7a] Following these seminal studies, the area of catalytic reductive C–C bond formation has undergone explosive growth, culminating in the emergence of a unique field of research encompassing a remarkably diverse range of transformations. Accordingly, several excellent monographs that include metal-catalyzed reductive C–C bond formation are now reported.[5,8,8a–8m,16a] (For selected reviews encompassing catalytic reductive carbocyclization, see Refs: 8, 8a–8m.)

In this review, an attempt is made to exhaustively catalog the rapidly growing subset of metal-catalyzed reductive C–C bond formations comprising the hydrometallative and hydrogenative carbocyclization of π-unsaturated substrates, and application of these methods in target-oriented synthesis. Content is organized on the basis of reaction

type, and is categorized further on the basis of catalyst type (e.g., early transition metals, group III metals and lanthanides, and late transition metals). Reductive cyclization involving σ-bond activation is not covered. Hence, reductive Heck cyclizations,[9,9a–9c] Nozaki–Hiyama–Kishi-type cyclizations,[8d,8e,8f,10] intramolecular nucleophilic allylations of carbonyl groups,[11,11a,11b] and reductive cyclizations involving epoxides[12,12a–12c] are not cited in this review. Additionally, carbometallative reductive cyclizations and related multicomponent cascade or "domino" reactions,[5,8h,8k,13,13a] and reductive cyclizations that do not incorporate at least one hydrogen atom, such as distannylative cyclization,[14,14a–14m] fall outside the scope of this review. Finally, the cyclization of substrates that incorporate the terminal reductant into their structure, as exemplified by intramolecular alkene hydrosilylation,[15,15a–15c] represent cycloisomerizations and, hence, are not covered.

10.10.2 Reductive Cyclization Involving C═C and C≡C π-Bonds

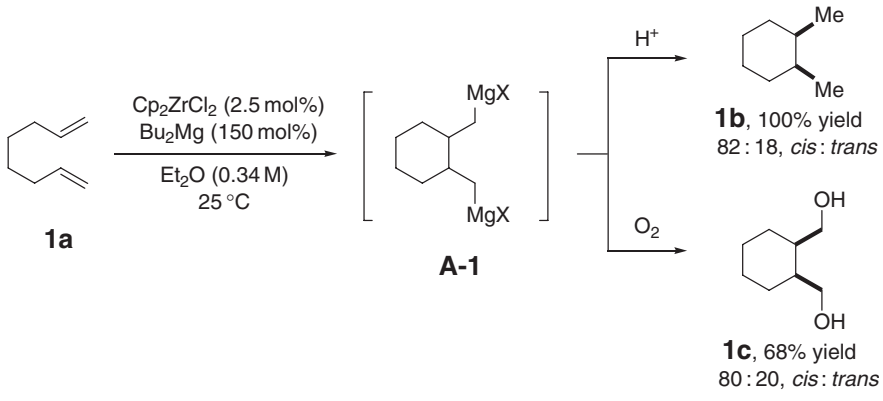
10.10.2.1 Reductive Cyclization of 1,5-, 1,6-, and 1,7-Dienes

10.10.2.1.1 Early transition metal catalysts

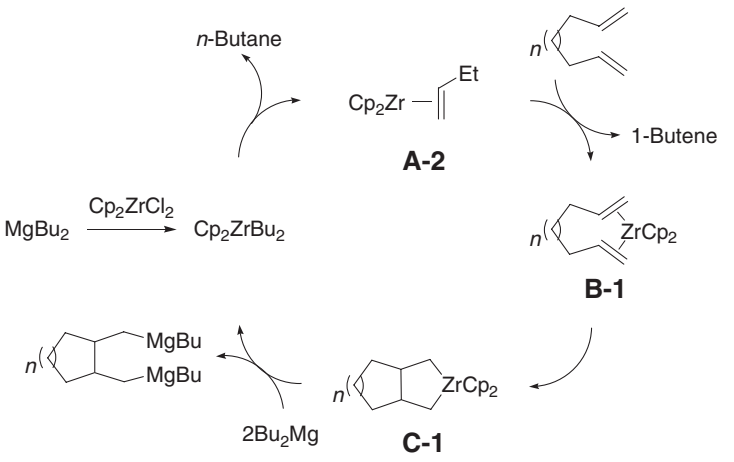
The transition metal-catalyzed cycloisomerization of 1,6- and 1,7-dienes has received considerable attention, and is the subject of several excellent reviews.[16,16a,16b] Corresponding catalytic reductive cyclizations are less developed.[5,8,8a–8m] The first reductive carbocyclizations of 1,6- and 1,7-dienes were performed using stoichiometric loadings of low-valent titanocene and zirconocene complexes.[17,17a,17b] Motivated by Dzhemilev's 1983 report of the zirconocene-catalyzed carbometallation of alkenes using dialkylmagnesium reagents,[18,18a–18c] the first catalytic reductive cyclizations of 1,6- and 1,7-dienes were described by Waymouth.[19,19a,19b] Exposure of 1,7-octadiene **1a** to substoichiometric quantities of zirconocene dichloride in the presence of excess dibutylmagnesium or butyl Grignard reagents provides the 1,2-disubstituted bis(magnesiomethyl)cyclohexane **A-1**, which may be proteolytically cleaved to provide 1,2-dimethylcyclohexane **1b** or exposed to elemental oxygen to afford the corresponding diol **1c**. Subsequent studies by Negishi revealed that subtle changes in reaction conditions can dramatically alter the outcome of the zirconocene-catalyzed reaction to favor formation of cyclized mono(magnesiomethyl) products or acyclic products that arise from independent carbomagnesiation of each alkene of the diene (Scheme 1).[20]

The mechanism proposed for the zirconocene-catalyzed reductive cyclization of 1,6- and 1,7-dienes is as follows. In analogy to the stoichiometric generation of zirconocene,[21] Cp_2ZrCl_2 reacts with the organomagnesium reagent to form Cp_2ZrBu_2, which undergoes β-hydride elimination to afford the zirconium(II)-butene complex **A-2**. Displacement of 1-butene by the substrate provides the diene complex **B-1**, which undergoes oxidative cyclization to furnish metallacyclopentane **C-1**. Transmetallation with the organomagnesium reagent cleaves the zirconium–carbon bond of the metallacyclopentane **C** to deliver the bis(magnesiomethyl)carbocycle and regenerate Cp_2ZrBu_2 to close the catalytic cycle (Scheme 2).

Studies of the reaction kinetics at low concentrations of dibutylmagnesium ($\leq$0.35 M) reveal a first-order dependence of reaction rate on both zirconocene and dibutylmagnesium concentration, which is consistent with rate-determining transmetallation. At higher concentration of dibutylmagnesium ($\geq$0.35 M), the reaction is first order in



Scheme 1



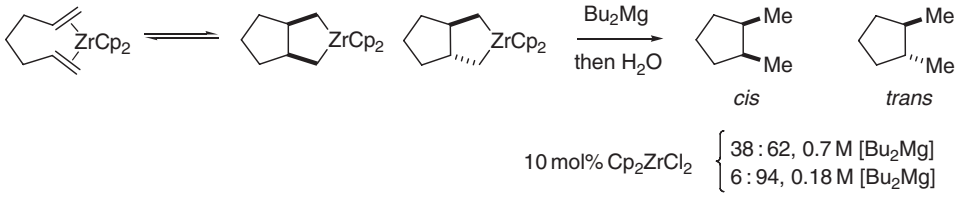
Scheme 2

zirconocene alone, indicating transmetallation is no longer rate determining. Product stereochemistry also depends upon dibutylmagnesium concentration. For example, in the cyclization of 1,6-heptadiene, diastereomeric ratios (*cis*:*trans*) of 38:62 and 6:94 are observed at 0.7 M and 0.18 M dibutylmagnesium concentrations, respectively. The collective data suggest that transmetallation competes with *cis*/*trans*-isomerization of the metallacycle by way of reversible oxidative cyclization. At high concentration of dibutylmagnesium, transmetallation is accelerated to suppress equilibration of the kinetic product mixture. At low concentration of dibutylmagnesium, oxidative cyclization occurs reversibly to provide the thermodynamically more stable *trans*-metallacycle. The catalytic competence of metallacyclic intermediates is established by effective use of isolable metallacycles as catalyst precursors. As related stoichiometric reactions exhibit high *trans*-selectivity,[22,22a] such transformations appear to be thermodynamically controlled (Scheme 3).[23]

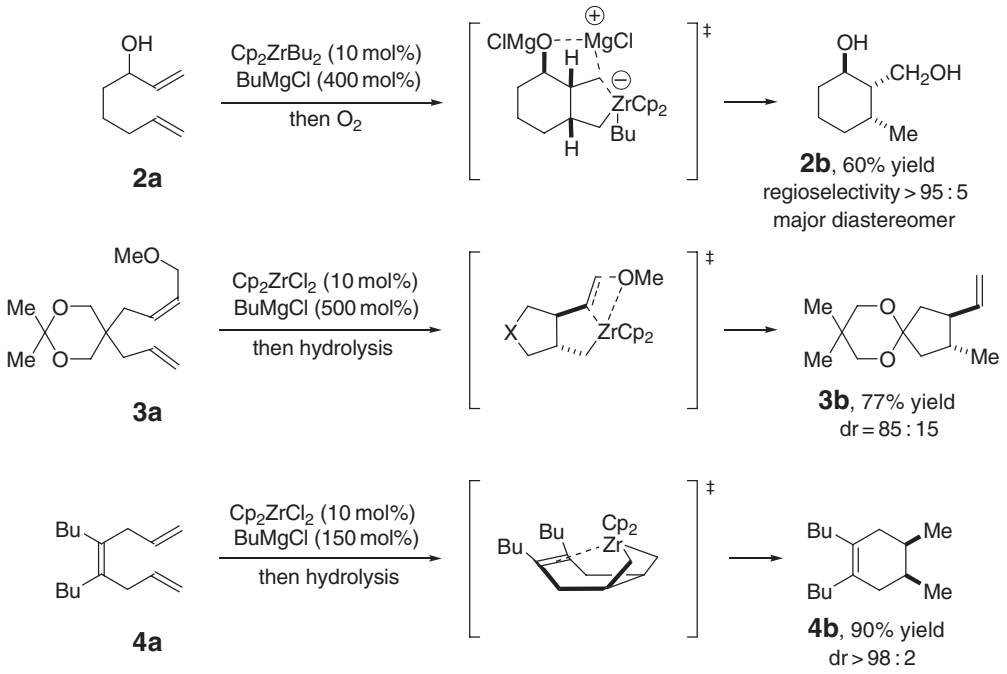
Due to the Lewis acidic nature of zirconium(IV), the zirconocene-catalyzed reductive cyclization of dienes is highly responsive to substrate-directed regio- and stereoselection. For example, as demonstrated by the conversion of 1,7-diene **2a** to cyclohexanol **2b**, dienes possessing hydroxyl groups in the tether at the allylic position direct regioselective cleavage of the metallacyclic intermediate by the organomagnesium reagent.[24] Dienes with allylic alkoxy groups exocyclic with respect to the incipient metallacycle, such as **3a**, eliminate to form products of reductive cycloallylation **3b**.[25,25a] Finally, the highly diastereoselective reductive cyclization of 1,4,7-triene **4a** reveals that Lewis basic sites in the form of olefinic residues are highly effective stereochemical control elements (Scheme 4).[26]

With the advent of enantioselective zirconocene-catalyzed alkene carbomagnesiation,[27,27a–27c,28,28a] chirally modified zirconocenes soon were applied to asymmetric reductive diene carbocyclization.[29,29a–29c] As demonstrated by the reductive cyclization of **5a**,[29] highly enantioselective cyclization is enabled through the use Brintzinger's chiral *ansa*-zirconocene.[30,30a] (For the preparation and resolution of chiral *ansa*-zirconocene **6**, see Refs: 30, 30a.) However, moderate diastereoselectivities and yields are generally observed (Scheme 5).

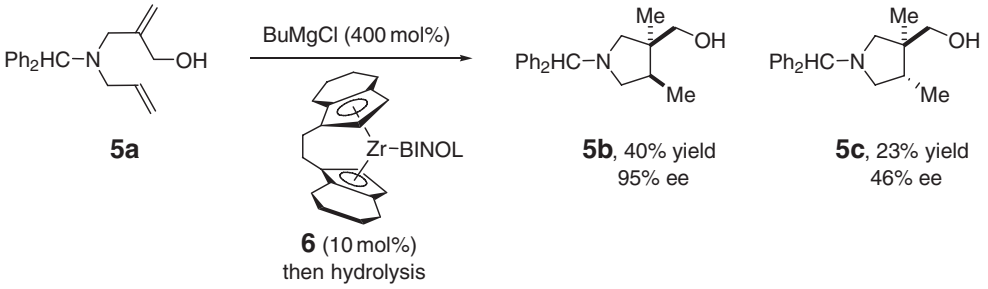
The use of organomagnesium reagents as terminal reductants in zirconocene-catalyzed diene reductive cyclization permits derivatization of the resulting bis(magnesiomethyl)cycloalkanes. However, the use of other stoichiometric reductants is likely to afford catalytic systems that exhibit complementary selectivity profiles. Molander reports the



Scheme 3

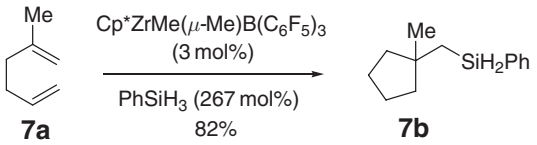


Scheme 4



Scheme 5

sole examples of silane-mediated diene reductive cyclization, which employ a cationic zirconocene catalyst.[31] Unlike the organomagnesium-mediated counterpart, the silane-based catalyst system is applicable to the cyclization of 1,5-dienes, as demonstrated by the conversion of **7a** to **7b**. The collective data suggest that the silane-mediated transformation proceeds through a mechanism involving olefin hydrometallation-insertion, rather than oxidative coupling to afford metallacyclic intermediates (Scheme 6).

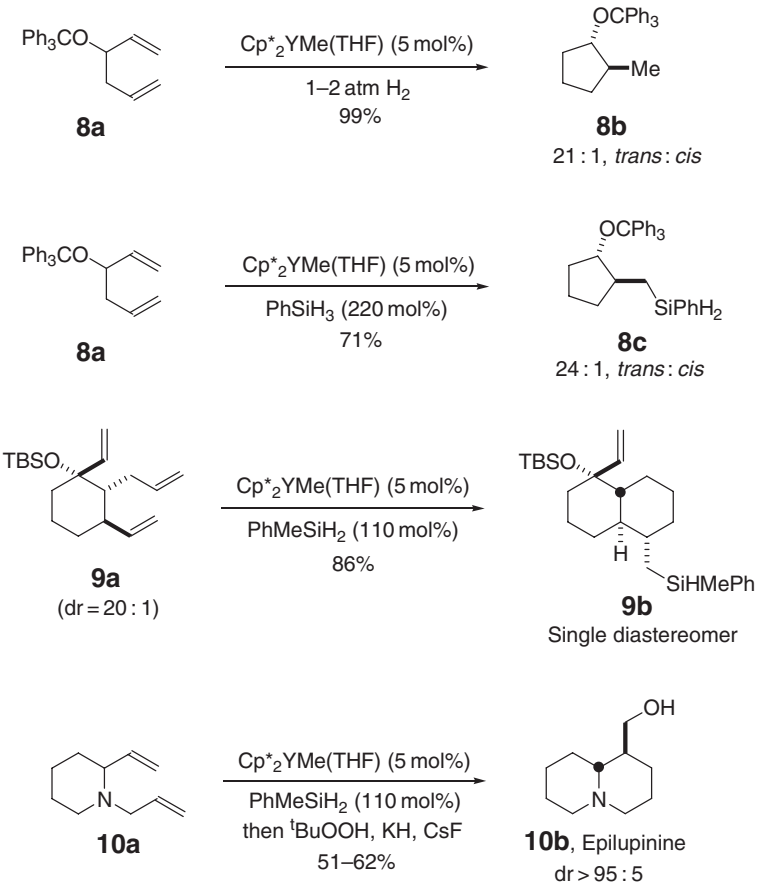


Scheme 6

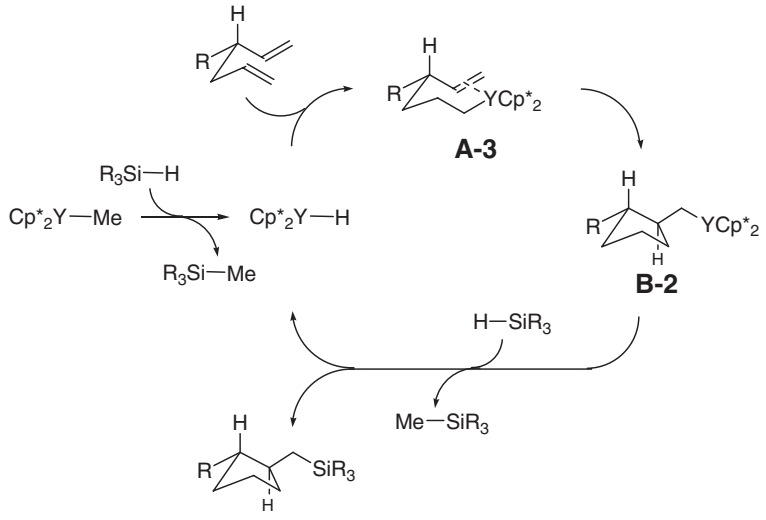
10.10.2.1.2 Group III and lanthanide catalysts

The development of group III and organolanthanide catalysts applicable to the reductive cyclization of non-conjugated dienes was facilitated by prior use of such complexes in alkene hydrogenation, hydrosilylation, hydroboration, and hydrostannylation.[8c,8g,8i] Yttrocene catalysts possessing pentamethylcyclopentadienyl ligands catalyze the reductive cyclization of 1,5- and 1,6-dienes using hydrogen[32] or silane[33,33a,33b] as terminal reductant. Due to the sensitivity of the catalyst with respect to the steric demands of the substrate, diene cyclization is initiated by hydrometallation of the sterically less-encumbered alkene.[34] Consequently, as demonstrated by the conversion of the non-symmetric 1,5-diene **8a** to cyclopentanes **8b** or **8c**, both the hydrogen- and silane-mediated reactions exhibit high levels of regio- and stereocontrol. The extraordinary selectivity of the permethylyttrocene catalyst is highlighted by the cyclization of triene **9a** to afford *trans*-decalin **9b**, in which three monosubstituted alkenes are discriminated successfully based on subtle differences in their steric environments.[33b] Taking advantage of such selectivity, the silane-mediated variant of this methodology was applied as a key bond formation in a concise synthetic approach to (±)-epilupinine **10b**.[33a] Here, the organosilane derived upon cyclization is oxidized to furnish the corresponding primary alcohol (Scheme 7).

A catalytic mechanism accounting for the observed selectivity has been proposed.[33] Entry into the catalytic cycle occurs via σ-bond metathesis of $Cp^*_2YMe(THF)$ with silane to afford an yttrocene hydride. Diene hydrometallation occurs at the sterically less-encumbered alkene partner to afford intermediate **A-3**. The chair-like conformation of **A-3** directs stereoselective insertion of the appendant alkene into the carbon–yttrium bond to provide alkylyttrocene species **B-2**. σ-Bond metathesis of **B-2** with silane liberates the cyclized product and regenerates the yttrium hydride to close the catalytic cycle. While kinetic analyses of the yttrocene-catalyzed reductive cyclization have not been performed, σ-bond metathesis is the rate-determining step in related yttrocene-catalyzed alkene hydrosilylations (Scheme 8).[34]



Scheme 7



Scheme 8

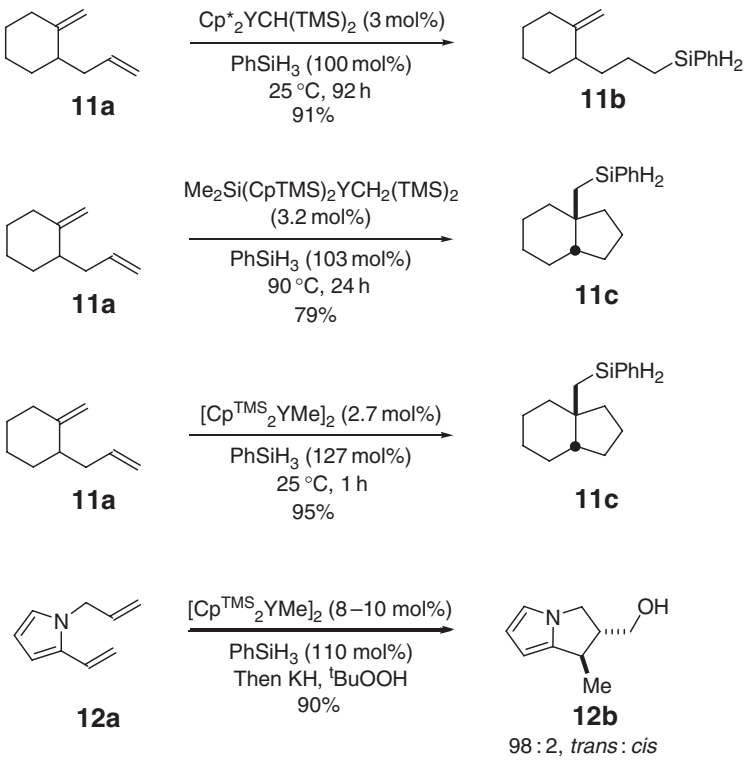
A corollary to the exquisite ability of the permethylyttrocene catalyst to discriminate amongst monosubstituted olefins is the diminished reactivity of this catalyst toward substrates that incorporate more highly substituted alkenes. To address this deficiency, the structurally modified yttrocene catalysts $Me_2Si(CpTMS)_2YCH_2(TMS)_2$ and $[Cp^{TMS}{}_2YMe]_2$ which bear sterically less-encumbered cyclopentadienyl ligands were developed.[33c] Whereas the permethylyttrocene catalyst does not effect cyclization of diene **11a**, instead providing the simple product of alkene hydrosilylation **11b**,[35] use of $Me_2Si(CpTMS)_2YCH_2(TMS)_2$ results in formation of the desired reductive cyclization product **11c** in 79% yield after 24 h at 90 °C. Even milder conditions for cyclization are achieved using $[Cp^{TMS}{}_2YMe]_2$, which enables conversion of diene **11a** to hydrindane **11c** in 95% yield after 1 h at 25 °C. Indeed, the reduced steric demand of $[Cp^{TMS}{}_2YMe]_2$ results in the first examples of yttrocene-catalyzed contrasteric reductive cyclization. As demonstrated by the conversion of **12a** to **12b**, cyclization is initiated via hydrometallation of the sterically more encumbered alkene, presumably due to electronic stabilization of the incipient alkylyttrocene conferred by the adjacent aromatic ring (Scheme 9).[33d]

To date, a single study pertaining to enantioselective yttrocene-catalyzed reductive diene cyclization is reported.[36] Using the C_2-symmetric yttrocene $[(R,S)$-BnBpY-H$]_2$, a range of 1,5- and 1,6-dienes are transformed to the corresponding cyclopentanes and cyclohexanes. In terms of asymmetric induction, the formation of cyclopentane **13b** in 50% ee from 1,5-diene **13a** represents the most favorable result (Scheme 10).

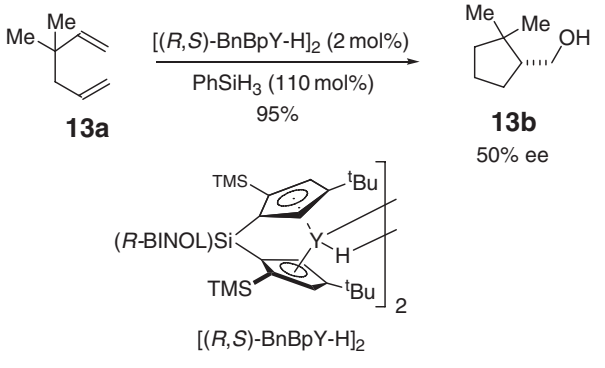
Among early and group III transition metals, the yttrocene catalysts have been studied in greatest detail. However, related metallocenes show great promise as catalysts for reductive cyclization. Neodymocene-catalyzed cyclization of 1,5- and 1,6-dienes **14a** and **15a** proceeds readily in the presence of silane to afford cyclopentanes **14b** and **15b**.[37] Lutetocenes and samarocenes also catalyze silane-mediated cyclization of 1,5-diene **14a** to cyclopentane **14b**.[38,39] In the case of the samarium-based metallocenes, the feasibility of borane-mediated cyclization has been established, as demonstrated by the highly diastereoselective conversion of phenyl-substituted diene **16a** to cyclopentane **16b** (Scheme 11).[40]

10.10.2.1.3 Late transition metal catalysts

The ability of high-valent early transition metals, group III metals, and lanthanides to catalyze diene reductive cyclization is closely linked to their coordinative unsaturation and favorable reactivity with respect to alkene insertion and σ-bond metathesis. Cationic palladium(II) complexes display similar insertion-metathesis reactivity, which has led to their use as catalysts for alkene polymerization[41] and hydrosilylation.[42,42a] The information gleaned from these earlier studies, coupled with the prospect of retaining the functional group compatibility characteristic of late transition metals, motivated development of diene cyclization-hydrosilylation catalysts based on cationic palladium(II).[43,43a–43l,8j] In a seminal report,[43] exposure of 1,6-diene **17a** to Et_3SiH in the presence of substoichiometric cationic palladium(II) affords cyclopentane **17b** in good yield and excellent *trans*-selectivity. Related transformations mediated by Me_2PhSiH were also developed.[43c] Reductive cyclization of 1,7-dienes is

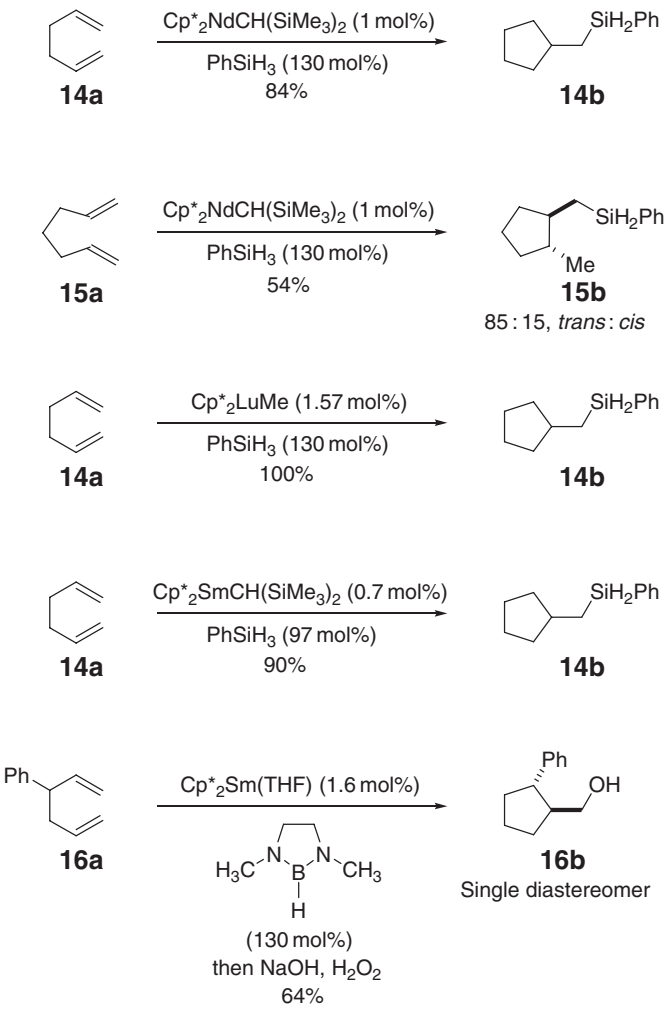


Scheme 9



Scheme 10

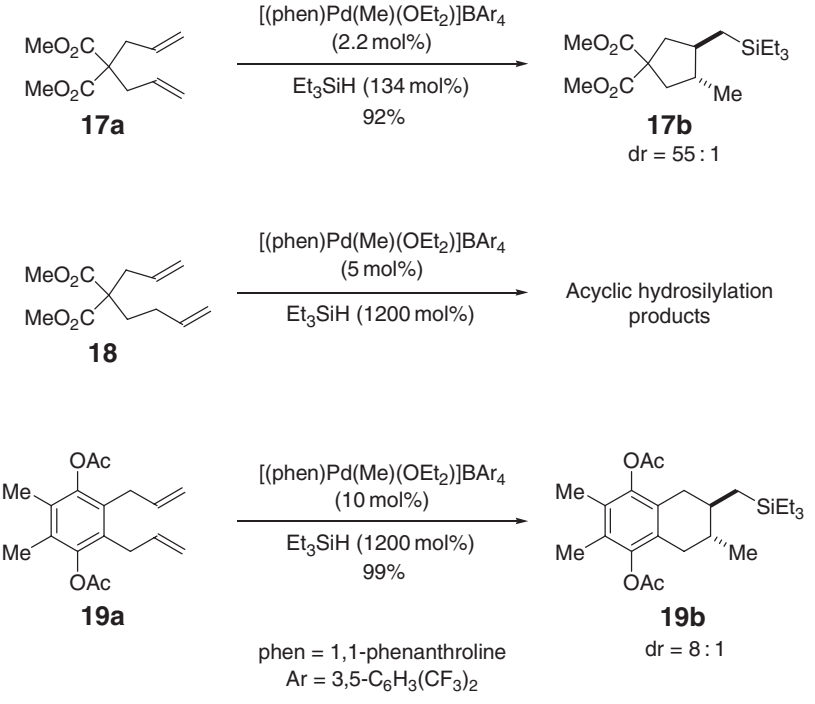
feasible, but exhibits significant substrate dependence.[43a,43b] While 1,7-diene **18** provides acyclic hydrosilylation products, the benzo-fused 1,7-diene **19a** provides a 99% yield of cyclohexane **19b**. In all cases, conformationally predisposed dienes possessing backbone substitution are required to facilitate cyclization via Thorpe–Ingold effect (Scheme 12).[44]



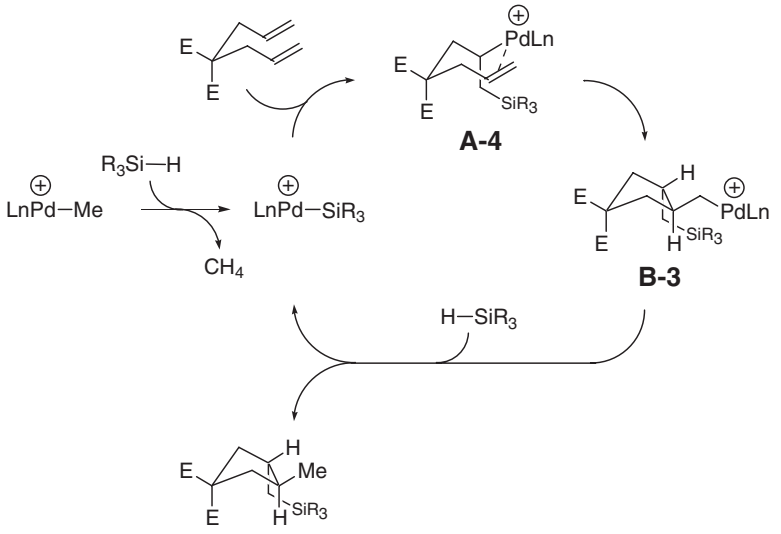
Scheme 11

The proposed mechanism of the palladium-catalyzed hydrosilylation–cyclization is similar to that previously outlined for related group III and organolanthanide-catalyzed transformations (*vide infra*, Scheme 8). However, whereas σ-bond metathesis of group III and organolanthanide alkyl complexes with silane results in metal hydride formation, corresponding σ-bond metathesis of late transition metal alkyl complexes produces complexes bearing a metal–silicon bond.[45,45a–45c] Accordingly, the initial step of the catalytic cycle involves irreversible alkene migratory insertion into the metal–silicon bond to provide intermediate **A-4**,[45,45a–45c] rather than alkene hydrometallation. Insertion of the appendant alkene in intermediate **A-4** occurs stereoselectively through a chair-like transition structure to afford the alkylpalladium complex **B-3**. Related olefin migratory insertions have been observed through low-temperature NMR analysis.[43j,43k] Finally, σ-bond metathesis of alkylpalladium complex **B-3** with silane provides the cyclized product along with the starting silylpalladium complex to close the catalytic cycle (Scheme 13).

An enantioselective variant of palladium-catalyzed hydrosilylation–cyclization was developed using a palladium pyridine-oxazoline complex.[43d–43i] As demonstrated by the cyclization of 1,6-diene **20a** to cyclopentane **20b**, high levels of relative and absolute stereocontrol are observed.[43d,43e] Conducting the reaction under anhydrous conditions is critical, as the presence of water in the reaction mixture leads to competitive formation of cyclized materials that do not incorporate silane.[43f] These initial studies involve use of Et_3SiH as terminal reductant. To facilitate oxidation of the silane-containing products to the corresponding alcohols, cyclizations employing other silanes were developed, including pentamethyldisiloxane (PMDS),[43g] 1-*tert*-butyl-3,3-dimethyl-1,1-diphenyldisiloxane



Scheme 12

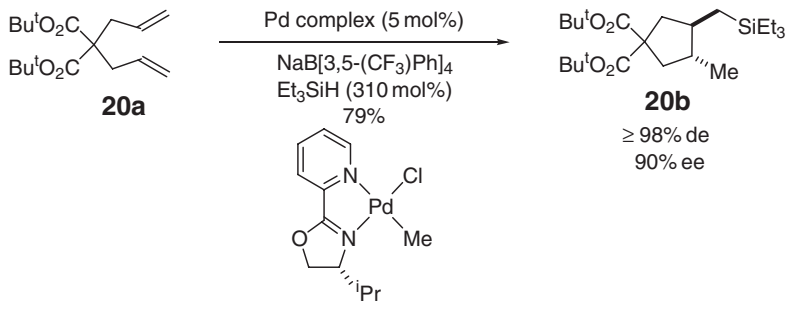


Scheme 13

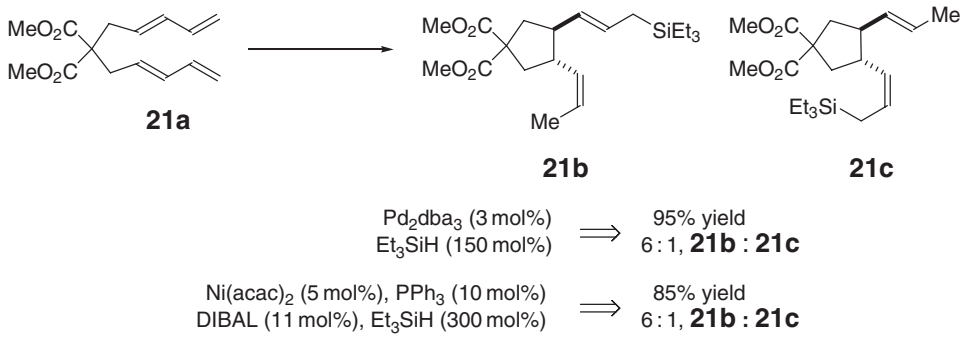
(HSiMe$_2$OTBDPS),[43h] and benzhydryldimethylsilane (HSiMe$_2$CHPh$_2$).[43i] As in the racemic variant, efficient cyclization generally requires preorganization of the 1,6-diene through homoallylic geminal disubstitution (Scheme 14).

10.10.2.2 Reductive Cyclization Involving Activated Alkenes

To date, the reductive cyclization of allenic alkenes remains undeveloped. However, the reductive cyclization of activated alkene partners in the form of 1,3-dienes and conjugated enones has been achieved using late transition metal catalysts. Indeed, the hydrosilylative dimerization of 1,3-dienes reported in 1969 appears to be the first reductive



Scheme 14



Scheme 15

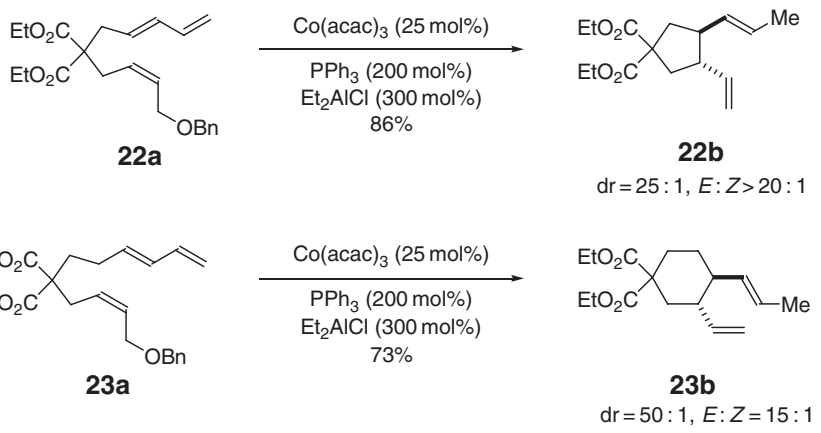
C–C bond formation mediated by silane.[6,6a–6f] With respect to the development of intramolecular variants, these seminal studies lay fallow until 1990, at which point the palladium- and nickel-catalyzed reductive cyclization of tethered 1,3-dienes mediated by silane was disclosed. As demonstrated by the hydrosilylation–cyclization of 1,3,8,10-tetraene **21a,** the *trans*-divinylcyclopentanes **21b** and **21c** are produced in excellent yield, but with modest stereoselectivity.[46] Bu_3SnH was shown to participate in an analogous cyclization.[46] Isotopic labeling and crossover experiments provide evidence against a mechanism involving initial diene hydrosilylation. Rather, the collective data corroborate a mechanism involving oxidative coupling of the diene followed by silane activation (Scheme 15).

In a related cobalt-catalyzed transformation, 1,3-dienes tethered to allylic ethers engage in Et_2AlCl-mediated reductive cyclization.[46a] Exposure of benzylic ether **22a** to $Co(acac)_3$–PPh_3 in the presence of Et_2AlCl results in formation of divinylcyclopentane **22b** with excellent *trans*-diastereoselectivity. As demonstrated by the conversion of **23a** to **23b**, this method is also applicable to the stereocontrolled formation of six-membered rings (Scheme 16).

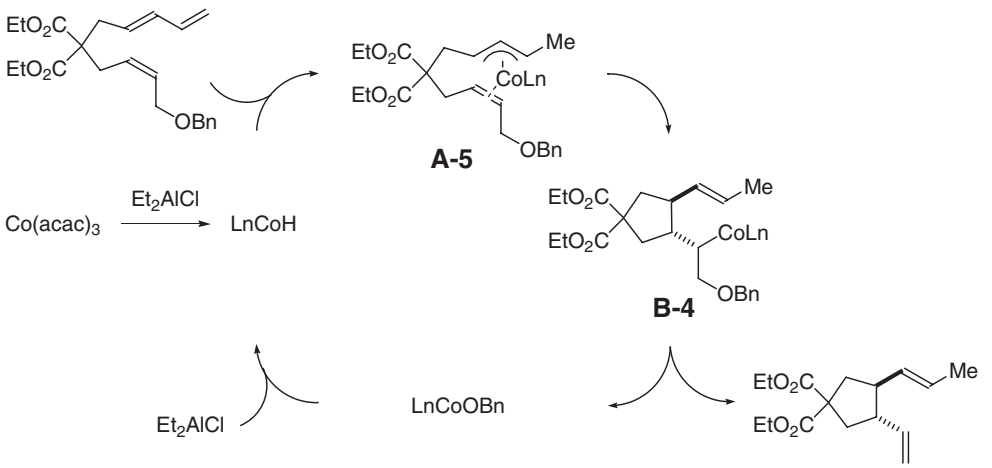
A mechanism was proposed in which entry into the catalytic cycle is achieved via Et_2AlCl-mediated cobalt hydride generation. Diene hydrometallation affords the cobalt-complexed π-allyl **A-5**, which inserts the tethered alkene to furnish intermediate **B-4**. Elimination of LnCoOBn provides the cyclization product. Reduction of LnCoOBn by Et_2AlCl regenerates cobalt hydride to complete the catalytic cycle (Scheme 17).

Nickel-based catalysts enable reductive cyclization of enone-dienes and bis(enones) in the presence of organozincs.[5,8h,8k,47,47a–47c] Exposure of enone-diene **24a** to nickel(0) in the presence of Et_2Zn provides cyclopentane **24b** in good yield along with small quantities of a diastereomeric product. Exposure of bis(enone) **25a** to related conditions results in formation of the β,β-coupled product **25b** and, to a greater extent, the bicyclic product **25c**, which derives from **25b** through aldol cyclization. Although details regarding the reaction mechanism are not fully resolved, the intermediacy of a nickel hydride is suggested by the fact that in order to suppress competitive enone conjugate addition, organozincs possessing β-hydrogens are required (Scheme 18).

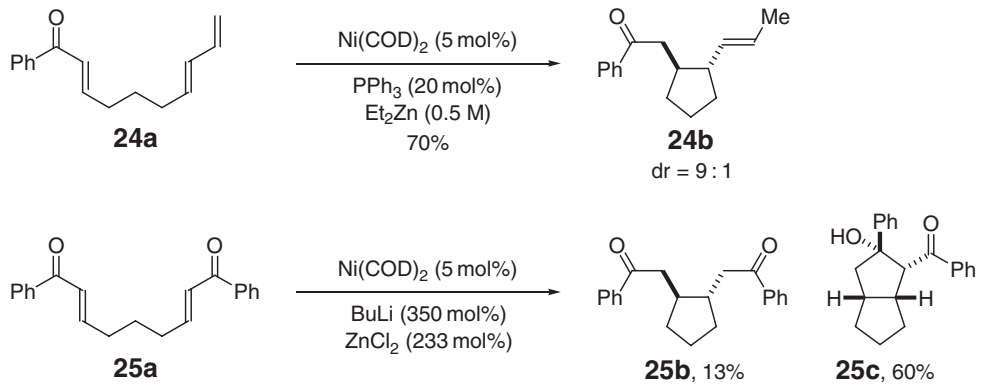
In contrast to the nickel–organozinc catalyst system, which induces β,β-coupling of bis(enones), the use of cobalt(II) catalysts in the presence of silane results in α,β-coupling to provide products of reductive Michael cyclization.[48,48a,48b] Both five- and six-membered ring products **26b** and **25d** are formed in good yields and with complete diastereoselection. The choice of silane is critical. Whereas exposure of bis(enone) **25a** to $Co(dpm)_2$



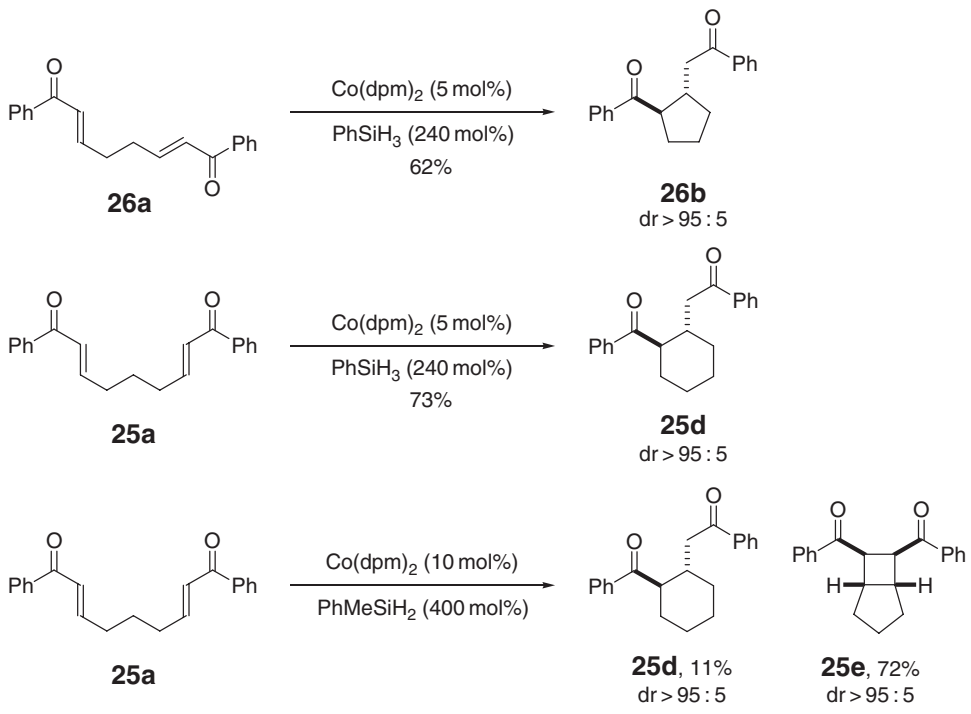
Scheme 16



Scheme 17



Scheme 18



Scheme 19

(dpm = dipivaloylmethane) in the presence of $PhSiH_3$ provides the reductive Michael cyclization product **25d**, use of $PhMeSiH_2$ promotes formation of the [2 + 2]-cycloadduct **25e** (Scheme 19).[48a]

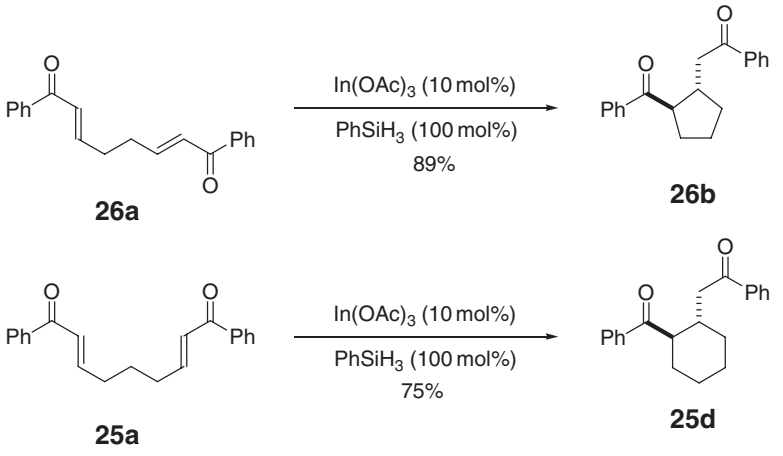
Mechanistic studies corroborate the intermediacy of anion radicals in the metal-catalyzed [2 + 2]-cycloaddition.[49,49a,49b] The very same [2 + 2]-cycloadducts are produced under cathodic reduction,[49] electron transfer from arene anion radicals,[49a] and electron transfer from Gilman reagents.[49b] As both [2 + 2]-cycloaddition and reductive Michael cyclization are possible only for easily reduced aromatic bis(enones), it is likely that reductive Michael cyclization products arise via enone reduction by low-valent cobalt to generate an oxy-π-allyl complex, which is a mesomeric form of the enone anion radical. Abstraction of hydrogen atom from $PhSiH_3$ at the former enone β-position generates a cobalt enolate that undergoes conjugate addition to the tethered enone.

Most recently, reductive Michael cyclization catalyzed by $In(OAc)_3$ in the presence of $PhSiH_3$ was reported.[50] As demonstrated by the reductive cyclization of the homologous bis(enones) **25a** and **26a**, both five- and six-membered ring formation occurs in good yield to afford cycloalkanes **25d** and **26b** as single *trans*-diastereomers (Scheme 20).

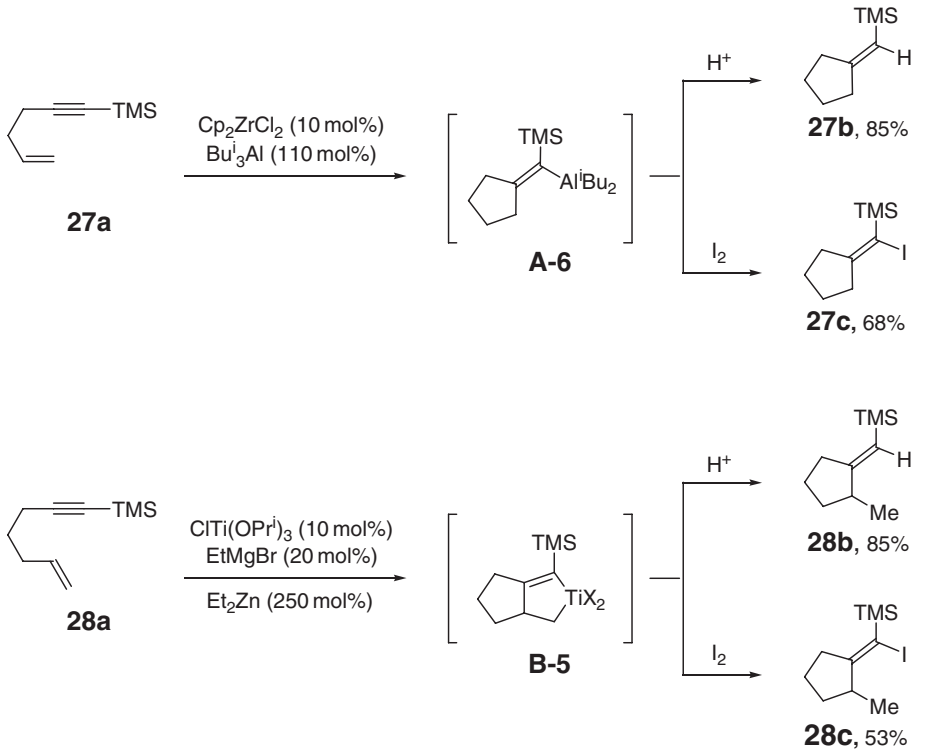
10.10.2.3 Reductive Cyclization of 1,5-, 1,6- and 1,7-Enynes

10.10.2.3.1 Early transition metal, group III, and lanthanide catalysts

Catalytic transformations of non-conjugated enynes are well developed in the context of cycloisomerization[16,16a,16b] and related Pauson–Khand reactions.[51,51a,51b] While there is an extensive literature documenting the stoichiometric reductive cyclization of non-conjugated enynes mediated by low-valent early transition metal complexes based on titanium[52,52a] and zirconium,[53,53a] there are very few examples of corresponding catalytic processes. The first early transition metal-catalyzed reductive enyne cyclization was reported in 1984.[54,54a] Upon exposure of 1,5-enyne **27a** to substoichiometric quantities of zirconocene dichloride in the presence of excess Bu^i_3Al, the alkylidene cyclopentane **27b** was generated in 85% yield upon hydrolysis. Upon iodinolysis of the reaction mixture the vinylic iodide **27c** was generated, implicating intermediacy of the vinyl alane **A-6**. Subsequently, it was shown that alkoxytitanium catalysts effect the reductive cyclization of 1,6-enynes mediated by Et_2Zn.[55] The proposed mechanism for this reaction invokes formation of a metallacyclopentene **B-5**, which undergoes transmetallation to zinc. Hydrolysis or iodinolysis of the reaction mixture provides alkylidenecyclopentanes **28b** and **28c**, respectively (Scheme 21).

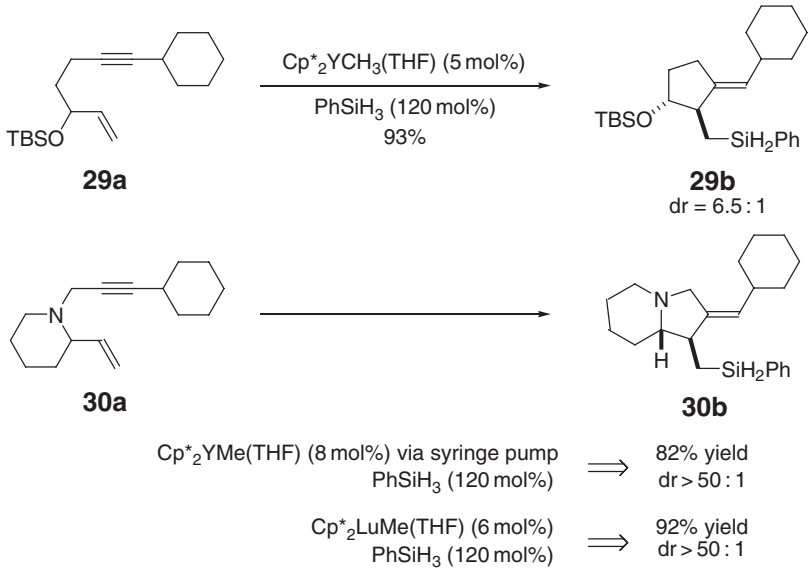


Scheme 20



Scheme 21

Pursuant to the development of yttrocene-catalyzed diene reductive cyclization, corresponding reductive enyne cyclizations were explored.[56,56a] Exposure of 1,6-enyne **29a** to reaction conditions optimized for diene reductive cyclization provides the cyclized products **29b** in good yield and moderate diastereoselectivity.[56] While the aforementioned conditions are not suited to substrates incorporating Lewis basic amine residues, this limitation is overcome through slow syringe-pump addition of the catalyst or through the use of analogous lutetocene catalysts (Scheme 22).[56a]



Scheme 22

10.10.2.3.2 Late transition metal catalysts

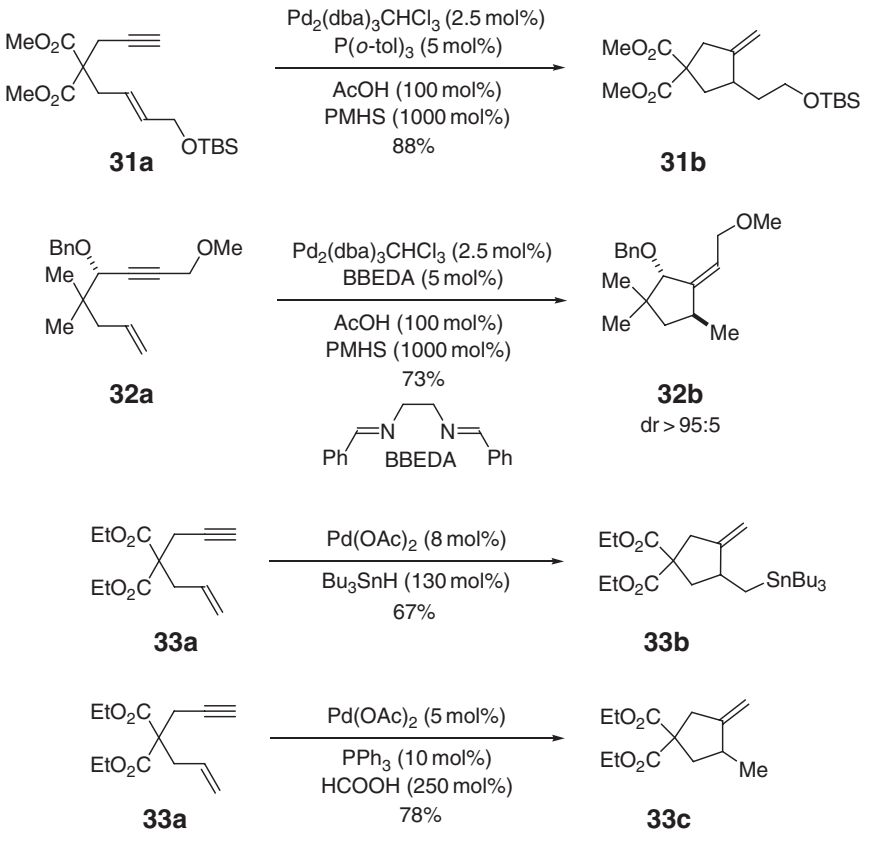
The first late transition metal-catalyzed enyne reductive cyclization was reported in 1987.[57] As revealed by the reductive cyclization of 1,6-enyne **31a**, the transformation is catalyzed by palladium and mediated by polymethylhydrosiloxane (PMHS). The high stereoselectivity of this process is underscored by the conversion of 1,6-enyne **32a** to cyclopentane **32b**, which is produced as a single diastereomer. Although complete partitioning of the competitive reductive cyclization and cycloisomerization pathways requires use of excess PMHS (1000 mol%), corresponding reductive cyclizations mediated by tributylstannane[58] or formic acid[58a–58c] require only a slight excess of the hydride donor, as illustrated by the reductive cyclization of **33a** (Scheme 23).

To probe the reaction mechanism of the silane-mediated reaction, Et_3SiD was substituted for PMHS in the cyclization of 1,6-enyne **34a**.[57] The mono-deuterated reductive cyclization product **34b** was obtained as a single diastereomer. This result is consistent with entry of palladium into the catalytic cycle as the hydride derived from its reaction with acetic acid. Alkyne hydrometallation provides intermediate **A-7**, which upon *cis*-carbopalladation gives rise to cyclic intermediate **B-6**. Delivery of deuterium to the palladium center provides **C-2**, which upon reductive elimination provides the mono-deuterated product **34b**, along with palladium(0) to close the catalytic cycle. The relative stereochemistry of **34b** was not determined but was inferred on the basis of the aforementioned mechanism (Scheme 24).

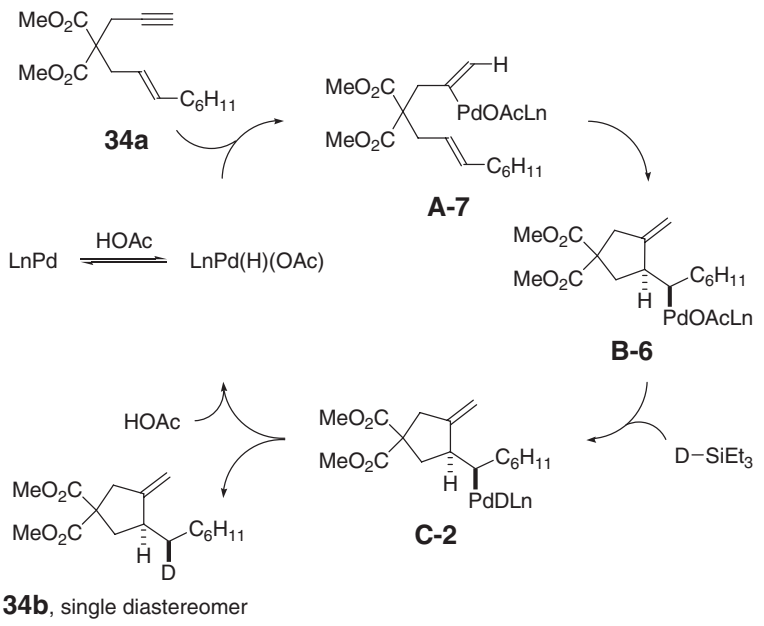
The stereocontrol and functional group tolerance exhibited by the palladium-catalyzed silane-mediated reductive enyne cyclization has led to its use as a key bond formation en route to structurally complex natural products. These include β-necrodol,[59] (−)-4a,5-dihydrostreptazolin,[59b] (±)-laurene,[59c] and, as illustrated by the conversion of 1,6-enyne **35a** to furan **35b**, (±)-phyllanthocin (Scheme 25).[59a]

A single report appears in the literature regarding the use of chirally modified palladium catalysts in reductive enyne cyclization.[60] Upon exposure of 1,6-enyne **36a** to the indicated palladium pyridine-oxazoline complex in the presence of Et_3SiH, cyclization product **36b** is formed in good yield, but with only modest levels of asymmetric induction (Scheme 26).

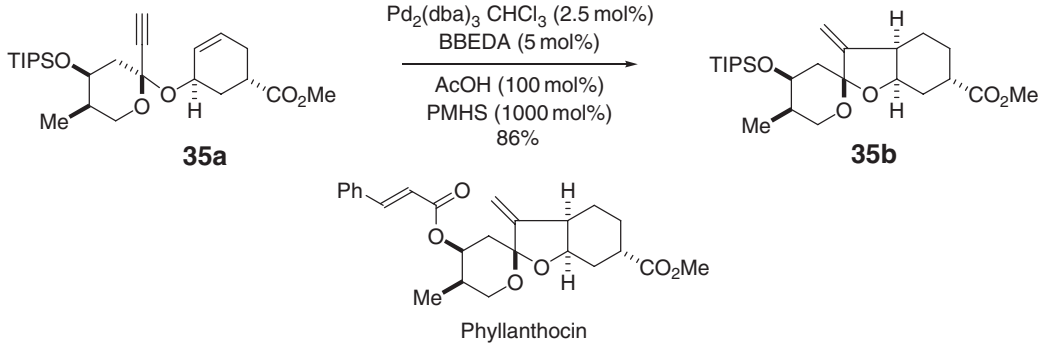
The first rhodium-catalyzed reductive cyclization of enynes was reported in 1992.[61,61a] As demonstrated by the cyclization of 1,6-enyne **37a** to vinylsilane **37b**, the rhodium-catalyzed reaction is a hydrosilylative transformation and, hence, complements its palladium-catalyzed counterpart, which is a formal hydrogenative process mediated by silane. Following this seminal report, improved catalyst systems were developed enabling cyclization at progressively lower temperatures and shorter reaction times. For example, it was found that *N*-heterocyclic carbene complexes of rhodium catalyze the reaction at 40 °C,[62] and through the use of immobilized cobalt–rhodium bimetallic nanoparticle catalysts, the hydrosilylative cyclization proceeds at ambient temperature.[63]



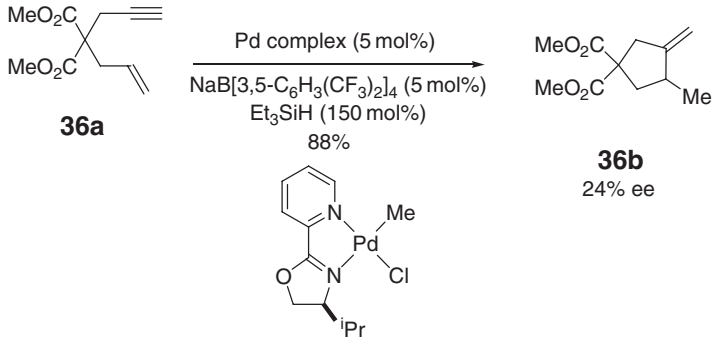
Scheme 23



Scheme 24



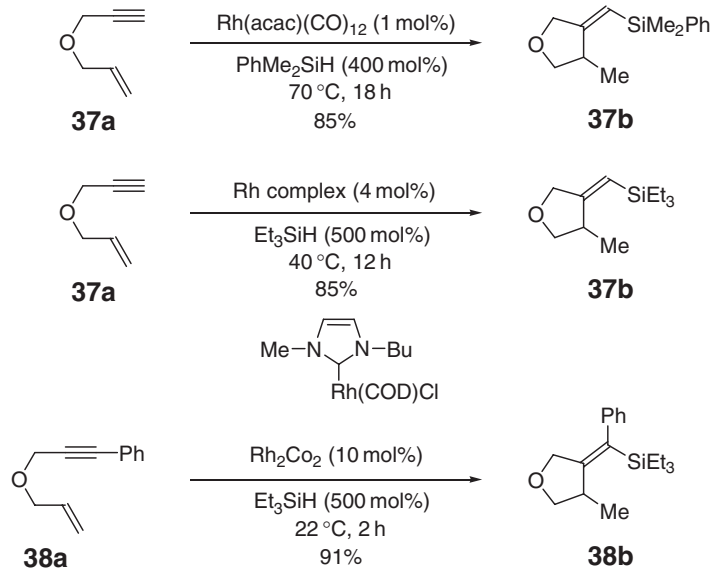
Scheme 25



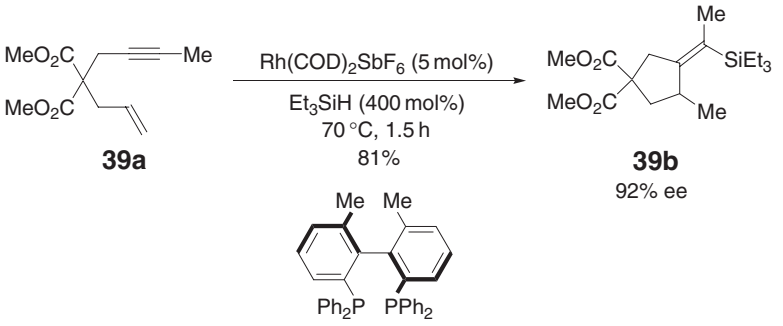
Scheme 26

Catalytic cycles involving both alkyne hydrorhodation and silylrhodation are proposed.[61a] However, mechanistic studies performed on related hydrogen-mediated enyne reductive cyclizations (*vide supra*) suggest oxidative cyclization of the enyne followed by hydrosilylytic cleavage of the resulting metallacycle via σ-bond metathesis is also plausible (Scheme 27).

A solitary report of enantioselective hydrosilylative cyclization appears in the literature.[64] Here, a variety of 1,6-enyne substrates are cyclized in good yields and enantioselectivities, using chirally modified cationic rhodium



Scheme 27

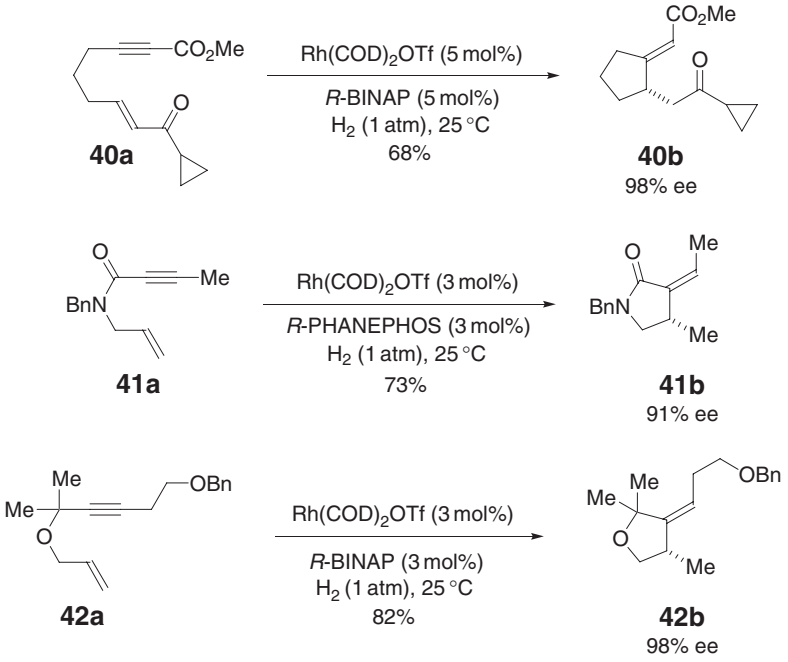


Scheme 28

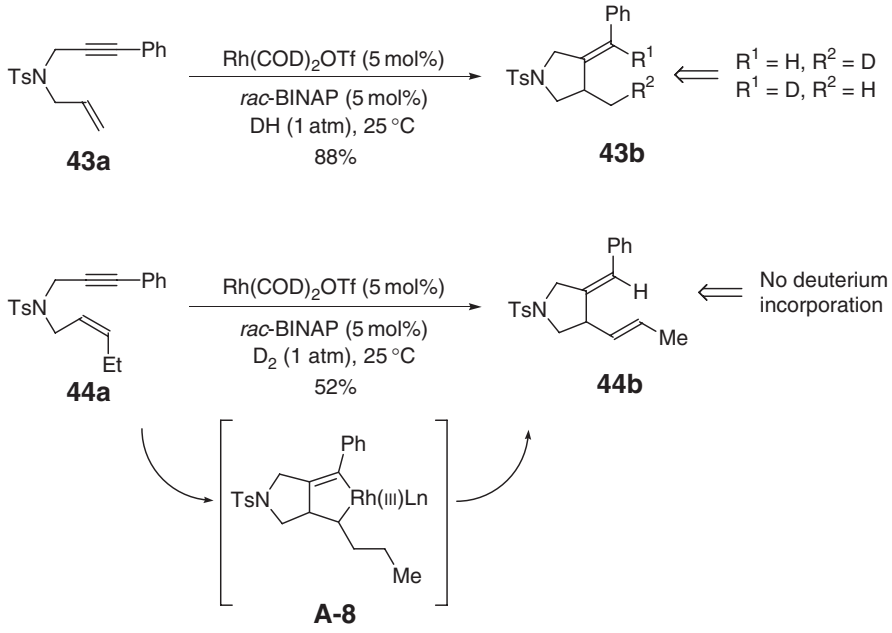
catalysts derived from $Rh(COD)_2SbF_6$ and *R*-BIPHEMP. The most favorable result in terms of asymmetric induction is observed for 1,6-enyne **39a**, which is converted to cyclopentane **39b** in 81% yield and 92% ee (Scheme 28).

Recently, it was demonstrated that elemental hydrogen could replace other hydride sources in a range of different reductive C–C bond formations.[8m,65,65a] The hydrogen-mediated reductive cyclization of 1,6-enynes catalyzed by cationic rhodium complex proceeds readily at ambient temperature and pressure to afford cyclized products in good yield.[66,66a] Through the use of chirally modified catalysts, a structurally diverse set of 1,6-enynes engage in highly enantioselective reductive cyclization, as demonstrated by the cyclization of 1,6-enynes **40a**, **41a**, and **42a**. Remarkably, over-hydrogenation of the unsaturated products **40b**, **41b**, and **42b** is not observed (Scheme 29).

A mechanistic hypothesis pertaining to the hydrogen-mediated reductive cyclization of 1,6-enynes was formulated on the basis of the following experiments. While hydrogenation of **43a** provides an excellent yield of reductive cyclization product **43b**, under identical reaction conditions the related 1,6-enyne **44a**, which incorporates a 1,2-disubstituted alkene, provides cycloisomerization product **44b**. The differential behavior of **43a** and **44a** may be rationalized on the basis of a catalytic mechanism involving initial formation of a rhodium(III) metallacyclopentene such as **A-8**. For substrate **44a**, β-hydride insertion from the intermediate metallacycle **A-8** followed by C–H reductive elimination delivers the nonconjugated cycloisomerization product **44b**. Metallacycles derived from substrate **43a**, which does not possess a suitably oriented β-hydrogen, are subject to hydrogenolytic cleavage via sigma bond metathesis. Isotopic labeling experiments performed on both **43a** and **44a** are consistent with this interpretation (Scheme 30).

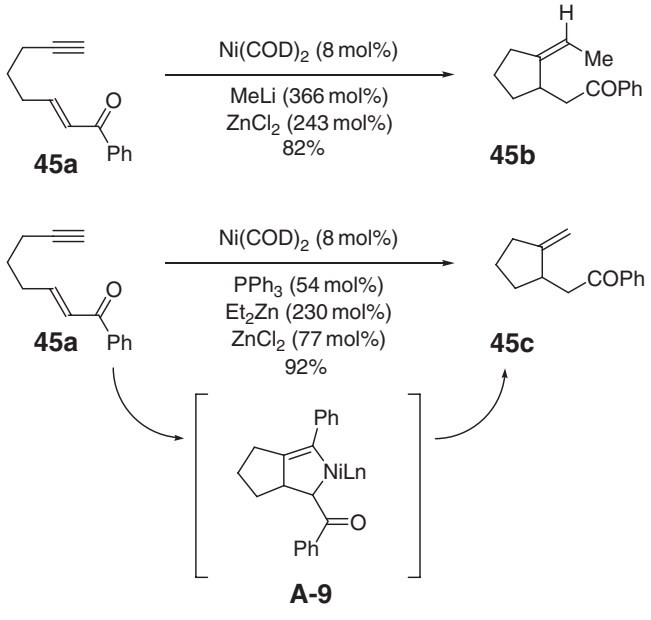


Scheme 29



Scheme 30

In the course of exploring the interaction nickel oxy-π-allyls[67,67a] with tethered unsaturation, a nickel-catalyzed reductive cyclization of acetylenic enones mediated by organozincs was discovered.[47,47a,47b] Both alkylative and hydrogenative cyclization products form competitively. However, as illustrated by the cyclization of acetylenic enone **45a**, complete partitioning of these reaction manifolds may be achieved. Through the introduction of PPh_3 and use of organozincs possessing β-hydrogens, such as Et_2Zn, the hydrogenative cyclization product **45c** is formed in excellent yield. Although detailed aspects of the reaction mechanism remain uncertain, the intermediacy of nickel(II) metallacycle **A-9** is suggested by the stoichiometric generation of a related O-bound nickel(II) metallacycle, which was characterized by single crystal X-ray diffraction analysis (Scheme 31).[68]

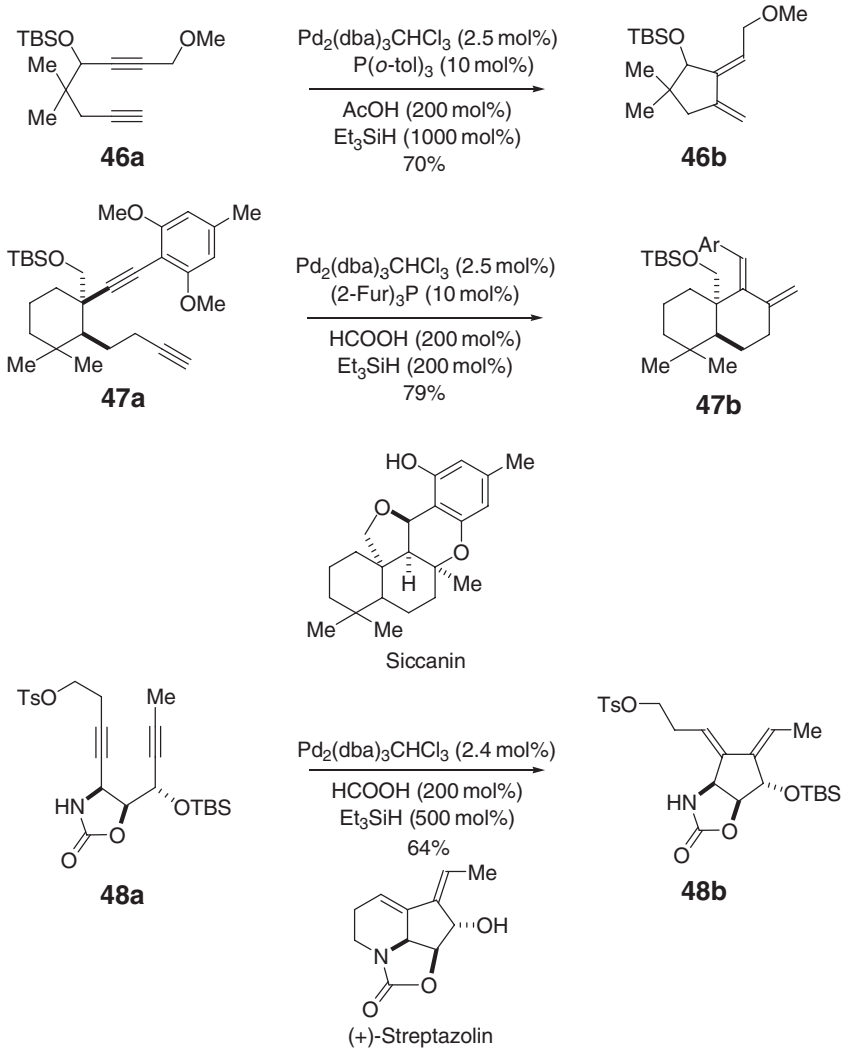


Scheme 31

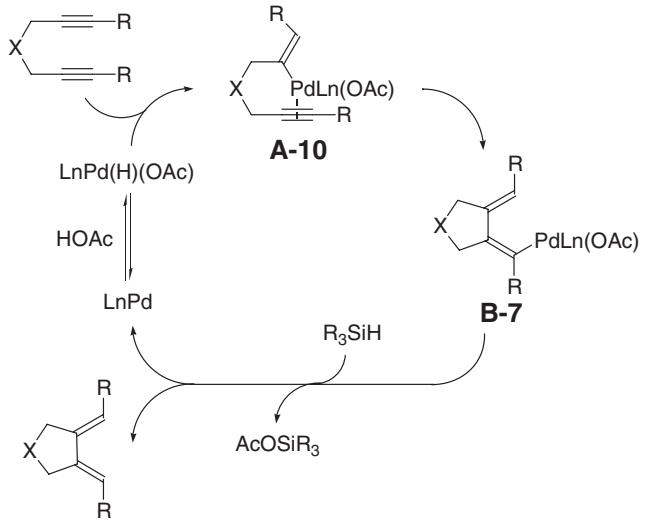
10.10.2.4 Reductive Cyclization of 1,6- and 1,7-Diynes

The reductive cyclization of non-conjugated diynes is readily accomplished by treatment of the acetylenic substrate with stoichiometric amounts of low-valent titanium[52,52a] and zirconium complexes.[53,53a] Hence, it is interesting to note that while early transition metal complexes figure prominently as mediators of diyne reductive cyclization, to date, all catalyzed variants of this transformation employ late transition metal complexes based on nickel, palladium, platinum, and rhodium. Nevertheless, catalytic diyne reductive cyclization has received considerable attention and is a topic featured in several review articles.[8,8b]

The first catalytic reductive cyclization of a non-conjugated diyne was accomplished by exposure of a 1,6-diyne to palladium(0) in the presence of acetic acid and excess Et_3SiH.[69,69a,69b] Exposure of 1,6-diyne **46a** to these conditions provides the 1,2-dialkylidenecyclopentane **46b** in good yield and with excellent control of alkene geometry. The synthetic utility of this methodology is illustrated by the syntheses of siccanin and (+)-streptazolin. In the former case, cyclization of 1,7-diyne **47a** proceeds smoothly to form *cis*-decalin **47b** in 79% yield despite considerable $A_{1,3}$-strain posed by the juxtaposition of the arene moiety and adjacent quaternary carbon center.[69a] For the total synthesis of (+)-streptazolin, cyclization of the optically enriched diyne **48a** occurring under "ligandless conditions" sets the geometry of two contiguous trisubstituted alkenes evident in the target structure (Scheme 32).[69b]



Scheme 32



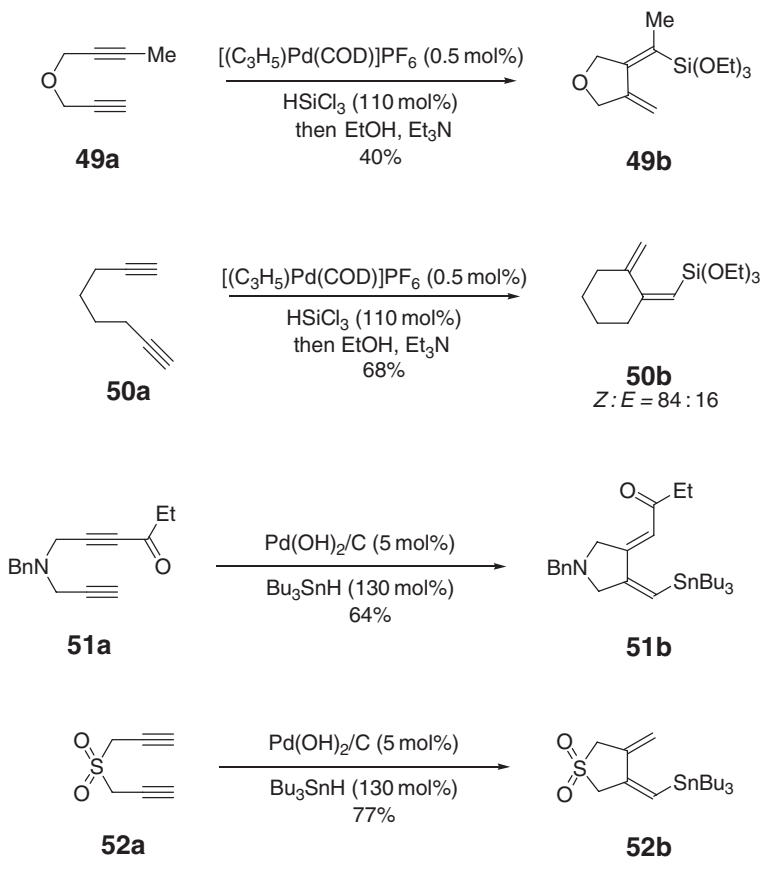
Scheme 33

In analogy to the mechanism of the palladium-catalyzed enyne cyclization, it is postulated that exposure of palladium(0) to acetic acid promotes *in situ* generation of hydridopalladium acetate $LnPd^{II}(H)(OAc)$. Alkyne hydrometallation affords the vinylpalladium complex **A-10**, which upon *cis*-carbopalladation of the appendant alkyne provides intermediate **B-7**. Silane-mediated cleavage of carbon–palladium bond liberates the cyclized product along palladium(0), which reacts with acetic acid to regenerate hydridopalladium acetate to close the cycle (Scheme 33).

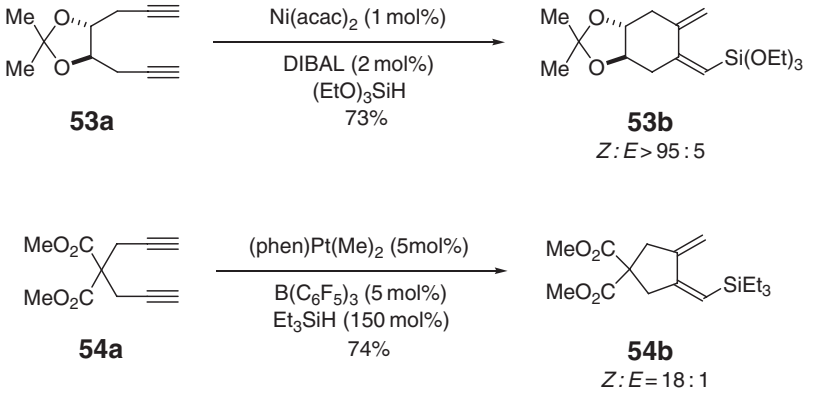
Alternate catalytic systems for diyne reductive cyclization based on palladium have been developed and offer complementary selectivities and substrate scope.[70,70a] In the absence of phosphine ligands, the cationic palladium complex $[(\eta^3\text{-}C_3H_5)Pd(cod)]PF_6$ in conjunction with $HSiCl_3$ catalyzes reductive cyclization of 1,6- and 1,7-diynes to afford five- and six-membered 1,2-dialkylidenecycloalkanes in moderate yields.[70] Interestingly, reductive cyclization of 1,6-diynes which possess both mono- and disubstituted alkynes results in exclusive formation of the more highly substituted vinylsilane, as shown in the conversion of **49a** to **49b**. This result suggests that the initial step of the reaction is hydropalladation, rather than silylpalladation, of the sterically less-encumbered unsubstituted alkyne. Under heterogeneous conditions, using Pearlman's catalyst $Pd(OH)_2/C$ and Bu_3SnH, diyne reductive cyclization also can be achieved.[70a] This stannylative cyclization is inhibited by the addition of PPh_3 and proceeds best under ligandless conditions. The reductive cyclization of **51a** and **52a** provides the 1,2-dialkylidenecyclopentanes **51b** and **52b**, revealing applicability of this catalyst to both activated and non-activated alkynes (Scheme 34).

Beyond palladium, it has recently been shown that isoelectronic metal complexes based on nickel and platinum are active catalysts for diyne reductive cyclization. While the stoichiometric reaction of nickel(0) complexes with non-conjugated diynes represents a robust area of research,[8] only one example of nickel-catalyzed diyne reductive cyclization, which involves the hydrosilylative cyclization of 1,7-diynes to afford 1,2-dialkylidenecyclohexanes appears in the literature.[71] The reductive cyclization of unsubstituted 1,7-diyne **53a** illustrates the ability of this catalyst system to deliver cyclic *Z*-vinylsilanes in good yield with excellent control of alkene geometry. Cationic platinum catalysts, generated *in situ* from $(phen)Pt(Me)_2$ and $B(C_6F_5)_3$, are also excellent catalysts for highly *Z*-selective reductive cyclization of 1,6-diynes, as demonstrated by the cyclization of 1,6-diyne **54a**.[72] The related platinum bis(imine) complex $[PhN{=}C(Me)C(Me){=}NPh]_2Pt(Me)_2$ also catalyzes diyne hydrosilylation–cyclization (Scheme 35).[72a]

The stoichiometric reaction of low-valent rhodium salts with 1,*n*-diynes to afford rhodacyclopentadiene complexes is well established and has been reviewed.[73,73a] The first rhodium-catalyzed reductive cyclization of a non-conjugated diyne has been reported only recently.[74,74a] The stereochemical outcome of the rhodium-catalyzed hydrosilylation–cyclization is dependent upon the choice of catalyst. Whereas reductive cyclization of 1,6-diyne **54a** catalyzed by $Rh_4(CO)_{12}$ provides modest yields of the *Z*-vinylsilane **54c**, exposure of **54a** to Wilkinson's catalyst

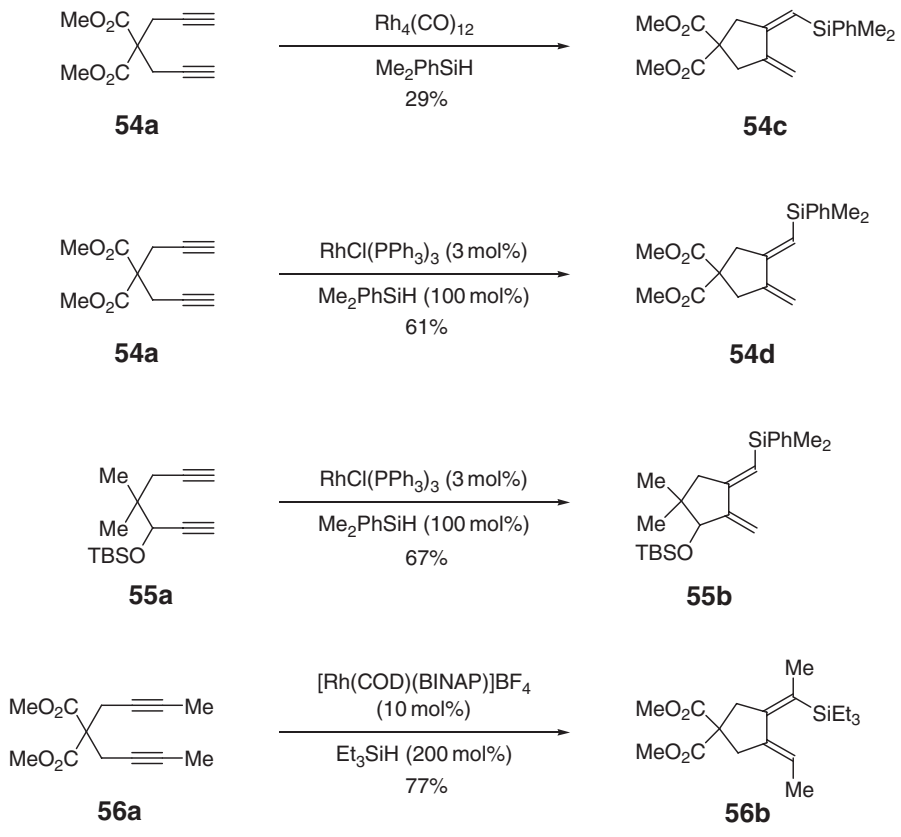


Scheme 34



Scheme 35

results in a good yield of the isomeric *E*-vinylsilane **54d**. Under the latter conditions, the non-symmetric 1,6-diyne **55a** provides hydrosilylation–cyclization product **55b**, in which the $SiPhMe_2$ moiety is incorporated at the terminus of the conjugated diene distal with respect to the resident silyloxy residue. This result suggests that hydrosilylation–cyclization promoted by Wilkinson's catalyst proceeds via initial silane oxidative addition followed by silylrhodation of the sterically more accessible alkyne partner. Initial silane activation is corroborated further by stoichiometric reaction of the preformed complex $LnRh(H)(SiPhMe_2)$ with non-symmetric 1,6-diyne **55a**, which provides

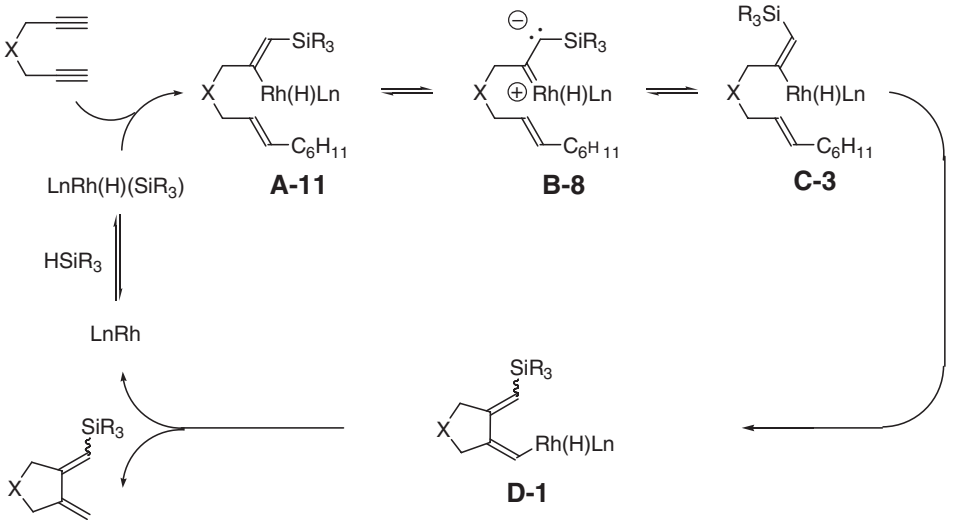


Scheme 36

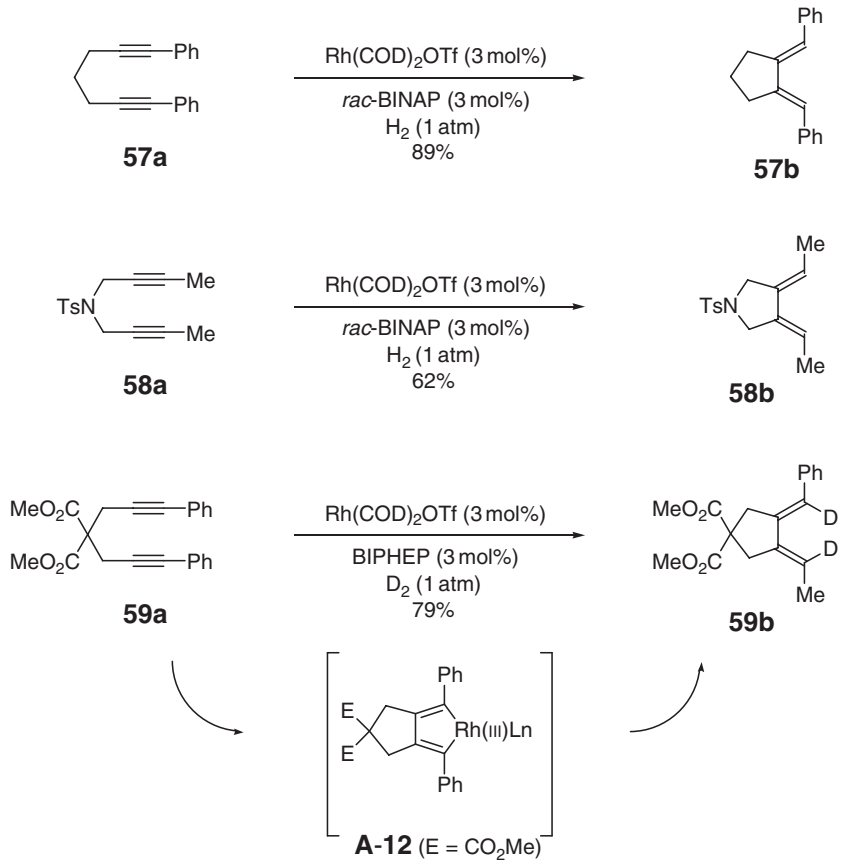
hydrosilylation–cyclization product **55b** in 94% yield. The stereoselectivity of the hydrosilylation–cyclization is also subject to substrate control. Whereas diyne **54a**, which possesses terminal alkyne partners, provides the *E*-vinylsilane **54d**, diyne **56a**, which possesses internal alkyne partners, provides the *Z*-vinylsilane **56b** (Scheme 36).[75]

A mechanism accounting for the stereochemical dichotomy observed in the rhodium-catalyzed hydrosilylation–cyclization of 1,6-diynes has been proposed.[74a] Silane oxidative addition by low-valent rhodium is followed by alkyne silylrhodation to provide vinylrhodium complex **A-11**. Intramolecular carbometallation produces carbocycle **D-1**, which upon C–H reductive elimination delivers the product along with low-valent rhodium to close the cycle. Intervention of the zwitterionic intermediate **B-8** is believed to provide a kinetic pathway for isomerization of the vinylsilane. For electron-rich rhodium centers, as in the case of the phosphine-ligated rhodium complex $RhCl(PPh_3)_3$, isomerization via intermediate **B-8** is fast with respect to carbocyclization, promoting formation of the *E*-product. In contrast, electron-deficient rhodium centers, such as those possessing CO ligands, disfavor formation of intermediate **B-8** and directly provide the *Z*-product. The high *Z*-selectivity exhibited by internal alkynes may stem from destabilization of intermediate **B-8** due to increased substitution at the carbanionic center adjacent to silicon (Scheme 37).

Catalytic hydrogenation of 1,6-diynes using cationic rhodium pre-catalysts at ambient temperature and pressure enables reductive carbocyclization to afford 1,2-dialkylidene cyclopentanes as single alkene stereoisomers. As demonstrated by the hydrogen-mediated reductive cyclization of diynes **57a**, **58a** and **59a**, conformational pre-organization of the substrate via Thorpe–Ingold effect is not a perquisite for cyclization. Remarkably, the diene-containing products **57b**, **58b**, and **59b** are not subject to further hydrogenation, highlighting the chemoselectivity of the catalytic system. Reductive cyclization of 1,6-diyne **59a** under an atmosphere of D_2 provides the doubly deuterated 1,2-dialkylidenecyclopentane **59b**. This result is consistent with a catalytic mechanism involving oxidative coupling of the diyne to form rhodacyclopentadiene **A-12**, followed by deuteriolytic cleavage of the metallacycle (Scheme 38).[8m,66]



Scheme 37

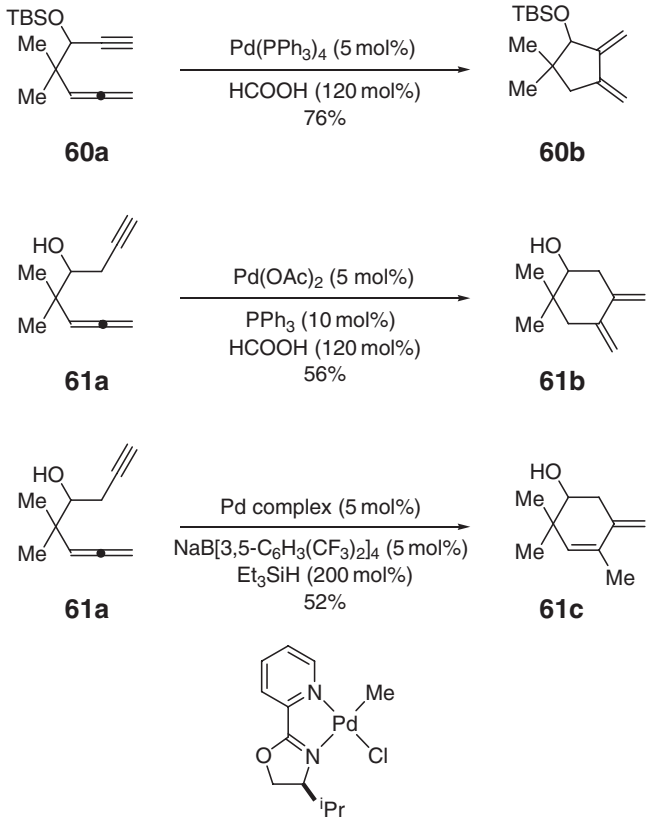


Scheme 38

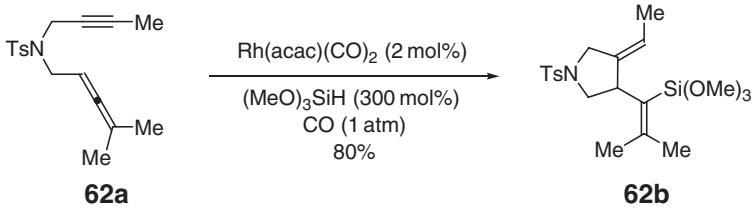
10.10.2.5 Reductive Cyclization of 1,6- and 1,7-Allenynes

There are very few reports dealing with the reductive cyclization of non-conjugated allenynes. The palladium-catalyzed reductive cyclization of allenynes mediated by formic acid or silane provides products of formal hydrogenative reductive cyclization.[76,76a] As demonstrated by the cyclization of allenynes **60a** and **61a**, both 1,5- and 1,6-allenynes are viable substrates, furnishing the homologous 1,2-dialkylidenecycloalkanes **60b** and **61b**, respectively. The formation of 1,2-dialkylidenecycloalkanes in the formate-mediated reaction was rationalized on the basis of a mechanism involving regioselective allene hydropalladation to afford a vinylpalladium intermediate, which carbopalladates the appendant alkyne. Interestingly, the palladium-catalyzed cyclization of 1,6-allenyne **61a** mediated by silane provides the isomeric reductive cyclization product **61c**. Based on this alternate outcome, the authors suggest a reaction mechanism whereby initial alkyne hydropalladation is followed by allene carbopalladation to afford an allyl palladium intermediate (Scheme 39).

Rhodium complexes catalyze hydrosilylation–cyclization of 1,6-allenynes in the presence of $(MeO)_3SiH$.[77] To avoid complex product distributions, the use of substrates possessing fully substituted alkyne and allene termini is imperative. As shown in the cyclization of 1,6-allenyne **62a**, the regiochemistry of silane incorporation differs from that observed in the rhodium-catalyzed hydrosilylation–cyclization of 1,6-enynes (see Section 10.10.2.3.2). For allenyne substrates, allene silylation occurs in preference to alkyne silylation (Scheme 40).



Scheme 39



Scheme 40

10.10.3 Reductive Cyclization Involving Coupling of C═C, C≡C with C═O π-Bonds

10.10.3.1 Reductive Cyclization of Unactivated Olefinic Carbonyl Compounds

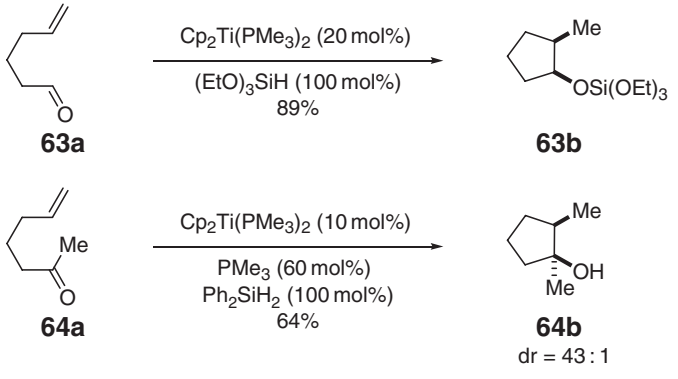
While there are numerous accounts of catalytic reductive cyclizations predicated on the coupling of two C–C π-bonds, related transformations involving the coupling of unactivated alkenes with carbonyl partners are exceptionally rare.[8d,8f] Titanocene-mediated variants of this transformation involving the stoichiometric formation of bicyclic titanium oxametallacycles have been reported.[52,52a] A key issue that must be addressed for the development of corresponding catalytic processes resides in the identification of a terminal reductant capable of cleaving the strong Ti–O bond to regenerate titanocene. Taking into account studies pertaining to the titanium-catalyzed hydrosilylation of alkenes and carbonyl compounds,[78] the titanocene-catalyzed reductive cyclization of unactivated olefinic carbonyl compounds mediated by silane was achieved.[79,79a,80] Two closely related protocols were developed. In one case, $Cp_2Ti(PMe_3)_2$ is used in conjunction with $(EtO)_3SiH$ as terminal reductant. This protocol is especially effective for the reductive cyclization of olefinic aldehydes, such as **63a**. However, when these conditions are applied to olefinic ketones, substantial quantities of carbonyl reduction products are observed. As demonstrated by the cyclization of **64a**, competitive carbonyl reduction is virtually eliminated when the reductive cyclization is conducted in the presence of excess trimethylphosphine using Ph_2SiH_2 as reductant. This latter protocol also allows the reaction to proceed at lower catalyst loadings. Though restricted to five-membered ring formation, exceptionally high levels of *syn*-diastereoselectivity are observed (Scheme 41).

The proposed catalytic cycle begins with release of trimethylphosphine from the titanium complex to generate the coordinatively and electronically unsaturated fragment [Cp_2Ti], which promotes oxidative coupling of the olefinic aldehyde to form bicyclic titanium oxametallacycle **A-13**. Cleavage of the Ti–O bond via σ-bond metathesis with silane provides the (alkyl)(hydrido)titanocene complex **B-9**. Finally, C–H reductive elimination provides the cyclized product and regenerates the catalytically active species [Cp_2Ti]. The absence of late transition metal catalysts applicable to the reductive cyclization of olefinic aldehydes may stem from the fact that low-valent late transition metals are not strong enough reductants to promote alkene–aldehyde oxidative coupling (Scheme 42).

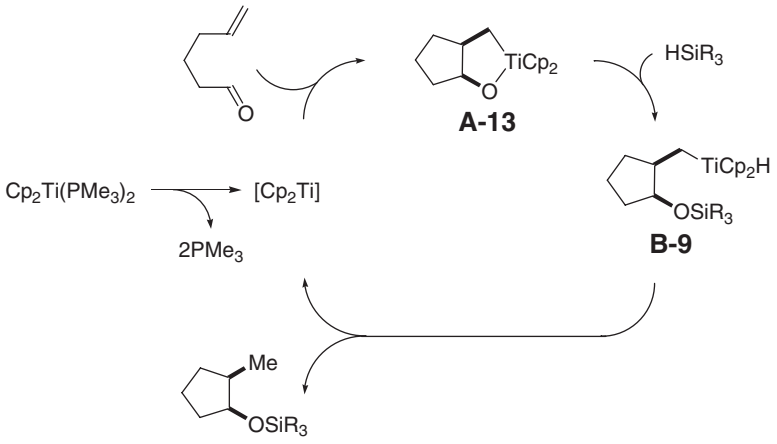
10.10.3.2 Reductive Cyclization of Activated Olefinic Carbonyl Compounds

10.10.3.2.1 Reductive aldol cyclization

The aldol reaction has been known for over a century. Though largely attributed to Würtz, the first aldol reaction was reported several years earlier by Borodin.[81,81a] Stimulated by the observation that (*Z*)- and (*E*)-enolates react stereospecifically to provide *syn*- and *anti*-aldol addition products,[82,82a,82b] several catalytic systems for aldol addition have been developed that successfully address relative and absolute stereocontrol.[83,83a–83d] In contrast, much less attention has been devoted to the more fundamental issues of chemo-, regio-, and stereoselectivity pertaining to the enolization event preceding carbonyl addition. Regiocontrolled enolate generation by way of enone reduction was first accomplished by Stork, who reported the dissolving metal reduction of enones with trapping of the resultant enolates by diverse *C*-electrophiles.[84,84a] Subsequent to Stork's seminal findings, numerous catalytic systems for the conjugate reduction of enones to afford enol derivatives were reported. (Selected examples of rhodium-, platinum-,



Scheme 41

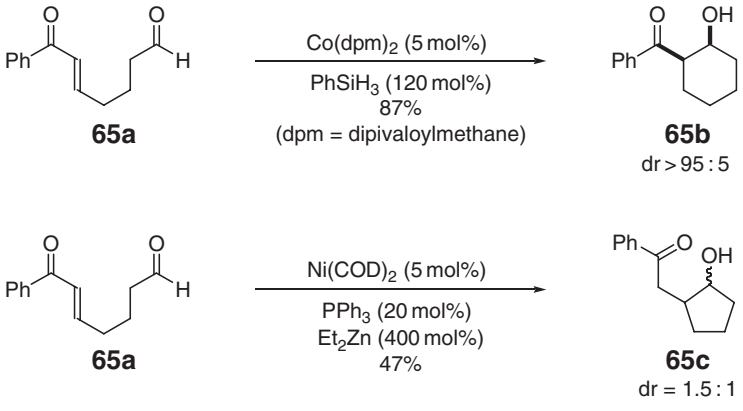


Scheme 42

nickel-, and copper-catalyzed reduction of α,β-unsaturated carbonyl compounds affording enol derivatives, are discussed.)[85,85a–85d,86,86a,87,88,88a,88b] Additionally, catalytic methods involving sequential 1,4-enone reduction-electrophilic trapping have been described.[89,89a–89c] Finally, the direct metal-catalyzed reductive coupling of enones to aldehydes, termed "reductive aldol reactions," has been developed.[8m,65,65a,90,90a] To date, catalytic reductive aldol coupling has been achieved using metal complexes based on cobalt,[48,48b,91] rhodium,[92,92a–92g,93,93a–93d] iridium,[94] palladium,[95] copper,[96] and indium.[50]

Though several intermolecular catalytic reductive aldol additions are reported, corresponding reductive cyclizations have received less attention. The first reported reductive aldol cyclization involves use of a (diketonato)cobalt(II) precatalyst in conjunction with $PhSiH_3$ as terminal reductant.[48,48b] The reductive cyclization is applicable to aromatic and heteroaromatic enone partners to form five- and six-membered rings. As demonstrated by the reductive cyclization of mono-enone mono-aldehyde **65a** to afford aldol **65b**, exceptionally high levels of *syn*-diastereoselectivity are observed. Interestingly, exposure of the substrate **65a** to low-valent nickel in the presence of excess Et_2Zn provides the isomeric homoaldol cyclization product **65c** via reductive coupling to the enone β-position (Scheme 43).[47a]

With regard to the catalytic mechanism, it is proposed that the pre-catalyst $Co(dpm)_2$ engages in single-electron oxidative addition with silane followed by reductive elimination to afford a cobalt(I) complex. Single-electron oxidative addition is a well-established reactivity mode for tetrahedral d^7 metal ions such as $Co(dpm)_2$.[97] Conventional silane oxidative addition to the cobalt(I) center provides $LnCo^{III}(SiR_3)(H)$, which enters the catalytic cycle via enone hydrometallation. The resulting cobalt enolate **A-14** undergoes addition to the appendant aldehyde to afford cobalt(III)-complexed aldolate **B-10**. Oxygen–silicon reductive elimination provides the silylated product and LnCo(I), which upon conventional silane oxidative addition affords $LnCo^{III}(SiR_3)(H)$ to close the catalytic cycle.

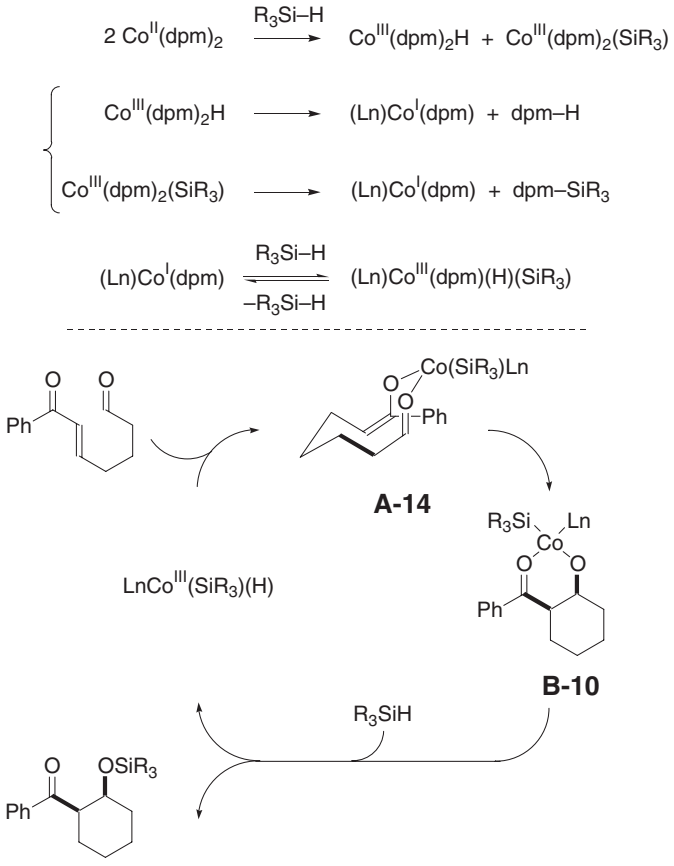


Scheme 43

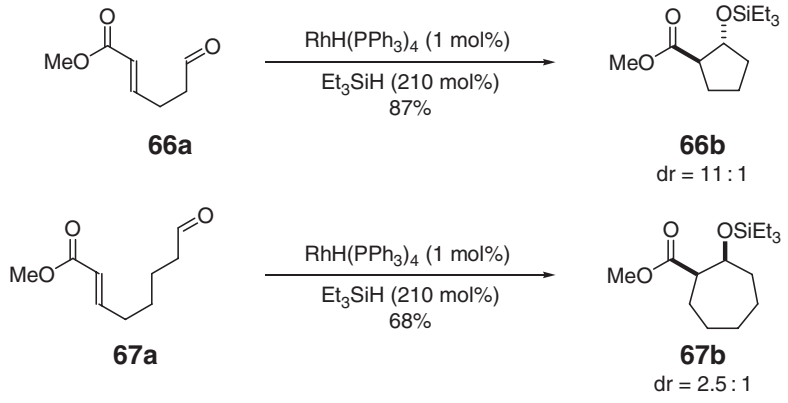
The high levels of *syn*-diastereoselectivity suggest aldolization through a closed Zimmerman–Traxler-type transition structure via intermediacy of the *Z*-enolate. When the transformation is performed using $PhSiD_3$, a single deuterium is incorporated at the β-position of the product as an equimolar mixture of epimers, inferring rapid isomerization of the kinetically formed cobalt enolate prior to cyclization or reversible aldol addition. The stereochemistry of the deuterated product was established by single crystal neutron diffraction analysis (Scheme 44).

Under the conditions of rhodium catalysis, a silane-mediated aldol reductive cyclization was devised.[92d,92e] Upon exposure of enoate **66a** to the rhodium(I) hydride complex $RhH(PPh_3)_4$ in the presence of Et_3SiH, the silyl-protected cyclic aldol product **66b** was obtained in excellent yield with high levels of *anti*-stereoselectivity. In addition to five-membered ring formation, the production of six- and, remarkably, seven-membered cycloaldols occurs in good yields. Interestingly, in the case of seven-membered ring formation, the *syn*-aldol product **67b** predominates. The postulated mechanism is similar to that described for cobalt-catalyzed aldol reductive cyclization. Silane oxidative addition to the rhodium(I) center is followed by hydrometallative enolate generation with subsequent aldol addition and, finally, oxygen–silicon reductive elimination (Scheme 45).

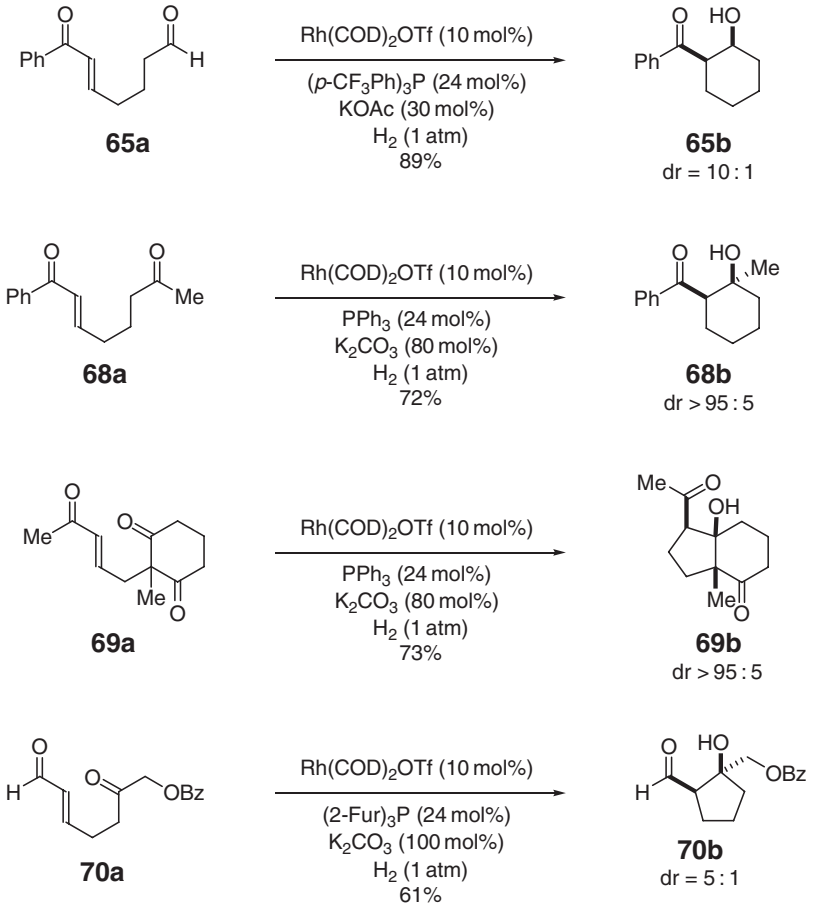
Hydrogen-mediated aldol reductive cyclizations are achieved using cationic rhodium catalysts in conjunction with mild basic additives. Additions to both aldehyde and ketone partners are feasible.[93,93a–93d] For example, exposure of phenyl-substituted enone **65a** to rhodium-catalyzed hydrogenation conditions at ambient temperature and pressure provides the cyclized product **65b** in 89% yield with high levels of diastereocontrol. Competitive conventional hydrogenation to form acyclic reduction products is suppressed through the addition of potassium acetate. Ketone aldols **68b** and **69b** are formed with even higher levels of stereocontrol via rhodium-catalyzed hydrogenation of enones **68a** and **69a**, respectively. Finally, as demonstrated by the reductive cyclization of enal **70a**, hydrogen-mediated enolate generation enables the intramolecular addition of aldehyde enolates to ketones. The latter result is significant in view of the fact that alkali aldehyde enolates are typically prone to polyaldolization and are not known to participate in additions to ketones (Scheme 46).



Scheme 44



Scheme 45

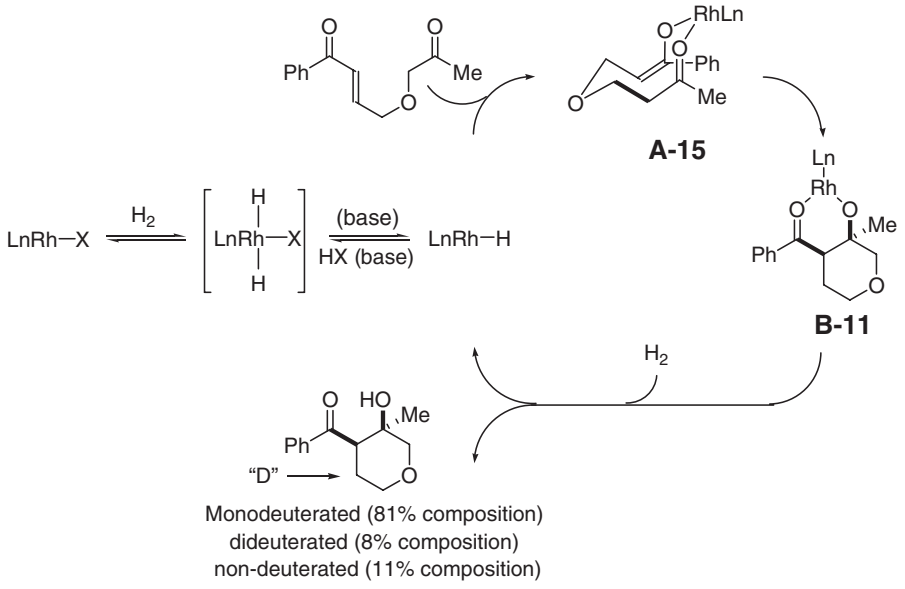


Scheme 46

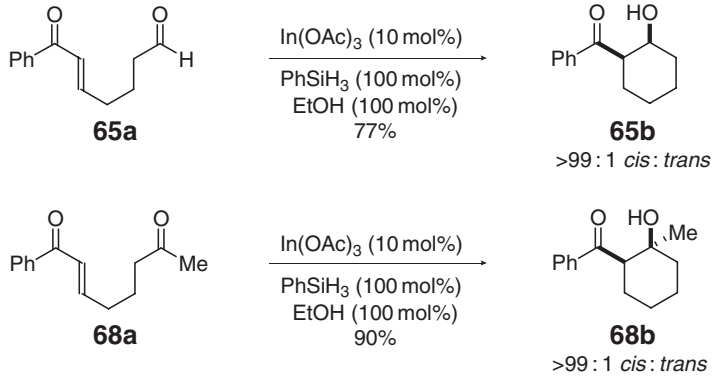
Detailed aspects of the catalytic mechanism remain unclear. However, influence of basic additives on the partitioning of the conventional hydrogenation and reductive cyclization manifolds coupled with the requirement of cationic rhodium pre-catalysts suggests deprotonation of a cationic rhodium(III) dihydride intermediate. Cationic rhodium hydrides are more acidic than their neutral counterparts and, in the context of hydrogenation, their deprotonation is believed to give rise to monohydride-based catalytic cycles.[98,98a,98b] Predicated on this

analysis, a monohydride-based catalytic cycle for hydrogen-mediated aldol reductive cyclization was proposed. Entry into the catalytic cycle requires hydrogen oxidative addition followed by deprotonation of the resulting cationic rhodium(III) dihydride, representing a formal heterolytic activation of elemental hydrogen. Enone hydrometallation provides rhodium enolate **A-15**, which upon carbonyl addition gives rise to rhodium aldolate **B-11**. Finally, hydrogenolytic cleavage of the rhodium–oxygen bond provides the cycloaldol product along with starting rhodium monohydride to close the catalytic cycle. This mechanism is consistent with the results of a deuterium labeling experiment, in which reductive cyclization of the indicated keto-enone substrate is conducted under a deuterium atmosphere. Incorporation of deuterium at the former enone β-position of the cyclized product is observed. Interestingly, reversible enone hydrometallation is implicated by the characterization of monodeuterated (81% composition), dideuterated (8% composition), and non-deuterated (11% composition) products (Scheme 47).[93a]

Most recently, reductive aldol cyclization catalyzed by $In(OAc)_3$ in the presence of $PhSiH_3$ was reported.[50] This catalytic system is applicable to both aldehyde and ketone acceptors. As demonstrated by the reductive cyclization of **65a** and **68a**, cycloaldol products are produced in good yields and excellent *syn*-diastereoselectivity (Scheme 48).



Scheme 47



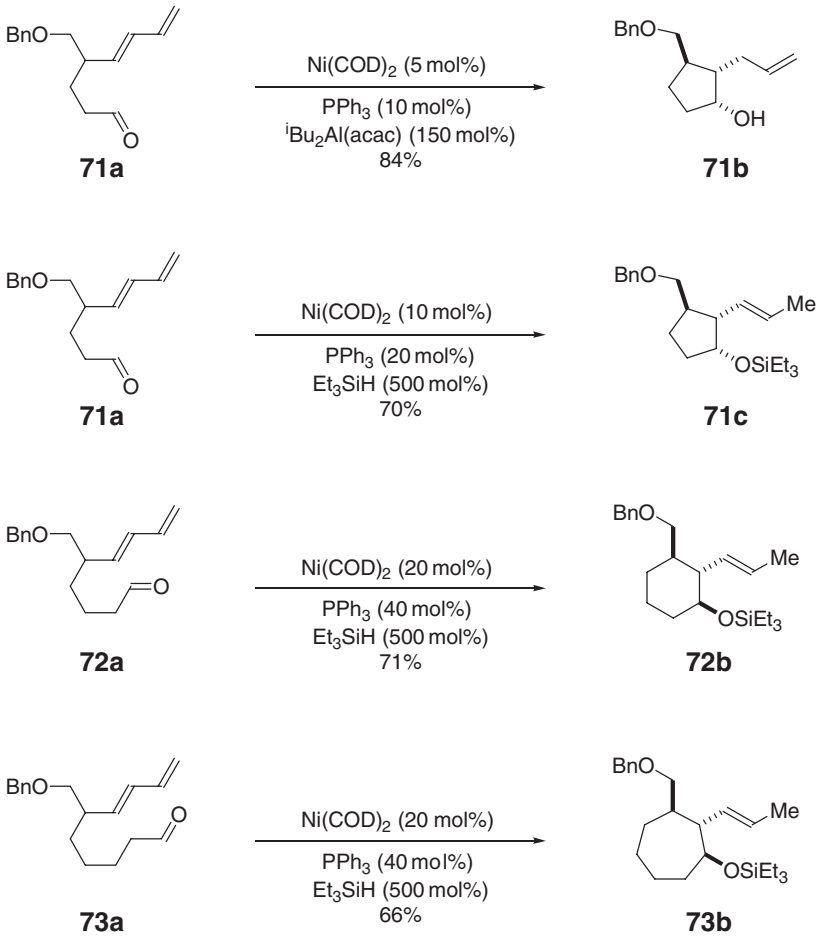
Scheme 48

10.10.3.2.2 Reductive cyclization of 1,3-dienyl carbonyl compounds

Stoichiometric intermolecular reductive couplings of dienes and carbonyl compounds mediated by zirconium[99,99a] and titanium[52,52a] have been reported. An indication that catalytic variants of this reaction type might be feasible stems from reports of nickel-catalyzed co-oligomerization of conjugated dienes and aldehydes.[100,100a] Indeed, the first preparatively useful catalytic reductive coupling of conjugated dienes and carbonyl compounds involves the nickel-catalyzed reductive cyclization of 1,3-dienyl aldehydes.[101,101a,101b] Corresponding intermolecular variants were reported subsequently.[8e,102]

For the reductive cyclization of dienyl aldehydes, two nickel-based catalyst systems have been developed.[101,101b] As demonstrated by the reductive cyclization of dienyl aldehyde **71a**, use of diisobutylaluminum acetylacetonate as terminal reductant results in production of **71b**, whereas conditions employing Et_3SiH generate the isomeric olefinic product **71c**. In each case, a single stereoisomer is formed. Using the silane-based catalyst system, five-, six- and seven-membered ring products **71c**, **72b** and **73b** are produced in stereoisomerically pure form. In a related study, it was shown that the reductive cyclization of 1,3-dienyl aldehydes may be conducted using $Ni(acac)_2$ as precatalyst and triethylborane or diethylzinc Et_2Zn as terminal reductant under ligandless conditions.[103] However, decreased levels of stereocontrol are observed (Scheme 49).

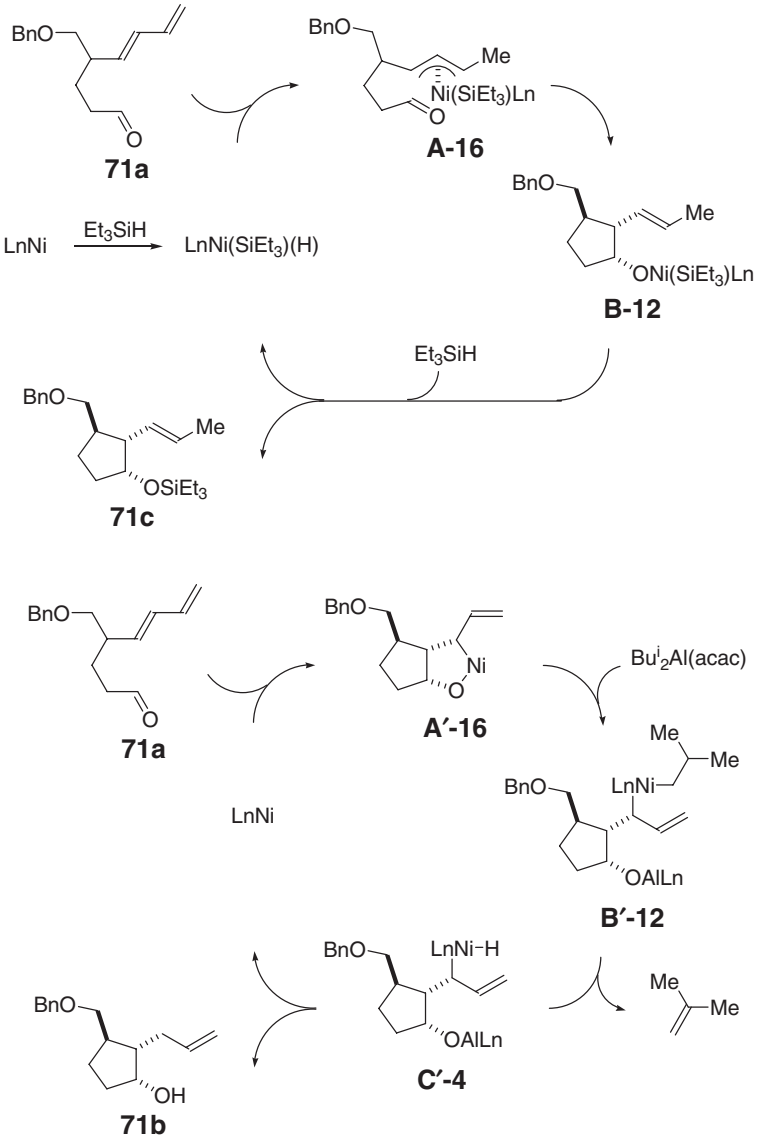
It is postulated that the mechanism of the silane-mediated reaction involves silane oxidative addition to nickel(0) followed by diene hydrometallation to afford the nickel π-allyl complex **A-16**. Insertion of the appendant aldehyde provides the nickel alkoxide **B-12**, which upon oxygen–silicon reductive elimination affords the silyl protected product **71c** along with nickel(0). Silane oxidative addition to nickel(0) closes the catalytic cycle. In contrast, the $Bu^i{}_2Al(acac)$-mediated reaction is believed to involve a pathway initiated by oxidative coupling of the diene and



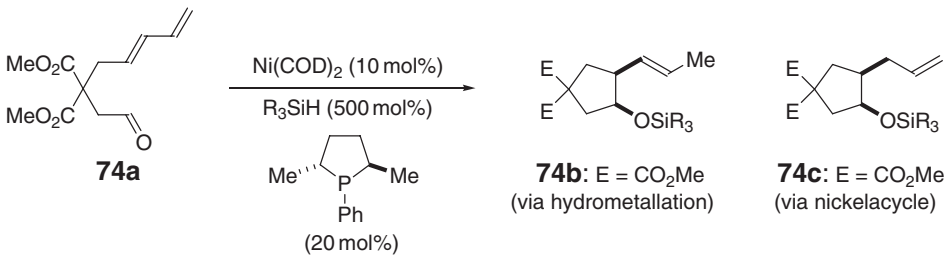
Scheme 49

aldehyde moieties to afford nickelacycle **A′-16**. Transmetallation of nickelacycle **A′-16** with $Bu^i_2Al(acac)$ furnishes the σ-allyl complex **B′-12**, which upon β-hydride elimination produces the σ-allyl nickel hydride **C′-4**. Reductive elimination from the indicated σ-allyl haptomer provides the isomeric product **71b**. This mechanistic interpretation is corroborated by the influence of exogenous 1,3-cyclohexadiene in the stoichiometric reaction of **71a** using $Ni(COD)_2$ (100 mol%), PPh_3 (200 mol%), and $Bu^i_2Al(acac)$ (220 mol%). In the absence of 1,3-cyclohexadiene, product **71c** is produced in 82% yield. However, in the presence of added 1,3-cyclohexadiene (150 mol%), conditions that mimic the catalytic reaction in the sense that nickel is present in substoichiometric quantities with respect to diene, the isomeric product **71b** is formed as the major species (98 : 2, **71b** : **71c**). Hence, it appears that the haptomeric equilibria of the intermediate σ-allylnickel hydride **C′-4** is influenced by the presence of excess diene, which presumably ligates nickel to enforce the observed regiochemistry of C–H reductive elimination. An exhaustive depiction of the possible allylic haptomers of **A′-16**, **B′-12** and **C′-4** has been omitted for the sake of clarity (Scheme 50).

Attempts at enantioselective cyclization have met with only limited success, but provide further insight into the catalytic mechanism.[104,104a] Silane-mediated reductive cyclization of dienyl aldehyde **74a** in the presence of



Scheme 50



R_3SiH	*Yield* (**74b** + **74c**)	*Ratio* (**74b**/**74c**)	*ee* (**74b**/**74c**)
Bu^tMe_2SiH	83%	>50/1	16/-
Et_3SiH	84%	4.3/1	2/47
Ph_2MeSiH	83%	1.2/1	27/78

Scheme 51

the indicated chiral phosphine ligand provides a mixture of isomeric alkene products **74b** and **74c**. Formation of the terminal alkene **74c** is not consistent with the aforementioned hydrometallative mechanism. Rather, terminal alkene **74c** appears to arise by way of oxidative cyclization followed by hydrosilylytic cleavage of the resulting metallacycle via σ-bond metathesis. The fact that the enantioselectivities of the isomeric products **74b** and **74c** formed under a given set of conditions differ substantially suggests that both oxidative coupling and hydrometallative reaction manifolds operate competitively (Scheme 51).

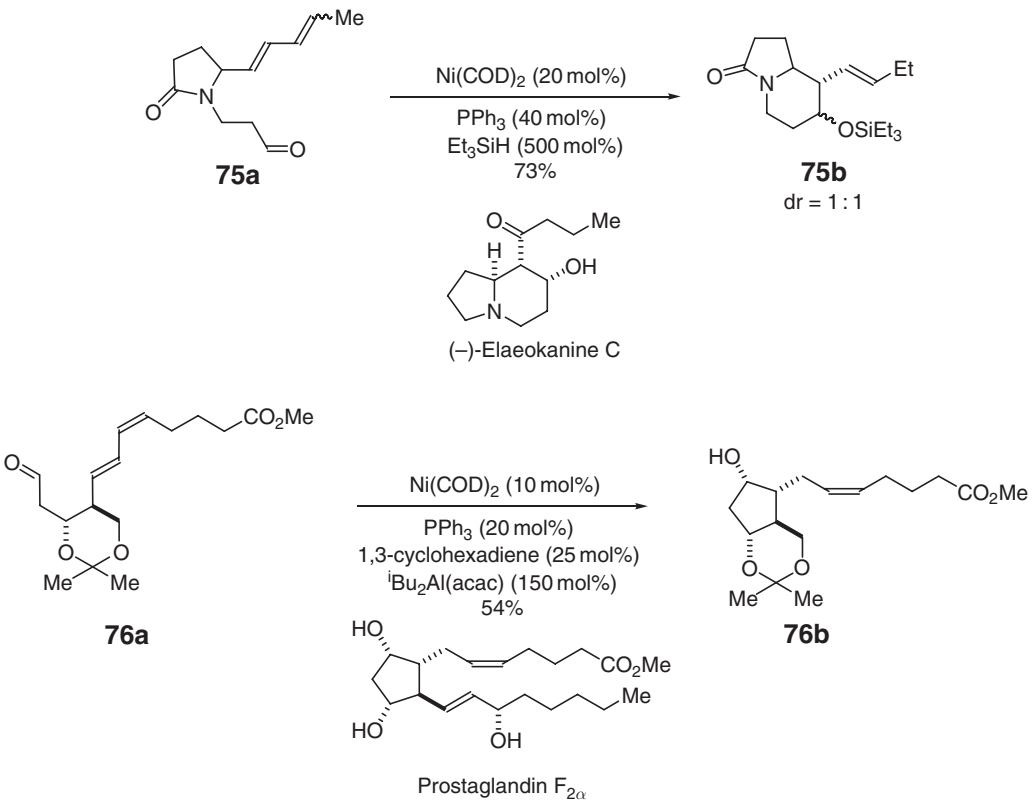
The nickel-catalyzed reductive cyclization of 1,3-dienyl aldehydes has been applied as a strategic bond formation in the formal synthesis of (−)-elaeokanine C.[105,105a] Specifically, diene **75a** was exposed to conditions for silane-mediated cyclization, enabling construction of **75b**, which possesses an intact indolizidine ring system. In a synthetic approach to prostaglandin $F_{2\alpha}$, the conjugated diene **76a** is exposed to conditions for $Bu^i_2Al(acac)$-mediated reductive cyclization.[106] Notably, the geometrical integrity of the *cis*-alkene moiety evident in substrate **76a** is retained in the product **76b**, which is produced as a single diastereomer. The presence of 1,3-cyclohexadiene is required to direct alkene regiochemistry (Scheme 52).

10.10.3.3 Reductive Cyclization of Acetylenic and Allenic Carbonyl Compounds

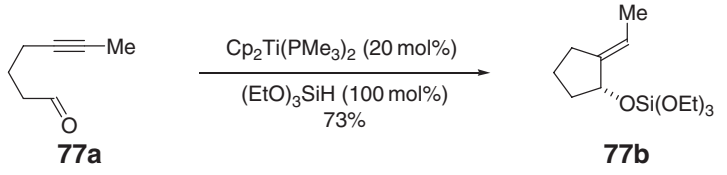
The inter- and intramolecular catalytic reductive couplings of alkynes and aldehydes recently have experienced rapid growth and are the topic of several recent reviews.[5,8h,8k,107] With respect to early transition metal catalysts, there exists a single example of the catalytic reductive cyclization of an acetylenic aldehyde, which involves the titanocene-catalyzed conversion of **77a** to ethylidene cyclopentane **77b** mediated by $(EtO)_3SiH$.[80] This process is restricted to terminally substituted alkyne partners (Scheme 53).

The very first example of the catalytic reductive cyclization of an acetylenic aldehyde involves the use of a late transition metal catalyst. Exposure of alkynal **78a** to a catalytic amount of $Rh_2Co_2(CO)_{12}$ in the presence of Et_3SiH induces highly stereoselective hydrosilylation–cyclization to provide the allylic alcohol **78b**.[108] This rhodium-based catalytic system is applicable to the cyclization of terminal alkynes to form five-membered rings, thus complementing the scope of the titanocene-catalyzed reaction (Scheme 54).

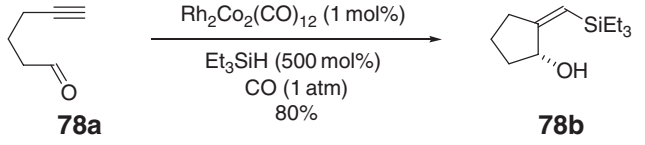
Nickel-based catalysts for the reductive cyclizations of acetylenic aldehydes exhibit remarkably broad scope.[5,8h,8k,107] The first reported nickel-catalyzed reaction of this type employs Et_2Zn as the terminal reductant.[109] As demonstrated by the reductive cyclization of alkynal **79a** to form either **79b** or **79c**, both alkylative and hydrogenative cyclization is possible. Notably, these reaction manifolds are completely partitioned in favor of hydrogenative cyclization by pre-treatment of the pre-catalyst with PBu_3 and use of organozincs possessing β-hydrogens, such as Et_2Zn. For substrates that incorporate Lewis basic functional groups, such as alkynal **80a**, mediation by Et_2Zn is not feasible due to direct addition of the organozinc to the aldehyde. However, by substituting Et_2Zn with Et_3SiH, nickel-catalyzed reductive cyclization proceeds smoothly to provide **80b** in good yield and excellent stereoselectivity (Scheme 55).



Scheme 52

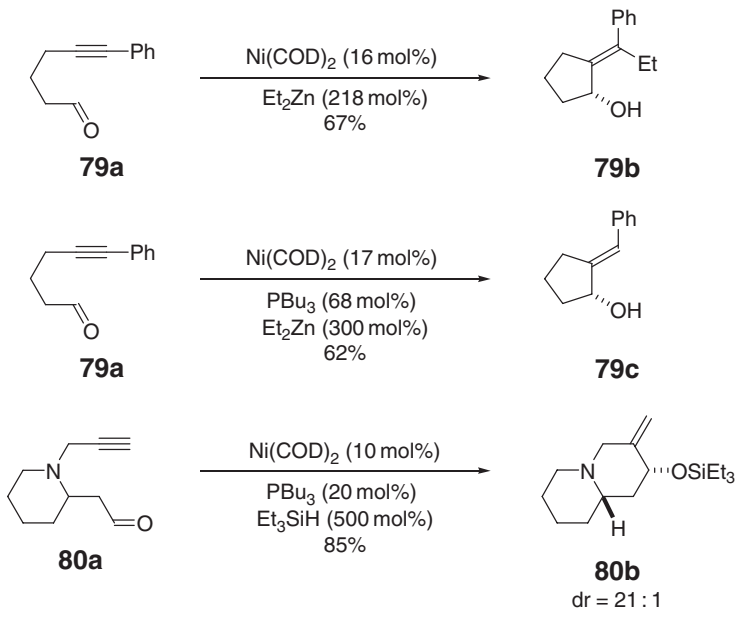


Scheme 53

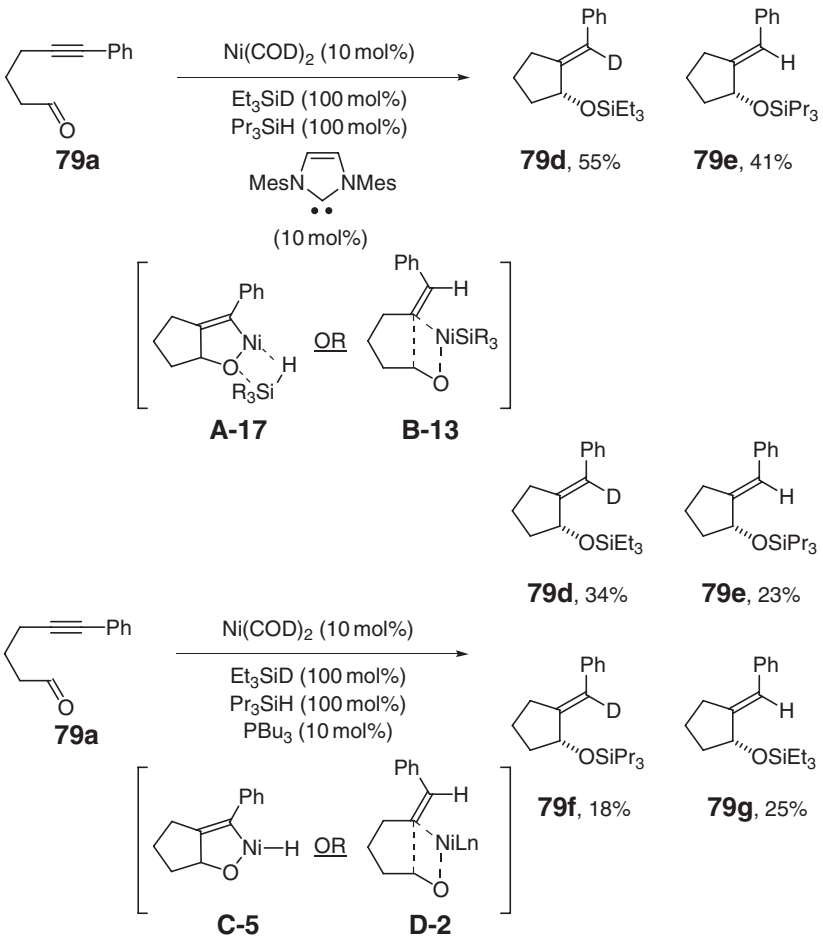


Scheme 54

The mechanism of the nickel-catalyzed reductive cyclization of acetylenic aldehydes was probed through elegant crossover experiments involving the reductive cyclization of alkynal **79a** in the presence of equimolar quantities of Et_3SiD and Pr_3SiH.[109c] It was found that transformations employing the indicated *N*-heterocyclic carbene complex of nickel exclusively provide products **79d** and **79e** without crossover, suggesting σ-bond metathesis of silane with nickelacycle **A-17** or alkyne carbometallation with subsequent oxygen–silicon reduction elimination as in **B-13**. Interestingly, the corresponding experiment employing PBu_3 as ligand results in a product distribution that includes crossover products **79f** and **79g**, implicating the intermediacy of **C-5** or **D-2** en route to nickel alkoxides that may engage in σ-bond metathesis with silane (Scheme 56).



Scheme 55



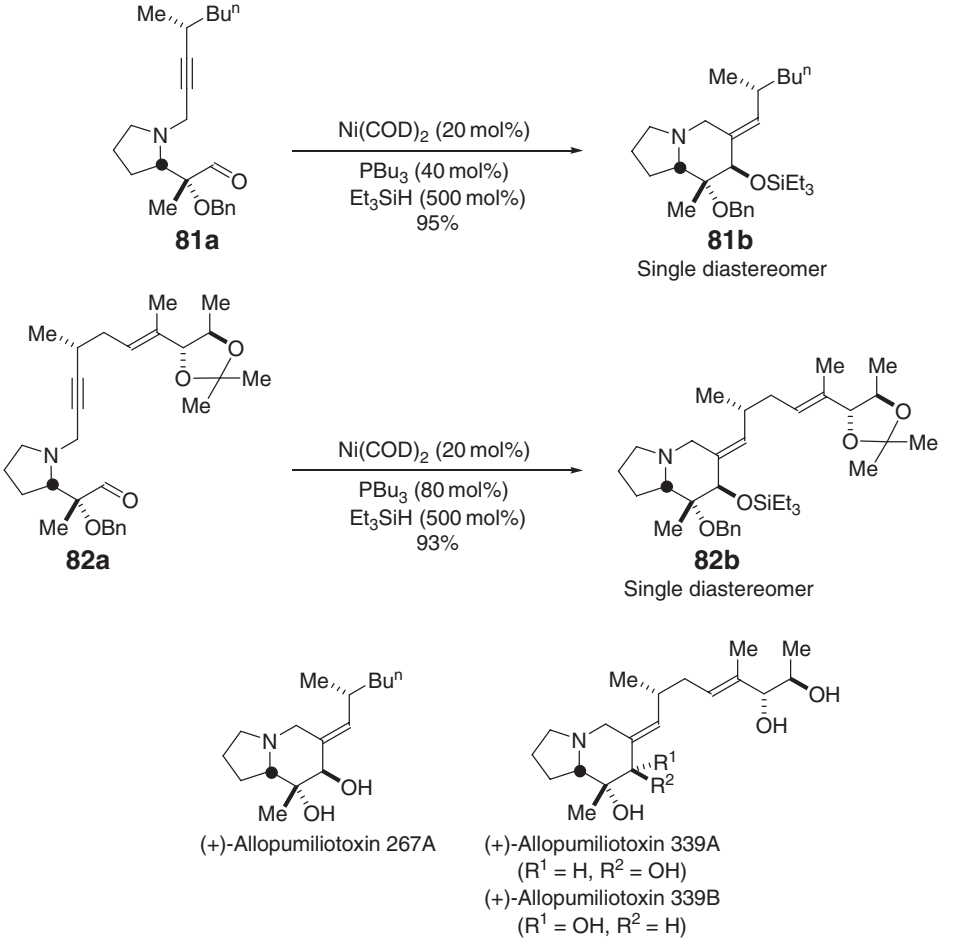
Scheme 56

The chemoselectivity of the nickel-catalyzed reductive cyclization of alkynals is highlighted by its use as a key bond formation in a general synthetic approach to members of the allopumiliotoxin alkaloid family, including (+)-allopumiliotoxin 267A, (+)-allopumiliotoxin 339A and (+)-allopumiliotoxin 339B.[109a,109b] For the synthesis of (+)-allopumiliotoxin 267A, exposure of L-proline derived alkynal **81a** to silane-mediated reductive cyclization conditions affords the indolizidine **81b** as a single diastereomer. Deprotection of the oxygen functional groups provides (+)-allopumiliotoxin 267A. Exposure of alkynal **82a** to similar conditions provides indolizidine **82b** as a single diastereomer, which was subsequently converted to (+)-allopumiliotoxin 339A and 339B (Scheme 57).

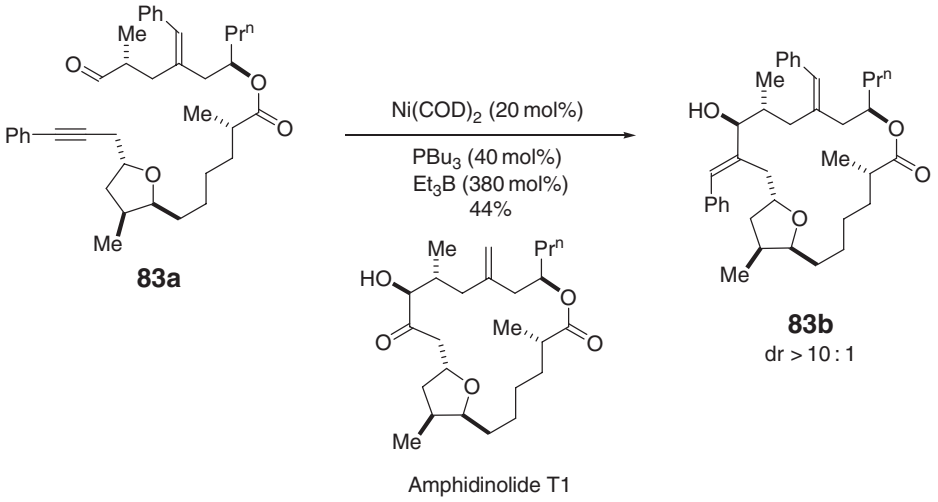
In the context of developing nickel-based catalysts applicable to intermolecular alkyne–aldehyde coupling, Et_3B was introduced as a terminal reductant[107,110,110a–110d] This borane-mediated coupling also serves as a method for macrocyclization, as illustrated by the total synthesis of amphidinolide T1.[111,111a] In the event, acetylenic aldehyde **83a** engages in stereoselective macrocyclization to afford the 18-membered ring lactone **83b** in moderate yield, which was elaborated to the target structure (Scheme 58).

Recently, the silane-mediated reductive cyclization of activated alkynes with tethered ketones using Stryker's reagent as a catalyst was reported.[112,90b] Alkynyl ketone substrate **84a** was treated with a catalytic amount of Stryker's reagent in the presence of polymethylhydrosiloxane (PMHS) to afford the *cis*-fused hydrindane **84b** as a single diastereomer. This method is applicable to both five- and six-membered ring formation, but often suffers from competitive over-reduction of the reaction products (Scheme 59).

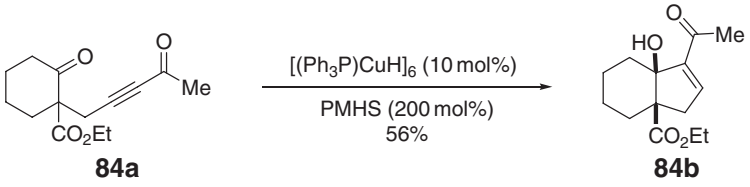
A single example of the reductive cyclization of allenic carbonyl compounds is reported, which employs a rhodium-based catalyst in conjunction with Et_3SiH as terminal reductant.[113] This protocol promotes hydrosilylation–cyclization to form both five- and six-membered rings with exceptional levels of *syn*-diastereocontrol. As revealed



Scheme 57



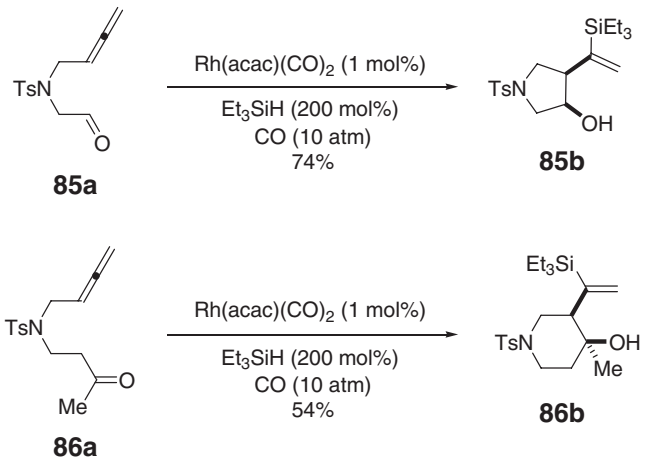
Scheme 58



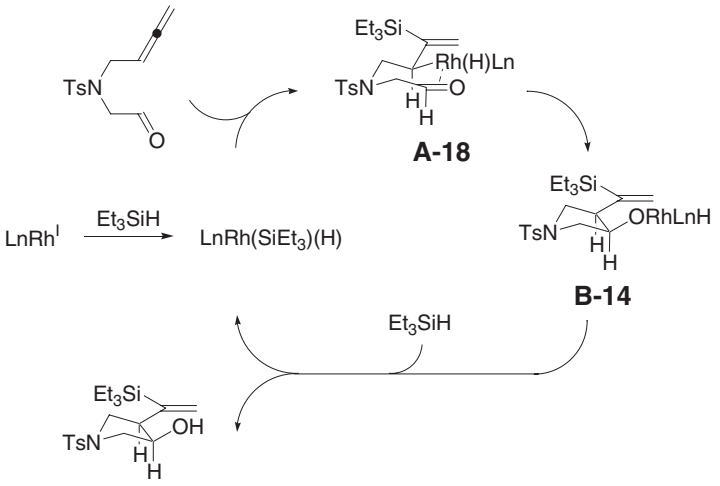
Scheme 59

by the reductive cyclization of allene **86a**, allenic ketones participate in the reductive cyclization to form six-membered rings in moderate yield. Elevated pressures of CO are required for catalytic turnover (Scheme 60).

Although detailed mechanistic studies are not reported, the postulated mechanism for the reductive cyclization of allenic carbonyl compounds involves entry into the catalytic cycle via silane oxidative addition. Allene silylrhodation then provides the σ-allylrhodium hydride **A-18**, which upon carbometallation of the appendant aldehyde gives rise to rhodium alkoxide **B-14**. Oxygen–hydrogen reductive elimination furnishes the hydrosilylation–cyclization product



Scheme 60



Scheme 61

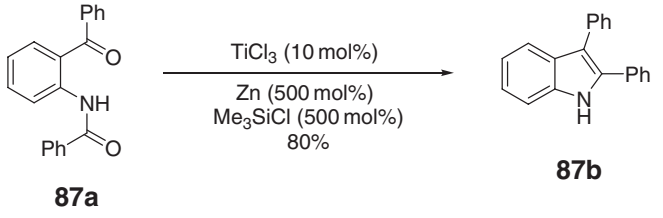
along with low-valent rhodium, which upon silane oxidative addition regenerates the $LnRh(SiEt_3)(H)$ to close the catalytic cycle. The major *cis*-isomer was produced via coordination of the aldehyde with the allylic rhodium complexes **A-18**. A mechanism involving oxidative coupling of the reacting partners followed by hydrosilylytic cleavage of the resulting metallacycle via σ-bond metathesis was not considered, but also may account for formation of the observed product (Scheme 61).

10.10.4 Reductive Cyclizations of Dicarbonyl Compounds (Pinacol and McMurry Couplings)

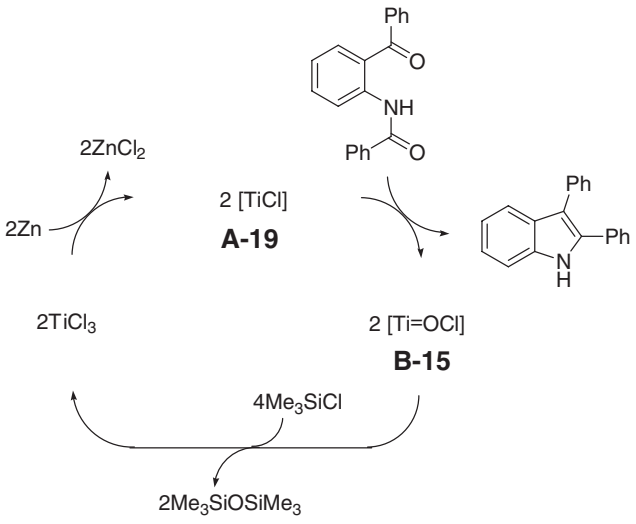
The intermolecular reductive coupling of carbonyl compounds represents an effective means of preparing 1,2-diols (Pinacol reaction) and alkenes (McMurry reaction) from readily available precursors.[114,114a–114e] Uncatalyzed transformations of this type typically employ strongly reducing conditions. With the goal of developing milder and more efficient protocols, several catalytic systems for the reductive coupling of carbonyl compounds have been developed.[8d–8f,12,115]

The first titanium-catalyzed reductive cyclization of dicarbonyl compounds utilizes zinc powder as the terminal reductant.[116] A key feature of this catalytic system involves the use of Me_3SiCl as an additive, which both activates the zinc surface through removal of oxide coating and cleaves the Ti–O bonds of reactive intermediates to promote catalytic turnover. In this way, large loadings of zinc may be avoided. Ketoamide **87a** was treated with substoichiometric amounts of titanium chloride, zinc powder, and Me_3SiCl to generate McMurry coupling product **87b** in 80% yield (Scheme 62).

The proposed catalytic mechanism for intramolecular McMurry reaction begins with the reduction of $TiCl_3$ by zinc metal to generate the activated titanium species **A-19**. Reductive cyclization of the dicarbonyl substrate forms the McMurry coupling product, along with titanium oxide complex **B-15**. To close the catalytic cycle, the oxide complex **B-15** is converted to $TiCl_3$ by Me_3SiCl (Scheme 63).[8d,8e]



Scheme 62



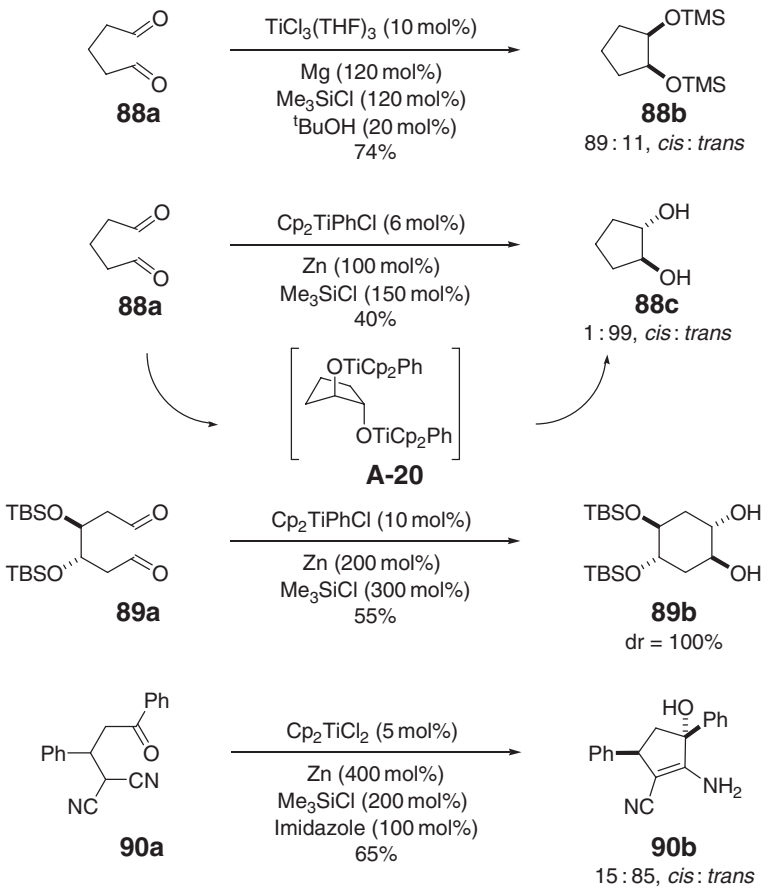
Scheme 63

Subsequent to these seminal studies, titanium-catalyzed Pinacol cyclizations were developed. Substoichiometric loadings of $TiCl_3(THF)_3$ in conjunction with magnesium metal, Me_3SiCl, and ^tBuOH promote the reductive cyclization of aliphatic dialdehydes, such as **88a**, to provide *cis*-diol-containing cycloalkanes.[117] In contrast, exposure of dialdehyde **88a** to $Cp_2Ti(Ph)Cl$ in the presence of zinc metal provides the isomeric *trans*-compound with high levels of stereocontrol.[118,118a] To account for the high *trans*-selectivity, it is postulated that the two bulky titanocene moieties attached to substrate **88a** project away from one another to avoid non-bonded interactions. The sensitivity of the titanocene catalyst with respect to steric features of the substrate is underscored by the reductive cyclization of the chiral dialdehyde **89a**, which proceeds with exceptionally high levels of diastereocontrol to afford tetrasubstituted cyclohexane **89b** as a single stereoisomer. Finally, using a related titanocene-based catalyst system, the reductive cyclization of ketonitriles is achieved.[119] In analogy to the reductive cyclization of dicarbonyl compounds, exposure of ketonitrile **90a** to titanocene dichloride in the presence of excess zinc metal, Me_3SiCl, and imidazole affords the reductive cyclization product with moderate *trans*-selectivity. Notably, two cyano groups are necessary for acquisition of the cyclized product (Scheme 64).

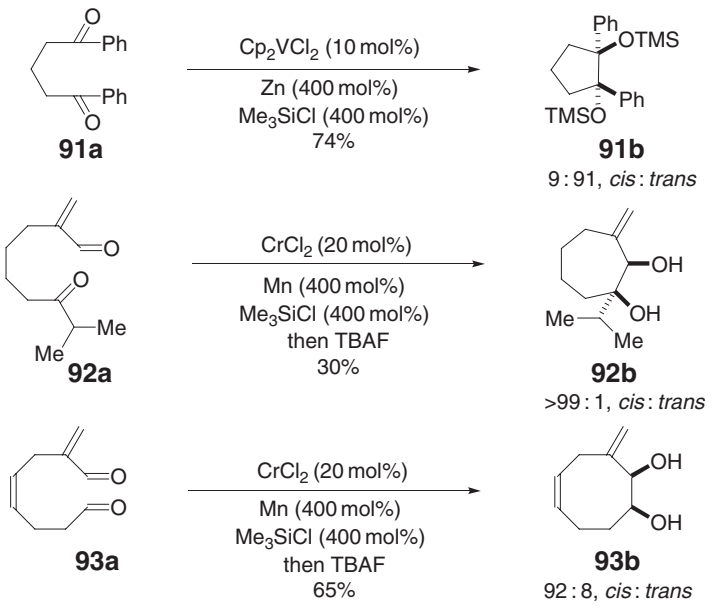
Beyond titanium, it has recently been shown that pinacol cyclization may be catalyzed by other metals. Through the use of vanadium-based catalysts, the Pinacol cyclization of 1,5-diketones may be achieved.[120] Diketone **91a** was exposed to substoichiometric amounts of Cp_2VCl_2 and excess zinc metal and Me_3SiCl to afford the cyclized product **91b** with good *trans*-diastereoselectivity. Using chromium-based catalysts, the formation of medium rings may be achieved.[121] As demonstrated by the reductive cyclization of **92a** and **93a**, seven- and eight-membered ring products form in moderate to good yield with excellent *cis*-selectivity (Scheme 65).

10.10.5 Conclusion

The development of catalytic methods for the reductive cyclization of π-unsaturated substrates is of inherent interest and has emerged as a robust field of research.[122] Nevertheless, it should be recognized that the greatest impact of the aforementioned studies does not reside in the generation of new cyclization methodologies. Rather, it derives from insight into the structural features of the various catalytic systems as they govern reactivity and, ultimately, as they propel the evolution of corresponding intermolecular reductive couplings, in particular those involving basic feedstocks. Hence, while much has been accomplished, it can be seen that many challenges remain. Beyond engineering catalytic systems that adequately address relative and absolute stereochemical control, the development of reductive couplings applicable to σ-bond activation remains an under-developed area of research. Additionally, catalytic systems that employ cost-effective terminal reductants which minimize the generation of byproducts should be devised. In this regard, it is interesting to note that while elemental hydrogen would enable completely atom economical couplings, and served as the progenitor of catalytic reductive coupling chemistry *vis-à-vis* the Fischer–Tropsch reaction (1922)[1,1a–1d] and alkene hydroformylation (1938),[2] hydrogen-mediated couplings that do not involve insertion of carbon monoxide are



Scheme 64



Scheme 65

highly uncommon.[93,93a–93d,123,123a–123d] (For metal-catalyzed intermolecular reductive coupling mediated by hydrogen, see Refs: 123, 123a–123d.) Ostwald once wrote that "there is probably no chemical reaction which can not be influenced catalytically,"[122] and it is certain that the very challenges cited above should fan the flames of discovery in this burgeoning area of research.

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10.11 C–C Bond Formation through Reaction of CO_2 with C≡C and C=C–C=C

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10.11.1 Introduction

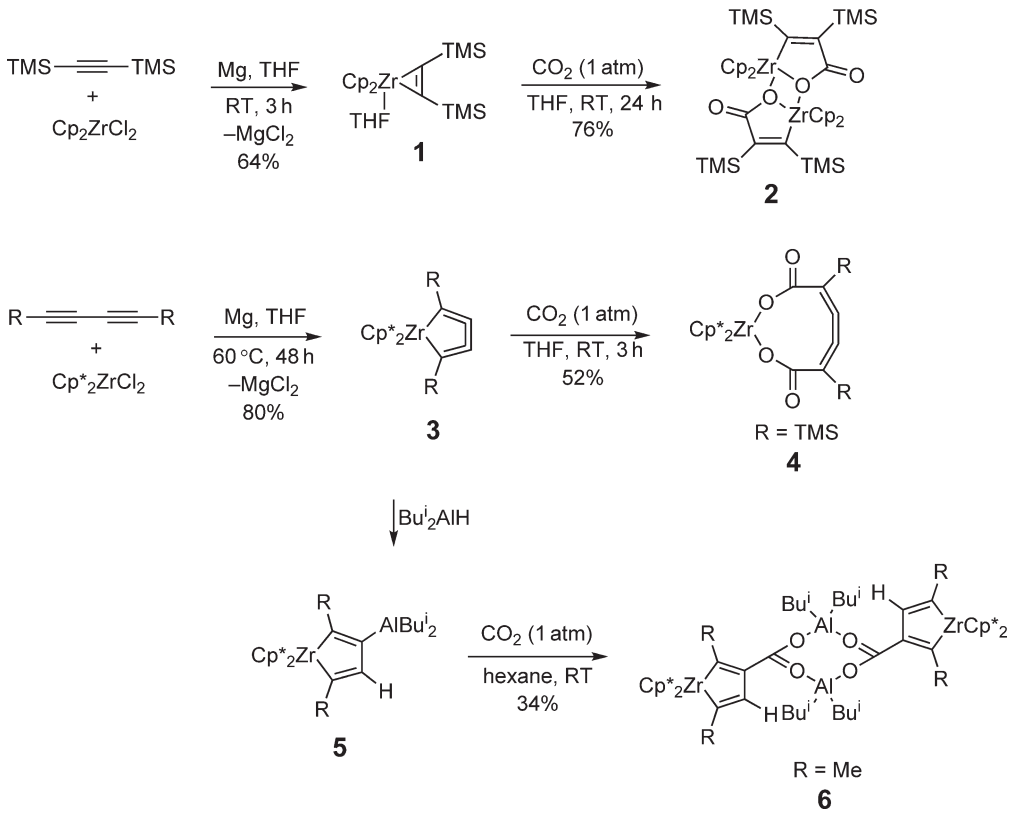
Carbon–carbon bond formation is the most important reaction in synthetic organic chemistry. Various carbon sources can be utilized for the construction of carbon skeletons. Carbon dioxide (CO_2) is a nontoxic, cheap, and attractive C_1-source.[1,1a–1d] The incorporation of CO_2 into organic compounds can be achieved by use of various organometallic reagents or catalysts, especially those of transition metals.[2,2a–2d] This chapter focuses on the carbon–carbon bond formation reactions between CO_2 and acetylenes and dienes, and covers literature from 1993 to 2004. Subsections are categorized according to metals.

10.11.2 Ti- and Zr-Mediated Reactions

10.11.2.1 Reaction with Acetylenes

Ti (IV) or Zr (IV) can be reduced by various reducing agents such as alkaline metals, alkaline earth metals, metal hydrides, alkyllithium, or Grignard reagents to give the corresponding low-valent metal species.[3,3a] The latter can react with unsaturated hydrocarbons such as alkynes to yield the corresponding metallacyclopropenes.[4] The resulting metallacyclopropenes may be intercepted by various substrates.[5,5a]

The zirconacyclopropene **1**, which was prepared by treatment of Cp_2ZrCl_2 with magnesium metal in the presence of bis(trimethylsilyl)acetylene, reacted with one molecule of CO_2 under atmospheric pressure at room temperature to give the dimeric zirconacycle **2** in good yield (Scheme 1).[6,6a,6b] Further insertion of CO_2 did not occur, although **2** has

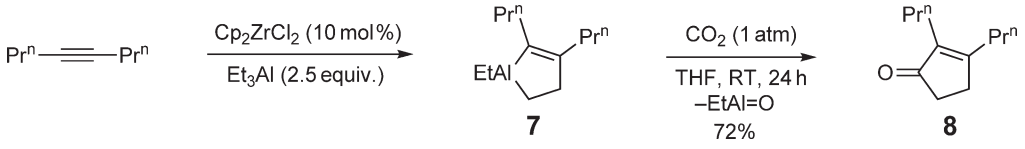


Scheme 1

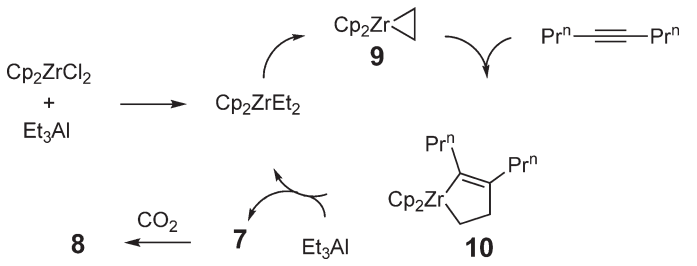
a carbon–zirconium bond. The similar reaction of Cp_2ZrCl_2/Mg with 1,4-bis(trimethylsilyl)-1,3-butadiyne produced the five-membered zirconacyclocumulenes **3** in 80% yield (Scheme 1). In contrast with **2**, the zirconacyclocumulene **3** incorporated two molecules of CO_2 to form the cumulenic dicarboxylate **4** under similar conditions.[7] Hydroalumination of **3** with diisobutylaluminum hydride, followed by the insertion of CO_2 into the resultant carbon–aluminum bond, gave the zirconacyclopentadienyl carboxylate **6**.[8]

In the presence of a catalytic amount of Cp_2ZrCl_2, 4-octyne could be carboaluminated by Et_3Al to give the aluminumcyclopenetene **7** (Scheme 2). The reaction of **7** with CO_2 gave cyclopentenone **8** in 72% yield.[9,9a] The reaction mechanism is shown in Scheme 3. First, Cp_2ZrCl_2 reacts with Et_3Al to yield Cp_2ZrEt_2, which after elimination of ethane affords the zirconacyclopropane **9**. The insertion of 4-octyne in **9** yields zirconacyclopentene **10**. Transmetallation between **10** and Et_3Al releases **7** and Cp_2ZrEt_2. When an enyne compound such as **11** was used, the bicylic cyclopentenone **13** was obtained via the intermediate **12** (Scheme 4).[9]

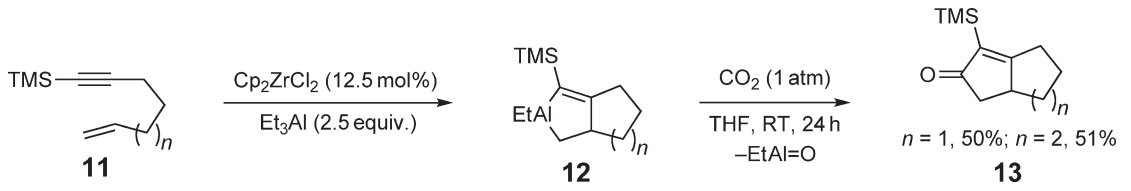
Similar to the reaction of zirconacyclopropene **1**, titanacyclopropene **14** reacted with CO_2 to give titanacycle **15** (Scheme 5).[10,10a–10c] However, the reaction of $Cp^*_2TiCl_2$/Mg with 1,4-bis(trimethylsilyl)-1,3-butadiyne did not afford a titanacyclocumulene species, but yielded titanacyclopropene instead **16**, which on reaction with CO_2 gave the titanacycle complex **17**.[7] In the case of the titanium half-metallocene complex **18**, the five-membered titanacyclocumulene **19** was obtained but the insertion of CO_2 took place only at one of the two Ti–carbon bonds, leading to the formation of **20** (Scheme 5),[11] which is in contrast with what was observed in the case of the Zr analog **3**. The



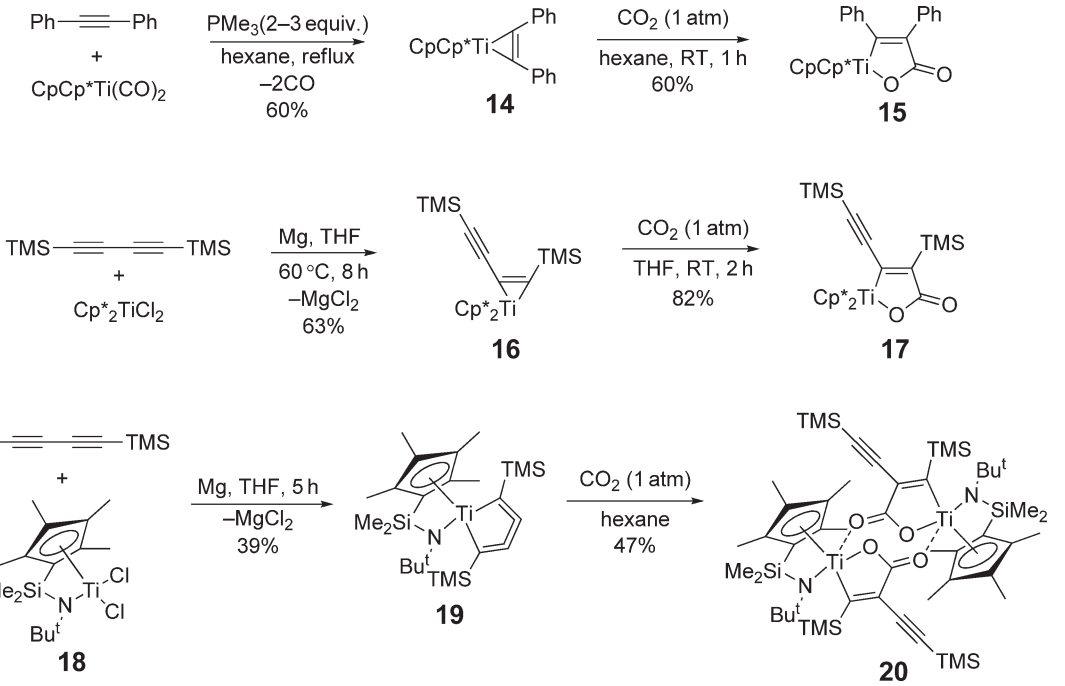
Scheme 2



Scheme 3



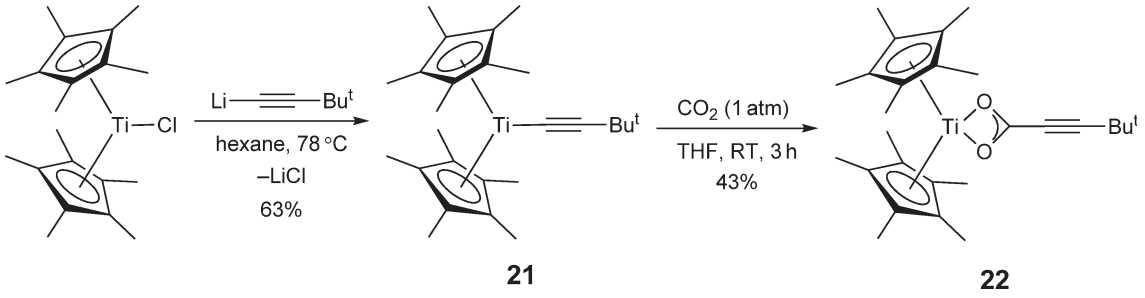
Scheme 4



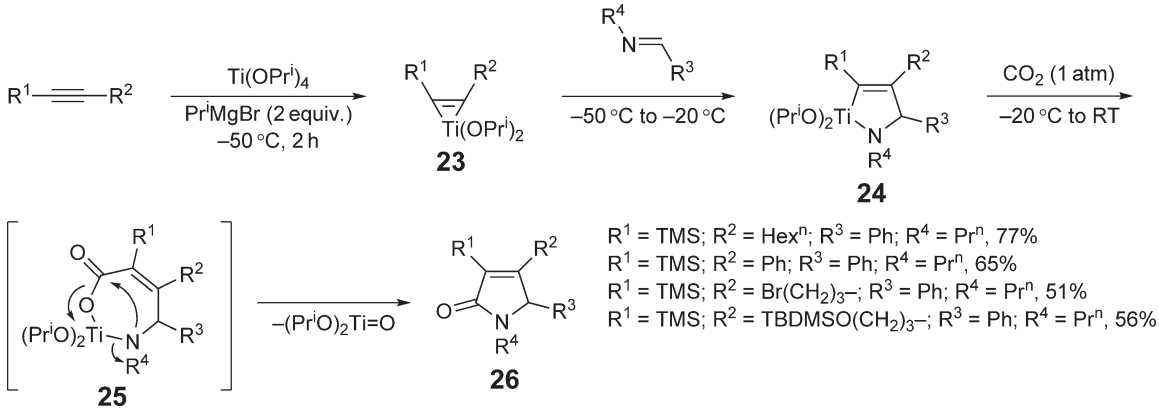
Scheme 5

reaction of the terminal acetylide complex **21** with CO_2 afforded directly titanium carboxylate **22** in 89% yield (Scheme 6).[12]

Similar to Cp_2TiCl_2, $Ti(OPr^i)_4$, as a less expensive precursor, can also be utilized for the synthesis of titanium–alkyne complexes.[13] The reactivity of the $(Pr^iO)_2Ti$–alkyne complexes toward a variety of substrates has been investigated.[14] In the case of unsymmetrical alkynes as a starting material, the less hindered carbon of the resultant



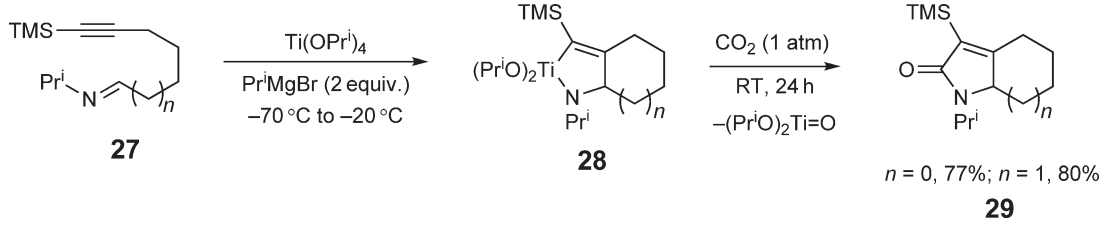
Scheme 6



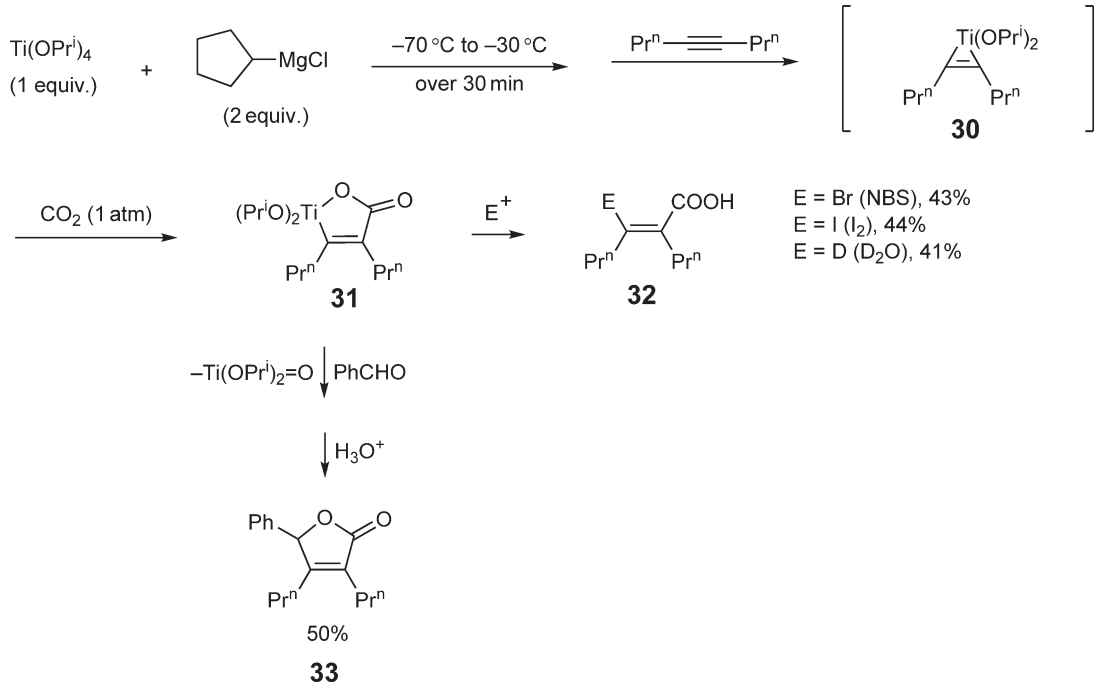
Scheme 7

unsymmetrical titanacyclopropenes such as **23** regioselectively reacted with imines to give the azatitanacyclopentene complexes **24** (Scheme 7). When **24** was allowed to react with CO_2 under atmospheric pressure, 3-pyrrolin-2-ones **26** were obtained in moderate to high yields with the release of $(Pr^iO)_2Ti{=}O$.[15] These reactions were done in one pot. Intramolecular cycloaddition of the alkynylimines **27** produced the bicyclic azatitanacycles **28**, which on treatment with CO_2 afforded the bicyclic pyrrolinone derivatives **29** in high yields (Scheme 8).[15] This reaction can be applied for the construction of indolin-2-one, a structure often seen in naturally occurring alkaloids such as thomandersine.[16]

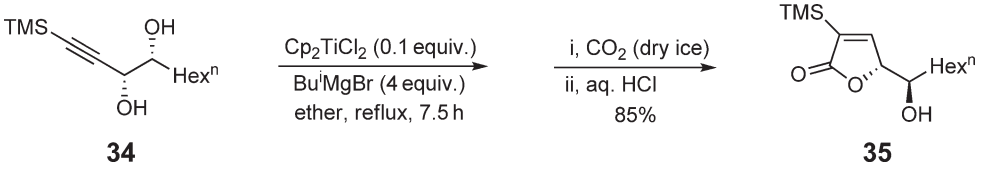
The bisfunctionalization of alkynes by both CO_2 and another electrophile can also be achieved, as shown in Scheme 9.[17,17a] The titanium–carbon bond in the titanacycle complex **31**, which was formed by reaction of CO_2 with the titanacyclopropene **30**, can be substituted with various electrophiles. For example, its reaction with NBS or I_2 afforded the synthetically useful vinyl bromide or iodide **32**, respectively, while the reaction with D_2O yielded the β-deuterated α,β-unsaturated carboxylic acid. When an aldehyde such as PhCHO was used as an electrophile, butenolide **33** was produced after acidic workup.



Scheme 8



Scheme 9

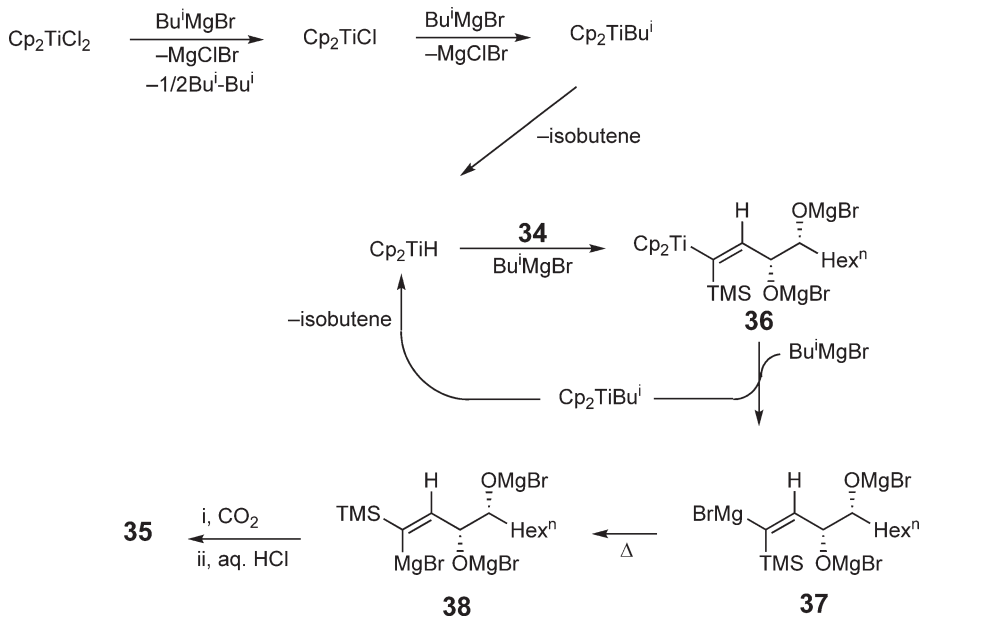


Scheme 10

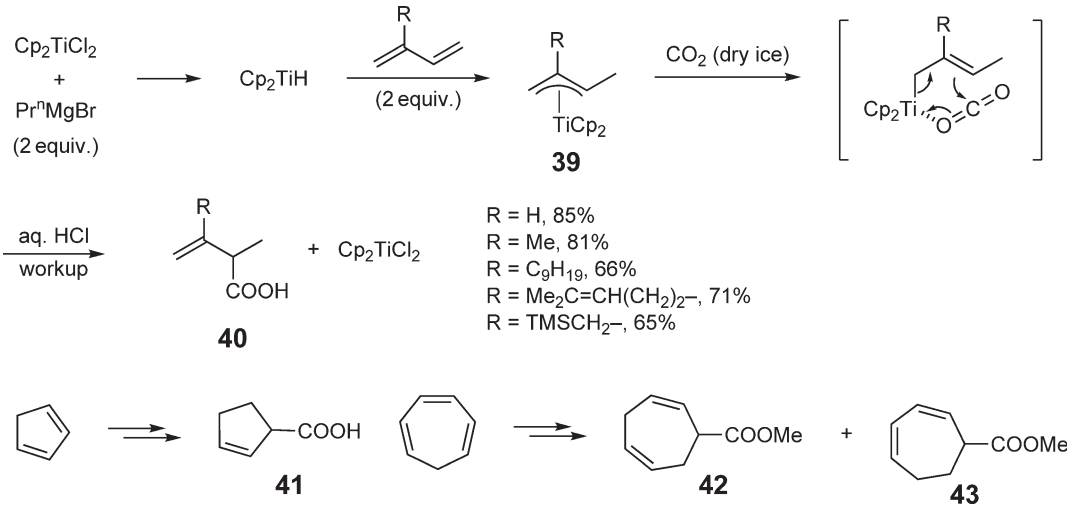
Transition metal-catalyzed hydromagnesation of unsaturated hydrocarbons is a well-known methodology for the preparation of highly functionalized Grignard reagents.[18] Ti-catalyzed hydromagnesation of γ-(trimethylsilyl)propargyl alcohol **34** followed by carboxylation gave the chiral butenolide **35** in high yield (Scheme 10).[19] The reaction mechanism is shown in Scheme 11. The reaction of Cp_2TiCl_2 with Bu^{i}MgBr gave Cp_2TiH, which on reaction with **34** yields the hydrotitanation product **36** with *cis*-configuration. Transmetallation between **36** and Bu^{i}MgBr should afford Cp_2TiBu^i and **37**. Elimination of isobutene from Cp_2TiBu^i would regenerate Cp_2TiH. The vinylmagnesium species **37** can be isomerized to **38** under reflux condition,[20] which after carboxylation with CO_2, followed by hydrolysis, gives the butenolide **35**. The chiral butenolide **35** can serve as a useful precursor to various kinds of butenolides and saturated γ-lactones, which are important building blocks for the synthesis of biologically active natural products.[21,22]

10.11.2.2 Reaction with Dienes

Metal–allyl species is one of the most important reagents in organic synthesis.[23] Generaly, π-allyltitanium compounds can be prepared by transmetallation reaction with titanium halides or by hydrotitanation of dienes.[15] Treatment of Cp_2TiCl_2 with Pr^{n}MgBr in the presence of dienes gave the π-allyltitanium complex **39** through hydrotitanation of the dienes with the *in situ* generated Cp_2TiH intermediate (Scheme 12). The regioselectivity of the hydrotitanation reaction was controlled by steric effect, and the reaction proceeded at the less hindered C–C double bond. However,



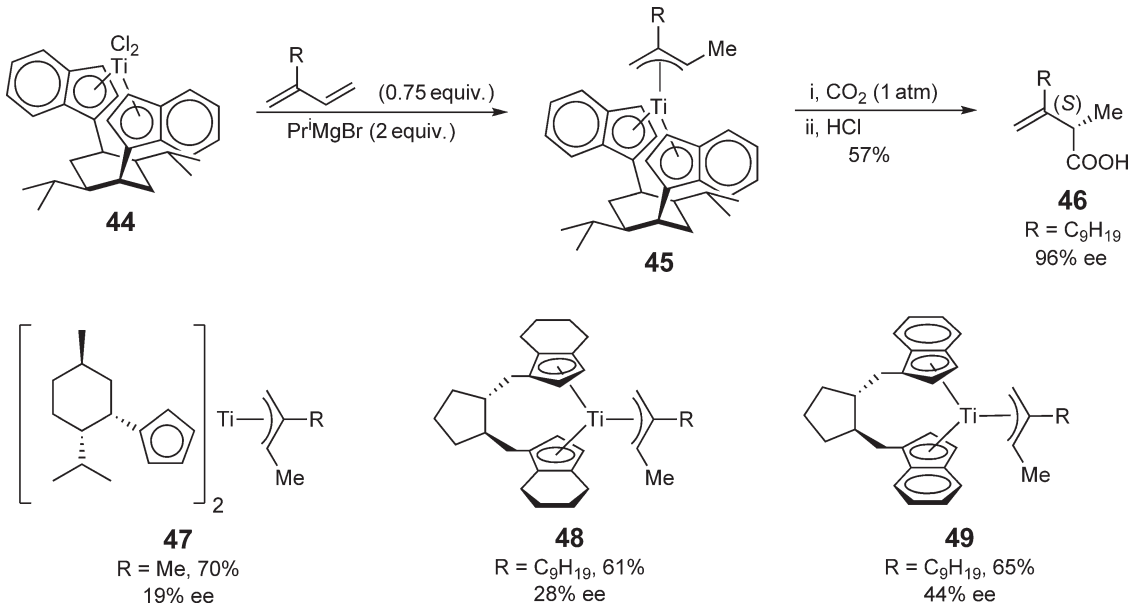
Scheme 11



Scheme 12

the reaction of the resulting π-allyltitanium complex **39** with CO_2 occurred at the substituted terminal allyl carbon and yielded the β,γ-unsaturated carboxylic acid **40** as shown in Scheme 12.[24] A variety of β,γ-unsaturated carboxylic acids can be obtained thus in moderate to good yields. Although a stoichiometric amount of titanium complex was required in this reaction, the starting Cp_2TiCl_2 was easily recovered by simple workup. This carboxylation can be applied to cyclic dienes as well. For example, in the case of cyclopentadiene, the reaction took place smoothly to give the corresponding β,γ-unsaturated carboxylic acid **41**. In the case of cycloheptatriene, two different regioisomers **42** and **43** were isolated after treatment with diazomethane,[25] which indicates that a mixture of π-allyltitanium regioisomers should exist in this reaction.

Asymmetric carboxylation was also achieved by use of π-allyltitanium complexes bearing chiral ligands (Scheme 13).[26] The enantiomeric selectivity was significantly influenced by the chiral auxiliary ligands used. In the case of **45**, the chiral β,γ-unsaturated carboxylic acid **46** was obtained with excellent ee.[27,28]



Scheme 13

10.11.3 Ni-Mediated Reactions

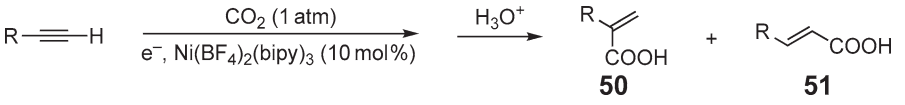
10.11.3.1 Reaction with Acetylenes

10.11.3.1.1 Terminal acetylenes

Under electrolytic conditions, the catalytic incorporation of CO_2 into terminal alkynes was achieved by use of $Ni(BF_4)_2(bipy)_3$ as a catalyst precursor, which yielded the α-substituted α,β-unsaturated carboxylic acids **50** as a predominant product (Scheme 14).[29] An Ni(0) species generated *in situ* at the Mg anode was thought to be a true active species. However, when $Ni(cod)_2$ was used as a catalyst in the presence of a bis(amidine) ligand such as **54**, the β-substituted α,β-unsaturated carboxylic acids **52** were obtained as a major product in some cases (Scheme 15).[30] The regio- and stereoselective carboxylation of various alkynes were achieved when DBU was used as a ligand, which led to the exclusive formation of the β-substituted α,β-unsaturated carboxylic acids **56** after hydrolysis (Scheme 16).[31] The DBU-coordinated nickelacycle species **55** was believed to be a key intermediate. When the nickelacycle **55** was allowed to react with Me_2Zn, the β,β-disubstituted α,β-unsaturated carboxylic acids **58** were obtained in moderate to high yields after hydrolysis (Scheme 16).[32]

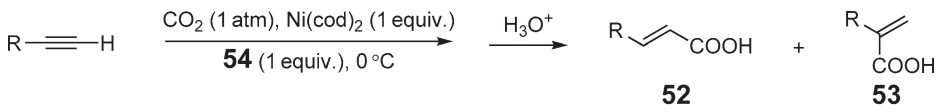
A variety of organozinc reagents can be utilized in this reaction as shown in Scheme 17.[32] In the case of Et_2Zn, however, the H-substituted α,β-unsaturated carboxylic acid, such as $BnOCCH_2CH_2CH{=}CHCO_2H$, was obtained as a major product as a result of β-hydride elimination of the ethylnickel intermediate followed by reductive elimination of the resultant hydride species (entry 3).

The Ni-mediated alkyne carboxylation/Zn-transmetallation can be applied for the construction of heterocycles (when appropriate Michael-donor-containing terminal alkynes are used). As shown in Scheme 18, carboxylation of **60**

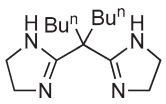


R	*Yield* (%)	*Ratio* **50**:**51**
Hex^n	60	90:10
Cyclopentyl	50	91:9

Scheme 14



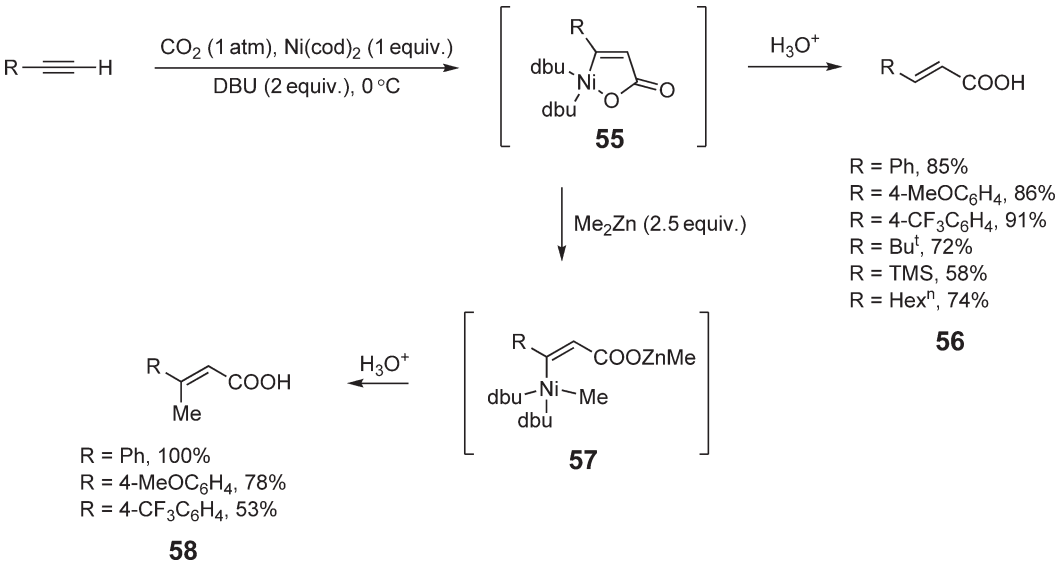
52 53



54

R	*Yield* (%)	*Ratio* **52** : **53**
Ph	63	98 : 2
Cyclohexen-1-yl	67	92 : 8
$PhCH_2CH_2$	38	47 : 53

Scheme 15



55

R = Ph, 85%
R = 4-$MeOC_6H_4$, 86%
R = 4-$CF_3C_6H_4$, 91%
R = Bu^t, 72%
R = TMS, 58%
R = Hex^n, 74%

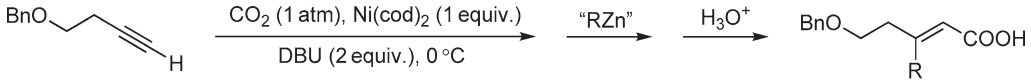
56

R = Ph, 100%
R = 4-$MeOC_6H_4$, 78%
R = 4-$CF_3C_6H_4$, 53%

58

57

Scheme 16

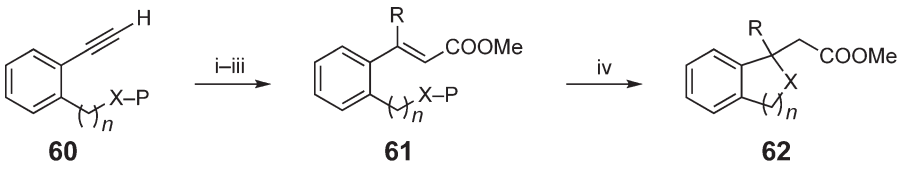


59

Entry	"*RZn*" (equiv.)	*Yield* (%)
1	PhZnCl (2)	69
2	BnZnCl (1.5)	81
3	Et_2Zn (1.5)	9[a]
4	Bu^nZnCl (3)	68
5	4-$MeOOCC_6H_4$ZnI (2)	70
6	MeO_2CCH_2ZnI (3)	33
7	$MeO_2C(CH_2)_3$ZnI (3)	81
8	$MeO_2C(CH_2)_4$ZnI (3)	82

[a] $BnOCCH_2CH_2CH{=}CHCO_2H$ (**59**, R = H) was obtained in 78%.

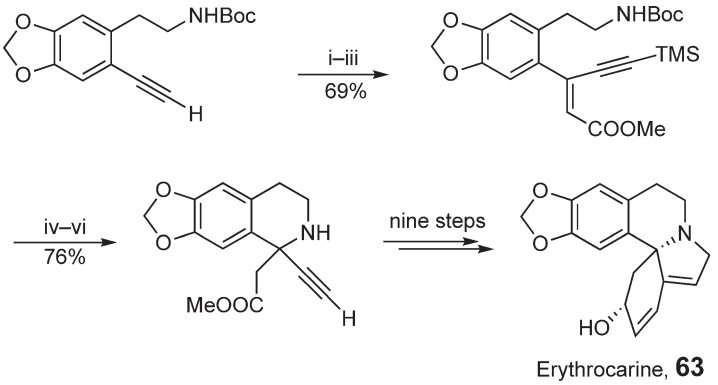
Scheme 17



n	*R*	*X–P*	**61** (%)	*X*	**62** (%)
1	Me	OTBDMS	81	O	81
2	Me	OTBDMS	67	O	81
1	Me	NBnBoc	75	NBn	83
2	Me	NBnBoc	76	NBn	79
1	TMS	NBnBoc	71	NBn	85

i, CO_2 (1 atm), $Ni(cod)_2$ (1.1 equiv.), DBU (3.3 equiv.), THF, 0 °C, 1 h; ii, RZnX (3 equiv.), 0 °C, 5 h; iii, CH_2N_2; iv, $Bu^n{}_4NF$ (X-P = OTBDMS) or CF_3COOH (X-P=NBnBoc).

Scheme 18

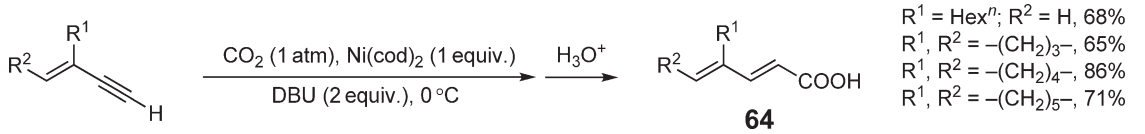


i, CO_2 (1 atm), $Ni(cod)_2$ (1.1 equiv.), DBU (3.3 equiv.), 0 °C, 1 h; ii, TMS(ethynyl)zinc chloride (3 equiv.), 0 °C, 24 h; iii, CH_2N_2; iv, CF_3COOH, RT, 3 h; v, MeOH, reflux, 18 h; vi, $Bu^n{}_4NF$, THF

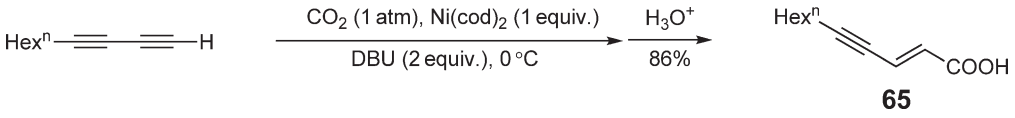
Scheme 19

in the presence of $Ni(cod)_2$/DBU, followed by transmetallation with RZnX and treatment with CH_2N_2, yielded the corresponding α,β-unsaturated esters **61**.[33] On removal of the protecting groups in **61**, intramolecular hetero-Michael addition occurred rapidly to afford the heterocyclic compounds **62** in high yields. This reaction has been utilized for the total synthesis of natural product erythrocarine **63**, as shown in Scheme 19.[34]

In the case of enynes, the CO_2 insertion took place selectively at the terminal position of the alkyne unit to give the corresponding dienoic acids **64** in good yields (Scheme 20).[31] Similarly, the reaction of 1,3-decadiyne with CO_2 yielded **65** as the only product (Scheme 21).



Scheme 20



Scheme 21

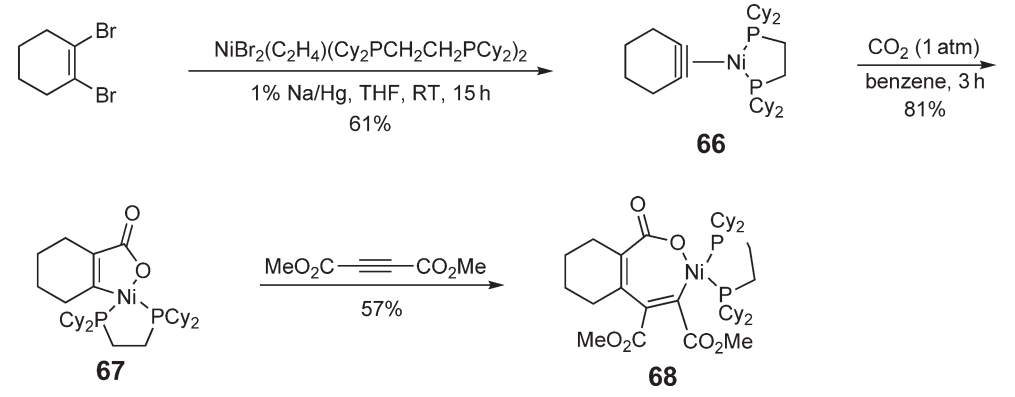
10.11.3.1.2 Internal acetylenes

Generally, cyclohexyne is an unstable molecule because of its ring strain. However, it can be stabilized by coordination to transition metals.[35] The reduction of 1,2-dibromocyclohexene by sodium/mercury in the presence of a nickel–bromide complex afforded the Ni–alkyne complex **66** as a thermally stable and isolable compound (Scheme 22).[36] Complex **66** smoothly reacted with CO_2 under atmospheric pressure to give nickelacycle **67** in good yield. Dimethyl acetylenedicarboxylate was inserted into the vinyl–nickel bond in **67** to give the seven-membered oxanickelacycle **68**.

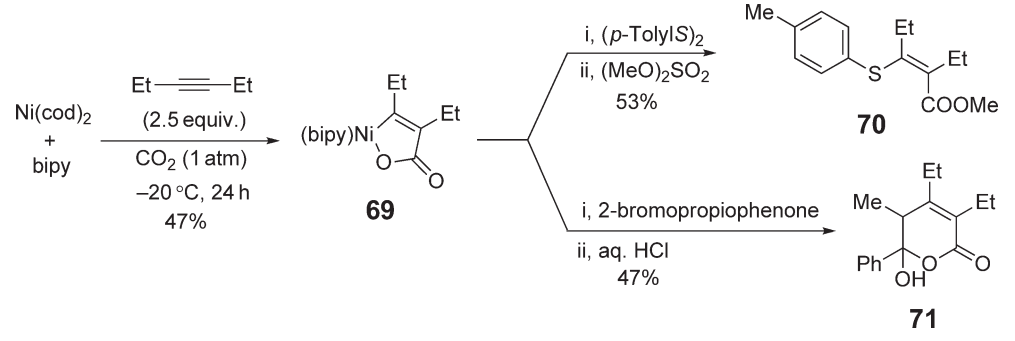
Similar to **67**, the oxanickelacycle **69** prepared from 3-hexyne, $Ni(cod)_2$/bipy, and CO_2 also acted as a nucleophilic reagent. The reaction of **69** with *p*-tolyl disulfide took place at the Ni–C bond to give vinyl sulfide **70** in 53% yield after esterification (Scheme 23).[37] In the case of 2-bromopropiophenone as an electrophile, the cycloadduct **71** was obtained in 47% yield after acidic workup.

In the case of unsymmetrical alkynes, the carboxylation yielded a mixture of regioisomers. But the reaction in the carbon atom having an alkyl substituent in the alkyne unit seemed to be more preferred than the one with an aryl substituent (Scheme 24).[30] The carboxylation of conjugated diynes by Ni/PTMDA under electrolytic conditions took place predominantly at an "internal" carbon atom of the diyne unit to give **74** as a major product (Scheme 25).[38] When $Ni(cod)_2$/DBU was used as a catalyst, however, the carboxylation occurred exclusively at the "terminal" carbon (Scheme 26).[31]

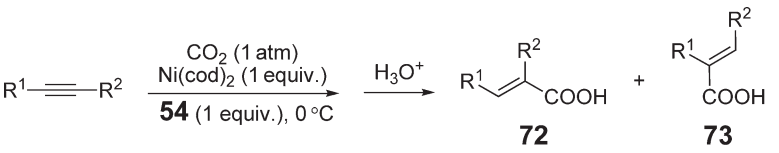
Under supercritical CO_2 at 102 °C, the [2 + 2 + 2]-cyclotrimerization of 3-hexyne with CO_2 was achieved by use of $Ni(cod)_2$/dppb as a catalyst system (Scheme 27).[39,40] In the case of diynes, the intramolecular cyclization/carboxylation took place under high pressure and high temperature (Scheme 28).[41,41a]



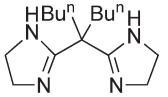
Scheme 22



Scheme 23



72 73



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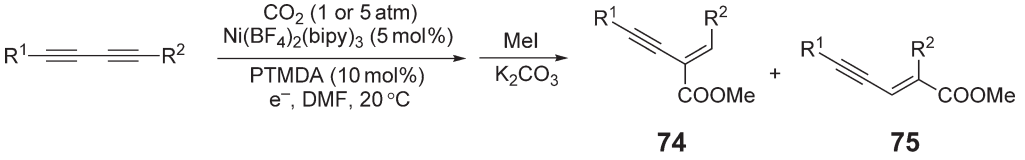
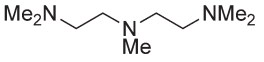
R^1, R^2	*Yield* (%)	*Ratio* **72**:**73**
R^1 = Ph; R^2 = Me	80	95:5
R^1 = 4-$MeOC_6H_4$; R^2 = Me	84	98:2
R^1 = 4-$CF_3OC_6H_4$; R^2 = Me	56	81:19
R^1 = $PhCH_2CH_2$; R^2 = Me	80	40:60

Scheme 24



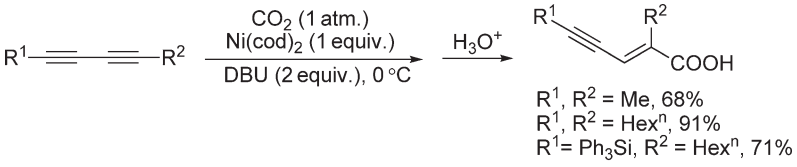
74 75



PTMDA
Pentamethyldiethylenetriamine

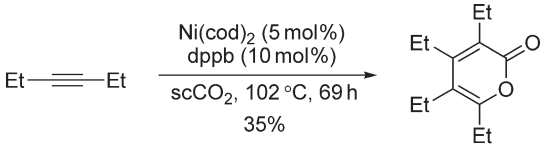
R^1, R^2	*Yield* (%)	*Ratio* **74**:**75**
Pentyl^n	70	70:30
Cyclopentyl	60	97:3
Ph	40	100:0
CH_2OMe	45	98:2
CH_2OPh	35	98:2

Scheme 25



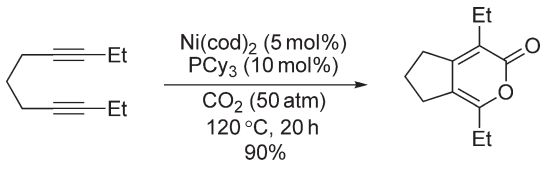
76

Scheme 26



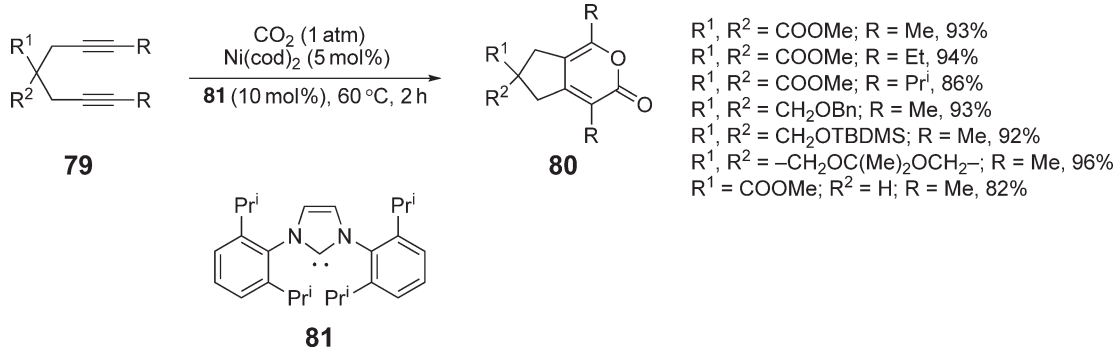
77

Scheme 27



78

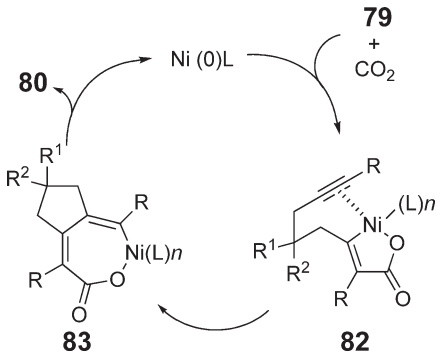
Scheme 28



79 80 81

R^1, R^2 = COOMe; R = Me, 93%
R^1, R^2 = COOMe; R = Et, 94%
R^1, R^2 = COOMe; R = Pr^i, 86%
R^1, R^2 = CH_2OBn; R = Me, 93%
R^1, R^2 = $CH_2OTBDMS$; R = Me, 92%
R^1, R^2 = $–CH_2OC(Me)_2OCH_2–$; R = Me, 96%
R^1 = COOMe; R^2 = H; R = Me, 82%

Scheme 29

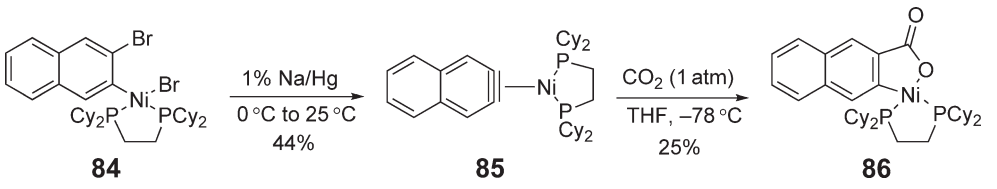


Scheme 30

When an *N*-heterocyclic carbene compound such as **81**[42,42a] was used as a ligand, the intramolecular cyclization/carboxylation of diynes occurred more efficiently. As shown in Scheme 29,[43,43a] various diynes **79** were smoothly converted into the corresponding pyrones **80** in excellent yields under mild conditions (60 °C, 2 h, 1 atm). Ester, benzyl ether, silyl ether, and isopropylidene groups in the starting diynes remained unchanged under the given conditions. A possible reaction mechanism is shown in Scheme 30. Oxidative cyclization to Ni(0)L by diyne **79** and CO_2 would first take place at one of the two C–C triple bonds to yield the oxanickelacycle intermediate **82**. Insertion of the remaining C–C triple bond into the Ni–C bond in **82** should give the seven-membered metallacycle **83**, which after reductive elimination affords **80** and regenerates Ni(0)L. The high electron-donating ability and steric hindrance of the L ligand, such as **81**, which could accelerate the oxidative cyclization and the reductive elimination processes, (respectively,) are thought to be important factors for the promotion of the present reaction.

10.11.3.1.3 Benzynes

Benzynes are highly strained molecules, which are recognized as useful intermediates in organic synthesis.[44] They can be isolated by coordination to transition metals.[45] Similar to the reaction of the cyclohexyne species **66**, Ni–benzyne complex such as **85** reacted with CO_2 to give the corresponding five-membered oxanickelacyle complex **86** (Scheme 31).[46]



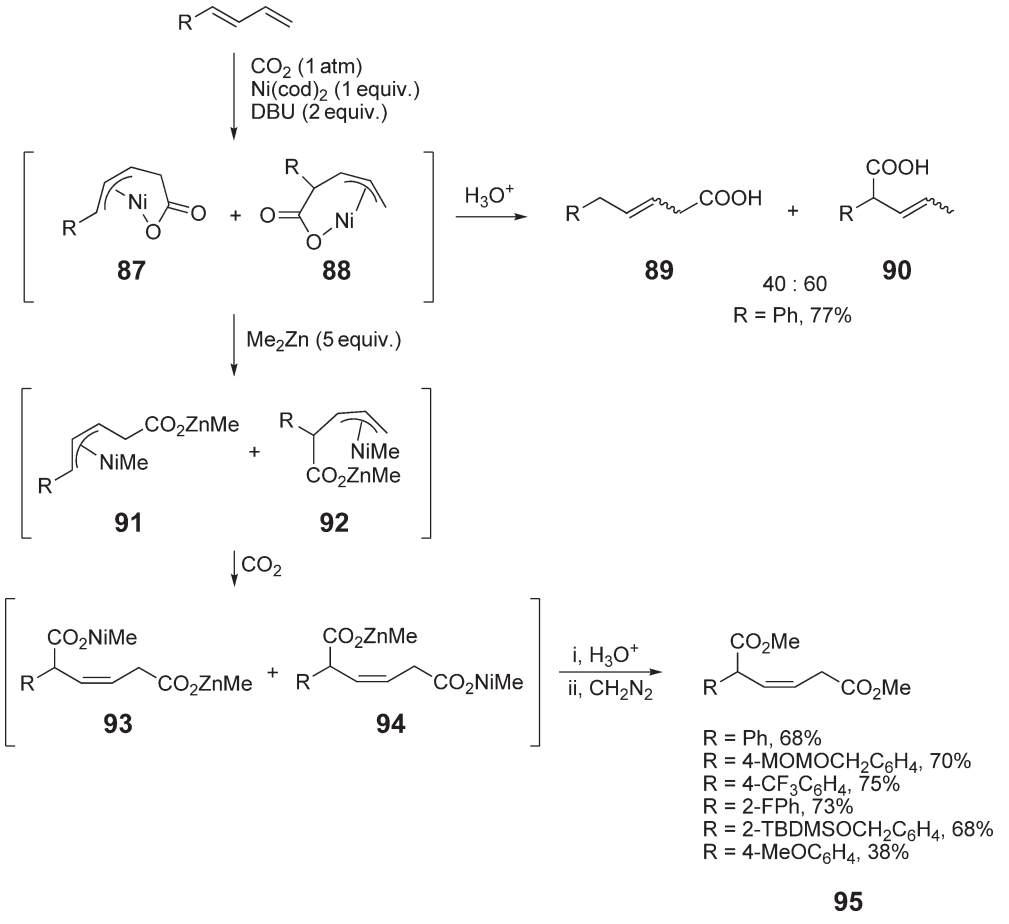
84 85 86

Scheme 31

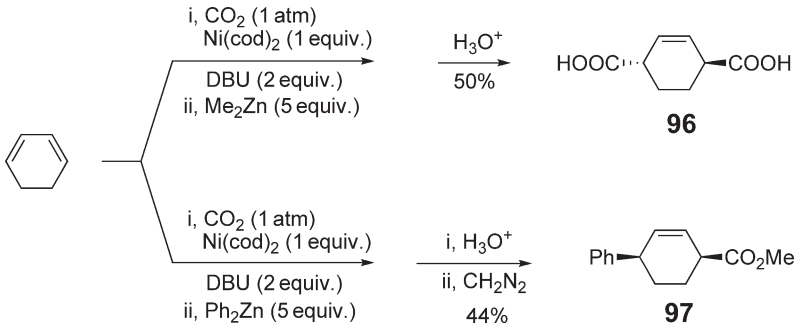
10.11.3.2 Reaction with Dienes

The reaction of CO_2 with 1,3-butadienes in the presence of Ni catalysts usually gave an isomeric mixture of carboxylic acids **89** and **90** after hydrolysis (Scheme 32).[47,48] The oxa-π-allylnickel complexes **87** and **88** might be the reaction intermediates, which could be formed through oxidative cyclization of Ni(0) with CO_2 and the dienes. When Me_2Zn was used as a transmetallation agent to react with the oxa-π-allylnickel intermediates under a CO_2 atmosphere, further carboxylation took place at the π-allylnickel unit. Thus, the 1,4-diesters **95** were obtained after acidic hydrolysis and treatment with diazomethane as shown in Scheme 32.[47]

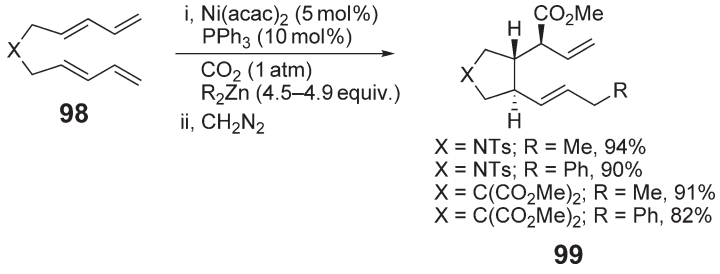
In the case of 1,3-cyclohexadiene with Me_2Zn, the dicarboxylation afforded the *trans*-1,4-dicarboxylic acid **96** (Scheme 33). In contrast, when Ph_2Zn was used instead of Me_2Zn as a transmetallation agent, the phenylative carboxylation occurred in high regio- and stereoselectivity to give the 1,4-*cis*-substituted-2-cyclohexene **97**, as a result of reductive elimination from the phenyl-π-allylnickel intermediate, prior to the second carboxylation reaction (Scheme 33).[47]



Scheme 32

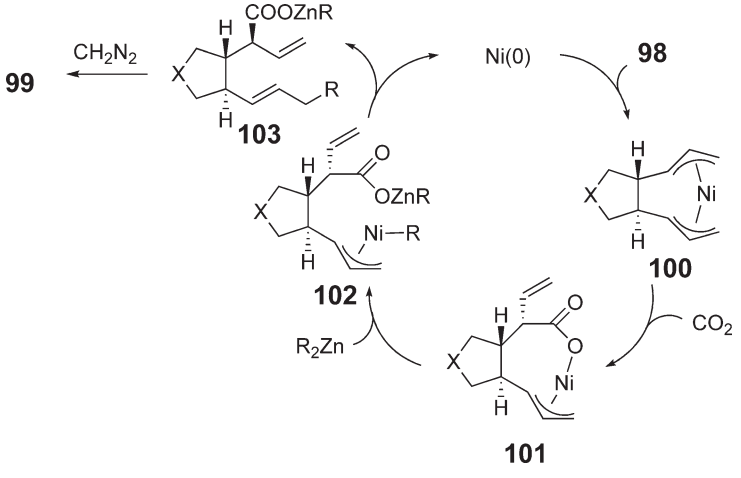


Scheme 33

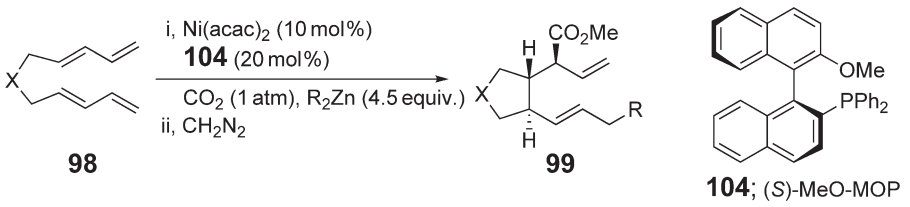


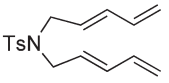
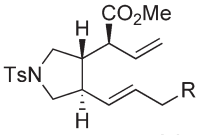
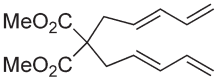
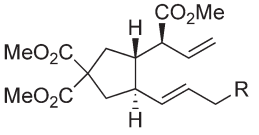
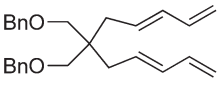
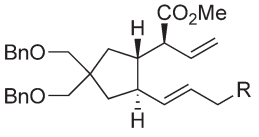
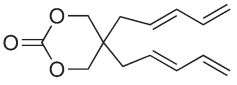
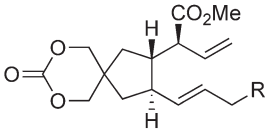
Scheme 34

Transition metal-catalyzed cyclization of bis-1,3-dienes is a highly effective method for the construction of cyclic molecules.[49] The Ni-catalyzed cyclization of the bis-1,3-dienes **98**, in combination with carboxylation, transmetallation with R_2Zn, and treatment with CH_2N_2, under mild conditions, afforded the esters **99** in excellent yields (Scheme 34).[50] As a technical advantage, air stable $Ni(acac)_2$ can be utilized as a catalyst precursor instead of $Ni(cod)_2$. The reaction mechanism is shown in Scheme 35. The reaction is initiated by oxidative cycloaddition of Ni(0) into **98** to produce the bis-π-allylnickel species **100** with *anti*-stereoselectivity at the junction of the cycloadduct. The subsequent insertion of CO_2 into one of the two π-allylnickel units affords the carboxylate **101** stereoselectively. Transmetallation between **101** and R_2Zn gives the nickel π-allyl/R complex **102** which, after reductive elimination, yields **103** and regenerates Ni(0). Treatment of the zinc carboxylate **103** with diazomethane gives methyl ester **99** as the final product.

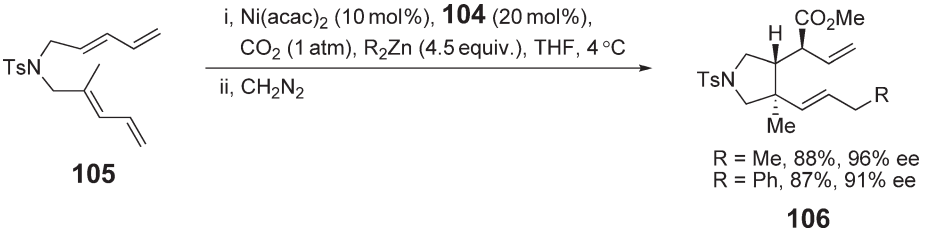


Scheme 35



Entry	*Substrate*	R_2Zn	*Product*	*R, Yield* (%), ee (%)
1		Me_2Zn		Me, 71, 93
2		Ph_2Zn		Ph, 81, 95
3		Me_2Zn		Me, 100, 94
4		Ph_2Zn		Ph, 89, 92
5		Me_2Zn		Me, 95, 95
6		Ph_2Zn		Ph, 80, 90
7		Me_2Zn		Me, 90, 94
8		Ph_2Zn		Ph, 83, 95

Scheme 36



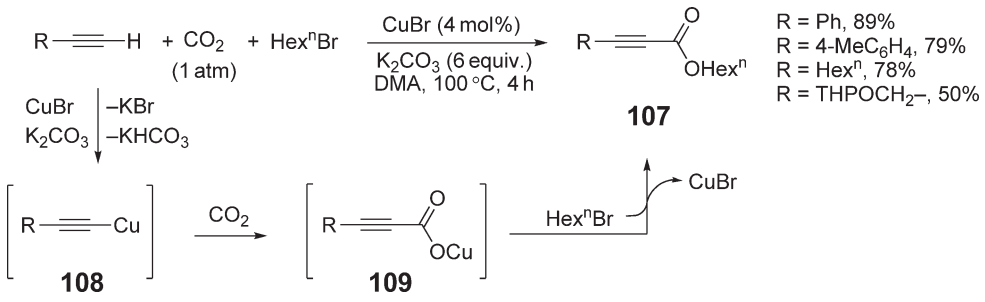
Scheme 37

When a chiral phosphine ligand such as (*S*)-MeO-MOP **104**[52] was used, enantioselective incorporation of CO_2 was achieved as shown in Scheme 36.[51] As a chiral auxiliary ligand, (*R*)-BINAP (52%, 12% ee), (*S*)-(*R*)-BPPFA (62%, 11% ee), (*R*, *R*)-DIOP (75%, 55% ee), (*S*)-NMDPP (67%, 3% ee), (*S*)-PHOX (38%, 15% ee), and (*S*)-(*R*)-PPFA (66%, 43% ee) were less effective for this reaction (R = Me, X = NTs). In the case of an unsymmetrical bis-diene such as **105**, the carboxylation occurred selectively at the less hindered diene part as shown in Scheme 37.

10.11.4 Cu-Mediated Reactions

10.11.4.1 Reaction with Acetylenes

Generally, organocopper compounds can be prepared by transmetallation between copper salts and organometallic reagents such as RLi, RMgX, and RZnX.[53,53a,53b] Copper alkynides can be obtained by reaction of terminal alkynes



Scheme 38

with a copper salt in the presence of a base. The copper alkynides play an important role in organic synthesis.[54,54a–54c] Direct esterification of terminal alkynes was achieved in the presence of CO_2 and 1-bromohexane by use of CuBr or CuI as a catalyst precursor, which afforded the corresponding α,β-unsaturated alkynyl esters **107** through the processes shown in Scheme 38.[55] AgI or $AgNO_3$ was also effective for this reaction.

10.11.4.2 Reaction with Dienes

The 1,4-addition of RCu to a diene compound can generate allylcopper species, which is active toward electrophiles.[53] The silylcupration of 1,3-dienes with $PhMe_2SiCuCNLi$[56] followed by reaction with CO_2 yielded the β,γ-unsaturated carboxylic acids **110** as shown in Scheme 39.[57] The carboxylation took place regioselectively at the γ-position of the σ-allylcopper intermediate **113**.

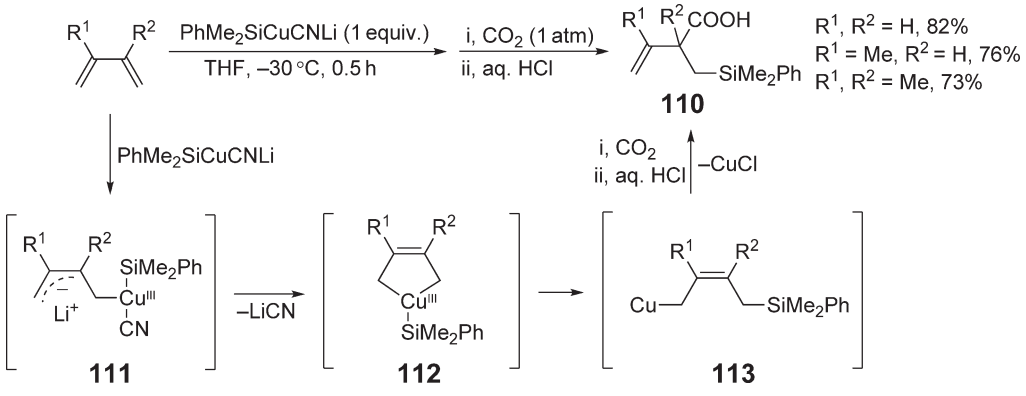
10.11.5 Reactions Mediated by Other Metals

10.11.5.1 Ta-mediated Reaction

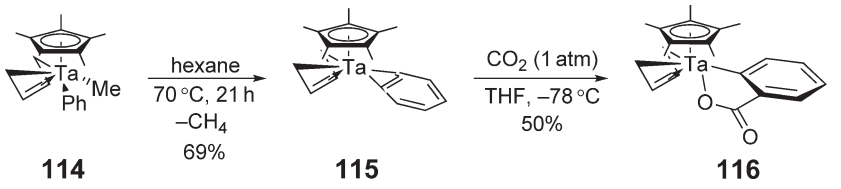
Thermolysis of the tantalum–phenyl/methyl complex **114** led to the formation of the Ta–benzyne complex **115** and the elimination of CH_4.[58] Similar to the reaction of the Ni–benzyne complex **85**, one molecule of CO_2 could be incorporated into the carbon–tantalum bond to form the tantalumcycle **116** as shown in Scheme 40.[59]

10.11.5.2 Ru-mediated Reaction

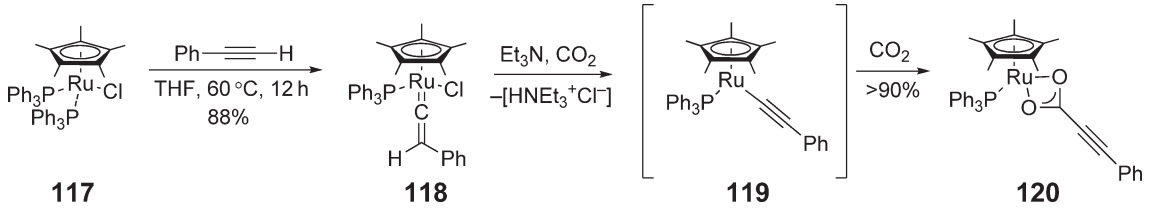
Ru–vinylidene complexes can be easily prepared by reaction of low-valent ruthenium complexes with terminal acetylenes. Treatment of the Ru(II) complex **117** with phenylacetylene gave the Ru(IV)–vinylidene complex **118** in 88% yield (Scheme 41).[60] The reaction of **118** with CO_2 in the presence of Et_3N afforded selectively the Ru–carboxylate complex **120**, probably via the terminal alkynide intermediate **119**.



Scheme 39



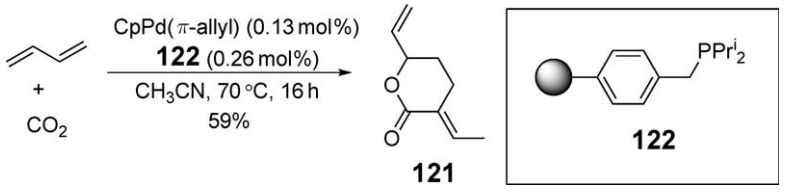
Scheme 40



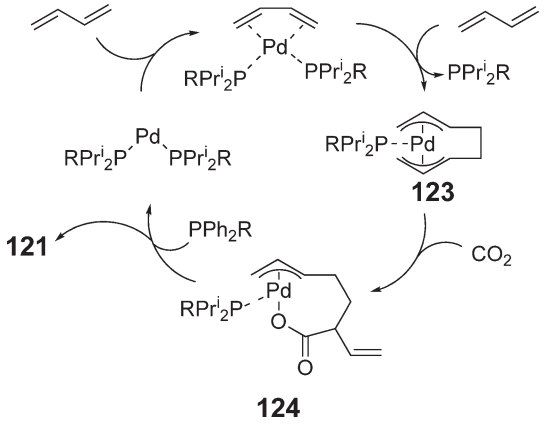
Scheme 41

10.11.5.3 Pd-mediated Reaction

Palladium-catalyzed cyclic carboxylation of dienes can be utilized for the synthesis of lactones.[2] Polymer-supported Pd catalyst could also be used for this reaction (Scheme 42).[61] The reaction is initiated by dimerization of two molecules of diene to give a bis-π-allylpalladium intermediate such as **123**. The incorporation of CO_2 takes place at the internal position of an allyl unit to afford the π-allylpalladium carboxylate **124** which, after reductive elimination/cyclization, yields the δ-lactone **121** (Scheme 43).



Scheme 42



Scheme 43

10.11.6 Conclusion

Transition metal-mediated C–C bond formation through reaction of CO_2 with acetylenes and dienes can serve as a useful method for the construction of various carbon skeletons, such as linear and cyclic carboxylic acids, and esters and lactams. Enantioselective incorporation of CO_2 can also be achieved, especially when combined with sterically controlled formation of cyclic carbo- or heterocyclic skeletons. In perspective of the future in this area, development of more efficient and more selective catalytic systems for incorporation or transformation of CO_2 into useful fine chemicals and polymer materials will continue to be an important and attractive research target.

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10.12 C–C Bond Formation (Part 1) by Addition Reactions: Alder-ene Reaction

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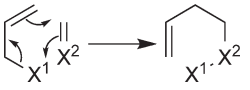
10.12.1 Introduction

The ene reaction, an electronic relative of the Diels–Alder cycloaddition, is a six-electron process involving the reaction of the π and allylic σ-bonds of an ene and the π-bond of an enophile (Equation (1)). Cases in which $X^1 = H$ and $X^2 = C$ are termed Alder-ene reactions; these reactions are reviewed in detail (for reviews of the Alder-ene reaction and related chemistry, see Refs: 1,1a, and 1b). Recent developments in the area of hetero-ene chemistry ($X^1 = H$, $X^2 = N,O$) are also surveyed.



(1)

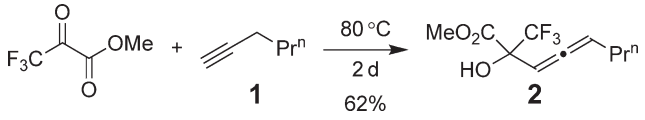
Like so many other reactions, the ene reaction has been given "new life" by metal catalysis. The use of metals ranges from common Lewis acids, which simply lower the barrier of activation of the hetero-ene reactions to transition metal catalysts which are directly involved in the bond-breaking and -forming events, rendering reactions "formal" ene processes. This review is meant to serve as a guide to the vast amount of data that have accumulated in this area over the past decade (1994–2004). If a particular subject has been reviewed recently, the citation is provided and only work done since the time of that review is included here. Finally, the examples included within are meant to capture the essence of the field, the scope, limitations, and synthetic utility; therefore, this review is not exhaustive.

10.12.2 Carbonyl–Ene Reactions and Derivatives Thereof

Synthetic activity associated with the carbonyl-ene reaction is extensive. During the past decade, the trend has been to perform these reactions in the presence of a Lewis acid in an enantioselective fashion. Efforts to find a general catalyst that affords homoallylic alcohols in high yields and enantioselectivities are continual. The synthetic utility of this reaction has been validated by its application to the synthesis of a number of natural products (see Section 10.12.6) and many structurally novel motifs that have found a place in drug discovery (*vide infra*). It is the latter application that has resulted in research efforts aimed at large-scale production of carbonyl–ene adducts.

10.12.2.1 Lewis Acid-catalyzed Carbonyl–Ene Reactions

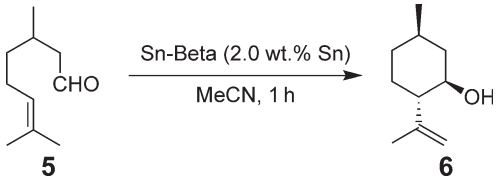
Burger[2] has shown that alkynes undergo both Lewis acid-catalyzed and thermal carbonyl–yne reactions with 3,3,3-trifluoropyruvates to give allenes. Reaction of **1** (Equation (2)) occurs to give a 1 : 1 mixture of diastereomeric allenyl carbinols **2**. Alternatively, reaction of hexyne **1** and methyl trifluoropyruvate with $MgBr_2{\cdot}OEt_2$ at low temperature afforded **2** as an 8 : 1 mixture of diastereomers. The thermal reaction does not suffer from allylic alcohol byproducts arising from reaction of the substrate with the Lewis acid.[3]



(2)

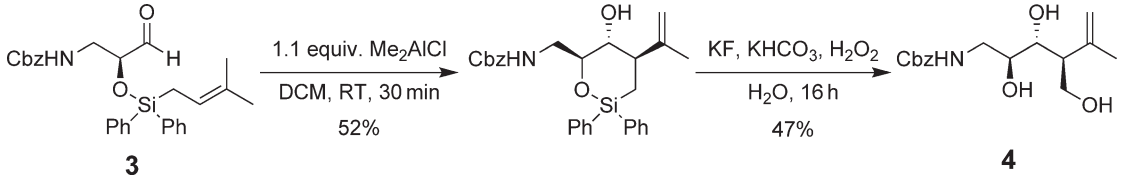
Type I and II silicon-tethered carbonyl–ene reactions were first performed by Robertson.[4,4a,4b] One particularly striking application of this method is the conversion of isoserine derivative **3** (Scheme 1) into amino triol **4** via a carbonyl–ene reaction followed by Tamao–Fleming oxidation.[5]

Corma and Renz[6] developed an effective heterogeneous catalyst system. Incorporation of tin into a beta zeolite network (Sn-Beta) gave a catalyst that was used to convert citronellal **5** to racemic isopulegol (**6**, Equation (3)) with 85% diastereoselectivity. It was calculated that each metal site performed 11,500 reaction cycles. No leaching of the tin was detected. This catalyst system is advantageous over normal Lewis acids, since precautions against humidity are not required, and it is suitable for use in a fixed bed continuous reactor.

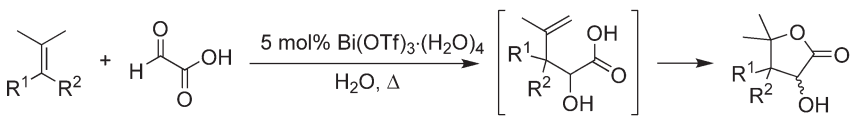


(3)

Structurally novel β-lactams were obtained using enantiopure 4-oxoazetidine-2-carbaldehydes and methylene cyclohexane and α-methyl styrene (Equation (4)).[7] Boron trifluoride diethyletherate and tin(IV) chloride produced the products in the highest yields, and all ene products possessed *syn*-stereochemistry.

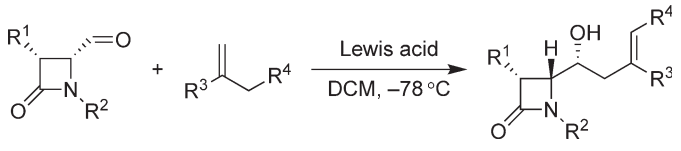


Scheme 1



R^1	R^2	Yield (%)	cis : trans
H	Me	85	36 : 64
H	Et	81	44 : 56
Me	Me	83	

Scheme 2



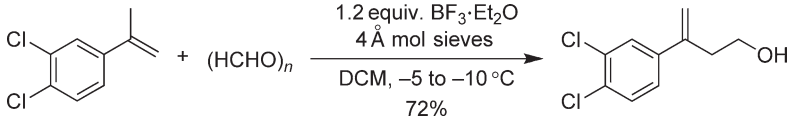
R^1	R^2	R^3	R^4	Lewis acid	Yield (%)
OMe	PMP	–$(CH_2)_3$–		$SnCl_4$	45
OPh	PMP	–$(CH_2)_3$–		$SnCl_4$	60
O-propargyl	PMP	–$(CH_2)_3$–		$BF_3{\cdot}Et_2O$	85[a]
OBn	2-propenyl	–$(CH_2)_4$–		$BF_3{\cdot}Et_2O$	15
OBn	3-butenyl	Ph	H	$BF_3{\cdot}Et_2O$	60
OMe	3-butynyl	Ph	H	$BF_3{\cdot}Et_2O$	52

[a]Reaction run at –40 °C.

(4)

α-Hydroxy-γ-valerolactones were prepared from alkenes and glyoxylic acid in the presence of 0.05 equiv. of bismuth triflate and water (Scheme 2).[8]

A carbonyl–ene reaction between a variety of α-methyl styrenes and paraformaldehyde was effected using the combined boron trifluoride and 4 Å molecular sieves (Equation (5)).[9] The reaction worked best when electron-withdrawing groups (Cl or F) were present on the aromatic ring.



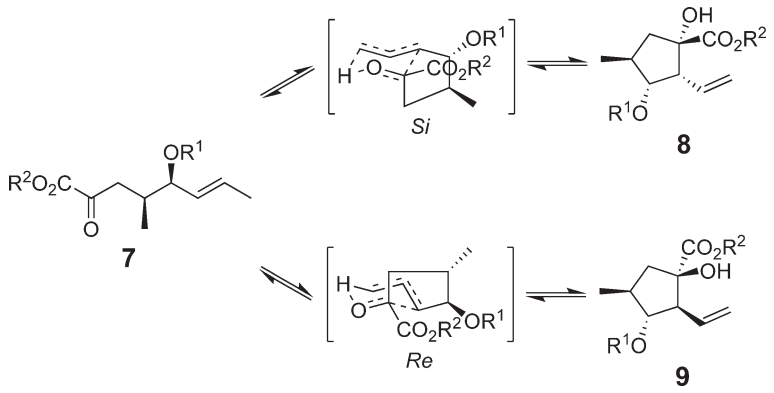
(5)

10.12.2.2 Asymmetric Carbonyl–Ene Reactions

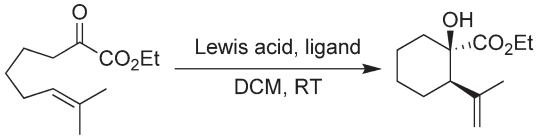
The first catalytic enantioselective ene reaction was reported by Yamamoto in 1988. Since this report there has been a lot of activity in this area, and this reaction has been the subject of two recent reviews.[10,10a] Thus, this section is focused on only the most current developments.

A diastereoselective intramolecular thermal carbonyl–ene reaction of a single enantiomer of keto ester **7** afforded the C5–C14 fragment of the jatrophane skeleton (Scheme 3).[11] The key reaction was performed under thermal conditions (180 °C, 3 days) to afford only the *cis*-compounds **8** and **9** in a 5 : 1 diastereomeric ratio. The kinetic preference for the *cis*-isomers was explained by the less strained *cis*-annulated transition states.

Yang[12] has effected an intramolecular asymmetric carbonyl–ene reaction between an alkene and an α-keto ester. Reaction optimization studies were performed by changing the Lewis acid, solvent, and chiral ligand. Ligand-accelerated catalysis was observed for $Sc(OTf)_3$, $Cu(OTf)_2$, and $Zn(OTf)_2$ (Equation (6)). The resulting optically active *cis*-1-hydroxyl-2-allyl esters provide an entry into multiple natural products.

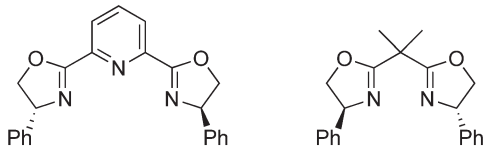


Scheme 3

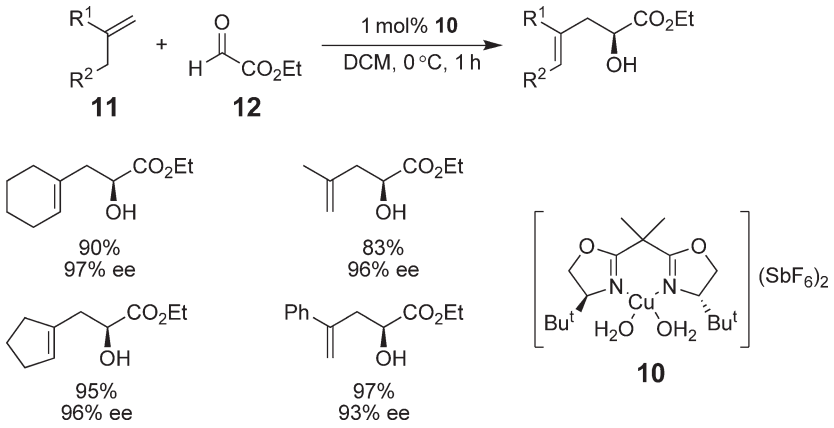


Lewis acid (equiv.)	*Ligand* (equiv.)	*Time* (h)	*Yield* (%)	*ee* (%)
$Sc(OTf)_3$ (0.2)	**L¹** (0.22)	6	86	88
$Cu(OTf)_2$ (1.0)	**L²** (1.1)	6	90	87
$Zn(OTf)_2$ (1.0)	**L²** (1.1)	48	54	54

(6)

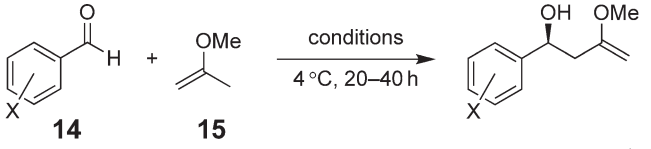


Evans[13] extended the scope of the intermolecular Lewis acid-catalyzed enantioselective carbonyl–ene reaction by increasing the Lewis acidity of the catalyst. Numerous bis(oxazolinyl) (box) Cu(II) complexes were examined. The bis(aquo) complex [Cu((*S*,*S*)-Bu^t-box)$(H_2O)_2$]$(SbF_6)_2$ **10**, a bench-stable solid, was found to be an effective catalyst. Simple and functionalized 1,1-disubstituted alkenes **11** react with ethyl glyoxalate **12** to give high yields of the α-hydroxy esters in high enantioselectivity (Equation (7)). In cases where R^1 does not equal R^2, enantioselectivities were still high but regioselectivities of the product olefins ranged from 1 : 1 to >99 : 1. For 1,2-disubstituted olefins, ee's remained high, but diastereoselectivity ranged from 40 : 60 to 86 : 14.



(7)

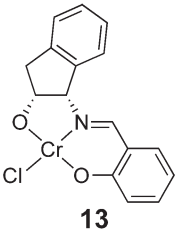
Jacobsen and co-workers[14] have shown that a tridentate Schiff base chromium complex **13** catalyzed an asymmetric carbonyl–ene reaction between a variety of aryl aldehydes (**14**, Equation (8)) and 2-methoxy propene **15** or 2-trimethylsiloxypropene. The highest yields were afforded when the aryl ring was substituted with an electron-withdrawing group; however, the substituent did not seem to affect the enantioselectivity.



14 **15**

X	*Conditions*[a]	*Yield* (%)	*ee* (%)
o-Br	A	97	96
p-Me	B	26	89
m-Cl	A	97	84
o-OMe	B	75	95
p-CN	A	92	84
m-NO_2	A	85	90
2,6-di-Cl	A	82	86

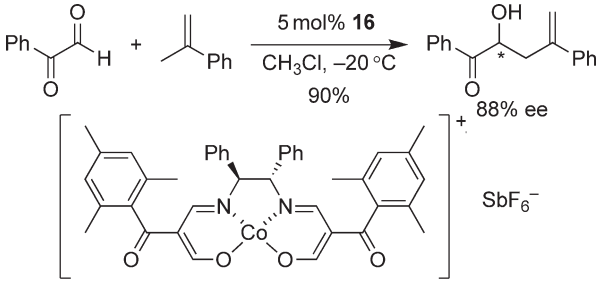
[a]Conditions A: 5 mol% **13**, 5 h pre-stir with 90 mol% BaO and acetone; Conditions B: 7.5 mol% **13**, 5 h prestir with 97 mol% BaO and EtOAc.



13

(8)

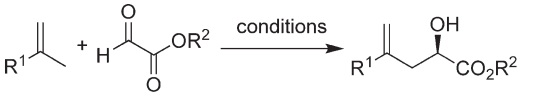
Cationic cobalt(III) complexes have successfully been applied to the asymmetric carbonyl–ene reaction.[15] The yield and enantioselectivity were dependent, to a large extent, upon the counterion, with SbF_6^- giving the best results (**16**, Equation (9)). The conditions were general for a variety of alkenes, but only glyoxaldehydes were used as the carbonyl component.



16

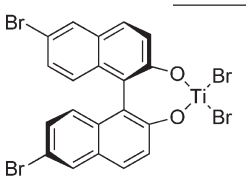
(9)

Mikami and co-workers[16–19] have done extensive work for developing catalysts for the asymmetric carbonyl–ene reaction. Excellent enantioselectivites are accessible with the binol-titanium catalyst **17** (Equation (10)) for the condensation of 2-methyl butadiene (R^1 = vinyl) and glyoxalates (binol = 1,1′-binaphthalene-2,2′-diol).[16] The products were further manipulated toward the total synthesis of (*R*)-(–)-ipsdienol. The oxo-titanium species **18** also provides excellent enantioselectivity in the coupling of α-methyl styrene with methyl glyoxalate.[17] Reasonable yields and good enantioselectivites are also obtained when the catalyst **19** is formed *in situ* from titanium isopropoxide and the binol and biphenol derivatives.[18]

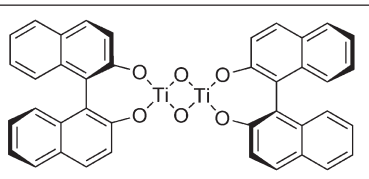


R^1	R^2	*Conditions*	*Yield* (%)	*ee* (%)
CH=CH_2	CH_2CF_3	2 mol% **17**, DCM, –30 °C, 1 h	84	>99
Ph	Me	0.2 mol% **18**, DCM, –30 °C, 2 h	88	98.7
Ph	Bu^n	10 mol% **19**, toluene, 0 °C, 4 h	66	97

(10)



17



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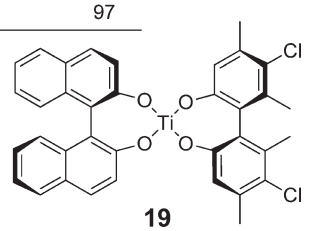
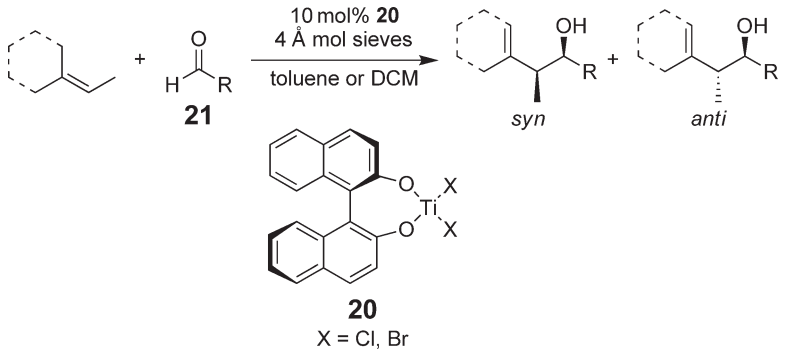


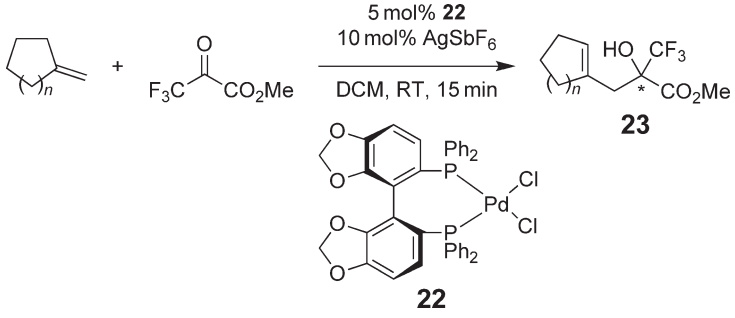
19

A related catalyst **20** was used in the diastereoselective carbonyl–ene reaction between ethylidenecyclohexane, ethylidenecycloheptane, or 2-methyl-2-butene and trifluoroacetaldehyde (**21**, R = CF_3, Equation (11))[19] or methyl glyoxylate (R = CO_2Me).[20] The best results were obtained when X = Br; 63–85% yields are obtained with *syn*/*anti* ratios of 95 : 5 or better, and ee's of the *syn*-isomer of 74–89%.



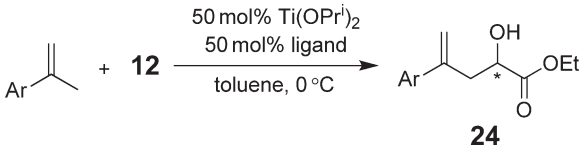
(11)

Mikami *et al.*[21] developed a palladium-based catalyst system **22**, capable of forming quaternary centers via a carbonyl–ene reaction. This is one of the few recent examples of a carbonyl–ene reaction that uses a ketone rather than an aldehyde and affords 84% yields in the case of the five-membered ring (**23**, $n = 1$) to near quantitative yields for the six-membered ring (**23**, $n = 2$), with 96% ee or better in both cases (Equation (12)). This catalyst system also shows selectivity when other ene partners are used, giving *syn*/*anti* ratios equal to or better than the titanium systems and affords linear products with complete (*E*)-selectivity.



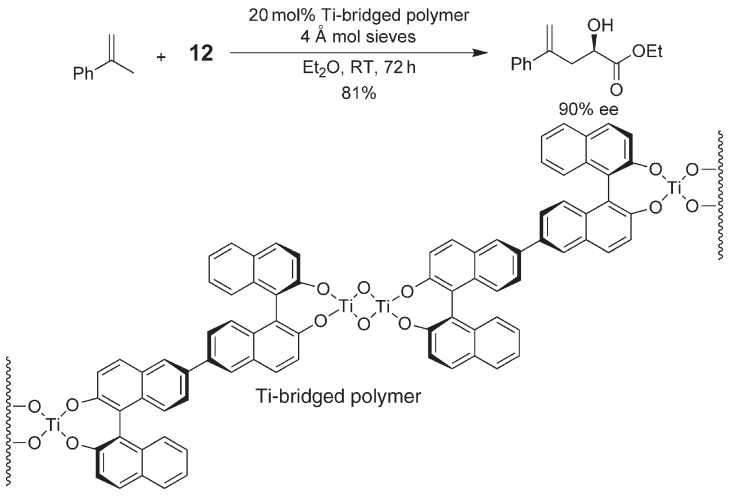
(12)

Ding[22] has performed an enantioselective carbonyl–ene reaction under quasi-solvent-free conditions. For example, 22 g of **24** was produced using 1 ml of toluene and 100 µl of dichloromethane (Equation (13)). A variety of substrates were examined, and high yields and high ee's were reported.



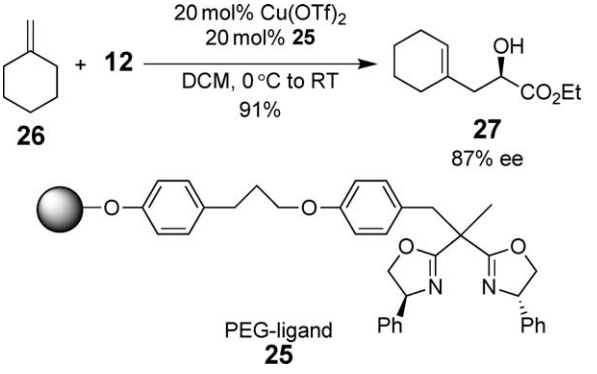
(13)

A number of insoluble or immobilized catalysts have been developed and applied to the carbonyl–ene reaction. As is evidenced by the entries below, the enantioselectivities are variable. Sasai[23] has utilized a titanium-bridged polymer to effect an enantioselective carbonyl–ene (Equation (14)). A single substrate was examined, and the polymer could be reused up to five times without loss of enantioselectivity in the ene reaction.



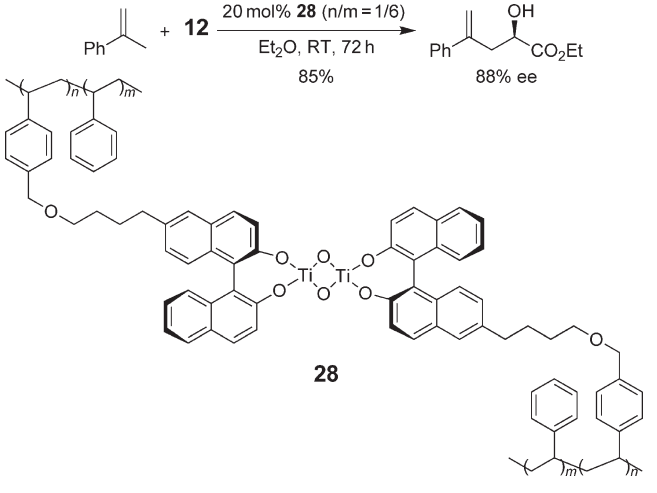
(14)

Chiral bisoxazolines (box) ligands have been attached to a polyethylene glycol (PEG) matrix **25**.[24] The supported ligands were tested on a variety of reactions for their enantioselectivity. The carbonyl–ene reaction between α-methyl styrene or methylene cyclohexane (**26**, Equation (15)) and ethylglyoxalate **12** afforded the corresponding ene adduct **27** in 96% and 91% yield and 95% and 85% ee, respectively.



(15)

Ikegami[25] focused on a self-assembled process between non-cross-linked co-polymer ligands and inorganics. Using the homogeneous protocol developed by Nakai for an enantioselective carbonyl–ene reaction, binaphthols were attached to a polystyrene support and titanium isopropoxide was added. The resulting catalysts **28** were examined for their efficiency. The highest-performing catalyst gave the homoallyllic alcohol in 85% yield with 88% ee (Equation (16)). The catalyst could be reused five times with no loss in activity or enantioselectivity.

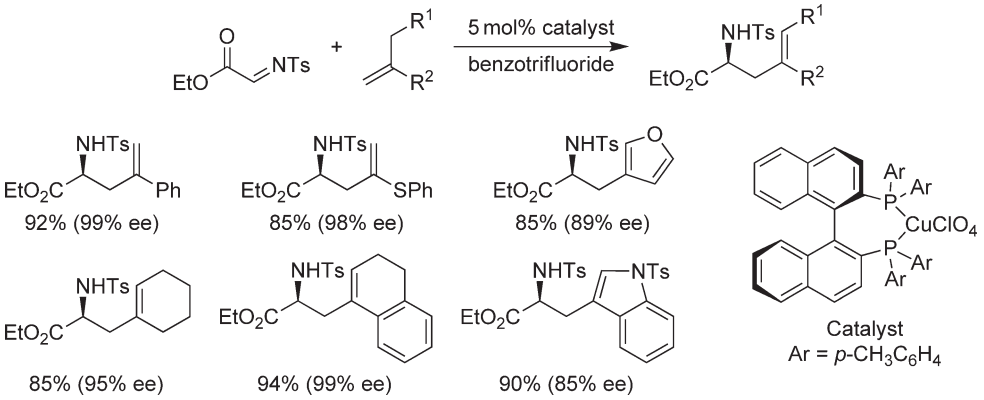


(16)

10.12.2.3 Imino–Ene Reactions

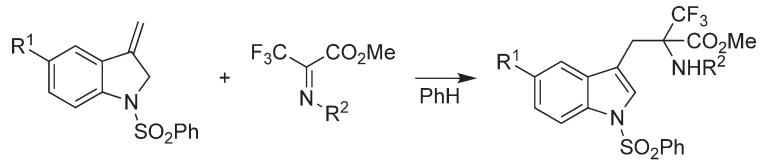
The imino–ene reaction has been recently reviewed; thus, this work only consists of research done since that time.[26] During the past decade there has been some expansion of the scope of the imino–ene reaction (*vide infra*); however, much of the work done in this area has involved its application to the synthesis of biologically relevant compounds (see Section 10.12.7).

An enantioselective imino–ene reaction was developed by Lectka to provide α-amino acid derivatives.[27] Aryl alkenes (α-methyl styrene, tetralene), aliphatic alkenes (methylene cyclohexane), and heteroatom-containing enes, all gave high yields and high ee's of the homoallylic amides (Equation (17)). The mechanism of this reaction has been proposed to proceed through a concerted pathway. This mechanism is evidenced by a large kinetic isotope effect observed in the transfer of H(D).



(17)

Racemic fluorinated tryptophan derivatives **31** were obtained from 3-methylene indole **29** and fluorinated imines **30** using the imino–ene reaction (Equation (18)).[28] The highest yields were obtained for the more electrophilic imines ($R^2 = SO_2Ph$, Ts, SO_2Me). Moreover, these reactions took place at ambient temperature.

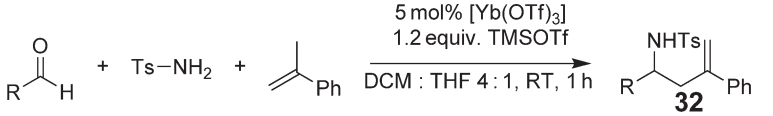


29 **30** **31**

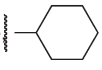
R^1 = H, F
R^2 = SO_2Ph, Ts, SO_2Me

(18)

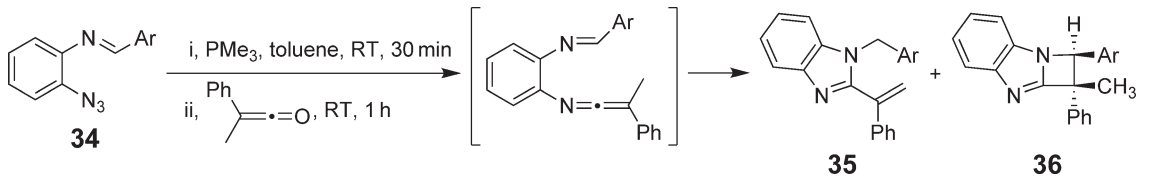
Ytterbium triflate [Yb(OTf)$_3$] combined with TMSCl or TMSOTf are excellent reagents for the conversion of α-methyl styrene and tosyl–imines into homoallylic amides **32** (Equation (19)) (TMS = trimethylsilyl).[29] These conditions produce the first examples of intermolecular imino–ene reactions with less reactive imines. Typically, glyoxalate imines are necessary. A comprehensive examination of the lanthanoid metal triflates was done and the activity was shown to directly correlate with the oxophilicity scale. The first report used preformed imines, and subsequently it was found that a three-component coupling reaction could be effected, bypassing the isolation of the intermediate imine.[30] Particularly noteworthy was the successful participation of aliphatic aldehydes to yield homoallylic amines.



32

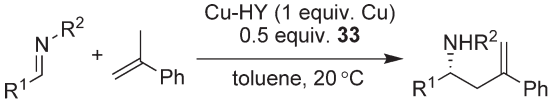
R = Ph (92%), Me (79%), Pr^i (71%), Bu^t (45%), CO_2Et (66%)  (85%),  (76%)

(19)

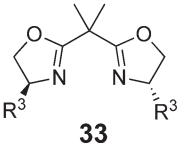


Scheme 4

A heterogeneously catalyzed imino–ene reaction has been accomplished enantioselectively using immobilized bis(oxazoline)-modified copper zeolite Y catalysts (**33**, Equation (20)).[31] The catalyst can be reused without loss of activity. Higher enantioselectivity was observed when compared to homogeneous catalysis. Notably, an electron-withdrawing group on the imine was not a requirement, since amines possessing N-benzyl and isovalerimine groups gave high yields of the homoallylic amines (Equation (20)).



R^1	R^2	R^3	*Yield* (%)	*ee* (%)
CO_2Et	diphenylmethyl	Ph	87	90
Bn	Pr^i	Bu^t	83	92

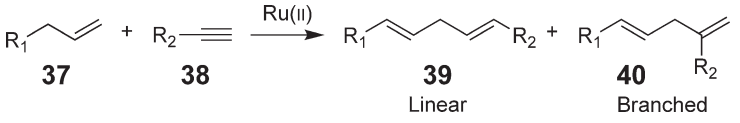


(20)

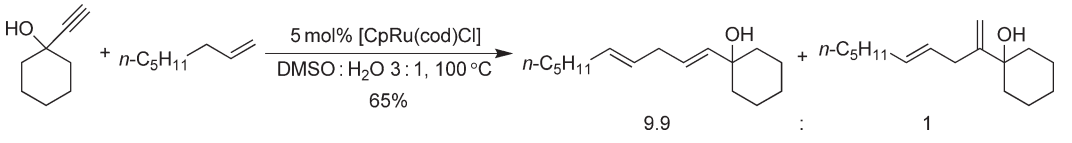
Ketenimines have been observed to participate in imino–ene reactions.[32] Conversion of **34** into **35** could be controlled by *ortho*-substitution on the aryl rings (Scheme 4). For example, if Ar = 2,6-$(CH_3)_2$-C_6H_3, only **35** was obtained in 70% yield and none of the [2 + 2]-cycloadduct **36** was observed.

10.12.3 Transition Metal-Catalyzed Intermolecular Alder-Ene Reactions

Transition metal-catalyzed Alder-ene reactions have proved to be extraordinarily advantageous over their thermal counterparts. Trost and co-workers have extensively explored the scope and limitations of the ruthenium-catalyzed intermolecular Alder-ene reaction between alkynes and alkenes (for reviews of related ruthenium-catalyzed reactions, see Refs: 33,34). Preliminary studies showed that the desired transformation of alkenes and alkynes to skipped dienes could be effected using a variety of ruthenium catalysts, with [CpRu(cod)Cl] being the most efficient. These reactions were remarkably stereoselective, but controlling the regiochemistry was problematic (Equation (21)). For example, the reaction of alkene **37** and alkyne **38** with a ruthenium(II) catalyst afforded the corresponding linear **39** and branched **40** dienes in nearly 1 : 1 ratios. These ratios could be controlled by additional branching at the *alpha*-position of the alkyne that afforded linear to branched ratios as high as 9.9 : 1 (Equation (22)). However, this higher selectivity was only seen for terminal alkynes.[35]



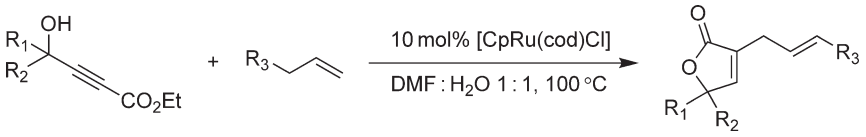
(21)



(22)

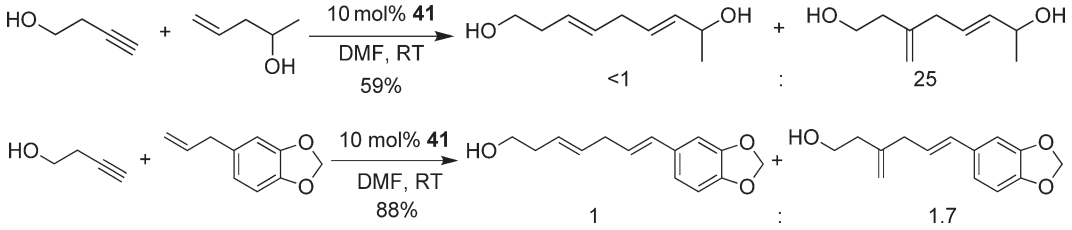
This excellent regiocontrol was exploited by subjecting terminal alkenes and hydroxyalkynoates to ruthenium catalysis conditions to afford butenolides and pentenolides (Equation (23)).[36] The Alder-ene reaction occurs preferentially to form the C–C bond at the *alpha*-carbon of the alkynoate. The unusually high regioselectivity is attributed to a synergistic effect derived from an enhanced coordination of the hydroxyl group to the ruthenium.

This effect is due to the increased electrophilicity of the metal as a result of its conjugation with the ester in the intermediate metallocycle.



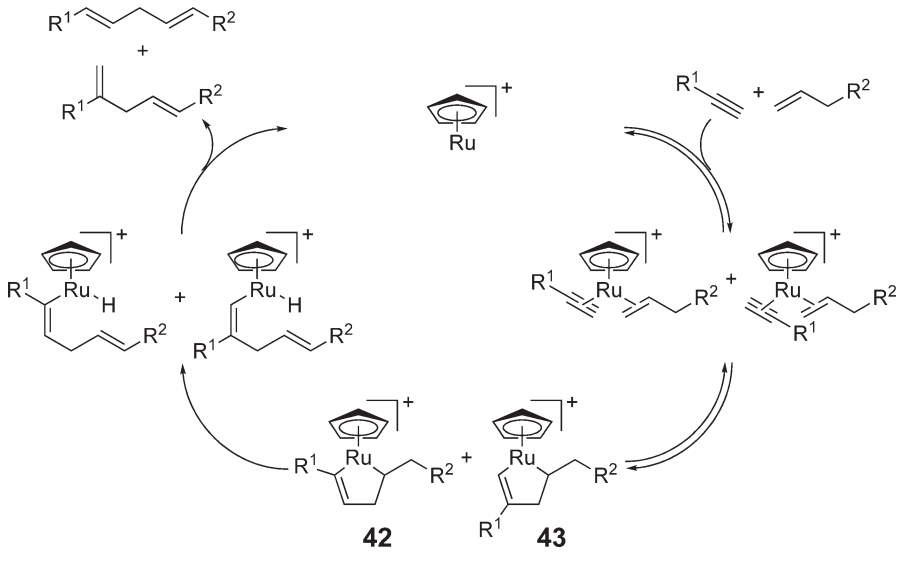
(23)

Soon after the discovery of this reaction, the synthetic utility was greatly increased by the more reactive catalyst $[CpRu(MeCN)_3]PF_6$ **41**.[37] A ruthenium-catalyzed Alder-ene reaction between a terminal alkyne and a vinyl substituent gave good yields of dienes.[38] The regioselectivity of the Alder-ene reaction with respect to the alkyne was significantly improved and polar functional groups were not required for regiocontrol. However, the best branched to linear ratios were still obtained for alkynes possessing coordinating atoms (Equation (24)). The lowest regioselectivities were observed when the alkene possessed a β-hydrogen that is allylic or benzylic (Equation (25)). Notably, for the first time disubstituted alkenes participated in the ruthenium-catalyzed Alder-ene reaction.



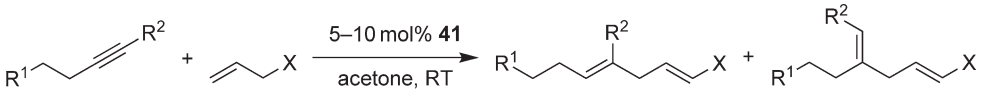
A mechanistic pathway is proposed based upon the observed regioselectivities and other results that were obtained during the exploration of the scope and limitations of the Alder-ene reaction.[38] Initially, coordination of the alkene and alkyne to the ruthenium catalyst takes place (Scheme 5). Next, oxidative addition affords the metallocycles **42** and **43**. It is postulated that β-hydride elimination is slow and that the oxidative addition step is reversible. Thus, the product ratio is determined by the rate at which **42** and **43** undergo β-hydride elimination.

The intermolecular ruthenium enyne Alder-ene reaction has been extended to the stereoselective preparation of enamines (Equation (26)).[39] The yields obtained for this reaction were high with allylacetamides, -benzamides,



Scheme 5

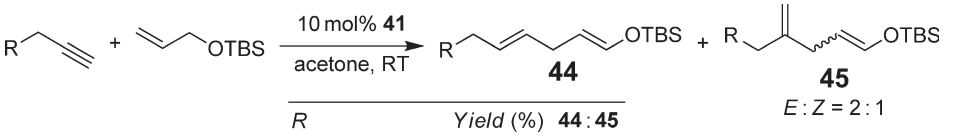
-tosylamides, and -tert-butyloxycarbonyl (BOC)-protected amines (BOC = butyloxycarbonyl). However, the linear to branched ratios were in the range of 2–3 : 1, with the linear isomer predominating. Exceptions to this involved compounds containing a quaternary propargylic position that gave only the linear product.

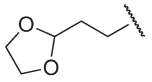
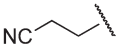
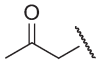
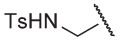
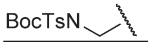


(26)

X = NHTs, NHAc, NHBz, NHBOC

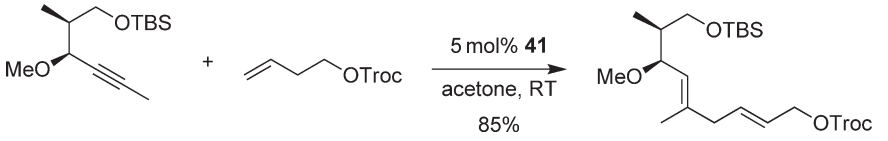
Similarly, enolsilanes **44** and **45** are afforded when silyl-protected alcohols and alkynes are reacted with ruthenium catalyst **41** (Equation (27)).[40] The linear to branched ratio typically ranged from 2–4 : 1, except when the alkyne terminus was substituted with a TMS group. These internal alkynes afforded only the branched products.



R	*Yield* (%)	**44** : **45**
	76	3.4 : 1
	82	3.6 : 1
	51	3.6 : 1
	83	2.3 : 1
	79	3.4 : 1

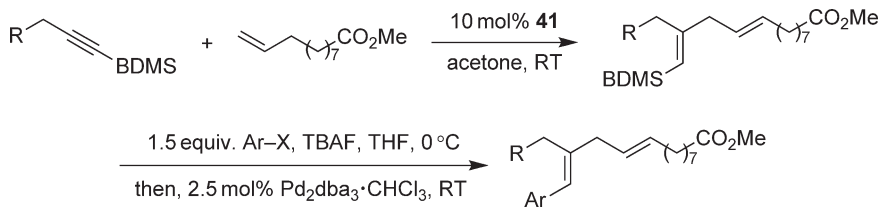
(27)

Internal alkynes subjected to the ruthenium-catalyzed Alder-ene reaction afforded good yields of the trisubstituted alkenes (Equation (28)).[41] Alkene and alkyne substitutents adjacent to the newly formed C–C bond are more important than the alkynyl substituent interaction with the Cp group. There are over 20 examples in this paper demonstrating regioisomeric ratios greater than 20 : 1. The regioselectivity is observed when the positions adjacent to the alkyne are occupied by two groups that represent very different steric environments, that is, a quaternary carbon and a methylene unit. As the size of these groups approaches unity, the ratio of regioisomers is decreased to nearly 1 : 1.

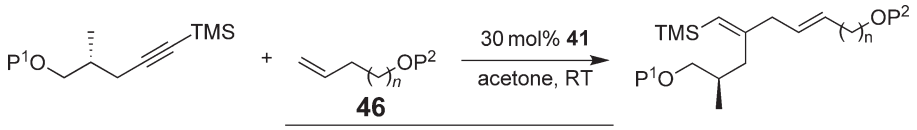


(28)

The nature of the protecting group has a dramatic effect on the efficiency of the ruthenium-catalyzed Alder-ene reaction.[42] Electron-withdrawing groups at the P^2 position of **46** (Equation (29)) such as acetyl or *p*-nitrobenzyl groups afforded high yields of the dienes. Electron-donating groups at the P^2 position of **46** such as methyl or *p*-methoxybenzyl gave low yields of the products. A free hydroxyl group (P^2 = H) gave high yields when removed by four or five carbons from the alkene; no diene was observed for the bis-homoallylic alcohol. Moreover, the new carbon–carbon bond is always formed distal to the TMS group on the alkyne and the new double bond geometry is always (*E*).



Scheme 6



46

n	P^1	P^2	*Yield* (%)
1	PMB	H	0
1	PMB	TBDPS	50
1	TBDPS	H	0
1	TBDPS	PMB	14
1	TBDPS	Ac	85
1	TBDPS	Me	0
1	TBDPS	PNB	98[a]
2	TBDPS	H	96
3	TBDPS	H	99

[a]20 mol% catalyst.

(29)

The scope of this remarkable regioselectivity imparted by the TMS group was further advanced by replacement of the TMS group with a benzyldimethylsilyl (BDMS) group.[43] Trost has shown that the BDMS group functions as a synthon and is suitable for palladium-catalyzed cross-coupling reactions (Scheme 6).

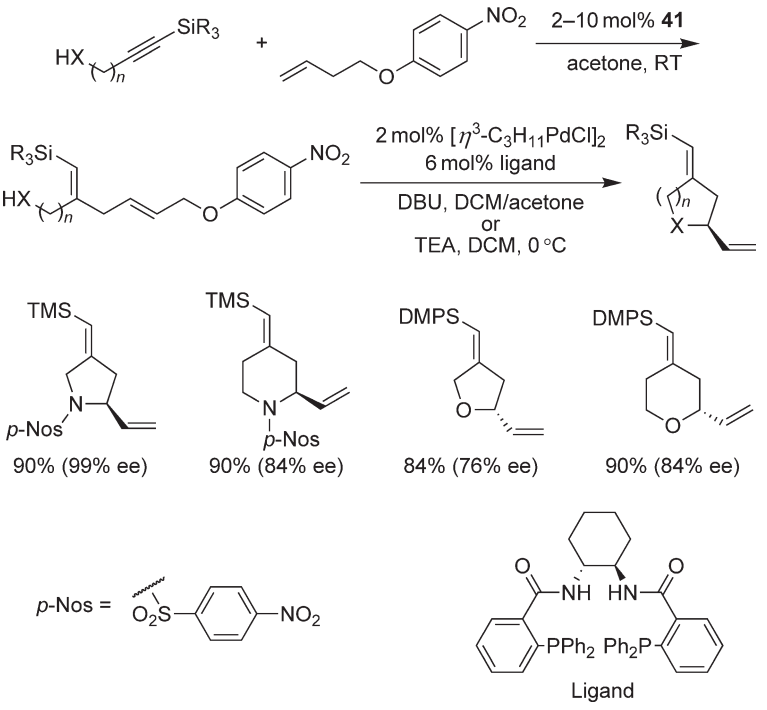
Enantio- and diastereoselective syntheses of a variety of heterocycles were accomplished by combining the ruthenium-catalyzed Alder-ene reaction with a palladium-catalyzed asymmetric allylic alkylation (AAA) (Scheme 7).[44] For the AAA, *p*-nitrophenol was found to function as a suitable leaving group and yet was stable to the Alder-ene conditions. Extensive solvent studies were performed to determine the best conditions for the one-pot procedure.

10.12.4 Transition Metal-Catalyzed Intramolecular Alder-Ene Reactions

The Alder-ene reaction has traditionally been performed under thermal conditions—generally at temperatures in excess of 200 °C. Transition metal catalysis not only maintains the attractive atom-economical feature of the Alder-ene reaction, but also allows for regiocontrol and, in many cases, stereoselectivity. A multitude of transition metal complexes has shown the ability to catalyze the intramolecular Alder-ene reaction. Each possesses a unique reactivity that is reflected in the diversity of carbocyclic and heterocyclic products accessible via the transition metal-catalyzed intramolecular Alder-ene reaction. Presumably for these reasons, investigation of the thermal Alder-ene reaction seems to have stopped almost completely. For example, more than 40 papers pertaining to the transition metal-catalyzed intramolecular Alder-ene reaction have been published over the last decade. In the process of writing this review, we encountered only three recent examples of the thermal intramolecular Alder-ene reaction, two of which were applications to the synthesis of biologically relevant compounds (see Section 10.12.6).

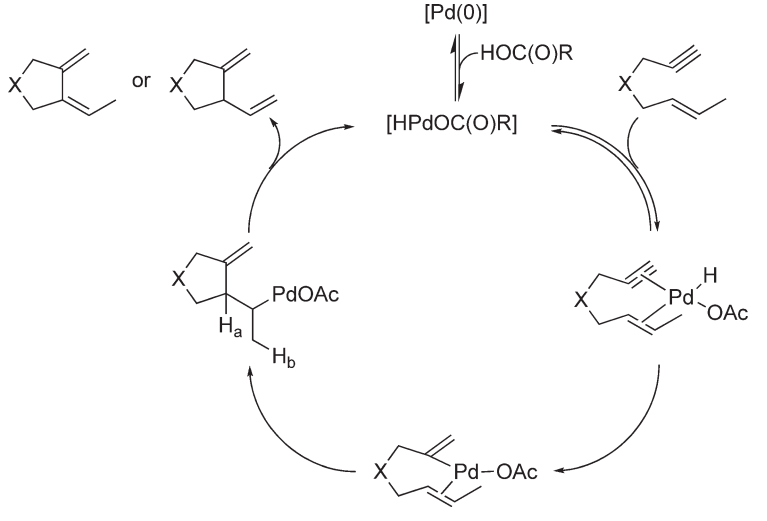
10.12.4.1 Palladium

Palladium(II) catalysts are among the most popular for use in the Alder-ene reaction. The active metal species is often generated *in situ* from a palladium(0) precursor such as tris-(dibenzylideneacetone)dipalladium chloroform adduct ($Pd_2dba_3{\cdot}CHCl_3$) using a weak organic acid. Acetic acid and formic acid are among the most common acids used and are often added in a large excess to shift the equilibrium in the direction of the hydridopalladium(II) species.[45]

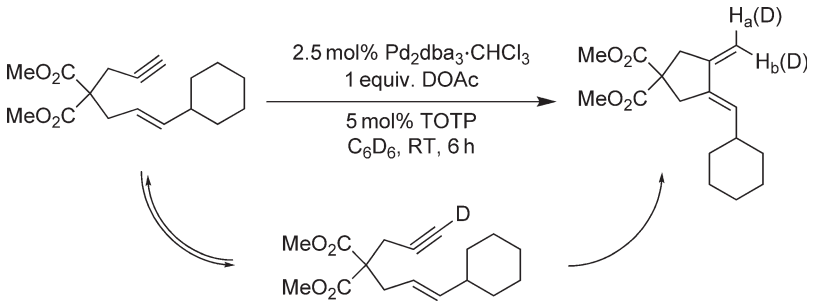


Scheme 7

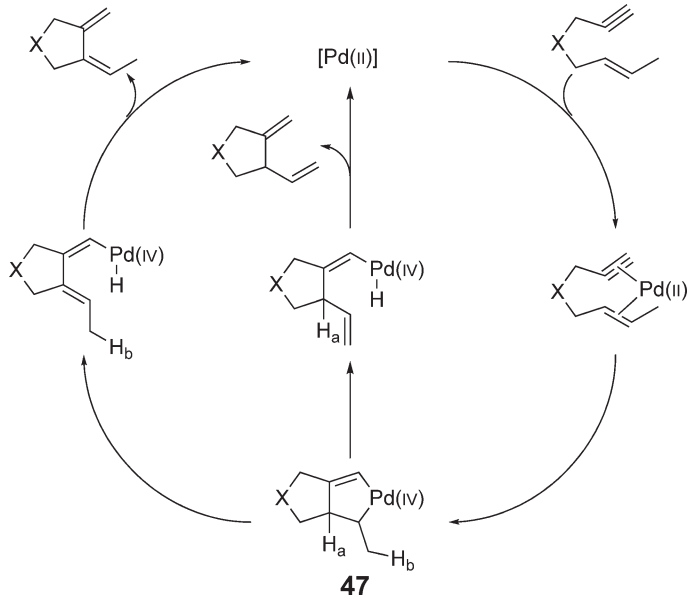
Insertion of the alkyne into the Pd–H bond is the first step in the proposed catalytic cycle (Scheme 8), followed by insertion of the alkene and β-hydride elimination to yield either the 1,4-diene (Alder-ene) or 1,3-diene product. The results of a deuterium-labeling experiment performed by Trost *et al.*[46] support this mechanism. ^{1}H NMR studies revealed 13% deuterium incorporation in the place of H_a, presumably due to exchange of the acetylenic proton, and 32% deuterium incorporation in the place of H_b (Scheme 9). An alternative Pd(II)–Pd(IV) mechanism involving palladocycle **47** (Scheme 10) has been suggested for Alder-ene processes not involving a hydridopalladium species.[47] While the palladium acetate and hydridopalladium acetate systems both lead to comparable products, support for the existence of a unique mechanism for each catalyst is derived from the observation that in some cases the efficacies of the catalysts differ dramatically.[46]



Scheme 8

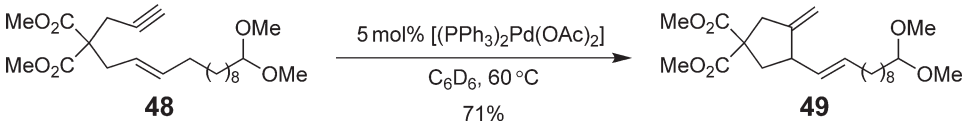


Scheme 9

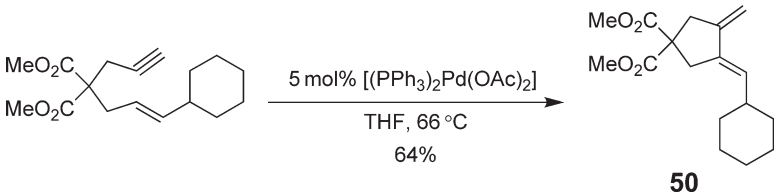


Scheme 10

Trost *et al.*[47] have observed product distribution to be dependent in part on the steric and electronic properties of the substrate. For example, linear enyne **48** (Equation (30)) cyclized exclusively to the Alder-ene product **49**, whereas branching at the allylic position led to the formation of 1,3-diene **50** (Equation (31)) under similar conditions. Allylic ethers also give 1,3-dienes; this effect was determined not to be the result of chelation, as methyl ethers and *tert*-butyldimethylsilyl ethers both gave dialkylidene cyclopentanes despite the large difference in coordinating ability.



48 **49** (30)



50 (31)

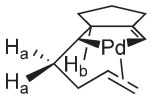
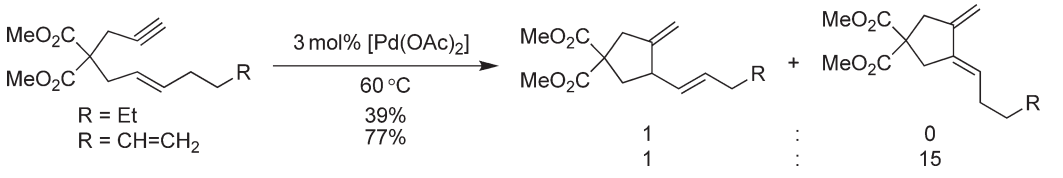


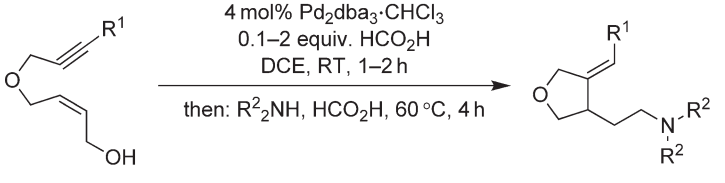
Figure 1 Remote olefin binding in transition state.

Substrates containing remote double bonds, however, are presumed to lead to preferential formation of 1,3-dienes due to coordination of the remote olefin to the metal (Equation (32)). The constrained geometry of the coordinated molecule (Figure 1) makes elimination of both H_a and H_b unfavorable; thus, the weaker bond strength of the C–H_b leads to elimination of H_b and formation of the 1,3-diene as the major product.



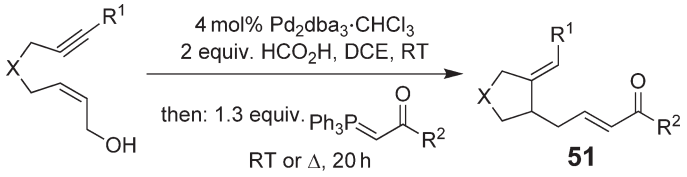
(32)

The mild conditions and chemoselectivity of the palladium-catalyzed Alder-ene reaction lend themselves nicely to the development of one-pot sequential transformations. Müller and Kressierer[48,49] have taken advantage of the tautomerization of enol Alder-ene products and developed methodology for the synthesis of amines and olefins via reductive amination and Wittig reaction, respectively, of aldehyde cycloisomerization products. The use of formic acid to activate the $Pd_2dba_3{\cdot}CHCl_3$ catalyst set the stage for use of Leuckart–Wallach reductive amination conditions[50] to produce a variety of β-amino ethyl alkylidene furans (Equation (33)); primary amines and bulky secondary amines, however, failed to yield amination products.[48] Müller and Kressierer[49] also synthesized 2,3,6,7-bis-unsaturated carbonyl compounds **51** (Equation (34)) through sequential Alder-ene cyclization and Wittig olefination.



R^1	HNR^2_2	*Yield* (%)
TMS	$HNEt_2$	61
CH_2OMe		64
TMS		89
TMS		87

(33)



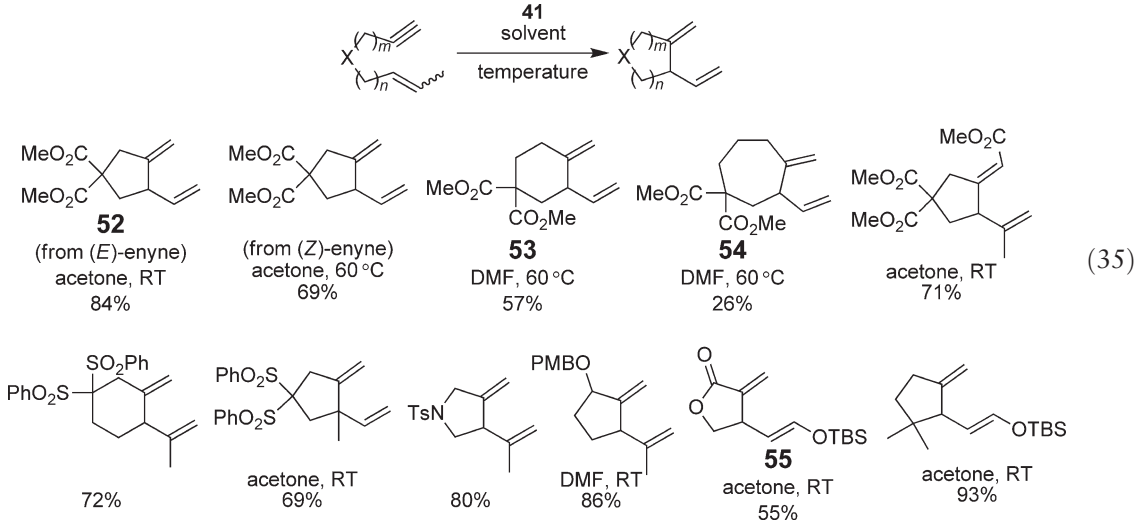
(34)

X	R^1	R^2	*Yield* (%)
$C(CO_2Me)_2$	CH_2OMe	OEt	71
$C(CO_2Me)_2$	Ph	Me	67
O	TMS	OEt	69
O	Ph	OEt	44

10.12.4.2 Ruthenium

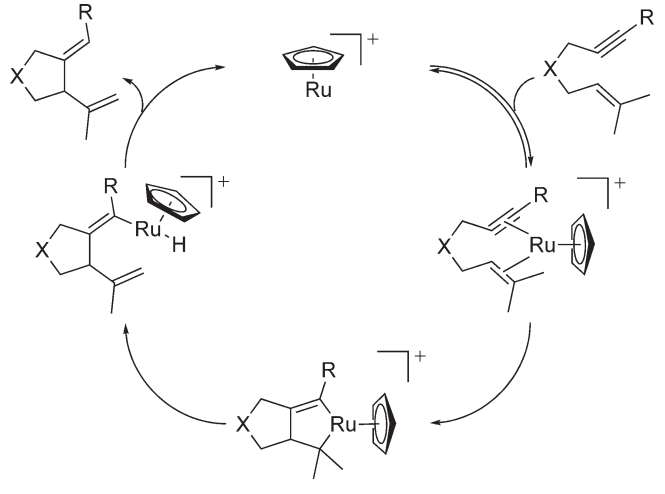
Trost and others have extensively studied the ruthenium-catalyzed intermolecular Alder-ene reaction (see Section 10.12.3); however, conditions developed for the intermolecular coupling of alkenes and alkynes failed to lead to intramolecular cycloisomerization due the sensitivity of the [CpRu(cod)Cl] catalyst system to substitution patterns on the alkene.[51] Trost and Toste instead found success using cationic $[CpRu(MeCN)_3]PF_6$ **41**. In contrast to the analogous palladium conditions, this catalyst gives exclusively 1,4-diene cycloisomerization products. The absence of 1,3-dienes supports the suggestion that the ruthenium-catalyzed cycloisomerization of enynes proceeds through a ruthenacycle intermediate (Scheme 11).

A variety of functionalities, tether lengths, and alkene substitution patterns were tolerated (Equation (35)).[52,53] Of particular significance is the synthesis of α-methylene-γ-butyrolactone **55**, as only Zhang had reported successfully using Alder-ene chemistry to gain access to this novel system (see Section 10.12.4.3). The reaction was sensitive to the length of the tether, since there was a marked decrease in yield for the formation of the six- and seven-membered carbocycles (**53** and **54**, respectively) compared to the five-membered case **52**.



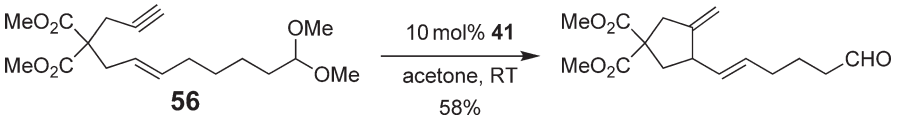
(35)

The ruthenium-based reaction conditions were, however, demonstrated to be acidic in acetone. Tandem acetal hydrolysis was observed in the cycloisomerization of **56** (Equation (36)) and unexpected 1,5-diene **59** arose from the

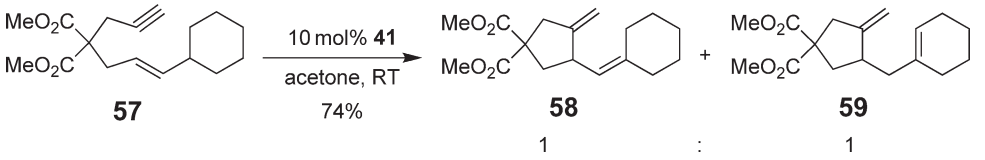


Scheme 11

cycloisomerization of **57**. This is thought to be the result of acid-catalyzed isomerization of **58** (Equation (37)). Performing the Alder-ene cyclization of **57** in DMF gave only the expected 1,4-diene **58** in 69% yield.

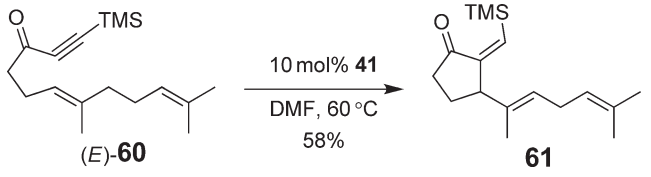


(36)

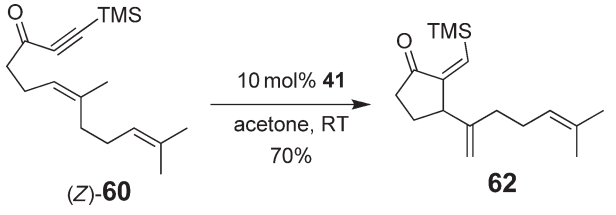


(37)

Cycloisomerization of a disubstituted alkyne sometimes required activation of the alkyne by the addition of a conjugated carbonyl and performing the reaction at a higher temperature as in Equation (38). The geometry of the alkene determines the regioselectivity of the β-hydride elimination, as (*E*)-**60** gave predominantly **61** (Equation (38)), while **62** was the major product of the cycloisomerization of (*Z*)-**60** (Equation (39)).

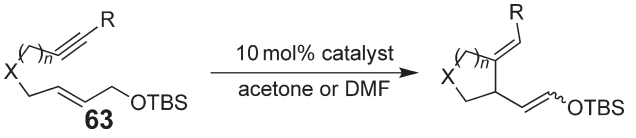


(38)



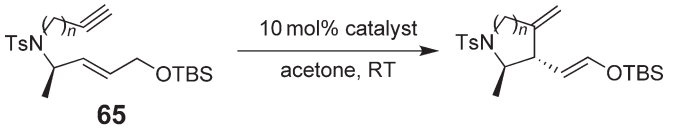
(39)

The Alder-ene cyclization of allylic silyl ethers represents a clever use of cycloisomerization chemistry, as the enol ether products can be easily unmasked to yield aldehydes. Palladium-catalyzed cycloisomerization of 1,6- and 1,7-enynes containing an allylic oxygen most often gives rise to 1,3-dienes (see Section 10.12.4.1). However, enynes of type **63** underwent facile Alder-ene cyclization to the corresponding five- or six-membered rings (Equation (40)) using both $[CpRu(MeCN)_3]PF_6$ **41** and the Cp^* analog ($[Cp^*Ru(MeCN)_3]PF_6$, **64**).[53]



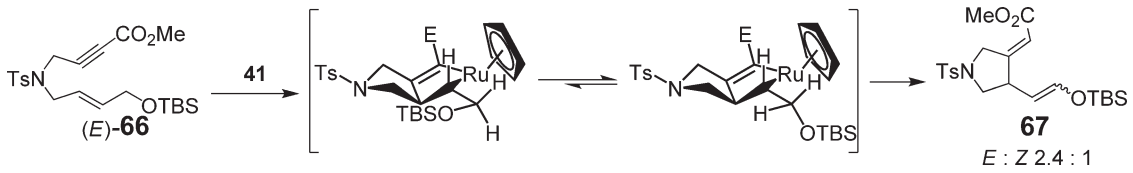
(40)

Diastereoselectivity was observed as the result of stereoinduction (Equation (41)), giving preferential formation of the 1,2-*trans* products. Enhancement of the diastereoselectivity in the cycloisomerization of enyne **65a** ($n = 1$) was observed with the use of the catalyst bearing the sterically demanding Cp^* ligand **64**.

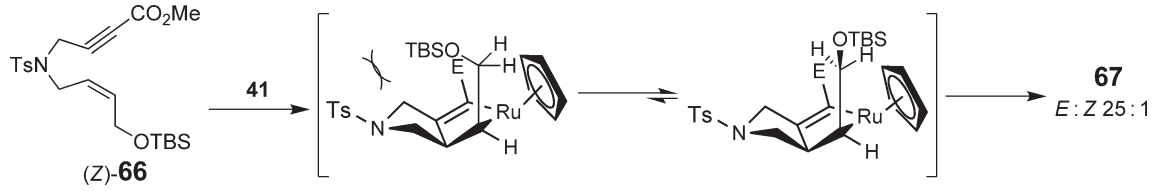


(41)

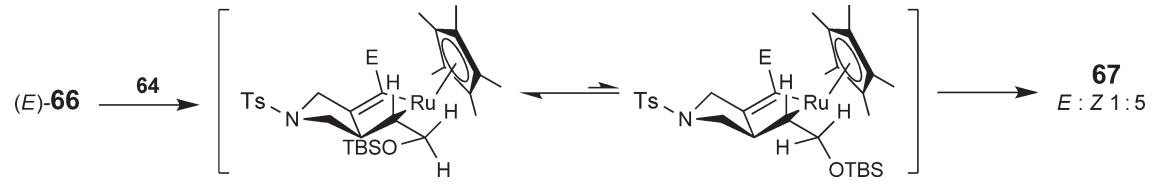
Substrate	*n*	*Catalyst*	*Yield* (%)	*dr*
65a	1	**41**	94	2.2 : 1
65a	1	**64**	74	32 : 1
65b	2	**41**	96	Only *trans*



Scheme 12



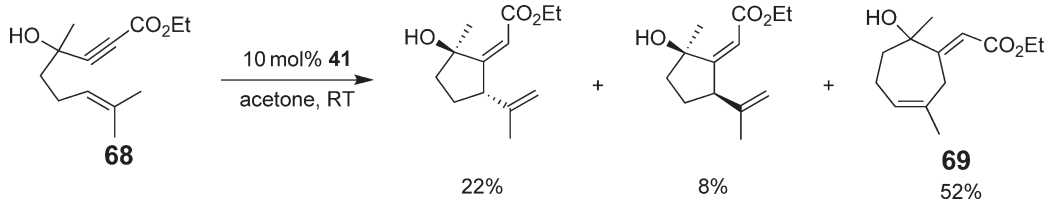
Scheme 13



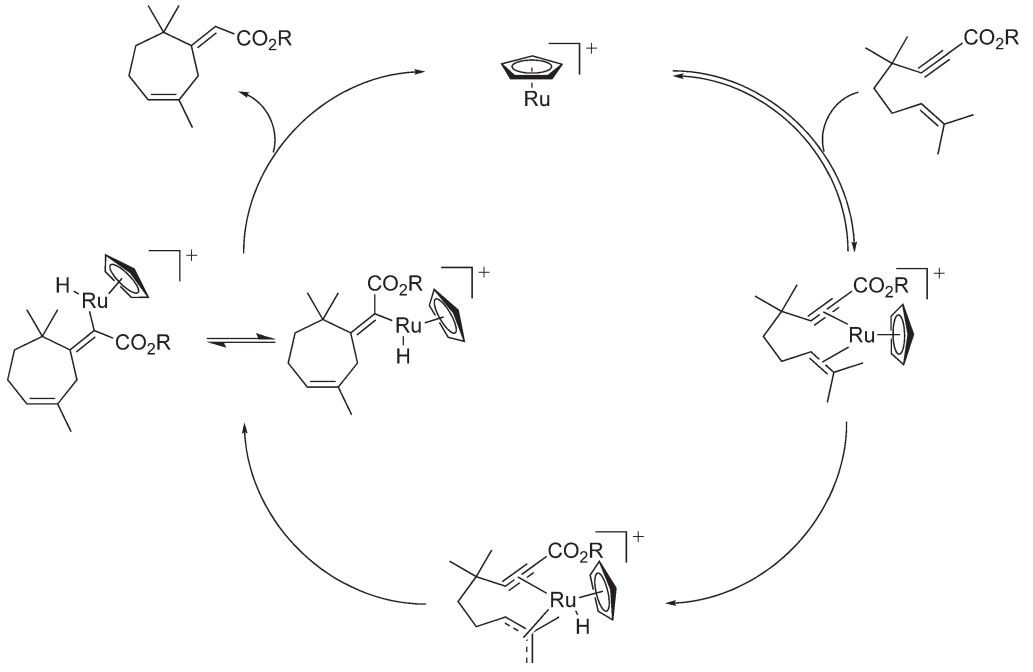
Scheme 14

The stereoselectivity was determined to depend on both the substrate and the steric demands of the cyclopentadienyl ligand. In the presence of **41**, both (*E*)-**66** and (*Z*)-**66** cyclize to form **67**, enriched in the (*E*)-isomer. However, substrates with (*Z*)-geometry favor higher *E* : *Z* ratios, as is rationalized by conformational analysis of the proposed intermediate metallocycles (Schemes 12 and 13). Use of catalyst **64** actually leads to a decrease in selectivity for the (*E*)-isomer and in some cases inverts the regioselectivity. A similar conformational analysis explains the observed change in selectivities (Scheme 14). The overall result is that the product distribution can be easily tuned by modification of the steric properties of the Cp ligand and to some extent by the olefin geometry of the starting material.

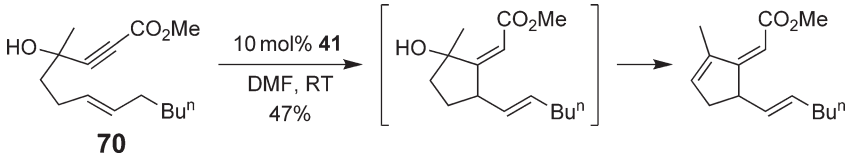
Trost and Toste[51] isolated unexpected cycloheptene **69** upon exposing enyne **68** to their optimized ruthenium-based Alder-ene conditions (Equation (42)). Further exploration into the effects of quaternary substitution at the propargylic carbon revealed the ability of ruthenium to catalyze a non-Alder-ene cycloisomerization to form seven-membered rings, presumably via allylic C–H activation (Scheme 15).



As the steric bulk of the propargylic substituents increased, the preference for the formation of the seven-membered ring increased as well. Formation of a ruthenacyclopentene intermediate with sterically hindered substrates involves a large amount of $A^{(1,3)}$ strain, leading to preferential formation of a π-allyl species. This novel cycloisomerization process is very sensitive to alkene substitution; the requirement for a *cis*-methyl group was evidenced by the failure of **70** to give

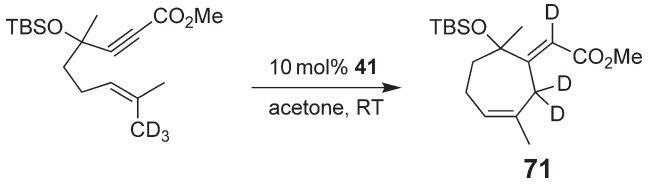


Scheme 15



Scheme 16

a seven-membered ring (Scheme 16). Additionally, a deuterium-labeling experiment showed 95% incorporation of deuterium only at the doubly allylic and newly formed vinylic positions of cycloheptene **71** (Equation (43)).



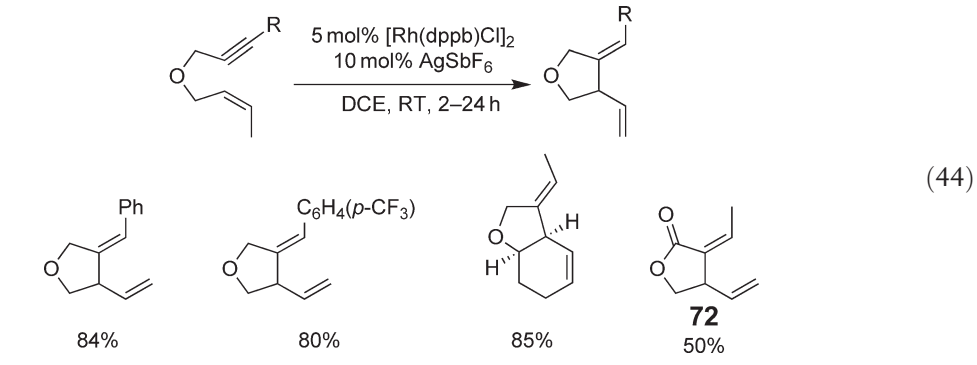
(43)

10.12.4.3 Rhodium

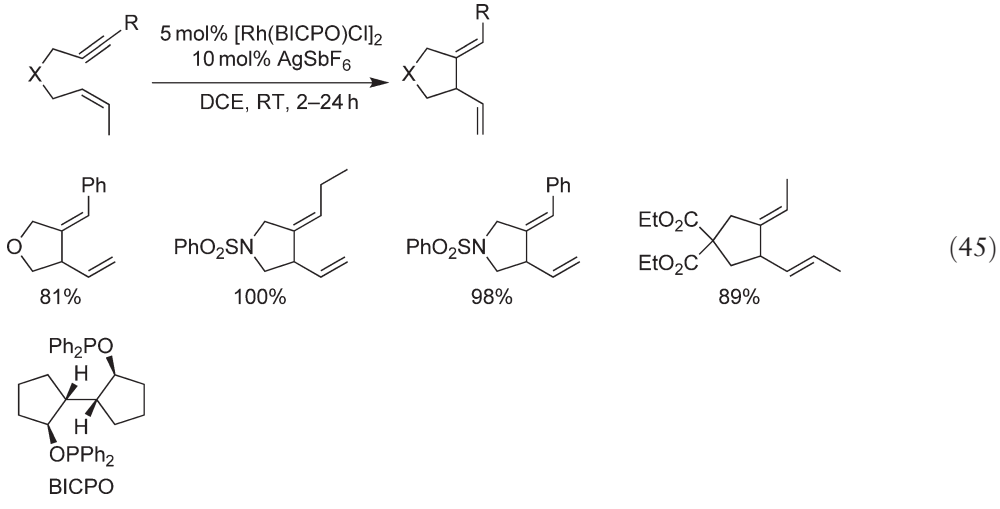
Zhang[54] published the first and only account of a non-asymmetric rhodium-catalyzed Alder-ene cycloisomerization of 1,6-enynes.[55] The conditions developed by Zhang and co-workers are advantageous in that, similar to the ruthenium conditions developed by Trost, selectivity for 1,4-diene products is exhibited. The rhodium conditions are dissimilar from many other transition metal conditions in that only (*Z*)-olefins give cycloisomerization products.

The active Rh(I) catalyst was generated *in situ* by the addition of $AgSbF_6$ to $[Rh(ligand)Cl]_2$ in the presence of substrate. Zhang postulates that the coordinatively unsaturated metal complex generated by this process facilitates coordination to enyne substrates and smooth conversion into the Alder-ene products. 1,4-Bis(diphenylphosphino)butane (dppb) and

1,4-diphosphinite (bis(diphenylphosphinoxy)-(1R,1′R)-dicyclopentane (2S,2′S)-bis(diphenylphosphinoxy)-(1R,1′R)-dicyclopentane (BICPO), Equation (45)), ligands developed by Zhang's group, were shown to be most effective for the rhodium species. Cycloisomerizations of oxygen-tethered 1,6-enynes proceeded in generally high yield in the presence of Rh–dppb catalyst (Equation (44)). The efficacy of this reaction in the synthesis of α-methylene γ-butyrolactone **72** is notable; at the time of publication, this was the first example of the use of a transition metal-catalyzed Alder-ene reaction in forming the novel α,β-unsaturated lactone (see also Section 10.12.6). More recently, Trost published the synthesis of an α-methylene γ-butyrolactone via an Ru-catalyzed Alder-ene transformation (see section 10.12.4.2). The Rh–dppb species did, however, demonstrate sensitivity to non-oxygen tethers. The rate of cycloisomerization of sulfonamides was significantly slowed compared to ether substrates; substrates containing carbon tethers failed to undergo Alder-ene cyclization under the Rh–dppb conditions.



(44)



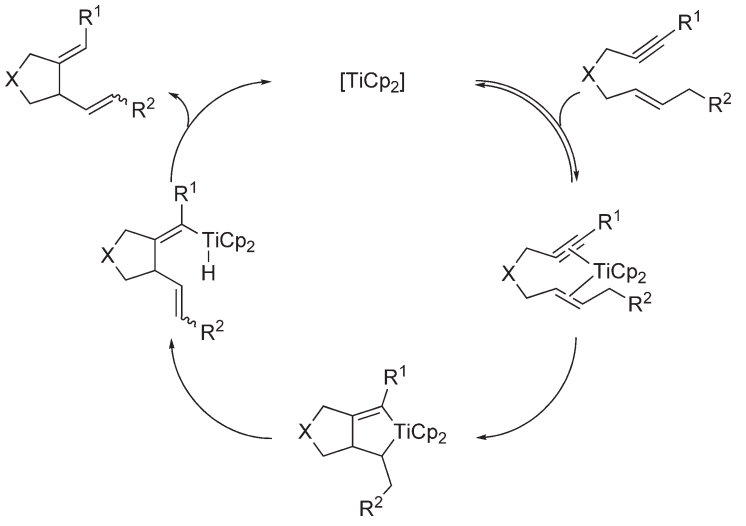
(45)

The Rh–BICPO system proved to be more general. Sulfonamide- and carbon-tethered enynes were cyclized in high yield (Equation (45)).

10.12.4.4 Miscellaneous Metals

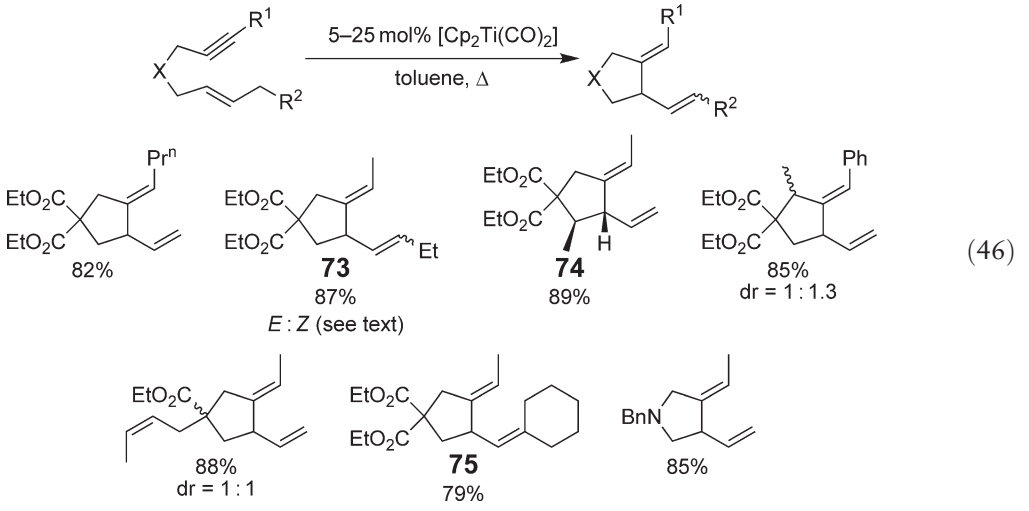
While palladium, ruthenium, and rhodium are the most common metal catalysts used to facilitate Alder-ene cyclization, a few successful examples of catalysis using different metals have been published. Both of the references reviewed in this section demonstrate chemistry that is novel and complimentary to the patterns of reactivity exhibited by late transition metals in the Alder-ene cyclization.

Buchwald and co-workers[56] found that (*E*)-olefins cycloisomerized upon exposure to $[Cp_2'Ti(CO)_2]$ giving exclusively the 1,4-diene Alder-ene products (Equation (46)). In contrast to the palladium conditions developed by Trost (see Section 10.12.4.1), the 1,4-diene is formed exclusively, even from substrates containing a tertiary carbon at the allylic position **75**. It was noted, however, that heating the reaction mixture for an extended period of time in some instances led to olefin isomerization, forming 1,3-dienes. The mechanism of this titanium-catalyzed



Scheme 17

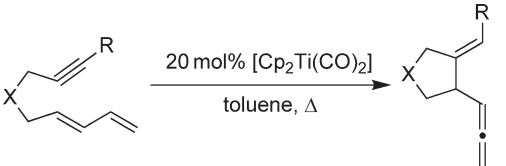
cycloisomerization (Scheme 17) is proposed to be similar to that for the ruthenium- and rhodium-mediated Alder-ene processes, proceeding via a titanocyclopentene intermediate.



(46)

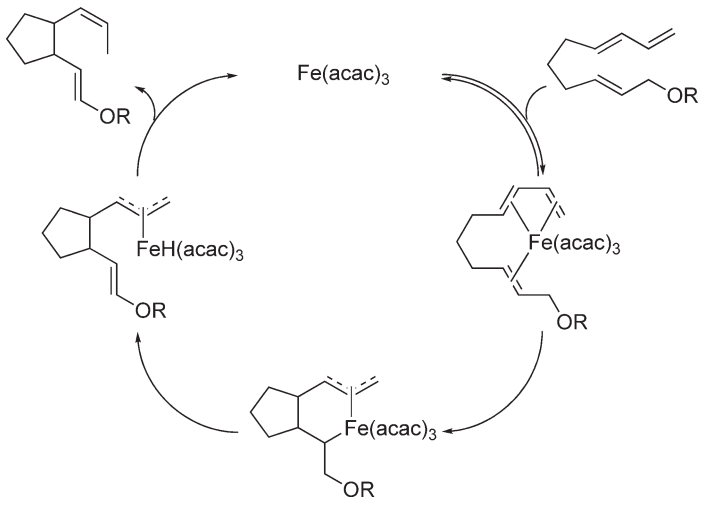
1,2-Stereoinduction was observed, as in the formation of **74** (Equation (46)) as a single diastereomer; 1,3-stereoinduction was not successful. Most substrates contained only methyl-substituted olefins, leading to terminal alkenes. In the case of the cycloisomerization of an *n*-propyl-substituted enyne, a modicum of selectivity with respect to olefin geometry was exhibited: **73** was produced in an isomeric ratio of 1 : 3.5. The authors do not specify whether the (*E*)- or (*Z*)-geometry was preferred.

A novel use of Buchwald's titanium-based Alder-ene protocol is the cycloisomerization of dienynes to allenes (Equation (47)). Somewhat surprisingly, the Diels–Alder product was observed in trace amounts only in the cycloisomerization of amine **76**.



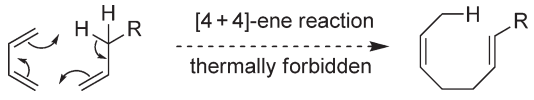
(47)

X = $C(CO_2Et)_2$; R = Me; 54%
X = $C(CO_2Bu^t)_2$; R = Me; 44%
76: X = NPh; R = n-C_5H_{11}; 36% (NMR)

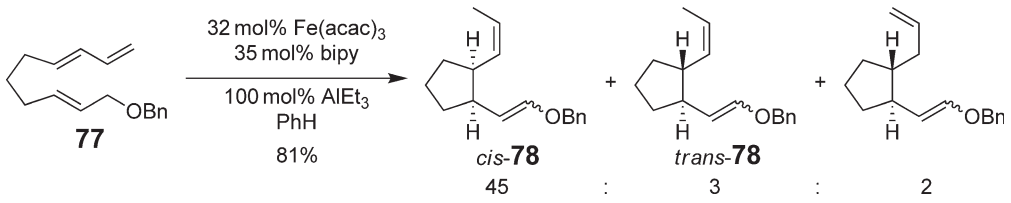


Scheme 18

The [4 + 4]-homolog of the [4 + 2]-Alder-ene reaction (Equation (48)) is thermally forbidden. However, in the presence of iron(III) 2,4-pentanedioate ($Fe(acac)_3$) and 2,2′-bipyridine (bipy) ligand, Takacs[57] found that triene **77** cyclizes to form cyclopentane **78** (Equation (49)), constituting an unprecedented formal [4 + 4]-ene cycloisomerization. The proposed mechanism for this transformation involves oxidative cyclization followed by β-hydride elimination and reductive elimination to yield the cyclized product (Scheme 18).

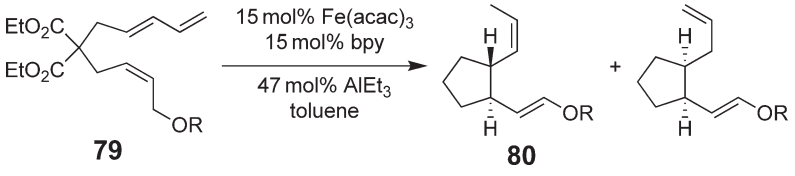


(48)



(49)

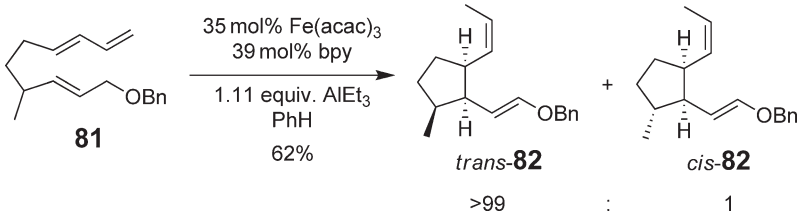
(2*E*,7*E*)-2,7,9-decatrienes are the preferred substrates for the transformation, generally giving both high yield and high diastereoselectivity (Equation (50)). Trienes with (2*Z*,7*E*)-geometry, such as **79** (Equation (50)), most often give the *trans*-substituted cyclopentane **80** as the major product, but the yield and selectivity are often low. Additionally, the nature of the oxygen protecting group was found to have a significant influence on the product distribution for the cyclizations of (2*Z*,7*E*) substrates (Equation (50)).



(50)

R = Bn	63%	2	:	1
R = Me	43%	1	:	2

1,2-Stereoinduction was an efficient means to generate substituted cyclopentanes in a highly diastereoselective manner using the $Fe(acac)_3$ conditions. Cyclization of triene **81** gave *trans*- and *cis*-**82** in a >99 : 1 ratio (Equation (51)). Unfortunately, 1,3-stereoinduction did not lead to useful amounts of diastereoselectivity.

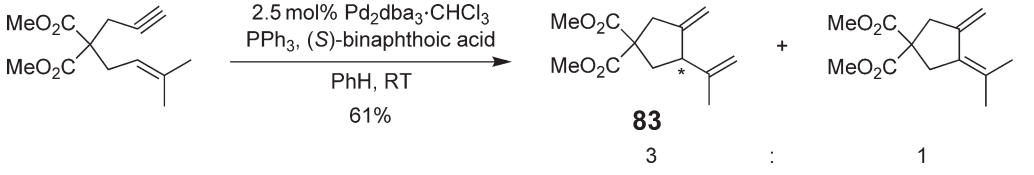


(51)

10.12.4.5 Asymmetric Alder-ene Reactions

While the transition metal-catalyzed Alder-ene reaction has been developed to offer excellent regio- and chemoselectivity, stereoselective variants have only recently begun to appear in the literature.[58] The scope and limitations of many of these protocols have yet to be established. Nonetheless, several groups have published exciting examples of asymmetric Alder-ene cyclizations.

Trost *et al.*[59] were the first to report enantioselectivity in the transition metal-catalyzed Alder-ene reaction. Several different acids were surveyed for the degree of efficacy in oxidizing the Pd(0) precursor to the active Pd(II) species and for compatibility with the catalyst, substrate, and product. Among acids surveyed were several chiral carboxylic acids; products of reactions using these optically active acids were formed with modest enantioselectivity. (*S*)-binaphthoic acid gave the most promising result, with the cyclized product **83** obtained with 33% ee (Equation (52)).



(52)

Incorporation of the carboxylic acid group into the substrate also had an effect on the stereochemistry of the Alder-ene products. Trost and Gelling[60] observed diastereoselectivity in the palladium-catalyzed cycloisomerization of 1,7-enynes when the reactions were conducted in the presence of *N*,*N*-bis(benzylidene)ethylene diamine (BBEDA, Figure 2). They were able to synthesize substituted cyclohexanes possessing vicinal (Equation (53)) and

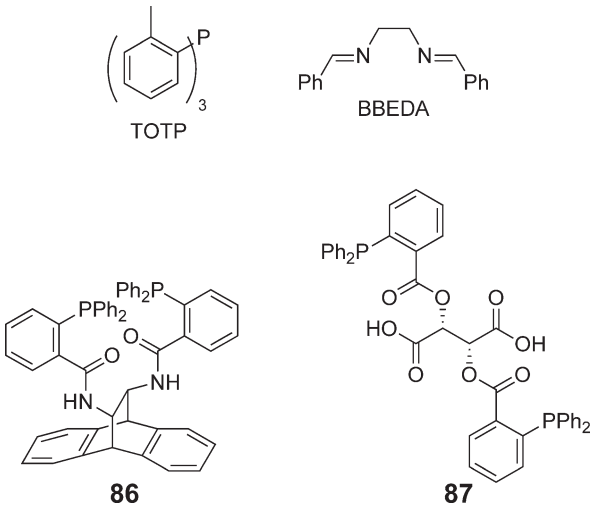
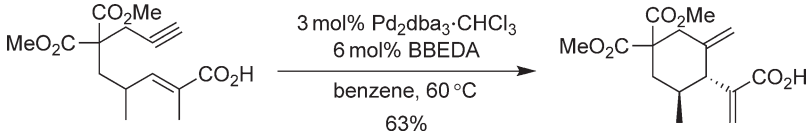
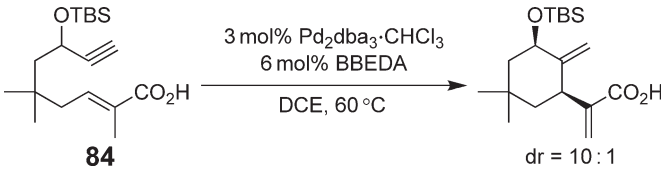


Figure 2 Ligands for effecting asymmetric transition metal-catalyzed Alder-ene cycloisomerization.

1,3-stereogenic centers (Equation (54)) with high diastereoselectivity; 1,4-stereogenic centers, however, were not produced diastereoselectively via this methodology. Trost and Gelling proposed an intermediate in which the enoic acid functions as a bidentate ligand, thus controlling the conformation of the intermediate and the resulting stereochemistry of the product.

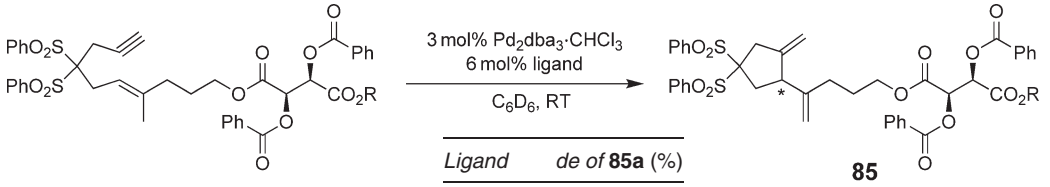


(53)



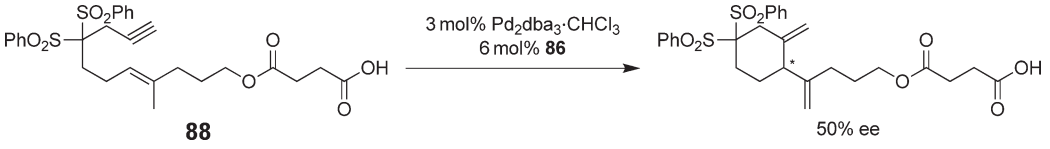
(54)

Better diastereoselectivities were obtained by Trost and Czeskis[61] through asymmetric induction. Enynes were appended with tartaric acid derivatives and subjected to $Pd_2dba_3{\cdot}CHCl_3$ in the presence of BBEDA, triphenylphosphine (TPP), or tri-*o*-tolylphosphine (TOTP) in benzene at room temperature (Equation (55)). Cyclized product **85a** was formed in 60–70% yield with diastereoselectivities ranging from 21% to 50%; methyl ester **85b** was formed in 71% de in the presence of TOTP ligand. Trost and Czeskis probed the possibility of improving the diastereoselectivity through double asymmetric induction using chiral ligands. Although diamide **86** (Figure 2) did not improve the de, it did cause a reversal in diastereoselectivity. Ligand **86** was shown to control stereochemistry of the product independent of the chiral substrate and gave moderate enantioselectivity in the cyclization of achiral substrate **88** (Equation (56)). This project culminated in the rational design of a chiral ligand (**87**, Figure 2) that incorporated both carboxylic acid and 2-diphenylphosphinobenzoyl moieties. Unfortunately, higher temperatures were required when the reaction was conducted in the presence of this ligand, which may have compromised selectivity; only minor enhancement to the stereoselectivities of cycloisomerization of some substrates was observed.



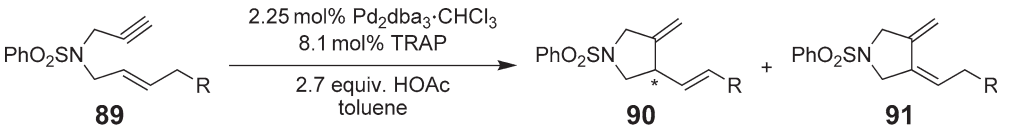
Ligand	*de of* **85a** (%)
TPP	27
TOTP	50
BBEDA	21

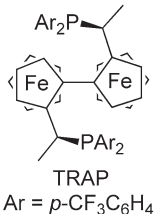
(55)



(56)

Ito and co-workers[62] found a use for a previously developed chiral *trans*-chelating diphosphine ligand[63] in the asymmetric Alder-ene reaction of 1,6-enynes. Cycloisomerization of enyne **89** in the presence of 2.25 mol.% $Pd_2dba_3{\cdot}CHCl_3$, 8.1 mol.% *p*-$CF_3C_6H_4$-TRAP, and acetic acid gave heterocycles **90** in 34–95% ee (Equation (57)). This is in contrast to selectivities of only 5–16% ee achieved using common *cis*-chelating phosphine ligands.

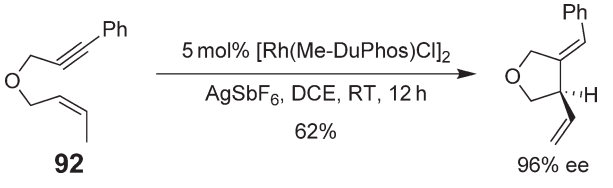




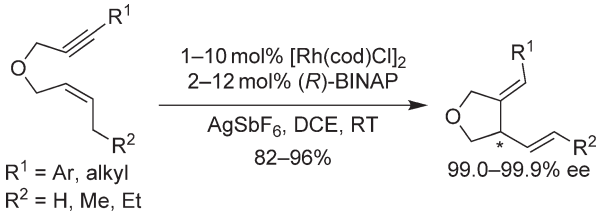
R	**90 : 91**	*Yield* (%) *ee* (%)	*(Config.)*
TMS	>98 : 2	24	76 (*R*)
DMPS	>98 : 2	27	66 (*R*)
C_2H_4TMS	>15 : 1	71	65 (*R*)
Et (*E*)	8.9 : 1	74	69 (*R*)
Et (*Z*)	>15 : 1	66	59 (*S*)
Et (*Z*)	>15 : 1	80	53 (*R*)

(57)

The first Rh(I)-catalyzed enantioselective Alder-ene reaction was reported by Zhang and Cao.[64] Of several ligand–Rh(I) complexes tested, $[Rh(Me\text{-}DuPhos)Cl]_2$ (Figure 3) gave the best conversion and selectivity in the cycloisomerization of enyne **92** (Equation (58)). The catalyst system was, however, sensitive to subtle variation of the acetylenic substituent. Under Rh/Me-DuPhos conditions, substrates with aryl moieties on the terminus of the alkyne were cyclized in moderate to good yield with high enantioselectivity; however, substrates bearing alkyl or cycloalkyl groups on the terminus of the alkyne failed to react. The use of other ligands gave better yields and high enantioselectivity for the cyclizations of these substrates. Zhang and colleagues[65] improved the efficacy of their Rh(I) catalyst system by using a cationic catalyst that was prepared *in situ* from air stable $[Rh(cod)Cl]_2$, enantiopure 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene (BINAP), and $AgSbF_6$. This catalyst was shown to give 99% conversion (>99.9% ee) at a catalyst loading as low as 1 mol% within 2 min for a variety of ether substrates (Equation (59)).



(58)



(59)

Kinetic resolution is achieved when racemic enynes are subjected to Zhang's Alder-ene conditions (Scheme 19).[66] A single diastereomer of *trans*-**94** (>99% ee) is accessible through the exposure of racemic enyne **93** to the Rh(I) catalyst in the presence of optically pure BINAP ligand.

The $[Rh(cod)Cl]_2$/BINAP/$AgSbF_6$ catalyst system demonstrated excellent functional group tolerance and was able to efficiently catalyze cycloisomerizations to form lactams[67] and lactones[68] (Equation (60)) and gave both heterocycles in high yield and greater than 99% ee for a variety of substrates. Among the functionalities that were formed

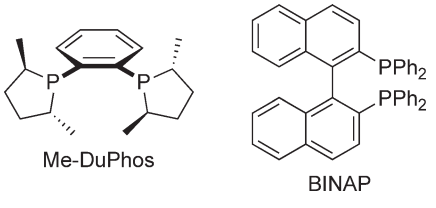
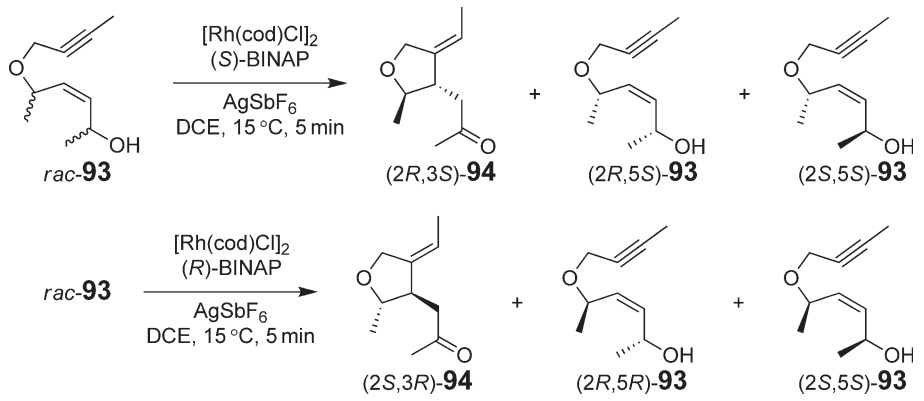
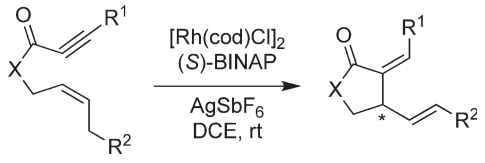


Figure 3 Chiral bisphosphine ligands.



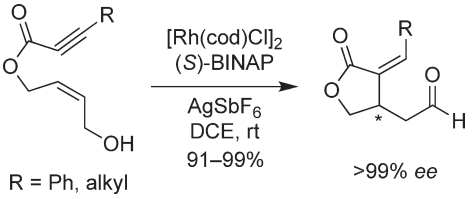
Scheme 19

using this methodology were vinyl ethers and acetates as well as aldehydes and ketones via tautomerizaton of the enol Alder-ene products (Equation (61)).



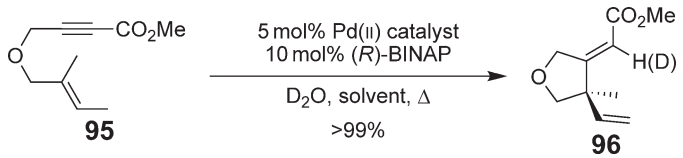
X	R^1	R^2	Yield (%)	ee (%)
NBn	Ph	Et	95	>99
NBn	Me	Me	96	>99
NBn	n-C_5H_{11}	Me	93	>99
NBn	n-C_5H_{11}	OMe	92	>99
NBn	Ph	OAc	89	>99
O	Ph	H	94	>99
O	Me	Me	98	>99
O	Ph	OMe	96	>99

(60)



(61)

Effects of solvent polarity on enantioselectivity have been observed by several groups. Trost and Gelling[60] reported an increase in the diastereoselectivity of the cycloisomerization of **84** (Equation (54)) when switching from benzene (dr = 4 : 1) to 1,2-dichloroethane (dr = 10 : 1). Working with both neutral and cationic Pd(II) catalysts, Mikami and co-workers[69] noticed a marked decrease in enantioselectivity in the cycloisomerization of oxygen-tethered 1,6-enynes when the reaction was performed in dimethyl sulfoxide (DMSO) rather than benzene; however, the reaction temperature was lower and reaction time was shorter under more polar conditions. A surprising exception occurred with the use of sterically demanding (*S*)-xylyl-H_8-BINAP (Figure 4); diene **94** was formed in 94% ee in DMSO and only 12% ee in deuterated benzene. In an attempt to elucidate the active catalyst species, Mikami added an excess of D_2O and observed similar results in the cycloisomerization of **95**, using (*R*)-BINAP as the ligand (Equation (62)). Conducting the reaction in DMSO led to only 68% ee, while using deuterated benzene solvent gave 93% ee.



(62)

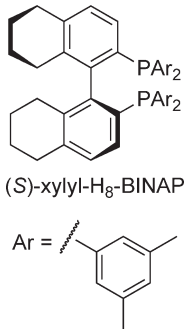
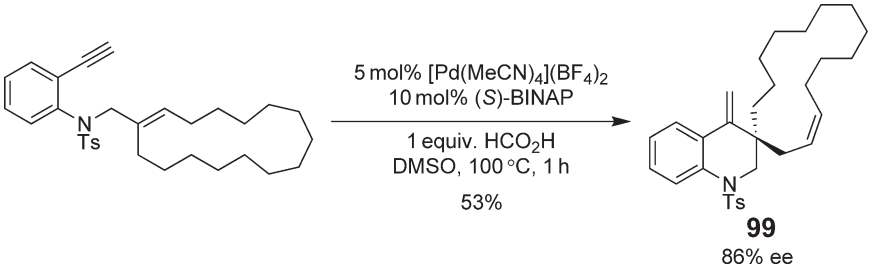


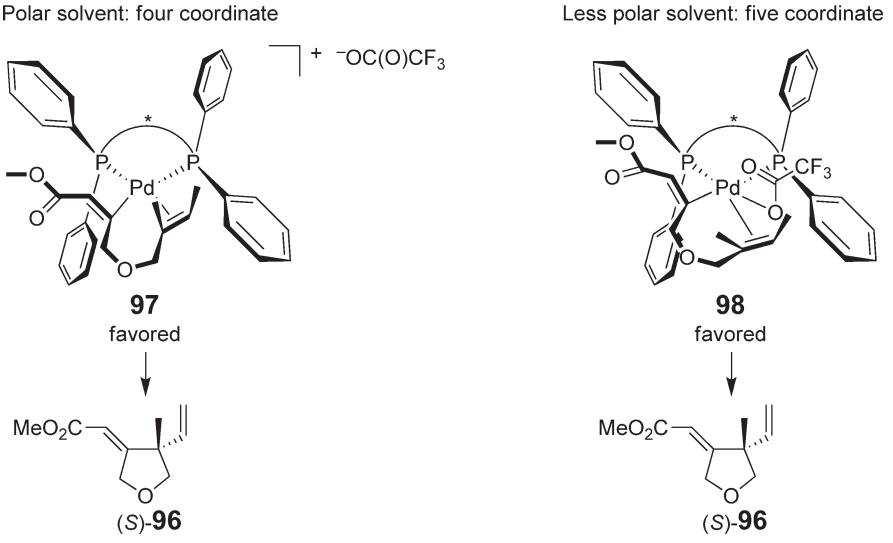
Figure 4 (*S*)-xylyl-H_8-BINAP.

Concluding that hydridopalladium was the active catalyst species, Mikami rationalized the observed solvent effects through the proposal of two different transition states. The preferred four-coordinate complex (**97**, Scheme 20) is formed in DMSO, where the polarity of the solvent facilitates outer-shell association of the counteranion to the metal species. A less polar solvent promotes coordination of the anion to the metal, leading to a neutral and relatively unstable five-coordinate complex **98**. The steric demands of a five-coordinate metal–ligand complex are greater than that of a comparable four-coordinate complex, leading to higher enantioselectivity in less polar solvent. However, the size of the (*S*)-xylyl-H_8-BINAP ligand is large enough to cause its dissociation from the congested metal center under less polar conditions, compromising the enantioselectivity of the cycloisomerization.

Mikami and Hatano[70] demonstrated the efficiency of the dicationic $[Pd(MeCN)_4](BF_4)_2$/BINAP catalyst system in DMSO with the highly enantioselective synthesis of a variety of quinoline derivatives, including *spiro*-compound **99** (Equation (63)), resulting from olefin isomerization of the Alder-ene product.



(63)

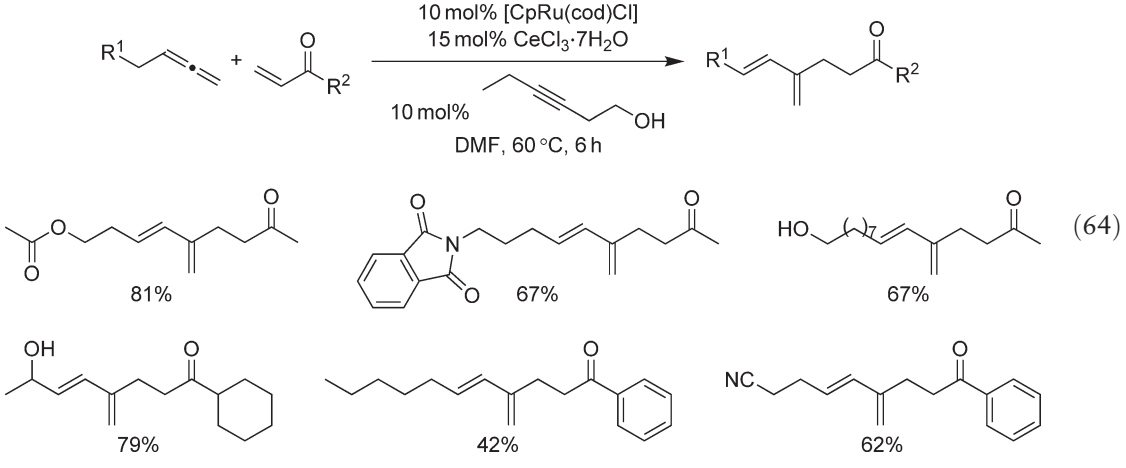


Scheme 20

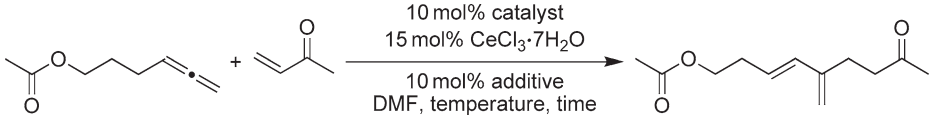
10.12.5 Allenic Alder-Ene Reactions

Allenes, while arguably underused in synthesis as a whole, have become popular functionalities in cycloisomerization chemistry and provide access to a wide variety of products. Ruthenium, cobalt, platinum, palladium, rhodium, and iridium catalysts are efficient in the transition metal-catalyzed Alder-ene reactions of allenes.

Intermolecular Alder-ene coupling of allenes and alkenes produces 1,3-dienes suitable for subsequent Diels–Alder transformations. In the presence of a ruthenium(II) catalyst, vinyl ketones and monosubstituted allenes undergo Alder-ene coupling with excellent regio- and chemoselectivity (Equation (64)).[71,72] Both [CpRu(cod)Cl] and cationic $[CpRu(MeCN)_3]PF_6$ **41** complexes efficiently catalyzed the intermolecular Alder-ene coupling with hydrated cerium trichloride as a co-catalyst. In the case of [CpRu(cod)Cl], an alkyne activator is required. Trost proposed that the addition of 3-hexyn-1-ol to the reaction mixture leads to a coordinatively unsaturated metal complex by undergoing [2 + 2 + 2]-cycloaddition with cyclooctadiene, thus removing the ligand from the coordination sphere;[72,73] however, corresponding cycloaddition products were not observed. An additional advantage of the $[CpRu(MeCN)_3]PF_6$ system was the ability of the catalyst to lead to coupled product at room temperature in comparable yield (Equation (65)).



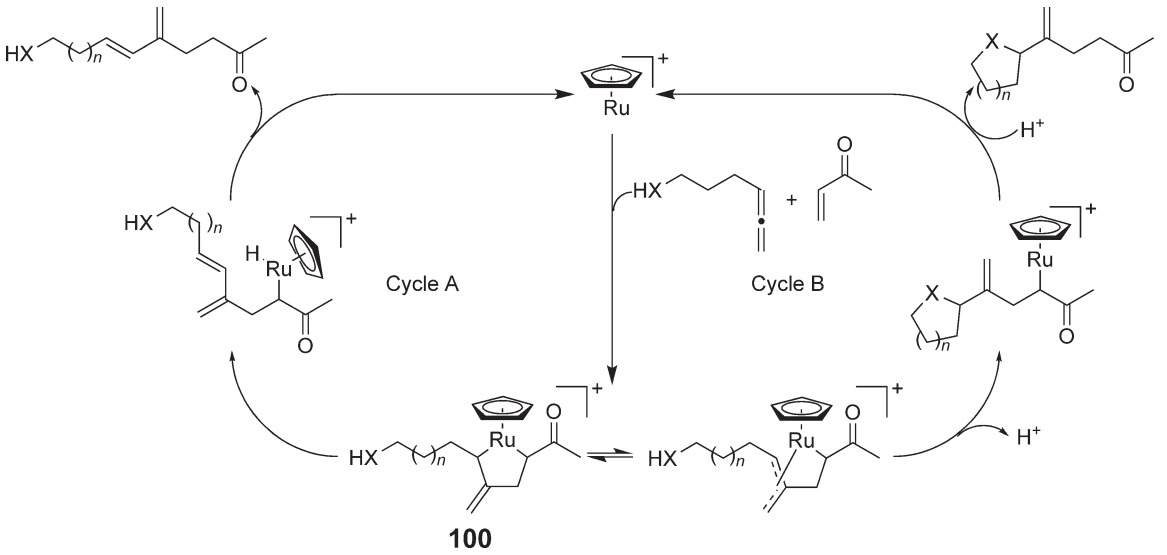
(64)



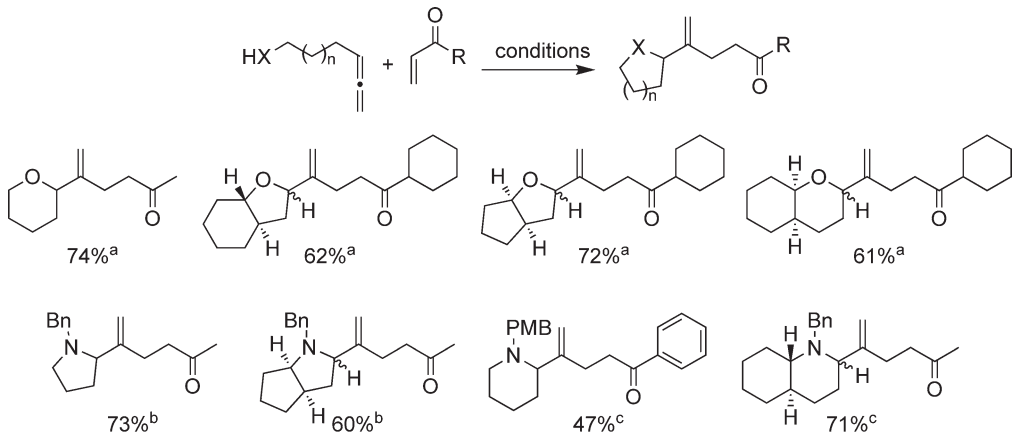
Catalyst	*Additive*	*Temperature*	*Time*	*Yield* (%)
[CpRu(cod)Cl]	3-hexyn-1-ol	60 °C	6 h	70
41	none	60 °C	6 h	76
41	none	RT	4 h	70

(65)

The proposed catalytic cycle of the ruthenium-catalyzed intermolecular Alder-ene reaction is shown in Scheme 21 (cycle A) and proceeds via ruthenacyclopentane **100**. Support for this mechanism is derived from the observation that the intermediate can be trapped intramolecularly by an alcohol or amine nucleophile to form the corresponding five- or six-membered heterocycle (Scheme 21, cycle B and Equation (66)).[74,75] Four- and seven-membered rings cannot be formed via this methodology, presumably because the competing β-hydride elimination is faster than interception of the transition state; for these substrates, **101** and **102**, only the formal Alder-ene product is observed (Equations (67) and (68)).

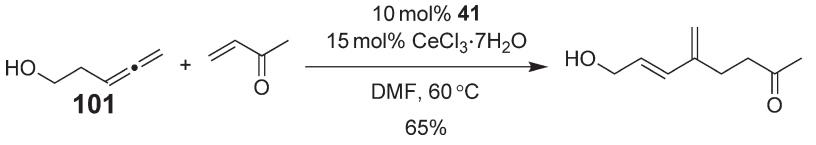


Scheme 21

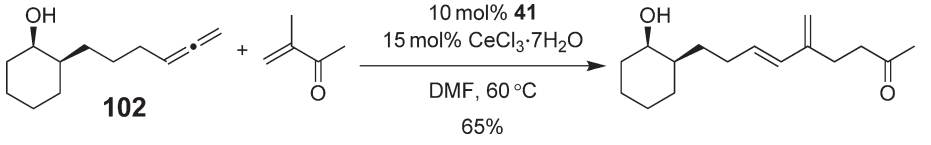


(66)

[a]Method A: 10 mol% $[CpRu(NCCH_3)_3]PF_6$, 15 mol% $CeCl_3{\cdot}7H_2O$ in DMF, 60 °C
[b]Method B: 10 mol% $[CpRu(NCCH_3)_3]PF_6$, 15 mol% $TiCl_4$ in DMF, 60 °C, workup with pyrrolidine
[c]Method C: 10 mol% $[CpRu(NCCH_3)_3]PF_6$, 15 mol% CH_3AlCl_2 in DMF, 40 °C, workup with pyrrolidine.

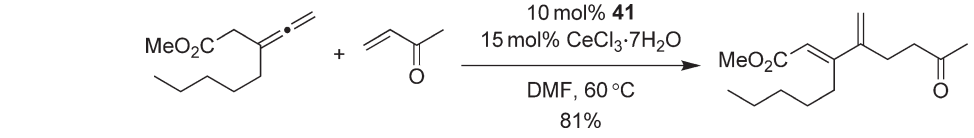


(67)

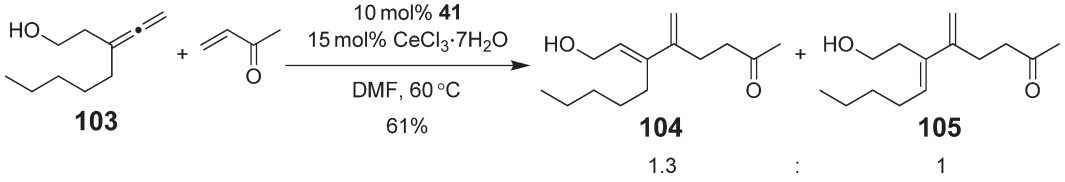


(68)

Trost *et al.*[72] also explored the compatibility of di-, tri-, and tetrasubstituted allenes with their intermolecular Alder-ene protocol. Multiple substituents present the opportunity for a mixture of products to arise from differing regio- and chemoselectivity. 1,1-Disubstituted allenes were coupled to methyl vinyl ketone with excellent chemoselectivity only when one set of β-hydrogens was activated by an α-ester or amide (Equation (69)). If the β-hydrogens were of similar acidity, a mixture of products was obtained, as in the coupling of allenol **103** with methyl vinyl ketone; dienes **104** and **105** are produced in a 1.3 : 1 mixture (Equation (70)).

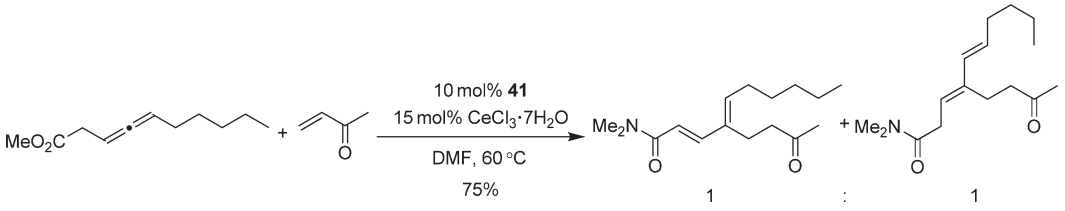


(69)

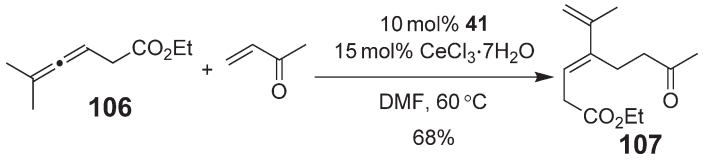


(70)

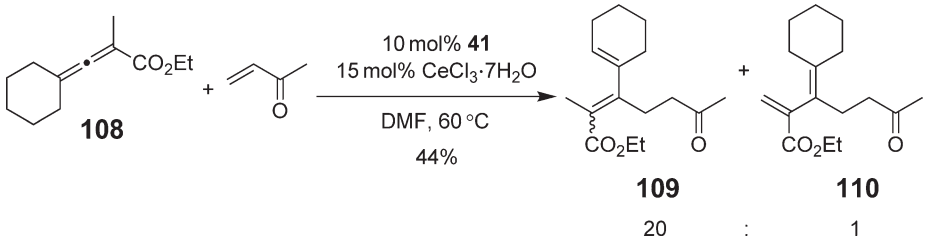
1,3-Disubstituted allenes generally gave a 1 : 1 mixture of regioisomeric products (Equation (71)). Trisubstituted allenes exhibited some selectivity; for example, allenic ester **106** coupled with methyl vinyl ketone to give exclusively diene **107** in 68% yield (Equation (72)). Some couplings were performed using tetrasubstituted allenes. However, it was noted that these reactions required longer reaction times and led to products in diminished yield. Nonetheless, allene **108** underwent Alder-ene coupling with methyl vinyl ketone in the presence of $[CpRu(MeCN)_3]PF_6$ **41** and $CeCl_3 \cdot 7H_2O$ to give products **109** and **110** in a 20 : 1 ratio and 44% combined yield (Equation (73)). This result implies that ruthenium complexes with the more electron-rich double bond of the allene before undergoing oxidative cyclization. For Alder-ene reactions involving tri- or tetrasubstituted allenes, bulky substituents led to lower yields and in some cases a complete lack of reactivity.



(71)

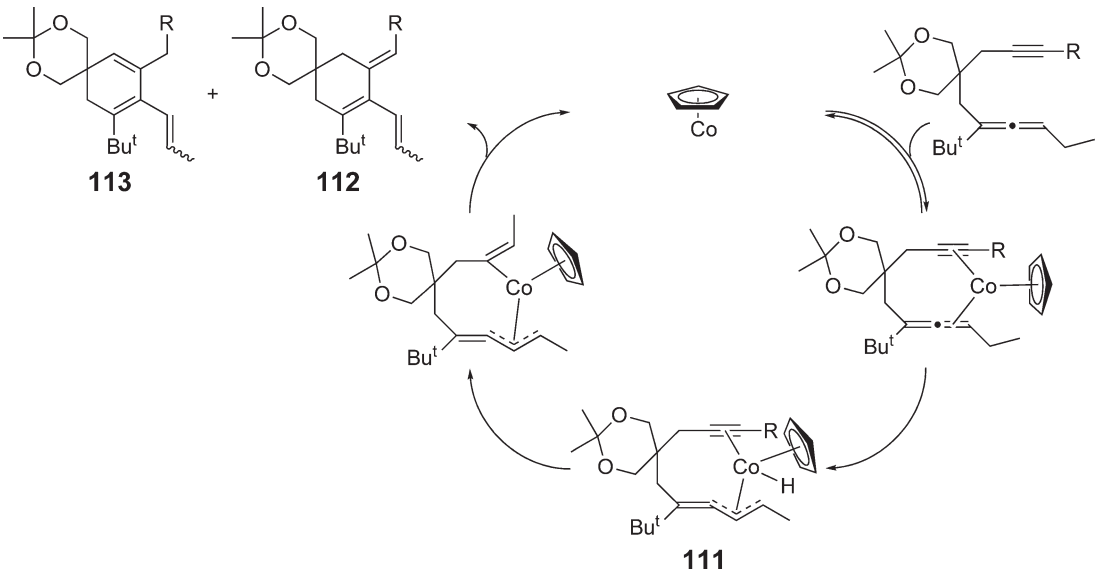


(72)



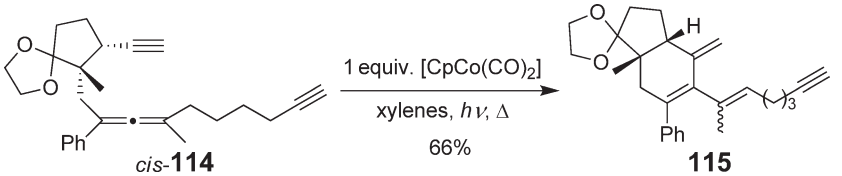
(73)

Trost *et al.*[72] briefly explored using non-enone enophiles. Simple alkenes led to the formation of complex mixtures of isomers due to the presence of an additional set of β-hydrogens. Many other types of substrates were incompatible with reaction conditions. Vinyl ketones were, therefore, the only coupling partners shown to be effective in the ruthenium-catalyzed Alder-ene couplings of allenes and alkenes.

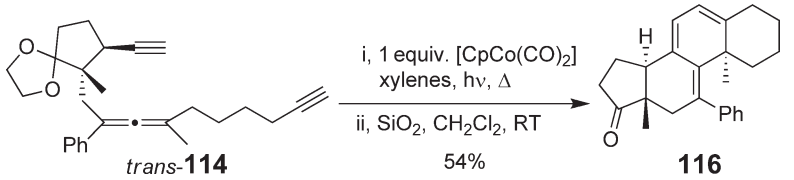


Scheme 22

Malacria and co-workers[76] were the first to report the transition metal-catalyzed intramolecular cycloisomerization of allenynes in 1996. The cobalt-mediated process was presumed to proceed via a π-allyl intermediate (**111**, Scheme 22) following C–H activation. Alkyne insertion and reductive elimination give cross-conjugated triene **112**; cobalt-catalyzed olefin isomerization of the Alder-ene product is presumed to be the mechanism by which **113** is formed. While exploring the cobalt(I)-catalyzed synthesis of steroidal skeletons, Malacria and co-workers[77] observed the formation of Alder-ene product **115** from *cis*-**114** (Equation (74)); in contrast, *trans*-**114** underwent [2 + 2 + 2]-cyclization under identical conditions to form **116** (Equation (75)).

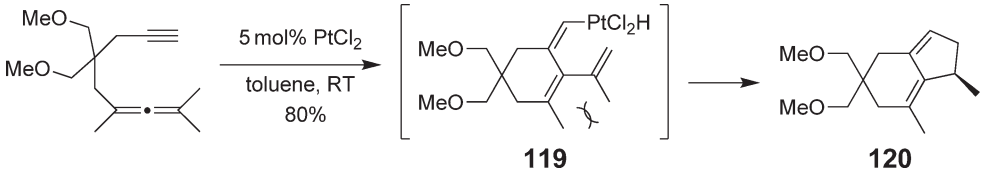


(74)

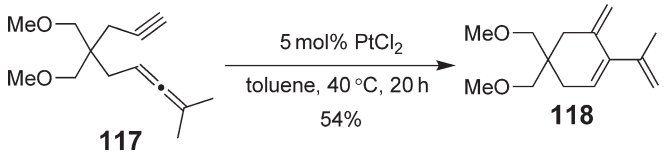


(75)

$PtCl_2$ was shown to catalyze a similar Alder-ene transformation, as in the cycloisomerization of allenyne **117** to triene **118** (Equation (76)).[78] In the same study, it was noticed that tetrasubstituted allenes cyclized to bicyclic compounds, such as **120** (Scheme 23), under identical $PtCl_2$ conditions, presumably due to $A^{(1,3)}$ strain in intermediate **119**.



Scheme 23

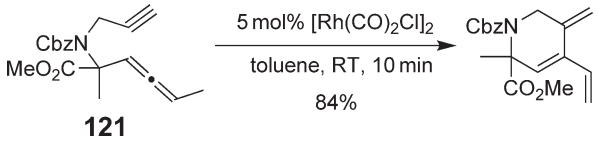


(76)

Brummond[79,80] and Shibata[81] independently reported the Rh(I)-catalyzed cycloisomerization of allenynes to cross-conjugated trienes. The rhodium conditions were shown to have broad functional group tolerance. Brummond *et al.*[79] observed rate and selectivity enhancements when they switched to an iridium catalyst (Equation (77)). The rate acceleration observed in the Alder-ene cyclization of aminoester containing allenyne **121** (Equation (78)) was attributed to the Thorpe–Ingold effect.[80]

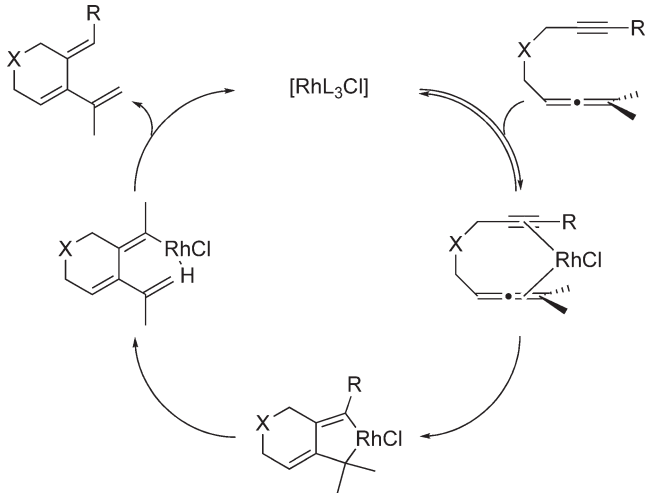
(77)

Conditions	*Time*	*E* : *Z*	*Yield* (%)
2 mol% $[Rh(CO)_2Cl]_2$, toluene, 90 °C	1 h	5 : 1	72
10 mol% $[Ir(cod)Cl]_2$, 20 mol% $AgBF_4$, DCE, 60 °C	5 min	>20 : 1	57



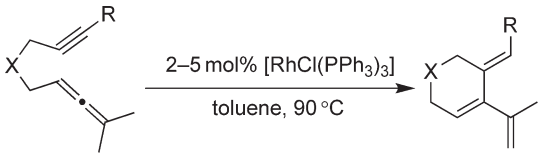
(78)

A variety of six-membered carbocycles and heterocycles were synthesized by Shibata *et al.*[81] using Wilkinson's catalyst (Equation (79)). The proposed catalytic cycle (Scheme 24) rationalizes the exclusive formation of the (*Z*)-isomer. Additionally, the mechanism is supported by the results of a isotope-labeling study reported by Brummond



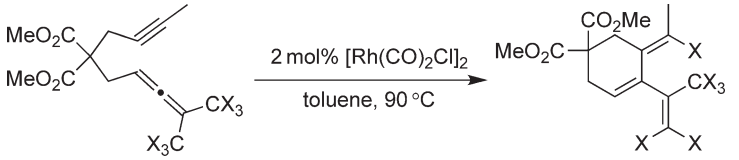
Scheme 24

et al. (Equation (80)).[79] Complete incorporation of deuterium on the exocyclic olefin of **123a** was seen. Also, no deuterium scrambling was observed when a 1 : 1 mixture of **122a** and **122b** was subjected to reaction conditions.



X	*R*	*Yield* (%)
O	Me	43
NTs	Ph	76
$C(CO_2Et)_2$	Ph	81

(79)

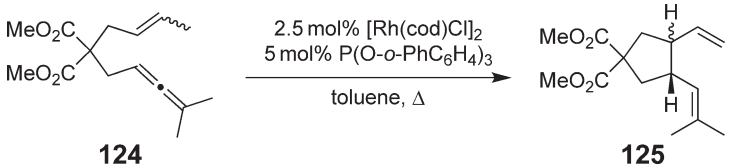


122
a: X = D
b: X = H

123

(80)

While investigating the scope of the Rh(I)-catalyzed ene-type cyclization of enallenes, Itoh and Makino[82] observed the formation of 1,4-dienes via ene-type cycloisomerization of enallenes containing terminal olefins. However, enallene **124** (Equation (81)) bearing a methyl substituent on the external carbon of the olefin gave exclusively the Alder-ene product **125** as a mixture of diastereomers. The distribution of products was determined not to be dependent on the olefin geometry in the starting material; varying the *E*/*Z* ratio of the starting material did not have a significant impact on diastereoselectivity.



124

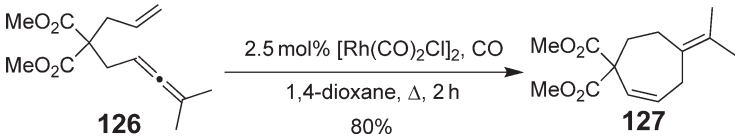
125

(81)

E : *Z* ratio of **124**	*Yield* (%)	*cis* : *trans* ratio of **125**
3 : 1	93	3 : 1
30 : 1	91	2.8 : 1

Using a protocol for tandem carbonylation and cycloisomerization, Mandai *et al.*[83] were able to synthesize cyclopentene and cyclohexene derivatives in high yield, including fused and *spiro*-bicycles (Scheme 25). The cyclohexene Alder-ene products were not isolable; methanol addition across the exocyclic double bond (in MeOH/toluene solvent) and olefin migration (in Bu^tOH/toluene solvent) were observed. The mechanism of methanol addition under the mild reaction conditions is unknown. In contrast to many of the other Pd conditions developed for the Alder-ene reaction, Mandai found phosphine ligands essential; additionally, bidentate ligands were more effective than triphenylphosphine.

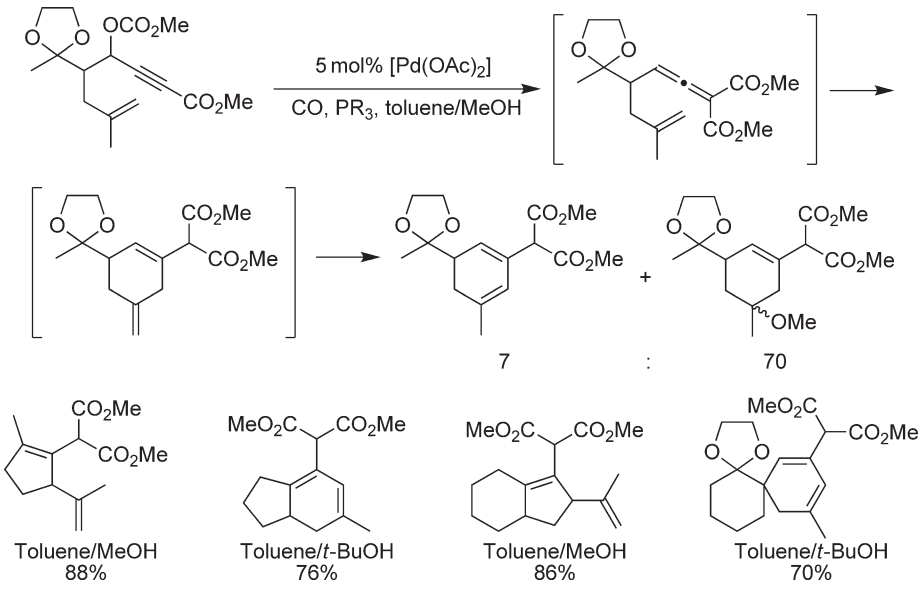
Seven-membered rings have been formed via *endo*-mode cycloisomerization of enallenes. Itoh and Makino[84] have reported a single example of *endo*-cyclization of a carbon-tethered enallene; they determined the mode of cyclization to be highly dependent on the auxiliary ligands. The use of $[Rh(cod)Cl]_2$ in the cycloisomerization of **126** led to formation of the seven-membered carbocycle **127** in only 33% yield; moderate yields of **127** and a mixture of unidentified isomers were obtained when the reaction was run in the presence of phosphine ligands. In the presence of rhodium biscarbonyl chloride dimer, enallene **126** gave a 70% yield of heptene **127** under argon atomosphere, while an 80% yield was obtained under CO atmosphere (Equation (82)).



126

127

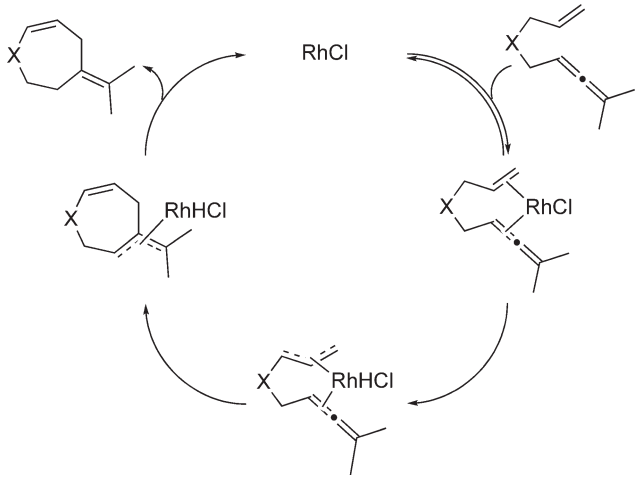
(82)



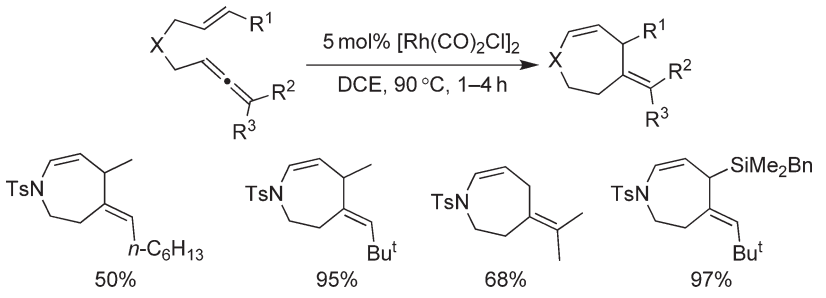
Scheme 25

The authors proposed two mechanisms. The first proceeds through a cationic intermediate and was ruled out after failed efforts to trap the cationic intermediate. The favored mechanism proceeds by allylic C–H activation, forming a π-allyl complex, which undergoes insertion and reductive elimination to give the cyclic product (Scheme 26).

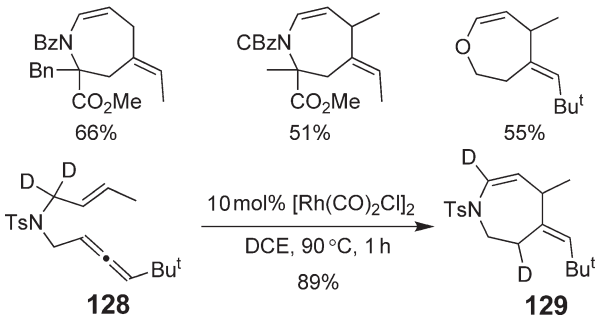
A variety of substituted azepines and oxepines were synthesized by Brummond *et al.*,[85] also using $[Rh(CO)_2Cl]_2$ (Equation (83)). Excellent functional group compatibility was demonstrated. Some insight into the mechanism of the Rh(I)-catalyzed *endo*-cycloisomerization was gained through a deuterium-labeling experiment. Enallene **128** (Equation (84)) was labeled with deuterium at the allyl position proximal to the heteroatom and was subjected to 10 mol% rhodium catalyst. The isolated product showed complete incorporation of deuterium at C2 and C6, supporting the mechanism shown in Scheme 26.



Scheme 26

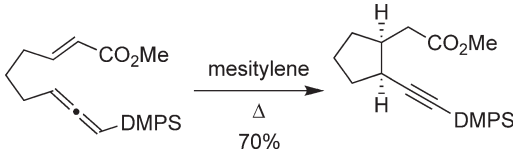


(83)

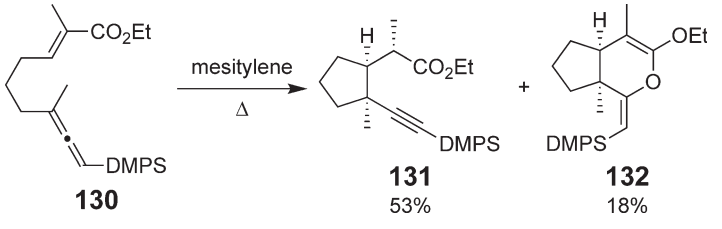


(84)

Weinreb[86] has reported the Alder-ene cyclization of enallenes under thermal conditions (Equation (85)). Varying the substitution pattern of alkene and allene groups had little effect on the yield of cyclized product. One exception was α,β-unsaturated ester **130**(Equation (86)); cycloisomerization under thermal conditions led to the formation of the Alder-ene product **131** and the unexpected hetero-Diels–Alder product **132** in a 3 : 1 ratio.

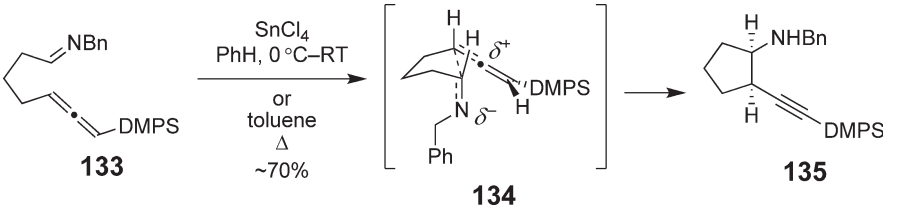


(85)



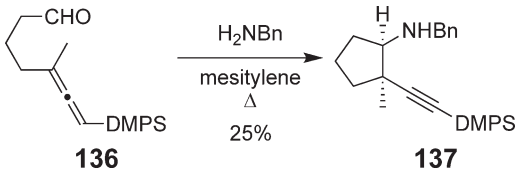
(86)

Weinreb *et al.*[86] have also studied the participation of allenes in imino–ene and carbonyl–ene reactions. Cycloisomerization of imine **133** in the presence of stannic chloride gave exclusively the *cis*-substituted cyclopentyl isomer **135** (Scheme 27). The thermal imino–ene reaction of **136** was equally effective. More highly substituted



Scheme 27

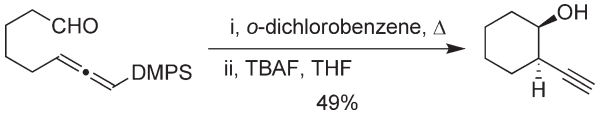
allenylsilane **136** (Equation (87)) was observed to decompose under Lewis-acidic conditions; refluxing in mesitylene, however, led to imino–ene product **137** in 25% yield.



136 **137** (87)

The silyl moiety was deemed essential; terminally unsubstituted allenes and allenes bearing a methyl substituent on the terminus failed to cyclize under either thermal or Lewis-acidic conditions. Weinreb explains this observation by proposing dipolar transition state **134** (Scheme 27), rationalizing that the β-silyl group provides necessary stabilization for the partial positive charge developing on the central carbon of the allene.

Thermal conditions were effective in the stereoselective oxa–ene cycloisomerization of allenylsilanes, furnishing both substituted cyclopentanes and, as in Equation (88), substituted cyclohexanes.



(88)

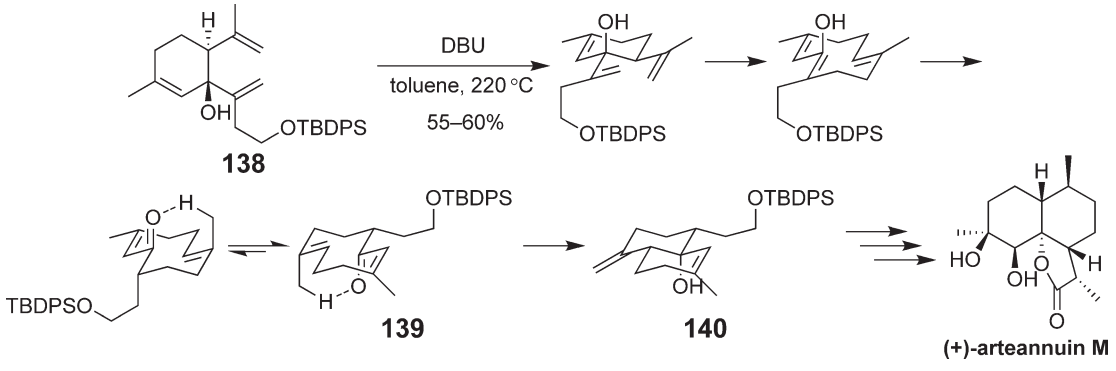
10.12.6 Applications of the Alder-Ene Reaction to the Synthesis of Biologically Relevant Compounds

The robustness and versatility of the Alder-ene and hetero-ene reactions are evidenced by their wide-ranging application to the synthesis of biologically relevant substrates over the past decade. In the section below, we have highlighted a few of these examples.

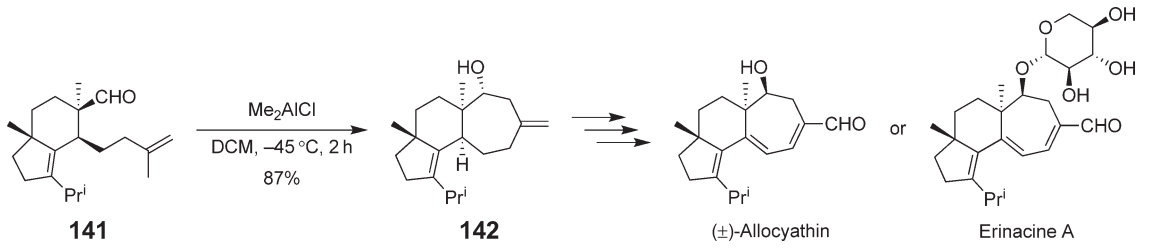
The first total synthesis of (+)-arteannuin M was accessed using a tandem oxy-Cope/ene reaction.[87] Divinylcyclohexanol **138** was heated in toluene and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give compound **140** as a single diastereomer in 55–60% yield (Scheme 28). The diastereoselectivity is controlled by the pseudo-equatorial position of the alkyl group in the transition state **139**.

Snider *et al.*[88] have shown that compound **141** undergoes a stereoselective carbonyl–ene reaction to afford alcohol **142** as a single diastereomer in 87% yield (Scheme 29). Alcohol **142** served as a synthetic intermediate for the preparation of (±)-allocyathin and erinacine A.

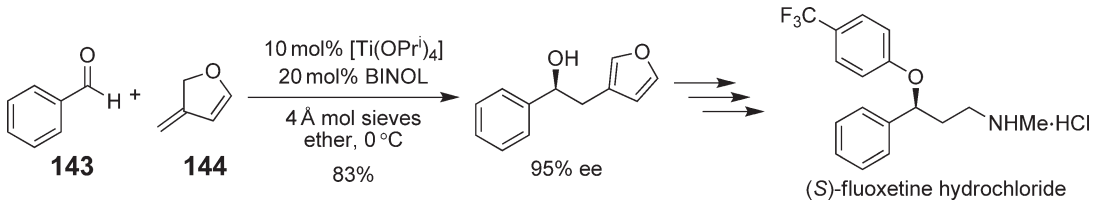
An extensive study was undertaken to optimize the carbonyl–ene reaction between benzaldehyde (**143**, Scheme 30) and 3-methylene-2,3-dihydrofuran **144**, which was utilized in the enantioselective synthesis of fluoxetine hydrochloride, a selective seratonin reuptake inhibitor.[89] The degree of hydration of the molecular sieves proved important in the stereoselectivity of the reaction, with lower enantioselectivities reported both with highly active



Scheme 28



Scheme 29



Scheme 30

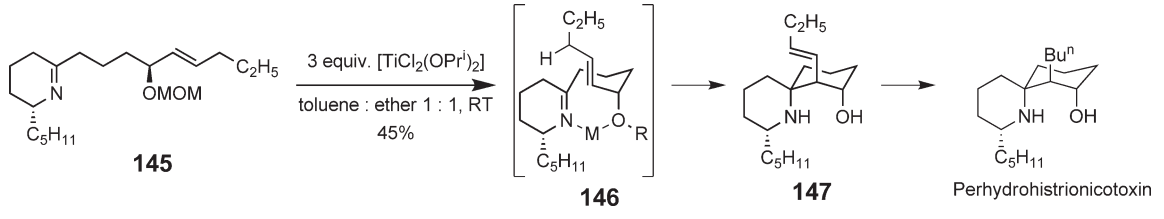
sieves and in the absence of molecular sieves. Additionally, it was determined that small-scale reactions (5 mmol) could be performed in refluxing ether, while larger-scale reactions (60 mmol) were run at 0 °C.

An intramolecular imino–ene reaction was used as the key step in the synthesis of the non-natural perhydrohistrionicotoxin.[90] The spirocycle **147** was obtained as a single diastereomer upon exposure of **145** to $TiCl_2(O^iPr)_2$ (Scheme 31). The transition structure **146** was proposed to explain the high diastereoselectivity of this reaction.

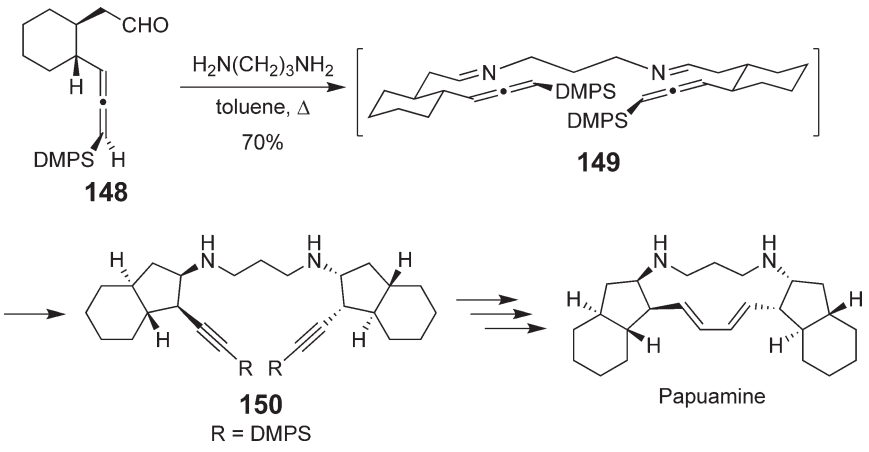
An elegant and concise synthesis of (–)-papuamine has been carried out by Weinreb and Borzilleri[91] using an intramolecular imino–ene reaction. Treatment of allenyl aldehyde **148** with 1,3-diaminopropane and heating for 16 h provided a 70% yield of **150** as a single stereoisomer. The intermediate bisamine **149** is presumably undergoing simultaneous imino–ene reactions. Interestingly, the reaction products are silyl alkynes and are shown to be completely stereospecific suggesting that the reaction is a concerted process. The tetracycle **150** was easily converted into (–)-papuamine (Scheme 32).

A stereospecific intramolecular imino–ene reaction was used by Weinreb and co-workers[92] to provide the enantioselective total syntheses of (–)-montanine, (–)-coccinine, and (–)-pancracine. Refluxing the imine resulting from the condensation of **151** and **152** in mesitylene produces the amine **153** (Scheme 33) as a single stereoisomer in 63% yield after removal of the silyl group from the alkyne. The high stereoselectivity is thought to arise from a concerted ene process.

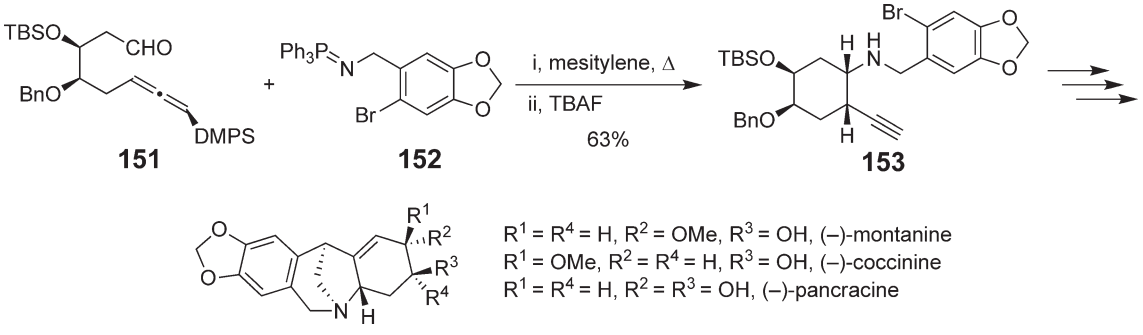
Assignment of the absolute and relative configuration of callipeltoside A was made possible by the completion of its total synthesis.[93] The key C–C bond-forming transformation in the synthesis was the intermolecular ruthenium-catalyzed Alder-ene reaction between alkyne **154** and alkene **155**, providing access to the tetrasubstituted alkene of the C7–C11 fragment **156** (Scheme 34). Remarkably high regioselectivity was observed for the Alder-ene reaction, which was attributed to the directing effect of the metal coordinating propargylic methyl ether. Varying the



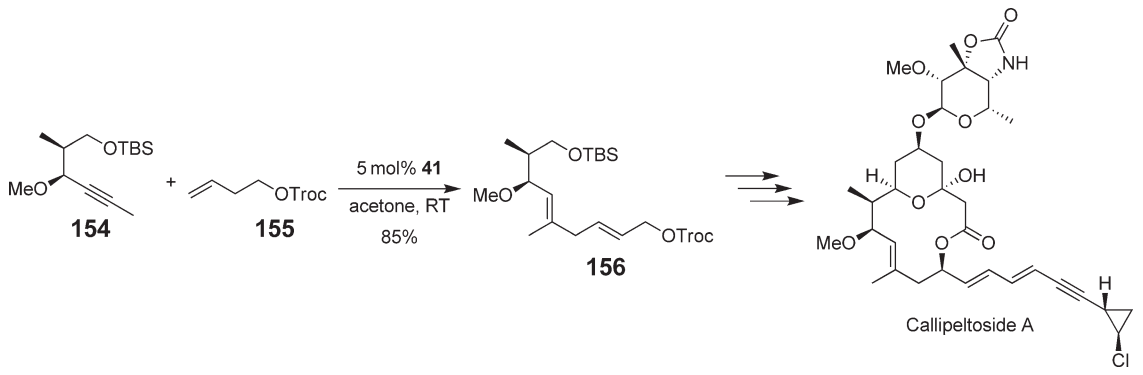
Scheme 31



Scheme 32



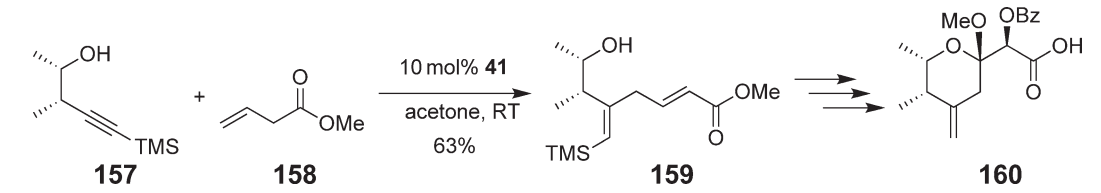
Scheme 33



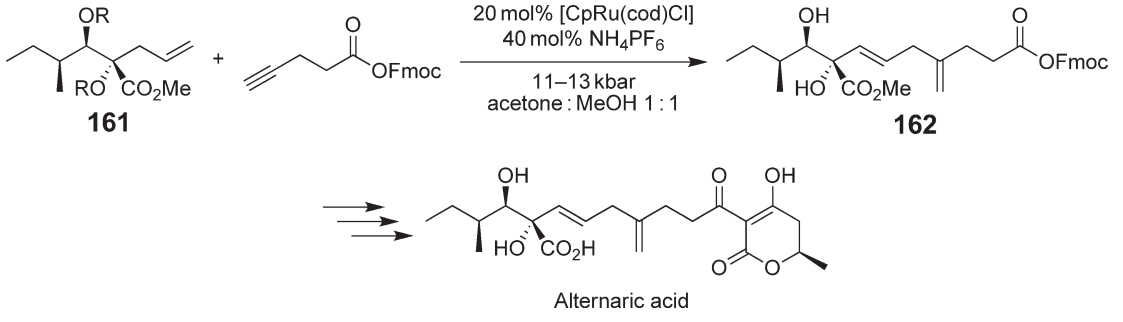
Scheme 34

protecting groups on fragments **154** and **155** had an effect on the efficiency and rate of this reaction, but it did not affect the regioselectivity.

A key reaction in the formal total synthesis of (–)-mycalamide A involved the intermolecular ruthenium-catalyzed Alder-ene reaction between **157** and **158** to give the dienoate **159** (Scheme 35).[94] This regioselective reaction provided a 63% yield of **159**, which was subsequently transformed to a key building block **160** which was taken on to (–)-mycalamide A.



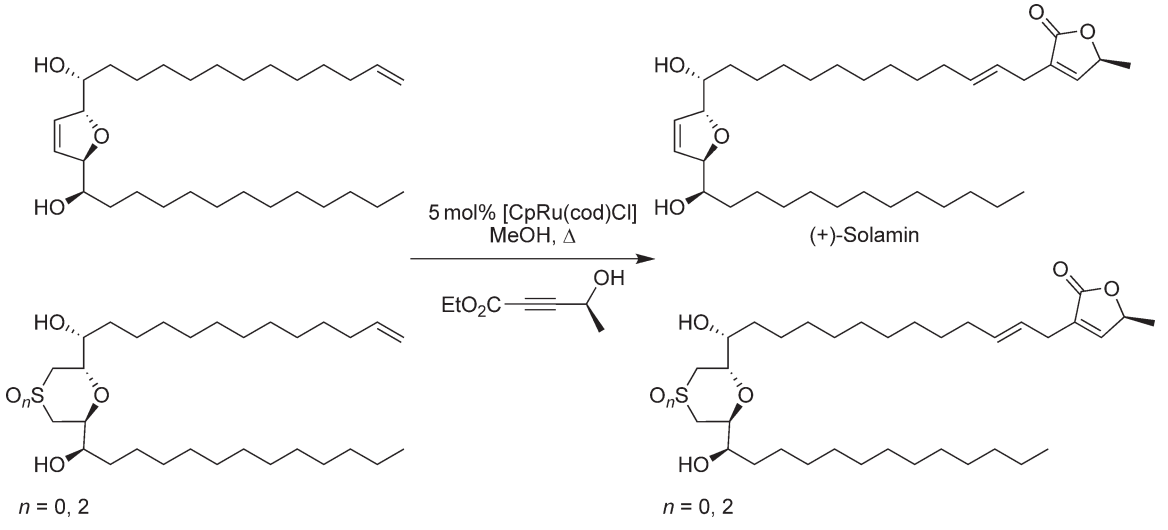
Scheme 35



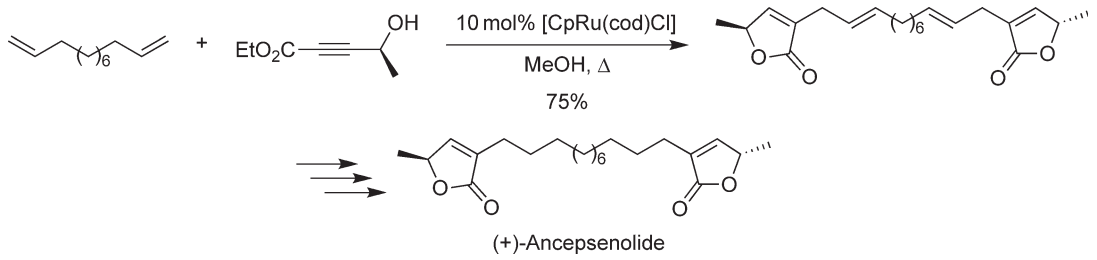
Scheme 36

A formal synthesis of the antifungal agent alternaric acid was realized in the Trost group.[95] The skipped diene portion of the natural product was obtained via a ruthenium-catalyzed intermolecular Alder-ene reaction (Scheme 36). Several attempts to produce **162** from the protected fragment **161** gave low yields and unremarkable regioselectivity. The diol (R = H), however, performed satisfactorily, allowing the reaction to be carried out at room temperature. The product **162** was obtained in 51% isolated yield as an 8.9 : 1 mixture of branched to linear isomers.

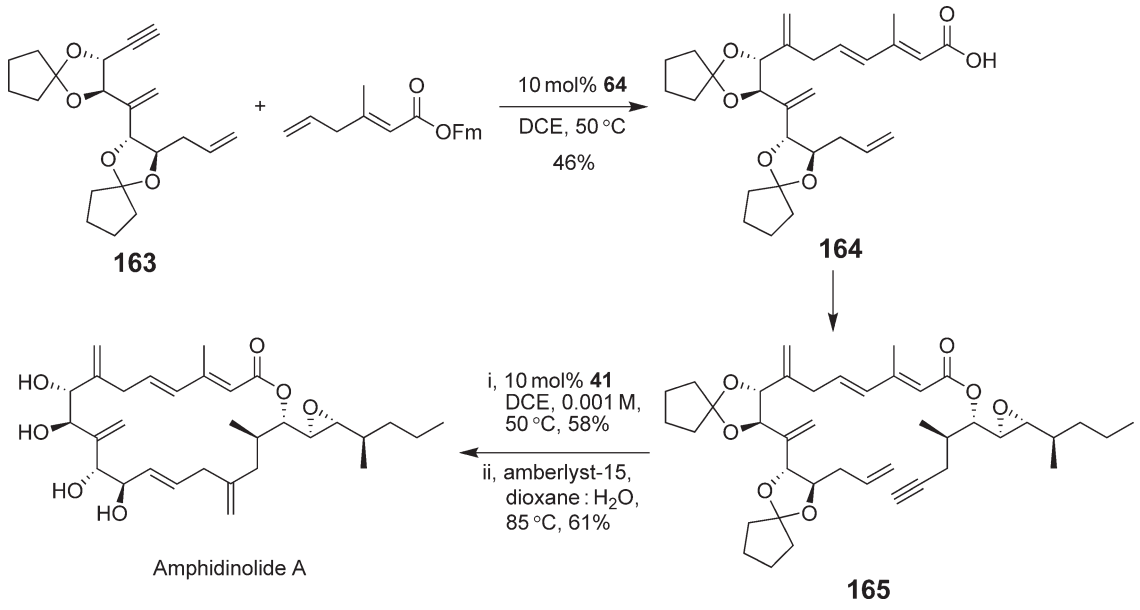
The acetogenin (+)-solamin and analogs were prepared via a ruthenium-catalyzed Alder-ene reaction/butenolide formation (Scheme 37).[96] Of particular note is the ability of the ruthenium to catalyze the reaction in the presence of free hydroxyls, sulfides, and sulfones. Yields ranged from 65% for the sulfide to 88% for the sulfone. Trost has also applied this reaction to the total synthesis of (+)-ancepsenolide, which features a bis-Alder-ene reaction (Scheme 38).[97]



Scheme 37



Scheme 38

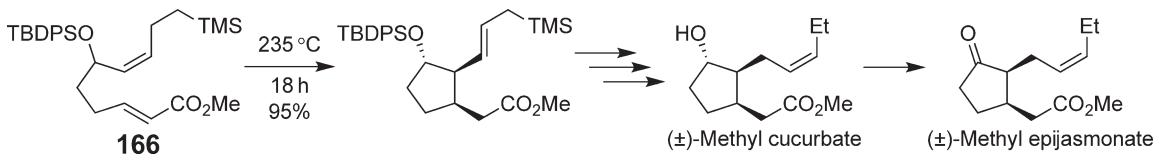


Scheme 39

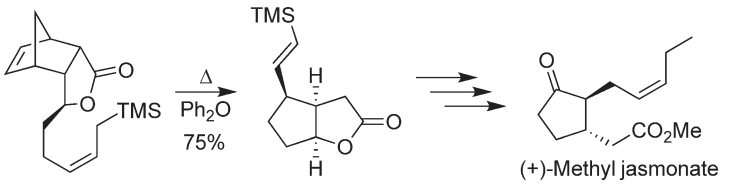
Inter- and intramolecular ruthenium-catalyzed Alder-ene reactions were utilized to synthesize the proposed structures of amphidinolide A.[98] Conversion of dienyne **163** into pentaene **164** was accomplished in 46% yield with the products obtained as a 3.5 : 1 mixture of the branched to linear forms (Scheme 39). It is notable that the Cp^* variant of the ruthenium catalyst **64** was used for the intermolecular Alder-ene reaction. Conversion of **164** into protected amphidinolide A was performed using high dilution conditions with the normal catalyst to give a 58% yield of the macrolide which was then deprotected to provide the natural product.

Racemic methyl cucurbate and racemic methyl epijasmonate were synthesized via a thermal Alder-ene reaction (Scheme 40).[99] The newly formed stereocenters are controlled by the existing protected hydroxyl group of **166** in an *anti*/*syn* relationship.

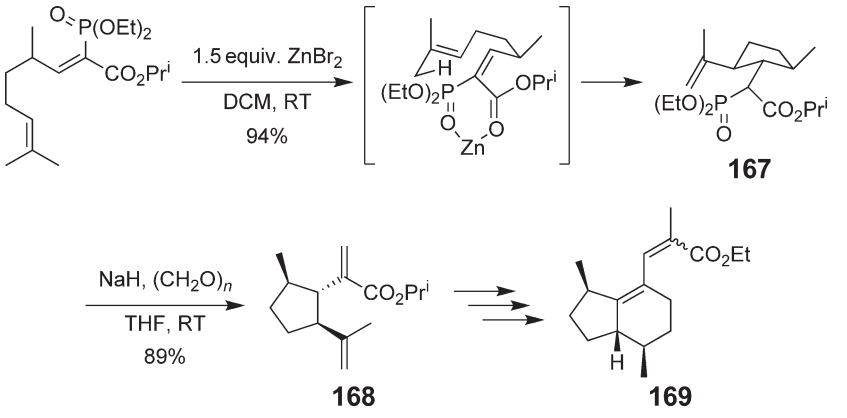
Inomata[100] utilized a tandem retro-Diels–Alder-ene reaction for an enantioselective total synthesis of (+)-methyl jasmonate (Scheme 41). The TMS group on the alkene was essential to the efficiency of the reaction, by producing a higher energy level of the HOMO for the ene reaction.



Scheme 40



Scheme 41



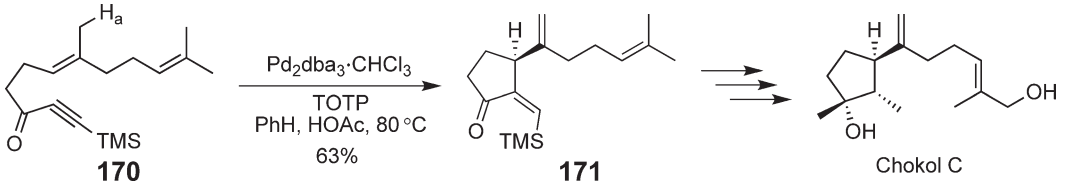
Scheme 42

Vinyl phosphonates have been used in the construction of valerenic acid terpenoids **169** (Scheme 42).[101] Both five- and six-membered rings can be formed via the vinyl phosphonate Alder-ene reaction which can be catalyzed by a variety of Lewis acids. The resulting structures **167** are suitable for Wittig–Horner reaction to give diene **168**. Subsequent reactions access valerenic acid terpenoids **169**. The chirality of the carbon bearing the phosphonate and ester is transferred, but is subsequently lost in the Wittig–Horner step.

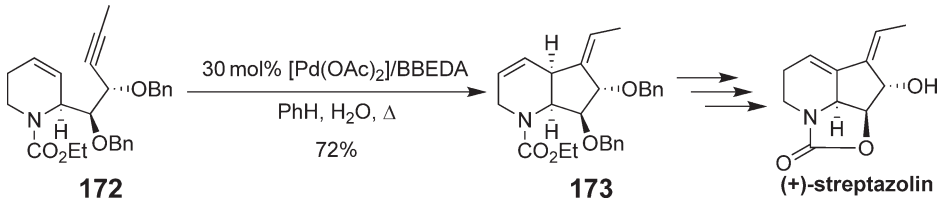
An intramolecular palladium-catalyzed cycloisomerization of enyne **170** was used to access the antifungal agent, chokol C (Scheme 43).[102] The choice of ligand and catalyst was essential to the efficiency of the Alder-ene reaction. Enone **171** was obtained as a single olefinic isomer resulting from migration of only H_a during the cycloisomerization reaction.

Kibayashi and co-workers[103] implemented the palladium-catalyzed cycloisomerization reaction in a stereoselective total synthesis of enantiomerically pure (+)-streptazolin. The cycloisomerization of enyne **172** to provide diene **173** was remarkably selective when performed in the presence of *N*,*N*′-bis(benzylidene)ethylenediamine (BBEDA) as a ligand and water as a proton source (Scheme 44).

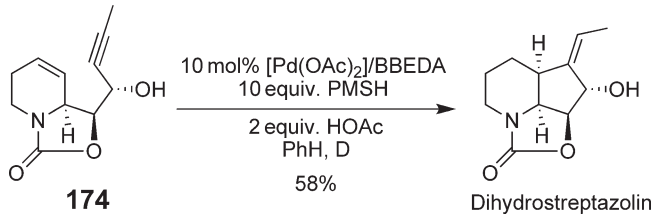
A synthesis of (–)-4a,5-dihydrostreptazolin was accomplished in a similar manner; only a reductive palladium-catalyzed cyclization was utilized.[104] The hydride source was polymethylhydroxysilane (PMHS), and the unprotected hydroxyl group of **174** (Equation (89)) had an accelerating effect, since the reaction was completed in minutes instead of hours, as in the example above.



Scheme 43



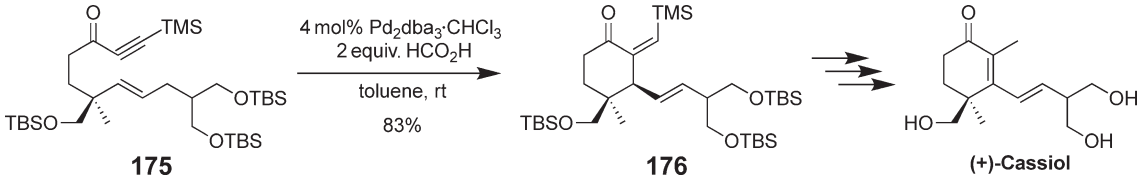
Scheme 44



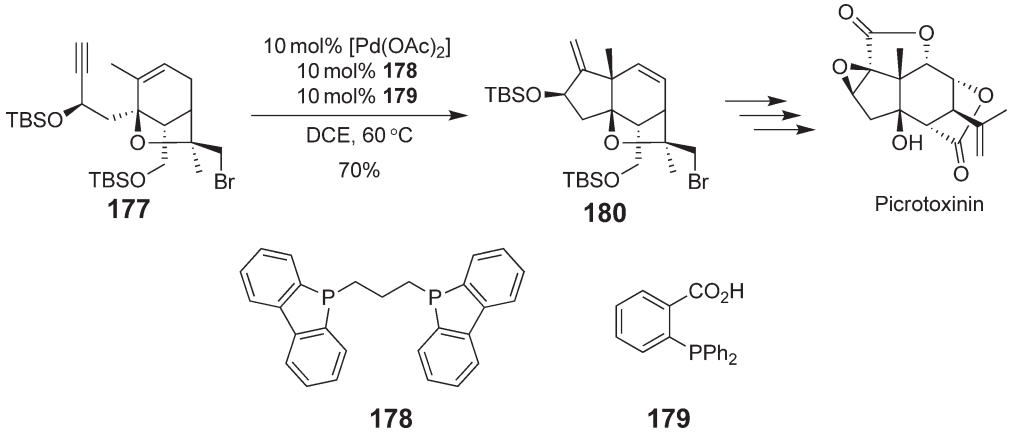
(89)

Trost and Li[45] have extended the scope of the palladium-catalyzed enyne Alder-ene cycloisomerization reaction by showing its effectiveness for six-membered ring formation. Conversion of **175** into **176** was accomplished using their so-called "ligandless" conditions (Scheme 45). Enone **176** was obtained as a 3 : 1 mixture of diastereomers in 83% yield and was taken on to complete the synthesis of cassiol. It was concluded that rate-retarding effect of ligands was also contributing to substrate decomposition; thus, the reaction was preformed in the presence of an acid. A systematic study was done varying the acids based upon their pK_a's, and formic acid was found to give the best results (see also Section 10.12.4.1).

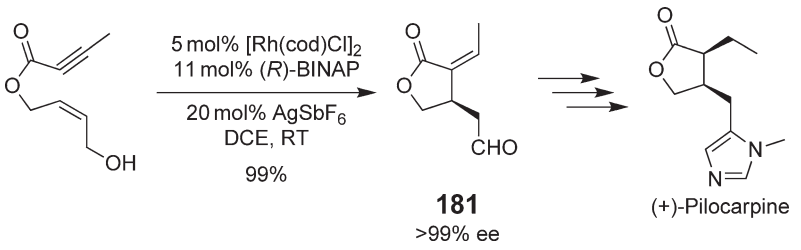
An asymmetric synthesis of the γ-aminobutyric acid (GABA) antagonist, picrotoxinin, was made possible using a palladium-catalyzed Alder-ene reaction.[105] Trost and Krische showed that, by subjecting enyne **177** to palladium acetate and ligands **178** and **179**, the core substructure **180** was afforded and taken on to complete the synthesis of the target (Scheme 46). The bis-phosphine ligand was designed to tie back the diphenylphosphine moiety, producing



Scheme 45



Scheme 46



Scheme 47

a smaller phosphine ligand. The smaller ligand proved to be advantageous as it eliminated steric interference in the transition state. Acidic ligand **179** was responsible for an internal proton delivery.

Zhang[68] has applied the cyclization of esters to the formation of α-methylene-γ-butyrolactones, thus offering a novel and enantioselective entry to these substructures. The importance of this unsaturated lactone is evidenced by its ubiquitous presence in nearly a third of all naturally occurring secondary metabolites. The Alder-ene reaction has been applied to a formal total synthesis of (+)-pilocarpine, a leading therapeutic reagent for the treatment of narrow and wide glaucoma. Zhang intersected Büchi's synthetic intermediate (*R*)-**181** (Scheme 47) in only two steps with a 99% ee and a 91% overall yield. In comparison, Büchi synthesized (*R*)-**181** in five steps with a 92% ee and a 20% overall yield.

10.12.7 Conclusion

In conclusion, the ene reaction has undergone a synthetic renaissance with the advent of Lewis acid and transition metal-catalyzed protocols. The carbonyl–ene, imino–ene, and Alder-ene reactions have all experienced tremendous growth due to the mild conditions in which these reactions can be performed, the high functional group compatibility and high stereoselectivity. As a confirmation of the synthetic utility of the ene reaction, there are many applications to **natural** product synthesis, and some of these are highlighted in Section 10.12.6. Finally, it should be mentioned that these catalyzed ene reactions are still in their infancy, so much remains to be learned.

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10.13 C–C Bond Formation (Part 1) by Addition Reactions: Higher-order Cycloadditions

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10.13.1 Introduction

Higher-order cycloadditions comprise a broad and versatile class of reactions that provide strategically unique and often industrially practical access to rings of seven or more members. The term higher-order cycloaddition was originally used to describe pericyclic cycloaddition reactions involving one or more extended π-systems relative to the Diels–Alder [4π + 2π]-cycloaddition. For example, Woodward and Houk described the [6π + 4π]-cycloaddition of cycloheptatriene and 2,5-dimethyl-3,4-diphenylcyclopentadienone as being a cycloaddition of "order greater than [4 + 2]."[1] More recently, this terminology has been extended through use to include non-pericyclic cycloaddition processes that produce rings of seven or more members.[2,3] Partly to avoid mechanistic implications and partly to codify reactions for synthetic applications, cycloadditions in general, and higher-order cycloadditions in particular,

7-membered rings
2-*component* 6+1 **5+2** **4+3**
3-*component* 5+1+1 **4+2+1** 3+3+1 **3+2+2**
4-*component* 4+1+1+1 3+2+1+1 **2+2+2+1**
5-*component* 3+1+1+1+1 2+2+1+1+1
6-*component* 2+1+1+1+1+1
7-*component* 1+1+1+1+1+1+1

8-membered rings
2-*component* 7+1 **6+2** **5+3** **4+4**
3-*component* 6+1+1 **5+2+1** 4+3+1 **4+2+2** 3+3+2
4-*component* 5+1+1+1 4+2+1+1 3+3+1+1 3+2+2+1 **2+2+2+2**
5-*component* 4+1+1+1+1 3+2+1+1+1 2+2+2+1+1
6-*component* 3+1+1+1+1+1 2+2+1+1+1+1
7-*component* 2+1+1+1+1+1+1
8-*component* 1+1+1+1+1+1+1+1

9-membered rings
2-*component* 8+1 7+2 **6+3** **5+4**
3-*component* 7+1+1 6+2+1 5+3+1 **4+4+1** **5+2+2** 4+3+2 3+3+3
4-*component* 6+1+1+1 **5+2+1+1** 4+3+1+1 4+2+2+1 3+3+2+1 3+2+2+2
5-*component* 5+1+1+1+1 4+2+1+1+1 3+3+1+1+1 3+2+2+1+1 2+2+2+2+1
6-*component* 4+1+1+1+1+1 3+2+1+1+1+1 2+2+2+1+1+1
7-*component* 3+1+1+1+1+1+1 2+2+1+1+1+1+1
8-*component* 2+1+1+1+1+1+1+1
9-*component* 1+1+1+1+1+1+1+1+1

Figure 1 Higher-order cycloaddition reactions.

have come to be designated in terms of the number of participating atoms in the reacting functionalities that map into the product ring. This terminology is not intended to indicate the number of electrons involved. Thus, the $[4\pi + 2\pi]$ Diels–Alder cycloaddition is considered to be an example of a more general class of [4 atom + 2 atom]- or more simply $[4 + 2]$-cycloaddition reactions that produce six-membered rings. This broader designation of $[m + n + \cdots (+x)]$ cycloadditions does not imply a mechanism as the reaction could be concerted or stepwise.

Figure 1 illustrates all possible higher-order cycloadditions leading to seven-, eight-, and nine-membered ring products. It is apparent from this compilation that most types of higher-order cycloadditions have not yet been reported. The focus of this chapter is higher-order cycloaddition reactions in which a metal mediates or catalyzes bond formation. The cycloadditions discussed in this chapter are highlighted in Figure 1. Pertinent literature from 1993 to mid-2005 is described along with some coverage of pioneering work in the respective areas. The reactions covered require the use of either a substoichiometric amount of a metal (metal-catalyzed) or at least 1 equiv. (metal-mediated) and involve a carbon–metal bond at some point in the ring-forming reaction. The higher-order cycloaddition reactions described here are classified by the number of components that are brought together to form the ring system. Those reported in the literature thus far fall into three general categories: $[m + n]$-, $[m + n + o]$-, and $[m + n + o + p]$-cycloaddition reactions representing two-, three-, and four-component processes, respectively.

For calibration, the nickel-catalyzed $[2 + 2 + 2 + 2]$-cycloaddition reaction of acetylene to form cyclooctatetraene reported by Reppe in the 1940s is an early example of what is now considered a metal-catalyzed higher-order cycloaddition reaction.[4] It is also a relatively uncommon but obviously powerful example of a four-component cycloaddition. As evidenced by the content of this chapter, most metal-mediated and metal-catalyzed higher-order cycloadditions were discovered long after Reppe's first report due in part to the challenging nature of the problem and to the relatively recent interest in rings of seven or more members heightened by synthetically challenging and biologically active molecules such as the phorbol esters and taxol. Higher-order metal-mediated and metal-catalyzed cycloadditions provide the synthetic chemist with new ways of thinking about and approaching the construction of medium ring-containing targets, often involving processes that in the absence of metals would be forbidden or difficult to achieve. These new processes in turn afford the synthetic chemist with options for route selection and thereby for achieving step-economical, if not ideal syntheses, processes in which cost, time, waste, and environmental impact are minimized.

This chapter is the first review whose sole focus is only on metal-catalyzed and metal-mediated higher-order cycloaddition reactions where all of the reaction types are discussed. Previous reviews have focused on specific types of higher-order cycloadditions (referenced in individual chapters), on the general topics of metal-mediated and metal-catalyzed cycloaddition reactions,[5–8] and on methods for forming medium-sized rings.[9]

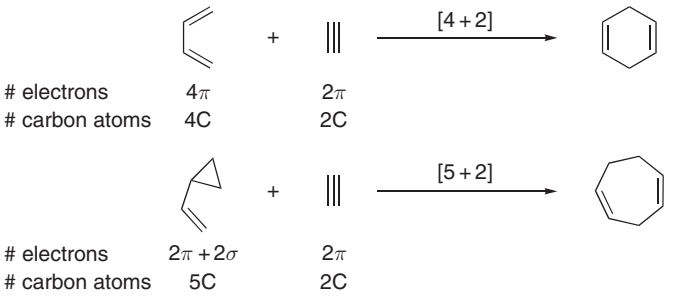
10.13.2 [*m* + *n*]-Cycloadditions

10.13.2.1 [5 + 2]-Cycloadditions

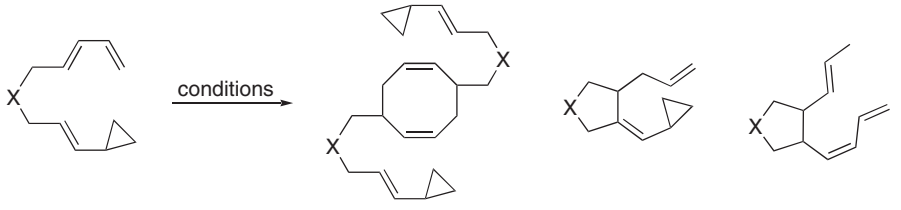
10.13.2.1.1 Metal-catalyzed [5 + 2]-cycloadditions of vinylcyclopropanes and π-systems

The first examples of transition metal-catalyzed [5 + 2]-cycloadditions between vinylcyclopropanes (VCPs) and π-systems were reported in 1995 by Wender and co-workers.[10] This [5 + 2]-reaction was based conceptually on the Diels–Alder reaction, replacing the four-carbon, four-π-electron diene with a five-carbon, four-electron VCP (Scheme 1). Although the [5 + 2]-reaction of VCPs and π-systems can be thought of as a homolog of the Diels–Alder [4 + 2]-reaction, the kinetic stability of VCPs (activation barrier for the thermal isomerization of VCP to cyclopentene has been reported as 51.7 kcal mol^{-1})[11] makes the thermal [5 + 2]-reactions involving VCPs and π-systems very difficult to achieve. A report of a thermal [5 + 2]-cycloaddition between maleic anhydride and a VCP has been published,[12] but this reaction has not been reproduced by others.[13,14] Based on the metal-catalyzed isomerization of VCPs to cyclopentenes and dienes,[15–20] Wender and co-workers hypothesized that a metal might be used to convert a VCP to a metallocyclohexene which in turn might be trapped by a π-system to produce a [5 + 2]-cycloadduct. Based on its previous effectiveness in catalyzed [4 + 2]-[21] and [4 + 4]-cycloadditions (Section 10.13.2.4), nickel(0) was initially selected to explore the potential of VCPs as four-electron, five-carbon components in [5 + 2]-cycloadditions.

In the presence of nickel(0), tethered diene–VCPs react to produce eight- and five-membered ring products (Scheme 2). Palladium(0) and cobalt(III) were also tried but produced only decomposition products. However, in the presence of Wilkinson's catalyst ($RhCl(PPh_3)_3$), tethered diene–VCP **1** was cleanly converted to triene **4** in 91% yield. Although the desired cycloaddition reaction was not obtained, the cleavage of the cyclopropane ring was encouraging.[22]



Scheme 1



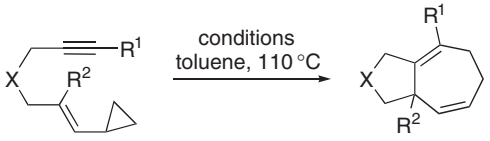
1 **2** **3** **4**

Conditions	*X*	*Result*
$Ni(cod)_2$, THF, 55 °C	$CH(CO_2Me)$	**2**
$Ni(cod)_2$, $P(OPh)_3$, toluene, Rt	$CH(CO_2Me)$	**2**
$Ni(cod)_2$, $P(Cy)_3$, toluene, 85 °C	$C(CO_2Me)_2$	**3**
$Co(acac)_3$, dppe, Et_2AlCl, benzene, 55 °C	$CH(CO_2Me)$	Decomposition
$Pd_2(dba)_3$, dppe, DMSO, 80 °C	$CH(CO_2Me)$	Decomposition
$RhCl(PPh_3)_3$, toluene, 100 °C	$C(CO_2Me)_2$	**4**

Scheme 2

Subsequent examination of a tethered alkyne–VCP with rhodium(I) resulted in the first metal-catalyzed [5 + 2]-reaction. Excellent yields were obtained with a variety of substrates (Scheme 3) irrespective of the steric and electronic nature of the R^1 group. Notably, quaternary centers are accessed in high yield. Since this first report, in-depth studies on catalysts, substrate scope, selectivity, and applications to total synthesis have been carried out. Work in this area has been reviewed.[23–26]

In addition to the cycloaddition of tethered alkyne–VCPs, the [5 + 2]-cycloaddition reactions of tethered alkene–VCPs and tethered allene–VCPs have also been achieved. The examples shown in Scheme 4 and Equation (1) indicate some key features of this powerful process. The [5 + 2]-reactions of tethered alkene–VCPs, catalyzed by a modified Wilkinson's catalyst (Wilkinson's catalyst treated with 1 equiv. of silver triflate to open a coordination site on rhodium), function at very low catalyst loading and can be scaled to produce gram (and presumably larger) quantities of product. Wilkinson's catalyst can be used without silver triflate if increased dilution and higher catalyst loading are employed. The [5 + 2]-cycloaddition of the methyl-substituted tethered alkene–VCP **7b** gives rise to a *cis*-fused bicyclo[5.3.0]decene containing an angular methyl group. The [5 + 2]-reaction of a substrate with a tether extended by one methylene unit provides the bicyclo[5.4.0]undecene **8c** in good yield.[27] Wilkinson's catalyst has also

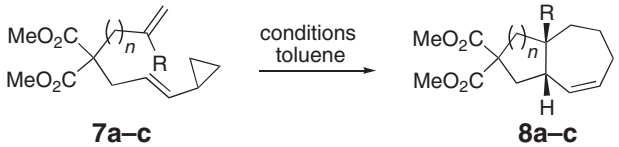


5a–f **6a–f**

Conditions A: $RhCl(PPh_3)_3$ (0.5 mol%), AgOTf (0.5 mol%)
Conditions B: $RhCl(PPh_3)_3$ (10 mol%)
Conditions C: $RhCl(PPh_3)_3$ (10 mol%), AgOTf (10 mol%)

Conditions	*Alkyne–VCP*	*X*	R^1	R^2	*Time* (h)	*Yield* **6** (%)
A	**5a**	$C(CO_2Me)_2$	Me	H	0.3	83
B	**5a**	$C(CO_2Me)_2$	Me	H	48.0	84
B	**5b**	O	Me	H	1.5	88
B	**5c**	O	TMS	H	3.5	83
B	**5d**	O	Ph	H	1.5	80
B	**5e**	O	CO_2Me	H	1.3	74
C	**5f**	$C(CO_2Me)_2$	Me	Me	0.5	82

Scheme 3



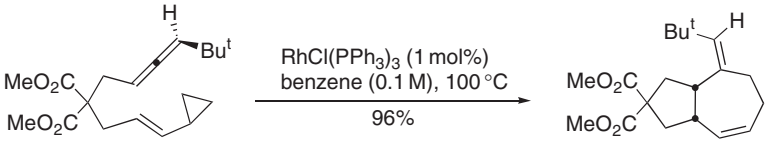
7a–c **8a–c**

Conditions A: $RhCl(PPh_3)_3$ (0.1 mol%), AgOTf (0.1 mol%)
Conditions B: $RhCl(PPh_3)_3$ (10 mol %)
Conditions C: $RhCl(PPh_3)_3$ (10 mol%), AgOTf (10 mol%)

Conditions	*Alkene–VCP*	*Concentration* (M)	*Temperature* (°C)	*R*	*n*	*Time* (h)	*Yield* **8** (%)
A	**7a**	1.0	110	H	1	17	86 (1 g)
B	**7a**	0.005	110	H	1	2.5	91
C	**7b**	0.01	110	Me	1	1	94
C	**7c**	0.02	100	H	2	120	77

Scheme 4

been used to catalyze the [5 + 2]-cycloaddition of tethered allene–VCPs. When the allene is chiral, an excellent yield of the cycloadduct is obtained with complete transfer of allene chirality (Equation (1)).[28]



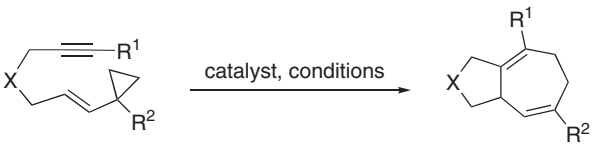
9
91% ee

10
92% ee

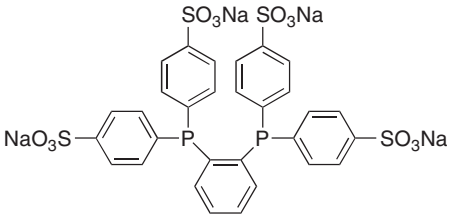
(1)

As shown in Scheme 5, various metal complexes have been found to be effective catalysts in the [5 + 2]-cycloaddition of tethered alkyne–VCPs. The commercially available $[RhCl(CO)_2]_2$ complex is an effective catalyst for the [5 + 2]-reaction[29] and several Rh(I) complexes catalyze the [5 + 2]-cycloaddition at ambient temperature.[30,31,32] The naphthalene-Rh(I) complex also minimizes some side-reactions when compared to the modified Wilkinson catalyst. As shown in Scheme 6, secondary isomerization of the initial cycloadducts can be either favored or suppressed, depending on the choice of catalyst. Water can be used as an inexpensive and environmentally friendly solvent (Scheme 5) allowing for the reuse of the water-soluble catalyst up to eight times with negligible decrease in cycloadduct yield. Furthermore, this catalyst-solvent system allows the product to be easily separated from the solvent via standard organic layer/aqueous layer extraction. Among other advantages, this allows the reaction to be conducted without organic solvent, often the most atom uneconomical aspect of a reaction.[33] In addition to rhodium(I) complexes, a ruthenium(II) complex[34] and a nickel(0) complex[35] have also been shown to catalyze the [5 + 2]-cycloadditions of tethered alkyne–VCPs.

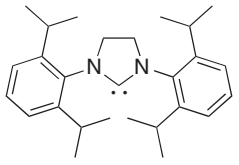
Thus far, rhodium(I) complexes are the most general, efficient, and selective catalysts, uniquely enabling [5 + 2]-cycloadditions of tethered alkyne–VCPs, alkene–VCPs, and allene–VCPs. For example, when tethered alkene–VCP **7a** (Equation (2)) is treated with $[(cod)Rh(C_{10}H_8)]SbF_6$, the bicyclo[5.3.0]decene is produced in 96% yield.



5a–c, 5g–i **6a–c, 6g–i**



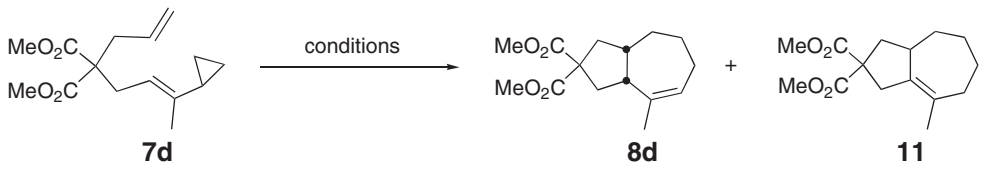
PAr$_3$



SIPr

Alkyne–VCP	*X*, R^1, R^2	*Catalyst* (mol%)	*Conditions*	*Yield* **6** (%)
5a	$C(CO_2Me)_2$, Me, H	$[RhCl(CO)_2]_2$ (5)	Toluene, 110 °C, 20 min	82
5g	O, H, H	$[Rh(dppe)(CH_2Cl_2)_2]SbF_6$ (6)	CH_2Cl_2, RT, 20 h	69
5b	O, Me, H	$[Rh(dppb)Cl]_2$, $AgSbF_6$ (1.25, 2.5)	DCE, RT, 1.5 h	91
5a	$C(CO_2Me)_2$, Me, H	$[(cod)Rh(C_{10}H_8)]SbF_6$ (2)	DCE, RT, 15 min	>99
5h	O, CO_2Me, Me	$[Rh(nbd)(\mathbf{PAr_3})]SbF_6$ (10)	H_2O, 90 °C, 12 h	80
5i	NTs, TMS, H	$[CpRu(CH_3CN)_3]PF_6$ (10)	Acetone, RT, 2 h	84
5c	O, TMS, H	$Ni(cod)_2$, **SIPr** (5, 5)	Toluene, RT, 2 h	88

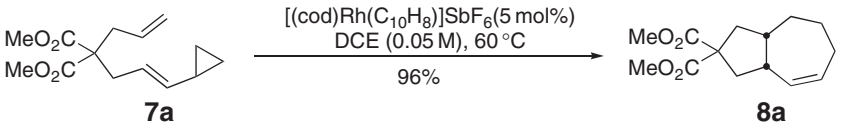
Scheme 5



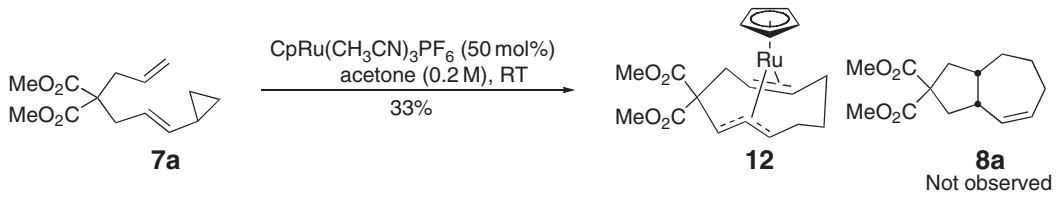
[(cod)Rh($C_{10}H_8$)]SbF_6 (10 mol%), 70 °C, DCE, 10 h	75%	0%
$RhCl(PPh_3)_3$ (5 mol.%), AgOTf (5 mol%), 110 °C, toluene, 15 h	0%	78%

Scheme 6

Alkynes often react with similar efficiency at room temperature (RT) in minutes. Treatment of the identical tethered alkene–VCP with a ruthenium catalyst leads to the formation of (1-3:6,7-η-cyclodecadienyl)ruthenium complex (Equation (3)).[36]

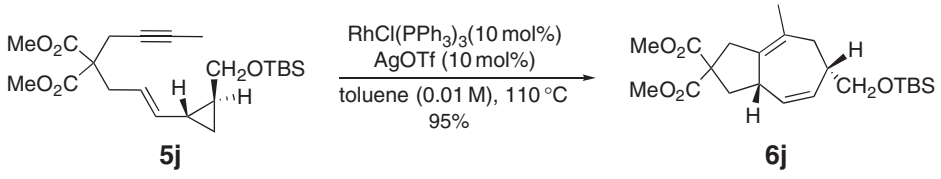


(2)

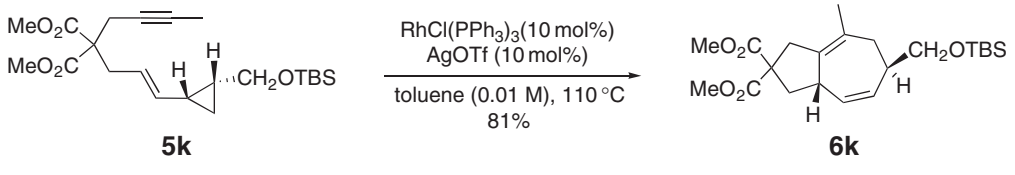


(3)

The [5 + 2]-cycloadditions of tethered alkyne–VCPs that are 1,2-disubstituted on the cyclopropane ring **5j–l** have been studied and a mechanism has been advanced to explain the regio- and stereoselectivities of the reactions.[37] In most cases, the product resulting from cleavage of the less-substituted (sterically less encumbered) carbon–carbon bond is obtained. The [5 + 2]-reaction is stereospecific in that a *trans*-relationship of the substituents on the cyclopropane leads to a *cis*-relationship of the substituents in the product and vice versa (Equations (4) and (5)). For some tethered alkyne–VCPs which contain a functional group that weakens the carbon–carbon bond of the cyclopropane system, the more substituted (weaker) carbon–carbon bond can be cleaved selectively depending on the choice of catalyst. Thus far, the rhodium(I)-catalysts are more selective catalysts than the ruthenium(0)-catalysts in the [5 + 2]-reaction of these substituted alkyne–VCPs (Scheme 7).[38]

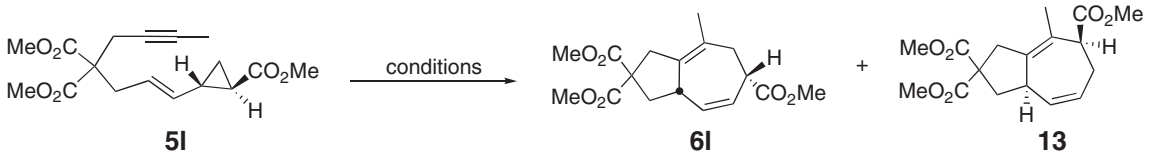


(4)



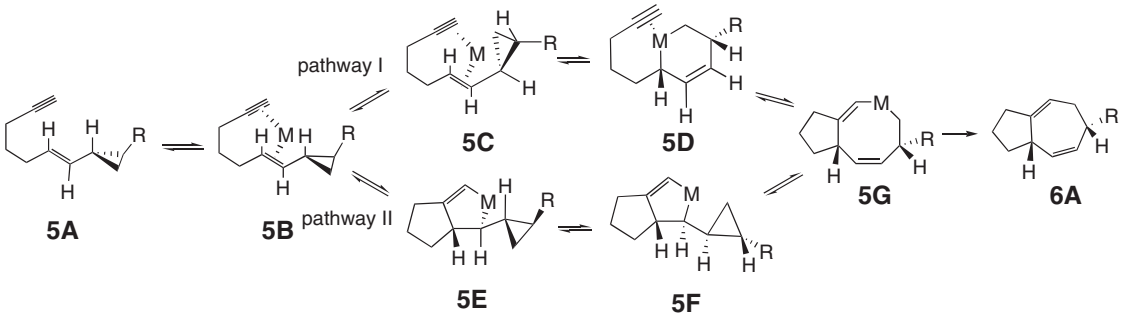
(5)

Possible mechanisms for this reaction are shown in Scheme 8. Pathway I involves an initial cleavage of the VCP (**5C** to **5D**) followed by migratory insertion of the alkyne (**5D** to **5G**), whereas pathway II involves first oxidative cyclization



$RhCl(PPh_3)_3$ (10 mol%), AgOTf (10 mol%), toluene, 110 °C	81%	20 : 1
$[RhCl(CO)_2]_2$ (5 mol %), toluene, 110 °C	93%	1 : 11
$[CpRu(CH_3CN)_3]PF_6$ (10 mol%), acetone, RT	88%	1 : 2.5

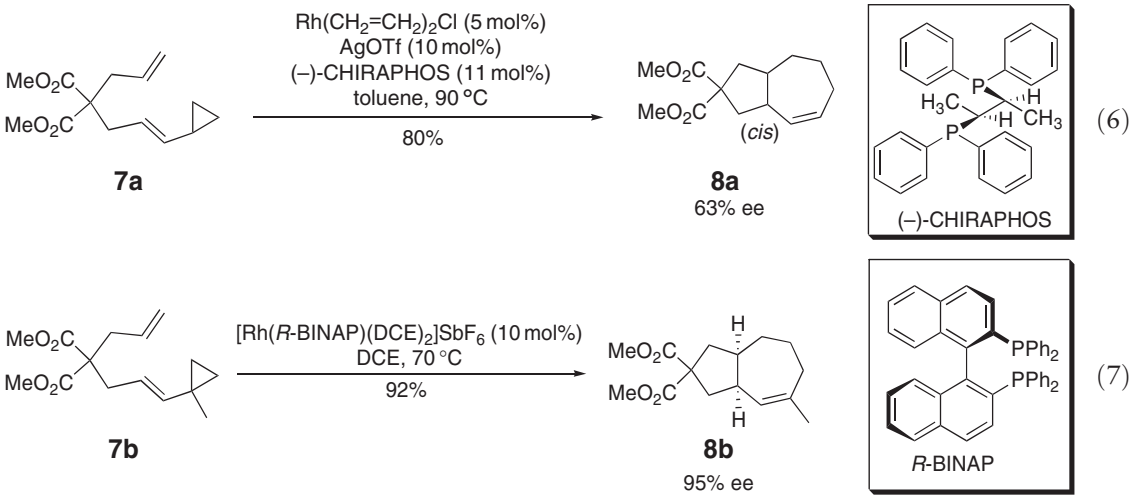
Scheme 7



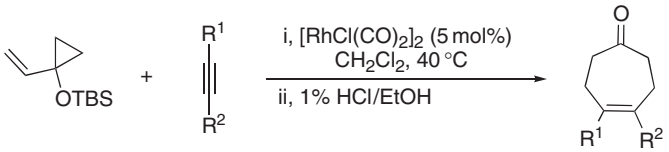
Scheme 8

of the alkene of the VCP with the alkyne (**5B** to **5E**) followed by ring expansion via opening of the cyclopropane (**5F** to **5G**). The proposed mechanisms illustrate how the *trans*-relationship of substituents on the cyclopropane map to a *cis*-relationship of groups in the product through cleavage of the less-substituted cyclopropane bond.

The first example of an enantioselective [5 + 2]-cycloaddition was reported for the tethered alkene–VCP **7a**, which upon treatment with a chiral rhodium complex afforded the *cis*-fused bicyclo[5.3.0]decene **8a** in 80% yield and 63% enantiomeric excess (ee) (Equation (6)).[39] A later study found that when a 2,2-bis(diphenyl-phosphanyl)-1,1-binaphthyl (BINAP)-modified rhodium(I) catalyst is used, good to excellent ee's and yields are achieved with a variety of substrates (Equation (7)).[40]



Given the commercial availability of alkynes as two-carbon components, the intermolecular [5 + 2]-cycloaddition of alkynes and VCPs represents a potentially practical route to seven-membered rings. However, initial attempts at an intermolecular [5 + 2]-reaction of alkynes and VCPs with modified Wilkinson's catalysts led to cyclotrimerization of the alkynes and/or isomerization of the VCPs. The first intermolecular [5 + 2]-cycloaddition of alkynes was realized

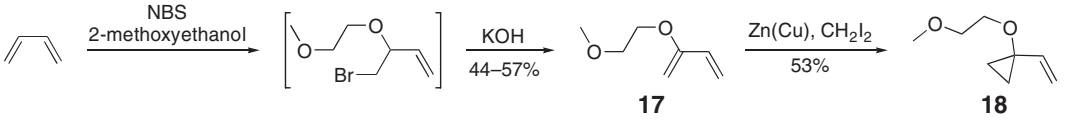


14 **15a–d** (1.1–1.5 equiv.) **16a–d**

Alkyne	R^1	R^2	*t* (h)	*Yield* **16** (%)
15a	CO_2Me	H	2	93
15b	CH_2OMe	H	1.5	88
15c	H	H	6	79
15d	CO_2Me	Me	1.5	92

Scheme 9

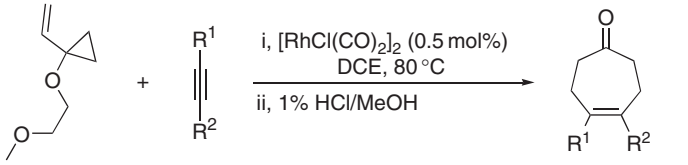
using $[RhCl(CO)_2]_2$ as the catalyst and the siloxy-substituted VCP **14** (Scheme 9).[41] The initial study revealed that internal, terminal, electron-rich, and electron-poor alkynes all participate in the [5 + 2]-cycloaddition with **14** giving excellent yields of the corresponding cycloheptenones after hydrolysis of the initially formed silylenolethers during workup. Even the simplest alkyne, acetylene, is an efficient two-carbon component in this reaction. Subsequently, a more cost-effective and now commercially available VCP **18** was prepared based on the cyclopropanation of readily available 2-alkoxybuta-1,3-dienes. The two-step synthesis of alkoxy-substituted VCP **18** can be performed on a preparative scale and has been conducted industrially (Equation (8)).[42] This alkoxy-substituted VCP is an excellent five-carbon component in the intermolecular [5 + 2]-reaction with alkynes (Scheme 10), providing cycloadducts often in minutes.



17 **18** (8)

In addition to siloxy- and alkoxy-substituted VCPs, alkyl- and H-substituted VCPs are also effective in the intermolecular [5 + 2]-cycloaddition reaction (Scheme 11). In general, an increase in the steric bulk of the cyclopropane substituent (H vs. Me vs. Pr^i) leads to increased reaction rates, putatively through preferential population of the more reactive *cis*-oid arrangement of the vinyl and cyclopropane moieties.[43]

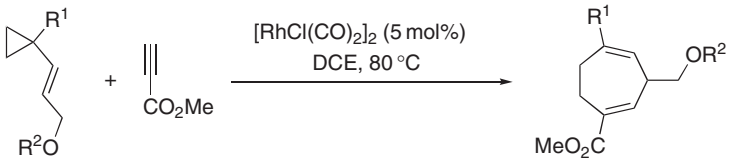
In contrast to the intramolecular process, simple allenes do not participate in the intermolecular [5 + 2]-reaction with VCP **18**. However, when a second functionality is incorporated into the allene, an efficient and facile cycloaddition occurs, presumably assisted by a directing effect of the secondary functional group. The [5 + 2]-reaction also works with styrenyl- and cyano-substituted allenes as directing groups (Scheme 12). As would be expected from



18 **15b, 15e–g** (1.2–1.3 equiv.) **16b, 16e–g**

Alkyne	R^1	R^2	*t* (h)	*Yield* **16** (%)
15b	CH_2OMe	H	0.25	92
15e	CO_2Me	CO_2Me	1	96
15f	CH_2OH	H	0.5	82
15g	CH_2NHTs	H	0.25	87

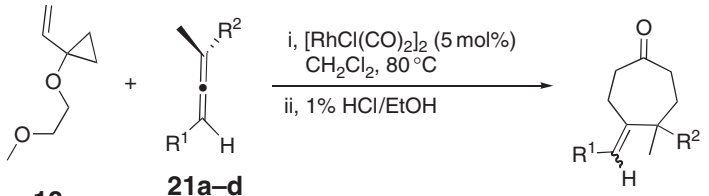
Scheme 10



19a–f **20a–f**

VCP	R^1	R^2	*t* (h)	*Yield* **20** (%)
19a	Pr^i	H	2	82
19b	Pr^i	TBS	2	93
19c	Me	TBS	8	81
19d	CH_2OTBS	H	2	82
19e	TMS	TBS	3	53
19f	H	H	30	23

Scheme 11



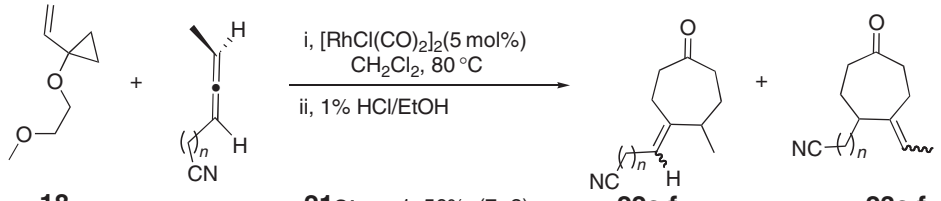
18 **21a–d** (1.2 equiv.) **22a–d**

Allene	R^1	R^2	*t* (h)	*Yield* **22** (%)
21a	CCTMS	Me	1	95
21b	CCPh	Me	1	83
21c	CHCHPh	Me	1	69
21d	CN	H	1	52

Scheme 12

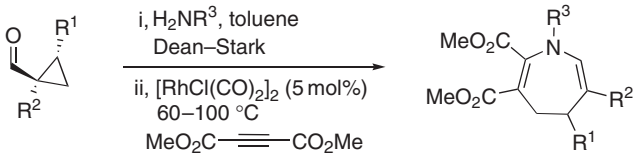
the role of the directing group, the intermolecular [5 + 2]-reaction is still observed when methylene units are inserted between the nitrile and allene functional groups (Scheme 13).[44]

Cyclopropyl imines can be used as five-atom components in intermolecular [5 + 2]-cycloaddition reactions with dimethylacetylene dicarboxylate (DMAD) (Scheme 14).[45] In this hetero-[5 + 2]-cycloaddition reaction, dihydroazepines are constructed from simple, readily available starting materials. The cyclopropyl imines can be preformed or made *in situ* by the condensation of cyclopropyl carboxaldehydes and amines. Although, thus far, DMAD is the only



18 **21e,f** **21e**: $n = 1$ 56% (7 : 2) **21f**: $n = 2$ 58% (1 : 1) **22e,f** **23e,f**

Scheme 13



24a–c **25a–c**

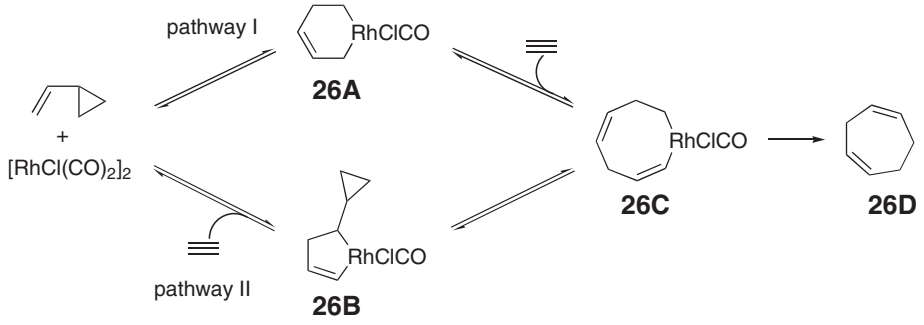
Cyclopropyl carboxaldehyde	R^1	R^2	R^3	*Yield* **25** (%)
24a	H	H	Bn	89
24b	Me	H	Bn	82
24c	H	Pr^i	Hx^n	74

Scheme 14

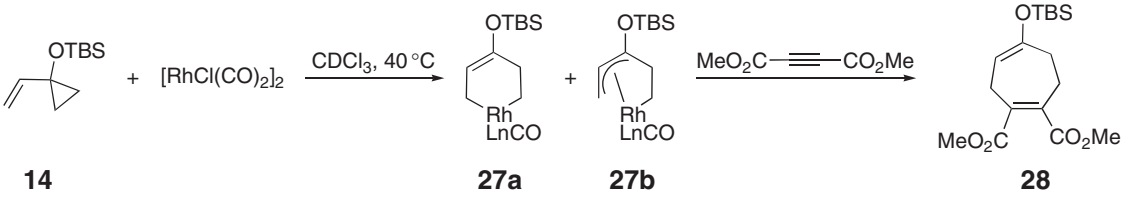
successful alkyne with this reaction, substitution of the cyclopropane is well-tolerated giving a variety of dihydrozepines in good to excellent yields. The specificity of this reaction for DMAD suggests that an alternative mechanism involving catalyzed addition of the imine to DMAD and subsequent rearrangement of the divinylaziridine could be involved. Rhodium is required for the reaction.

As mentioned previously and described originally by Wender and co-workers (Scheme 8),[37] the rhodium(I)-catalyzed [5 + 2]-cycloaddition can occur via two different pathways: cyclopropane cleavage before or after coupling with the two-carbon component (Scheme 15, pathway I or II, respectively). Density functional theory (DFT) calculations have shown a preference for pathway I in the intermolecular case.[46] In this pathway (the cleavage first mechanism), the VCP reacts with rhodium(I) to give a metallacyclohexene **26A**, which upon coordination and insertion of an alkyne gives a metallacyclooctadiene **26C**. The insertion of the alkyne was calculated to be the rate-determining step for this pathway. Cycloheptadienes are then formed via reductive elimination. In pathway II, the cyclopropane bond is cleaved after the rate-determining oxidative cyclization between the alkene of the VCP and the alkyne. This cleavage second mechanism was calculated to be approximately 9 $kcal^{-1}$ mol higher in energy compared to pathway I.

It was also found experimentally that the rhodacyclohexenes **27a** and **27b** can be identified by ^1H NMR when the siloxy-substituted VCP **14** is treated with a stoichiometric amount of $[RhCl(CO)_2]_2$ (Scheme 16). Addition of DMAD to the mixture of rhodacycles **27a** and **27b** gives the expected cycloheptadiene **28**.[47]

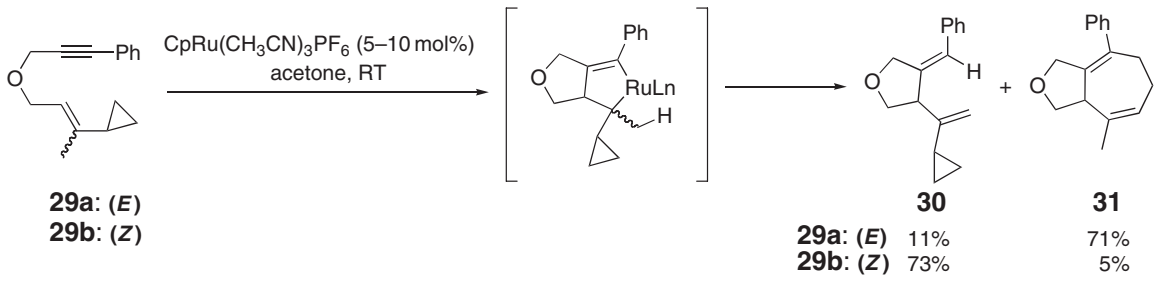


Scheme 15



14 **27a** **27b** **28**

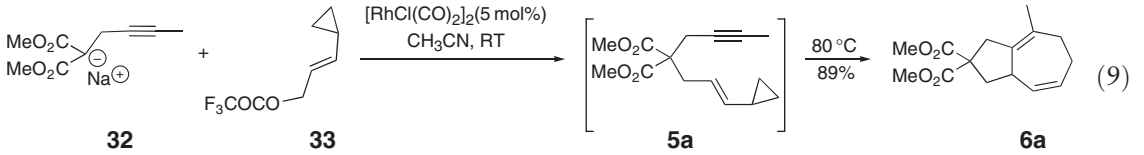
Scheme 16



Scheme 17

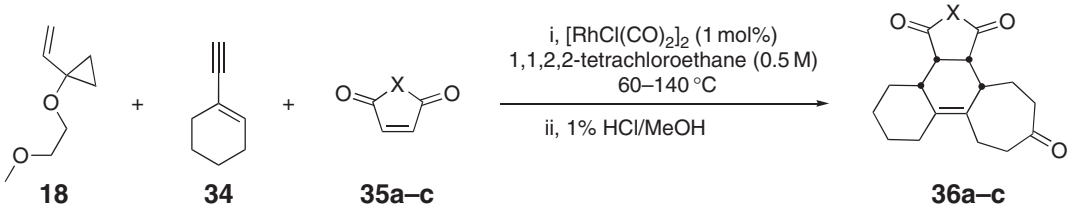
Interestingly, experimental results indicate that pathway II might be operative in some ruthenium(II)-catalyzed [5 + 2]-reactions. Cyclized products implicating β-hydride elimination and subsequent reductive elimination from ruthenacyclopentenes have been reported (Scheme 17).[26] A direct comparison with rhodium catalysts using these specific substrates has not been reported.

Representing an impressively straightforward route to bicyclo[5.3.0]decadiene derivatives, Martin and co-workers have designed a one-step route to the [5 + 2]-cycloadducts from alkynes and VCP building blocks through the use of a sequential $[RhCl(CO)_2]_2$-catalyzed allylic alkylation/[5 + 2]-cycloaddition (Equation (9)).[48]



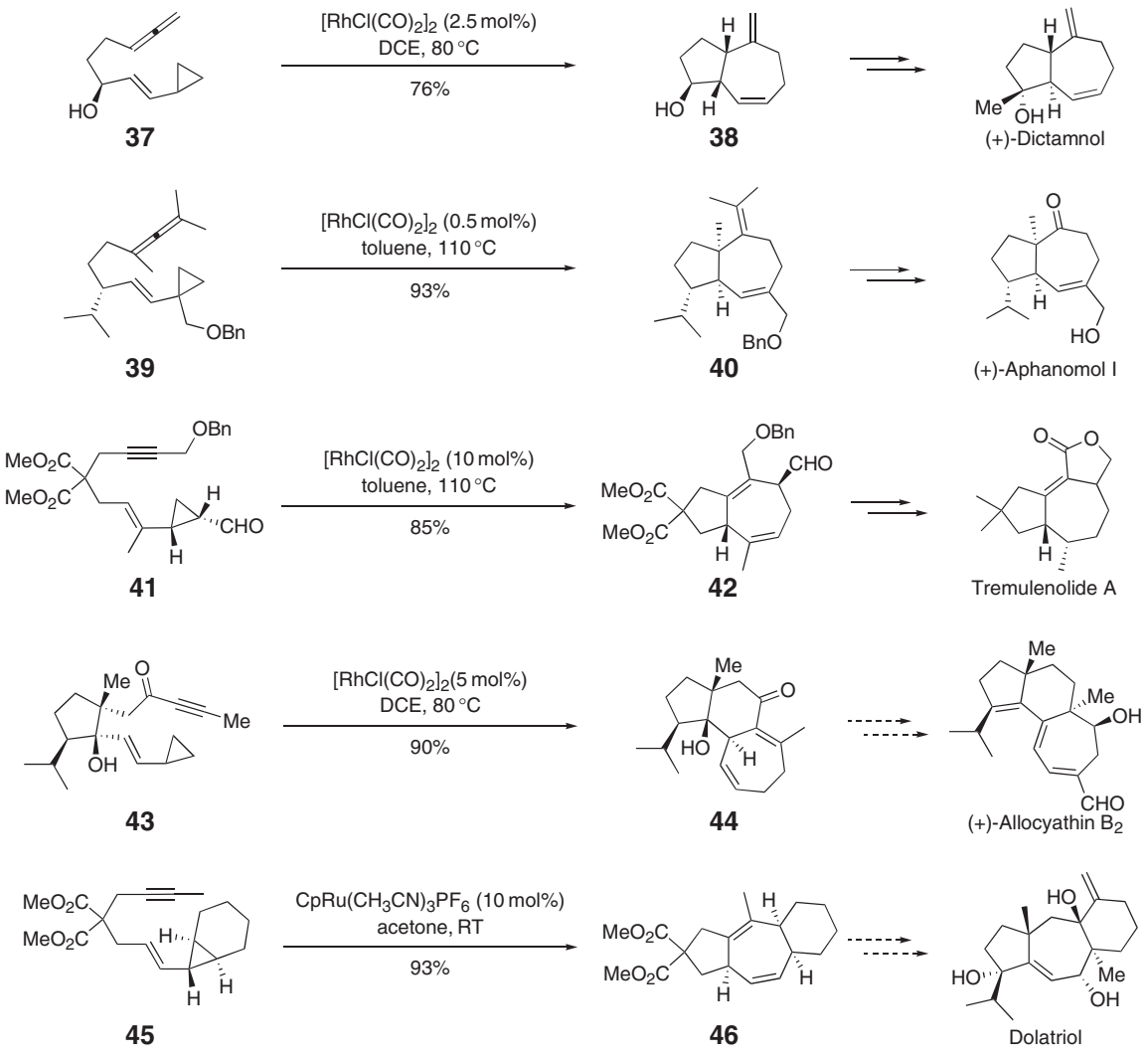
Taking advantage of the chemoselectivity of alkynes over alkenes in the intermolecular [5 + 2]-cycloaddition reaction, Wender and co-workers designed a serial [5 + 2]/[4 + 2]-reaction, allowing for a three-component construction of complex polycycles. Initially, the VCP reacts with the alkyne in a [5 + 2]-reaction to set up the seven-membered ring and a 1,3-diene. The conjugated diene is then trapped *in situ* by a dienophile in a [4 + 2]-cycloaddition (Scheme 18).[49] In this serial process, three commercially available components combine to form two rings, four carbon–carbon bonds, and four stereocenters. This powerful methodology has been used to access potent kinase inhibitors (13 nM) in a step-economical manner, illustrating one of the values of new reactions, that is, providing facile access to targets of functional (biological/potentially therapeutic) value.[50,51]

The metal-catalyzed [5 + 2]-cycloaddition of tethered VCPs and π-systems has been applied to the total syntheses of (+)-dictamnol,[52] (+)-aphanomol 1,[53] and tremulenolide A.[54] The tricyclic core of cyathane diterpenes such as (+)-allocyathin B_2[55] and the tricyclic carbon skeleton of polyhydroazulenes such as dolatriol[56] were also synthesized



Dienophile	*X*	*Yield* **36** (%)
32a	O	89
32b	NH	91
32c	NPh	92

Scheme 18



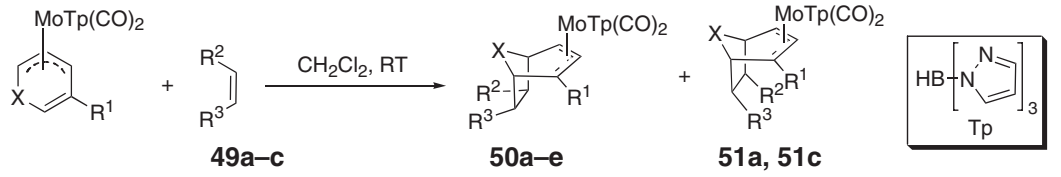
Scheme 19

(Scheme 19). These synthetic studies show the applicability and selectivity of the [5 + 2]-cycloaddition in total synthesis, in many cases generating products as single diastereomers (e.g., bicyclo[5.3.0]decenes **38**, **40**, and **42**). Studies exploring the diastereoselectivity of the ruthenium-catalyzed [5 + 2] have also been reported.[57] More generally, these metal-catalyzed [5 + 2]-cycloadditions serve to illustrate the value of new reactions, providing new ways of thinking about the construction of targets of interest in synthesis.

The metal-catalyzed [5 + 2]-cycloaddition reaction of VCPs and π-systems provides a new concept for seven-membered ring construction that has been significantly advanced over the last decade in the areas of catalyst development, chemo-, diastereo-, and enantioselectivity, substrate scope, and applications to total synthesis.

10.13.2.1.2 Metal-mediated [5 + 2]-cycloadditions

The [5 + 2]-cycloadditions of air-stable η^3-pyranyl and η^3-pyridinyl molybdenum π-complexes (**47**[58] and **48**,[59] respectively) with alkenes reported by Liebeskind and co-workers provide a novel method for the construction of oxabicyclo[3.2.1]octenes and highly functionalized tropanes (Scheme 20). This process involves the formation of a $TpMo(CO)_2$ complex which in the presence of $EtAlCl_2$ reacts with an alkene in a stereoselective [5 + 2]-cycloaddition to give metal-complexed cycloadducts **50** and **51** (Tp = hydridotrispyrazolylborato). Metal decomplexation via protiodemetalation or oxidation affords the products in good to excellent yields (Scheme 21).



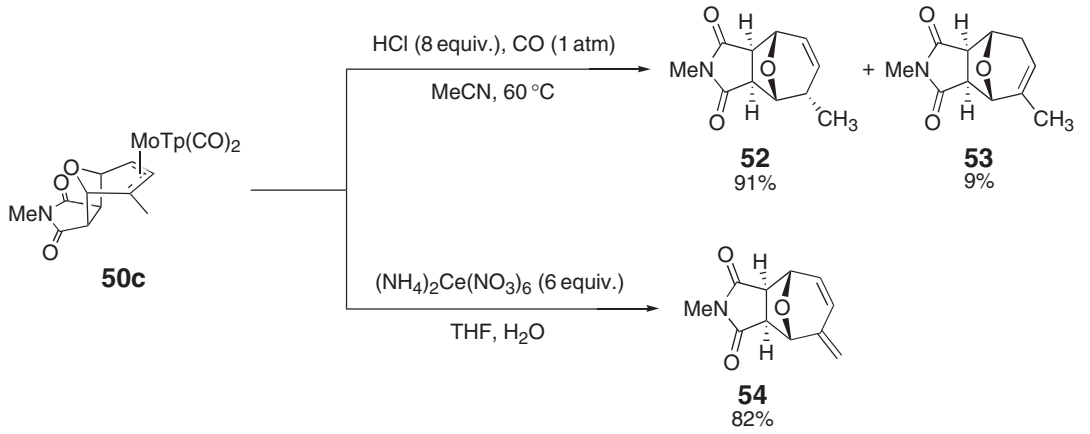
49a–c **50a–e** **51a, 51c**

47: X = O, R^1 = Me(+) 97% ee

48: X = NCO_2Me R^1 = OMe(+) 98% ee

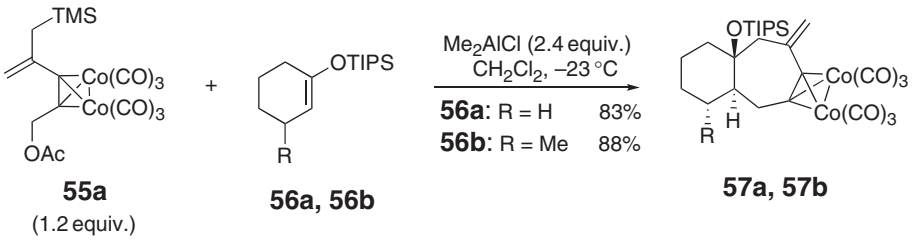
Mo-complex	*Alkene*	R^2, R^3	*$EtAlCl_2$* (mol%)	**50** (*Yield* (%), % *ee*)	**51** (*Yield* (%), % *ee*)
47	**49a**	CO_2Me, H	20	68, 95	20, 95
47	**49b**	–C(O)$(CH_2)_3$–	20	93, 96	–
47	**49c**	–C(O)N(Me)C(O)–	110	88, 97	11, >90
48	**49a**	CO_2Me, H	180	88, 98	–
48	**49b**	–C(O)$(CH_2)_3$–	50	87, 97	–

Scheme 20

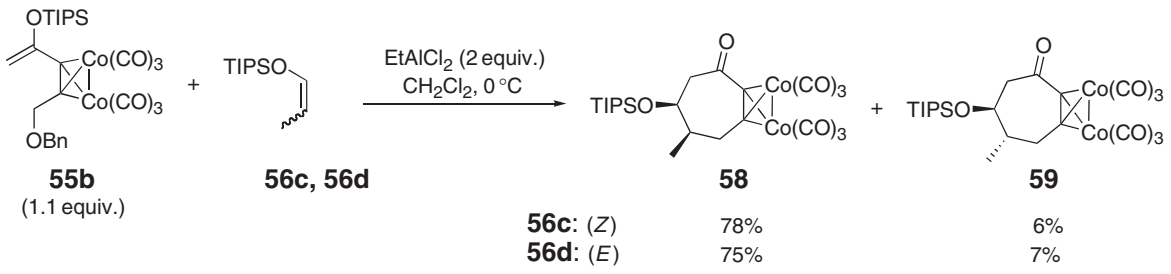


Scheme 21

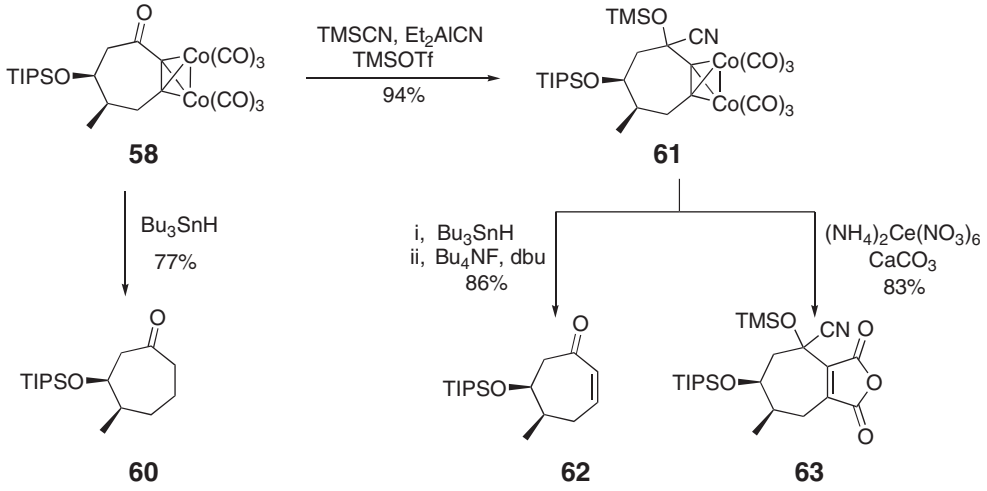
In another conceptually novel [5 + 2]-process, Tanino and co-workers synthesized cycloheptene derivatives by stereoselective [5 + 2]-cycloadditions involving hexacarbonyldicobalt–acetylene complexes as the five-carbon component and enol ethers as the two-carbon component (Schemes 22 and 23).[60,61] The role of the dicobalthexacarbonyl complex is to facilitate formation and reaction of the propargyl cation putatively involved as an intermediate in this reaction. The dicobalthexacarbonyl moiety can be removed using various conditions (Scheme 24) to provide alkane **60**, alkene **62**, and anhydride **63**.



Scheme 22



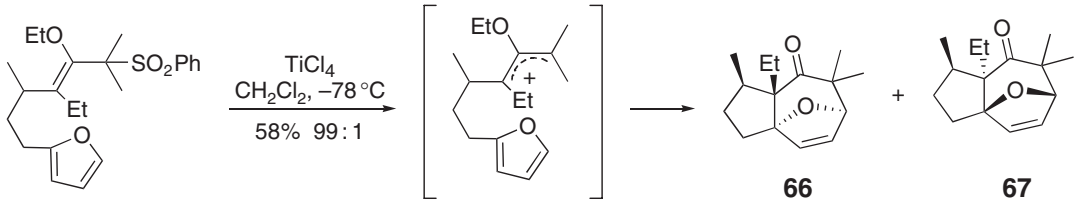
Scheme 23



Scheme 24

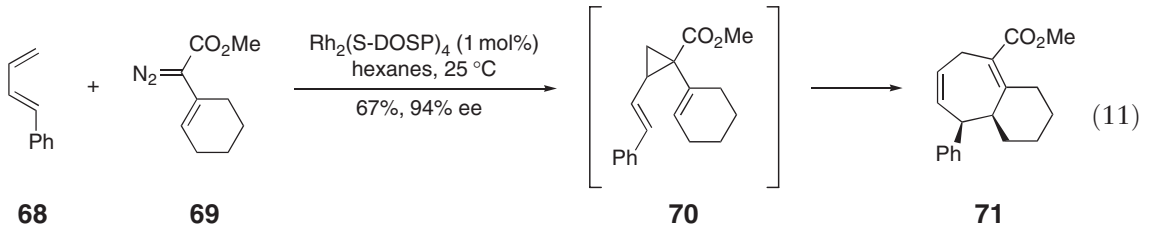
10.13.2.2 [4 + 3]-Cycloadditions

The [4 + 3]-cycloaddition is a commonly used method for the synthesis of seven-membered rings.[9] Many of these reactions involve metals, principally in the role of a Lewis acid as exemplified in Equation (10). These Lewis acid-catalyzed [4 + 3]-cycloadditions have been reviewed by Rigby,[62] Sarhan,[63] Harmata,[64,65] and Hoffmann,[66] and will not be reviewed here due to the role of the metal as a Lewis acid. Several computational papers on this subject have also been published.[67–71]

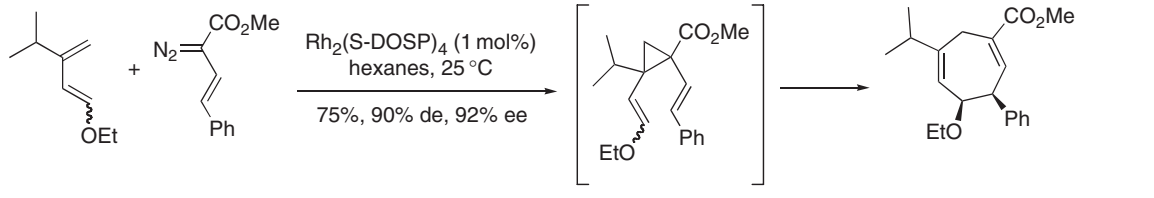


(10)

Davies and co-workers[72] have shown that cyclopropanation of a diene with a vinylcarbenoid produces a divinyl cyclopropane that, as shown in numerous earlier studies, reacts *in situ* via a thermal Cope rearrangement to give a seven-membered ring.[73–81] The Davies group has also shown that this reaction can be performed with control of absolute stereochemistry through the use of chiral rhodium complexes (Equations (11)[82] and (12)[83]). The overall process can be thought of as a [4 + 3]-reaction, but since the step resulting in the formation of the seven-membered ring is not thought to involve an organometallic species and because of numerous reviews on the divinylcyclopropane rearrangement, this work will not be covered further.

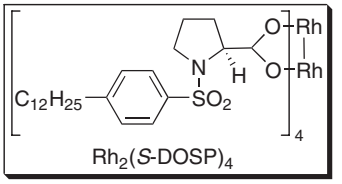


68 **69** **70** **71** (11)

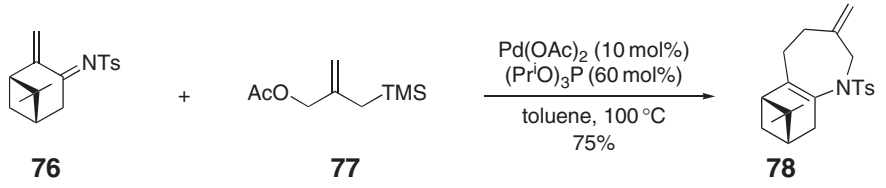


72 **73** **74** **75**

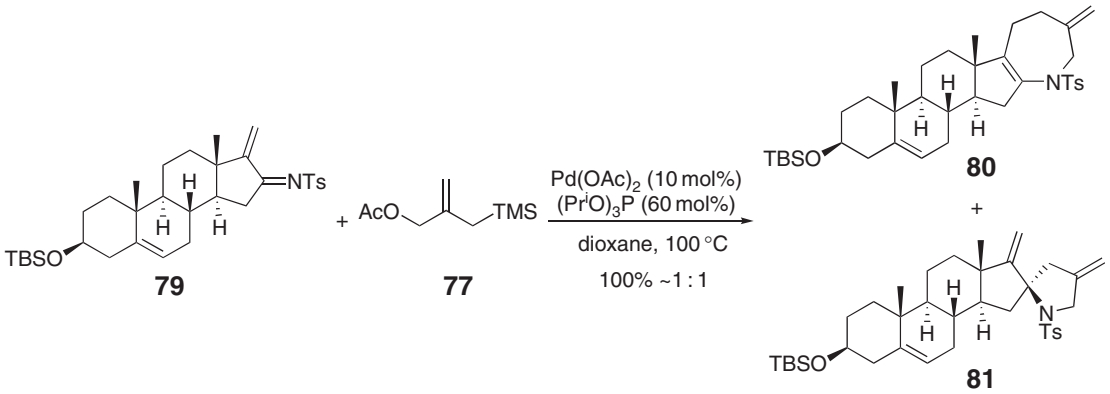
(3 : 1 *E*/*Z*) (0.5 equiv.) (12)



The palladium-catalyzed hetero-[4 + 3]-cycloadditions reported by Trost and Marrs utilize a metal-complexed trimethylenemethane as the three-carbon component. These complexes react with α,β-unsaturated imines to produce seven-membered heterocycles in moderate to good yields.[84] Two examples of this reaction were reported and are shown in Equations (13) and (14). Only the [4 + 3]-reaction was observed with α,β-unsaturated imine **76**; however, both the [4 + 3]- and the [3 + 2]-modes of reactivity are observed with α,β-unsaturated imine **79**.

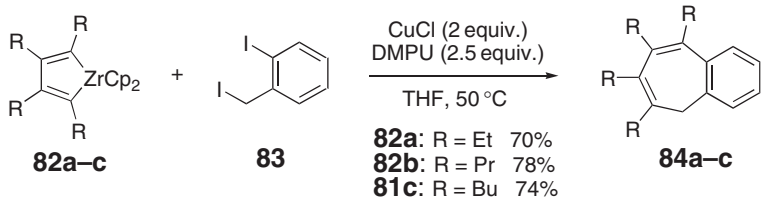


76 **77** **78** (13)

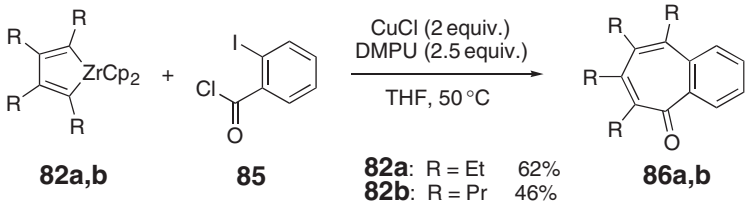


(14)

Takahashi and co-workers have designed a [4 + 3]-cycloaddition based on their previously reported [4 + 4]- and [4 + 5]-reactions (Sections 10.13.2.4 and 10.13.2.7) involving zirconacyclopentadienes as four-carbon components.[85] The zirconacyclopentadienes are prepared by the coupling of two alkynes with Cp_2ZrR_2 (where R = Et, Bu, or



Scheme 25



Scheme 26

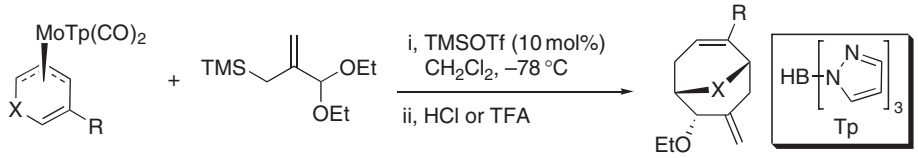
Ph).[86,87] A [4 + 3]-reaction occurs upon treatment of the zirconacyclopentadiene with a 2-iodobenzyl halide or 2-iodobenzoyl chloride and a copper catalyst (Schemes 25 and 26).[88] While based on serial substitution reactions, these processes qualify as cycloadditions in the broader sense of the term as they involve the addition of one entity across another functionality to produce a cyclic product.

10.13.2.3 [5 + 3]-Cycloadditions

A rare example of a higher-order [5 + 3]-cycloaddition was reported by Liesbeskind and Arrayas. Homochiral η^3-pyranyl- and η^3-pyridinyl-molybdenum π-complexes react with an oxyallyl cation that is generated *in situ* from the precursor 88. After decomplexation of the molybdenum, oxa- and azabicyclo[3.3.1]nonenes are obtained in moderate yields and in excellent ee's (Scheme 27).[89] Related work using η^3-pyranyl- and η^3-pyridinyl-molybdenum π-complexes as five-carbon components in [5 + 2]-cycloadditions is discussed in Section 10.13.2.1.2.

10.13.2.4 [4 + 4]-Cycloadditions

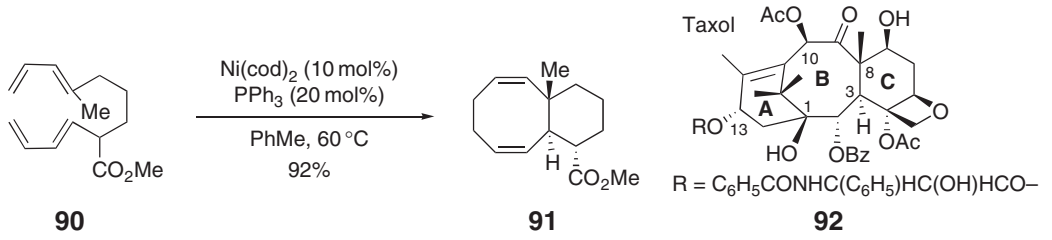
The nickel-catalyzed [4 + 4]-cycloaddition of butadiene to form cyclooctadiene was first reported by Reed in 1954.[90] Pioneering mechanistic and synthetic studies largely derived from the Wilke group advanced this process to an industrially important route to cyclodimers, trimers, and other molecules of interest.[91–94,94a,95,96] While successful with simple dienes, this process is not useful thus far with substitutionally complex dienes as needed in complex molecule synthesis. In 1986, Wender and Ihle reported the first intramolecular nickel-catalyzed [4 + 4]-reaction of



87a: X = NCbz; R = Me (> 99.5% ee) 64% yield (> 99.5% ee)
87b: X = O; R = Ph (> 98% ee) 64% yield (> 99% ee)

Scheme 27

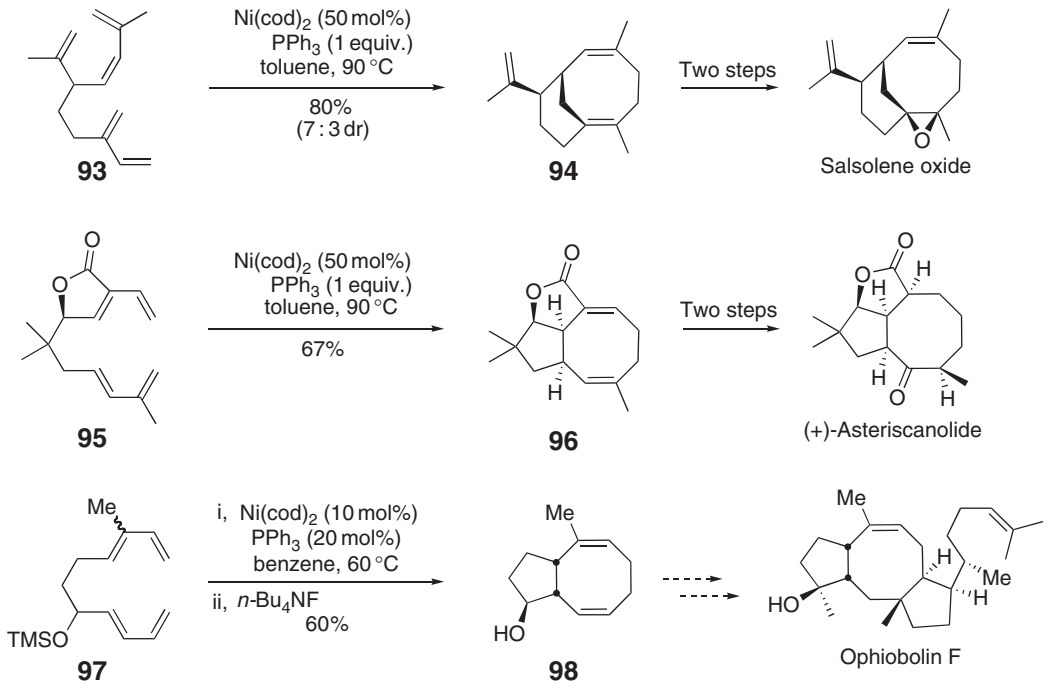
tethered bis-dienes, showing that the reaction can be conducted efficiently and selectively even with heavily substituted dienes.[97] The intramolecular [4 + 4]-reaction also circumvents problems associated with the intermolecular [4 + 4]-reaction, providing products in a highly regio- and stereoselective fashion and provides an exceptional route to taxol analogs, the original inspiration for the investigation of this novel intramolecular reaction (Equation (15)).[98]



90 **91** **92** (15)

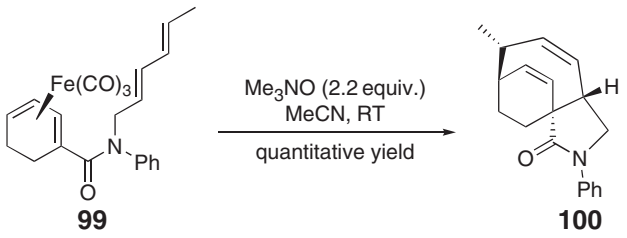
The [4 + 4]-cycloaddition reaction of tethered bis-dienes has been used by Wender and co-workers in total synthesis as exemplified in syntheses of (±)-salsolene oxide and (+)-asteriscanolide (Scheme 28). In the synthesis of (±)-salsolene oxide, a nickel(0)-catalyst cleanly effects the cycloaddition of the two conjugated dienes in compound **93** to afford the bicyclo[5.3.1]undecadiene in a good yield and with moderate selectivity.[99] The first synthesis of (+)-asteriscanolide was accomplished in only 13 steps. The key [4 + 4]-cycloaddition reaction efficiently set the requisite eight-membered ring of (+)-asteriscanolide in good yield and with excellent diastereoselectivity.[100] The diastereoselective [4 + 4]-cycloaddition has also been applied to the synthesis of the core ring system found in several sesterterpenes such as the ophiobolins (Scheme 28).[101]

Pearson and Wang report that upon treatment with Me_3NO, the cyclohexadiene–$Fe(CO)_3$ complex **99** will undergo an intramolecular [4 + 4]-cycloaddition with the pendant 1,3-diene to give cyclooctadiene **100** as a single diastereomer in quantitative yield (Equation (16)).[102]



93 **94** **95** **96** **97** **98**

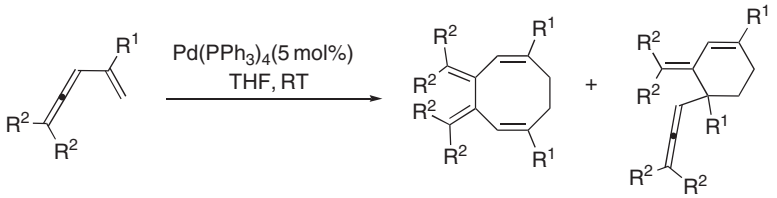
Scheme 28



99 **100** (16)

Murakami and co-workers have shown that phenyl- and vinyl-substituted vinylallenes react in a palladium-catalyzed intermolecular [4 + 4]-cycloaddition in the presence of a palladium complex to give the cyclooctadiene cycloadducts in moderate to good yields (Scheme 29).[103] In a method reported by Lee and Lee, bicyclo[6.4.0]-dodecatrienes are prepared in good overall yields via a two-step, one-flask procedure that involves a serial palladium-catalyzed cross-coupling/[4 + 4]-cycloaddition followed by [4 + 2]-cycloaddition (Scheme 30). Overall, this two-step process impressively brings together five simple components to form relatively complex bicyclic products.[104]

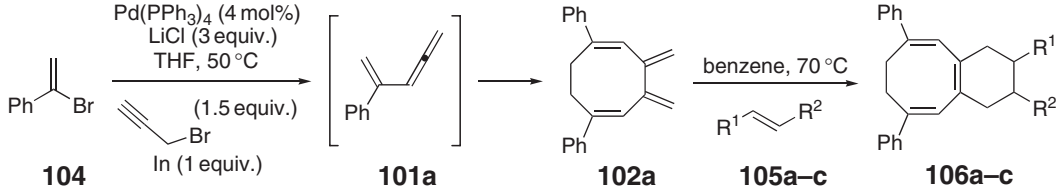
Based on their interest in medium-size ring synthesis, Takahashi and co-workers used a copper(I) salt to mediate the [4 + 4]-reaction of zirconacyclopentadienes **82a**, **82b** and **82d** and 1,2-bis(bromomethyl)arenes (Scheme 31).[85] The reaction works with substoichiometric amounts of copper(I) chloride (10 mol%), but in general higher yields and faster reaction times are observed with 2 equiv.



101a–c **102a–c** **103b,c**

			Yield (%)	
Vinylallene	R^1	R^2	**102**	**103**
101a	Ph	H	84	0
101b	Ph	Me	48	32
101c	$CHCH_2$	Me	23	53

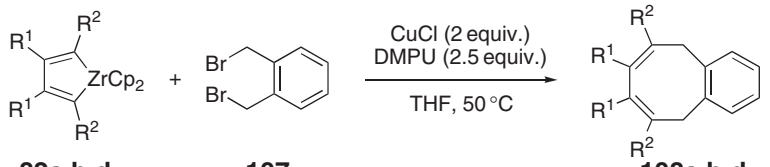
Scheme 29



104 **101a** **102a** **105a–c** **106a–c**

Alkene	R^1	R^2	*Yield* **106** (%)
105a	C(O)Me	H	72
105b	CO_2Et	H	71
105c	CO_2Me	CO_2Me	74

Scheme 30



82a,b,d **107** **108a,b,d**

82a: R^1 = Et; R^2 = Et 67%
82b: R^1 = Pr; R^2 = Pr 80%
82d: R^1 = $-(CH_2)_4-$; R^2 = Et 67%

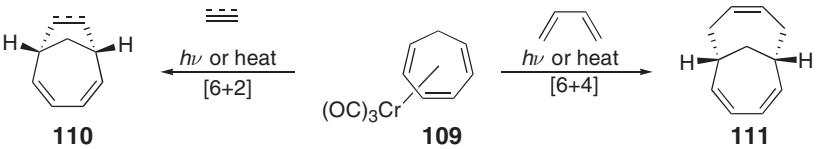
Scheme 31

10.13.2.5 [6 + 2]- and [6 + 4]-Cycloadditions

10.13.2.5.1 [6 + 2]- and [6 + 4]-Cycloadditions of trienes and π-systems

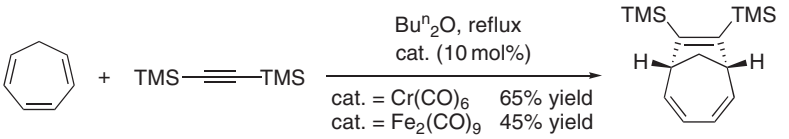
The metal-mediated and metal-catalyzed [6 + 2]- and [6 + 4]-cycloaddition reactions, pioneered by Pettit and co-workers[105,106] and Kreiter and co-workers,[107] respectively, involve the cycloaddition of metal-complexed cyclic trienes with π-systems such as alkenes, alkynes, and dienes. The [6 + 2]-reactions produce bicyclo[4.2.1]nonadiene derivatives and the [6 + 4]-reactions produce bicyclo[4.4.1]undecatrienes (Scheme 32). Trienes complexed to chromium, which can be prepared on large scale (40 g) as reported by Rigby and co-workers,[108] react with π-systems upon thermolysis or irradiation.[109–111] Chromium and iron-catalyzed [6 + 2]-reactions of cycloheptatrienes and disubstituted alkynes (Scheme 33) have also been reported by Sheridan and co-workers.[112] Since these [6 + 2]- and [6 + 4]-reactions have been extensively reviewed, only some of the recent advances are discussed in this chapter for comparative purposes.[2,113–118]

Two methods have been developed to provide enantiomerically enriched cycloadducts using the chromium-mediated [6 + 2]- and [6 + 4]-cycloadditions: one involving a chiral resolution and the other involving the attachment of a chiral auxiliary to the triene. The lipase resolution method provides access to either enantiomer of the chromium complex, albeit with moderate enantiomeric excesses (Scheme 34).[119] The [6 + 4]- and [6 + 2]-reactions of chiral substrates such as **116** which are available by the attachment of a removable chiral auxiliary (R^*) to the triene moiety are highly diastereoselective (Equation (17)).[120]



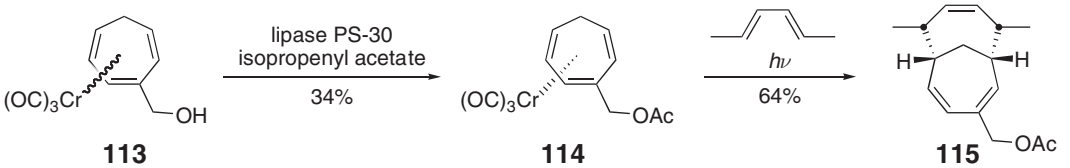
110 **109** **111**

Scheme 32



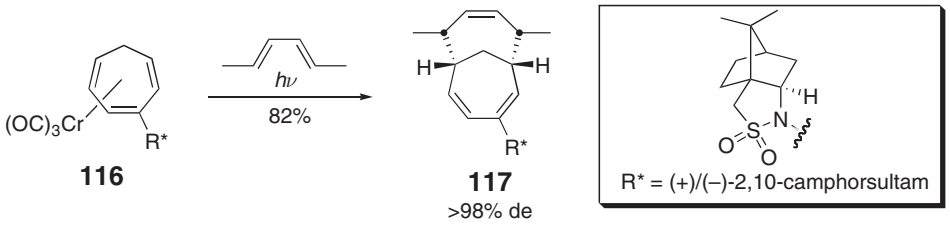
112

Scheme 33

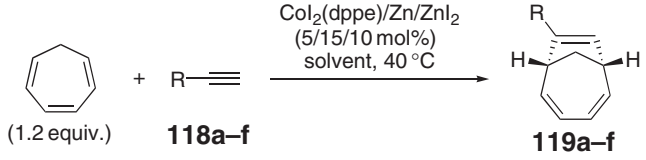


113 **114** 75% ee **115** 75% ee

Scheme 34



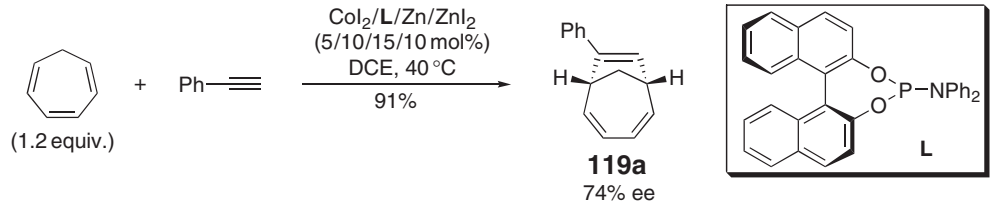
(17)



Alkyne	*R*	*Solvent*	*Yield* **119** (%)
118a	Ph	DCE	75
118b	TMS	DCE	92
118c	CO_2Me	DCE	21
118d	CH_2CH_2OAc	DCE	83
118e	$(CH_2)_3CN$	DCE	90
118f	CH_2OH	TFE	60

Scheme 35

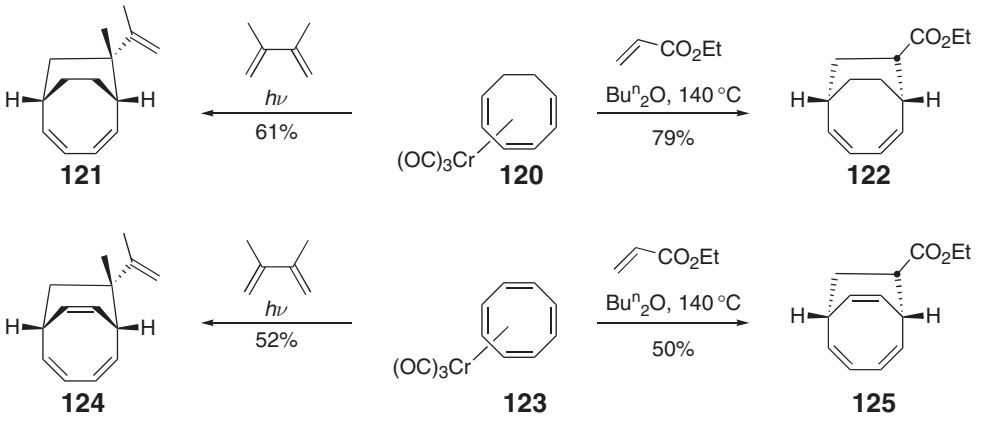
Although disubstituted alkynes are used successfully as two-carbon components in chromium-mediated and -catalyzed [6 + 2]-reactions, the use of terminal alkynes produces a [6 + 2 + 2]-reaction (Section 10.13.3.7). Buono and co-workers have discovered that when a cobalt catalyst is employed, several monosubstituted alkynes can be used in [6 + 2]-cycloadditions with cycloheptatriene (Scheme 35). The use of a chiral BINOL-phosphoramidite cobalt complex affords an enantioselective [6 + 2]-cycloaddition reaction (Equation (18)).[121]



(18)

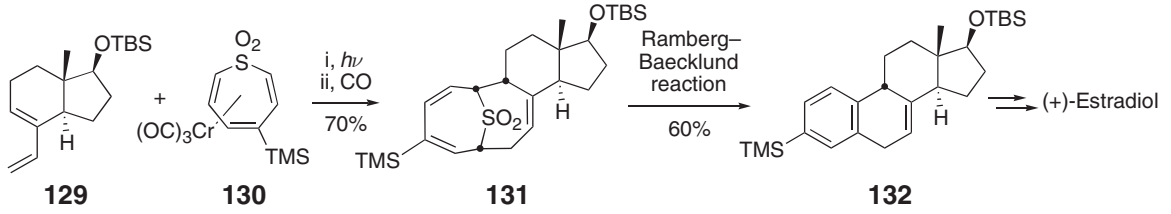
In addition to cycloheptatriene, cyclooctatriene and cyclooctatetraene systems can be used as six-carbon components in the [6 + 2]-cycloaddition with π-systems (Scheme 36). Interestingly, in these cases, dienes react exclusively as two-carbon components instead of four-carbon components as they do in the [6 + 4]-cycloaddition with cycloheptatrienes.[122]

N-Cyanoazepines[123,124] and cyclic sulfonate trienes also react as six-carbon components in [6 + 2]- and [6 + 4]-cycloadditions with π-systems (Equations (19), (20), and Scheme 37). The products of the reactions of sulfonate trienes have been shown to undergo Ramberg–Baecklund rearrangements.[125] This strategy has been used in the total synthesis of (+)-estradiol (Scheme 37).[126]



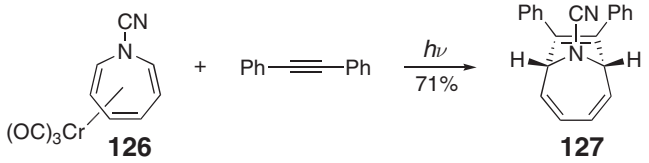
121 **120** **122** **124** **123** **125**

Scheme 36

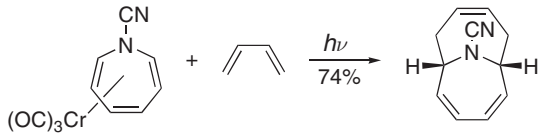


129 **130** **131** **132**

Scheme 37



126 **127** (19)

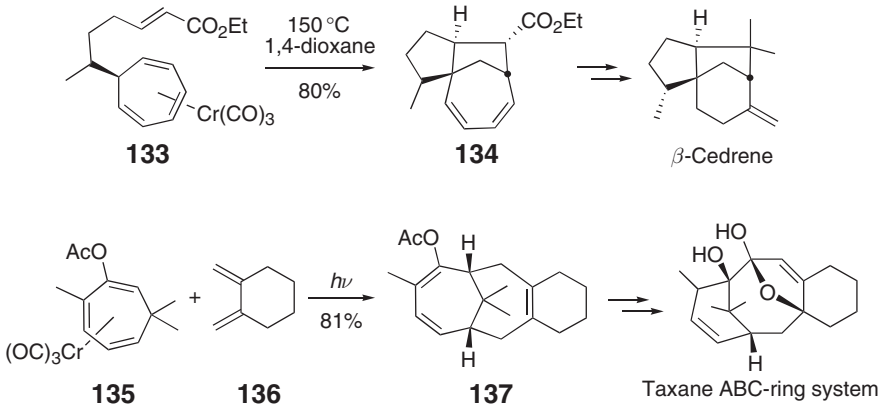


126 **128** (20)

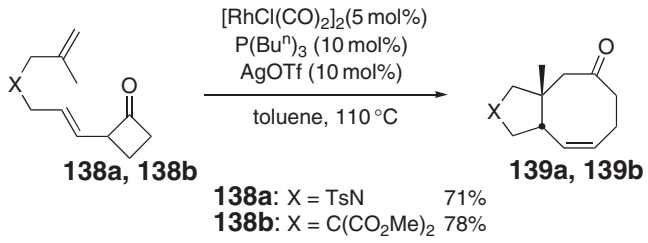
Other applications of the [6 + 2]- and [6 + 4]-cycloaddition reactions in total synthesis have been reviewed.[127] The two representative examples shown in Scheme 38 illustrate their use in the total synthesis of β-cedrene and the taxane ABC ring system. The total synthesis of β-cedrene utilized an intramolecular [6 + 2]-reaction[128] to set up a tricyclic intermediate and the synthesis of the taxane ABC ring system is accomplished via a [6 + 4]-cycloaddition.

10.13.2.5.2 [6 + 2]-Cycloadditions of vinylcyclobutanones and π-systems

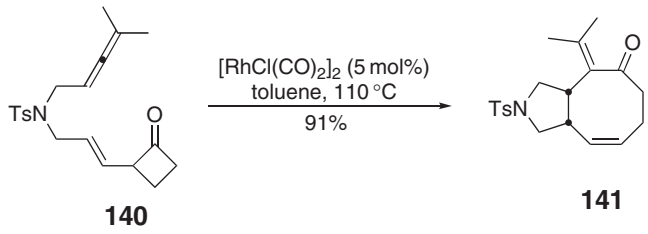
The rhodium(I)-catalyzed [6 + 2]-cycloaddition of vinylcyclobutanones and π-systems was designed by Wender and co-workers based on interest in both the synthesis of eight-membered rings and metal-catalyzed carbon–carbon bond activation reactions (analogous to the reaction of VCPs and π-systems in the [5 + 2]-cycloaddition, Section 10.13.2.1.1). Initial attempts to effect the [6 + 2]-cycloaddition with simple vinylcyclobutanes as the six-carbon component were unsuccessful, but the reactions of tethered alkene–vinylcyclobutanones and allene–vinylcyclobutanones were found to proceed efficiently to give cyclooctenones in good to excellent yields (Scheme 39 and Equation (21)).



Scheme 38

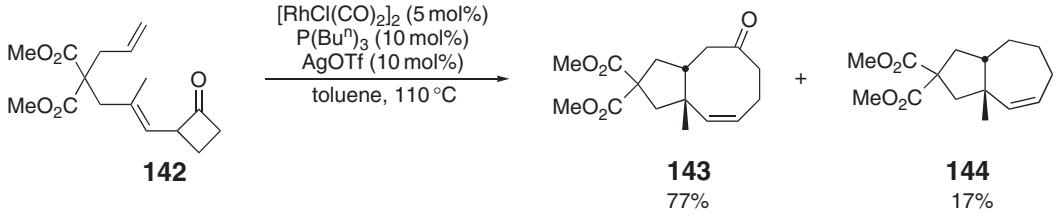


Scheme 39



(21)

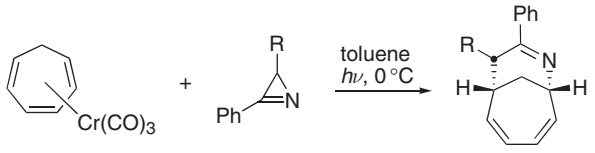
In addition to cyclooctenone **143**, the reaction of tethered alkene–vinylcyclobutanone **142** also produces cycloheptene **144** as a byproduct (Equation (22)). This product is thought to result from a decarbonylation reaction of a rhodacyclononenone intermediate. This result is discussed further in Section 10.13.3.3.[129]



(22)

10.13.2.6 [6 + 3]-Cycloadditions

The palladium-catalyzed trimethylenemethane reaction with tropanones was reported in 1987 by Trost and Seoane and is the first example of a [6 + 3]-cycloaddition.[130] Chromium-mediated [6 + 3]-cycloadditions of two types have been described–one in which the chromium complex activates the six-carbon component and one in which the chromium complex activates the three-atom component. An example of the first type involves the reaction of a cycloheptatriene–$Cr(CO)_3$ complex with azirines to give cyclic imines in moderate yields (Scheme 40).[131]

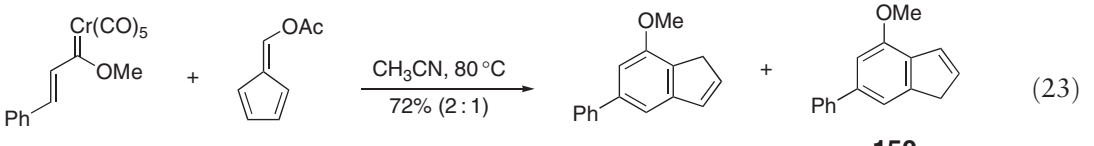


109 **145a–c** **146a–c**

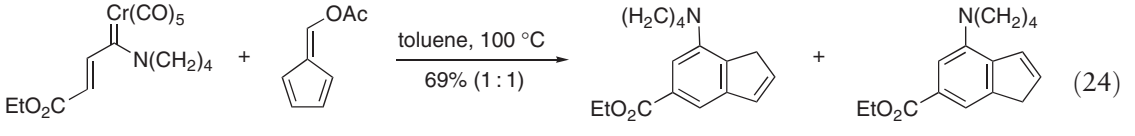
145a: R = Ph, 53%
145b: R = Me, 48%
145c: R = H, 77%

Scheme 40

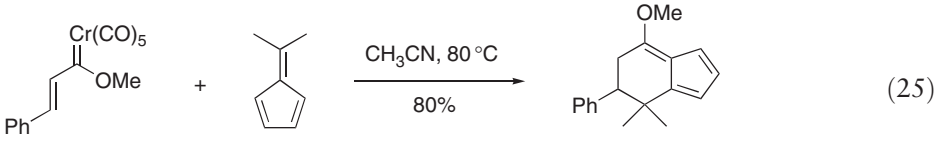
Alkenyl Fischer carbene complexes can serve as three-carbon components in the [6 + 3]-reactions of vinylchromium carbenes and fulvenes (Equations (23)–(25)), providing rapid access to indanone and indene structures.[132] This reaction tolerates substitution of the fulvene, but the carbene complex requires extended conjugation to a carbonyl or aromatic ring. This reaction is proposed to be initiated by 1,2-addition of the electron-rich fulvene to the chromium carbene followed by a 1,2-shift of the chromium with simultaneous ring closure. Reductive elimination of the chromium metal and elimination/isomerization gives the products (Scheme 41).



147a **148** **149** **150** (23)



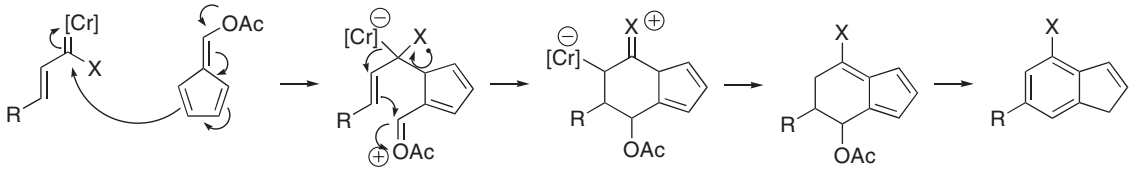
147b **148** **151** **152** (24)



147a **153** **154** (25)

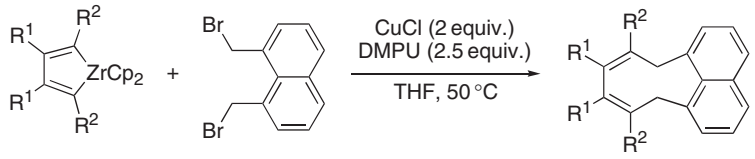
10.13.2.7 [5 + 4]-Cycloadditions

As an extension of their work on the [4 + 4]-reaction of zirconacyclopentadienes and 1,2-bis(bromomethyl)arenes (Section 10.13.2.4), Takahashi and co-workers reported a [5 + 4]-reaction based on the use of 1,8-bis(bromomethyl)-naphthalene as the five-carbon component.[85] As with the [4 + 4]-reaction, the [5 + 4]-reaction works with a catalytic amount of CuCl, but higher yields and faster reactions result when stoichiometric CuCl and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone(*N*,*N*′-dimethylpropyleneurea) (DMPU) are used (Scheme 42).



147 **148** **147A** **147B** **147C** **147D**

Scheme 41



82a,b,d **155** **156a–c**

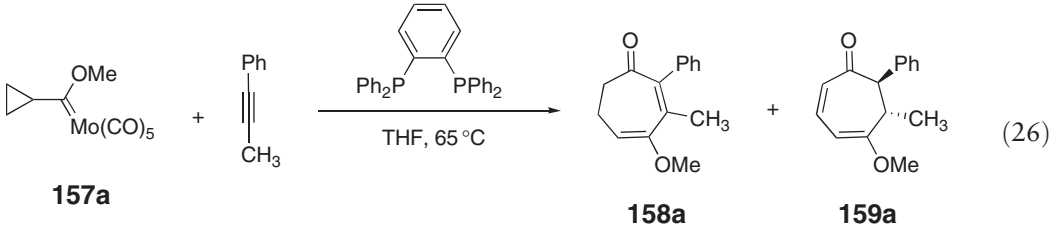
82a: R^1 = Et R^2 = Et 74%
82b: R^1 = Pr R^2 = Pr 72%
82d: R^1 = -$(CH_2)_4$- R^2 = Et 64%

Scheme 42

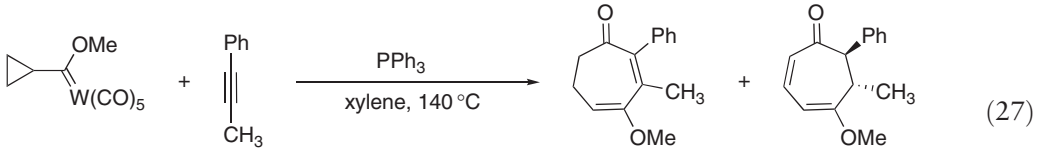
10.13.3 [*m* + *n* + *o*]-Cycloadditions

10.13.3.1 [4 + 2 + 1]-Cycloadditions

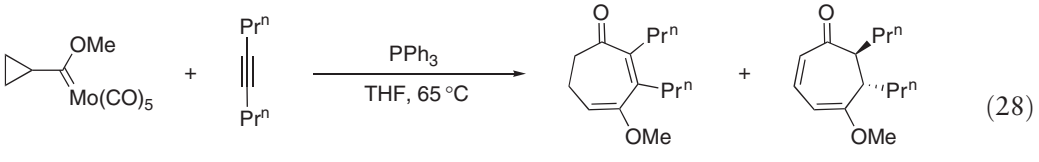
In a noteworthy series of studies, Herndon has shown that cyclopropylcarbenes can be used as four-carbon components in molybdenum- and tungsten-mediated [4 + 2 + 1]-reactions with alkynes and carbon monoxide (CO). These reactions give cycloheptadienones in moderate yields and with moderate selectivity (Equations (26)–(28)). The mechanism of this reaction is proposed to proceed through a series of steps involving metathesis, CO insertion, ketene formation, cyclopropane cleavage, and finally reductive elimination (Scheme 43).[133]



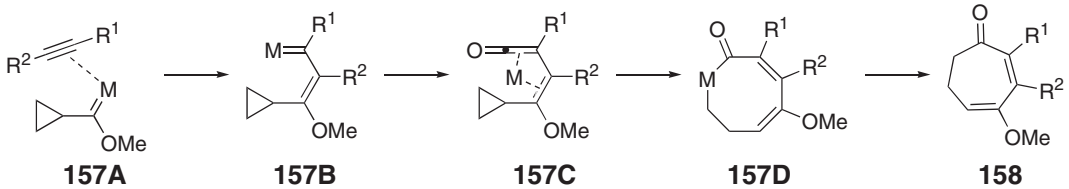
157a **158a** 45% **159a** 10% (26)



157b **158a** 3% **159a** 61% (27)



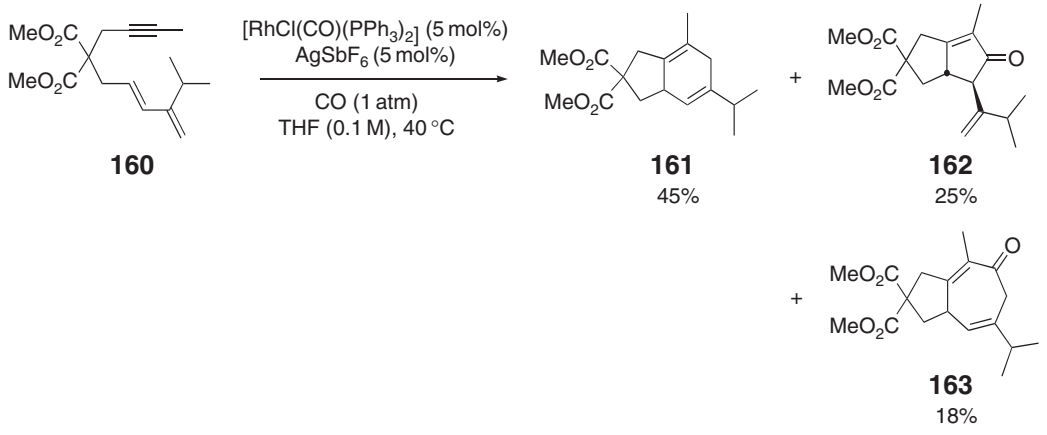
157a **158b** 23% **159b** 23% (28)



157A **157B** **157C** **157D** **158**

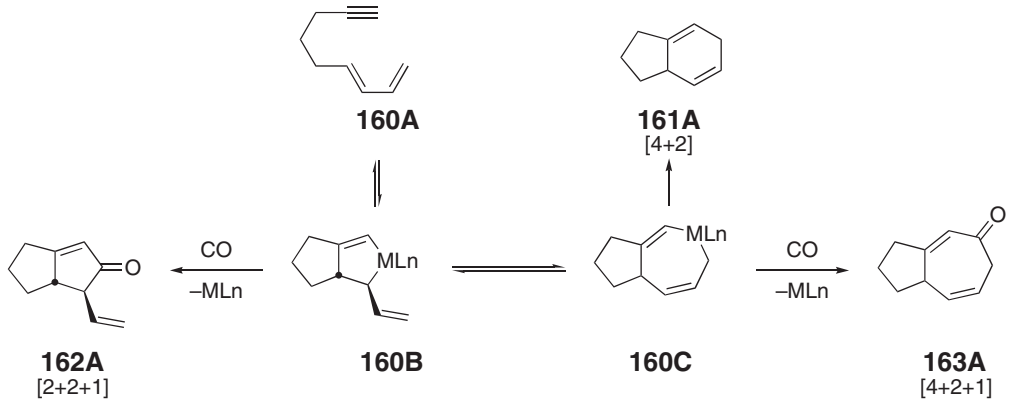
Scheme 43

The first metal-catalyzed [4 + 2]-reaction of tethered dienes with π-systems was reported by Wender and Jenkins using alkynes initially as the two-carbon component.[21] This study was based on the earlier observation by Wender and Ihle that in the [4 + 4]-cycloaddition of bis-dienes a competing side-reaction is the [4 + 2]-cycloaddition of the diene with a mono-ene portion of a second diene. The extension of this reaction to the synthesis of seven-membered rings by trapping the metallacycloheptadiene with CO, a formal [4 + 2 + 1]-cycloaddition, has been shown in preliminary studies to be feasible. For example, tethered diene–yne **160** can be converted to cycloheptadienone **163** in an Rh(I)-catalyzed [4 + 2 + 1]-reaction with CO, albeit the [4 + 2]- and [2 + 2 + 1]-reaction products dominate (Equation (29)). The mechanistic scheme (Scheme 44) illustrates the possible metallacyclic intermediates leading to the observed products and provided the conceptual basis for the realization of three novel reaction types ([4 + 2], [2 + 2 + 1], and [4 + 2 + 1]).[134]

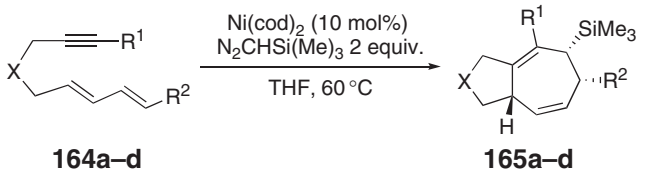


160 **161** 45% **162** 25% **163** 18% (29)

The use of a carbene as the one-carbon component provides an alternative and efficient entry into the [4 + 2 + 1]-reaction manifold. Montgomery and Ni have developed a nickel-catalyzed process where the carbene is generated from trimethylsilyldiazomethane (Scheme 45).[135] It is not known, however, if the seven-membered ring forms via a Cope rearrangement of a divinylcylopropane or if the metal is intimately involved in the step that leads directly to



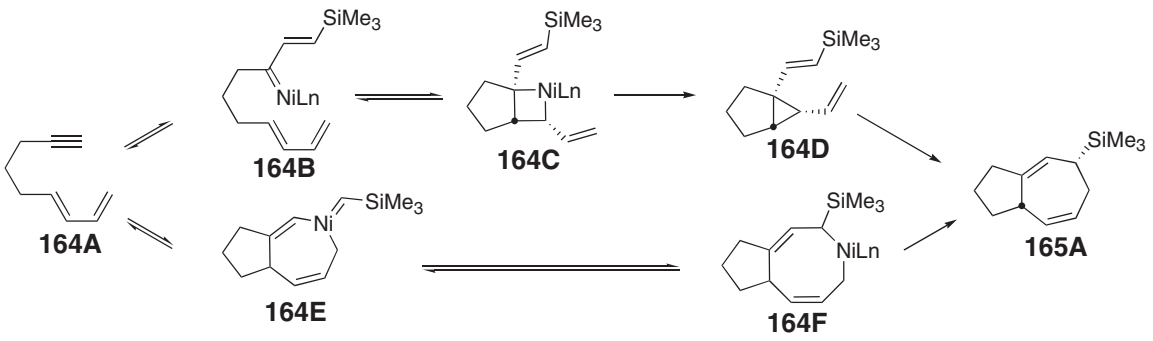
Scheme 44



164a–d **165a–d**

X	R^1	R^2	*dr*	*Yield* **164** (%)
$C(CO_2Me)_2$	H	H	13 : 1	76
NTs	H	H	>95 : 5	68
O	CH_3	H	16 : 1	62
O	CH_3	CH_3	>95 : 5	49

Scheme 45

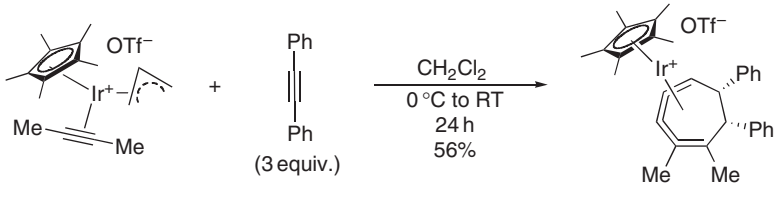


Scheme 46

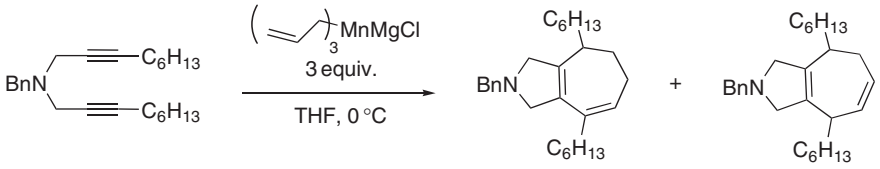
cycloheptadiene formation (Scheme 46). The former mechanism has been used by the Wulff[136] and Harvey[137,138] groups in syntheses of seven-membered rings.

10.13.3.2 [3 + 2 + 2]-Cycloadditions

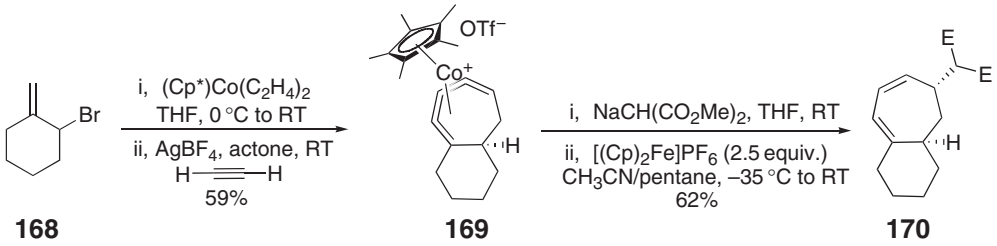
Metal-mediated and -catalyzed [3 + 2 + 2]-higher-order cycloaddition reactions have also proved to be viable and mechanistically novel methods for the synthesis of seven-membered rings. The reported [3 + 2 + 2]-cycloadditions of allyliridium (Equation (30)),[139] -allylcobalt (Scheme 47),[140] and allylmanganese (Equation (31))[141] complexes with alkynes involve the reaction of preformed allylmetal complexes with two separate alkynes, leading to a cycloheptadiene–metal complex.



(30)



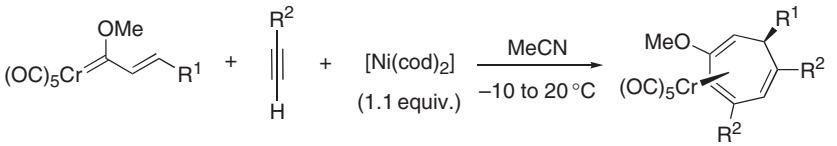
(31)



Scheme 47

Vinyl Fischer carbenes can be used as three-carbon components in Ni(0)-mediated and Rh(I)-catalyzed [3 + 2 + 2]-reactions with alkynes (Schemes 48 and 49)[142] and with allenes (Schemes 50 and 51).[143] All three of the proposed mechanisms for the [3 + 2 + 2]-cycloadditions involve an initial carbene transfer from chromium to nickel or rhodium (Schemes 49, 52, and 53). As is seen from the products of the two [3 + 2 + 2]-reactions with 1,1-dimethylallene, although the nickel and rhodium carbenes **147G** and **147K** appear similar, the initial insertion of the allene occurs with opposite regioselectivity.

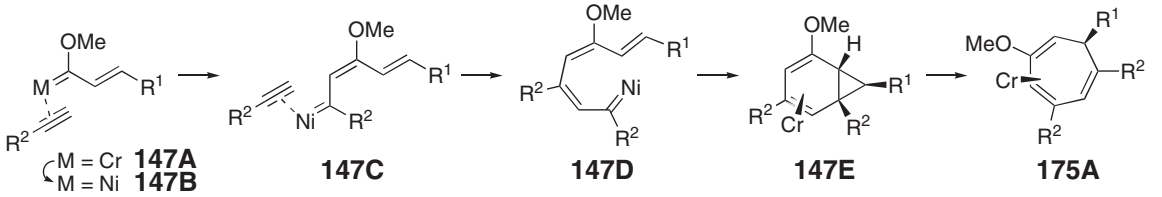
An alternative approach to [3 + 2 + 2]-cycloadditions has been reported by Saito and co-workers and involves cleavage of a methylenecyclopropane to produce, after capture with two alkynes, the cycloheptadiene products shown in Scheme 54.[144] In a mechanistically distinct [3 + 2 + 2]-reaction, Murakami and Miura report a route to a cycloheptadienone involving the capture of two alkynes initiated by a Suzuki coupling to 2-cyanophenylboronic acid (Equation (32)).[145]



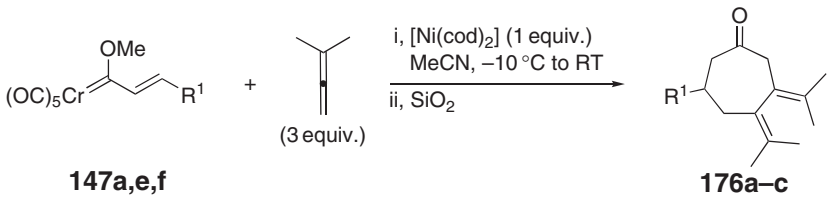
147a,c,d **174a–c** (3 equiv.) **175a,c,d**

Fischer carbene	R^1	*Alkyne*	R^2	*Yield* **175** (%)
147a	Ph	**174a**	Pr^n	86
147c	Pr^n	**174c**	Pr^n	62
147d	Ph	**174d**	Me_3Si	80

Scheme 48



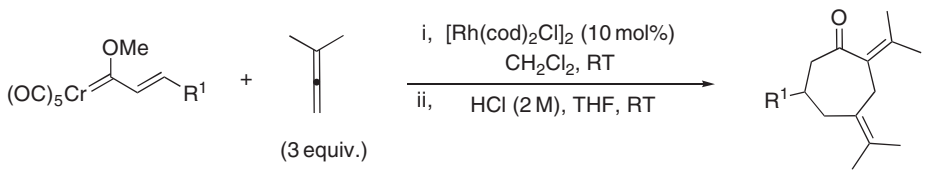
Scheme 49



147a,e,f **176a–c**

Fischer carbene	R^1	*Yield* **176** (%)
147a	Ph	52
147e	*p*-$MeOC_6H_4$	53
147f	Bu^n	40

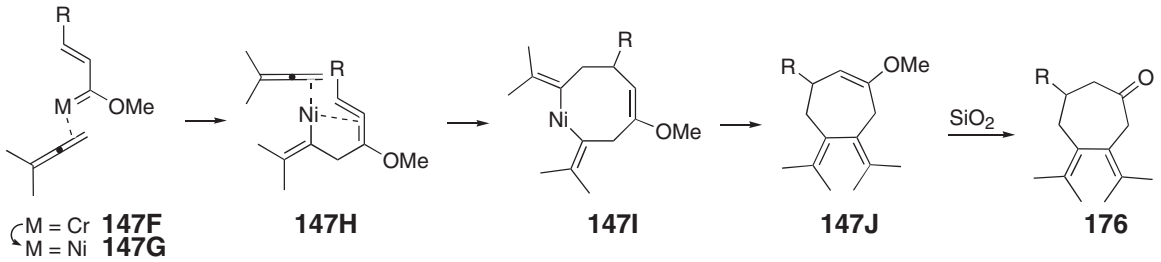
Scheme 50



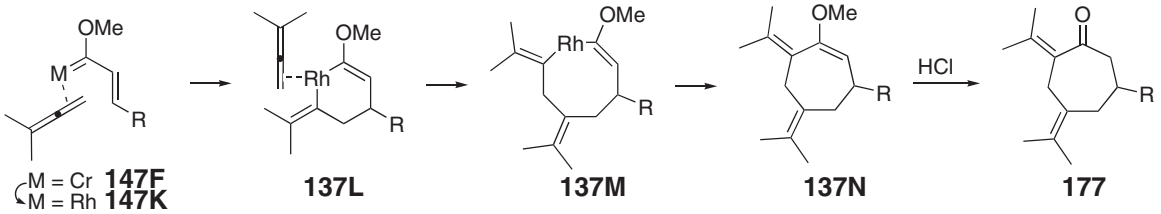
147e–g **177a–c**

Fischer carbene	R^1	*Yield* **177** (%)
147e	*p*-$MeOC_6H_4$	55
147f	Bu^n	61
147g	Bu^i	70

Scheme 51



Scheme 52

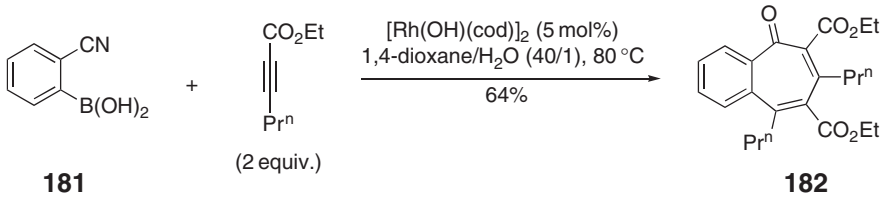


Scheme 53

178 **179a–c** (5 equiv.) **180a–c**

Alkyne	*R*	*Yield* **180** (%)
179a	Ph	74
179b	Me_3Si	70
179c	Me_3C	89

Scheme 54



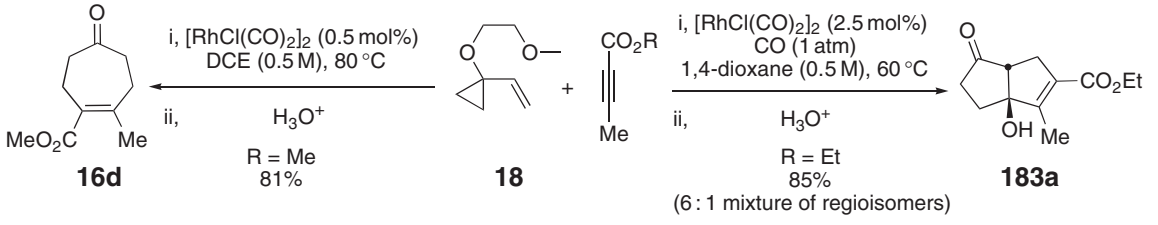
181 **182** (32)

10.13.3.3 [5 + 2 + 1]-Cycloadditions

Recognizing that intermediates in the [5 + 2]-reaction of VCPs and π-systems could be trapped with other components, Wender and co-workers reported a three-component [5 + 2 + 1]-cycloaddition involving VCPs, alkynes, and CO that provide efficient access to densely functionalized bicyclo[3.3.0]octenones via a cyclooctadienone intermediate (Scheme 55).[129] This reaction converts three commercially available materials to bicyclic products and creates two stereocenters and four C–C bonds.

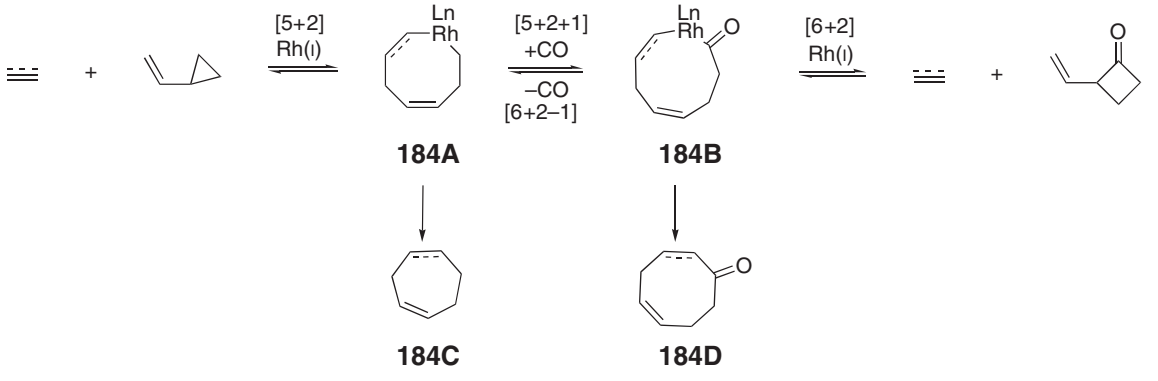
As seen in Scheme 55, with the simple addition of a balloon of CO to the [5 + 2]-reaction of VCPs and alkynes or allenes, the [5 + 2]-reaction can be diverted via a nine-membered metallacycle to produce initially an eight-membered ring product. This Rh(I)-catalyzed three-component [5 + 2 + 1]-reaction is mechanistically similar to the previously mentioned [6 + 2]-reaction (Section 10.13.2.5.2) differing only in regard to the insertion of CO in the pathway versus its incorporation in starting material (Scheme 56).

As indicated in Scheme 57, the formation of the secondary bicyclo[3.3.0]octenone product is thought to occur via an *in situ* transannular closure of the initially formed cyclooctadienone **185**. In some cases, cyclooctenediones and the [5 + 2]-cycloadducts are observed as minor products (Equations (33) and (34)).



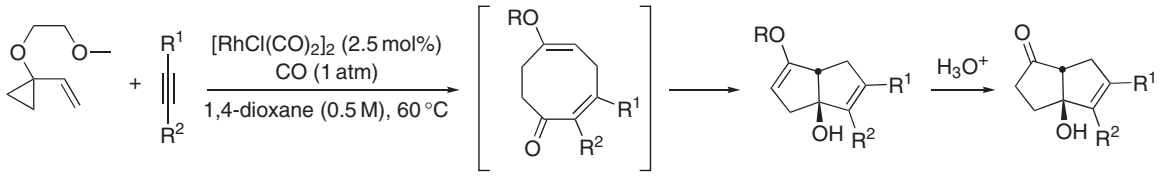
16d **18** **183a**

Scheme 55



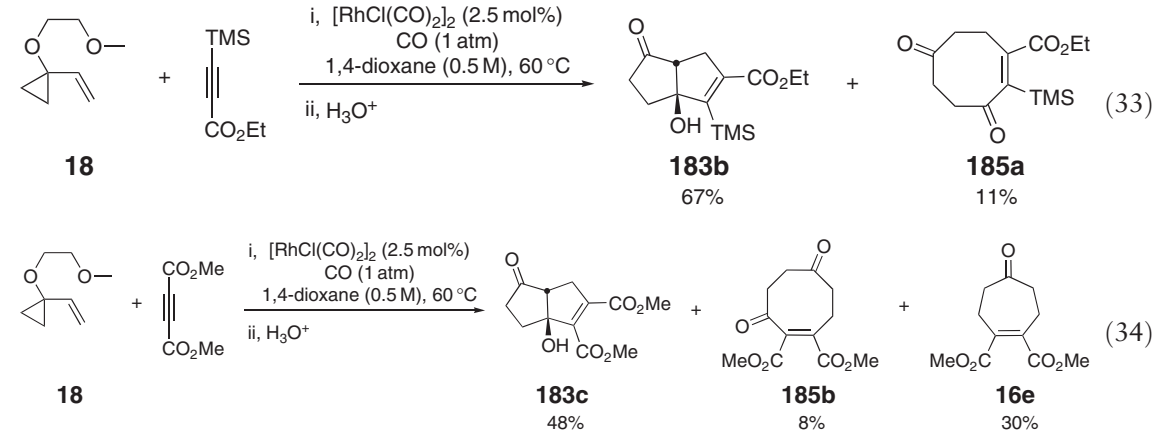
184A **184B** **184C** **184D**

Scheme 56



18 **185** **186** **183**

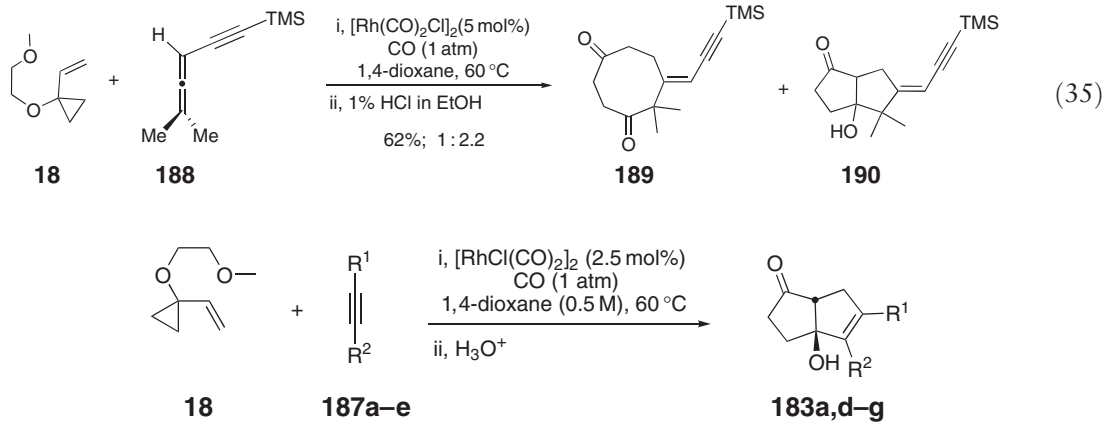
Scheme 57



(33)

(34)

Thus far, the [5 + 2 + 1]-reaction works efficiently with alkynyl esters, amides, aldehydes, and ketones or an alkynyl-substituted allene[44] as the two-carbon component (Scheme 58). Just as in the case of the [5 + 2]-cycloaddition of VCPs and allenynes, the [5 + 2 + 1]-reaction is selective for the allene over the alkyne subunit (Equation (35)).



18 **188** **189** **190**

(35)

18 **187a–e** **183a,d–g**

Alkyne	R^1	R^2	*t* (h)	*Yield* **183** (%)
187a	COMe	TMS	42	54
187b	COMe	Ph	26	88
187c	$CONH_2$	Ph	40	96
187d	CO_2Et	Ph	24	79
187e	CO_2Et	Me	20	85

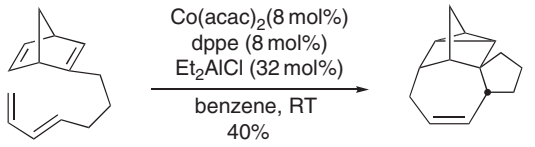
Scheme 58

10.13.3.4 [4 + 2 + 2]-Cycloadditions

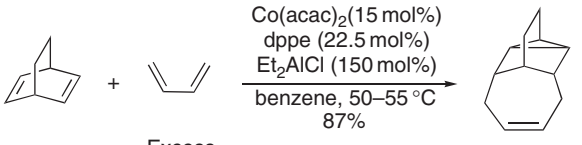
There are two main classes of [4 + 2 + 2]-metal-catalyzed higher-order cycloadditions that have been reported. The first class involves the reaction of 1,3-dienes (the four-carbon component) with norbornadienes (both two-carbon components) and the second involves the reaction of 1,3-dienes with either two alkynes or an alkyne and an alkene as the two-carbon components (Scheme 59).

Lautens and Snyder have shown that cobalt is an effective catalyst for the [4 + 2 + 2]-reaction of norbornadienes and 1,3-butadienes. Significant developments in this area include an enantioselective process described by Lautens[146] and a catalyst system that gives increased yields as described by Snyder (Scheme 60).[147,148]

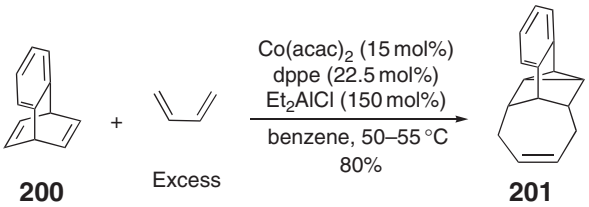
The reaction can be carried out intramolecularly to produce, in one step, three new rings in moderate yield (Equation (36)).[149] It is noteworthy that up to six stereogenic centers could be formed. Additionally, cobalt-catalyzed [4 + 2 + 2]-cycloadditions of bicyclo[2.2.2]octadienes have been reported (Equations (37) and (38)).[150]



(36)



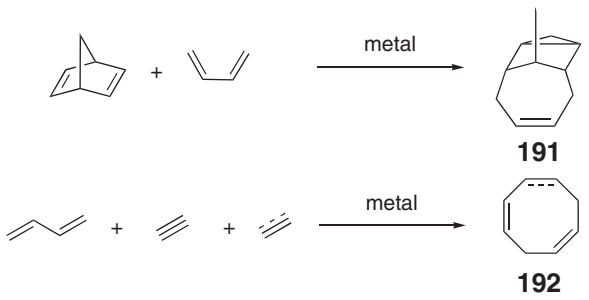
(37)



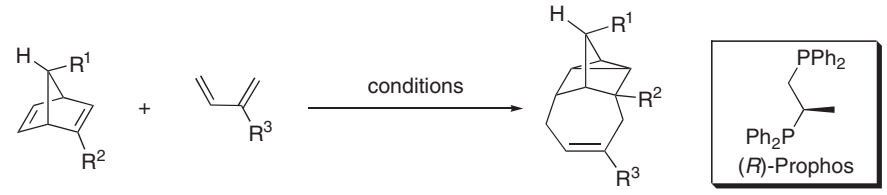
(38)

The products of these [4 + 2 + 2]-reactions have a high level of molecular complexity, which has been used to advantage in exploring the conversion of the [4 + 2 + 2]-cycloadducts into commonly encountered ring systems. Zeise's dimer, for example, has been employed to carry out a skeletal rearrangement, as illustrated in Scheme 61,[151–153] producing fused and bridged bicyclic systems found in several natural product families.

Recognizing that intermediates in the [4 + 2]-reaction of dienes and alkynes could be intercepted with components in addition to CO as in the [4 + 2 + 1]-reaction, Gilbertson and Evans independently published two new methods for the synthesis of eight-membered carbocycles involving [4 + 2 + 2]-cycloadditions. Saá and co-workers report a



Scheme 59

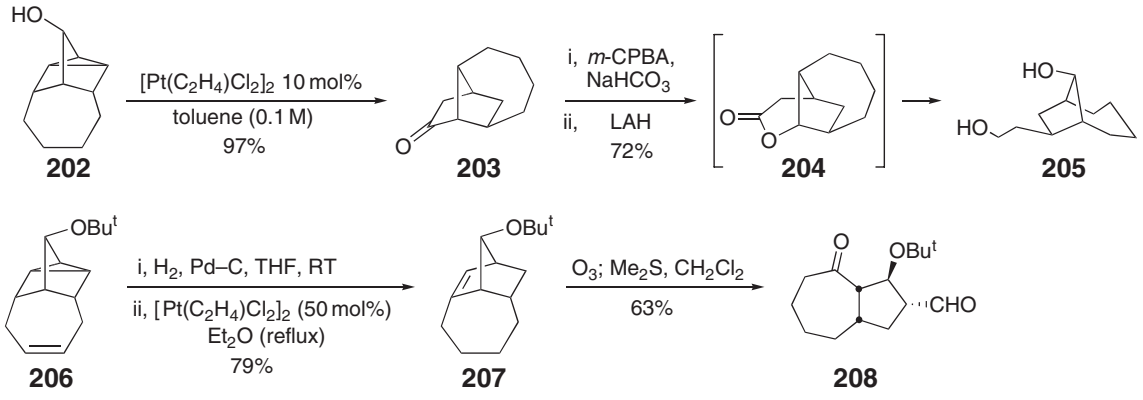


193a–c **194a–d** (1.5–3 equiv.) **195a–f**

Conditions A: $Co(acac)_2$ (2 mol%); (*R*)-Prophos (2 mol%); Et_2AlCl (10 mol%); benzene, RT
Conditions B: CoI_2 (5 mol%); dppe (5 mol.%); Zn (5 mol%); ZnI_2 (15 mol%); CH_2Cl_2; RT

Conditions	*Norbonadiene*	R^1	R^2	*Diene*	R^3	*Yield* **195** (%)	*ee* **195** (%)
A	**193a**	H	H	**194a**	Me	66	72
A	**193a**	H	H	**194b**	$(CH_2)_3OAc$	52	73
A	**193a**	H	H	**194c**	$(CH_2)TMS$	49	71
B	**193b**	OBz	H	**194d**	H	99	–
B	**193c**	OBu^t	Me	**194d**	H	96	–
B	**193a**	H	H	**194d**	H	87	–

Scheme 60



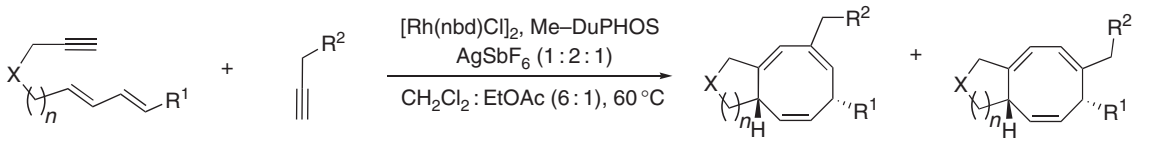
202 **203** **204** **205** **206** **207** **208**

Scheme 61

"formal" [4 + 2 + 2]-reaction, but the mechanism in that case involves the formation of an acyclic 1,3,5,7-tetraene which undergoes an eight-π-electron conrotatory ring closure, not dependent on a metal.[154] The Rh(I)-catalyzed [4 + 2 + 2]-reaction of tethered diene–ynes and alkynes, published by Gilbertson and DeBoef, involves the effective trapping of a metallacycloheptadiene intermediate **160C**, Scheme 44, Section 10.13.3.1 with an alkyne.[155] Several examples of this reaction were reported, all showing moderate to good yields of the eight-membered ring products and good to excellent regioselectivity with respect to the alkyne (Scheme 62).

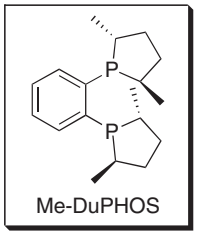
In the correspondingly innovative work by Evans and co-workers, a Rh(I) catalyst is used to effect a [4 + 2 + 2]-reaction of tethered ene–ynes with 1,3-butadienes, to produce bicyclo[3.6.0]undecadienes in good to excellent yields (Scheme 63).[156]

Studies aimed at expanding the scope of the reaction revealed that substitution of the alkene is tolerated if an *N*-heterocyclic carbene-complexed rhodium(I) species is used. Employing the RhCl(IMes)(cod) complex as the precatalyst also allowed for a reaction of substrates substituted at the allylic position, a previously problematic substitution pattern, and the diastereoselective formation of cycloadducts containing up to three contiguous stereocenters (Equation (39) and Scheme 64). This work represents the first use of such a rhodium complex in an [*m* + *n* + *o*]-cycloaddition reaction.[157] Further expanding on the scope of this reaction, it was shown that tethered 1,3-butadienes (Equations (40) and (41)) give the corresponding tricyclic products in good yields.[158]

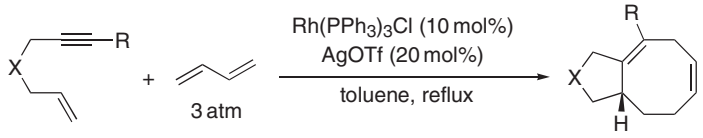


209a–c + **210a–d** (5 equiv.) → **211a–e** + **212**

Diene–yne	*X*	R^1	*Alkyne*	R^2	*n*	*Yield* **211** + **212** (%)	*ratio* **211 : 212**
209a	O	Me	**210a**	OBn	1	73	1 : 0
209a	O	Me	**210b**	Et	1	41	1 : 0
209a	O	Me	**210c**	OTMS	1	63	1 : 0
209b	O	H	**210a**	OBn	2	55	2.9 : 1
209c	NTs	Me	**210d**	NHTs	1	49	1 : 0



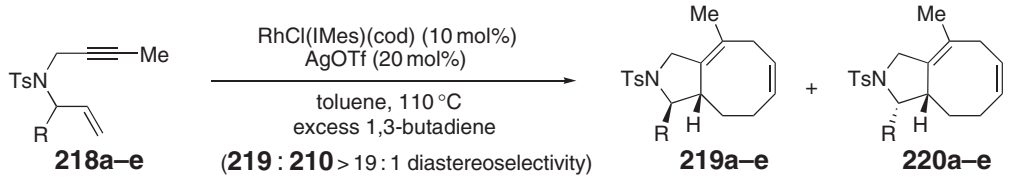
Scheme 62



213a–d → **214a–d**

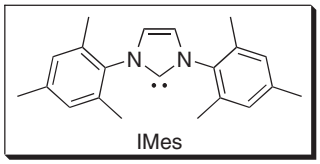
Ene–yne	*X*	*R*	*Yield* **214** (%)
213a	O	Me	81
213b	O	H	71
213c	NTs	Ph	87
213d	SO_2	Ph	87

Scheme 63

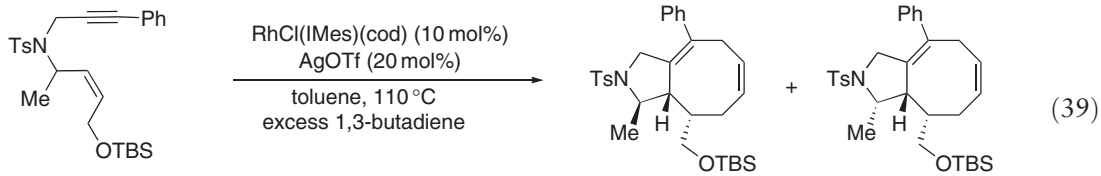


218a–e (**219** : **210** > 19 : 1 diastereoselectivity) → **219a–e** + **220a–e**

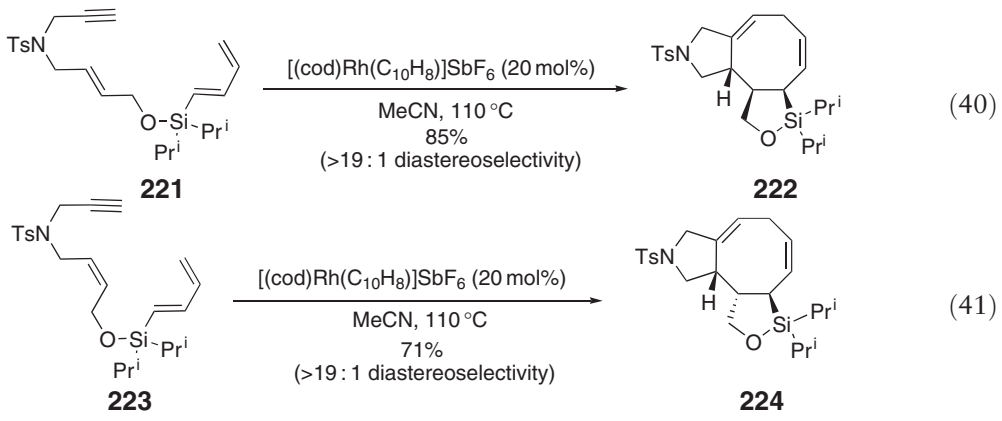
Ene–yne	*R*	*Yield* **219** + **220** (%)
218a	Bn	79
218b	Pr^i	84
218c	CO_2Me	71
218d	CH_2OH	55
218e	CH_2OTBS	83



Scheme 64



215 (70% (>19 : 1 diastereoselectivity)) → **216** + **217** (39)

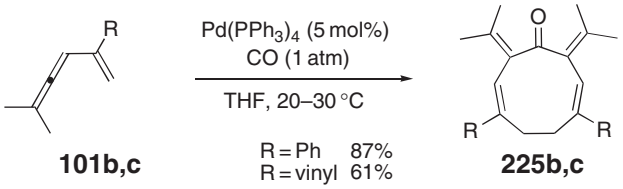


10.13.3.5 [4 + 4 + 1]-Cycloadditions

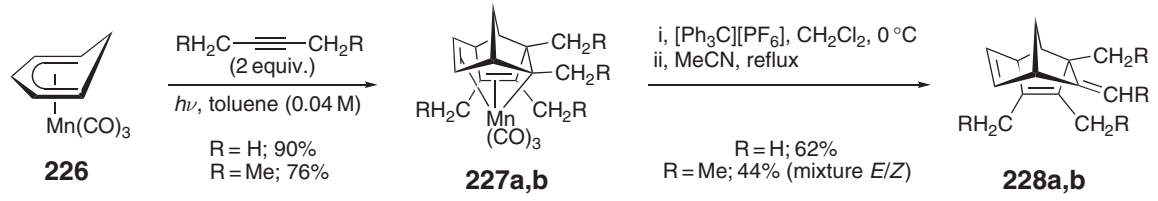
Based on the [4 + 4]-reaction of vinylallenes, Murakami and co-workers reported a novel route to phenyl- and vinyl-substituted cyclononadienones (Scheme 65).[159] It was found that the palladium-catalyzed [4 + 4]-reaction of vinylallenes could be converted to the [4 + 4 + 1]-reaction by the simple addition of CO (1 atm). The example reported reveals that the reaction is completely regioselective, giving head-to-head pairing of the vinylallenes. The methodology is thus far limited to the two examples shown in Scheme 65.

10.13.3.6 [5 + 2 + 2]-Cycloadditions

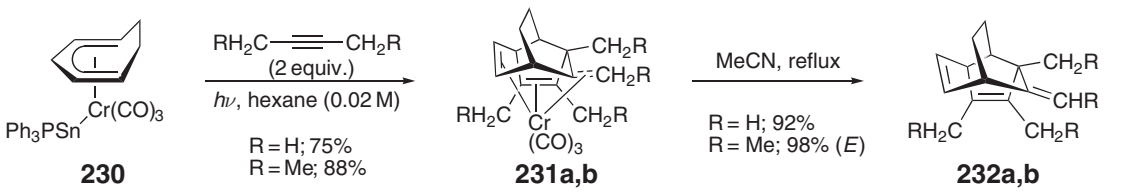
Sheridan and co-workers reported a novel photo-assisted [5 + 2 + 2]-reaction based on the reactions of η^5-cyclodienyl Mn complexes[160,161] or Cr complexes[162] and two alkynes. Decomplexation of the metal gives cycloadducts in moderate to good overall yields (Scheme 66, Equation (42), and Scheme 67). It should be noted that the authors refer to this reaction as a [5 + 2]-, [3 + 2]- or a [5 + 2]-, homo-[5 + 2]-reaction. This reaction leads to the formation of impressively complex tricyclic products that would be otherwise difficult to prepare with step economy.



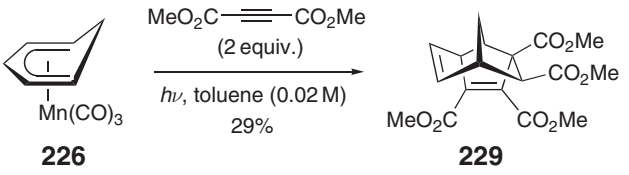
Scheme 65



Scheme 66



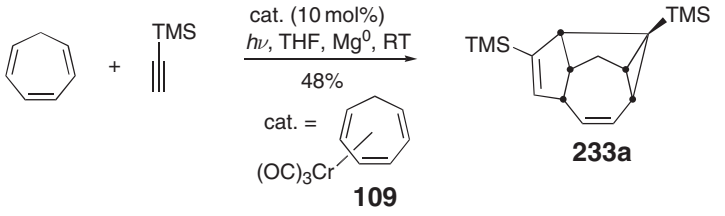
Scheme 67



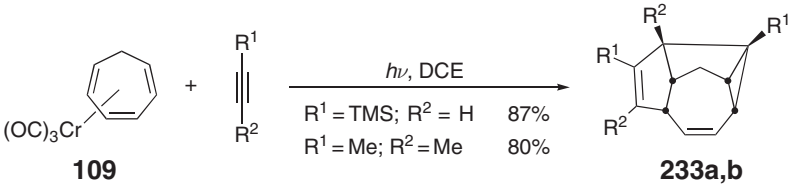
(42)

10.13.3.7 [6 + 2 + 2]- and [6 + 2 + 2 + 2]-Cycloadditions

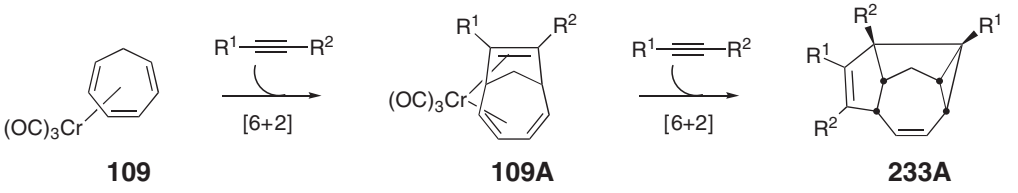
The remarkable [6 + 2 + 2]-cycloaddition reactions illustrated in Scheme 68 and Equation (43) were reported independently in 1996 by the Rigby[163] and Sheridan[164] groups. The mechanism of these reactions is thought to proceed via tandem [6 + 2]/[6 + 2]-reactions (Scheme 69). Although both initial reports involve the use of stoichiometric amounts of chromium complexes, later reports by Rigby and co-workers used chromium in catalytic amounts (10 mol.%) (Equation (43)).[165] This reaction has been employed as a key step in the total synthesis of 9-*epi*-pentalenic acid (Scheme 70).[166]



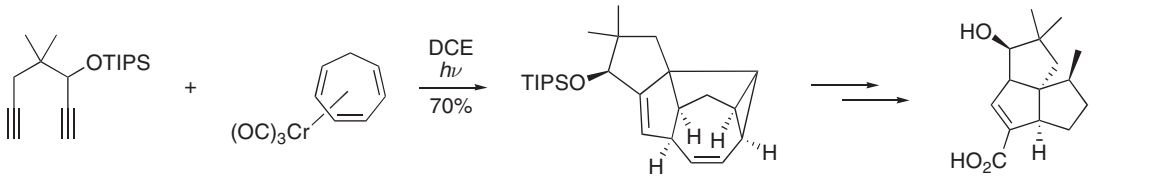
(43)



Scheme 68

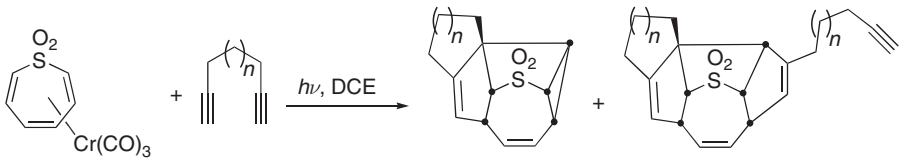


Scheme 69



234 **109** **233c** 9-*epi*-pentalenic acid

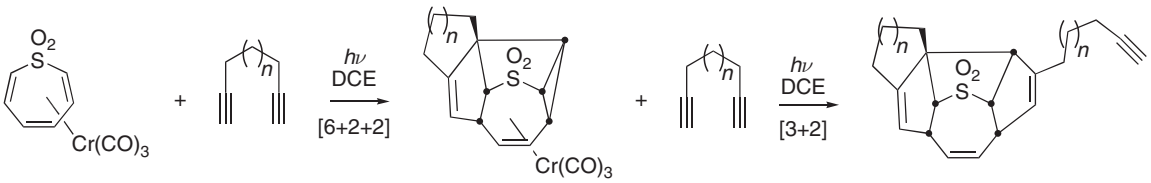
Scheme 70



235 **236a–c** **233d** **237a,b**

236a: $n = 1$ 56% 0%
236b: $n = 2$ 0% 45%
236c: $n = 3$ 0% 38%

Scheme 71



235 **236** **233A** **236** **237**

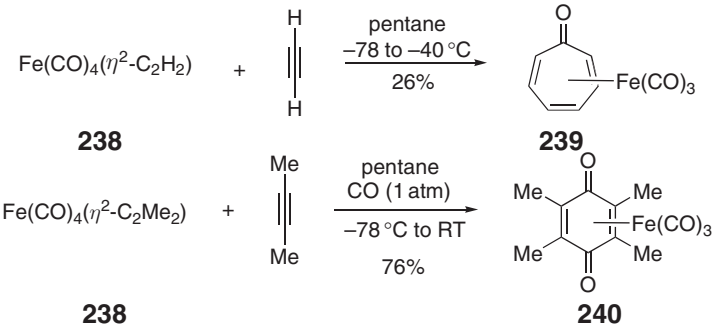
Scheme 72

During the course of their studies on the chromium-mediated [6 + 2]- and [6 + 2 + 2]-reactions, the Rigby group uncovered a new four-component [6 + 2 + 2 + 2]-cycloaddition.[167] When the two terminal alkynes are connected by three methylene units, an anticipated [6 + 2 + 2]-cycloaddition occurs in a moderate yield. Surprisingly, when the alkynes are tethered by four or five methylenes, a third alkyne is incorporated in an overall [6 + 2 + 2 + 2]-process (Scheme 71). The authors propose that the [6 + 2 + 2 + 2]-cycloaddition products arise from a [3 + 2] reaction of an alkyne with the initially formed [6 + 2 + 2]-reaction products (Scheme 72). These reactions greatly increase structural complexity by stereoselectively converting four achiral components to a pentacyclic product with six contiguous stereocenters.

10.13.4 [*m* + *n* + *o* + *p*]-Cycloadditions

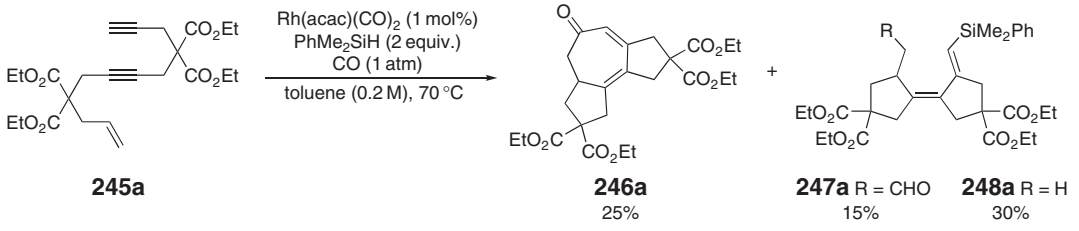
10.13.4.1 [2 + 2 + 2 + 1]-Cycloadditions

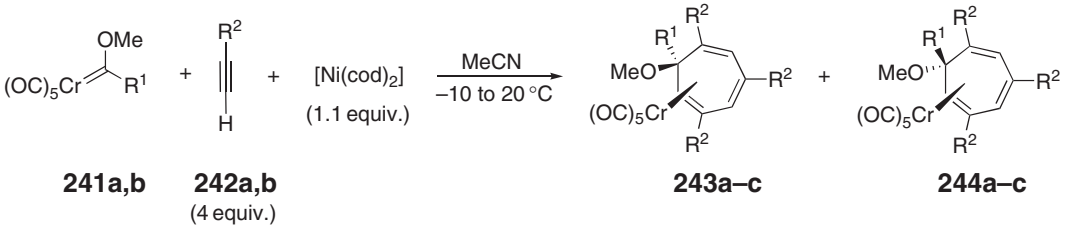
A single but noteworthy example of a [2 + 2 + 2 + 1]-cycloaddition reaction was reported by Takats and Cooke in 1997. In this process, $Fe(CO)_4(\eta^2\text{-}C_2H_2)$ reacts with acetylene to give an iron–tropanone complex in 26% yield (Equation (44)). When the analogous reaction was tried with substituted alkynes under an atmosphere of CO, iron–quinone complexes were observed (Equation (45)).[168]



Barluenga and co-workers reported a novel [2 + 2 + 2 + 1]-reaction based on the use of two metals, the nickel-mediated [2 + 2 + 2 + 1]-reaction of Fischer carbenes with alkynes (Scheme 73).[142] While, at present, this process requires the stoichiometric use of both metals, it is highly regioselective, affords good yields, and is a novel route to seven-membered rings.

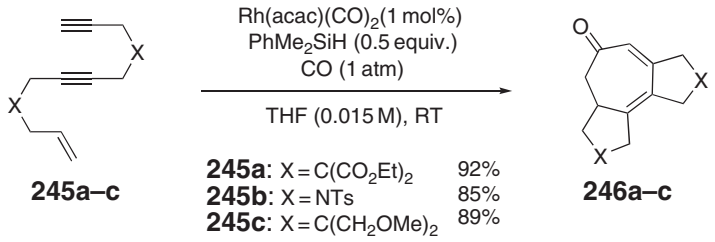
Starting in the year 2000, Ojima and co-workers have reported a series of innovative studies leading to the synthesis of seven-membered rings via a novel [2 + 2 + 2 + 1]-reaction. In addition to their novelty, these reactions have been shown to provide access to several synthetically interesting tricyclic products from relatively simple acyclic building blocks. Starting with 11,1,6-enediyne **245a** under an atmosphere of CO, Ojima and Lee reported the formation of three product types including the [2 + 2 + 2 + 1]-product through an Rh(I)-catalyzed silicon-initiated carbometalation pathway (Equation (46)).[169] By lowering the reaction temperature and running the reactions at higher dilution in THF, the [2 + 2 + 2 + 1]-reaction products were formed in good to excellent yields (Scheme 74). This impressive four-component reaction allows for the formation of three rings and four C–C bonds with notable step economy.





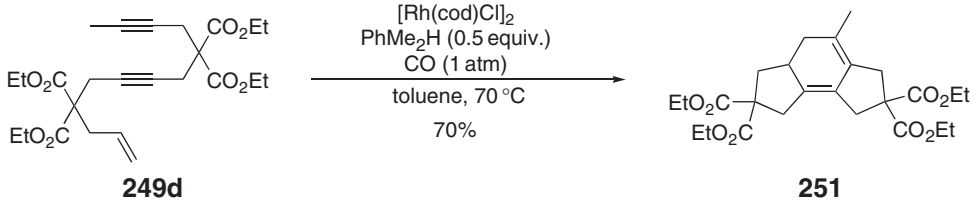
Fischer carbene	R^1	*Alkyne*	R^2	*Yield* **243** + **244**(%)	*Ratio* **243** : **244**
241a	Me	**242a**	Pr^n	92	>98 : 2
241a	Me	**242b**	$(CH_2)_3CN$	96	>98 : 2
241b	Ph	**242a**	Pr^n	68	6 : 4

Scheme 73

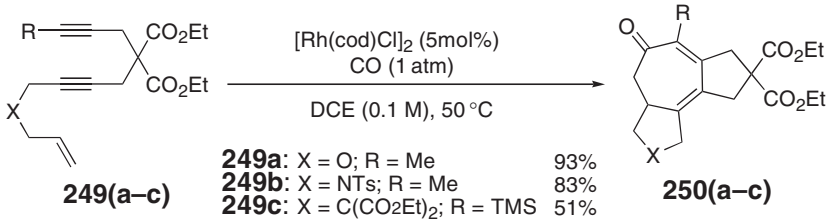


Scheme 74

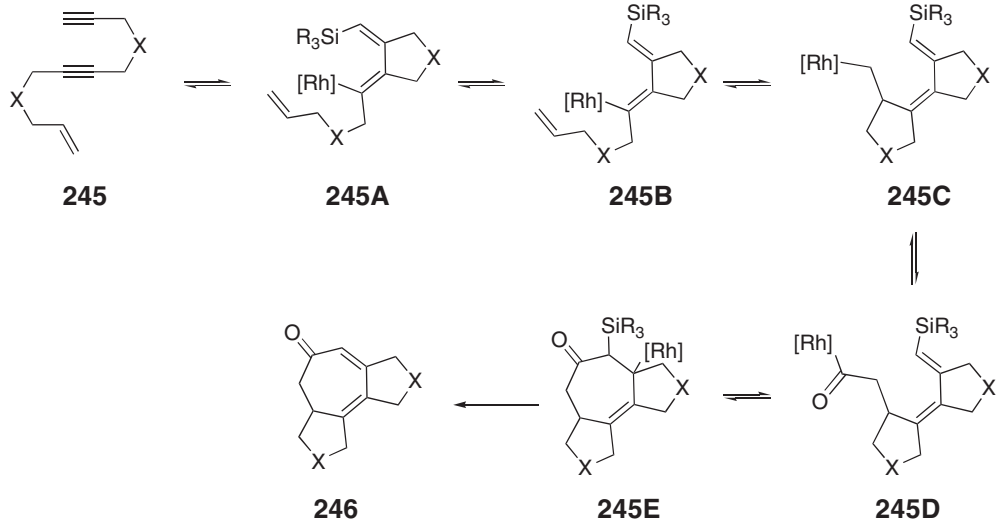
When internal alkynes are used, no silane is necessary for the reaction, although slightly elevated temperatures are required (Scheme 75).[3] Interestingly, it was determined that terminal alkynes yield more of the [2 + 2 + 2]-cycloadducts when no silanes are used in the reaction while internal alkynes only produce the [2 + 2 + 2]-products when silanes are present (Equation (47)). Two distinct mechanisms for the [2 + 2 + 2 + 1]-reactions, both leading to the seven-membered ring products, have been proposed (Schemes 76 and 77).



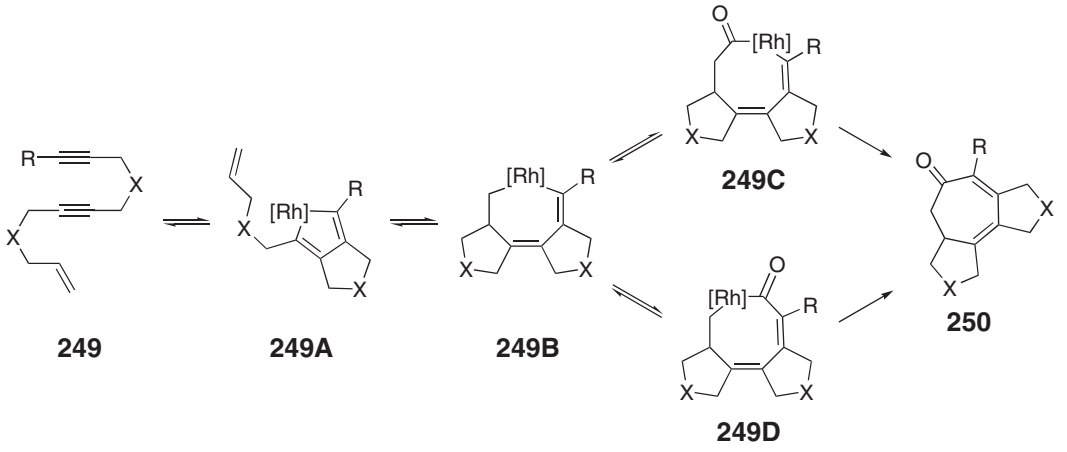
(47)



Scheme 75



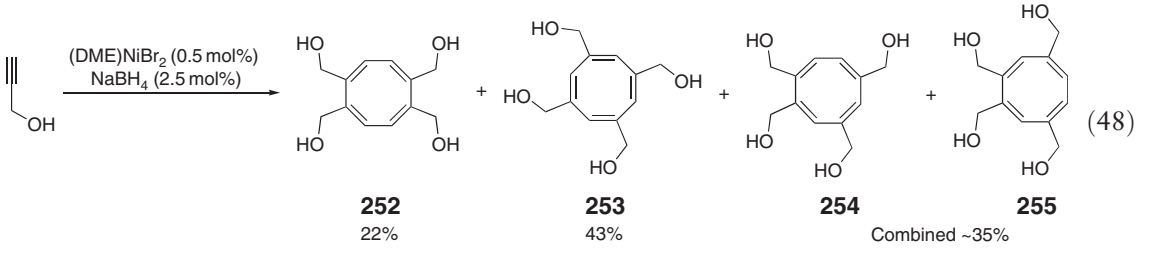
Scheme 76



Scheme 77

10.13.4.2 [2 + 2 + 2 + 2]-Cycloadditions

The nickel-catalyzed [2 + 2 + 2 + 2]-reaction of acetylene reported by the Reppe group in the 1940s is the first example of what is now considered a metal-catalyzed higher-order cycloaddition reaction.[170] Although the first reaction was reported in 1948, the selective and efficient cyclotetramerization of four different alkynes is still an unsolved problem, suffering from issues related to regioselectivity and chemoselectivity. In 1993, Streitweiser and Boussie reported the nickel-catalyzed [2 + 2 + 2 + 2]-reaction of propargyl alcohol providing facile albeit relatively unselective access to the four possible cyclooctatetraene regioisomers (Equation (48)).[171] The 1,2,5,6- and 1,3,5,7-substituted isomers were separable via derivatization with dimethoxypropane. Although this reaction does not solve the issue related to the regiochemistry in the [2 + 2 + 2 + 2]-reaction, this method offers an alternative way to get to the isomers by chemical separation. The resulting allylic alcohols can be derivatized to access other alkyl-substituted cyclooctatetraenes.



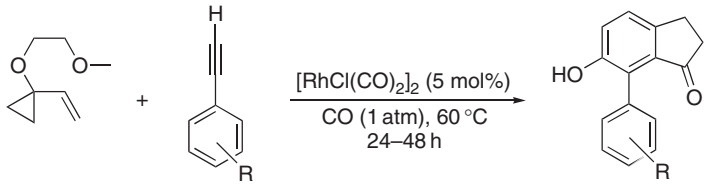
(48)

10.13.4.3 [5 + 2 + 1 + 1]-Cycloadditions

Following their studies on the trapping of intermediates in the [5 + 2]-cycloaddition with CO, which led to the [5 + 2 + 1]-process, the Wender group found that when related reactions were conducted with aryl alkynes under an atmosphere of CO, a novel four-component [5 + 2 + 1 + 1]-product was observed.[172] A VCP, an alkyne, and 2 equiv. of CO react to give the biaryl compounds shown (Scheme 78) via the formation of a nine-membered ring intermediate.

The mechanism of this novel process is proposed to involve formation of a nine-membered ring, which after tautomerization undergoes an electrocylic ring closure to form the bicyclo[4.3.0]nonadienone intermediate. Elimination of ROH gives the aromatic product observed (Scheme 79).

As indicated in Scheme 78, *ortho*-, *meta*-, and *para*-substituted aryl alkynes were studied and were all shown to be effective two carbon components in this process. Alkyl alkynes were also studied and were found to give moderate yields of the [5 + 2 + 1 + 1]-products (Equations (49) and (50)).

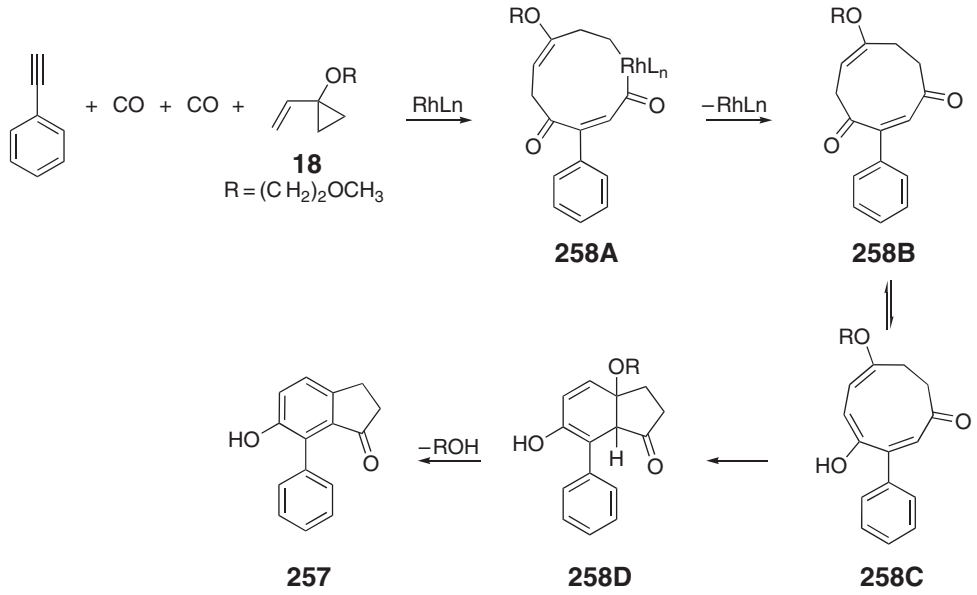


18 (2 equiv.) **256a–g** **257a–g**

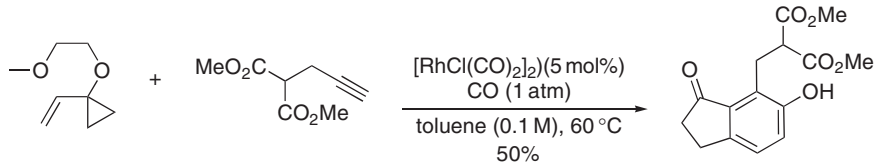
Alkyne	*R*	*Solvent*	*Yield* **257** (%)
256a	H	toluene	57
256b	*p*-Ph	toluene	92
256c	*o*-MeO	toluene	42
256d	*m*-MeO	toluene	59
256e	*p*-MeO	mixed[a]	75
256f	*p*-F	mixed[a]	81
256g	*p*-(TBSCC)	mixed[a]	78

[a]Mixed solvent = toluene : decane (3 : 1).

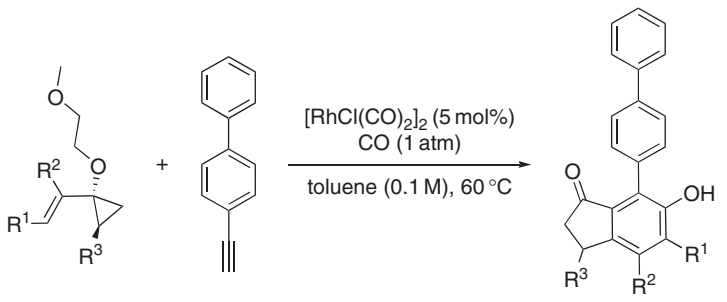
Scheme 78



Scheme 79

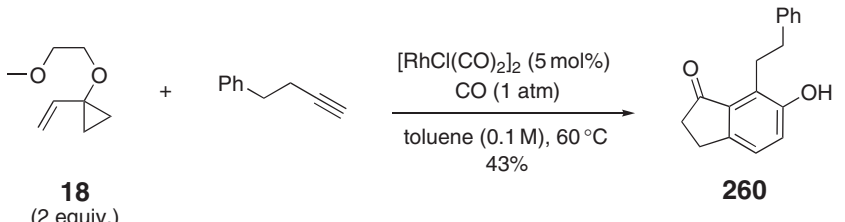


18 (2 equiv.) **259** (49)



VCP	R^1	R^2	R^3	*Yield* **262** (%)
261a	Me	H	H	74
261b	H	Me	H	64
261c	H	H	CH_2OTBS	52 (33 : 1 regioselectivity)

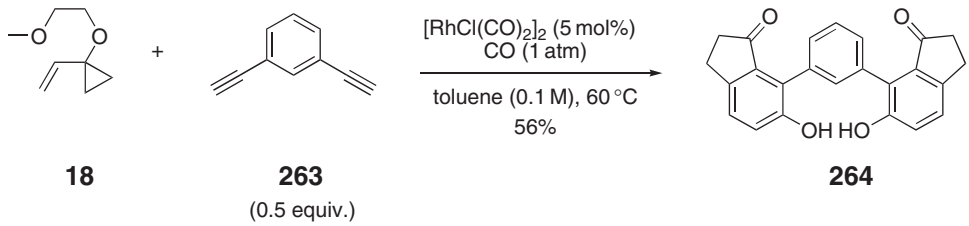
Scheme 80



(50)

The study of substituted VCPs revealed that methyl substitution of the alkene gives the expected products and substitution of the cyclopropane gives, with high regioselectivity, the product shown in Scheme 80.

Substituted bis-alkyne **263** gives a bidirectional product (Equation (51)). In this case, seven components are brought together in a step-economical process that forms 10 carbon–carbon bonds and four rings in one transformation, providing potential building blocks for novel materials, medicinal leads, and ligands for catalysis.



(51)

10.13.5 Conclusion

While interest in medium and large rings dates back to the early twentieth century and to a lesser extent before, the synthesis of rings of seven or more members only recently attracted significant attention in organic synthesis, taking shape largely in the 1970s with the identification of an increasing number of natural and non-natural products containing such ring systems that exhibit interesting and often profound biological activities (e.g., taxol, phorbol esters, daphnanes, pseudoguaianes, colchicines, germacranes, macrolides). Highly innovative approaches to these problems have been designed or discovered, many, as evident in this review, based on metal-catalyzed or metal-mediated transformations. In numerous cases, these metal-based processes provide a method for achieving a reaction that in the absence of a metal would be forbidden (e.g., [4 + 4]-cycloadditions of dienes) or difficult to do

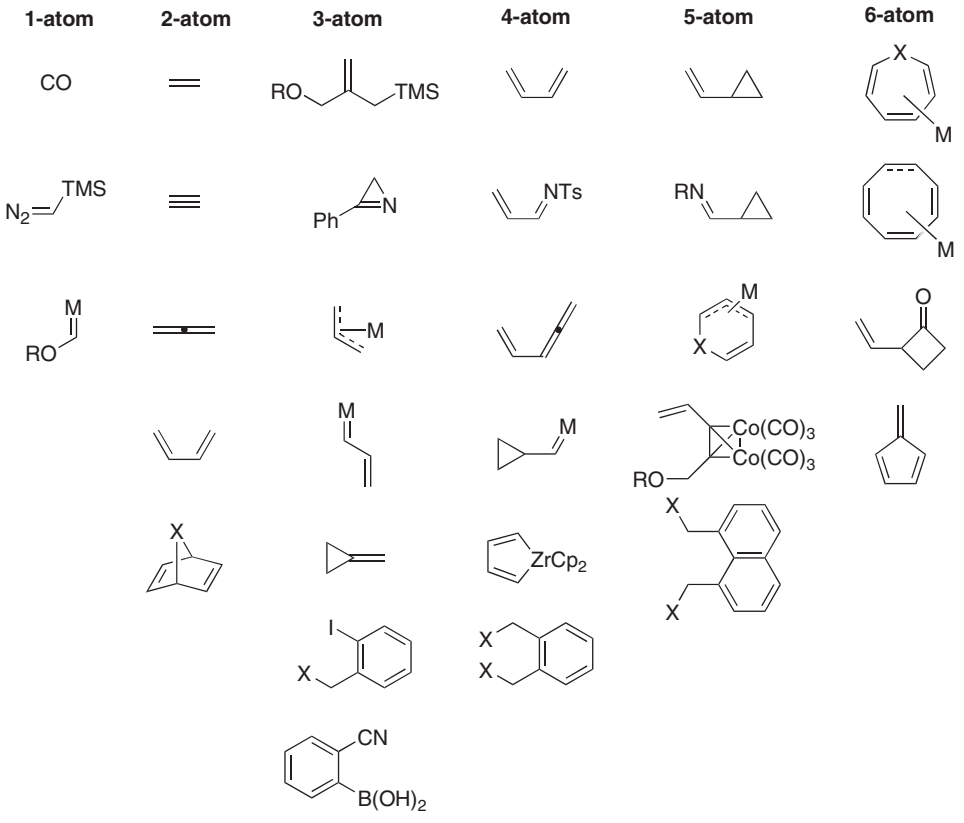


Figure 2 Various components discussed in this chapter.

(e.g., [4 + 2]-cycloadditions of unactivated dienes and π-systems). In other cases where a non-metal catalyzed counterpart of the metal-catalyzed reaction exists, the catalyst often provides a different means of controlling the selectivity or the facility of the process. Collectively, whether metals enable new reactions, improve, or complement the selectivities of known reactions, metal-based reactions offer the synthetic chemist new ways of thinking about target construction. These new theoretical and strategic options often influence route selection and therefore environmental acceptability, process costs, synthesis time, atom economy, and most importantly step economy. Shorter, that is, step-economical syntheses require less time, solvent, and development, and often facilitate the realization of goals associated with cost and environmentally effective solutions.

A list of one-, two-, three-, four-, five-, and six-atom components used in this chapter are compiled in Figure 2. This clearly portrays the creativity involved in the invention of new reactions and reaction components. A surprising feature of Figure 2 is the large number of components which can incorporate one to six atoms, but the complete absence of larger atom components. The design of seven- and eight-atom components will help fill this void in higher-order cycloadditions. Of the possible multicomponent [$m + n + o + \cdots + x$]-cycloadditions that create seven-, eight-, or nine-membered rings, less than one-fifth are known (Figure 1). As is evident from this overview, much progress has been made in the introduction of new reactions for medium ring synthesis. However, equally evident from this compilation is that much remains to be done. Relative to its common ring counterpart, the science of higher-order cycloadditions is relatively unexplored but rich in opportunities for the advancement of synthesis, biology, medicine, and materials science.

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10.14 C–O Bond Formation through Transition Metal-mediated Etherification

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10.14.1 Introduction

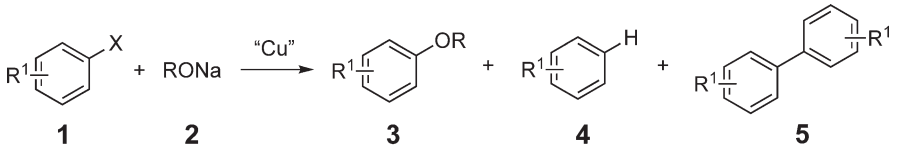
The ether linkage is a major structural motif found in a broad range of natural and unnatural structures. Due to the biomedical and industrial importance of these molecules, the efficient and selective construction of ether bonds has been a topic of long-standing interest. While numerous etherification processes have been developed ever since the discovery of the Williamson ether synthesis,[1] an increasingly large number of examples have employed transition

metal complexes. The use of these reagents for etherification offers a number of advantages over Williamson-type approaches. For example, the bond formation may be achieved through multiple mechanisms rather than relying solely on the substitution process. This feature enables expeditious preparation of various ether types with potential control of chemo-, regio-, and stereoselectivities. Moreover, the transformations usually occur under mild reaction conditions, often in the presence of only catalytic amounts of organometallic reagents. In recent years, the transition metal-mediated etherification reaction has undergone remarkable development to establish unquestionably broad synthetic utility. New processes based on various mechanistic motifs have been discovered and tested for novel C–O bond-forming transformations using a wide range of substrates. Consequently, the formation of ether linkages that have traditionally been considered difficult to achieve can now be routinely practiced, often on large scale, in high yield. This chapter presents an overview of the literature published between 1993 and 2005 in the chemistry of C–O bond formation through transition metal-mediated etherification.

10.14.2 Aryl/Alkenyl Ether Formation via Cross-Coupling Reactions

10.14.2.1 Copper-mediated Cross-coupling Reactions

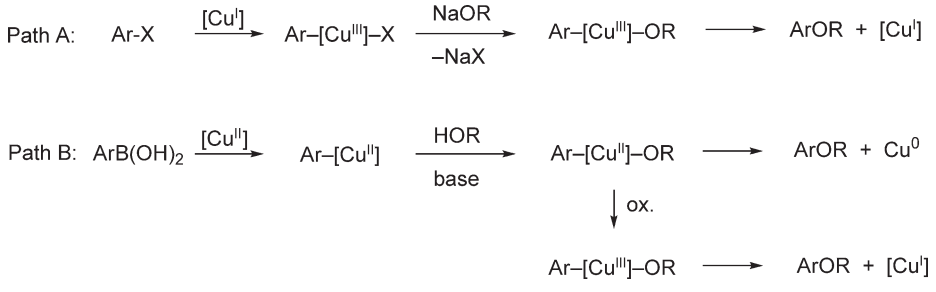
The Ullman reaction, discovered in 1903,[2] is the prototype cross-coupling method for the synthesis of aryl ether linkages through copper-mediated catalysis (Equation (1)). In this reaction, phenoxides (**2**, R = aryl) undergo a cross-coupling process with aryl halides **1** to give the products of *O*-arylation. The Ullman coupling in its classical form, however, suffers from several major drawbacks. Most notably, the reaction conditions are quite harsh, with high temperatures and polar solvents typically used, and the coupling partners must include an electron-deficient aryl halide and an electron-rich phenol for the attainment of good yields. In practice, the phenol is often employed in excess, which is an obvious limitation if it is a valuable starting material. Common byproducts are the arene **4** derived from simple reduction of the aryl halide, as well as the biaryl **5** resulting from its homocoupling.



R = aryl, alkyl
R^1 = EWG
X = Br, I

(1)

Although the detailed mechanism of the Ullmann reaction is still not well understood, an excellent review on this subject is available that provides a thorough discussion of the various mechanisms that may be operative under different conditions.[3] In most classical and modified Ullmann processes, the Cu(I) or Cu(II) salt employed for the reaction is a precursor to an arylcopper intermediate. For example, in the coupling of an aryl halide with a phenoxide, oxidative addition of the Cu(I) complex to the aryl halide generates a Cu(III) aryl species; coordination of the phenoxide and subsequent reductive elimination afford the product and regenerate the Cu(I) catalyst (path A in Scheme 1). In cross-coupling reactions where a boronic acid is used in place of an aryl halide, a slightly different mechanism is operative (path B). In this case, a Cu(II) intermediate, derived from transmetallation of the boronic acid and subsequent coordination of the phenoxide, may undergo reductive elimination directly to the product and a



Scheme 1

Cu(0) species. Alternatively, the Cu(II) species may first undergo oxidation by an external oxidant (or internal redox process) to a Cu(III) intermediate, and then undergo reductive elimination to provide the product and a Cu(I) species. Re-oxidation to Cu(II) would then, in theory, complete the catalytic cycle, but in practice, most reactions of this type have been performed with stoichiometric amounts of the copper reagent.

The last few decades have witnessed a great deal of effort to improve the Ullman processes that employ aryl halide donors for *O*-arylation.[4] Advances have come from simple modifications to otherwise typical Ullmann conditions to provide benefits on yields and operational simplicity. A common modification has been the introduction of a simple additive, which is believed either to enhance the solubility of the copper salt or to act as a ligand for the copper center to influence its electronic properties. Examples include the addition of esters[5] or CO_2[6,7] to the methoxylation of aryl bromides, and the use of a pyridine ligand for the hydration of aryl chlorides.[8] Improvements on the yields and reaction times have also been realized by sonication[9] or microwave heating.[10,11] Similarly, a few successful heterogeneous Ullmann reactions have been reported using Raney Ni–Al alloy as an additive in conjunction with a typical copper salt,[12] or using malachite, $CuCO_3{\cdot}Cu(OH)_2{\cdot}H_2O$, as an inexpensive, alternative copper source.[13] Ionic liquids have proved to be viable solvents for Ullmann couplings, albeit with moderate solvent recyclability.[14,15]

The resurgence of Ullmann chemistry has been due in no small part to the occurrence of a number of biologically important natural products that possess macrocyclic biaryl ether linkages in the context of complex molecular settings (Figure 1).[16] While a simple S_NAr approach has been employed in many cases for the synthesis of these biaryl ethers, a more attractive strategy has been the use of the Ullmann coupling, which in principle does not require the installment of additional activating groups.[17] This point is well illustrated by the work of Boger and co-workers, where the copper-mediated cross-coupling was used to prepare the biaryl ether linkages of RA-VII,[18] bouvardin and several of its derivatives **6**,[19] models of piperazinomycin **7**,[20] vancomycin **8** and **9**, and ristocetin.[21] Further examples of the usage of Ullmann conditions in either inter- or intramolecular settings have also appeared in the literature over the past years. These include the syntheses of the natural products isodityrosine,[22,23] renieramide,[24] combretastatin D1 and D2,[25] acerogenin C,[26] and marchantin I,[27] as well as the preparations of aryl ether derivatives of *tert*-butylcalix[4]arene,[28] 2,3-dihydrobenzofurans,[29,30] and various dibenzoxepino-4,5-d-pyrazoles **10**.[31]

A combination of the S_NAr feature and the coordination ability of a copper complex has led to the development of a new *O*-arylation method that makes use of a triazene as an activating and directing group (Equation (2)).[32,33] This protocol, though necessitating a three-step removal sequence of the triazene moiety, has been successfully applied to the total synthesis of vancomycin[17,34–36] and extended to a solid-phase synthesis in which the triazene unit serves as an anchor to the resin.[37]

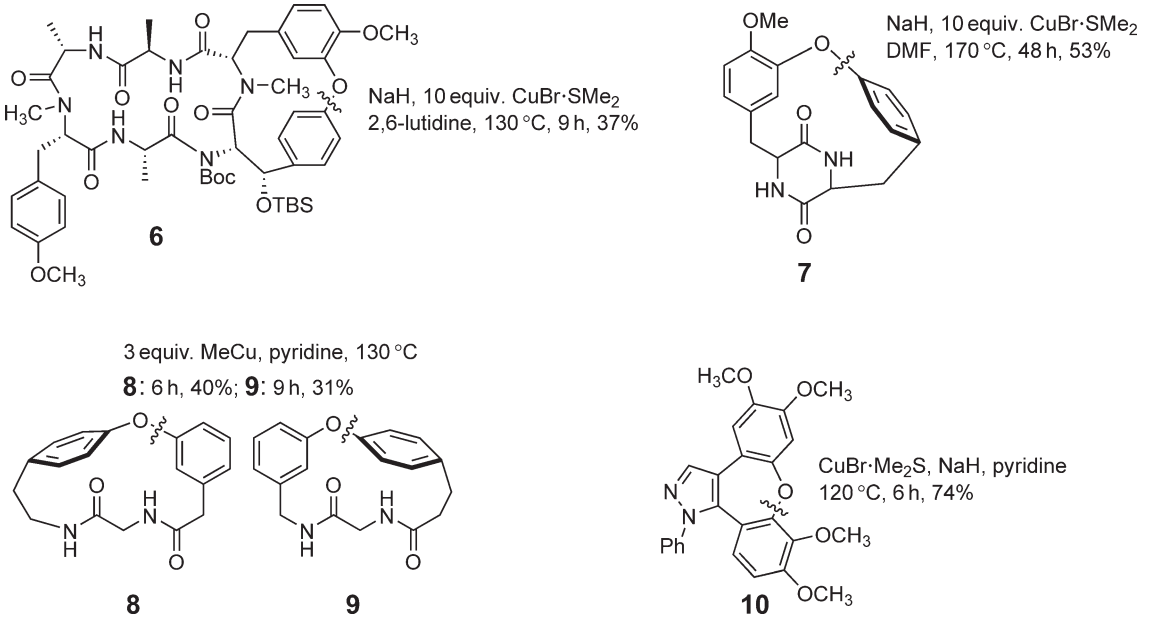
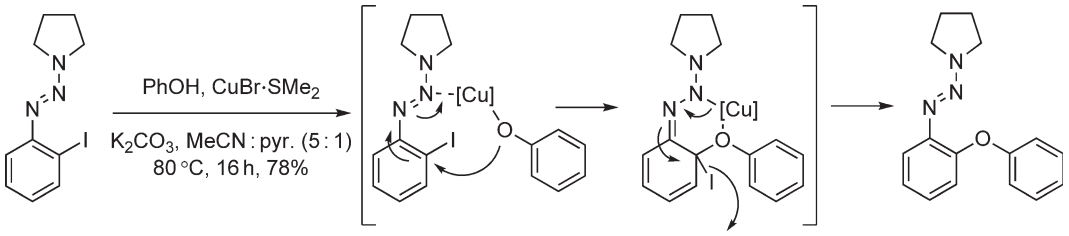
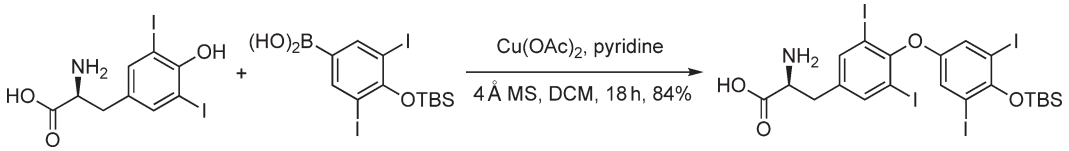


Figure 1 Selected examples of the Ullman coupling in complex syntheses.



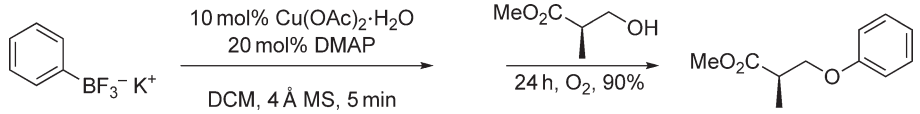
(2)

An important contribution to the field has been made independently by the groups of Chan[38] and Evans,[39] who have reported the copper-mediated cross-couplings of phenols with aryl boronic acids, instead of aryl halides, for the preparation of biaryl ethers (Scheme 1, path B). The notable features of this protocol are the use of Cu(II) rather than Cu(I) salts, the mild and simple reaction conditions (Et_3N or pyridine/CH_2Cl_2/25 °C), and the broad substrate scope (Equation (3)). Further studies have revealed that cyclic boroxines are excellent coupling partners as well.[40] Not surprisingly, the new cross-coupling method has already seen a great number of applications, such as in the syntheses of teicoplanin aglycone,[41] L,L-cycloisodityrosines,[42] (*S*,*S*)-isodityrosines,[43] (−)-tejedine,[44] a series of estrogen receptor modulators,[45] and metalloproteinase inhibitors.[46]

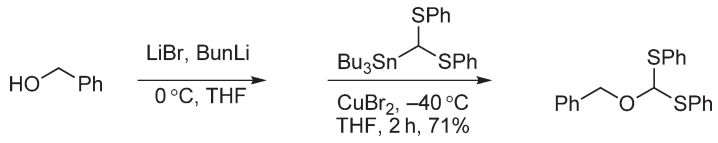


(3)

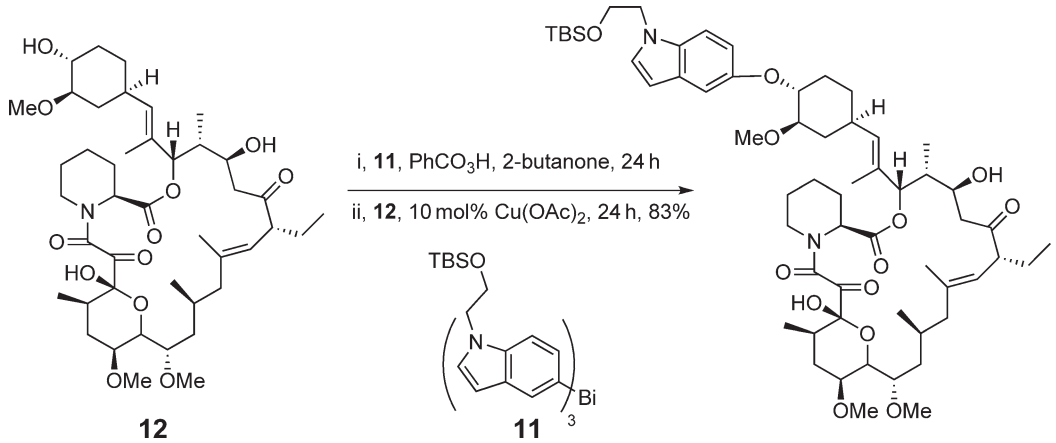
In addition to boronic acids, aryltrifluoroborates,[47] tetraalkyltin,[48] and organobismuth reagents have also been shown to be capable transmetallation partners (Equations (4) and (5)). In particular, due to the mildness and operational simplicity of the reaction, the copper-catalyzed *O*-arylation reaction using pentavalent organobismuth reagents has seen widespread utility.[49,50] While an inherent drawback of this method is that only one of the three aryl groups is transferred,[51] a number of aryl ethers have been prepared using various $Ar_3Bi(OAc)_2$ reagents[52–54] and pentavalent bismuth derivatives generated *in situ* by the oxidation of the corresponding trivalent compounds (Equation (6)).[55–57] In contrast to the bismuth systems, the corresponding arsenic reagents have seen little use over the past decade due to their diminished reactivity.[58,59]



(4)

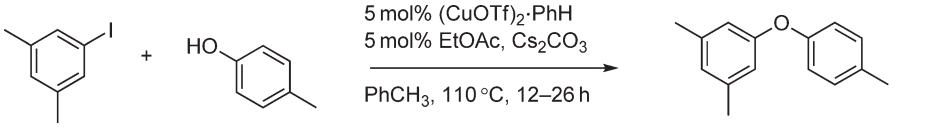


(5)

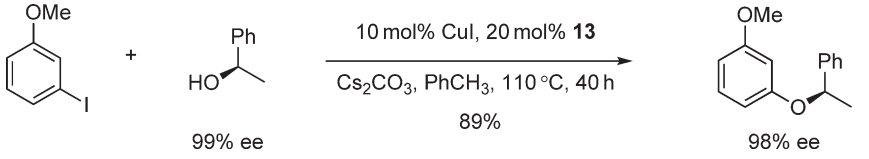


(6)

Efforts to improve the Ullmann procedure by employing new copper sources and/or specialized ligands have rendered the systems truly catalytic in copper. In 1997,[60] the Buchwald group reported the synthesis of biaryl ethers using $(CuOTf)_2{\cdot}PhH$ as the catalyst in the presence of Cs_2CO_3 and EtOAc (OTf = trifluoromethansulfonate). Although the copper source could be varied, the use of Cs_2CO_3 as base[61] and EtOAc as additive[5] was found to be crucial for stabilizing and solubilizing the copper complex. These reaction conditions allowed for the coupling of a wide variety of aryl halides and phenols, including highly hindered or electronically unactivated substrates (Equation (7)).[62–64] More recently, this *O*-arylation protocol has also been applied to the coupling of aryl halides with aliphatic alcohols (Equation (8))[61] using catalyst systems based on Cu(I)/1,10-phenanthroline **13**,[65,66] Cu(I)/neocuproine **14**,[65] and the even simpler $BrCu{\cdot}PPh_3$.[67]



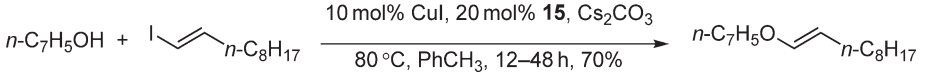
(7)



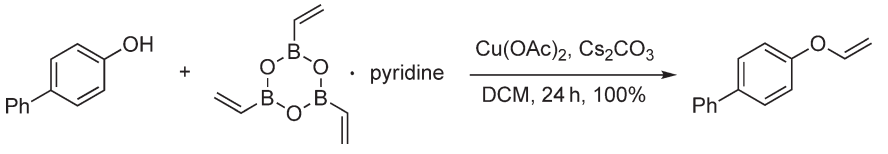
(8)

The discovery of the copper-catalyzed Ullmann reaction has further fueled the search for reactive catalysts based on Cu/ligand/base systems. For example, the phosphazene base P_4-*t*-Bu **17**[68] and KF/Al_2O_3[69] have been used as alternatives to Cs_2CO_3 for biaryl ether formation. Variants on the copper source have also been reported in which the air stable $CuPF_6(MeCN)_4$ catalyst[70] and the copper clusters $[Cu_8(S_2P(OR)_2)_6(\mu_8\text{-Cl})]PF_6$ (R = OMe or OPr^i)[71] proved to be effective for a broad range of substrates. For the CuCl-catalyzed phenoxylation and methoxylation of the challenging substrate 2-bromo-4,6-dimethylaniline, a library-based search led to the identification of 8-hydroxyquinoline **18** and 2-aminopyridine **19** as excellent ligands for these transformations.[72] Several other ligands for simple copper salts have been discovered (Figure 2), including a simple β-diketone **20**,[73,74] *N*,*N*-dimethylglycine,[75] and Chxn-Py-Al **21**,[76] the last of which promoted biaryl ether couplings at relatively low temperatures.

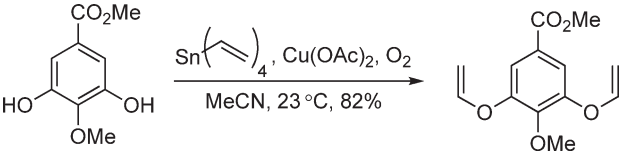
The Ullmann-type C–O bond formation reaction can also be applied to *O*-vinylation. For example, the efficient vinylation of phenols has been achieved using vinyl halides under the catalysis of Cu(I) with the amino ethyl ether ligand **22**[77] or with *N*,*N*-dimethylglycine as the ligand.[78] Similarly, the use of catalytic Cu(I) and the phenanthroline ligand **15** has allowed for the *O*-vinylation of primary aliphatic alcohols (Equation (9)).[79] Ketone enolates have also been shown to be viable nucleophiles for intramolecular *O*-vinylation with vinyl bromides.[80] Vinyl trifluoroborates,[47] boronic acids,[81] and boroxanes (Equation (10))[82] have also participated well in this type of reaction in the presence of $Cu(OAc)_2$. Finally, aryl vinyl ethers have been generated in good yields from the reactions of phenols with tetravinyltin (Equation (11)).[83–86]



(9)



(10)



(11)

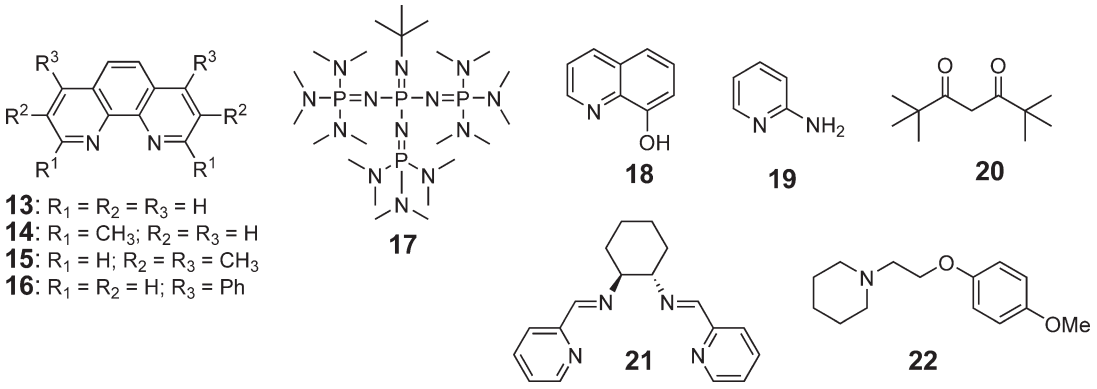


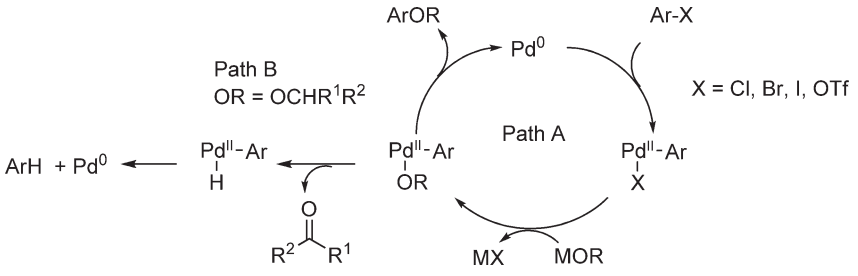
Figure 2 Recently developed ligands and bases for copper-catalyzed cross-coupling reactions.

10.14.2.2 Palladium-catalyzed Cross-coupling Reactions

Although the use of Cu reagents has historically been prevalent, tremendous progress in Pd-catalyzed C–O bond-forming cross-coupling reactions has been recorded during the last decade.[87,88] Copper is, of course, much less expensive than palladium and therefore potentially more attractive in industrial settings. Nevertheless, recent advances in the Pd catalyst systems, heralded by the pioneering efforts of the Buchwald and Hartwig groups, have rendered the Pd-catalyzed protocols versatile etherification methods of broad utility.

A general mechanistic picture for these processes consists of two competitive pathways, depending on the nature of the alcohol nucleophile (Scheme 2). The reaction proceeds by way of oxidative addition of Pd(0) to an aryl halide, coordination of an alcohol or alkoxide to the Pd(II) center, and reductive elimination to give the ether product and regenerate the Pd(0) catalyst (path A). If the alcohol has an α-hydrogen, however, a competing β-H elimination pathway can be observed (path B), which serves not only to destroy the alcohol nucleophile, but also to provide a pathway for the undesired reduction of the aryl halide to the corresponding arene. This competing pathway has been a major obstacle in the development of effective cross-coupling methodology for primary and secondary aliphatic alcohols, but progress has been made in overcoming this difficulty by tuning the properties of the ligand. It has been suggested that increased steric congestion around the Pd center destabilizes the arylpalladium alkoxide complex, thereby promoting reductive elimination.[89] For this reason, it has generally been observed that control of the steric properties of the ligands, more so than their electronic properties, has led to greater control over the outcome of the reaction.[90]

Due to the potential problems associated with β-H elimination, the first examples that were reported involved the intramolecular formation of C–O bonds between tertiary alcohols and aryl bromides using $Pd(OAc)_2$ with 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binapthyl (tol-BINAP) or bis(diphenylphosphino)ferrocene (dppf) as the ligands (Equation (12)).[91] Although the coupling with primary and secondary alcohols was troublesome with this system, the more recent introduction of ligands **23–28** (Figure 3) has ameliorated many of these difficulties (Equation (13)).[92]



Scheme 2

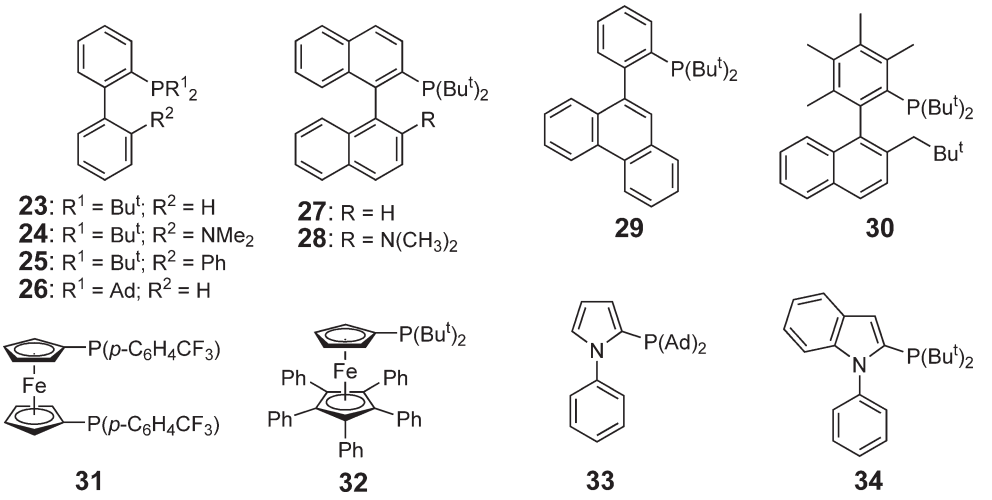
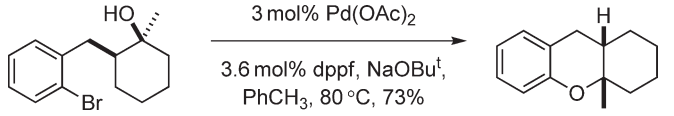
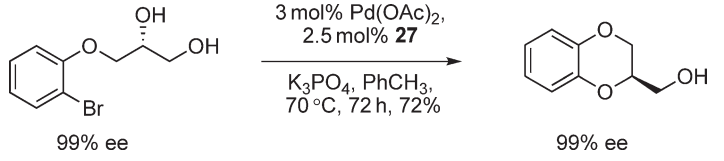


Figure 3 Recently developed ligands for palladium-catalyzed cross-coupling reactions.

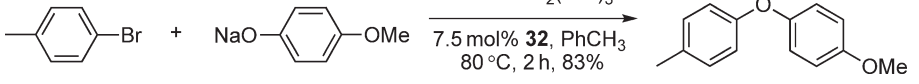


(12)



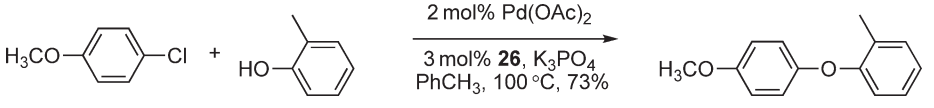
(13)

The feasibility of the Pd-catalyzed intermolecular *O*-arylation of alcohols was noted when Hartwig and co-workers observed the formation of *t*-butyl aryl ethers in the course of their studies on *N*-arylation using $Pd_2(dba)_3$/dppf as catalyst and $NaOBu^t$ as base (dibenzylidene acetone).[93] Later, the CF_3–dppf ligand **31** was found to be more effective for the formation of a range of biaryl ethers.[94] Further studies on this process have led to the discovery of the novel ferrocene-derived ligand Q-Phos, **32**, that was inadvertently generated *in situ* under the reaction conditions.[95] The independent preparation and use of this ligand allowed for highly efficient cross-couplings between $NaOBu^t$, NaOTBS, or sodium phenoxides with aryl halides, which, in some cases, could be performed at room temperature (Equation (14)).[96]



(14)

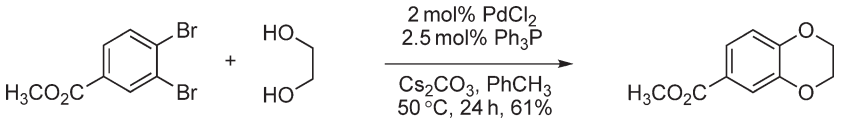
Mechanistic studies carried out by the Buchwald group[97,98] on the key C–O bond formation step in these reactions have reinforced the importance of the properties of the ligand, and have led to the adoption of a variety of more sterically hindered ligands (e.g., **23**, **24**, **27**, **29**, and **30**), which have given improved results for the preparation of biaryl ethers (Equation (15)),[89] *t*-butyl aryl ethers,[99] and aryl ethers of primary alcohols.[100]



(15)

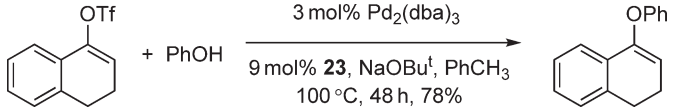
This methodical line of research has culminated in sets of catalyst systems with varying metals and ligands for the cross-coupling of a diverse array of aryl halides with primary, secondary, and allylic alcohols (Scheme 3).[101] The appropriate ligand for a given transformation can readily be selected based on the steric and electronic parameters of the particular aryl halide and aliphatic alcohol being employed. Other ligands which have been utilized in cross-couplings of this type include $P(Bu^t)_3$[102] and the heteroaryl phosphine ligands **33** and **34**,[103] which achieved turnover numbers (TONs) reaching 1,000.

Commensurately with the development of various catalyst systems, the Pd-catalyzed C–O cross-coupling has found a number of synthetic applications. Examples include the syntheses of the protein kinase C (PKC) activator (+)-decursin,[104] the natural product heliannuol E,[105] a chiral 2-methyl chroman,[106] and a series of aryloxy and alkoxy porphyrins.[107] The Buchwald–Hartwig coupling has also been utilized in the preparation of a heterocycle library.[108] Intramolecular *O*-arylation has also been achieved in the reactions of enolates with aryl halides leading to benzofurans.[109,110] Finally, a double cross-coupling between an *o*-dibromobenzene and a glycol has also been applied for the preparation of benzodioxanes (Equation (16)).[111]

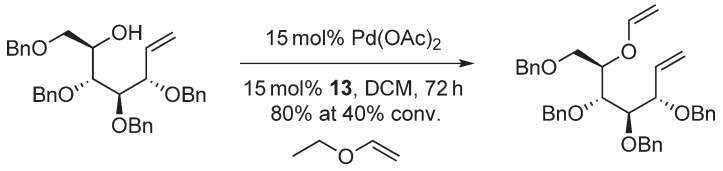


(16)

Similar to the Cu-catalyzed cases, the Pd-catalyzed cross-coupling reaction has also been extended to *O*-vinylation. Under $Pd(PPh_3)_4$ catalysis, certain vinyl bromides underwent cross-coupling with either Bu_3SnOMe or Bu_3SnOEt, but the success of these reactions was highly substrate dependent.[112] More promising results have been reported using vinyl triflates, where a range of phenols of varying electronic nature underwent *O*-vinylation (Equation (17)).[113] The use of Pd(II) catalysts in conjunction with the phenanthroline-based ligands **13**[114] and **16**[115] has led to the transfer vinylation of aliphatic alcohols with ethyl or propyl vinyl ether (Equation (18)).[116]

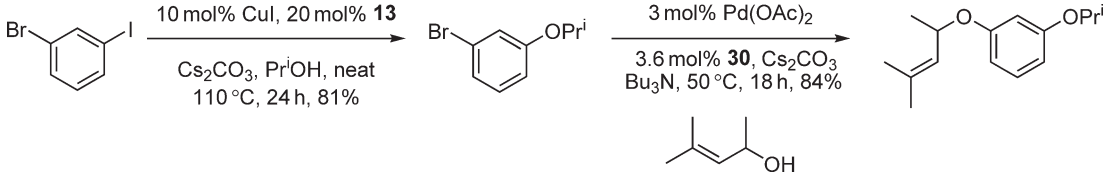


(17)

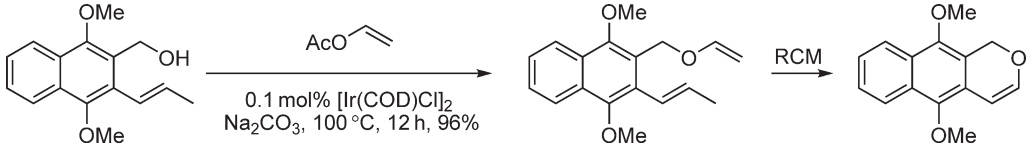


(18)

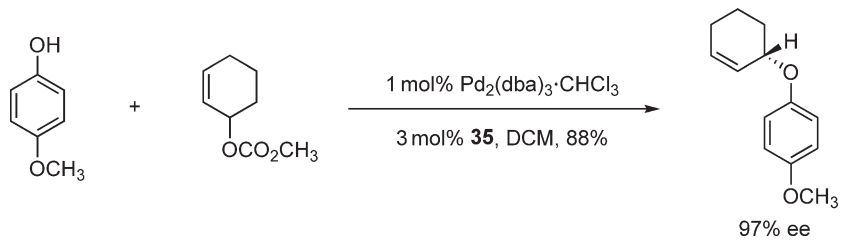
Another system for transfer vinylation has utilized $[Ir(COD)Cl]_2$ as the catalyst, and was applicable to the preparation of vinyl ethers from the reactions of aliphatic alcohols with vinyl acetate (COD = 1,4-cyclooctadiene; Scheme 4).[117] This protocol has been used for the preparation of chromenes by a vinylation–ring-closing metathesis sequence (Equation (19)).[118]



Scheme 3



Scheme 4



(19)

10.14.3 Allylic Etherification

10.14.3.1 Etherification with π-Allylmetals Generated from Allylic Alcohol Derivatives

Although transition metal-catalyzed allylic alkylation has become one of the most powerful methods in chemical synthesis, the formation of ether bonds using this process has been slow to evolve.[119–121] The main reasons for this disparity are the lower nucleophilicity and higher basicity of oxygen nucleophiles, particularly those derived from aliphatic alcohols, compared to their carbon or nitrogen analogs. However, this notion has rapidly been revised, as recent advances in the *O*-allylation area have largely addressed the issue of the reactivity mismatch between the hard alkoxide and the soft π-allylmetal species to provide a considerable body of literature.

10.14.3.1.1 *O*-allylation of phenols

The early examples[121] of allylic etherification mainly involved the *O*-allylation of phenols owing to the soft nature of the phenolic nucleophiles relative to aliphatic alkoxides. Particularly significant is the catalyst system developed by the Trost group that has realized great success in a variety of enantioselective allylic etherification reactions using the C_2-symmetric ligand **35** (Figure 4). For example, high ee's have been achieved using this ligand in the reactions of a range of phenols with various chiral racemic allylic carbonates through deracemization processes (Equation (19)).[122] The utility of these intermolecular etherifications has been demonstrated in the syntheses of a number of natural products, including galanthamine,[123,124] and codeine and morphine.[125]

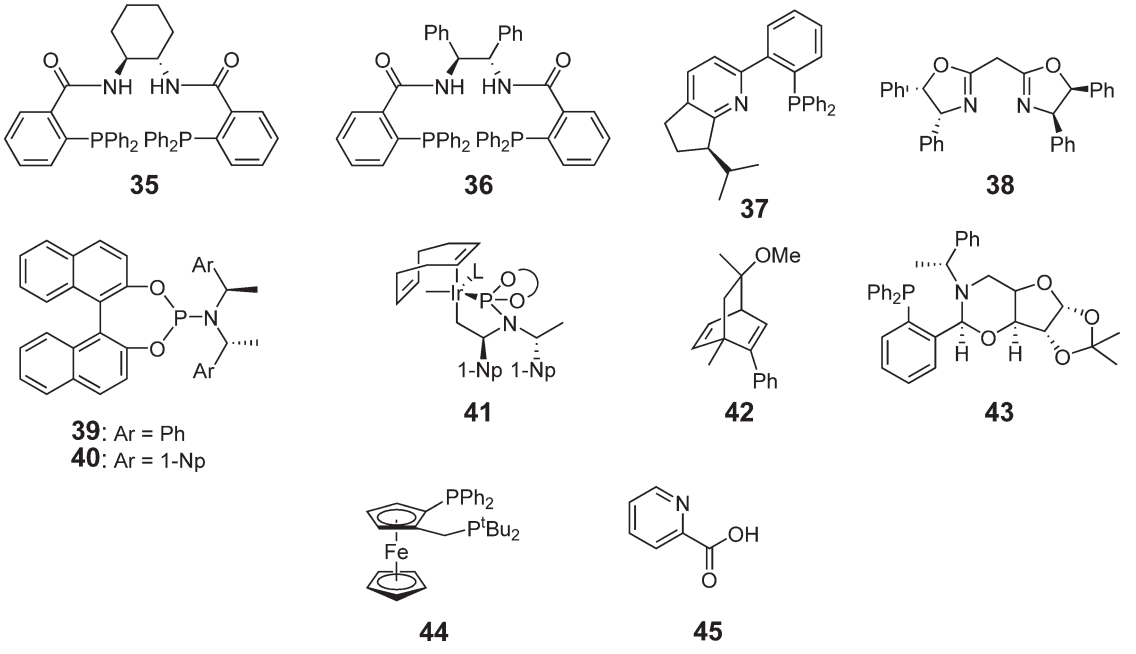
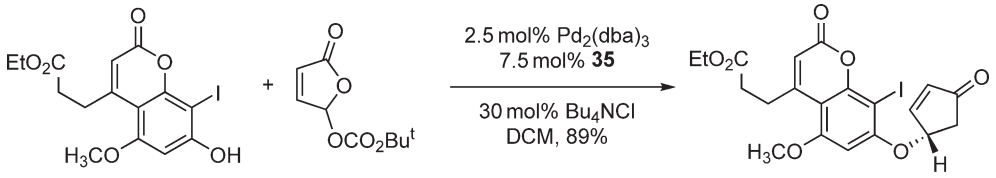
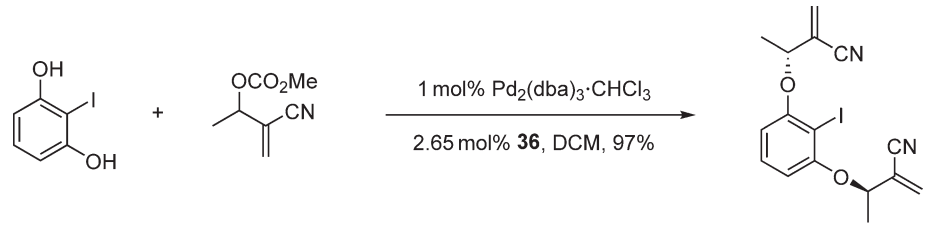


Figure 4 Recently developed ligands for transition metal-catalyzed allylic etherification.

Attaining both regio- and enantioselectivity in unsymmetrically substituted allylic systems has been a challenging problem, but the ligand has played an important role in controlling both of these aspects (Equations (20)–(22)).[126–129] Examples of the difficulties of employing unsymmetrical allylic carbonates can be found in the syntheses of calanolides A and B,[130] callipeltoside A,[131,132] and ustiloxin D (Equation (22)).[133,134]



(20)



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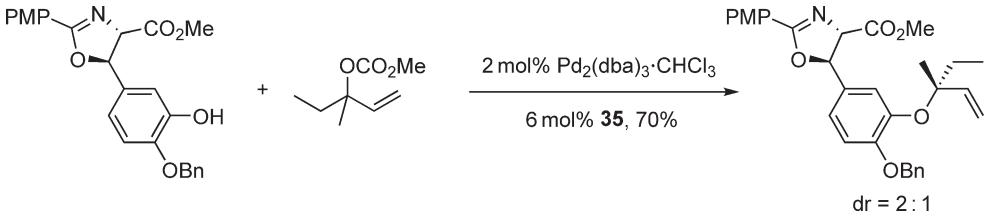
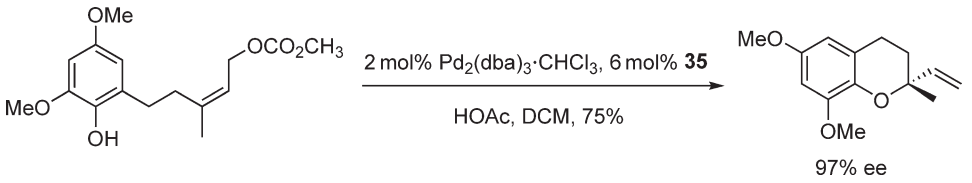


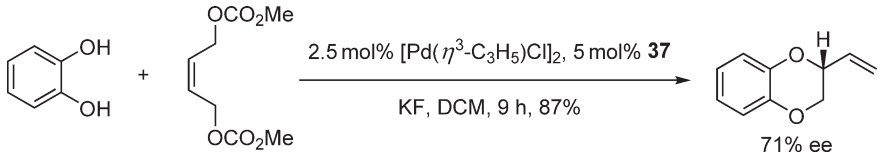
(22)

Due to the inherently fast rate of bond formation in intramolecular reactions, etherification reactions have frequently been carried out through cyclization in order to achieve high degrees of regio- and stereocontrol. This has been demonstrated in the synthesis of the chroman core of vitamin E, where the intramolecular allylic etherification gave the product as a single regioisomer in 97% ee (Equation (23)),[135,136] whereas the analogous intermolecular reaction provided the core with only 77% ee.[130]



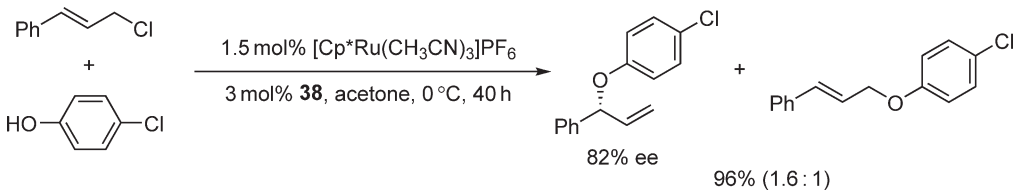
(23)

This intramolecular etherification approach has successfully been applied to the syntheses[136] of siccanin[137] and clusifoliol,[136] and a formal synthesis of morphine.[138] Examples of tandem inter- and intramolecular etherification reactions have also been reported which convert catechol and *o*-aminophenol derivatives into benzodioxins (Equation (24)),[139–141] benzodioxepines,[142] and morpholines.[139,140]



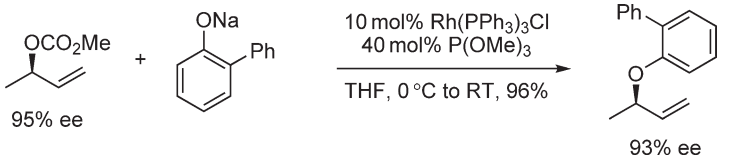
(24)

Although palladium catalysts have played the most prominent role in this area, other metals have also been found to catalyze allylic etherification reactions, often providing complementary stereochemical outcomes. A few ruthenium catalyst systems have been used for the *O*-allylation of phenols,[143,144] including an enantioselective version utilizing $[Cp^*Ru(MeCN)_3]PF_6$ that provides promising ee's, albeit with diminished control of regioselectivity (Equation (25)).[145]

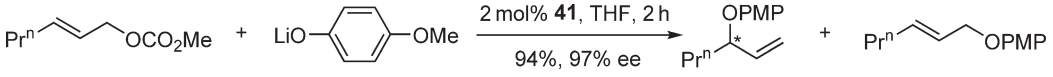


(25)

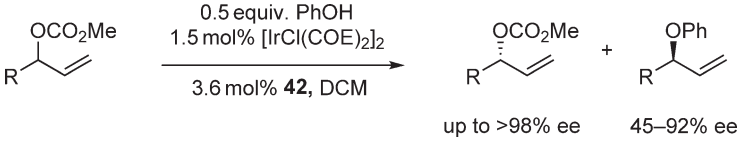
Rh and Ir catalysts have frequently been used for the allylic alkylation of phenoxides with monoalkyl-substituted allylic substrates, since these catalyst systems induce the formation of the branched regioisomer as the major or often exclusive product. For example, a highly regio- and enantiosepecific etherification of phenols has been accomplished using Wilkinson's catalyst and $P(OMe)_3$ as ligand (Equation (26)).[146] In a similar fashion, an Ir catalyst generated from $[Ir(COD)Cl]_2$ and the phosphoramidite ligand **39** was found to be capable of producing the branched product with high levels of chiral induction (Equation (27)).[147] This catalyst system has been further refined by the identification of an active iridium complex **41** and fine-tuning of the ligand.[148] An interesting use of the novel chiral diene ligand **42** has also been reported in which kinetic resolution of allylic carbonates is achieved with high selectivity by an Ir-catalyzed allylic etherification of phenols (Equation (28)).[149]



(26)



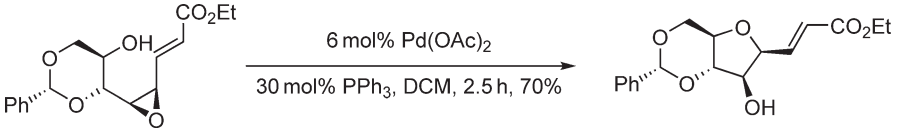
(27)



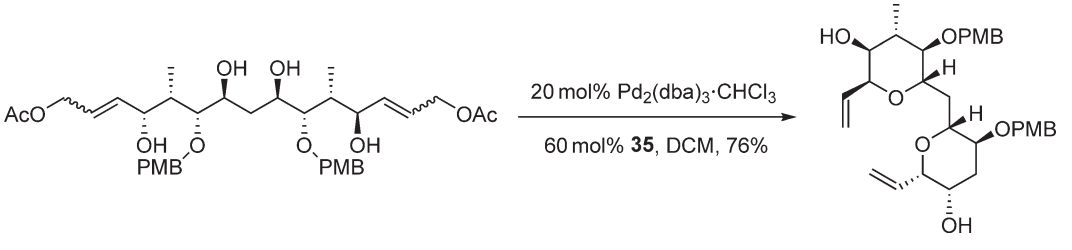
(28)

10.14.3.1.2 *O*-allylation of aliphatic alcohols

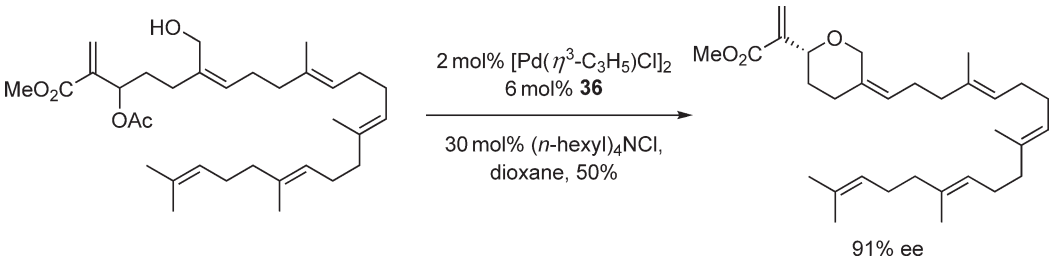
While the notion that the alkoxides derived from aliphatic alcohols are poor nucleophiles toward π-allylmetal complexes has prevailed over the years, much progress made in the recent past has rendered the transition metal-catalyzed allylic alkylation a powerful method for the *O*-allylation of aliphatic alcohols. In particular, owing to the facility of five- and six-membered ring formation, this process has found extensive utility in the synthesis of tetrahydrofurans (THFs) (Equation (29))[150–156] and tetrahydropyrans (THPs).[157–159] Of note was the simultaneous formation of two THP rings with high diastereoselectivity via a Pd-catalyzed double allylic etherification using **35** in a bidirectional synthetic approach to halichondrin B (Equation (30)).[157] The related ligand **36** was used in the enantioselective cyclization of a Baylis–Hillman adduct with a primary alcohol (Equation (31)).[159]



(29)

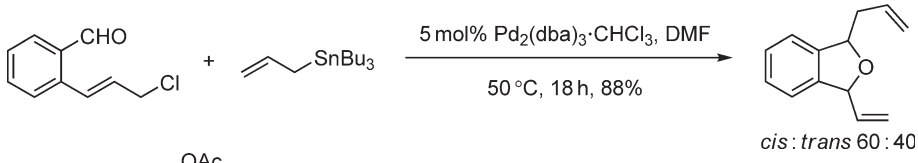


(30)

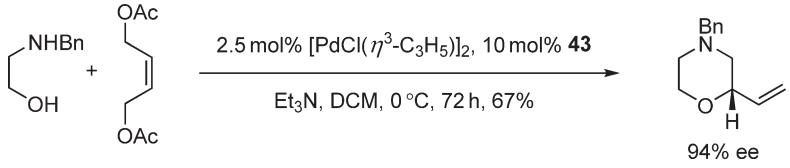


(31)

Pd-catalyzed intramolecular etherification reactions of aliphatic alcohols have also been practiced in tandem with other bond-forming processes, such as a Pd-catalyzed allyltin addition to an aldehyde (Equation (32)).[160] Similarly, a tandem C–N and C–O bond formation sequence occurs (Equation (33)) during the reactions of β-amino alcohols with biscarbonates in the presence of the *N*,*O*-acetal-derived ligand **43**.[161–163]

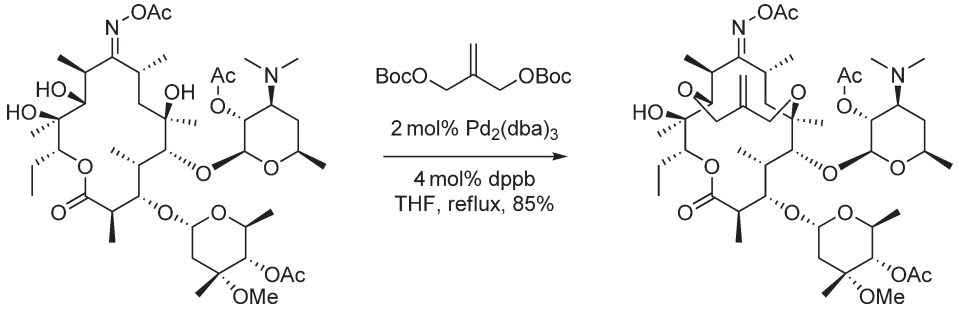


(32)



(33)

In rare cases, the Pd-catalyzed intramolecular allylic etherification has been extended to the construction of medium-sized rings. Both an 11-membered bis-ether ring (Equation (34))[164] and an eight-membered ether ring (Equations (35) and (36))[155] have been prepared in this fashion. In the latter case, the choice of ligand dictated the regiochemical outcome.



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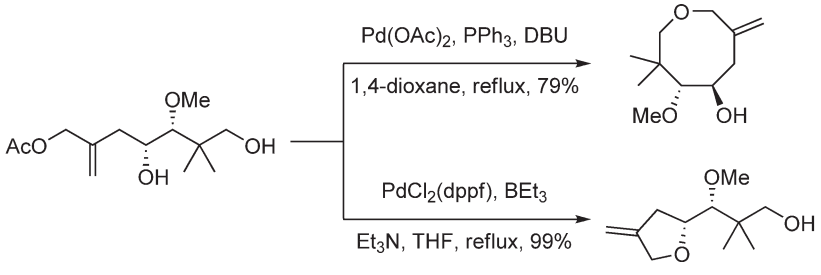
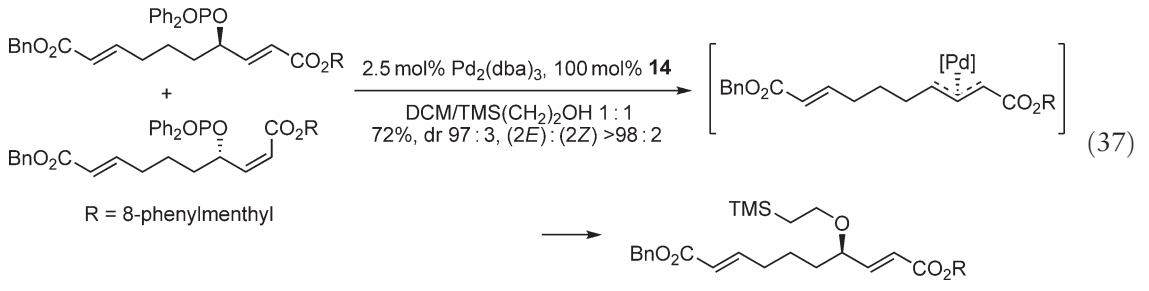


(35)

(36)

Due to the poor nucleophilicity of aliphatic alkoxides, the intermolecular *O*-allylation of aliphatic alcohols has been performed, for the most part, using a large excess of structurally simple primary alcohols (Equation (37))[165] and/or unsubstituted allylic substrates.[166,167] When allylic systems activated with an electron-withdrawing substituent were employed, only a slight excess of the alcohol was necessary to achieve complete stereospecificity, as exemplified by Equation (38).[168,169]



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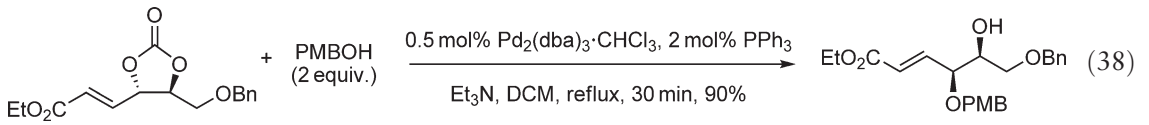
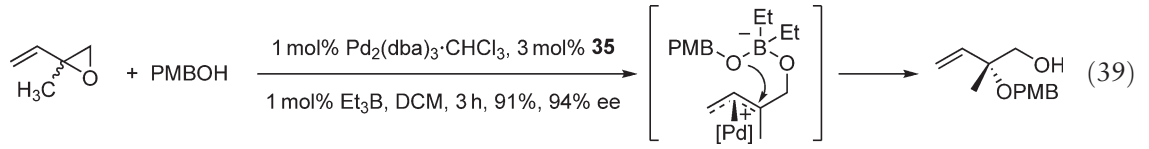
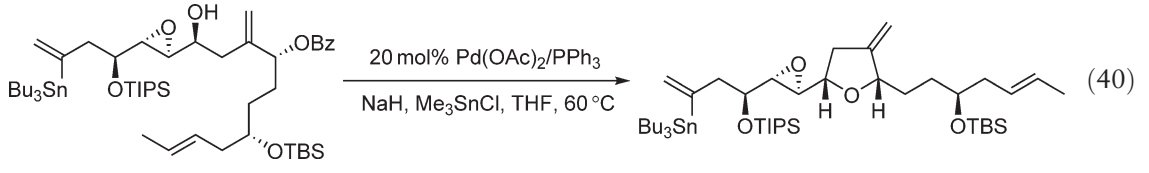


(38)

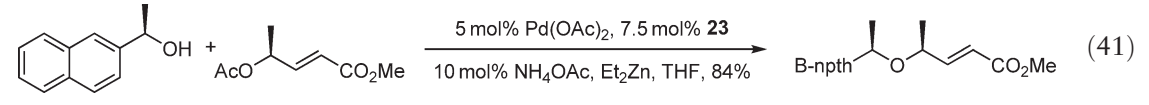
However, more general protocols involve modulation of the hardness of the alkoxide anions to enhance their reactivity toward π-allylmetal cations. Along this line, a temporary borate linker has been used to effect the highly enantio- and regioselective etherification of a wide range of alcohols with vinyl epoxides under palladium catalysis (Equation (39)).[170–174] This internal delivery approach via an "ate" complex affords the ether linkage of a more hindered alcohol leaving a primary alcohol unprotected. Similarly, trialkyl borates react with allylic carbonates to provide the corresponding branched alkyl ethers.[175] Tin alkoxides have also been used in the allylic etherification with aliphatic alcohols as a method for softening the basicity of the alkoxide. An example of the use of this approach has been reported in an intramolecular cyclization to form a THF unit of amphidinolide K (Equation (40)).[156] In addition to tin, the use of Zn(II) alkoxides as nucleophiles in the presence of $Pd(OAc)_2$ and ligand **23** has shown broad utility, giving rise to various ether linkages with high stereospecificity (Equation (41)).[176]



(39)

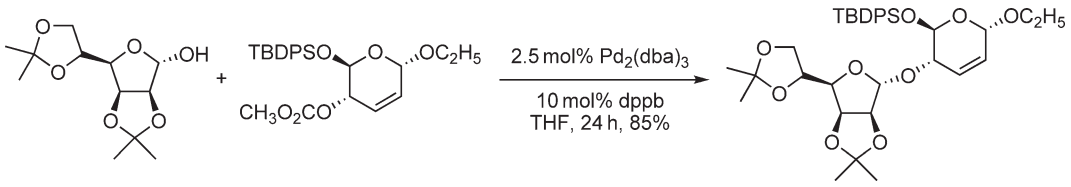


(40)

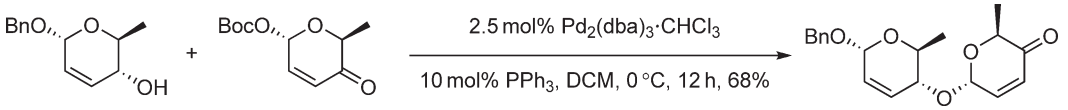


(41)

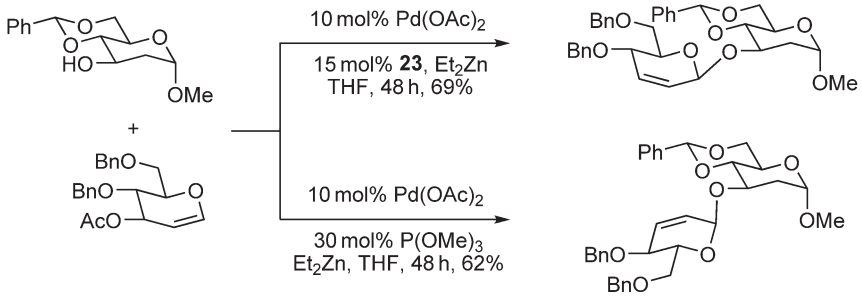
While the Pd-catalyzed allylic etherification of anomeric alcohols has been explored for the synthesis of 1,4-disaccharides (Equation (42)),[177–180] a more general glycosylation has been accomplished through allylic etherification with pyranone derivatives (Equation (43)).[181,182] Together with post-glycosylation functionalization reactions, this approach has served as an efficient strategy for the *de novo* synthesis of oligosaccharides.[183] When zinc alkoxides were employed as glycosyl acceptors, their reaction with glycal-derived glycosyl donors under Pd catalysis furnished disaccharides with high stereoselectivities (Equations (44) and (45)).[184] Notably, the stereochemistry at the anomeric center was dictated by a simple choice of the ligand used.



(42)



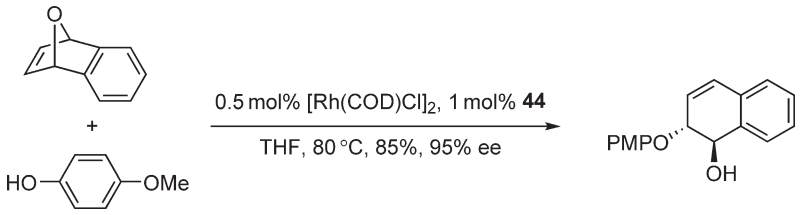
(43)



(44)

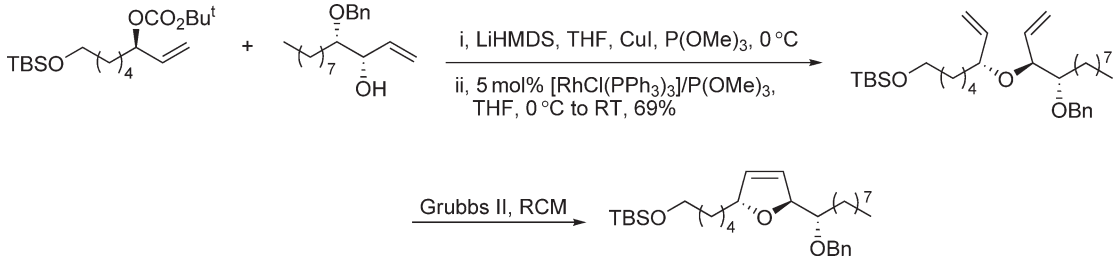
(45)

Rhodium catalysts have also been used with increasing frequency for the allylic etherification of aliphatic alcohols. The chiral π-allylrhodium complexes generated from asymmetric ring-opening (ARO) reactions have been shown to react with both aromatic and aliphatic alcohols (Equation (46)).[185–188] Mechanistic studies have shown that the reaction proceeds by an oxidative addition of Rh(I) into the oxabicyclic alkene system with retention of configuration, as directed by coordination of the oxygen atom, and subsequent S_N2' addition of the oxygen nucleophile.[189]



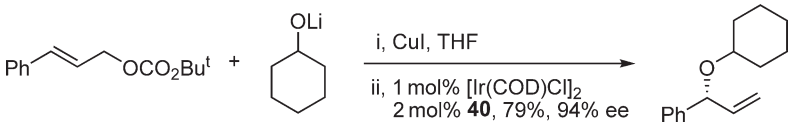
(46)

Another Rh-catalyzed protocol that has potentially broad utility has come from the reactions of Cu(I) alkoxides with allylic carbonates.[190,191] Under the action of Wilkinson's catalyst modified by $P(OMe)_3$, a variety of primary, secondary, and even tertiary aliphatic alcohols undergo an allylic etherification process with a high degree of retention of regio- and stereochemistry, thus providing expeditious access to α and/or α'-stereogenic ether linkages (Scheme 5).[192]



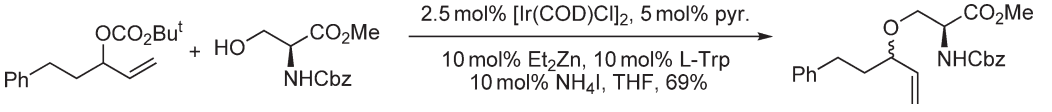
Scheme 5

The enantioselective preparation of dialkyl ether linkages conjoining α-stereogenic centers has also been achieved through iridium catalysis (Equation (47)).[193] Thus, the complex derived from $[Ir(COD)Cl]_2$ and phosphoramidite ligand **40** promotes the allylation of Cu(I) alkoxides with prochiral allylic substrates to give the corresponding branched allylic ethers with high ee's.



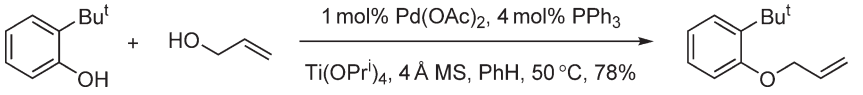
(47)

A two-component bimetallic catalytic system has been developed for the allylic etherification of aliphatic alcohols, where an Ir(I) catalyst acts on allylic carbonates to generate electrophiles, while the aliphatic alcohols are independently activated by Zn(II) coordination to function as nucleophiles (Equation (48)).[194] A cationic iridium complex, $[Ir(COD)_2]BF_4$,[195] and an Ru(II)-bipyridine complex[196] have also been reported to effectively catalyze the *O*-allylation of aliphatic alcohols, although allyl acetate and MeOH, respectively, are employed in excess in these examples.



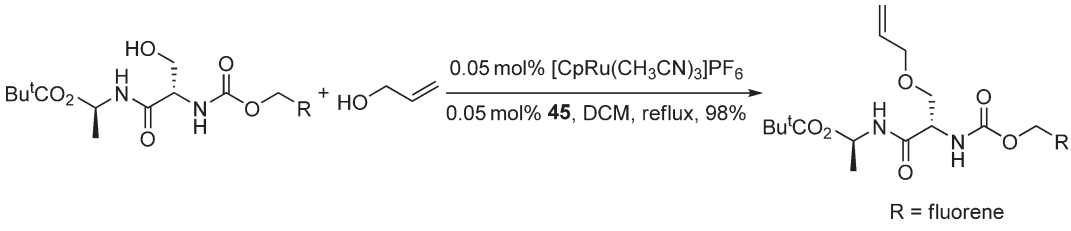
(48)

Although the majority of allylic etherification reactions have primarily utilized allylic carboxylates or carbonates as electrophiles (and occasionally allylic chlorides), the use of allylic alcohols for this transformation would be more desirable from a practical standpoint. Reported strategies involving Pd catalysis include the use of $P(OPh)_3$ as the ligand[197] and $Ti(OPr^i)_4$[198] as an additive for the *in situ* activation of the hydoxyl group (Equation (49)).[199]



(49)

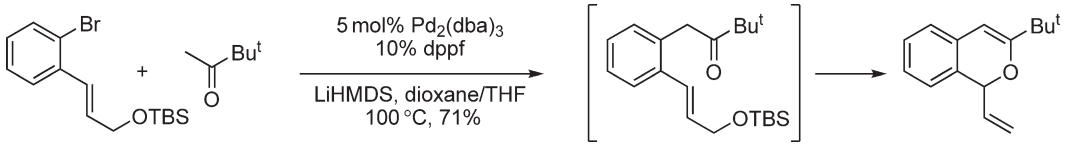
Ruthenium catalysts have also been used in this context.[200,201] In particular, the cationic ruthenium complex, $CpRu(CH_3CN)_3PF_6$, in conjunction with carboxylic acid ligand **3**, has been used to achieve the remarkably chemoselective allylation of a variety of alcohols via dehydrative condensation with allyl alcohol (Equation (50)).[202] It is worth noting that this transformation proceeds with 0.05 mol% catalyst loading and does not require the use of excess allyl alcohol.



(50)

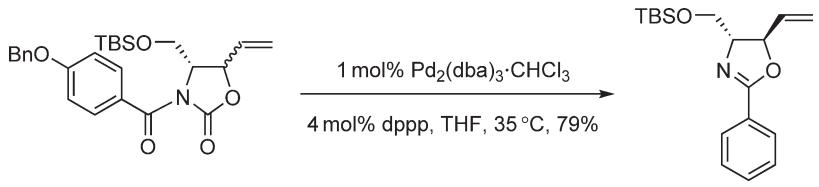
10.14.3.1.3 Allylation of other oxygen nucleophiles

In addition to alkoxides, carbonyl oxygens have occasionally been recruited to function as nucleophiles in allylic etherification processes. The cyclization reactions of ketones containing internal allylic systems occur through *O*-allylation under Pd catalysis to give rise to vinyl dihydrofurans[203] or vinyl dihydropyrans (Equation (51))[204,205] in good yields.



(51)

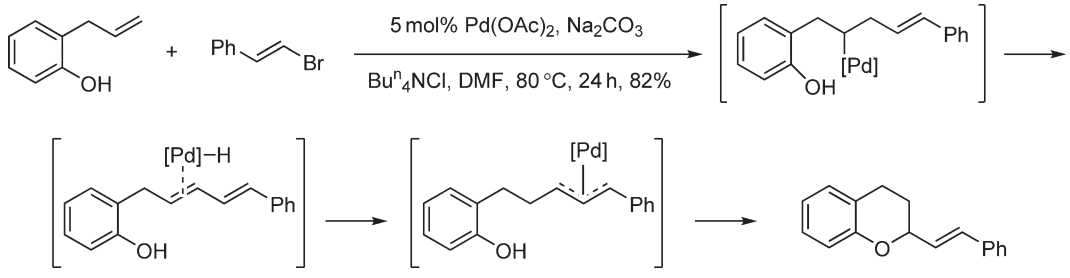
Similarly, amides react with an intramolecular π-allylpalladium through the carbonyl oxygen to form oxazolines in good yields.[206,207] An approach using 5-vinyloxazolidinones as precursors provides oxazolines via a sequence involving generation of a π-allylpalladium, decarboxylation, and *O*-allylation (Equation (52)).[208,209]



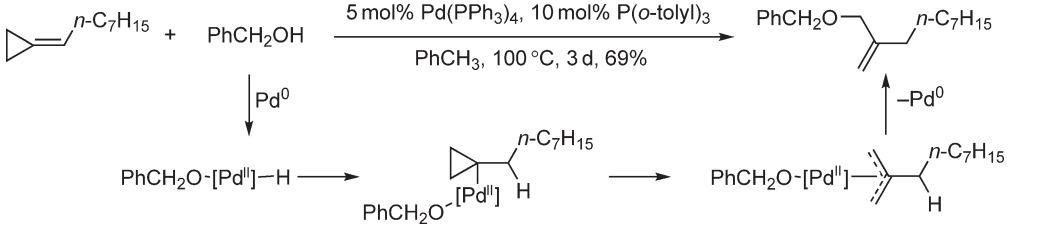
(52)

10.14.3.2 Etherification through π-Allyl Intermediates Generated by Other Means

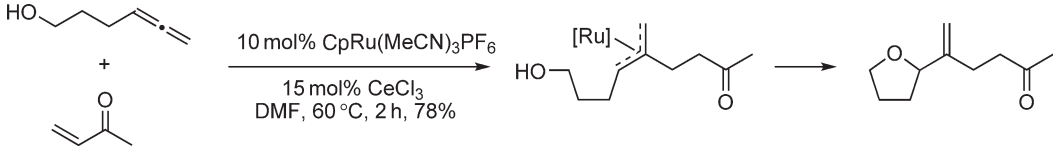
The π-allylmetals required for allylic etherification can emanate from reactions other than by the ionization of an allylic system (Equations (53)–(55)). For example, an assortment of ether linkages has been prepared from interrupted Heck processes in which the incipient σ-palladium arising from an initial migratory insertion undergoes β-H elimination and re-addition to generate a π-allyl species (Equation (53)).[210–217] Similar transformations have been reported utilizing alkylidene cyclopropanes, where β-H insertion leads to cyclopropylpalladium species that undergo ring opening to afford π-allyl intermediates; these then give allylic ethers by the reductive elimination of metal-coordinated alkoxides (Equation (54)).[218] Similarly, π-allyl intermediates have also been formed in the Ru(II)-promoted couplings of allenes with α,β-unsaturated ketones, and if alcohols are present in the substrate, intramolecular etherification can occur to provide THFs or THPs (Equation (55)).[219]



(53)



(54)

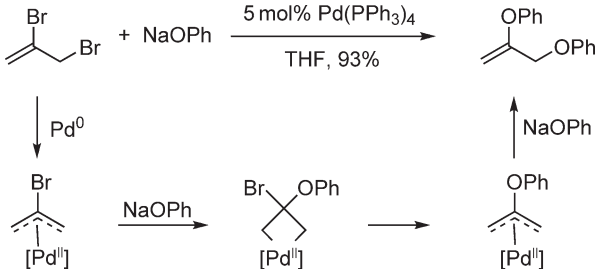


(55)

10.14.3.3 Etherification with Addition to the Central Carbon of a π-Allyl Species

Although unusual, a nucleophile has occasionally been observed to add to the central carbon of a metal π-allyl species to generate a metallacyclobutane intermediate, which can then undergo further transformations. In the reaction between 2,3-dibromopropene and sodium phenoxide under Pd catalysis (Equation (56)), the central carbon of the initially formed π-allyl intermediate is attacked by phenoxide to furnish a palladacyclobutane. Displacement of the

remaining bromide then regenerates a π-allyl species, which can accept another molecule of phenoxide to give the final product.[220] A related transformation using a platinum catalyst has also been reported.[221,222]



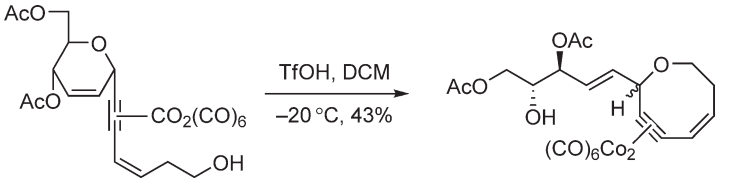
(56)

10.14.4 Propargylic Etherification

10.14.4.1 Cobalt-mediated Propargylic Etherification

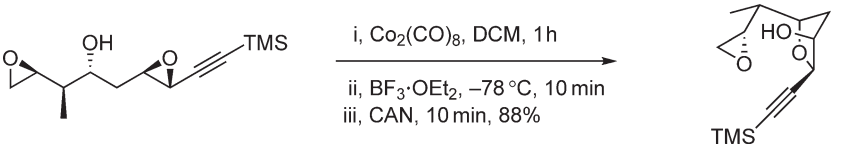
One of the most useful methods for propargylic substitution is the Nicholas reaction,[223–226] in which a propargylic leaving group can undergo a displacement process with a variety of nucleophiles by activation through cobalt complexation in the presence of a Lewis[227–229] or Brønsted[230–232] acid. The major limitations of this reaction, despite its well-recognized synthetic value, are the requirements of employing stoichiometric amounts of the cobalt complex and adding two extra synthetic steps (complexation and decomplexation) to accomplish the overall substitution. Nonetheless, the Nicholas reaction has found applications in the synthesis of various cyclic and acyclic propargyl ethers (Scheme 6).[233,234]

A notable feature of the etherification by the Nicholas reaction has been that, owing to the bond angle change caused by cobalt complexation, cyclization processes have enabled the installation of formal carbon–carbon triple bonds within oxacyclic frameworks, thereby lending themselves to efficient syntheses of these subunits in ladder toxins (Equation (57)).[231,232,235]

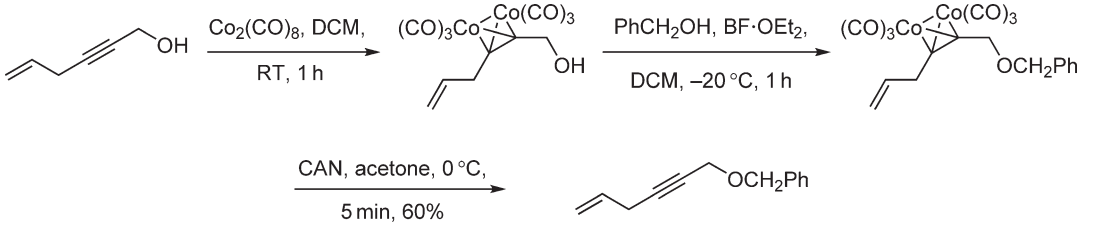


(57)

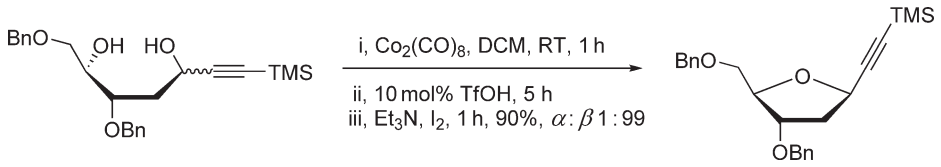
The more general use of the Nicholas process has typically involved the formation of five- and six-membered cyclic ethers through propargylic activation by cobalt complexes exogenous to the ring systems (Equations (58) and (59)).[230,236,237] These processes have also been carried out through epoxide openings that occur with complete *endo*-selectivity and high stereospecificity.[238–241]



(58)

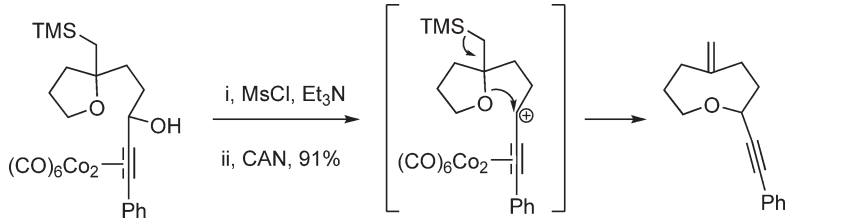


Scheme 6

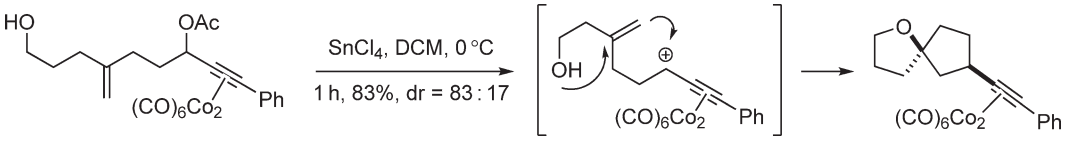


(59)

The high reactivity of the cobalt-complexed propargylic systems has also allowed for ether oxygens to serve as nucleophiles, which has led to the fashioning of medium-sized ring ethers via ring expansion (Equation (60)), and also to the formation of oxa *spiro*-skeletons by tandem C–C and C–O bond formation sequences (Equation (61)).[242,243] Not surprisingly, the cobalt-complexed ether products obtained by the Nicholas reaction can be subjected directly to the Pauson–Khand sequence (Scheme 7).[244]



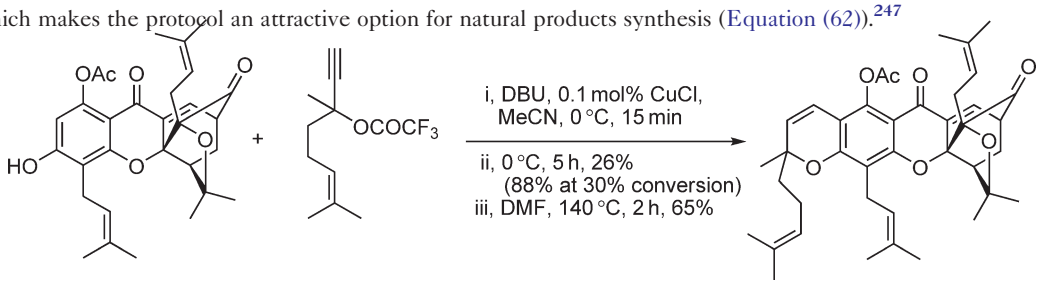
(60)



(61)

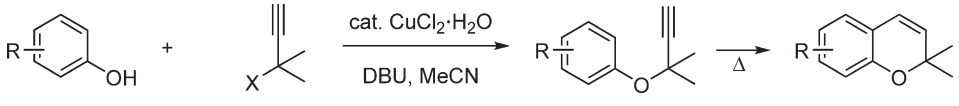
10.14.4.2 Transition Metal-catalyzed Propargylic Etherification

Important advances in propargylic etherification have come from the use of copper-based systems that achieve efficient, catalytic *O*-progargylation of phenols (Scheme 8).[245,246] While the mechanism of this transformation remains unclear, the products of these reactions have been readily converted into chromenes through subsequent Claisen rearrangement, which makes the protocol an attractive option for natural products synthesis (Equation (62)).[247]



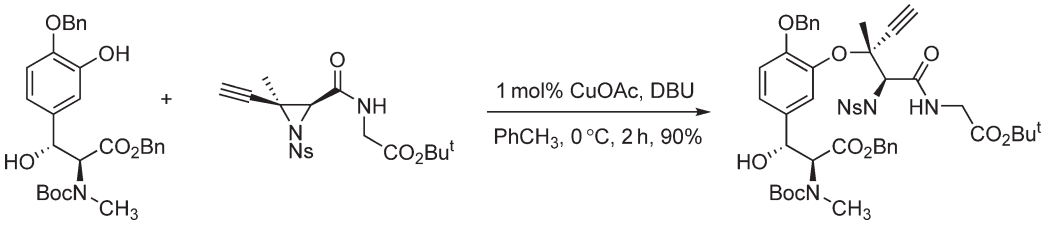
(62)

Scheme 7



Scheme 8

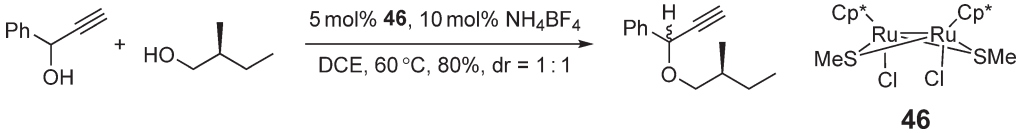
An application of copper-catalyzed propargylic etherification has been reported in the synthesis of ustiloxin D (Equation (63)).[248] Here, a quaternary center was generated from the unprecedented reaction of a phenol with an ethynyl aziridine.



(63)

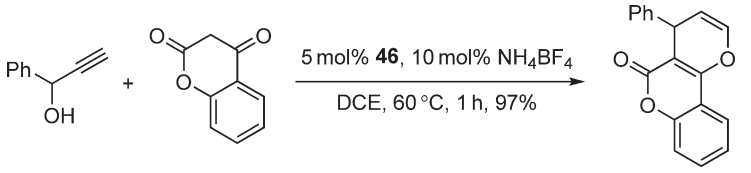
The propensity of propargylic systems to form allenylidene complexes with transition metals has also been harnessed for the development of catalytic *O*-propargylation processes (Scheme 9). Mechanistic studies suggest that the metal complexation of a terminal acetylene possessing a leaving group may induce the formation of a metal allenylidene intermediate whose α- and γ-carbons are electrophilic. Subsequent attack of an oxygen nucleophile at the γ-carbon leads to the generation of a vinylidene, which can then isomerize back to the corresponding alkyne complex and release the propargylic ether product.

The novel thiolate-bridged dinuclear Ru(III) catalyst **46** has been reported to promote the dehydrative etherification of propargylic alcohols through this type of mechanism (Equation (64)).[249] It appears that only one of the two metal centers is the active catalyst, while the other's function is to assist in charge-transfer processes.[250] With an ambident nucleophile such as a 1,3-diketone, the reaction takes place through a sequence involving initial attack of the active methylene carbon at the γ-carbon of the ruthenium allenylidene, followed by C–O bond formation at the α-carbon (Equation (65)).[251] The mononuclear complex, [Ru(η^3-2-C_3H_4Me)(CO)(dppf)]SbF_6, has also been used for propargylic etherification by this allenylidene mechanism (Equation (66)).[252]

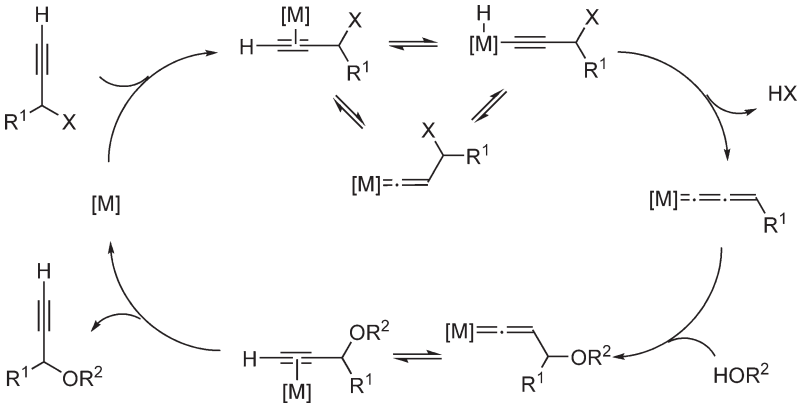


(64)

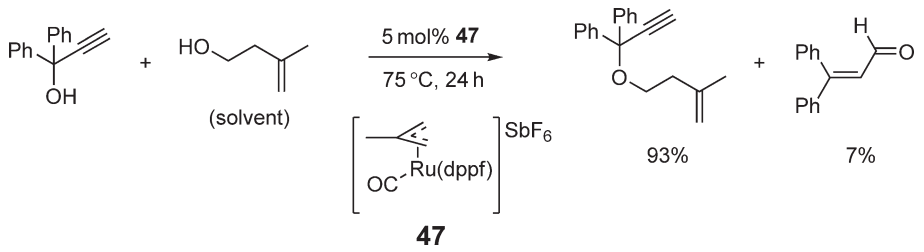
46



(65)

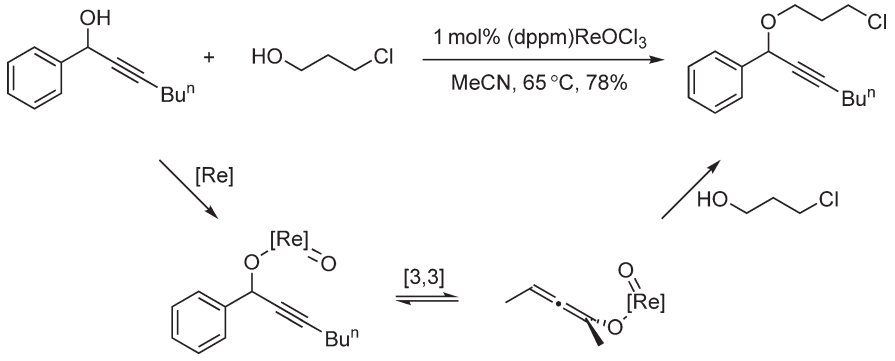


Scheme 9



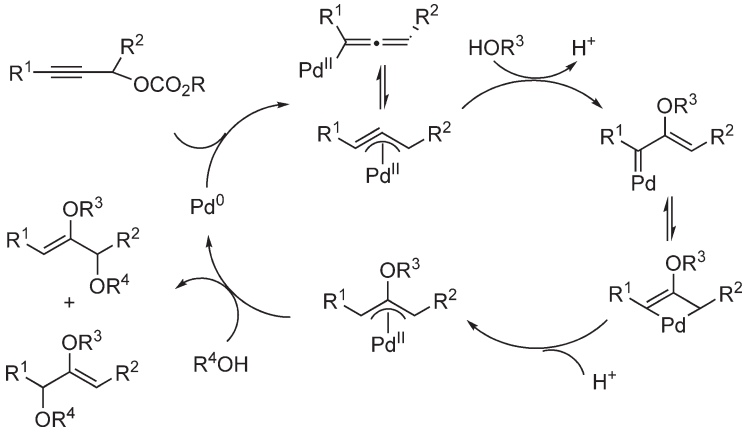
(66)

While most of the transition metal-catalyzed propargylic etherification reactions have been performed with terminal alkyne derivatives through the allenylidene mechanism or with highly activated propargylic substrates through a cationic pathway,[227–229] a novel rhenium catalyst system has been developed which is effective for the *O*-propargylation of internal alkynes (Equation (67)).[253] This reaction has been proposed to proceed by coordination of the alcohol to the rhenium center, followed by [3,3]-rearrangement to the corresponding allenyl rhenium species, and then displacement of the metal in an S_N2' fashion by the incoming alcohol. When an optically active substrate is employed, complete racemization occurs at the propargyl center due to rapid reversible sigmatropic rearrangement prior to C–O bond formation.



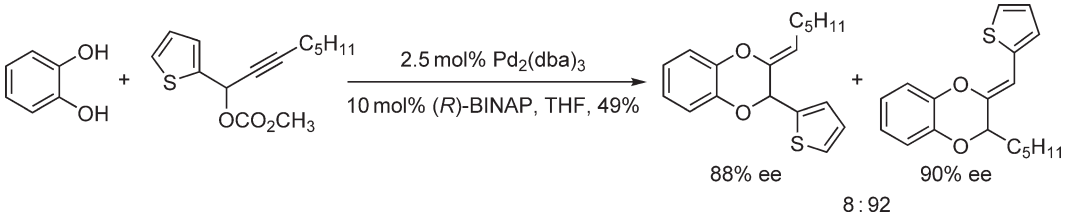
(67)

A different type of reactivity has been observed when propargylic acetates or carbonates are subjected to Pd catalysts in the presence of *O*-nucleophiles (Scheme 10).[254] Oxidative addition of Pd(0) to a propargyl system gives rise to an allenyl-Pd(II) species, in equilibrium with the corresponding π-propargyl species. A nucleophile can then add to the central carbon of this species, generating either a Pd carbene or a palladacyclobutene. A proton transfer then gives a π-allyl intermediate, and addition of a second nucleophile then expels Pd(0) so that the catalytic cycle can propagate further. In principle, one or both of these two can be oxygen nucleophiles, and thus these reactions can lead to the formation of up to two ether bonds.



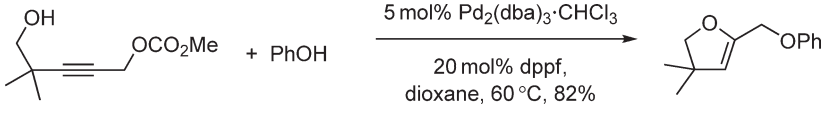
Scheme 10

This type of reactivity has been exploited for the preparation of 1,4-benzodioxanes from catechols and propargylic carbonates. Using 2,2′-bis(diphenylphosphino)-1,1′-binapthyl (BINAP), this process has been rendered asymmetric with ee's up to 97% (Equation (68)).[254,255]

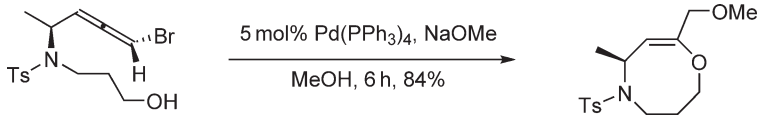


(68)

Propargylic substrates possessing a tethered alcohol have also been employed, leading to consecutive intra- and intermolecular bond formations, in which the propargylic system undergoes simultaneous substitution and addition processes with internal and external nucleophiles (Equation (69)).[256–259] The same types of intermediates have also been obtained by the oxidative addition of Pd(0) to allenyl bromides.[260] It is noteworthy that these reactions have been capable of forming medium-sized oxacycles in high yields through the intramolecular addition of a pendant alcohol to the allenyl palladium and the intermolecular quenching of the π-allylpalladium by methoxide (Equation (70)).



(69)



(70)

10.14.5 Etherification via Ring Opening of Epoxides

The formation of ether bonds by the opening of epoxides with oxygen nucleophiles provides rapid access to synthetically useful, monofunctionalized 1,2-diol systems. This seemingly straightforward approach has, however, been difficult in large part because of the poor nucleophilicity of alcohol nucleophiles. With the exception of facile cyclizations, strong Lewis or Brønsted acids are typically required to activate the epoxides, and the alcohol nucleophiles have frequently been used as the solvent. In the last decade, a number of transition metal-based catalysts have been developed for this important process, largely addressing the issues associated with traditional epoxide-opening reactions. In particular, the emergence of mild and highly efficient chiral catalyst systems has rendered the asymmetric ring-opening reaction a powerful tool for the synthesis of stereogenic ether linkages.[261]

A variety of transition metal catalysts have been employed for epoxide openings by oxygen nucleophiles, and these often exhibit both higher reactivity than the classical Lewis acids and improved functional group tolerance. For example, various iron catalysts have been utilized for the alcoholysis of epoxides with Markovnikov selectivity, including $FeCl_3$,[262] $FeCl_3/SiO_2$,[263] $Fe(ClO)_3$,[264] Fe(III)-montmorillonite,[265] and $Fe(O_2CCF_3)_3$.[266] Similarly, both titanium ($TiCl_3OTf$ and $TiO(O_2CCF_3)_3$)[267] and zirconium (Cp_2ZrCl_2)[268] complexes have been shown to be viable catalysts. A copper-based catalyst has also been used for epoxide openings with alcohols, providing the products with clean inversion of stereochemistry (Equation (71)).[269]

(71)

The most significant development in the etherification using epoxides is the ARO process that occurs through the catalysis of metallosalen complexes (Figure 5).[270] Mechanistic studies that have been carried out on these systems by

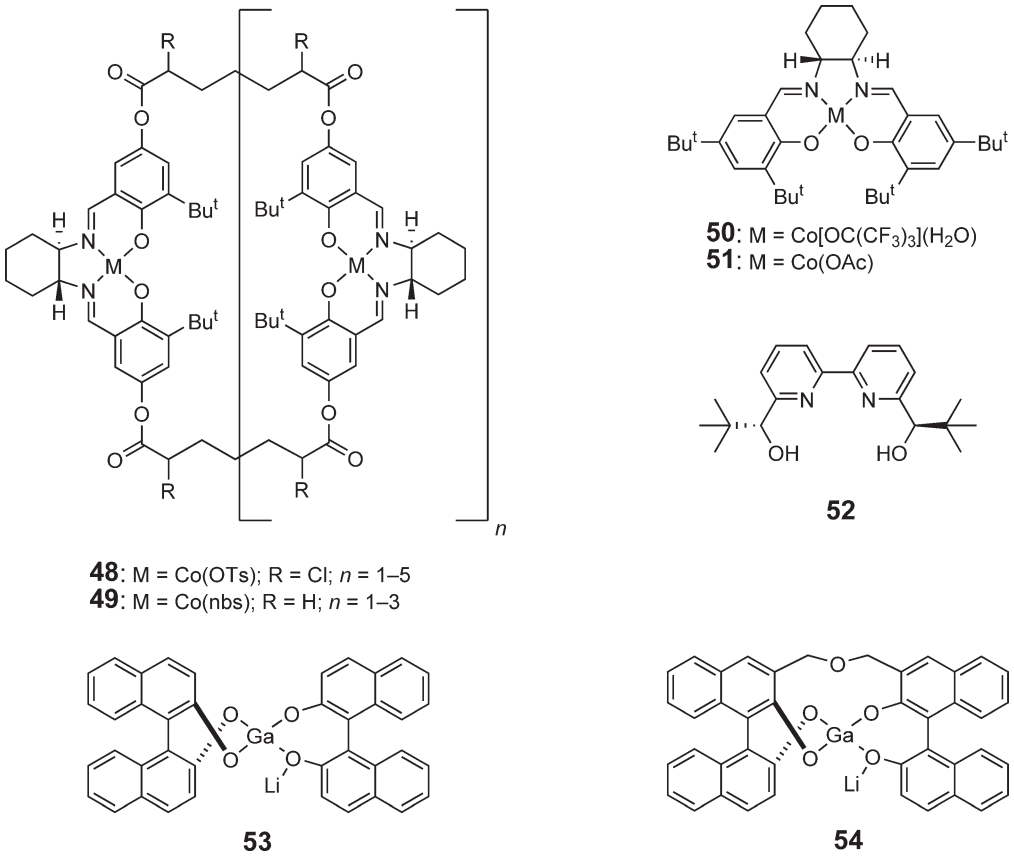
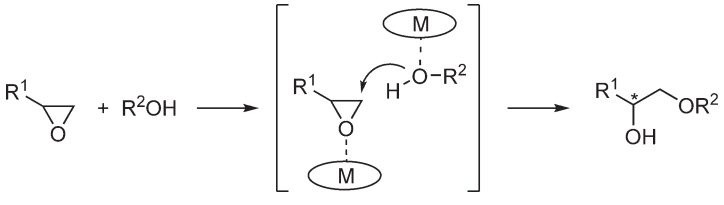


Figure 5 Catalysts and ligands for epoxide opening reactions.

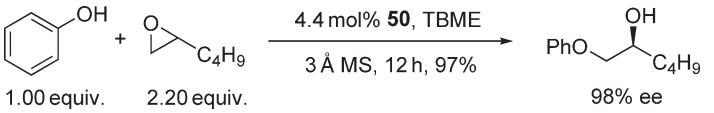
the Jacobsen group have shown that the efficacy of these reactions arises from the dual activation of both the nucleophile and the electrophile by the metal catalyst.[270,271] Furthermore, it has been shown that the reaction proceeds through the interaction of two separate metal centers in a cooperative event (Scheme 11).

The discovery of this bimetallic pathway has led to the design of tethered metal–salen dimers and oligomers **48** and **49**. These catalyst systems have been found to exhibit higher catalytic activity, both in terms of yields and ee's, than their monomeric counterparts **50** and **51**, which provides further evidence for the proposed cooperative bimolecular pathway.

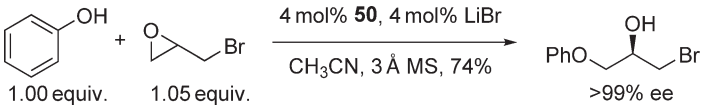
The monomeric Co(III)–salen complex **50** has proved to be an excellent catalyst for the opening of terminal expoxides (Equation (72)).[272] Using both electron-rich and electron-poor phenols as nucleophiles, the kinetic resolution of epoxides has been achieved in high yields and ee's through the formation of aryl alkyl ethers. When this catalyst was used for the ARO reaction of epibromohydrin, a dynamic kinetic resolution was possible simply by adding 4 mol% LiBr to the reaction mixture, owing to the facile racemization of the starting material induced by excess bromide ion (Equation (73)). It was also demonstrated that a polystyrene-immobilized form of this catalyst could be used to rapidly produce a library of 50 ether compounds.[273]



Scheme 11

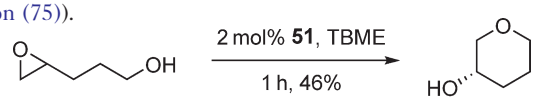


(72)

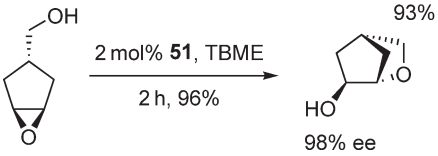


(73)

The kinetic resolution by etherification has also been conducted through the cyclization of epoxy aliphatic alcohols.[274] In these reactions catalyzed by monomeric complex **51**, the ring closure of acyclic substrates occurred with exclusive *endo*-selectivity (Equation (74)), whereas *exo*-openings were observed in the desymmetrization of cyclic *meso*-substrates (Equation (75)).

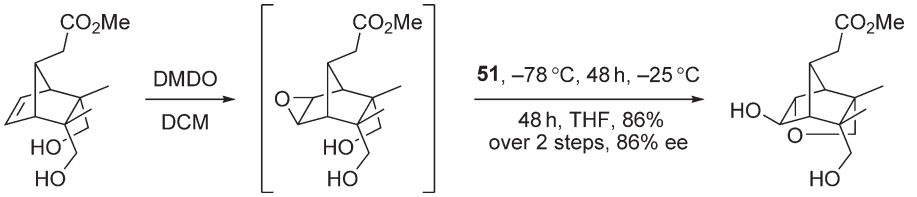


(74)



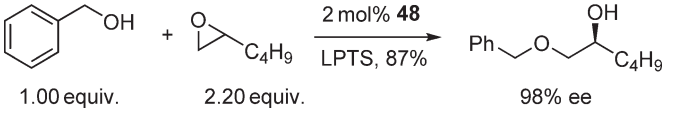
(75)

An elegant application of this protocol has recently been reported, which relied on the desymmetrization of a *meso*-epoxide to produce a key intermediate for the synthesis of merrilactone A (Equation (76)).[275]



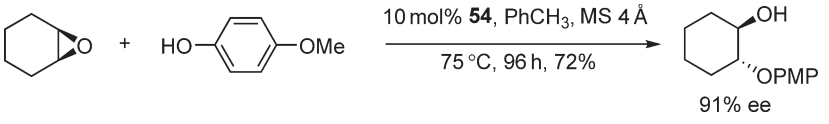
(76)

As mentioned above, since the general mechanistic pathway of the ARO reactions of epoxides has been shown to be bimetallic in character, oligomeric catalysts have been designed with the notion that enforcing several metal centers into close proximity would greatly facilitate their mutual interaction. Indeed, this expectation has been borne out in the kinetic resolution of epoxides with aliphatic alcohols (Equation (77)),[276] and was then further refined with the design of additional oligomeric catalysts **49**,[277] which were shown to be capable of carrying out the kinetic resolution with an eightfold decrease in catalyst loading and a fourfold decrease in reaction time.

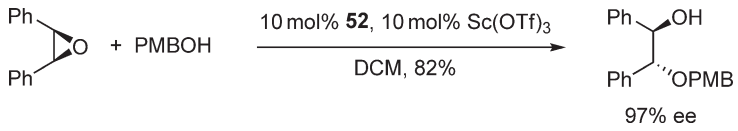


(77)

A heterobimetallic BINOL–Ga/Li complex **53** has been developed for the enantioselective ARO of *meso*-epoxides (BINOL = 1,1′-bi(2-naphthol)).[278] Using *p*-methoxyphenol as the nucleophile, this etherification reaction was observed to take place with a high level of asymmetric induction. An improved catalyst **54** has also been reported that exhibits greater stability under the reaction conditions and delivers higher yields and ee's (Equation (78)).[279] A simple catalyst derived from $Sc(OTf)_3$ and the chiral bipyridine ligand **52** has been shown to be effective for the ARO of aryl-substituted *meso*-epoxides with aliphatic alcohols to give high ee's (Equation (79)).[280]

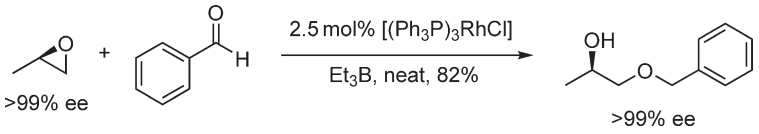


(78)



(79)

Recently, aldehydes have been developed as nucleophiles to open epoxides as a method for the formation of β-hydroxy ether linkages (Equation (80)).[281] This rhodium-catalyzed reductive coupling process effects the regioselective cleavage of the less-hindered C–O bond and transfer hydrogenation of the aldehyde using Et_3B as the hydrogen donor, with epoxide opening having been proposed to occur prior to reduction.



(80)

10.14.6 Etherification of Unsaturated Carbon–Carbon Bonds

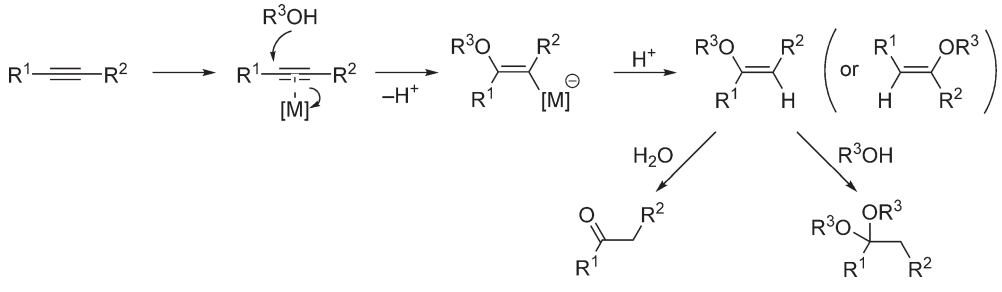
10.14.6.1 Transition Metal-catalyzed Additions of Oxygen Nucleophiles to Alkynes

The transition metal-catalyzed addition of nucleophiles to alkynes is a broad field that has been studied extensively for many years. A number of reviews have recently been published on the subject,[282–285] and thus this section will serve to highlight only the most noteworthy examples of this process in the context of etherification.

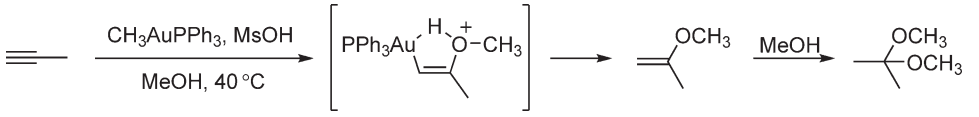
10.14.6.1.1 Inter- and intramolecular hydroalkoxylation

The transition metal-catalyzed hydroalkoxylation reaction of alkynes typically proceeds according to a mechanism consisting of two major steps (Scheme 12). The catalytic cycle is started by coordination of an electrophilic transition metal complex to an alkyne, thus rendering the π-system susceptible to attack by an oxygen nucleophile. The vinyl metal species arising from the nucleophilic addition is then protonated to regenerate the catalyst and release the vinyl ether product, which, depending on the reaction conditions and the nature of the substrate, may undergo ketalization or hydrolysis. Note that this mechanism results in a net *trans*-addition because of the *anti*-attack on the metal-coordinated alkyne.[286] Due to its inherent Markovnikov-type selectivity, the hydroalkoxylation process typically has made use of sterically or electronically biased alkynes to control regioselectivity.

For the intermolecular addition of simple alcohols to activated or terminal alkynes, Pd(II),[287] Pt(II),[287,288] or Ag(I) salts[288,289] and a $PdMo_3S_4$ cluster[290] have been employed, giving rise to vinyl ethers in high yields. These catalyst systems, however, gave mixtures of regioisomeric products when applied to dialkyl-substituted alkyne substrates. Of particular interest are Au(I) catalyst systems that have catalyzed the addition of aliphatic alcohols to unactivated alkynes with TONs as high as 10,000.[291] In these cases, cationic gold species ligated with phosphane, phosphite, or arsine ligands have been proposed to coordinate to alkynes and effect the addition of methanol via a *syn*-insertion pathway (Equation (81)). Good control of regioselectivity has also been observed for the addition of methanol to alkynes using an Ir_2Pd sulfido cluster.[292]

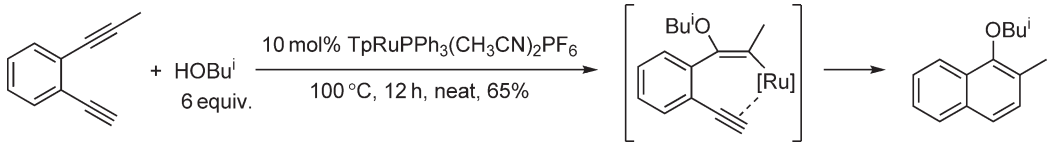


Scheme 12



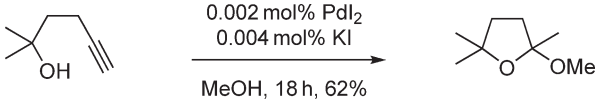
(81)

The vinyl metal intermediate arising from intermolecular nucleophilic addition of an oxygen nucleophile to a metal–alkyne complex has been harnessed for further transformations prior to protonation. An example is the ruthenium-catalyzed benzannulation of 1,5-enedyines that occurs through a tandem sequence involving hydroalkoxylation, carbometallation, and protonation (Equation (82)).[293]

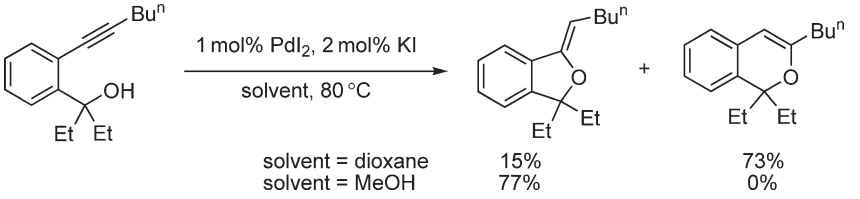


(82)

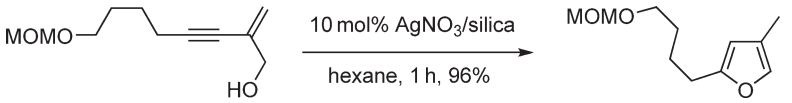
A large number of examples of the intramolecular hydroalkoxylation reaction of alkynes bearing pendant alcohols have been reported. In the reactions of enynols, the cyclization process has typically been accompanied by isomerization of the resulting enol ethers to give rise to furan or pyran products. These processes have been achieved using Pd(II),[294–297] Ru(II),[298,299] Au(I),[300] Au(III),[286,300,301] Ir(I),[302] Ir(III),[303] and Ag(I) [304] catalysts. Some examples are shown in Equations (83)–(87).



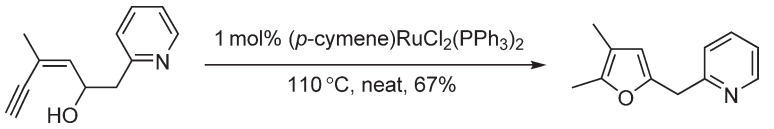
(83)



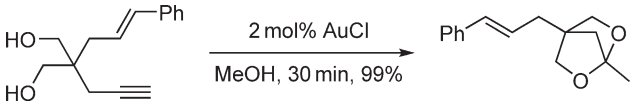
(84)



(85)



(86)

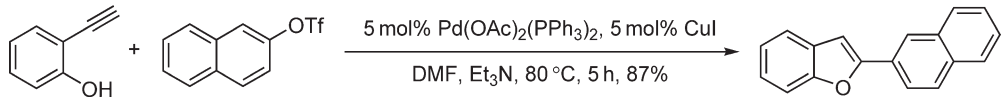


(87)

10.14.6.1.2 Cycloetherification with concomitant C–C bond formation using alkynes

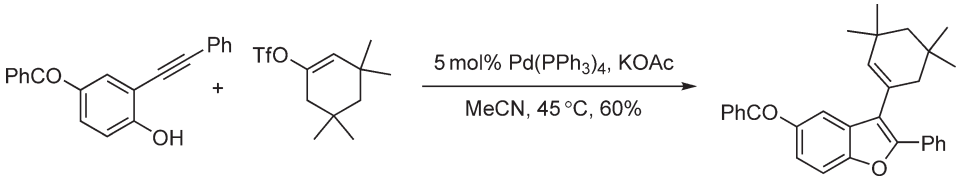
When an alkynyl moiety is prepared by a transition metal-catalyzed reaction, the very catalyst system affecting the C–C bond formation can also promote an efficient intramolecular C–O bond formation when a suitable oxygen nucleophile is present in the substrate. One example following this mechanism that has been reported is the Pd-catalyzed diyne cross-coupling reaction between terminal alkynes and propargyl alcohols, in which the initial enynol products undergo subsequent Pd-promoted cyclization to give furans[305] or dihydropyrans.[306] The Sonogashira reaction of *o*-iodophenols with terminal alkynes under Pd(0)/Cu(I) catalysis has also lead to the formation of benzofurans.[307–309] Based on a similar approach, a variety of structurally diverse 2-substituted benzofurans have been prepared from *o*-ethynylphenols, which undergo the Sonogashira cross-coupling reaction followed by 5-*endo*-ring

closure (Equation (88)).[310,311] A variation of this process has utilized a less expensive $[Cu(phen)(PPh_3)_2]NO_3$ catalyst in place of the usual Pd(0)/Cu(I) system.[312,313] Also of note is that the efficiency of this method has been translated to solid-phase syntheses.[314–316]

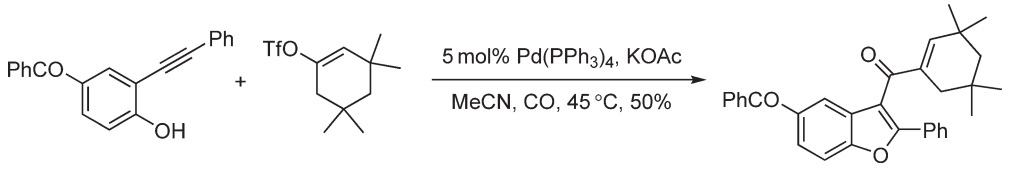


(88)

While the alkoxymetallation process has typically been affected by highly electrophilic metal salts, high-valent metal species generated by an oxidative addition have also been used to activate alkynes through the formation of π-complexes. In such cases, the metal–carbon σ-bond emerging from the attack of an oxygen nucleophile may enter a reaction manifold that leads to an additional C–C bond formation rather than a simple protic quench. This approach, pioneered by Arcadi and Cacci, has proved to be a powerful strategy for the synthesis of structurally diverse substituted benzofurans and has found numerous applications (Equation (89)).[311,317] When CO is incorporated into the reaction, a three-component coupling process occurs to provide 2-ketobenzofurans (Equation (90)).[311,318,319] In addition to benzofurans, benzo- and napthodioxins have also been prepared by this methodology.[320]

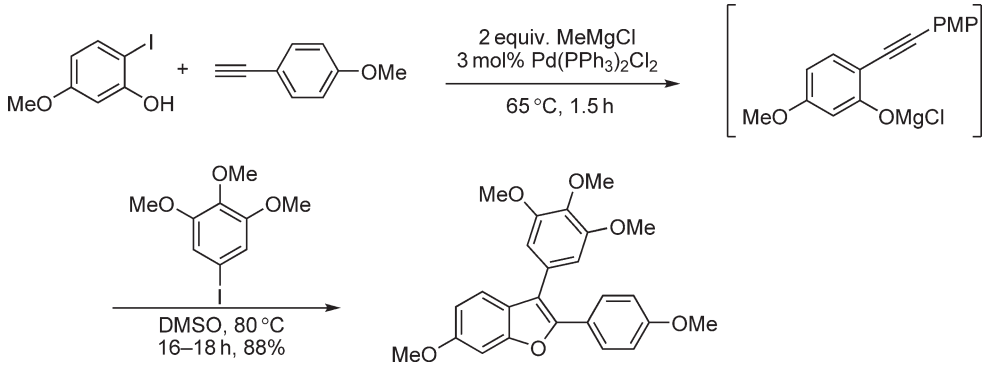


(89)



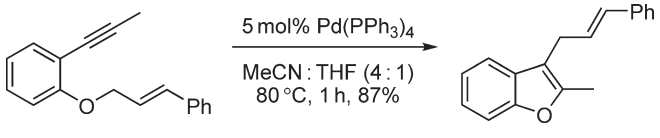
(90)

A common problem that has been encountered in these reactions is the premature cyclization of the intermediate *o*-alkynylphenol to the corresponding 2-substituted benzofuran under the influence of a simple base.[311] One strategy that has been found to suppress this premature cyclization is to deprotonate the phenol with MeMgCl prior to cyclization (Equation (91)).[321,322]

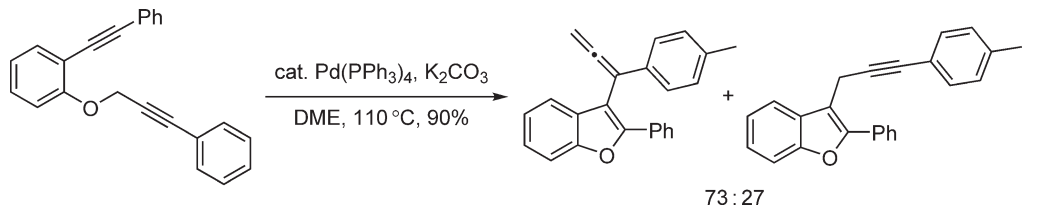


(91)

The high-valent metal species required for activation of an alkyne has also been generated by the oxidative addition to an allylic or propargylic system. For example, with an allyl aryl ether as the substrate, this type of reaction achieves a cycloisomerization that occurs through an *O*- to *C*-allyl migration (Equation (92));[323,324] similarly, *O*-propargyl derivatives lead to a mixture of allenyl and propargyl products (Equation (93)).[325,326]

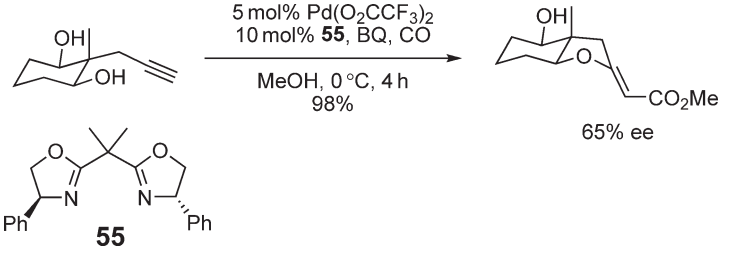


(92)



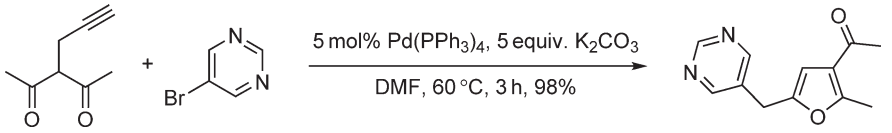
(93)

Another possible termination step that has been utilized for the cycloetherification of alkynols involves CO insertion and esterification of the resulting acyl metal with an exogenous alcohol. This process has typically employed MeOH as solvent and a stoichiometric oxidant since the catalyst is turned over in a reduced form. Following this mechanistic motif, a variety of alkynols have been cyclized under Pd(II) catalysis to five- and six-membered oxacycles with incorporation of methyl esters into the products.[294,327–329] For the formation of five-membered ring products, this reaction has been carried out in both *exo*-[330,331] and *endo*-mode[318,328,329,332–335] to provide 1- and 2-substituted furans. The use of a chiral bisoxazoline ligand gave modest ee's in the 5-*exo*-cyclization reaction of a *meso*-alkynediol (Equation (94)).[336]



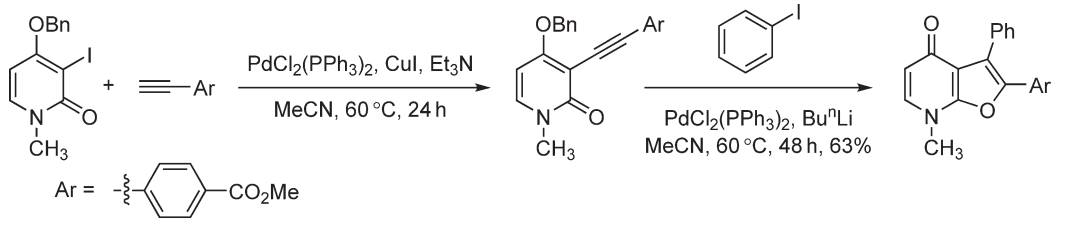
(94)

Aside from alcohols, other oxygen nucleophiles have also participated in hydroalkoxylation reactions with alkynes. The most common of these are 1,3-dicarbonyl compounds, whose enol oxygens are readily available to add to alkynes. Cyclization reactions of this type have been carried out under Pd(0) catalysis with various aryl or vinyl iodides or triflates, often in the presence of CO, affording the corresponding furan derivatives (Equation (95)).[337–340] A similar approach employing cyclic 1,3-diketones has also been reported to prepare THFs and dihydropyrans under Pd, Pt, or W catalysis.[341] Simple 1-alkyn-5-ones have also been isomerized to furans under the influence of $Hg(OTf)_2$.[342]



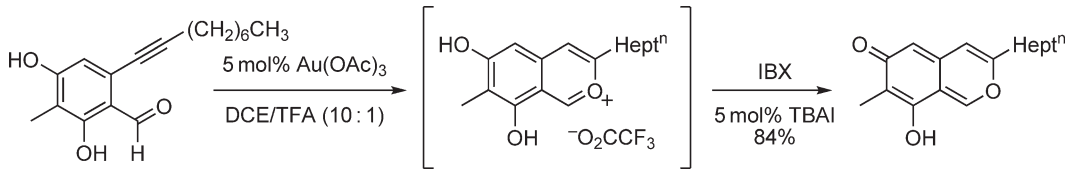
(95)

The carbonyl groups that participate in the alkyne-addition process have not been limited to those that can form enol tautomers. For example, amides have been used as nucleophiles in a one-pot reaction sequence for the preparation of 2,3-disubstituted furanopyridones using Pd catalysis (Equation (96)).[343] Furopyridines have also been obtained from the reaction of iodopyridones with alkynes under Pd catalysis,[344] and alkynyl pyrimidones have been converted into 2-substituted furanopyrimidones under the influence of an $AgNO_3$ catalyst.[345]



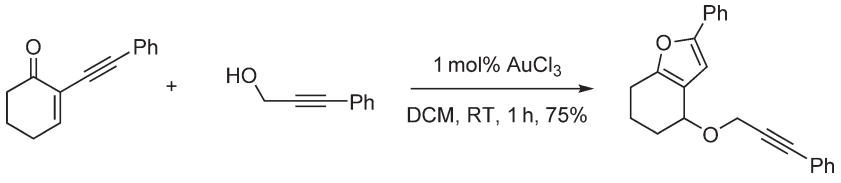
(96)

An Au(III) catalyst has been used for the cyclization of *o*-alkynylbenzaldehydes to benzopyrilium salts, which are readily oxidized to the corresponding azaphilones (Equation (97)).[346] Similar transformations have been realized with catalytic $AgSbF_6$.[347]



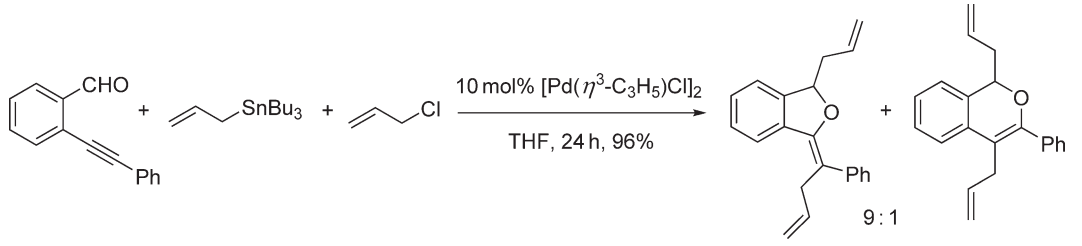
(97)

Enones have also served as latent enols in the hydroalkoxylation process. For example, an Au(III) catalyst has been used to effect the conjugate addition of alcohols (or other nucleophiles) to α,β-unsaturated ketones, thereby triggering a hydroalkoxylation pathway of the resulting enol to furnish furans as products. (Equation (98)).[348]



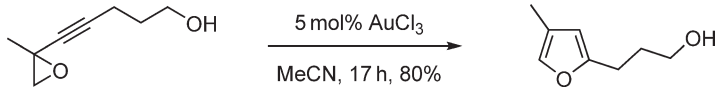
(98)

Alkoxides that arise from simple carbonyl additions have also functioned as excellent *in situ* nucleophiles for intramolecular hydroalkoxylation reactions. Carbinols derived from the addition of allyltin reagents have proved to be potent nucleophiles in reactions of this type (Equation (99)),[349] and this approach has also been used for the combined addition–cyclization of alkynals under Pd(II)[350] or Cu(I)[351] catalysis, and alkynones under Pd(II) catalysis.[352]



(99)

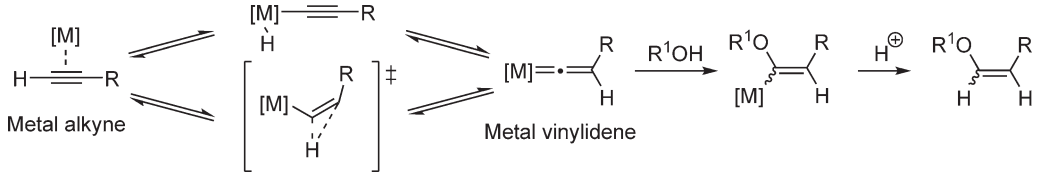
A few examples have recently appeared in the literature where epoxides can function as nucleophiles for the hydroalkoxylation of alkynes. Both $AuCl_3$[353] and HgO[354] in an acidic medium have been used as catalysts for this purpose (Equation (100)).



(100)

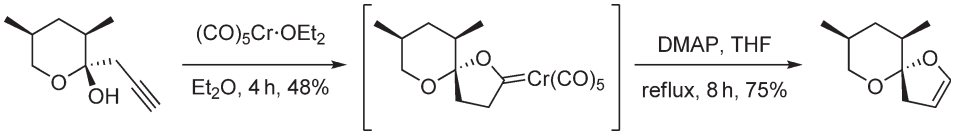
10.14.6.1.3 Addition of oxygen nucleophiles to alkynes via metal vinylidenes

Another approach toward C–O bond formation using alkynes that has been pursued involves the intermediacy of transition metal vinylidenes that can arise from the corresponding η^2-alkyne complexes (Scheme 13). Due to the electrophilicity of the α-carbon directly bound to the metal center, a nucleophilic addition can readily occur to form a vinyl metal species. Subsequent protonation of the resulting metal–carbon σ-bond yields the product with anti-Markovnikov selectivity and regenerates the catalyst.



Scheme 13

Although the intermolecular addition of alcohols to terminal alkynes following this vinylidene mechanism is known,[355] this chemistry has been performed more extensively in intramolecular settings. Using catalytic Mo or W complexes, or stoichiometric Cr complexes,[356,357] the cyclization of alkynols occurs with high *endo*-selectivity to give five-,[358,359] six-,[360–362] and seven-membered[363] oxacyclic products (Equations (101)–(103)) that are important subunits of various natural products.[362,364] For the $W(CO)_6$-catalyzed cycloisomerization reaction of 4-alkyn-1-ol, a computational study suggests that the 6-*endo*-pathway is greatly preferred over the competitive 5-*exo*-pathway, with formation of the vinylidene complex as the rate-limiting step.[365] However, the inclusion of a solvent molecule (THF) in the transition state narrows the energy difference between the 6-*endo*- and 5-*exo*-pathways to render the 5-*exo*-pathway competitive, which is frequently observed experimentally.[366] Systematic experiments have also been carried out to examine the impact of various propargylic substituents on the regiochemical outcome of these cycloisomerizatons.[367,368]



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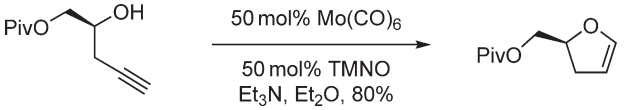
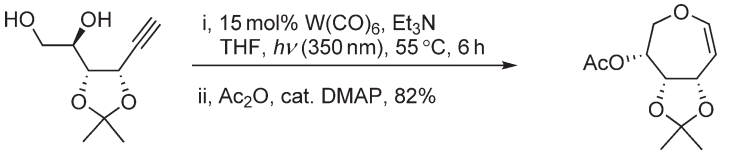
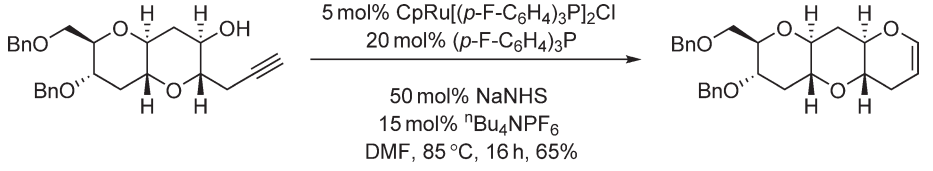


(102)



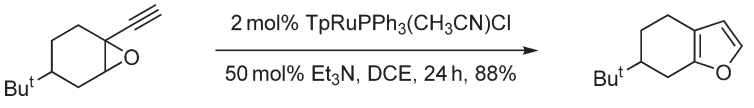
(103)

In addition to the W and Mo carbonyl complexes that have most commonly been used for the cycloisomerization of alkynols, an Rh-based catalyst system has recently been developed which uses substantially lower catalyst loadings (1.5–2.5 mol%) than have typically been required for the W and Mo systems (10–50 mol%).[369] Among the various ligands studied, P(*p*-F-C_6H_4)$_3$ proved to be particularly effective. Interestingly, this ligand has also been found to be optimal for an Ru system that catalyzes the same type of cycloisomerization (Equation (104)).[370,371]



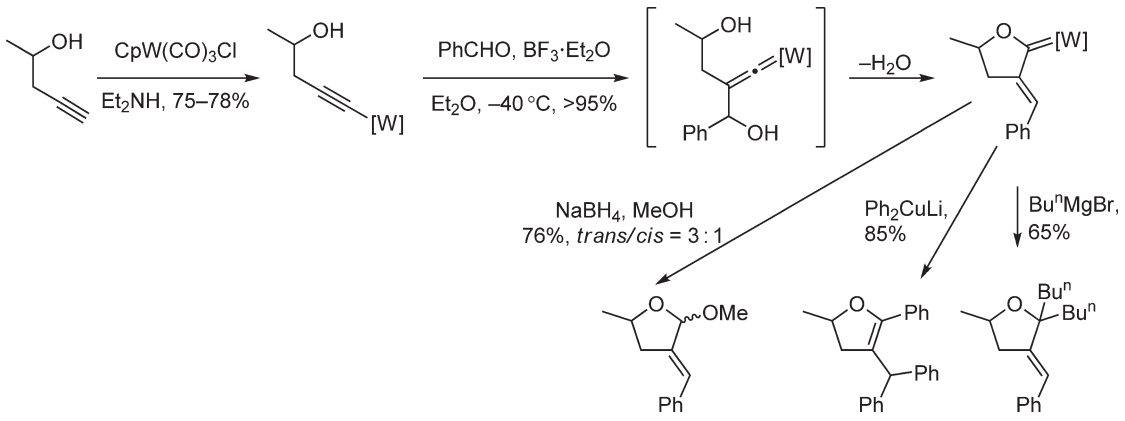
(104)

Alkynyl epoxides have also been shown to be competent nucleophiles in these processes. Both Mo[372] and Ru[373] catalyst systems have been used for the preparation of furans in this manner (Equation (105)), with lower catalyst loadings in the latter case (2–10 vs. 25–50 mol%).



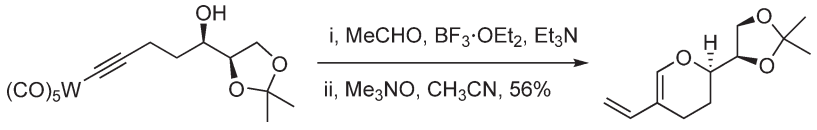
(105)

Etherification using a metal vinylidene has also been combined with C–C bond formation through the reaction of an alkynyl tungsten complex with benzaldehyde (Scheme 14). The addition of an internal alcohol to the incipient β,β-dialkylvinylidene that is generated leads to dehydration and the formation of a Fischer-type alkylidene complex. Further reactions of this carbene with a range of nucleophiles have provided access to various furan derivatives.[374,375]



Scheme 14

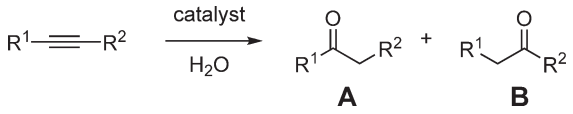
Aliphatic aldehydes have also been used, leading to intermediates that can undergo olefin isomerization under the action of mild base to generate metal-bound dienes; these have then been used in subsequent Diels–Alder reactions, either before[376] or after[377–379] demetallation of the metal complex (Equation (106)).



(106)

10.14.6.1.4 Transition metal-mediated hydration of alkynes

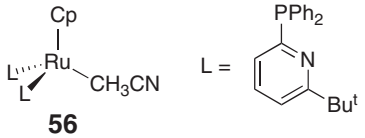
The hydration of alkynes represents a prime example in which simple coordinative activation by transition metal complexation greatly facilitates an otherwise very slow chemical process (Equation (107)). This reaction has been a long-studied problem, but only recently have alternatives to the classical use of catalysts such as Hg(II) salts been sought. These new catalyst systems typically display much enhanced reactivity, and some can mediate an anti-Markovnikov hydration through a novel mechanism (Table 1).

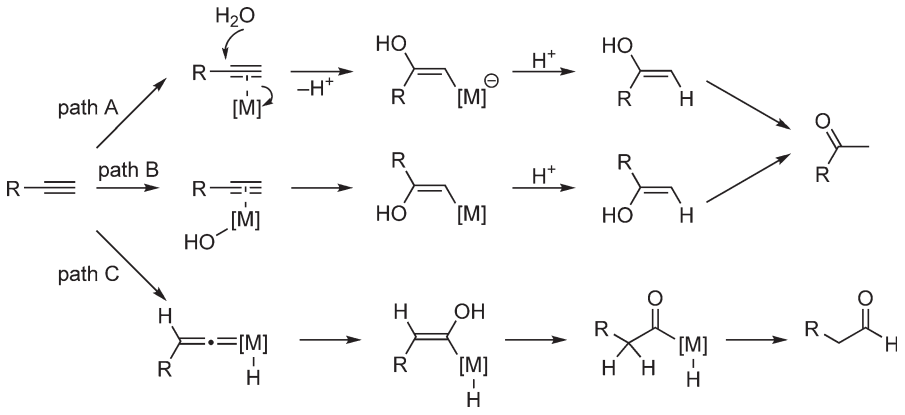


(107)

Table 1 Selected examples of transition metal-catalyzed alkyne hydration reactions

Entry	R^1	R^2	*Catalyst*	*Yield*, **A**:**B**	*References*
1	CH_3	Bu^t	1-4 mol% $[PtCl_2(C_2H_4)]_2$	89%, 27:73	392
2	CH_2CH_3	$CH_2OCH_2CH_3$	1-4 mol% $[PtCl_2(C_2H_4)]_2$	>95% conv., 88:12	392
3	*o*-$CH_3C_6H_4$	Ph	2 mol% $PtCl_4$, CO	83%, 0:100	393
4	*n*-C_3H_7	CH_3	0.2 mol% $[(Ph_3P)AuCH_3]$	76%, 45:54	383
5	$NC(CH_2)_3$	H	0.2 mol% $[(Ph_3P)AuCH_3]$	83%, 100:0	383
6	$NC(CH_2)_3$	H	10 mol% RuCpCl(dppm)	88%, 0:100	396
7	$CH_3(CH_2)_4CH(OH)$	H	5 mol% $[Ru(\eta^5\text{-}C_9H_7)Cl(PPh_3)_2]$	95% conv., 1.4:93	399
8	$THPOCH_2$	H	2 mol% **56**	98.0%, 0:100	400





Scheme 15

With an electrophilic transition metal complex, it is believed that the hydration of an alkyne occurs through a *trans*-addition of water to an η^2-alkyne metal complex (Scheme 15, path A),[380] although the *cis*-pathway via hydroxymetallation has also been proposed (path B).[381,382] However, distinguishing between the two pathways is difficult due to the rapid keto–enol tautomerization that renders isolation of the initial water adduct challenging.

Electrophilic metal complexes that have shown Markovnikov-type selectivity include catalysts based on Ru(II),[383–386] Fe(III),[387] Au(I) and Au(III),[380,388] and Ir(III).[389] Notable among these examples are Zeise's salt[390] (entries 1 and 2) and the $PtCl_4$/CO system (entry 3),[382,391] the latter of which has proved to be effective for the hydration of a wide range of alkynes. Additionally, a turnover frequency (TOF) as high as 15,600 h^{-1} has been achieved with the catalyst derived from CH_3AuPPh_3 (entries 4 and 5).[381]

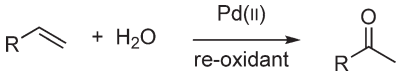
A most significant advance in the alkyne hydration area during the past decade has been the development of Ru(II) catalyst systems that have enabled the anti-Markovnikov hydration of terminal alkynes (entries 6 and 7). These reactions involve the addition of water to the α-carbon of a ruthenium vinylidene complex, followed by reductive elimination of the resulting hydridoruthenium acyl intermediate (path C).[392–395] While the use of CpRuCl(dppm) in aqueous dioxane (entry 6)[393–396] and an indenylruthenium catalyst in an aqueous medium including surfactants has proved to be effective (entry 7),[397] an Ru(II)/P,N-ligand system (entry 8) has recently been reported that displays enzyme-like rate acceleration ($>2.4 \times 10^{11}$) (dppm = bis(diphenylphosphino)methane).[398]

10.14.6.2 Transition Metal-catalyzed Additions to Alkenes

Like alkynes, a variety of mechanistic motifs are available for the transition metal-mediated etherification of alkenes. These reactions are typically initiated by the attack of an oxygen nucleophile onto an η^2-metalloalkene that leads to the formation of a σ-metal species. As described in the preceding section, the C–O bond formation event can be accompanied by a wide range of termination processes, such as β-H elimination, carbonylation, insertion into another π-bond, protonolysis, or reductive elimination, thus giving rise to various ether linkages.

10.14.6.2.1 Alkoxylation via Wacker-type reactions

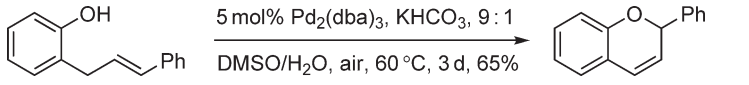
Since nucleophilic addition to a metal-coordinated alkene generates a σ-metal species bonded to an sp^3-hybridized carbon, facile β-H elimination may then ensue. An important example of pertinence to this mechanism is the Wacker reaction, in which alkenes are converted into carbonyl compounds by the oxidative addition of water (Equation (108)), typically in the presence of a Pd(II) catalyst and a stoichiometric reoxidant.[399] When an alcohol is employed as the nucleophile instead, the reaction produces a vinyl or allylic ether as the product, thus accomplishing an etherification process.



(108)

Early mechanistic studies have indicated that the oxypalladation step in the Wacker process proceeds through an *anti*-pathway,[399] although recent deuterium-labeling experiments have shown the viability of a *syn*-mechanism involving insertion of a metal-coordinated oxygen into the alkene.[400,401] For example, with excess chloride ion present, the Wacker-type cyclization of a deuterated phenol system occurred in a primarily *anti*-pathway, whereas the oxypalladation step favored a *syn*-mode in the absence of excess chloride ion (Scheme 16). Thus, either mechanism may be operative under a given set of experimental conditions.

A survey of Wacker-type etherification reactions reveals many reports on the formation of five- and six-membered oxacycles using various internal oxygen nucleophiles. For example, phenols[401,402] and aliphatic alcohols[401,403–406] have been shown to be competent nucleophiles in Pd-catalyzed 6-*endo*-cyclization reactions that afford chromenes (Equation (109)) and dihydropyranones (Equation (110)). Also effective is the carbonyl oxygen or enol of a 1,3-diketone (Equation (111)).[407] In this case, the initially formed *exo*-alkene is isomerized to a furan product. A similar 5-*exo*-cyclization has been reported using an Ru(II) catalyst derived *in situ* from the oxidative addition of $Ru_3(CO)_{12}$ to allyl acetate.[408]



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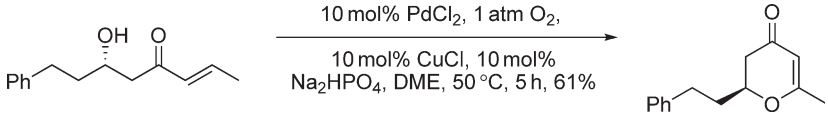

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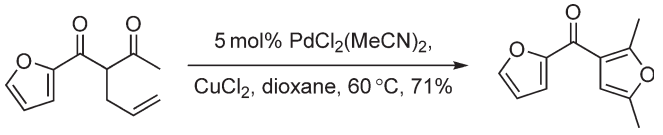
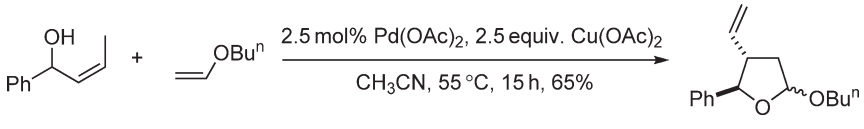


(111)

In the presence of additional unsaturation, the intermediate σ-palladium bond formed in these transformations can undergo a further Heck process to establish an additional C–C bond. The reactions of allylic alcohols with vinyl ethers proceed along this pathway and lead diastereoselectively to THFs (Equation (112)), with $Cu(OAc)_2$[409] and O_2[410] used as the stoichiometric oxidants. This methodology has been used to good effect in the syntheses of (−)-dihydroxanthatin,[409] fraxinellone limonoids,[411] and mycalamide A.[412]



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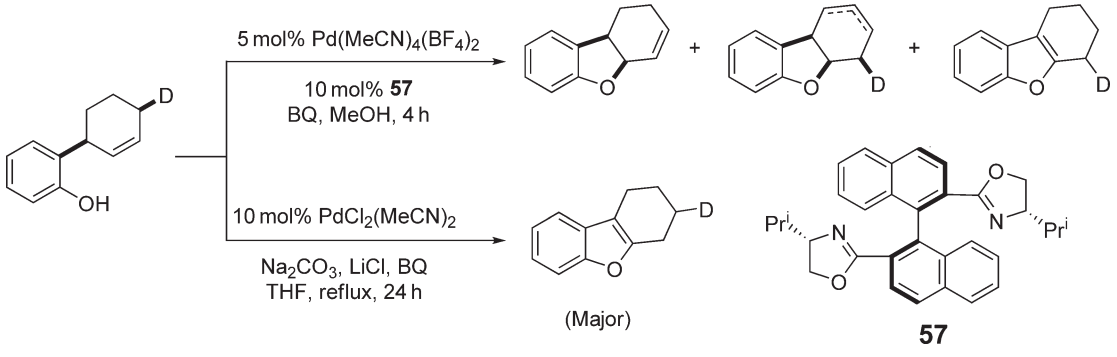
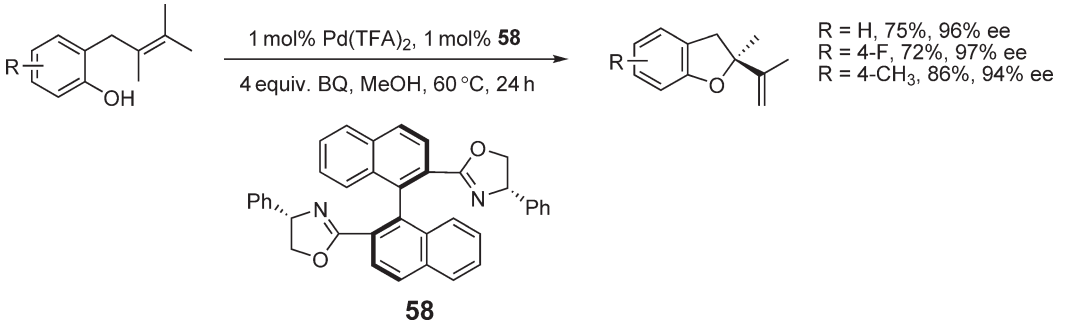


Scheme 16

A few reports have emerged concerning asymmetric Wacker-type etherifications. Notably, complexes derived from Pd(II) and dinitrogen ligands have proved to be effective for these reactions, whereas the use of more common phosphine ligands is precluded by the oxidative reaction conditions. High ee's have been attained in the cyclization of alkenyl phenols using an axially chiral bisoxazoline ligand, albeit with a narrow scope of substrates (Equation (113)).[413–415]



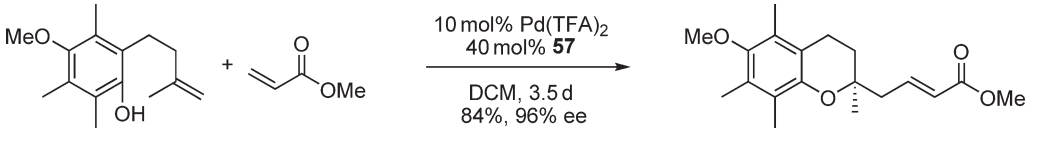
58 (113)

Asymmetric induction has also been achieved in the cyclization of aliphatic alcohol substrates where the catalyst derived from a spirocyclic ligand differentiates enantiotopic alcohols and alkenes (Equation (114)).[416] The catalyst system derived from $Pd(TFA)_2$ and (−)-sparteine has recently been reported for a similar cyclization process (Equation (115)).[417] In contrast to the previous cases, molecular oxygen was used as the stoichiometric oxidant, thereby eliminating the reliance on other co-oxidants such as CuCl or *p*-benzoquinone. Additional aerobic Wacker-type cyclizations have also been reported employing a Pd(II) system supported by *N*-heterocyclic carbene (NHC) ligands.[401,418]

59 (114)

(115)

The asymmetric Wacker methodology has also been extended to include a tandem Heck reaction.[416] An elegant demonstration of this strategy has recently been utilized to prepare the chroman core of vitamin E (Equation (116)).[419]

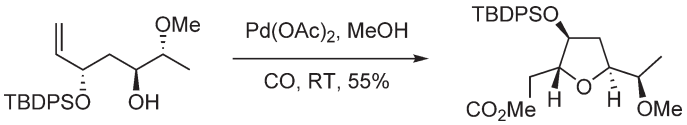


(116)

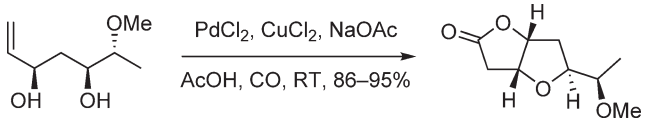
10.14.6.2.2 Wacker processes with subsequent carbonylation

When Wacker-type reactions are performed under a CO atmosphere, the β-H elimination pathway can be suppressed in favor of CO insertion and subsequent nucleophilic cleavage of the acyl metal species.[399] This alkoxycarbonylation process has found widespread utility, particularly in the synthesis of five- and six-membered oxacyclic natural products. For example, the THF core of tetronomycin was prepared by the Pd-catalyzed alkoxycarbonylation of 4-alkenol derivatives (Equations (117) and (118)), where stereocontrol was achieved by utilizing either the directing ability of a free hydroxyl or the conformational bias imposed by a bulky silyl ether.[420] Additional examples making

use of this chemistry include the syntheses of plakortone[421–423] and related δ-lactone systems,[424] goniofufurones,[425] goniothalesdiols,[426] and erythroskyrine.[427]

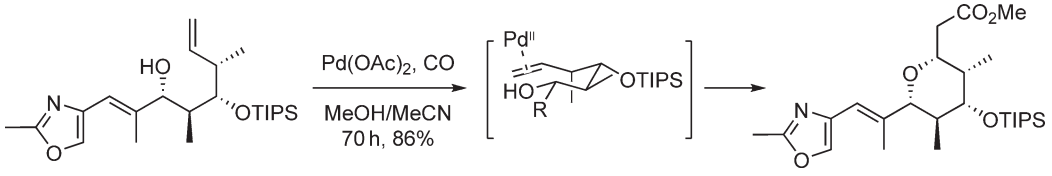


(117)



(118)

The alkoxycarbonylation reaction is also feasible with 6-*exo*-ring closure for the preparation of stereodefined THP rings. Using this process, the integral THP moieties of frenolicin B,[428] leucascandrolide A,[429] and phorboxazole A (Equation (119))[430,431] have been prepared. All of these reactions occur with 2,6-*cis*-selectivity, a rationale for which has been advanced by an analysis of chair-like transition states.[431]



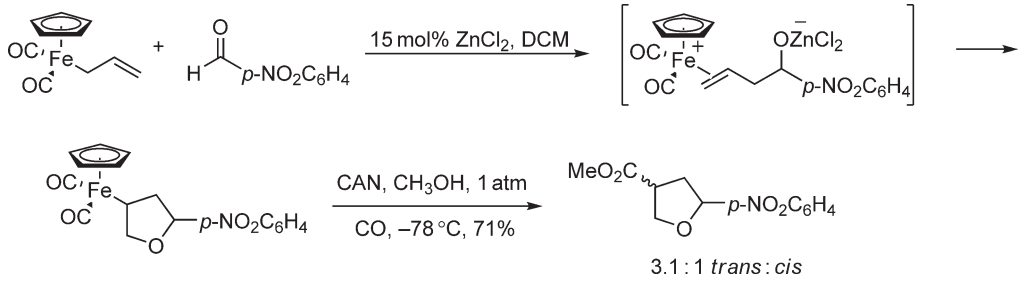
(119)

Cationic η^2-alkene iron complexes have been generated stoichiometrically from the allylation of aldehydes with the iron reagent $CpFe(CO)_2(CH_2CH{=}CH_2)$; the resulting carbinols undergo 5-*endo*-cyclization on treatment with base. The stable σ-iron complexes thus generated are incapable of mediating catalysis, but the C–Fe bonds can be converted into esters under oxidative carbonylation conditions, thus affording net alkoxycarbonylation products (Scheme 17).[432–434]

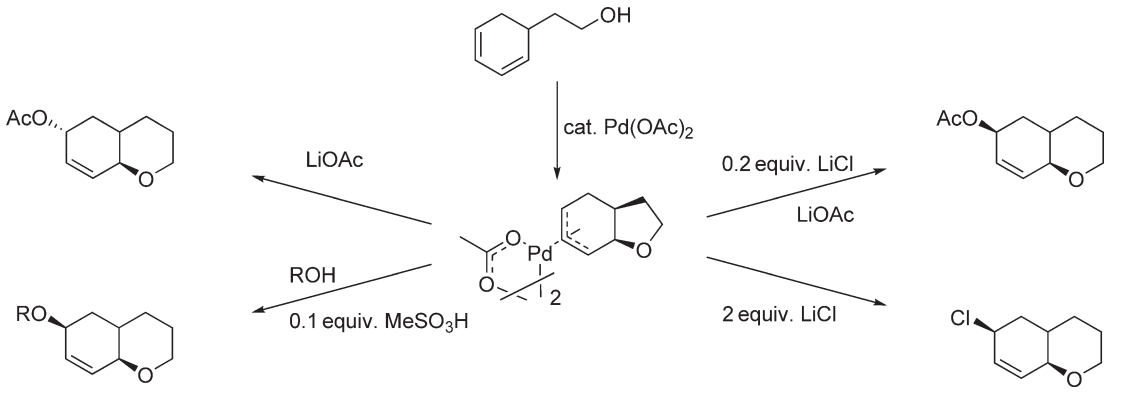
10.14.6.2.3 Wacker processes leading to π-allyl intermediates

When 1,3-dienes containing a tethered alcohol are subjected to Wacker-type reactions, the initial intramolecular oxypalladation event creates a π-allylpalladium species, which can then undergo an additional bond-forming process to effect an overall 1,4-difunctionalization of the diene with either *cis*- or *trans*-stereochemistry (Scheme 18).[399] An array of substrate types has been shown to participate in this reaction to generate both five- and six-membered fused or *spiro*-oxacycles.[435–437] Employing chiral benzoquinone ligands, progress toward the development of an asymmetric variant of this reaction has also been recorded, albeit with only modest levels of enantioselectivity (up to 55% ee).[438]

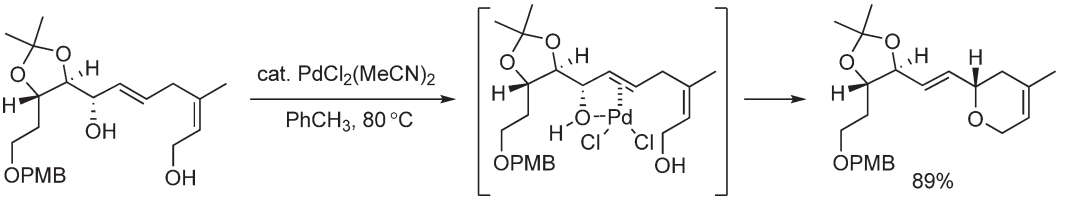
An interesting variant involves the use of an allylic alcohol as the alkene component. In this process, re-oxidation of the catalyst is unnecessary since the cyclization occurs with β-oxygen elimination of the incipient σ-Pd species to effect an S_N2' type of ring closure. Both five- and six-membered oxacycles have been prepared in this fashion using enol, hemiacetal, and aliphatic alcohol nucleophiles.[439,440] With a chiral allylic alcohol substrate, the initial π-complexation may be directed by the hydroxyl group,[441] as demonstrated by the diastereoselective cyclization used in the synthesis of (−)-laulimalide (Equation (120)).[442] Note that the oxypalladation takes place with *syn*-selectivity, in analogy with the cyclization of phenol nucleophiles (*vide supra*).



Scheme 17



Scheme 18

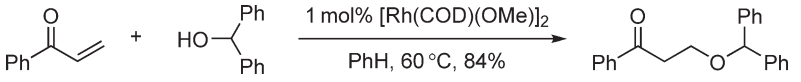


(120)

10.14.6.2.4 Hydro- and alkylative alkoxylation

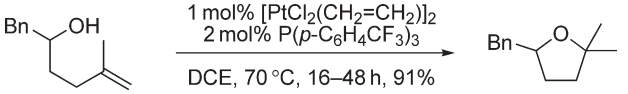
The carbon–metal σ-bond emanating from the addition of an alcohol nucleophile to a π-alkene complex may undergo a protonolytic cleavage to effect overall hydroalkoxylation of the alkene. While this process is difficult to achieve due to the propensity of the σ-metal species to undergo β-H elimination, some encouraging progress in this area has recently been forthcoming.

With conjugated enone substrates, the alkoxymetallation leads to the formation of a metal enolate that can undergo a facile protonation to accomplish the hydroalkoxylation. Following this mechanism, various β-alkoxyketones were obtained in good yields by the addition of primary and secondary alcohols to methyl vinyl ketone under cationic Pd(II) catalysis.[443] Similarly, $[Rh(COD)(OMe)]_2$ was found to catalyze the hydroalkoxylation of both methyl vinyl ketone and phenyl vinyl ketone (Equation (121)).[444]

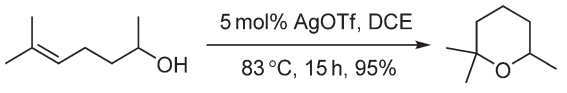


(121)

Progress in the more challenging area of the hydroalkoxylation of unactivated alkenes has also recently been reported, which achieves a Markovnikov-type addition making use of the catalysis of highly electrophilic metal complexes. For example, the cyclization of 4-alkenols to THFs (Equation (122)) and THPs (Equation (123)) has been catalyzed by both Pt(II)[445] and Ag(I)[446] complexes. In these transformations, the mode of ring closure (5-*exo* vs. 6-*endo*) depends on the substitution pattern of the alkene, implicating a buildup of cationic charge in the transition state leading to C–O bond formation. Other examples of intramolecular hydroalkoxylations include the 5-*exo*-cyclizations of *o*-allylphenols to dihydrobenzofurans as catalyzed by $ZrCl_4$[447] and $IrCl_3$/AgOTf.[448]



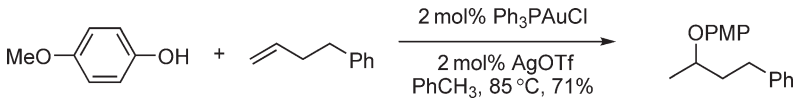
(122)



(123)

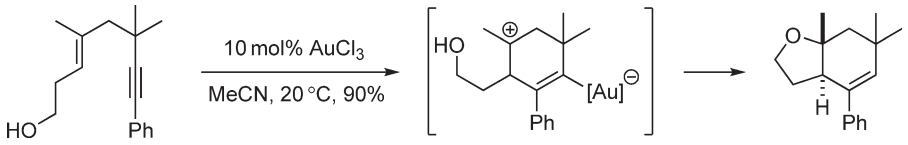
A few examples of the intermolecular hydroalkoxylation of unactivated alkenes have also appeared in the literature. While limited results have been obtained with aliphatic alcohols using a $Cp^*RuCl_2(PPh_3)$/AgOTf

system,[449] $Ph_3PAuCl/AgOTf$ appears to function as a more versatile catalyst for the hydroalkoxylation of terminal olefins with various phenols (Equation (124)).[450] In both cases, Markovnikov-type selectivity was observed.



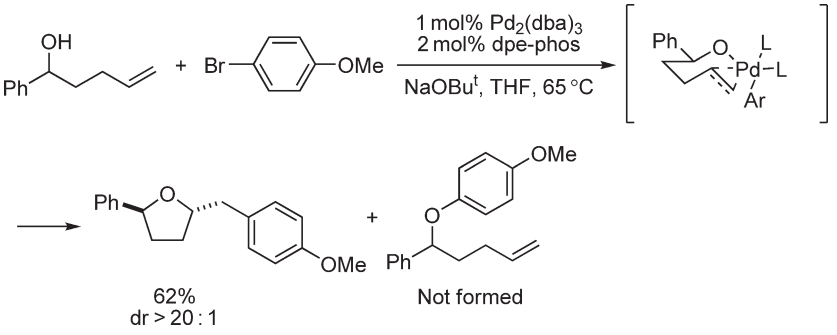
(124)

The cyclization of alkenols can also occur through an interesting relay mechanism (Equation (125)). Under $AuCl_3$ catalysis, the alkyne of an enynol is first activated to promote a cationic C–C bond-forming cyclization with the alkene. The C–O bond-forming ring closure then occurs via capture of the carbocation by the alcohol.[451]



(125)

In addition to β-H elimination, olefin insertion, and protonolysis, the σ-metal intermediate has also proved to be capable of undergoing a reductive elimination to bring about an alkylative alkoxylation. Under Pd catalysis, the reaction of 4-alkenols with aryl halides affords aryl-substituted THF rings instead of the aryl ethers that would be produced by a simple cross-coupling mechanism (Equation (126)).[452] It has been suggested that C–O bond formation occurs in this case by *syn*-insertion of a coordinated alcohol rather than *anti*-attack onto a π-alkene complex.[453]



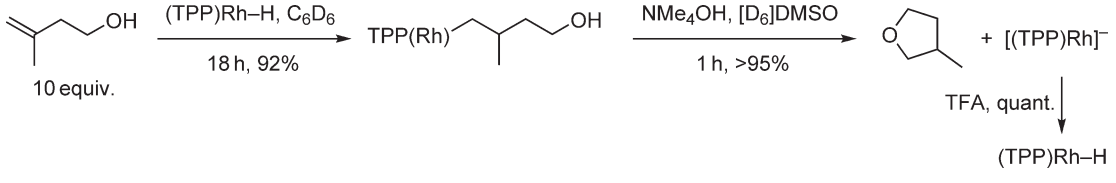
(126)

10.14.7 Miscellaneous Etherification

10.14.7.1 Etherification by S_N1 and S_N2 Processes

A variety of transition metal catalysts have been reported to catalyze the formation of ethers by the dehydration of alcohols via an S_N1 mechanism, including CH_3ReO_3,[454] $FeCl_3$ or $Fe(ClO_4)_3$,[455] $PdCl_2(MeCN)_2$,[456] (DIOP)$PdCl_2$/AgOTf,[457] and $PtCl_2/AgSbF_6$.[458] These methods have been used to form both symmetrical and unsymmetrical ethers, although in the latter case biased systems or a large excess of one alcohol must typically be employed for good yields. THFs and THPs have similarly been formed from diols by this method.[458]

Although extremely rare, a recent report documents the intramolecular S_N2-type displacements of (TPP)Rh–alkyl complexes (TPP = tetraphenylporphyrin) by alcohols and phenols to form THFs (Scheme 19). The intermediate rhodium alkyl complexes are themselves prepared by anti-Markovnikov hydrorhodation, and although the (TPP)Rh–H



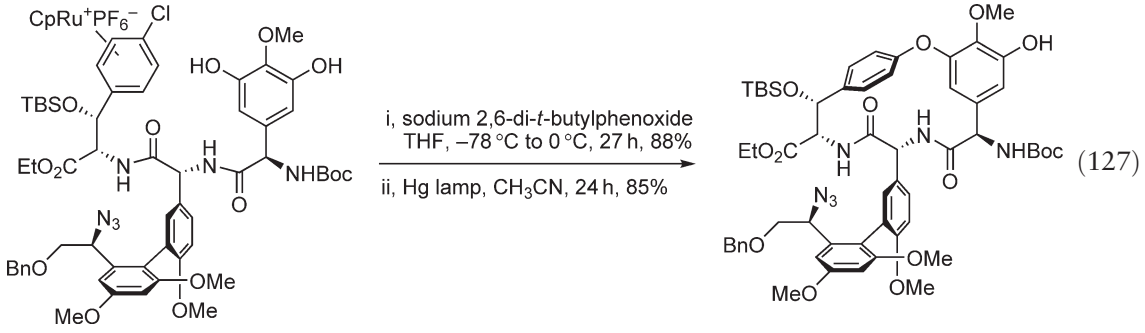
Scheme 19

complex can be recovered after the S_N2 etherification reaction by protonation with excess TFA, the entire sequence requires stoichiometric quantities of the rhodium porphyrin complex.[459]

10.14.7.2 Addition of Oxygen Nucleophiles to Transition Metal π-Arene Complexes

The coordination of an electrophilic transition metal complex to an aromatic ring can greatly enhance its electrophilicity such that S_NAr chemistry can become feasible without the need to introduce covalent activating groups. The addition of oxygen nucleophiles to transition metal arene complexes is an area that has seen a great deal of study, with Ru, Fe, and Cr[460,461] complexes having seen common use. One drawback of the use of this strategy is the necessity of using stoichiometric quantities of the transition metal complexes. Difficulties have also arisen in the purification of the metal-complexed products, as well as in the decomplexation step itself.[462] To alleviate some of these problems, approaches immobilizing the organic fragment[463] or the metal complex[461] onto the solid phase have been explored, as has the use of esoteric stationary phases[464–466] to allow for the chromatographic purification of the metal-complexed products.

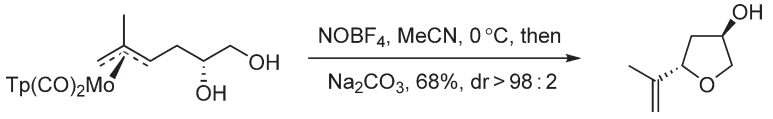
The most prominent application of the Ru–arene chemistry has been for the preparation of biaryl ethers in the syntheses of portions of vancomycin,[467] ristocetin (Equation (127)),[462,468–473] and teicoplanin (see also Section 10.14.1.2).[474–476] Additional applications[477–479] have included the syntheses of the macrocyclic biaryl ether-containing compounds K-13[480,481] and OF4949-III,[481,482] several macrocyclic depsipeptides,[483,484] and poly(phenylene oxide) polymers.[485]



(127)

Fe–arene complexes have been employed for the same purposes as their Ru counterparts, namely, in the preparation of monomeric aryl ethers,[463,486–488] polyaromatic ethers,[489,490] and macrocyclic aryl ethers.[491]

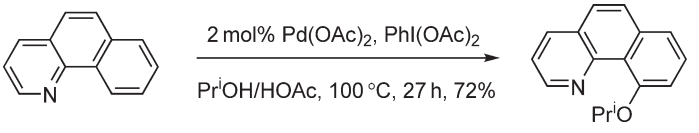
Both dienyl- and π-allylmetal complexes of Fe,[492] Mo,[493,494] and W[374] have also been prepared and undergone similar reactions with oxygen nucleophiles. One pertinent example is the reaction of π-allylmolybdenum complexes with internal alcohols leading to THFs (Equation (128));[493] additional examples of this chemistry have appeared in a recent review.[374]



(128)

10.14.7.3 Etherification through C–H Bond Functionalization

A recent publication has shown that aryl alkyl ethers can be formed through a C–H bond oxidative functionalization process in a regioselective manner when an adequate directing group is present (Equation (129)).[401,495] Mechanistic studies have provided evidence for the involvement of a Pd(IV) intermediate.[496]



(129)

10.14.8 Conclusion

The past decade has witnessed an explosive growth of interest and impressive progress in transition metal-catalyzed etherification reactions. A variety of approaches making use of novel mechanistic motifs have led to a better understanding of the organometallic chemistry involving C–O bond-forming processes and the emergence of powerful methods of broad utility in organic synthesis. A number of newly developed reactions can be performed under mild conditions with a high degree of stereocontrol, requiring only catalytic amounts of the metal complexes. In addition, owing to their mechanistic diversity, the transition metal-based methods can construct various types of ether linkages that are infeasible by classical etherification reactions. Moreover, the new reaction systems allow for multiple bond formations, thus lending themselves to strategic use in complex organic synthesis. As is evident from many examples in this chapter, the potential of the metal mediation in etherification processes will lead continuing efforts to discover more efficient reactions. Thus, it should not be surprising if research in this area undergoes more extensive developments over the years to come.

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10.15
C–N Bond Formation through Amination

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10.15.1 Introduction

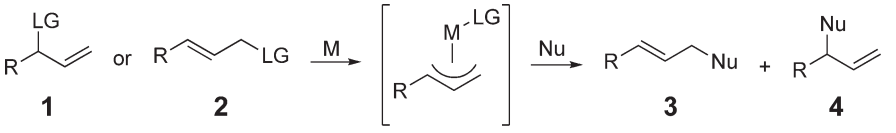
Transition metal complex-catalyzed carbon–nitrogen bond formations have been developed as fundamentally important reactions. This chapter highlights the allylic amination and its asymmetric version as well as all other possible aminations such as crosscoupling reactions, oxidative addition-β-elimination, and hydroamination, except for nitrene reactions. This chapter has been organized according to the different types of reactions and references to literature from 1993 to 2004 have been used.

10.15.2 Amination Through Allylic Substitution Reaction

An important variant for transition metal-catalyzed carbon–nitrogen bond formation is allylic substitution (for reviews, see[1,1a–1h]). Nucleophilic attack by an amine on an π-allyl intermediate, generated from either an allylic alcohol derivative,[2–16,16a–16f] an alkenyloxirane,[17–19,19a–19d] an alkenylaziridine[19,19a–19d], or a propargyl alcohol derivative,[21,21a–21d] gives an allylic amine derivative.

10.15.2.1 Reaction with Allylic Alcohol Derivatives

Palladium complexes are general and versatile catalysts for allylic amination.[1,1a–1h] The palladium-catalyzed allylic aminations of 1,3-symmetrically disubstituted substrates, including enantioselective versions, have been widely studied.[1,1a–1h] It has been important to control the regioselectivity in allylic amination of unsymmetrical substrates **1** or **2** (Equation (1)). In general, palladium-catalyzed allylic amination gives the (*E*)-linear product **3**;[1,1a–1h] thus, regiocontrol in amination has recently attracted much attention in approaches toward the branched product **4**.



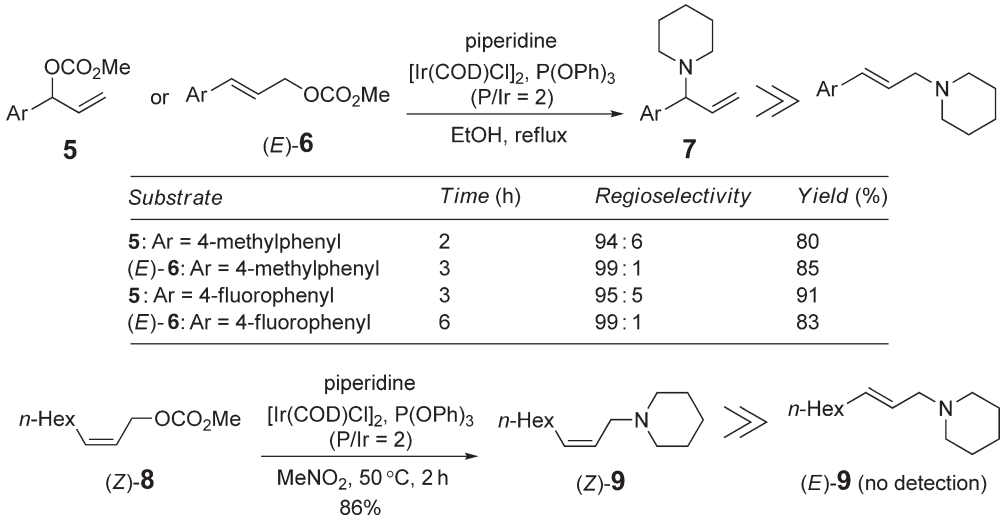
1 **2** **3** **4**

LG = leaving group
M = transition metal
Nu = nitrogen-atom nucleophile

(1)

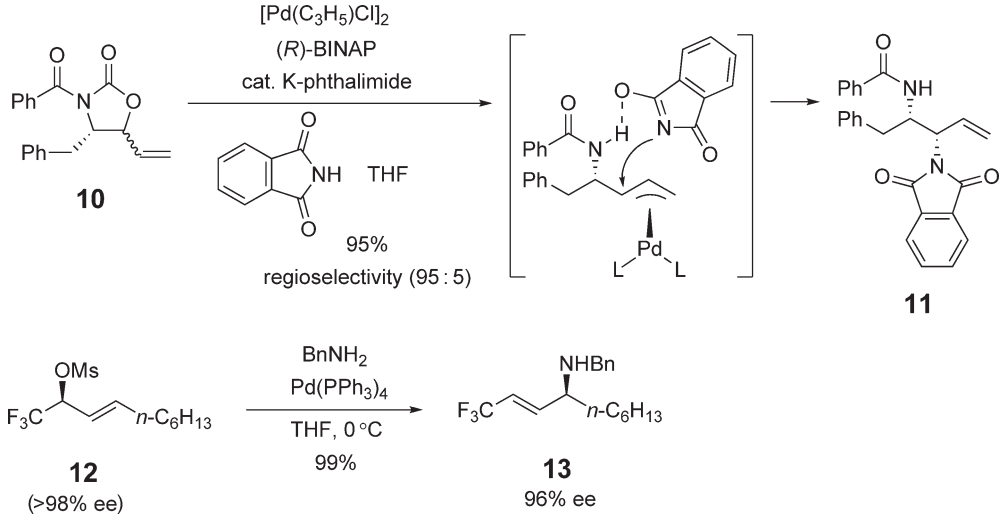
Allylic alkylation catalyzed by tungsten, molybdenum, ruthenium, iridium, and rhodium complexes often generates the branched products, and highly regio- and enantioselective allylic alkylations have been achieved by employing the chiral metal complexes.[1,1a–1h] Recent studies show that rhodium,[2,2a,2b] iridium,[3,3a,3b] ruthenium,[4,4a] iron,[4b] and nickel[4c–4f] complexes serve as catalysts for allylic amination. The regio- and stereoselectivities of amination using these catalysts are quite different from those of palladium-catalyzed amination, and the selective formation of the branched product **4** was mainly investigated by using rhodium, iridium, and ruthenium. For example, the regioselectivity of iridium-catalyzed allylic aminations was studied by Takeuchi's group.[3,3a,3b] The reaction of 1-substituted-2-propenyl carbonate **5** or (*E*)-3-substituted-2-propenyl carbonate (*E*)-**6** with piperidine in the presence of a catalytic amount of $[Ir(COD)Cl]_2$ and $P(OPh)_3$ (P/Ir = 2) gave a branched amine **7** with up to 99 : 1 regioselectivity (Scheme 1).[3] When a primary amine was used under the optimized conditions, selective monoallylation occurred without the formation of diallylation product. Additionally, the geometry of (*Z*)-3-substituted-2-alkenyl carbonate (*Z*)-**8** was retained in iridium-catalyzed allylic amination to give the linear (*Z*)-product, (*Z*)-**9**, selectively.[3,3a] In general, the retention of *Z* geometry in palladium-catalyzed allylic substitution has been difficult to achieve.

An unusually high regioselectivity was observed by Cook's group in palladium-catalyzed allylic amination of 5-vinyloxazolidinone **10** (Scheme 2).[5] An imide-type nucleophile was directed to the internal carbon, whereas



Substrate	*Time* (h)	*Regioselectivity*	*Yield* (%)
5: Ar = 4-methylphenyl	2	94 : 6	80
(*E*)-**6**: Ar = 4-methylphenyl	3	99 : 1	85
5: Ar = 4-fluorophenyl	3	95 : 5	91
(*E*)-**6**: Ar = 4-fluorophenyl	6	99 : 1	83

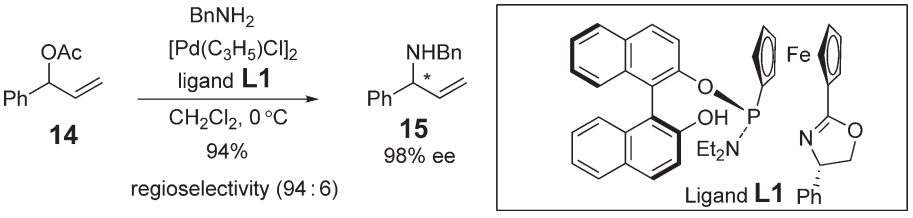
Scheme 1



Scheme 2

sulfonamide and amine were added only to the terminal carbon of the allyl complex. Hydrogen bonding was suggested in order to direct the introduction of nucleophiles to an allyl complex giving the branched product **11**. The regioselectivity of this reaction was influenced by the nature of substrates and solvents; relatively nonpolar solvents such as toluene and THF favored the branched product **11**. Kondo *et al.* reported that α-fluoroalkylated allyl mesylate reacted with amines to give an excellent yield of γ-fluoroalkylated (*E*)-allylic amine without the formation of the other regioisomer.[5a] In π-allyl complex, the palladium moiety might be closer to the CF_3 group than n-C_6H_{13} group because of the electron-withdrawing effect of the former. Therefore, the nucleophile attacks preferentially at the less hindered γ-carbon. Application of this reaction to chiral mesylate **12** affords chiral allylic amine **13**. The double inversion results in a net retention for this process.

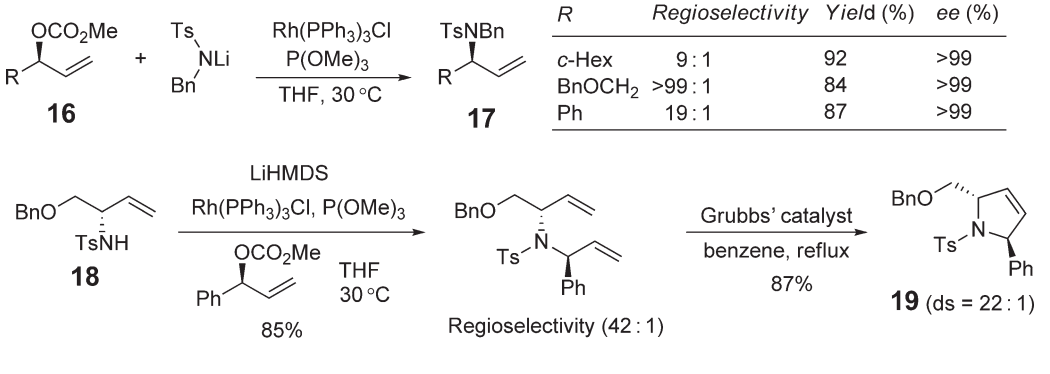
Extensive investigations into enantioselective allylic aminations of 1,3-symmetrically disubstituted substrates using a variety of metal complexes have been performed.[1,1a–1h] In contrast, the reaction of unsymmetrical substrates is challenging, since both regio- and enantioselectivities should be controlled to give the desired branched products with a high enantiopurity. Pioneering work in this field has been done by Hayashi and Ito, using chiral ferrocenyl-phospine–palladium complexes.[6] Highly regio- and enantioselective palladium-catalyzed allylic amination was achieved by Dai's group (Equation (2)).[7] The reaction of acetate **14** with benzylamine (3 equiv.) gave the branched amine **15** with 98% ee in the presence of ferrocene-based P,N-ligand **L1**. The X-ray structure of ligand **L1** showed that the OH group in the ligand **L1** is directed inwardly to the reaction site. In this reaction, a hydrogen bond between the free OH group and the benzylamine might be formed.



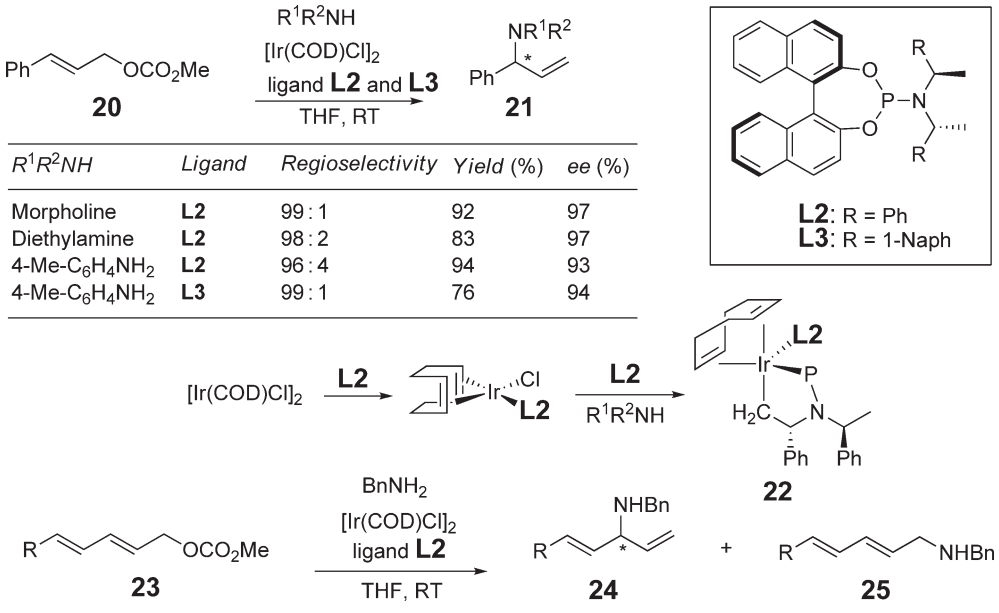
(2)

Evans *et al.* demonstrated that rhodium-catalyzed allylic substitutions proceed with excellent regioselectivity and retention of absolute configuration. The regioselective and enantiospecific rhodium-catalyzed allylic amination of chiral carbonate **16** was studied by his group (Scheme 3).[2] The nature of the counterion of a nucleophile, in which lithium was superior to both sodium and potassium in terms of reaction rate and regioselectivity, proved to be crucial. This amination proceeded with overall retention of absolute configuration, which is consistent with a double inversion process via the intermediacy of an enyl ($\sigma + \pi$) organorhodium intermediate. They demonstrated that the rhodium-catalyzed allylic amination using **18** could be combined with ring-closing metathesis for the synthesis of azacycle **19**.[2a] For the synthesis of arylamines, the reaction with *N*-(arylsulfonyl)anilines was also investigated.[2b]

The control of regio- and enantioselectivities in allylic substitution using chiral iridium complex has been a subject of recent interest. The regio- and enantioselective iridium-catalyzed allylic amination was mainly studied by Hartwig's group[8,8a,8b] and Helmchen's group[9,9a,9b] (Scheme 4). The iridium complex of Feringa's ligand **L2** catalyzed the allylic amination of **20** with good activity to form the branched product **21** with high enantioselectivity.[8]An activated form of the iridium-ligand **L2** complex was identified.[8a] A cyclometallation of a



Scheme 3



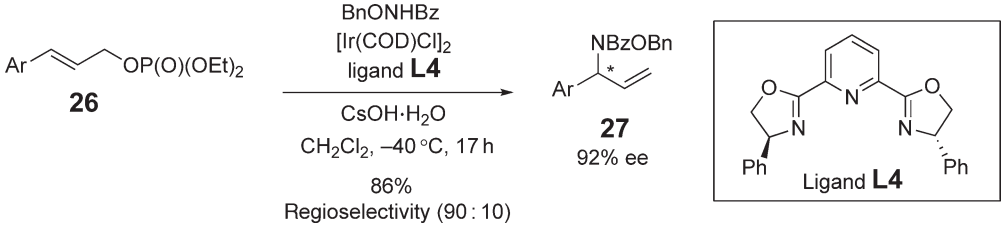
R	*Time* (h)	**24** : **25**	*Yield* (%)	*ee* (%)
Ph	24	99 : 1	61	97
$TBDMSOCH_2CH_2$	48	94 : 6	72	97
$PMBOCH_2CH_2$	14	96 : 4	71	97

Scheme 4

R^1*R*^{2}*NH*	*Ligand*	*Regioselectivity*	*Yield* (%)	*ee* (%)
Morpholine	**L2**	99 : 1	92	97
Diethylamine	**L2**	98 : 2	83	97
4-Me-$C_6H_4NH_2$	**L2**	96 : 4	94	93
4-Me-$C_6H_4NH_2$	**L3**	99 : 1	76	94

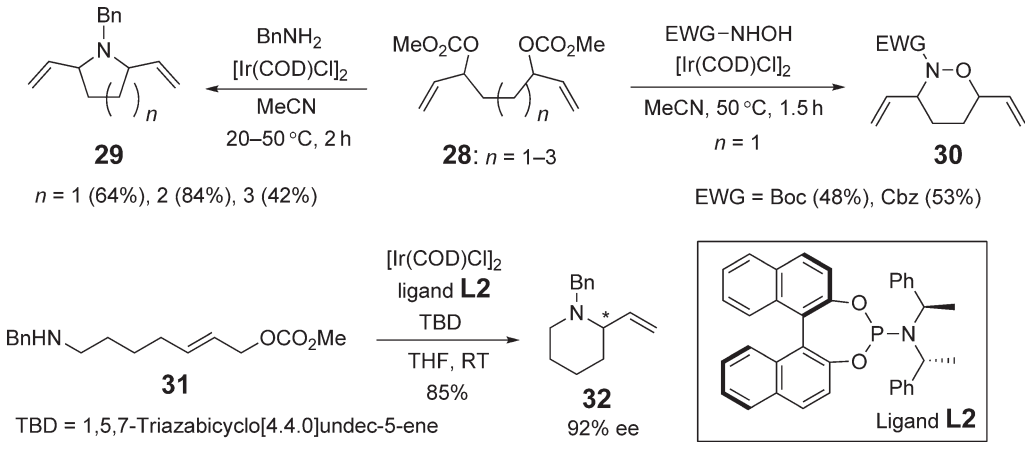
hindered phosphoramidate ligand generated more reactive species **22** and their use led to improved activity, selectivity, and broader substrate scope for allylic amination. The reactions with aromatic amines were also investigated.[8b] In these reactions, improvement in regioselectivity and enantioselectivity was achieved by conducting reaction with the bulkier ligand **L3**. The reaction of dienyl carbonates **23** was investigated by Helmchen. For both aryl- and alkyl-substituted substrates, high regioselectivity in favor of the desired internal substitution product **24** was obtained.[9] The aminations provided ee values up to 97%.

Takemoto and Miyabe recently found that the iridium complex of pybox **L4** catalyzed the reaction to form the branched product with good enantioselectivity (Equation (3)).[10] In the presence of $CsOH{\cdot}H_2O$, the reaction of phosphate **26** with BnONHBz proceeded smoothly to give the branched product **27** with 92% ee.



(3)

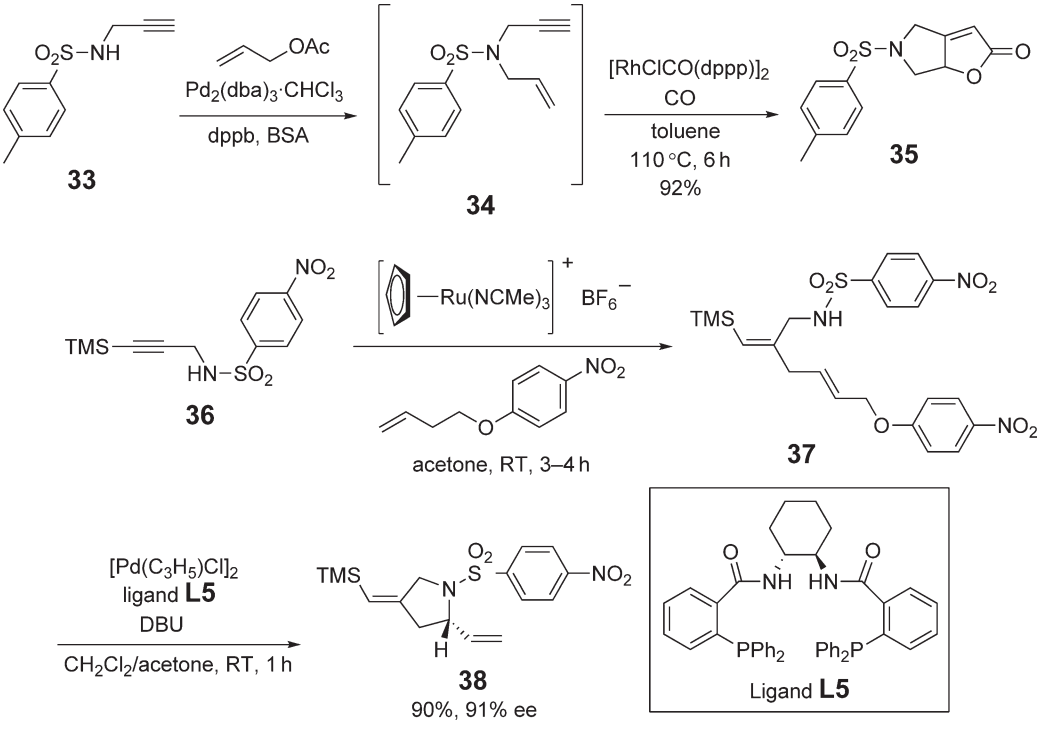
Allylic amination is important for the synthesis of nitrogen-containing heterocycles. Takemoto and Miyabe reported a novel method for preparing azacycles **29** based on the sequential allylic amination of **28** (Scheme 5).[10a] The success of this method reflects a high degree of regiocontrol in both intermolecular and intramolecular allylic aminations with the use of $[Ir(COD)Cl]_2$. Both nitrogen and oxygen atoms on hydroxylamines with an *N*-electron-withdrawing substituent acted as nucleophiles.[10b] Thus, the reaction with hydroxylamines was successfully applied to a cyclization giving six-membered products **30**. Recently, Helmchen's group reported the enantioselective intermolecular reaction of **31** by using the iridium complex with Feringa's ligand **L2**.[9a] The iridium–**L2** complex



Scheme 5

was treated with a variety of bases, because activated iridium complex is generated by C–H activation promoted by the nucleophile or base. The best enantioselectivity was obtained upon activation with 1,5,7-triazabicyclo[4.4.0]undec-5-ene (TBD) as base to give the cyclic product **32** with 92% ee.

For the synthesis of heterocycles, an efficient strategy has been introduced utilizing the dual transition metal sequences (Scheme 6).[11,11a] The key issue is the compatibility of the two catalyst systems. Jeong *et al.* studied the one-pot preparation of bicyclopentenone **35** from propargylsulfonamide **33** and allylic acetate.[11] This transformation includes two reactions: the first palladium-catalyzed allylation of **33** generates an enyne **34** and the following Pauson–Khand type reaction (PKR) of **34** yields a bicyclopentenone **35**. The success of this transformation reflects the right combination of catalysts which are compatible with each other because the allylic amination can be facilitated by the electron-rich palladium(0) catalyst and the PKR needs a Lewis-acidic catalyst. Trost *et al.* reported the one-pot enantioselective



Scheme 6

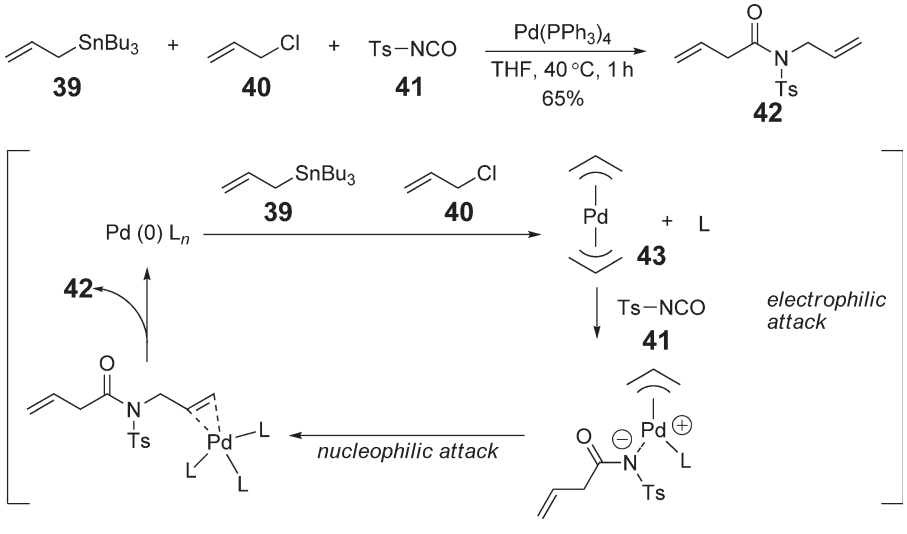
synthesis of azacycle **38**.[11a] This transformation comprises a ruthenium-catalyzed ene–yne addition followed by a palladium-catalyzed asymmetric allylic amination of intermediate **37**. For this reaction, the allylic alcohol derivative that was compatible with both asymmetric allylic amination and ene–yne coupling was required. *p*-Nitrophenyl ether was used to enhance the reactivity for the palladium-catalyzed step without disturbing the ruthenium-catalyzed step.

The palladium-catalyzed multicomponent coupling reactions have attracted considerable interest.[12,12a–12e] A reaction using allylstannane **39** and allyl chloride **40** was applied to the three-component diallylation of benzylidenemalonitrile and its congeners by Yamamoto *et al.*[12] Analogous diallylation of isocyanate **41** was studied by Szabó *et al.* (Scheme 7).[12a] The reaction mechanism can be explained by formation of an amphoteric bis-allylpalladium intermediate **43** which undergoes an initial electrophilic attack on one of the allyl moieties followed by a nucleophilic attack on the other.

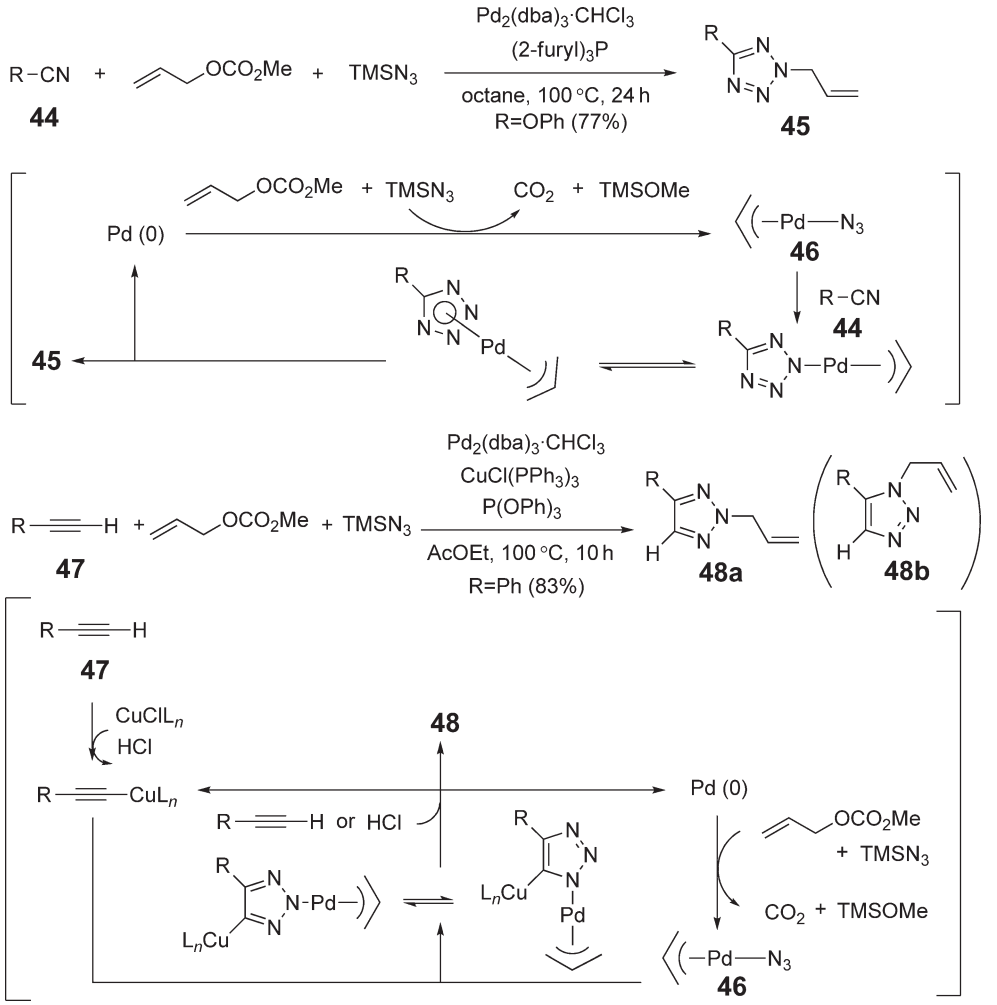
The palladium-catalyzed three-component coupling reaction of nitrile **44**, allyl carbonate, and trimethylsilyl azide gives 2-allyltetrazole **45** (Scheme 8).[12b,12c] In this reaction, palladium(0) initially reacts with allyl carbonate and trimethylsilyl azide to give the π-allylpalladium azide complex **46** as a key intermediate. Mechanistically, a new type of [3 + 2]-cycloaddition between the π-allylpalladium azide complex **46** and nitrile **44** is proposed. A three-component coupling reaction of terminal alkyne **47**, allyl carbonate, and trimethylsilyl azide promoted by a palladium and copper bimetallic catalyst gives allyltriazoles.[12d,12e] The combination of $Pd_2(dba)_3{\cdot}CHCl_3$–$CuCl(PPh_3)_3$–$P(OPh)_3$ catalyzes the selective formation of 2-allyltriazole **48a**. The selective synthesis of 1-allyltriazole **48b** as the single regioisomer is attained by using the combination of $Pd(OAc)_2$–$CuBr_2$–PPh_3. The copper catalyst probably behaves as an activator of the C–C triple bond of alkyne **47** by forming a copper–acetylide intermediate, thereby promoting the [3 + 2]-cycloaddition of the azide complex **46** and the copper–acetylide.

The direct use of allyl alcohols as the ally source potentially provides economical, technical, and environmental advantages because of the formation of water as a co-product derived from the living OH group. As an approach for promoting the allylic amination of allyl alcohols, some activators were employed (Scheme 9).[13,13a,13b] For example, the direct activation of C–O bond of allyl alcohols by a palladium complex was accelerated by using a Lewis acid. In the presence of $Ti(OPr^i)_4$, the palladium-catalyzed amination of allyl alcohol **50** with aniline **49** was studied by Yang *et al.*[13] In this reaction, allyl alcohol or an allyl titanate, formed through an alcohol exchange reaction with $Ti(OPr^i)_4$, reacts with palladium(0) to afford a π-allylpalladium intermediate. This method was applied to the regiospecific tandem allylation of 2-aminophenols **53** with 2-butene-1,4-diol **54**, leading to 3,4-hihydro-2-vinyl-2*H*-1,4-benzoxazines **55**.[13a] Kimura and Tamaru found that a combination of palladium(0) and Et_3B, both in a catalytic amount, promoted the amination of allyl alcohols.[13b] The di-allylation of primary amines and the mono-allylation secondary amines were also reported.

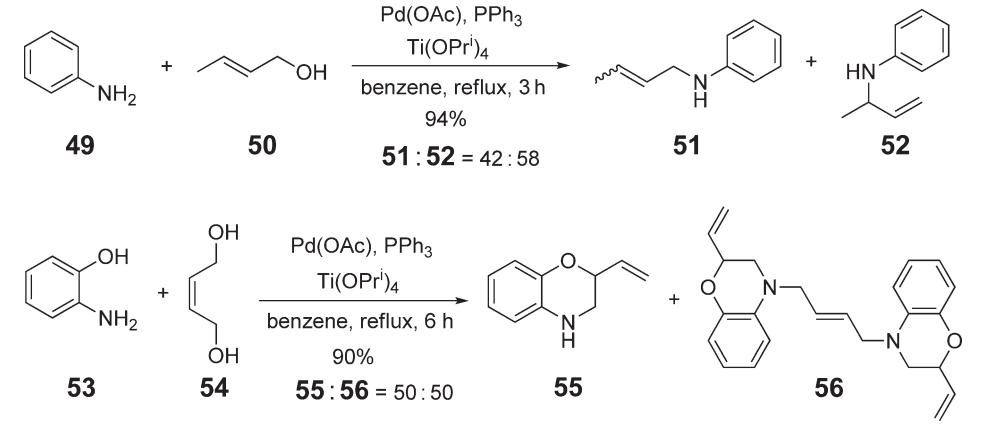
Recently, particular ligands have been reported to enable the amination of allyl alcohols without the aid of activators (Scheme 10).[13c,13d] Ozawa's group found that (π-allyl)palladium complex **58** bearing sp^2[2,2a,2b]-hybridized



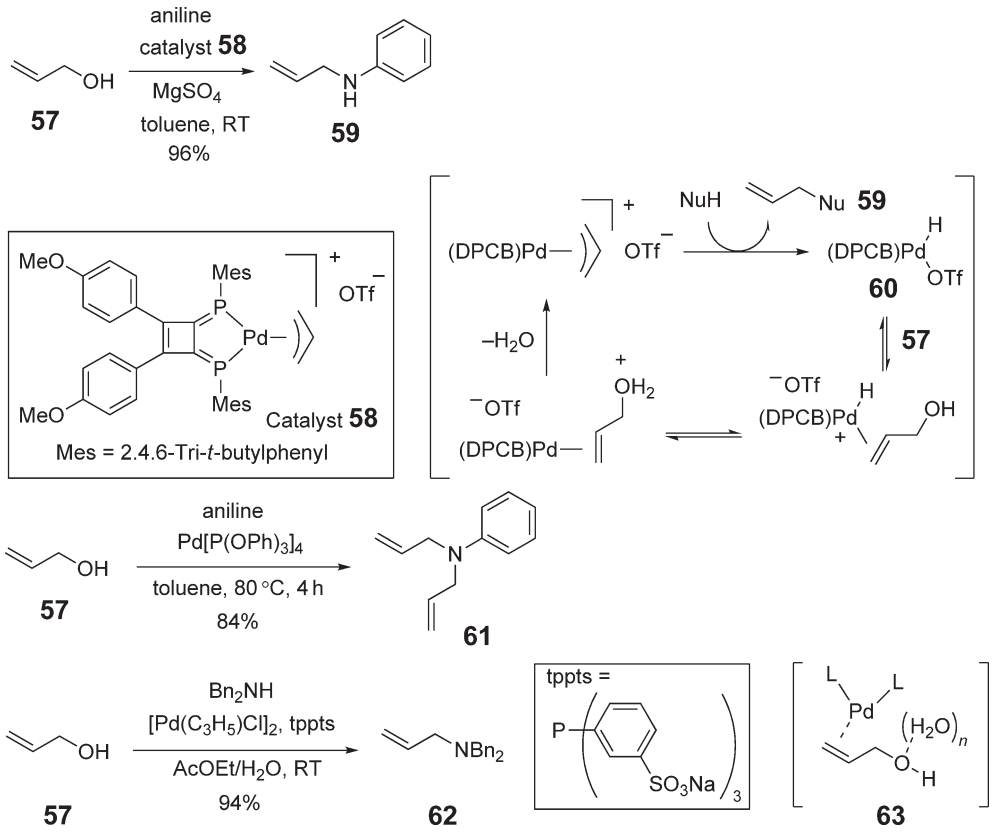
Scheme 7



Scheme 8



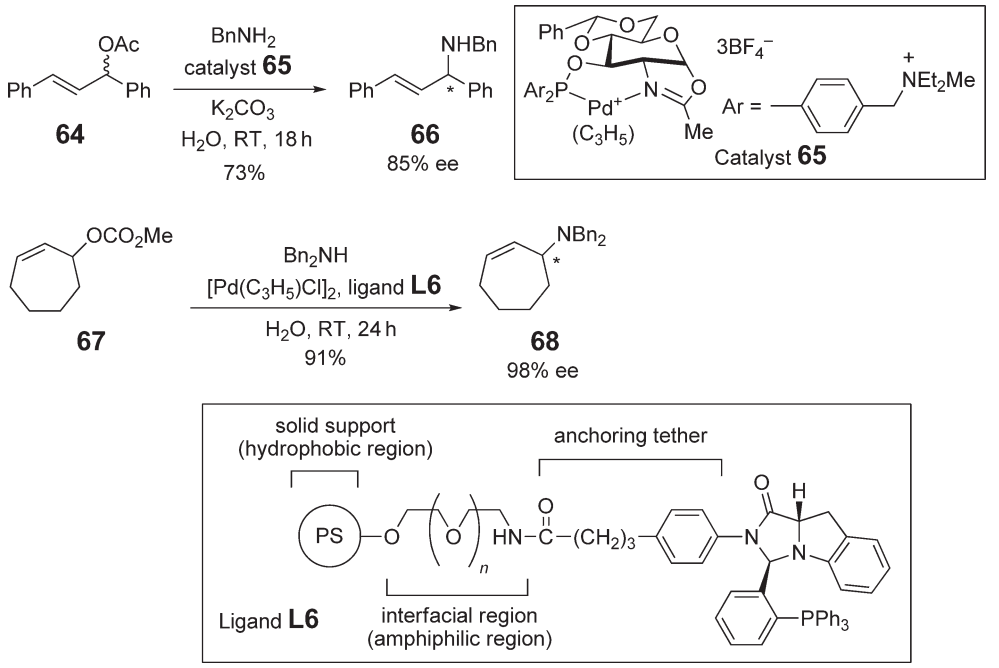
Scheme 9



Scheme 10

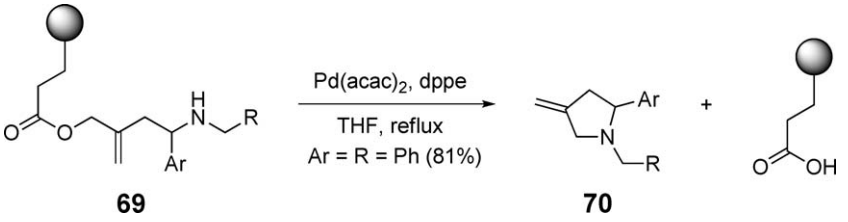
phosphorus ligand (DPCB) effectively catalyzed the direct conversion of allyl alcohol **57** to amine **59**.[13c] They assumed hydride complex **60** to be responsible for this process, giving a π-allylpalladium intermediate. Coordination of allyl alcohol **57** to hydride complex **60** followed by proton transfer from Pd to OH group results in the C–O bond cleavage. Ikariya's group has also shown that triphenylphosphite–palladium complex $Pd[P(OPh)_3]_4$ promoted allylic substitution of allyl alcohol **57** without cocatalyst and base.[13d] The direct use of allyl alcohol was also achieved in an aqueous system without any activator by Oshima's group.[13e] In an ethyl acetate–water biphasic system, the reaction of allyl alcohol **57** was conducted with the catalyst combination of $[Pd(C_3H_5)Cl]_2$ and tppts. Theoretical calculations have elucidated the importance of hydration **63** of the hydroxyl group for the smooth generation of π-allylpalladium intermediate.

Development of the aqueous medium transition metal-catalyzed reactions is becoming an important research subject in order to provide environmentally benign processes.[14,14a] The palladium-catalyzed reactions with water-soluble phosphines (e.g., sulfonated phosphines) provide advantages of the two-phase aqueous system: easy separation of the products and recycling the expensive palladium. For asymmetric allylic amination in water, an amphiphilic chiral catalyst **65** was prepared by Uemura's group (Scheme 11).[14b] The reaction of **64** proceeded even in H_2O, but the reaction was slower compared to that in MeCN–H_2O. In this case by using H_2O, the product **66** could be easily separated from the aqueous catalyst phase by simple extraction using hexane. Asymmetric allylic amination was achieved under heterogeneous conditions using an amphiphilic resin-supported chiral ligand **L6** by Uozumi's group.[14c] Amination of **67** with dibenzylamine was carried out in water in the presence of the palladium complex of **L6**, which was prepared by mixing **L6** and $[Pd(C_3H_5)Cl]_2$ just prior to use. It is interesting that, under these conditions, the allylic amination did not take place in an organic solvent such as dichloromethane, whereas the same system in water proceeded smoothly to give the product **68** with 98% ee. The hydrophobic organic substrates **67** and Bn_2NH must diffuse into the polystyrene matrix of **L6** in water to construct a highly concentrated reaction sphere to provide a significant increase in reactivity. Additionally, the recovered resin catalyst was used a second and third time.



Scheme 11

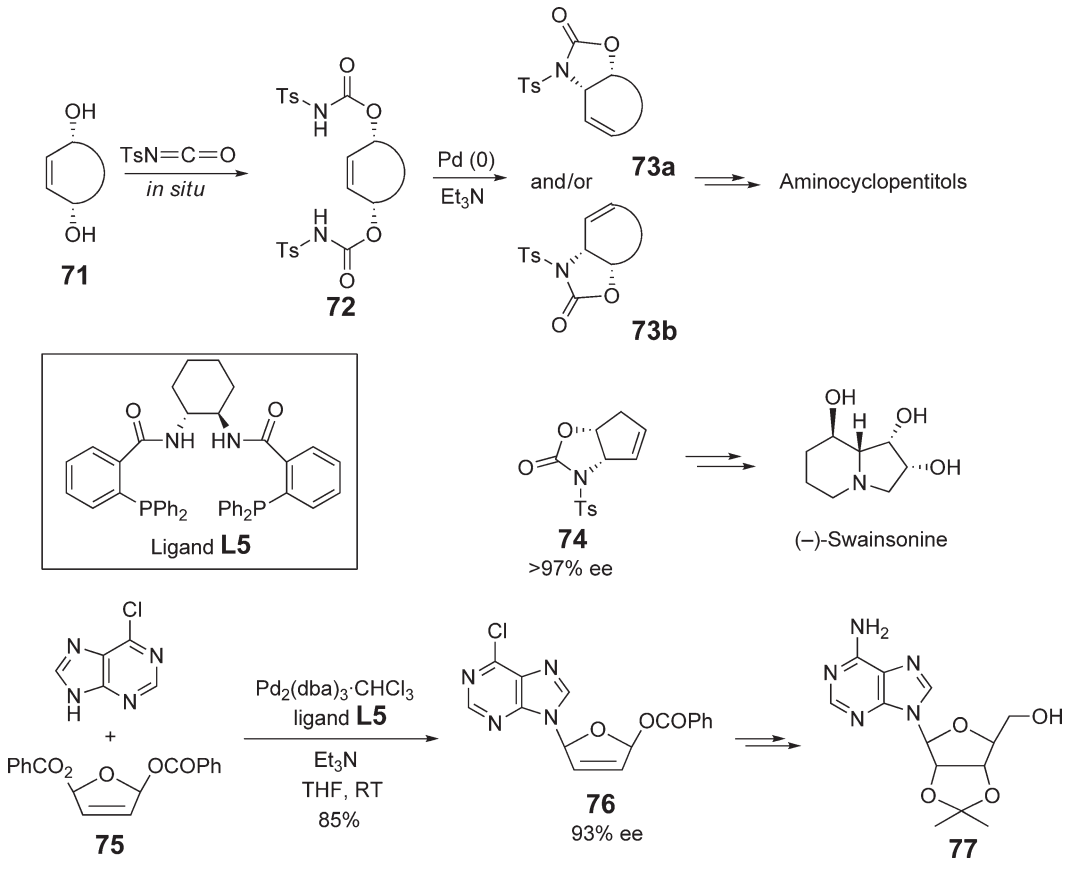
Allylic amination is important for the solid-phase organic synthesis.[15] The solid-phase allylic aminations are devised into the C–N bond formation on solid support and the deprotection of allyl ethers. As a novel deprotection method, the palladium-catalyzed cyclization-cleavage strategy was reported by Brown *et al.* (Equation (4)).[15a,15b] The solid-phase synthesis of several pyrrolidines **70** was achieved by using palladium-catalyzed nucleophilic cleavage of allylic linkages of **69**.



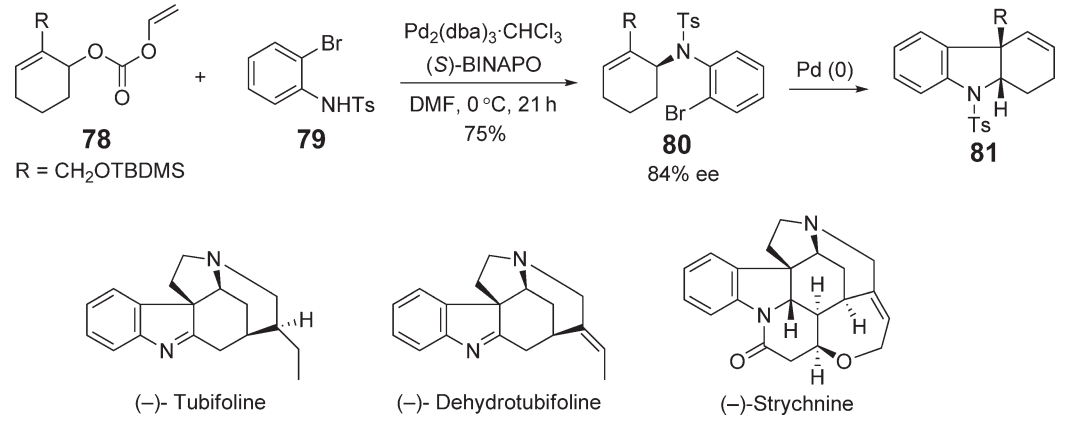
(4)

Enantioselective allylic amination has emerged as a powerful tool for the synthesis of natural products.[16] Desymetrization of *meso*-compounds led to the development of novel and efficient strategies in the total synthesis of natural products as demonstrated by Trost *et al.* (Scheme 12).[16a–16c,1g] The reaction of **71** provided easy access to chiral nitrogen-substituted carbocycles such as aminocyclopentitol glycosidase inhibitors.[16a] The *meso*-bis-carbamates **72** were generated *in situ* by the reaction of a diol **71** with 2 equiv. of *p*-tosyl isocyanate. In this transformation, Trost *et al.* reported that ligand **L5** gave excellent enantioselectivity when Et_3N was used as a base.[16b]The desymetrization product **74** served as a key building block for the synthesis of (−)-swainsonine, as demonstrated by Blechert and co-workers.[16c] Desymmetrization of *meso*-compound **75** with 6-chloropurine gave the functionalized intermediate **76** for the synthesis of the *ent*-adenosine acetonide **77**.[16d]

A novel procedure for the synthesis of an indole skeleton **81** was developed by Mori's group (Scheme 13).[16e,16f] Enantioselective allylic amination of **78** with *N*-sulfonated *ortho*-bromoaniline **79** followed by Heck cyclization of **80** provided chiral indoline **81**. The treatment of a cyclohexenol derivative **78** with **79** in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ and (*S*)-BINAPO gave compound **80** with 84% ee in 75% yield. Total syntheses of (−)-tubifoline, (−)-dehydrotubifoline, and (−)-strychnine were achieved from compound **80**.



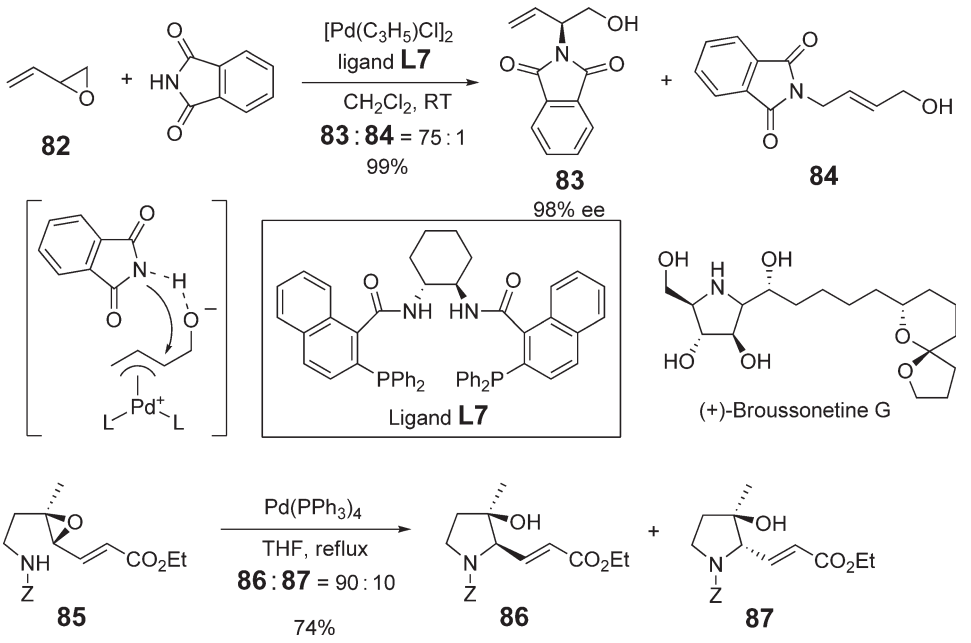
Scheme 12



Scheme 13

10.15.2.2 Reaction with Alkenyl Oxiranes and Aziridines

The ability to perform a dynamic kinetic asymmetric transformation (DYKAT) using the palladium-catalyzed reaction of racemic vinyloxirane **82** with phthalimide was explored by Trost's group (Scheme 14).[17,17a–17c] The 1,2-adduct **83** was obtained in nearly quantitative yield and 98% ee by using the conformationally rigidified ligand **L7**.[17,17a] In this reaction, the hydrogen bond of the nucleophile to the oxygen-leaving group would deliver the

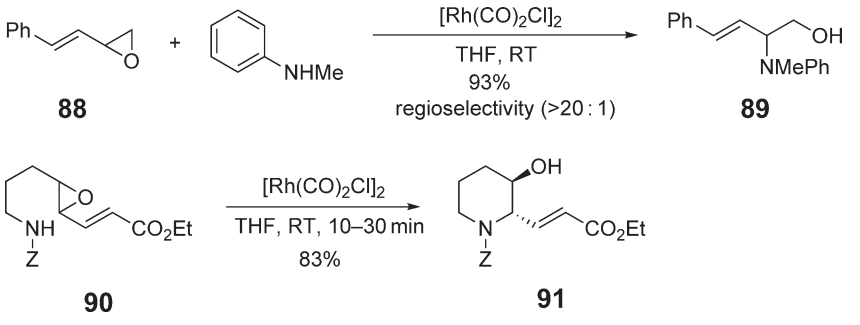


Scheme 14

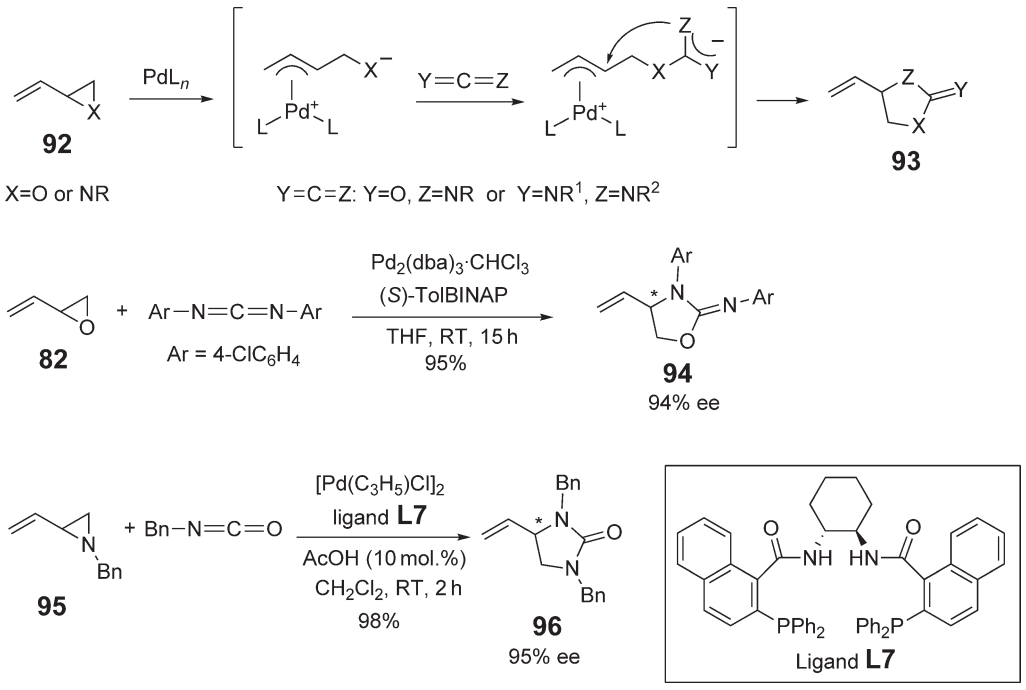
nucleophile to the adjacent carbon to give 1,2-adduct **83**. This DYKAT process potentially provides access to the broussonetine family such as (+)-broussonetine G.[17b] Kobayashi *et al.* studied the palladium-catalyzed intramolecular *N*-allylation of alkenyloxirane **85** to the pyrrolidines **86** and **87** for the synthesis of (2*S*,3*R*)-3-hydroxy-3-methylproline.[17c] The stereochemistry at C-2 and C- was controlled without a base to give pyrrolidine **86** as a major product.

Lautens *et al.* reported that $[Rh(CO)_2Cl]_2$ is an effective catalyst for the ring opening of alkenyloxiranes with aromatic amines under neutral conditions (Scheme 15).[18] The reaction of **88** with *N*-methylaniline occurred with excellent regioselectivity giving the 1,2-adduct **89**. Probably, rhodium(I) initially formed a π-complex with the alkenyl group of **88**, followed by an oxidative addition resulting in the formation of an enyl or π-allyl intermediate. Recently, the rhodium-catalyzed cyclization of alkenyloxirane **90** was studied by Ha's group.[18a]

The palladium-catalyzed cycloaddition reactions of three-membered-ring heterocycles such as oxirane and aziridine **92** with heterocumulenes (Y = C = Z) to form the five-membered-ring products **93** have been widely studied in the past 10 years (Scheme 16).[19,19a–19d] Asymmetric cycloaddition of vinyloxirane **82** with heterocumulenes was investigated by Alper's group. Reaction of **82** with symmetical carbodiimide using (*S*)-TolBINAP afforded product **94** with 94% ee.[19] Highly enantioselective cycloadducts were also formed in the reaction of **82** with unsymmetrical carbodiimide, although two regioisomers were always formed.[19a] Trost *et al.* reported the asymmetric cycloaddition of aziridine **95** with isocyanate. High yield and enantioselectivity were obtained by using chiral ligand **L7**.[19d] The



Scheme 15



Scheme 16

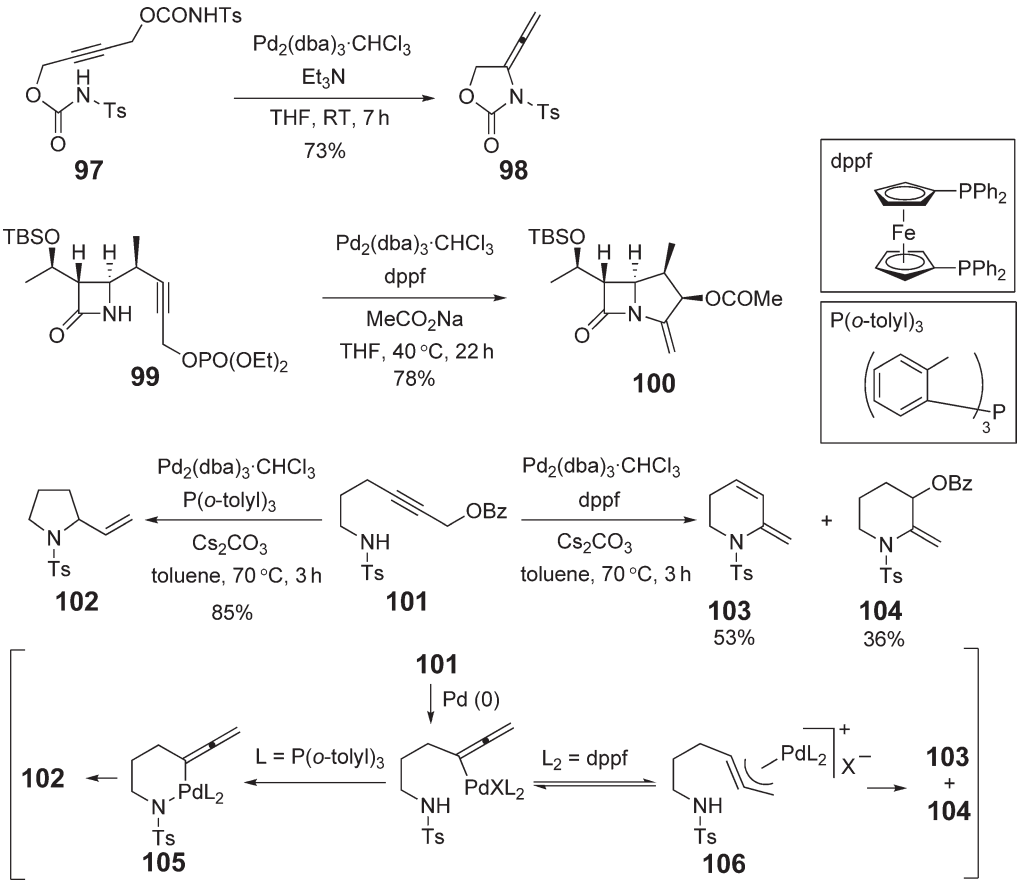
formation of various heterocycles has been successfully achieved by the cycloaddition reaction of thiiranes, oxetanes, azetidines, and pyrrolidines with heterocumulenes.[20,20a–20c]

10.15.2.3 Reaction with Propargyl Alcohol Derivatives

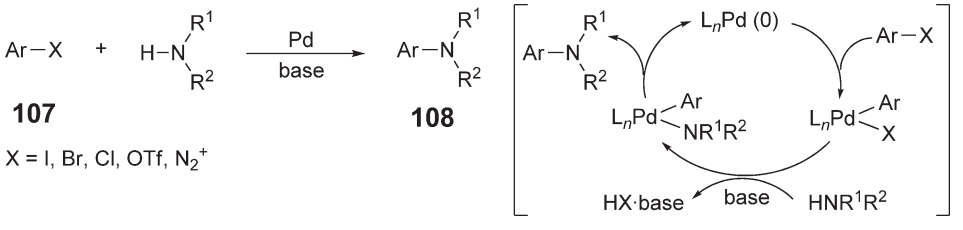
The reactivity of allenylpalladium complexes, which are obtained by oxidative addition of propargyl alcohol derivatives to palladium(0), is attractive in organic synthesis.[21] The synthesis of oxazolidinone **98** via the cyclization of propargyl alcohol derivative **97** was studied by Tamaru's group (Scheme 17).[21a] This transformation proceeded smoothly in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ and triethylamine at room temperature. The construction of a carbapenam skeleton **100** from β-lactam **99** having propargyl alcohol moiety was investigated by Mori's group.[21b,21c]By using bidentate ligand dppf, the palladium-catalyzed cyclization of **99** proceeded to give the desired carbapenam skeleton **100**. In these transformations, the nature of ligand on a palladium complex plays an important role in the determination of the ring size of the cyclic compound. In the case of the reaction of **101**, an intermediate palladium complex bearing a monodentate ligand P(*o*-tolyl)$_3$ gave a pyrrolidine **102** via palladacycle **105**, while that bearing a bidentate ligand dppf gave piperidines **103** and **104** via propargylpalladium complex **106**.

10.15.3 Amination Through Cross-Coupling Reaction

Transition metal-catalyzed cross-coupling reactions are attractive organometallic transformations for the generation of C–N bond (for reviews, see **22,22a–22e**). The palladium-catalyzed C–N bond-forming reactions of aryl halides or triflates with amines have been investigated mainly by Buchwald's group and Hartwig's group (Scheme 18).[23,23a–23f,24,24a–24f] Over the past several years, these two research groups and others have fine-tuned the catalytic system, allowing this type of transformation to be performed under very mild conditions and with a variety of coupling patterns.[23–25,25a–25f] Additionally, nickel complexes are well known to be effective catalysts for this transformation (for nickel-catalyzed reaction, see **26,26a–26g**). As related transformations, the copper-catalyzed Ullmann-type coupling reactions of aryl halides with amine have been extensively investigated (for copper-catalyzed reaction, see **27,27a–27n**).

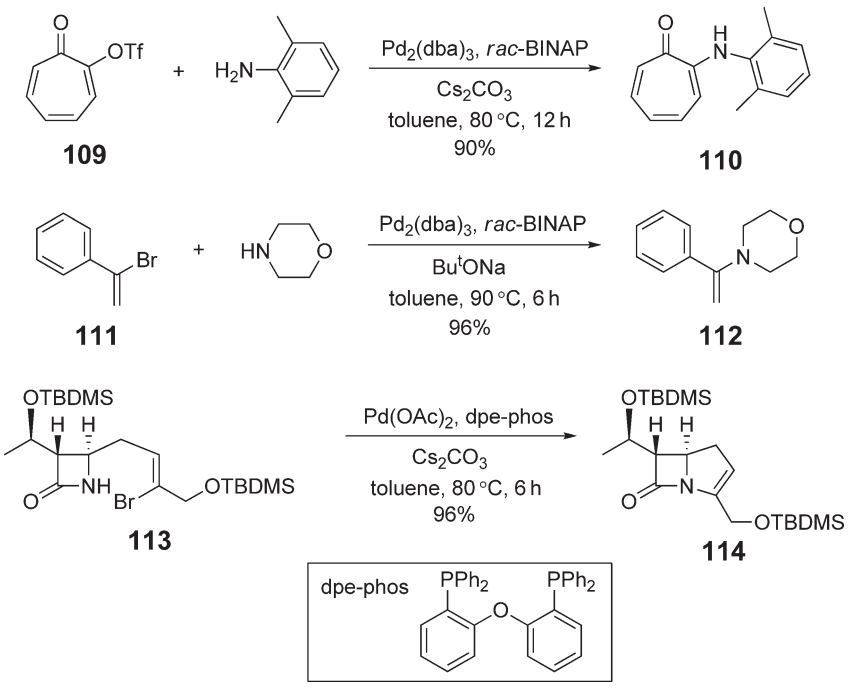


Scheme 17



Scheme 18

Most of the work on the C–N bond-forming crosscoupling reactions has concentrated on the formation of aromatic C–N bonds. Recent studies show that the application of cross-coupling reactions to alkenyl halides or triflates furnished enamines (Scheme 19) (for palladium-catalyzed reaction, see **28**,**28a–28d**, and for copper-catalyzed reaction, see **28e–28g**). Brookhart *et al.* studied the palladium-catalyzed amination of 2-triflatotropone **109** for the synthesis of 2-anilinotropone **110**.[28] It was found that the reaction of **109** proceeded effectively in the presence of racemic BINAP and a base. As a simple method for the synthesis of enamines, the palladium-catalyzed reactions of alkenyl bromide **111** with secondary amine were achieved under similar conditions.[28a] The water-sensitive enamine **112** was isolated as pure compound after dilution with hexane and filtration through Celite. The intramolecular cyclization of β-lactam **113**, having a vinyl bromide moiety, was investigated by Mori's

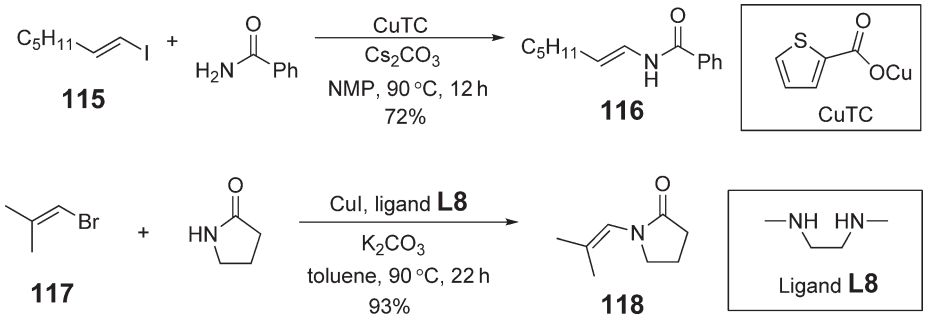


Scheme 19

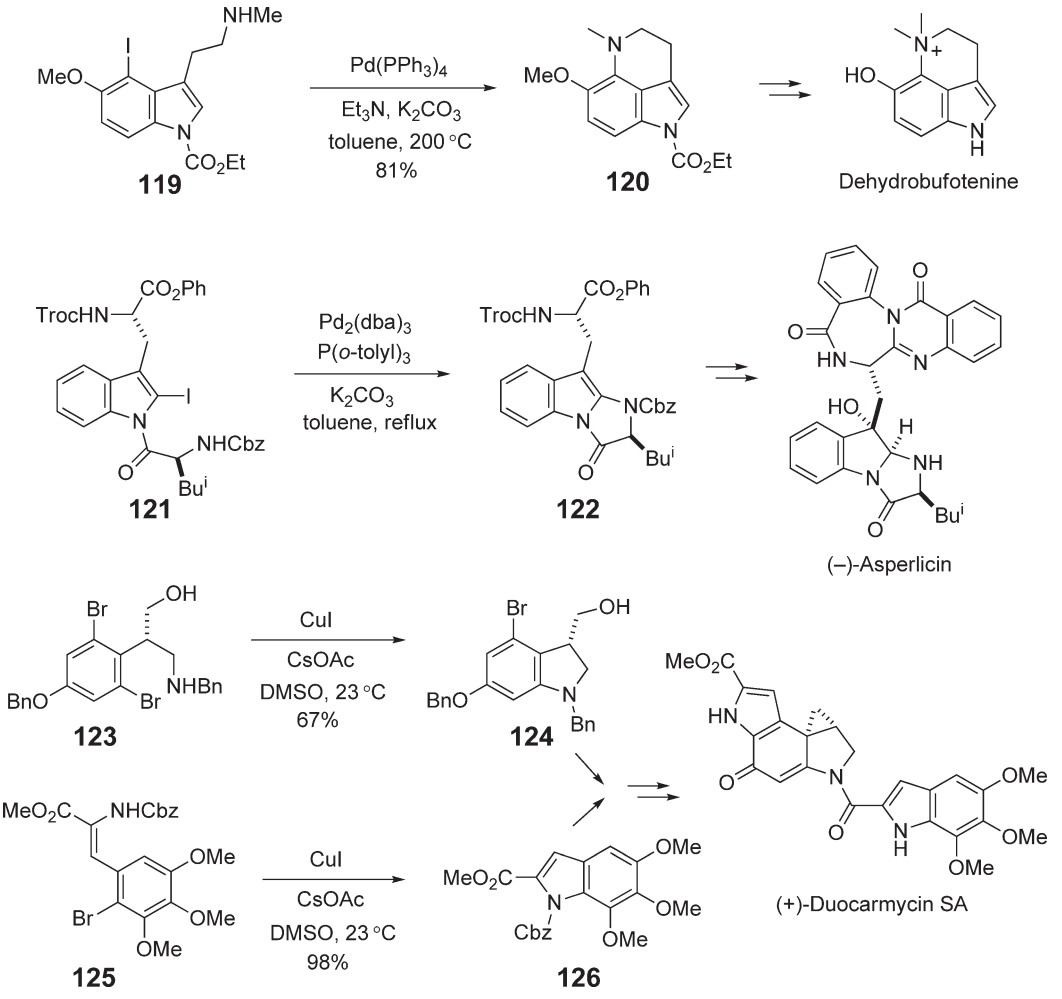
group.[28b] Among several palladium catalysts employed, the use of $Pd(OAc)_2$ and dpe-phos gave a good result in the formation of carbapenam **114**.

Parco *et al.* described a copper-catalyzed amidation of vinyl iodide **115** to give **116** (Scheme 20).[28e] Enhanced conversions were attained using copper(I) thiophenecarboxylate (CuTC) in a polar aprotic solvent such as NMP. The total synthesis of the antitumor natural product, lobatamide C, has been accomplished by using this reaction.[28f] Buchwald *et al.* developed a general and efficient copper-catalyzed method using *N*,*N*′-dimethyl ethylenediamine **L8**. The double-bond geometry of the alkenyl halides was retained under the reaction conditions.

The C–N bond-forming cross-coupling reaction has been extended to intramolecular reactions and these procedures have been utilized in many areas of organic synthesis including synthesis of natural products (Scheme 21).[29,29a–29g] Buchwald *et al.* studied the total synthesis of the South American toad poison dehydrobufotenine.[29] In this route, the tricyclic system **120** was formed via the palladium-catalyzed ring closure of a functionalized tryptamine derivative **119**, although unusually high temperatures were necessitated. Snider *et al.* developed a general route to imidazoindolone ring system and applied it to the total synthesis of



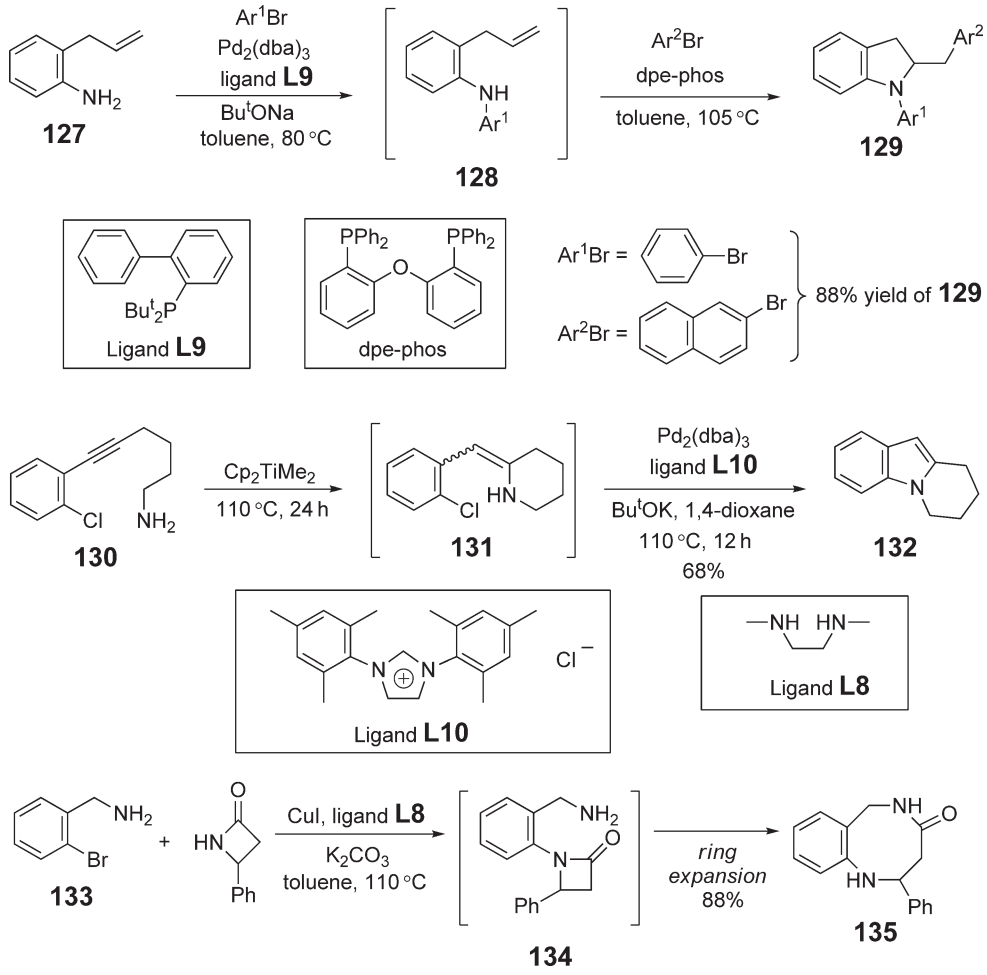
Scheme 20



Scheme 21

(−)-asperlicin.[29d] The palladium-catalyzed intramolecular amidation reaction of *N*-acylindole **121** provided the imidazoindolone **122**. Fukuyama *et al.* achieved the convergent total synthesis of (+)-duocarmycin SA.[29g] The key transformations were the copper-mediated aminations of aryl dibromide **123** and aryl bromide **125** under exceptionally mild conditions.

Recently, tandem or sequential reactions involving palladium-catalyzed *N*-arylation were developed (Scheme 22).[30,30a,30b] Wolf *et al.* reported the palladium-catalyzed sequential *N*-arylation/cyclization/*C*-arylation reaction between 2-allylaniline **127** and two different aryl halides.[30] This transformation led to the formation of two C–N bonds, one C–C bond, and one ring in a catalytic one-pot process. The selective diarylation was achieved by an *in situ* modification of palladium catalyst via phosphine ligand exchange. An electron-rich monodentate ligand **L9** facilitates *N*-arylation of **127** to give **128**, and then a key exchange with the chelating bis(phosphine) ligand such as dpe-phos ligand promotes olefin insertion into the intermediate palladium complex. Doye *et al.* reported a new method for the synthesis of indoles, in which two C–N bonds were formed during the one-pot procedure.[30a] The combination of titanium-catalyzed hydroamination of **130** with a palladium-catalyzed *N*-arylation of **131** produced the indole **132**. Buchwald *et al.* developed a novel method for the synthesis of medium ring nitrogen-heterocycles based on copper-catalyzed C–N bond formation.[30b] The tandem process involves a copper-catalyzed coupling of a β-lactam with an aryl bromide **133** followed by an intramolecular attack of a pendant amino group on the carbonyl group of **134**.



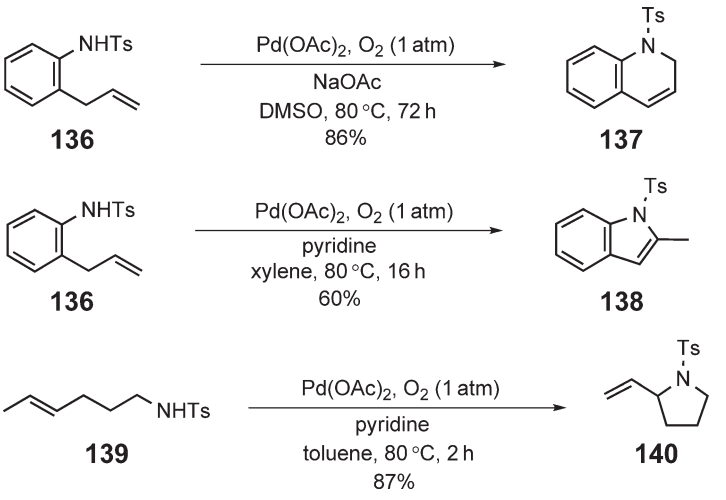
Scheme 22

10.15.4 Amination Through Oxidative Addition, β-Elimination, and Hydroamination

The synthesis of alcohols, ethers, and ketones by metal-catalyzed addition of water or alcohols to alkenes and alkynes is a well-established reaction in organic chemistry. Many regio- and stereoselective modifications of these reactions are known. In contrast, the analogous addition of ammonia or primary and secondary amines to nonactivated alkenes and alkynes has not had a comparable development, in spite of extensive efforts. In this section, we summarize the recent results of amination to unsaturated compounds.

10.15.4.1 Reaction with Alkenes

Transition-metal complex-catalyzed oxidative cyclization of aminoalkenes has proved to be a valuable route to a wide variety of unsaturated nitrogen-heterocycles such as cyclic imines, enamines, pyrroles, and indoles (for reviews, see **31,31a–31g**). However, palladium-catalyzed oxidative methods exhibit a complexity associated with redox catalysis, specifically the need for a stoichiometric oxidant such as benzoquinone or $CuCl_2$. Although these reagents are efficient in most of the cases, a simple and environmentally attractive catalyst system is more desirable. In practice, the catalytic oxidation system using $Pd(OAc)_2$ (5 mol%)/O_2/DMSO has been developed and acyclic, cyclic, and arene-containing tosylamides are transformed into five- and six-membered ring products containing an allylic nitrogen moiety.[32,32a–32c] Particularly interesting is the clean cyclization of tosylamide **136** to the dihydroquinoline

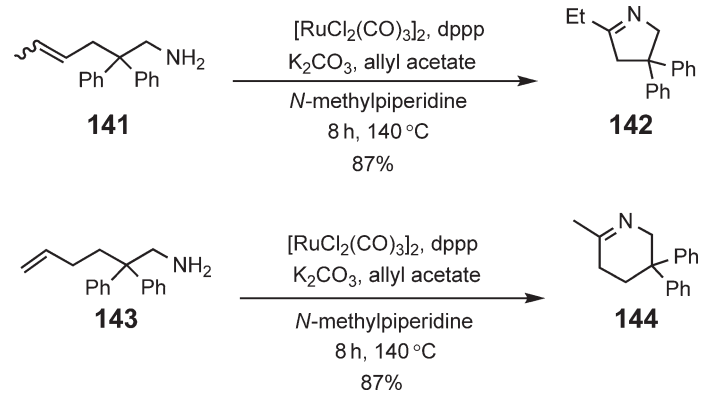


Scheme 23

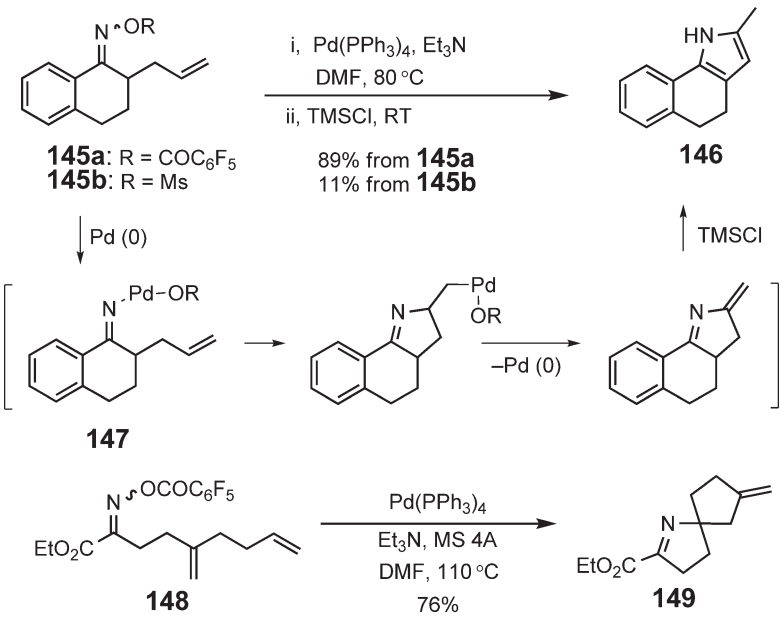
137 as the single product (Scheme 23).[32] This example contrasts with the following work, where the indole **138** was formed from the same substrate **136** just by adding pyridine as an additive.[32a] The recent mechanistic studies of this system revealed that pyridine promoted a palladium oxidation, thereby increasing catalytic efficiency in the oxidative amination reaction. Indeed, the oxidative cyclization of **139** worked remarkably well in the presence of pyridine [$Pd(OAc)_2$/pyridine = 1/2], giving pyrrolidine **140** in 87% yield within 2 h.

Although sulfonamides and carboxamides could be employed as a nucleophile for the cyclization, it is not easy to achieve the cyclization with aliphatic amines due to their strong coordination to the electrophilic palladium(II) catalyst. Recently, the first ruthenium-catalyzed oxidative amination of aminoalkenes to the corresponding cyclic imines was reported (Scheme 24).[33,33a] Treatment of **141** with 2 mol.% $[RuCl_2(CO)_3]_2$ and 5 mol% dppp in the presence of K_2CO_3 and allyl acetate in *N*-methylpiperidine at 140 °C for 8 h gave didehydropyrrolidine **142** in 87% yield. This method can be applied in the formation of didehydropiperidine **144** from terminal alkene **143**. The ring-size dependence of cyclization rates and yields follows the order 5 > 6 >> 7.

Though some palladium(II)-mediated cyclizations of unsaturated oximes were developed to synthesize nitrogen-heterocycles, palladium(0)-catalyzed cyclization involving the sp^2[2,2a,2b] nitrogen atom of oximes with the N–O bond cleavage has been developed by Narasaka's group.[34,34,34b] They reported that *O*-pentafluorobenzoyloxime **145a** readily afforded tricyclic pyrrole **146** in 89% yield after heating with triethylamine and a catalytic amount of $Pd(PPh_3)_4$ in DMF, followed by isomerization with TMSCl (Scheme 25). However, the Beckmann rearrangement mainly proceeded in the reaction of the corresponding *O*-methylsulfonyloxime **145b**, giving **146** in poor yield. The alkylideneaminopalladium(II) species **147** are proposed as intermediates for the cyclization. This nitrogen Heck-type reaction was successfully applied to the synthesis of spiro-imine **149** from the diene **148**.

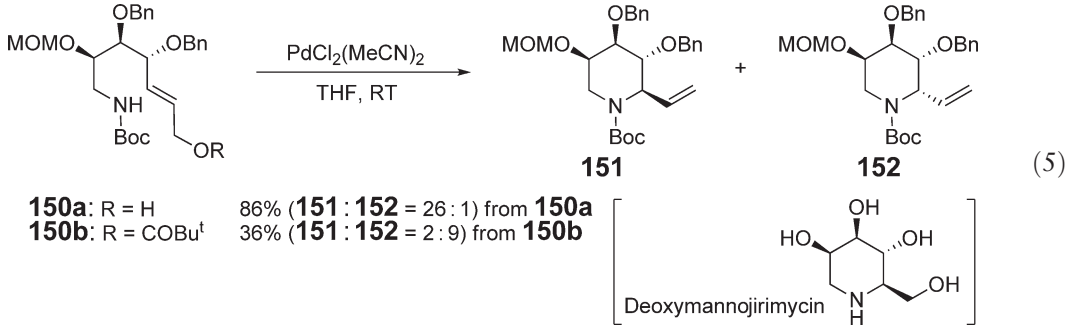


Scheme 24



Scheme 25

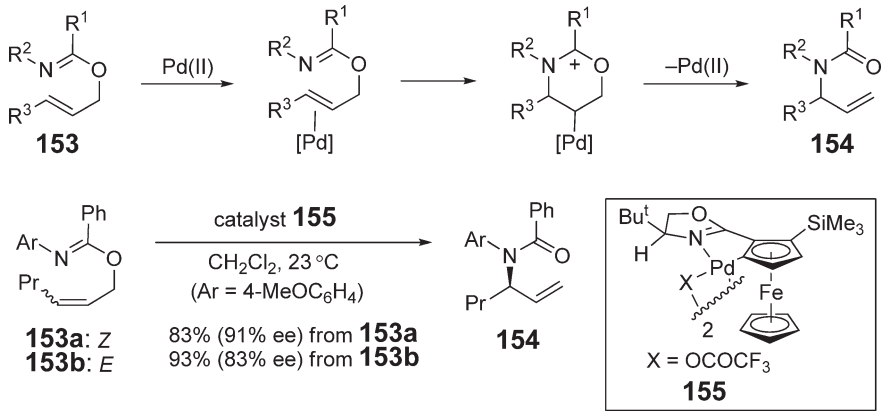
Nitrogen-heterocycles can also be readily synthesized from allylic alcohol derivatives bearing amino and amido groups.[35,35a,35b] During the synthetic studies on 1-deoxymannojirimycin, Hirai and co-workers reported the preparation of chiral piperidine **151** from the optically active urethane **150a** by palladium(II)-catalyzed cyclization and subsequent palladium hydroxide elimination (Equation (5)).[35,35a] They observed that the catalytic system worked well without any reoxidant due to regeneration of the palladium(II) species. In addition, the reaction proceeded with high diastereoselectivity, giving the *trans*-adduct **151**, whereas the same reaction of pivaloyl ester **150b** afforded the diastereomer **152** with moderate stereoselectivity.



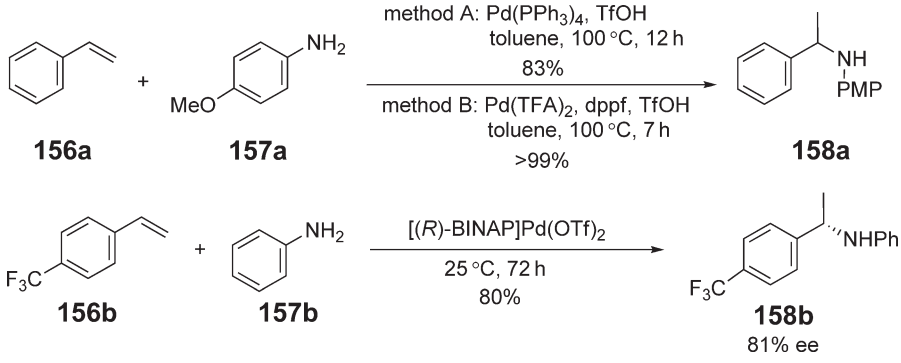
(5)

Overman *et al.* described an interesting palladium(II)-catalyzed rearrangement of allylic imidates **153** to obtain allylic amines **154** (Scheme 26).[36,36a–36c] A cyclization-induced rearrangement mechanism is proposed for this reaction, in which the attack of the imidate nitrogen on a palladium(II)-complexed alkene and subsequent deoxypalladation to yield amide are pivotal steps. To develop asymmetric reaction, they designed and synthesized the ferrocenyl oxazoline palladacycle **155**.[36] The reaction of *N*-PMP-imidate **153a** with 5 mol.% catalyst **155** provided the rearranged allylic amide **154** with high enaniopurity (91% ee). The *Z*-imidate **153a** rearranged with higher enantioselectivity than the *E*-imidate **153b**.

The catalytic intermolecular hydroamination of alkenes is a highly desirable, but difficult, process.[31b,31c,31e,37,37a–37f] Recently, the efficient method using a late transition metal-catalyst has been developed by Hartwig's group (Scheme 27).[37] They reported that both the palladium(0)- and palladium(II)-catalyzed hydroamination of vinylarene **156a** with aromatic amines **157a** in the presence of TfOH (methods A and B) proceeded smoothly to afford the *sec*-phenethylamine **158a** in good yield. In addition, the method was successfully applied to the asymmetric synthesis of **158b** by using BINAP as a chiral ligand.

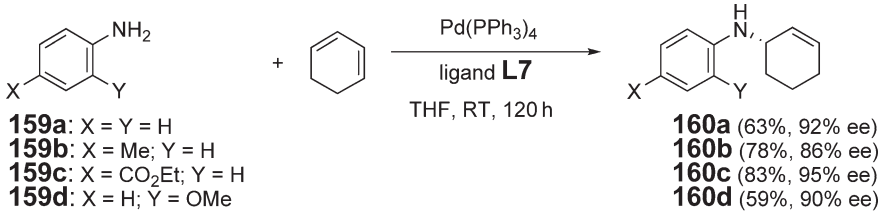


Scheme 26

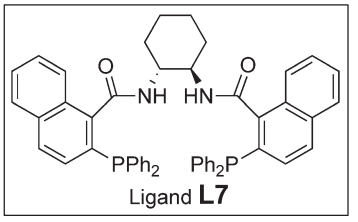


Scheme 27

Hartwig's group also discovered the palladium-catalyzed regioselective 1:1 hydroamination of 1,3-dienes with anilines by a high-throughput colorimetric assay to identify efficient catalysts (Equation (6)).[37a,37b] The reaction of cyclohexadiene with anilines **159a–d** in the presence of 2 mol.% $Pd(PPh_3)_4$ and 10 mol.% TFA as catalyst and cocatalyst, respectively, in toluene furnished the corresponding allylic anilines **160a–d** in high yields regardless of the substituents on the aniline. Furthermore, they sought an enantioselective version of this process and found that the same reaction with the chiral ligand **L7**, but without acid as cocatalyst, showed a promising stereoselectivity and conversion of various arylamines and cyclohexadiene.



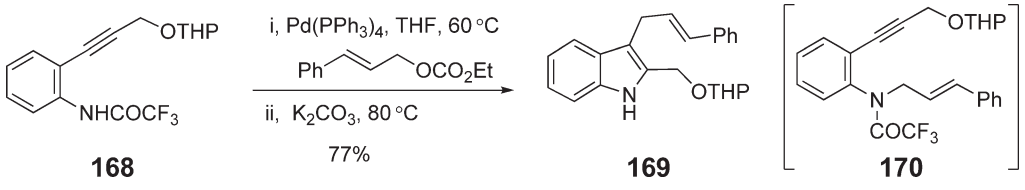
(6)



10.15.4.2 Reaction with Alkynes

The intramolecular reaction of alkynes bearing an amino or an imino group is promoted by various types of metal complexes such as palladium, gold, and tungsten. These reactions have been extensively studied to prepare a wide variety of nitrogen heterocycles, since the first palladium(II)-mediated synthesis of pyrroles was described by Utimoto's group in 1981. The cyclizations of 2-(1-alkynyl)anilines **161** to 3-substituted indoles **164** with organopalladium complexes are representative examples of these reactions (Scheme 28).[38,38a–38f,39,39a–39f] The cyclization is considered to proceed through the intermediacy of the (η^2-alkyne)organopalladium complex **162**, formed by coordination of the alkyne to an organopalladium complex R^1PdX generated *in situ*, that undergoes an intramolecular nucleophilic attack by the nitrogen atom on the carbon–carbon triple bond. Subsequently, the resultant σ-indolylpalladium intermediate **163** affords the 3-substituted indole **164** by a reductive elimination. This methodology was successfully applied to an elegant synthesis of the parent indolo[2,3-a]carbazole ring system **167**, common to several biologically active compounds such as arcyriaflavin A, from **165** and **166**.[39d]

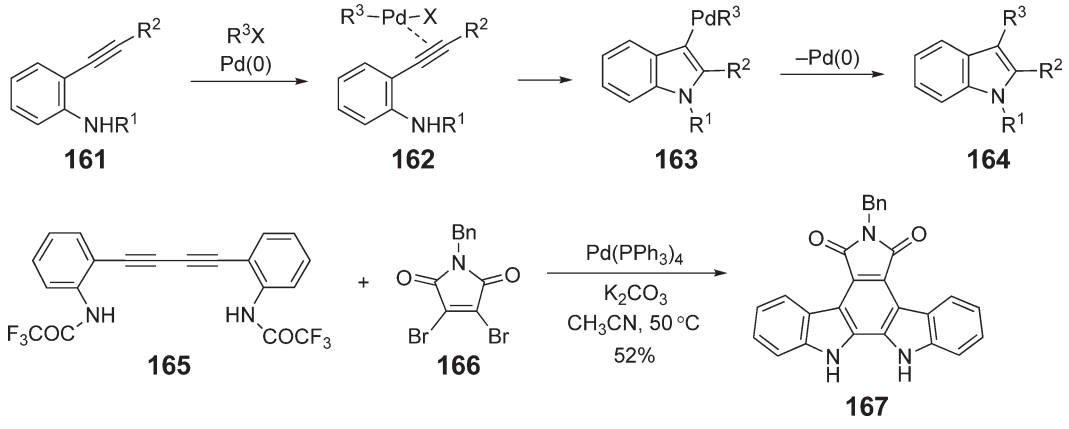
Similarly, η^3-allylpalladium complexes were also employed as promoters for the cyclization.[39,39a,39b] The palladium(0)-catalyzed reaction of alkyne **168** with allylic carbonate in THF at 60 °C gave the *N*-allyl product **170** instead of the desired product **169**. However, without isolation of **170**, the reaction mixture was heated at 80 °C with 5 equiv. of K_2CO_3, providing **169** in 77% yield (Equation (7)). The nitrogen atom intervenes in the process as a nucleophile in the *N*-allylation step and as a leaving group in the cyclization step.



168 **169** **170** (7)

On the other hand, palladium-catalyzed oxidative cyclocarbonylation of alkynes represents an efficient and versatile approach to the one-step synthesis of functionalized heterocycles. The reaction of *o*-ethynylaniline **171** was carried out in MeOH at 50 °C in the presence of PdI_2 and KI under a 4 : 1 CO/air mixture (20 atm) and afforded (*E*)-dihydroindol-2-one **172** as a single isomer in 64% yield (Scheme 29).[40] The reaction also proceeds smoothly in the cases of secondary amines but cannot be applied to substrates bearing an internal triple bond. Larock *et al.* reported the palladium(II)-catalyzed cyclization-olefination domino reaction of 2-(1-alkynyl)arylaldimine **173** in the presence of various alkenes to prepare a variety of 4-(1-alkenyl)isoquinolines **174** in good to excellent yields.[40b] The presence of a chelating methoxy group stabilizes the organopalladium intermediate formed by electrophilic attack of the palladium(II) salt on the alkyne. Subsequent Heck coupling with the olefin affords the final product.

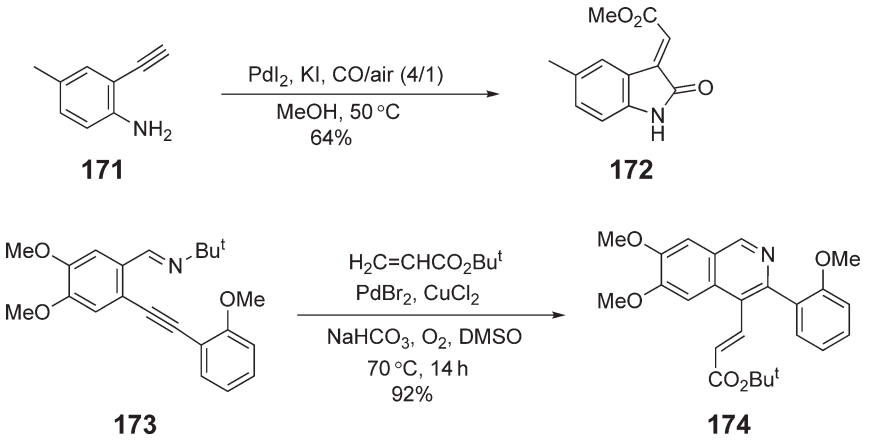
In contrast to the palladium-catalyzed reactions, little attention has been paid to other transition-metal catalysts. Recently some efficient reactions using copper(I or II), gold(III), platinum(II), and tungsten(0) have been developed for the synthesis of nitrogen-heterocycles. The copper-catalyzed cyclizations of 2-alkynylaniline derivatives into



161 **162** **163** **164**

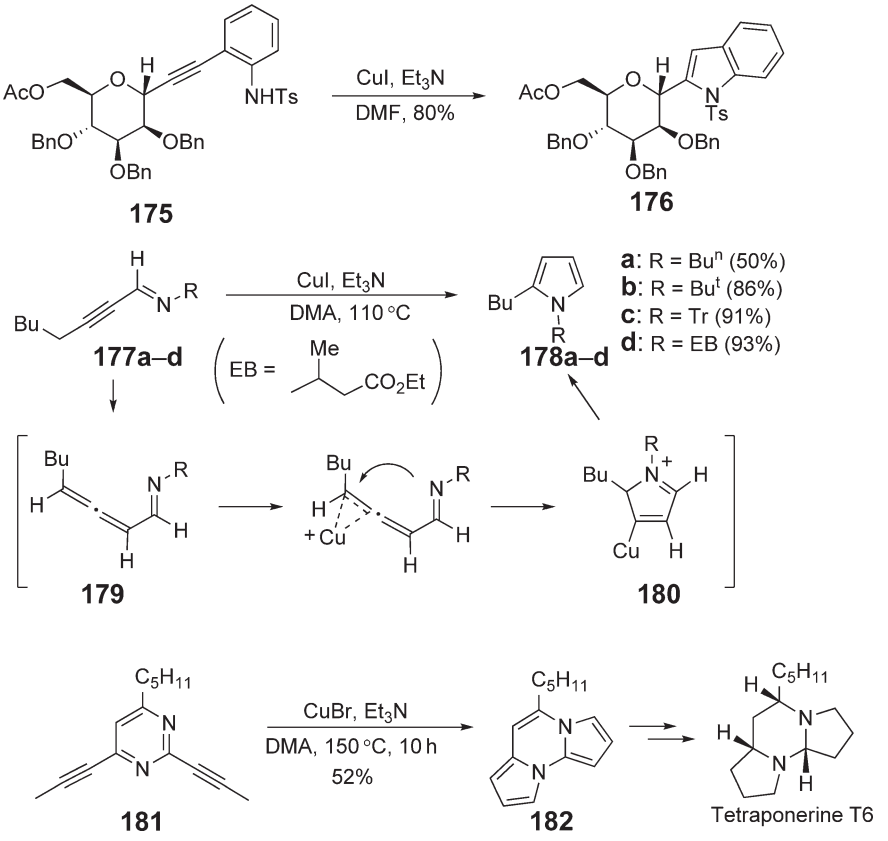
165 **166** **167**

Scheme 28



Scheme 29

2-substituted indoles were described by several groups.[41,41a–41e] Both copper(I) and copper(II) salts such as CuI and $Cu(OTf)_2$ can be employed for the cyclization. Indeed, the mannosylindole **176**, a key intermediate for the total synthesis of α-*C*-mannosyltryptophan, was synthesized in 80% yield by treatment of tosylanilide **175** with CuI and Et_3N in DMF (Scheme 30).[41a] Gevorgyan *et al.* reported the copper(I)-assisted cycloisomerization of alkynyl imines to pyrrole-containing heterocycles.[41d] The *N*-substituted alkynyl imines **177a–d** underwent cycloisomerization in the presence of CuI (30 mol.%) in Et_3N/DMA (1/7) at 110 °C to give pyrroles **178a–d** in moderate to good yields. They found that the 3-(ethylbutyryl) (EB) group was the best *N*-substituent for this reaction. Mechanistic studies revealed that the reaction consisted of three steps, that is, the base-catalyzed propargyl-allenyl isomerization of **177** to the

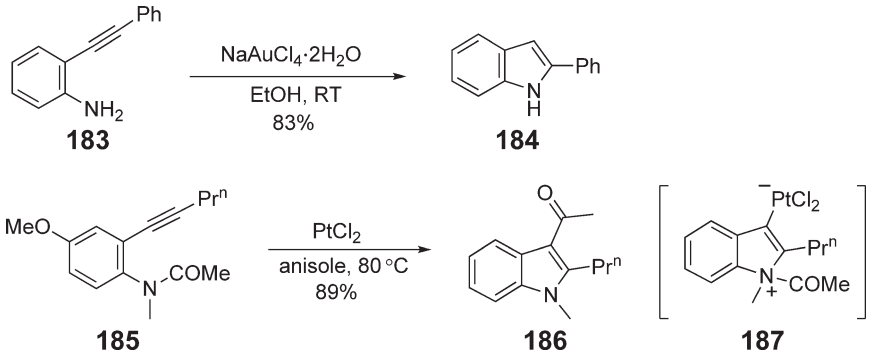


Scheme 30

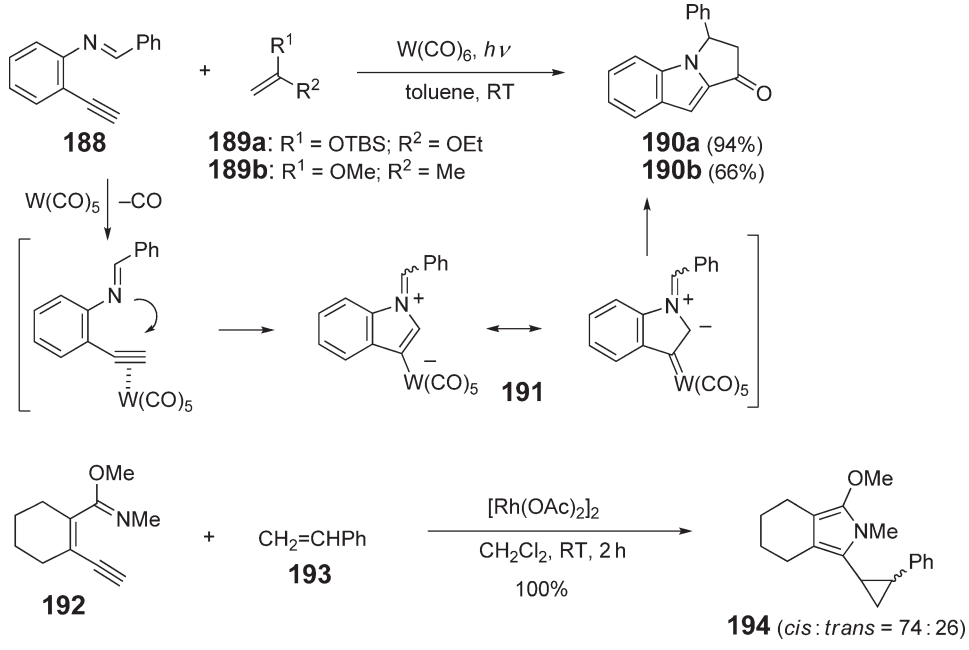
allenyl imine **179**, the copper(I)-assisted nucleophilic attack of the imine on the terminal double bond of the allene, and the subsequent isomerization of **180** into the pyrrole. Furthermore, the method can be applied to cyclic alkynyl imine **181**, giving fused heteroaromatic compound **182** via the double cycloisomerization. The resulting product **182** was successfully converted into (±)-tetraponerine T6.[41e]

Marinelli's group described an efficient synthesis of 2-alkynylanilines to 2-substituted indoles with gold(III) catalyst under mild conditions (Scheme 31).[42] Treatment of 2-alkynylaniline **183** with 4 mol.% of $NaAuCl_4 \cdot 2H_2O$ in EtOH at room temperature gave the indole **184** in 83% yield. Since the reaction does not require any protecting groups of nitrogen and harsh reaction conditions, the protocol is general and compatible with a large variety of functional groups. Yamamoto *et al.* reported the platinum(II)-catalyzed cyclization of 2-alkynylanilides with an intramolecular migration of *N*-acyl groups (Scheme 31).[42a] The reaction of **185** with 5 mol% $PtCl_2$ in anisole at 80 °C proceeded smoothly to afford the 3-acetylindole **186** in 89% yield. Not only can the methylamides but other amides such as formamides and benzamides can also be used. The zwitterionic Pt-complex **187** is proposed as an intermediate of this cyclization.

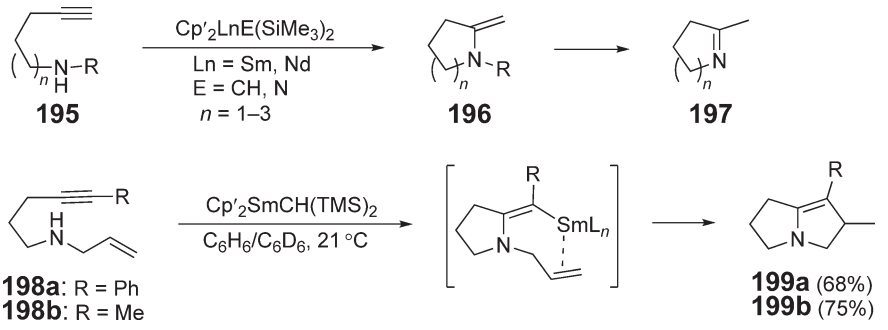
Iwasawa and co-workers developed a facile method for the construction of polycyclic indole derivatives **190a** and **190b** by the tungsten(0)-catalyzed reaction of *N*-(2-(1-alkynyl)phenyl)imine **188** with the electron-rich alkenes **189a** and **189b** (Scheme 32).[42b] Photoirradiation of a mixture of imine **188** and ketene silyl acetal **189a** with 10 mol% of



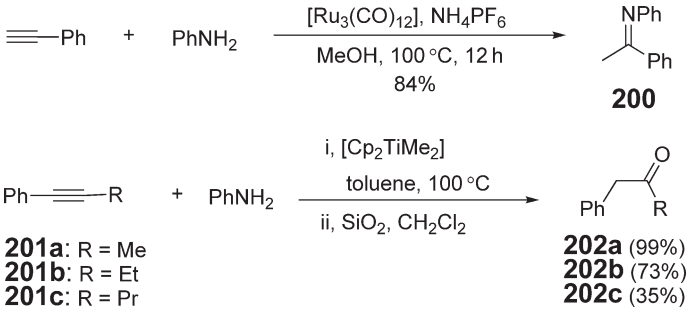
Scheme 31



Scheme 32



Scheme 33



Scheme 34

$W(CO)_6$ in toluene at room temperature gave the tricyclic adduct **190a** in 94% yield after acidic workup. This reaction forms the tungsten-containing azomethine ylide **191**, which undergoes the [3 + 2]-cycloaddition with **189a**. The rhodium(II)-catalyzed cyclization of the ene–yne–aldimine **192** with alkene **193** into the cyclopropane **194** was reported by Uemura and Ohe (Scheme 32).[42c]

The organolanthanide-catalyzed hydroamination of the aminoalkynes **195** gives the cyclic imines **196** or cyclic enamines **197** in good yields (Scheme 33).[43,43a–43g] Marks *et al.* reported that the reaction of the aminoenynes **198a** and **198b** in the presence of 2 mol% $Cp'_2SmCH(TMS)_2$ in benzene at 21 °C proceeded smoothly, providing the pyrrolizines **199a** and **199b** in good yields through a sequential amination-carbocyclization, resulting in bicylization.[43,43a]

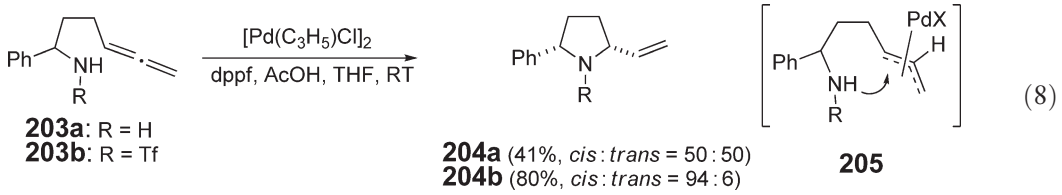
Compared to intramolecular cyclization, intermolecular hydroamination of alkynes is more difficult, and only a few approaches have been reported to date. Wakatsuki *et al.* reported the ruthenium-catalyzed hydroamination of terminal alkynes with anilines (Scheme 34).[43d] The reaction of phenylacetylene with aniline in the presence of 0.1 mol% $Ru_3(CO)_{12}$ and 0.3 mol% NH_4PF_6 in MeOH at 100 °C for 12 h gave ketimine **200** in 84% yield, while only a 2.6% yield of the product was obtained under the same conditions without the additive (NH_4PF_6). Later, Doye's group reported that dimethyltitanocene (Cp_2TiMe_2) could be employed for the reaction of unsymmetrically substituted alkyne **201a–c** with aniline, affording the anti-Markovnikov products **202a–c** as a single regioisomer in moderate to good yields.[43e]

10.15.4.3 Reaction with Allenes

In addition to alkenes and alkynes, allenes have attracted considerable interest due to their unique reactivity and multireaction sites. Therefore, transition-metal-catalyzed nucleophilic addition reaction of amines and imines to allenes has been extensively studied to prepare biologically important amines and nitrogen-heterocycles.[31,31d]

Yamamoto and co-workers found that amine **203a** or sulfonyl amide **203b**, bearing a terminal allene, underwent a facile intramolecular hydroamination in the presence of a catalytic amount of $[Pd(C_3H_5)Cl]_2$, dppf, and AcOH, giving pyrrolidines **204a** and **204b**, respectively, in good to high yields (Equation (8)).[44,44a–44c] Only *exo*-cyclization products were obtained. The proposed reaction mechanism is as follows. Initially, acetic acid undergoes oxidative

addition to the palladium(0) catalyst to give hydridopalladium(II) complex, H-Pd-OAc·L_2. Hydropalladation of the complex with allenic amines **203** and subsequent intramolecular nucleophilic addition of an amino group to the resultant π-allylpalladium species **205** furnish the cyclized products **204**.



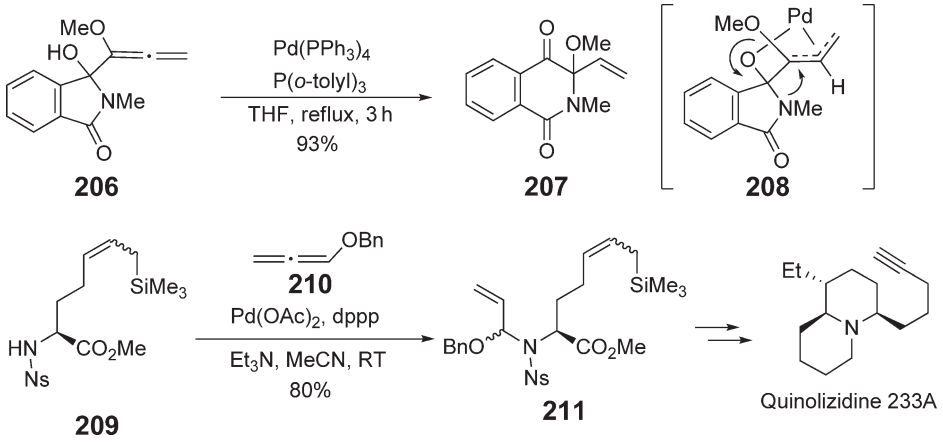
(8)

Nagao's group reported the palladium(0)-catalyzed ring expansion reaction of the methoxyallenylisoindolinone **206** to give the isoquinolone **207** in high yield (Scheme 35).[45,45a,45b] In this reaction, the oxidative addition of an O–H bond of **206** to the palladium(0) catalyst should be a key step to obtain a π-allylpalladium intermediate **208**. Recently, Hiemstra and Rutjes reported the intermolecular hydroamidation of **209** with benzyloxyallene **210** in the presence of a catalytic amount of $Pd(OAc)_2$ and dppp to synthesize the allylic *N*,*O*-acetal **211**, a key intermediate for a formal synthesis of quinolizidine 233A.[46,46a] Although the use of sulfonamides resulted in excellent chemical yields, less acidic amides such as a *N*-Boc amide can also be employed as the substrates in the presence of DBU instead of Et_3N.

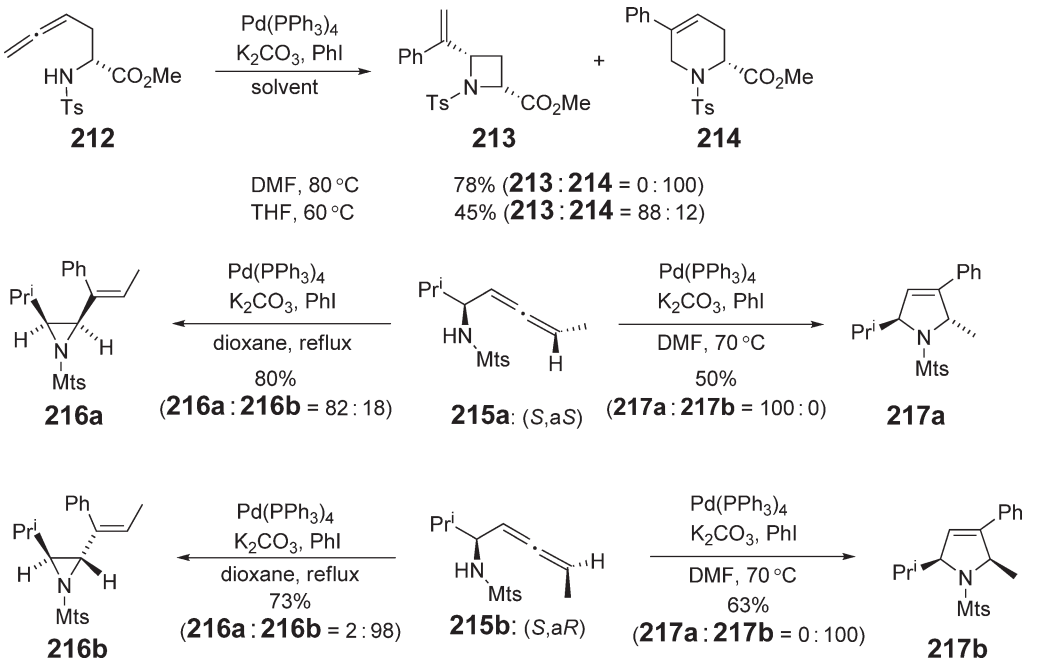
The palladium(0)-catalyzed cyclization of amide-allenes via a carbopalladation has been developed by several groups. The reaction proceeds through the carbopalladation of the allene moiety with an organopalladium species (R-Pd-X), generated by oxidative addition of R-X to palladium(0), and subsequent reductive elimination of the resultant π-allylpalladium intermediate.[47,47a–47f]

Hiemstra's group reported the selective formation of azetidine **213** and tetrahydropyridine **214** via the palladium-catalyzed cyclization of allene-substituted amino acid **212** (Scheme 36).[46b–46d] Although the thermodynamically more stable six-membered adduct **214** was obtained as the single product when the reaction was carried out in DMF at 80 °C, the use of THF as a solvent at a lower temperature resulted in the predominant formation of the *cis*-azetidine **213**. Ibuka and Ohno reported that the palladium(0)-catalyzed reaction of *N*-arylsulfonyl-α-aminoalkylallenes provided the corresponding 2-alkenylaziridines and 3-pyrrolines stereoselectively.[48,48a] Whereas the palladium(0)-catalyzed reaction of (*S*,a*S*)-amido-allene **215a** with PhI and K_2CO_3 in refluxing 1,4-dioxane yielded 2,3-*cis*-*E*-aziridine **216a** predominantly, the same reaction of (*S*,a*R*)-isomer **215b** afforded 2,3-*trans*-*E*-aziridine **216b** preferably. In contrast, palladium(0)-catalyzed cyclization of **215a** and **215b** in DMF gave 2,5-*trans*-pyrroline **217a** and 2,5-*cis*-pyrroline **217b**, respectively.

Ma *et al.* described the palladium(0)-catalyzed three-component tandem double-addition-cyclization reaction of 2-(2,3-allenyl)malonate **218**, PhI, and *N*-Ts-imine **219** for the stereoselective synthesis of 2,5-*cis*-pyrrolidine **220**

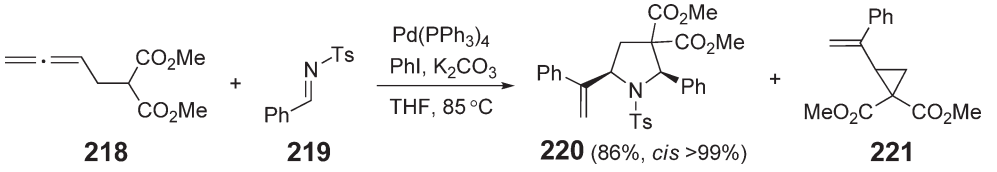


Scheme 35



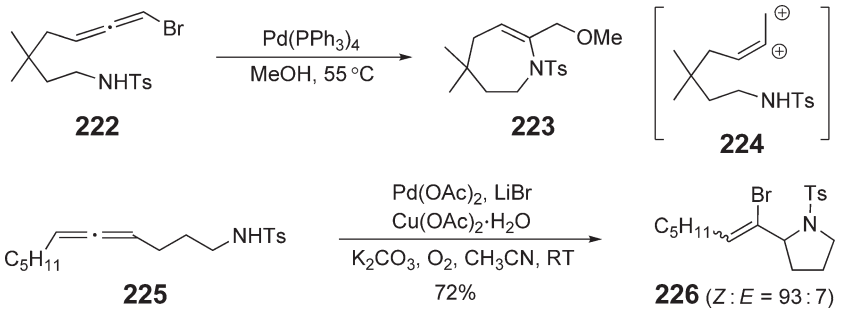
Scheme 36

(Equation (9)).[49,49a–49d] The solvent (THF or 1,4-dioxane) and reaction temperature (85 °C) are the keys to a smooth relay of the unit processes and high stereoselectivity of **220**. The electron-withdrawing tosyl group of the imine is important for this reaction, since the same reaction of **218** with *N*-(4-chlorobenzylidene)aniline instead of **219** afforded the cyclopropane **221** in 92% yield.

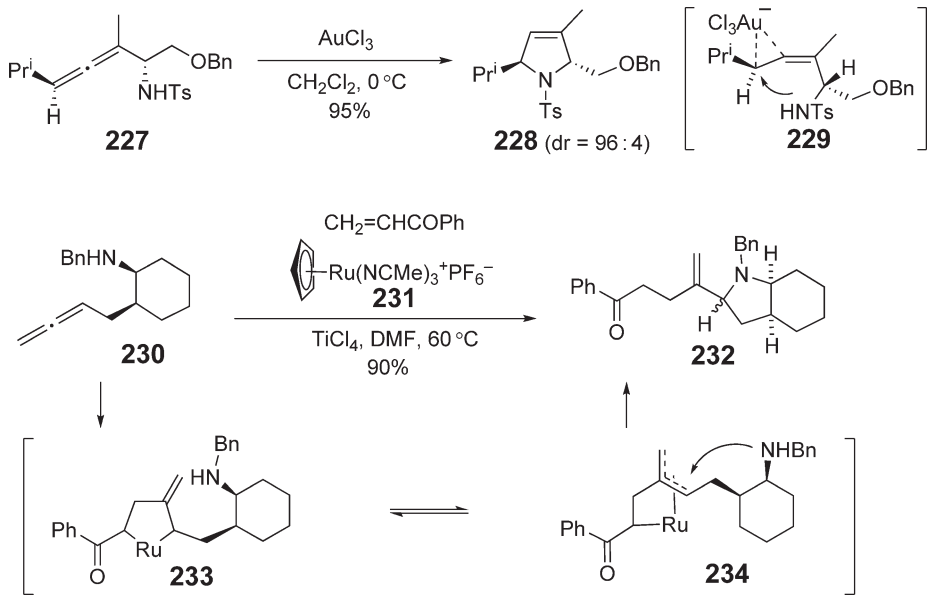


(9)

Tanaka and Ohno developed the palladium(0)-catalyzed cyclization of bromoallene **222** bearing a sulfonamide for the synthesis of medium-sized heterocycle **223** (Scheme 37).[48b] In this reaction, bromoallene acts as an allyl dication equivalent **224**, and two different nucleophiles can be introduced regioselectively. The intramolecular nucleophilic



Scheme 37



Scheme 38

attack takes place exclusively at the central carbon atom of the allene moiety, giving seven- and eight-membered ring adducts in good yields. Bäckvall's group reported that palladium(III)-catalyzed 1,2-oxidation of the allenic tosylamide **225** with LiBr and K_2CO_3 in the presence of $Cu(OAc)_2$ as a reoxidant afforded the 2-(1-bromoalkenyl)-*N*-tosylpyrrolidine **226** in good yield.[50,50a] The reaction works well with benzyl-ureas and carbamates as well as tosylamides with moderate to good *Z*-selectivity.

Krause's group reported a highly efficient gold(III)-catalyzed cycloisomerization of α-aminoalkylallenes that provides the corresponding 3-pyrrolines in high yields with efficient chirality transfer for an allene's axis to a carbon center (Scheme 38).[50b] Treatment of the diastereomerically pure α-amidoallene **227** with 2 mol% $AuCl_3$ in dry CH_2Cl_2 at 0 °C gave the 2,5-*trans* adduct **228** (dr = 96/4). In this reaction, they observed an interesting dependence of the chirality transfer and reactivity on the *N*-protecting group. The intermediate **229** was proposed to explain the stereoselectivity of this cyclization. Trost *et al.* discovered the ruthenium(I)-catalyzed cyclization of secondary γ- and δ-aminoalkylallenes to pyrrolidines and piperidines.[50c] The reaction of *N*-benzylaminoalkylallene **230** with phenyl vinyl ketone in the presence of the ruthenium(I) catalyst **231** (10 mol%) and $TiCl_4$ (15 mol%) gave the pyrrolidine **232** in 90% yield. Similarly, by switching the cocatalyst from $TiCl_4$ to $MeAlCl_2$, various piperidines were prepared from δ-(*N*-benzylamino)alkylallenes. The key step is the formation of ruthenacycle **233** from **230** and phenyl vinyl ketone, which is followed by the intramolecular nucleophilic addition of the amino group to the π-allyl complex **234**, generated from **233**.

10.15.5 Conclusion

We have shown the construction of a carbon–nitrogen bond based on transition metal-catalyzed reactions. In addition to the fundamental allylic amination and its asymmetric version, the reaction of the π-allyl intermediate, generated from alkenyloxirane, alkenylaziridine, or propargyl alcohol derivative, disclosed a broader aspect of the utility of transition metal-catalyzed amination for the synthesis of various types of amino compounds. We have also covered the carbon–nitrogen bond formation through the crosscoupling reaction, the oxidative addition-b-elimination, and the hydroamination. These transition metal-catalyzed aminations will be particularly useful because it does not require the excess of reagents and the use of moisture-sensitive irritant catalysts. This domain offers opportunities for further exploration with intriguing possibilities in transition metal-catalyzed reactions.

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10.16
C–E Bond Formation through Element–Element Addition to Carbon–Carbon Multiple Bonds

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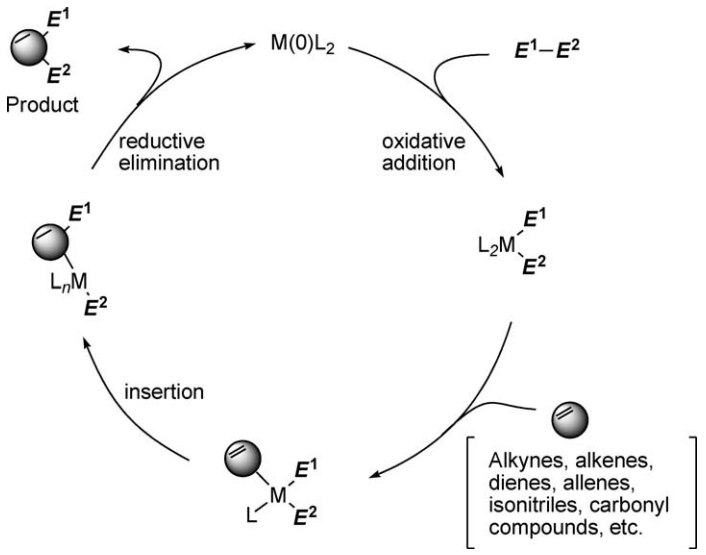
10.16.1 Overview

Addition of σ-bonds containing metallic elements to carbon–carbon multiple bonds is regarded as the most atom-economical and, thus, efficient method for the formation of metal–carbon bonds. Following the rapid development of hydrometallation reactions, additions of σ-bonds between non-hydrogen elements, that is, element–element bonds, have been developed with increasing demands for highly functionalized organometallic compounds. Typically, such element–element additions to unsaturated multiple compounds are accelerated by transition metal complexes. A brief overview is given here before describing the recent advancements in this field.

The chemistry of element–element additions began with the investigation of the nature of the silicon–silicon σ-bond, whose energy levels are comparable to those of carbon–carbon "double" bonds. It was assumed that the characteristic frontier molecular orbitals, that is, the high-lying HOMO and the low-lying LUMO, were able to interact with transition metal complexes easily, like carbon–carbon σ-bonds. Such orbital interaction was expected to lead to the activation of the Si–Si bonds for catalytic reactions. Catalytic addition of the Si–Si bonds to carbon–carbon unsaturated bonds, which might proceed through the activation of Si–H bonds of hydrodisilanes, was realized in 1972.[1,2] Following this finding, two independent groups reported bis-silylation of alkynes, which may involve direct



Scheme 1

activation of the Si–Si bonds.[3,4] The reaction mechanism is presumed to involve oxidative addition of the Si–Si bond to palladium(0) species, which results in the formation of bis(silyl)palladium(II) intermediate. The isolation and characterization of the bis(silyl)palladium complexes[5–10] and related nickel[11] and platinum complexes[12–15] have been reported. Subsequent insertion of an alkyne into the Si–Pd bond of the bis(silyl)palladium complex followed by reductive elimination of an Si–C linkage results in the production of the bis(silyl)alkenes. In accord to the presumed reaction mechanism, the catalytic bis-silylation proceeds in a *cis*-fashion.

Following the catalytic bis-silylation, important variants were reported, where element–element bonds other than Si–Si bonds are activated by transition metal catalysts and undergo insertion of unsaturated organic molecules. The addition of the Si–Sn bonds is one of the important and early developments, since it clearly demonstrated that addition of unsymmetrical element–element bonds proceeds in a regioselective manner. Following these findings, a variety of element–element bonds have been examined in the related addition reactions to a wide range of unsaturated organic compounds. Until now, additions of element–element bonds containing metallic or semimetallic elements such as boron, silicon, germanium, and tin, as well as heteroatoms such as sulfur, selenium, and phosphorus have been developed. In most reactions, reaction mechanisms similar to that of bis-silylation have been suggested, although some may involve a different mechanism. A general mechanism for the transition metal-catalyzed element–element addition is shown in Scheme 1. For the addition reactions of unsymmetrical element–element bonds ($E^1 \neq E^2$), the relative reactivities of E^1–M and E^2–M may have primary impact on the regiochemical outcome of the reaction. In this chapter, all those element–element additions are discussed for some mechanistic aspects and synthetic applications. Since the previous COMC series did not cover these reactions well, each section provides some background with more detailed description of the recent results. In cases where they are relevant, element–element additions that do not require transition metal catalysts are also described. Reviews and accounts related to this area have appeared.[16–35]

10.16.2 Homonuclear Element–Element Bonds

10.16.2.1 Addition of Boron–Boron Bonds

10.16.2.1.1 Addition to alkynes

Addition of a boron–boron bond across a carbon–carbon triple bond is known for some 40 years since the finding that diboron tetrahalides add to alkenes and alkynes in the absence of catalysts.[36] Although the reaction seemed to be potentially attractive, the instability of diboron tetrahalides was the critical drawback for the practical use in synthesis. In 1993, much more stable pinacol ester derivative of diboron was found to add to alkynes in the presence of platinum catalysts such as $Pt(PPh_3)_4$, $Pt(CH_2{=}CH_2)(PPh_3)_2$, and $Pt(CO)_2(PPh_3)_2$ (Figure 1, Scheme 2).[37,38] Other

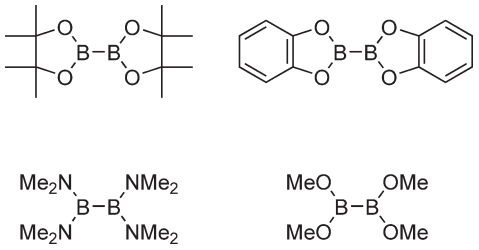
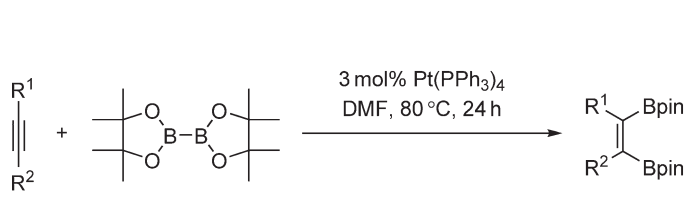


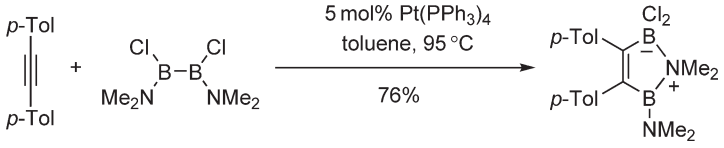
Figure 1 Representative diboron derivatives.



R^1	R^2	*Yield* (%)
n-C_8H_{17}	H	86
cyclo-C_6H_{11}	H	78
$H_2C{=}CH(CH_2)_4$	H	85
$Cl(CH_2)_3$	H	83
$MeO_2C(CH_2)_4$	H	89
$NC(CH_2)_3$	H	79
n-C_3H_7	*n*-C_3H_7	86

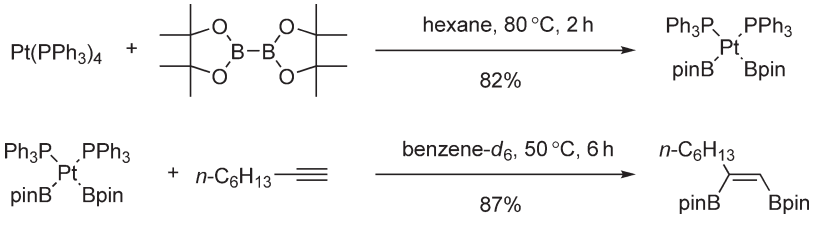
Scheme 2

(alkoxy)diborons such as tetrakis(methoxy)diboron and bis(catecholato)diboron were also effective for diboration, although the reaction of tetrakis(dimethylamino)diboron was found to be sluggish even at 120 °C. 1,2-Dichloro-1,2-bis(dimethylamino)diboron reacts with internal alkynes at 95 °C, affording a cyclic product which arises from redistribution of B–Cl and B–NMe_2 bonds (Equation (1)).[39] The platinum-catalyzed diboration of alkynes with bis(pinacolato)diboron is compatible with various functionalities, such as C═C, alkyl chloride, cyano, and carbonyl groups.



(1)

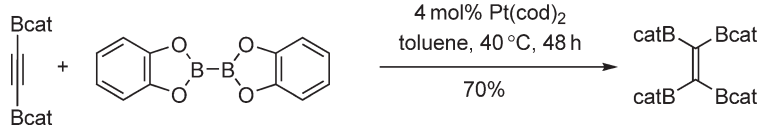
A stoichiometric reaction of tetrakis(triphenylphosphine)platinum(0) with bis(pinacolato)diboron gives *cis*-diborylplatinum(II) complex in high yield (Scheme 3).[38] The diborylplatinum complex then reacts with an alkyne, giving *cis*-diboration product.[40,41] These results indicate that the diboration proceeds through the general mechanism shown in Scheme 1 ($E^1 = E^2 =$ Bpin), which involves the formation of diborylplatinum(II), insertion of an alkyne into the B–Pt bond, and reductive elimination.



Scheme 3

To realize milder reaction conditions, modification of the platinum catalyst system has been examined. A combined use of bis(catecholato)diboron with phosphine-free divalent platinum complex, $PtCl_2$(cod), allows the diboration of alkynes to proceed at RT.[42] The room-temperature diboration has also been achieved with a $Pt(nbd)_3$–monophosphine (Pt/L = 1/1) catalyst.[43]

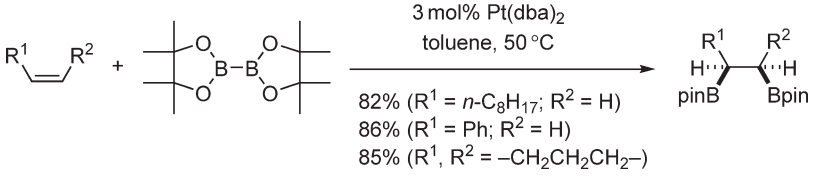
The platinum-catalyzed diboration has been applied to some functionalized alkynes such as 1,3-diynes,[44] 1-borylalkynes,[45] 1,2-diborylethynes,[46,47] and alkynylphosphonates.[45] In particular, diboration of 1,2-diborylethyne gives tetraborylethene, which is a potential precursor for new boron heterocycles (Equation (2)).[46,47]



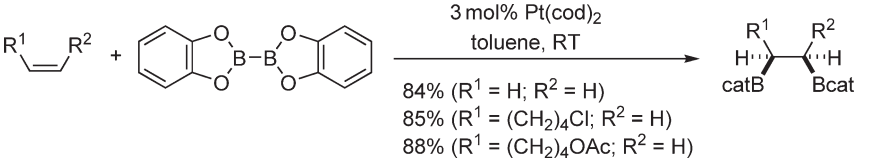
(2)

10.16.2.1.2 Addition to alkenes

Diboration of alkene is catalyzed by Pt(0),[42,48–51] Rh(I),[52–57] Au(I),[52] and Ag(I)[58] complexes. Phosphine-free platinum complexes such as $Pt(dba)_2$ and $Pt(cod)_2$ are efficient catalysts for diboration of alkene, whereas those with phosphine ligands show much lower catalytic activities (Equations (3) and (4)).[48,49] A $PtCl_2$(cod) complex, which may be readily reduced to Pt(0) species with diboron, also catalyzes the addition of bis(catecholato)diboron to alkenes.[42] Platinum-catalyzed diboration has so far been limited to terminal alkenes and strained cyclic alkenes.

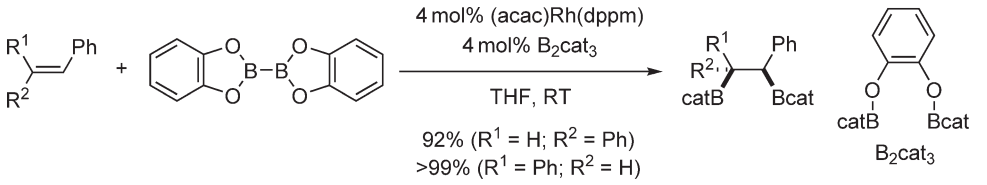


(3)

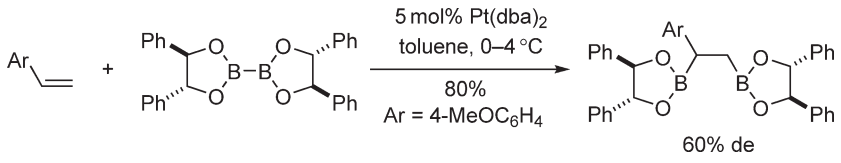


(4)

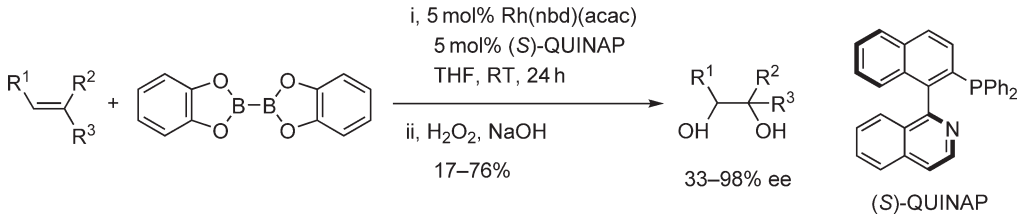
In comparison with the platinum catalysts, rhodium catalysts are much more reactive to effect addition of bis(catecholato)diboron even to non-strained internal alkenes under mild reaction conditions (Equation (5)).[53–55] This higher reactivity prompted trials on the asymmetric diboration of alkenes. Diastereoselective addition of optically active diboron derived from (1*R*,2*R*)-diphenylethanediol for *p*-methoxystyrene gives 60% de (Equation (6)).[50] Furthermore, enantioselective diboration of alkenes with bis(catecolato)diboron has been achieved by using Rh(nbd)(acac)/(*S*)-QUINAP catalyst (Equation (7)).[55,56] The reaction of internal (*E*)-alkenes with *tert*-butylethylene derivatives gives high enantioselectivities (up to 98% ee), whereas lower ee's are obtained in the reaction of internal (*Z*)-alkenes, styrene, and α-methylstyrene.



(5)



(6)

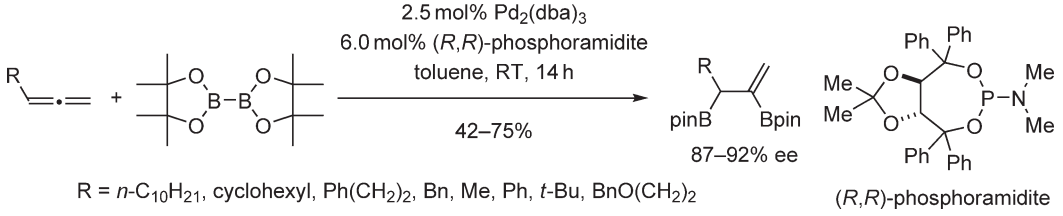


(7)

10.16.2.1.3 Addition to allenes

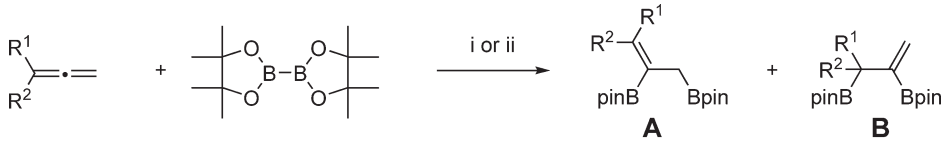
Bis(pinacolato)diboron adds to terminal allenes in the presence of $Pt(PPh_3)_4$ or $Pd(dba)_2/PCy_3$ as a catalyst (Scheme 4).[59] The addition occurs at either the internal or terminal double bond depending on the substituents and the conditions used. The phosphine ligands on platinum also affect the regioselectivity. *tert*-Phosphines having large cone angle, such as PCy_3, favor the terminal addition.

Use of a palladium catalyst bearing monodentate phosphine ligands dramatically improves the regioselectivity of the internal addition (Equation (8)).[60] Enantioselective diboration takes place with an optically active phosphoramidite ligand, giving β-bolylallylborane with up to 92% ee. On the other hand, highly regioselective terminal addition of a diboron takes place in the presence of a catalytic amount of organic iodide, such as 3-iodo-2-methyl-2-cyclohexenone, with phosphine-free palladium catalyst (Equation (9)).[61]



R = *n*-$C_{10}H_{21}$, cyclohexyl, Ph$(CH_2)_2$, Bn, Me, Ph, *t*-Bu, BnO$(CH_2)_2$

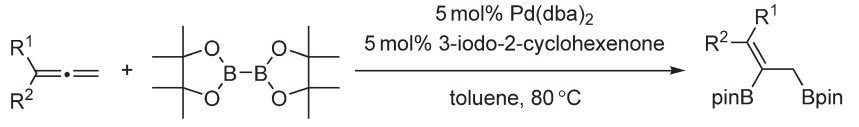
(8)



i, 3 mol% $Pt(PPh_3)_4$, toluene, 80 °C, 16 h
ii, 3 mol% $Pt(dba)_2$, 3 mol% PCy_3, toluene, 50 °C, 16 h

		Conditions i	*Conditions* ii
R^1	R^2	*Yield* (%) (**A** : **B**)	*Yield* (%) (**A** : **B**)
H	H	99	99
n-Bu	H	97 (6 : 94)	90 (16 : 84)
CH_2CO_2Et	H	90 (7 : 93)	82 (8 : 92)
Ph	H	94 (29 : 71)	84 (68 : 32)
$-(CH_2)_5-$		96 (50 : 50)	84 (85 : 15)
Me	Me	98 (76 : 24)	99 (98 : 2)
MeO	H	81 (100 : 0)	85 (100 : 0)
MeS	H	48 (50 : 50)	82 (82 : 18)

Scheme 4

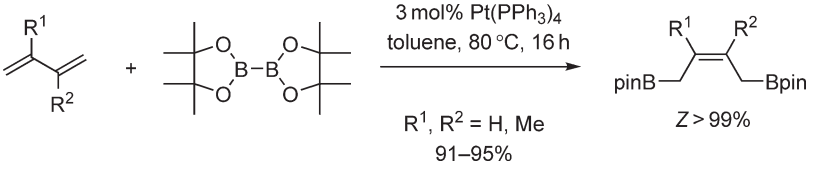


(9)

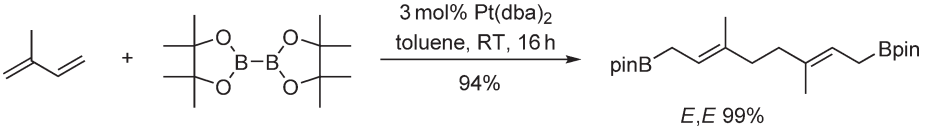
R^1 = H; R^2 = *n*-Bu, Ph, cyclohexyl, cyclopentyl, PhO, 2-IC_6H_4, 4-IC_6H_4 (52–88% yield (*Z* : *E* = 95 : 5–93 : 7))
$R_1 = R_2$ = Me (93% yield)

10.16.2.1.4 Addition to 1,3-dienes

Diborations of 1,3-dienes are carried out in the presence of platinum(0) catalyst. In the $Pt(PPh_3)_4$-catalyzed diboration of 1,3-dienes, 1,4-addition takes place to give (*Z*)-1,4-diboryl-2-alkenes stereoselectively (Equation (10)).[62] In contrast, the $Pt(dba)_2$-catalyzed reaction of 1,3-pentadiene affords 1,2-addition product, in which more substituted C═C bond is left intact (Scheme 5). The use of $Pt(dba)_2$ as catalyst also enables the diborative dimerization of isoprene to occur (Equation (11)).[48]



(10)



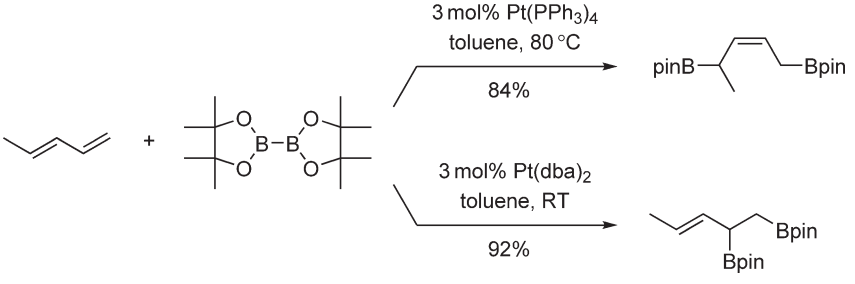
(11)

Attempted reaction of 1,3-pentadiene with the optically active diboron derived from dialkyl tartrate in the presence of a phosphine-free platinum catalyst gave poor diastereoselectivity (20% de).[63] Better selectivity has been attained with a modified platinum catalyst bearing a PCy_3 ligand (Scheme 6).[64] The reaction of allylborane thus obtained with an aldehyde followed by oxidation with basic hydrogen peroxide affords the corresponding diol derivative with moderate ee.

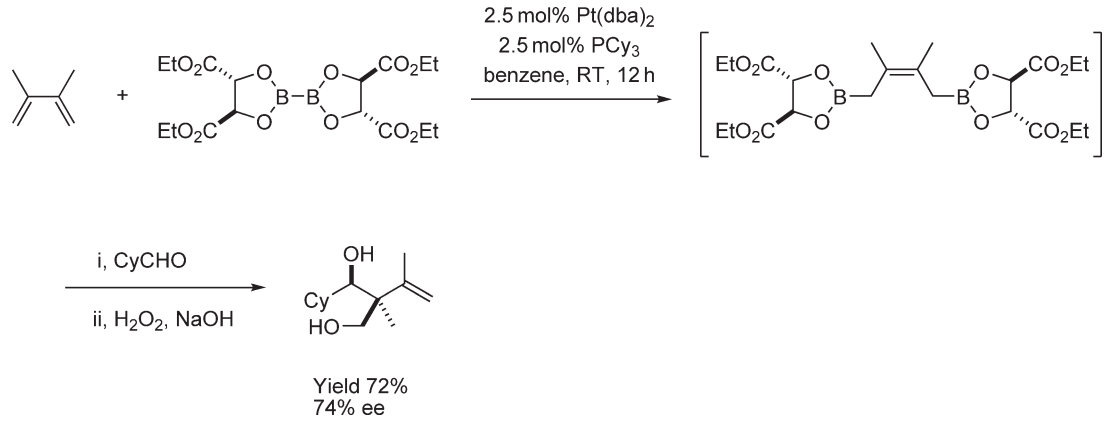
The combination of diboration and subsequent intramolecular allylboration has been applied for the diastereoselective synthesis of a cyclic diol (Scheme 7).[65]

10.16.2.1.5 Addition to activated alkenes

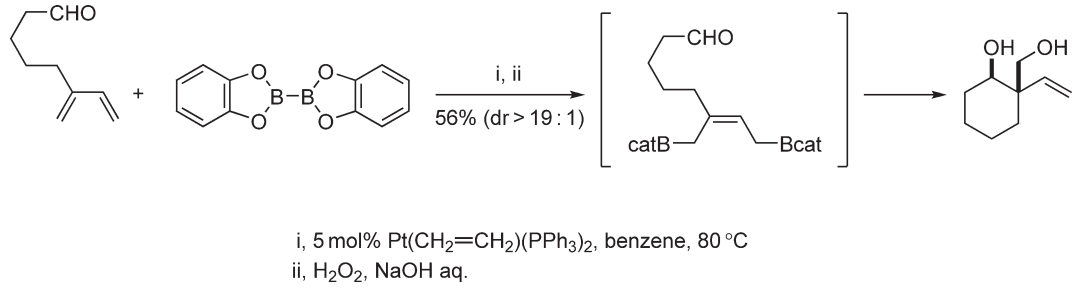
Diboration of α,β-unsaturated ketones is promoted by platinum(0) complexes. Reaction of 4-phenyl-3-buten-2-one with bis(pinacolato)diboron in the presence of a platinum catalyst affords a boryl-substituted (*Z*)-boron enolate, that is, a 1,4-diboration product, in high yield with high stereoselectivity (Scheme 8). The isolated boron enolate is easily hydrolyzed by exposure to water, giving β-boryl ketones in high yields.[66] Similar diboration of α,β-unsaturated ketones has also been achieved with Pt(bian)(dmfu) (bian = bis(phenylimino)acenaphthene, dmfu = dimethyl fumarate).[67] Although the



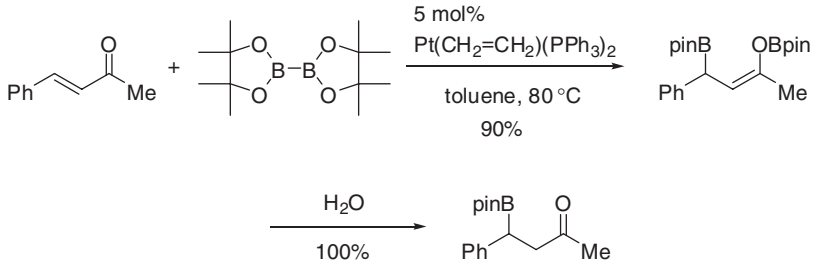
Scheme 5



Scheme 6

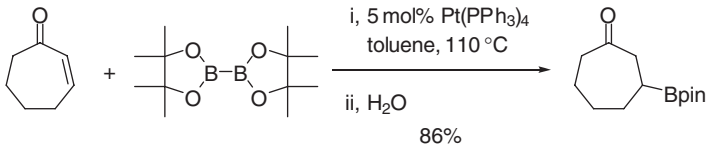


Scheme 7



Scheme 8

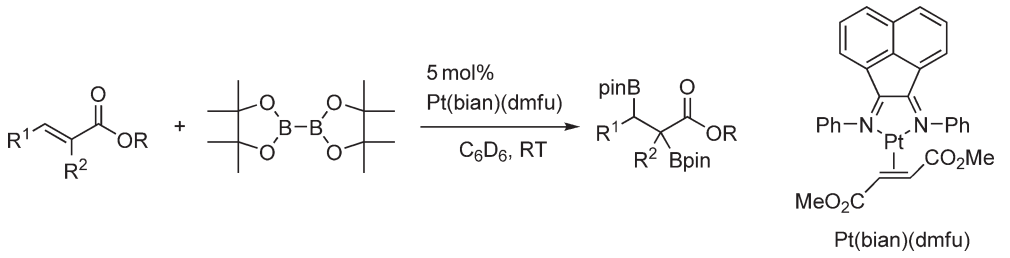
formation of diboryl compounds has not been confirmed, β-boryl ketones and aldehyde are obtained by $Pt(PPh_3)_4$-catalyzed reaction of diboron with α,β-unsaturated ketones including cycloalkenones (Equation (12)).[68] β-Boryl ketones have also been obtained by the reaction of diboron with α,β-unsaturated ketones in the presence of Rh(I)[69] or Cu(I)[70–73] complexes.



(12)

Diboration of α,β-unsaturated esters is catalyzed by the platinum(0)/diimine catalyst, giving α,β-diboryl esters, that is, 3,4-addition products (Equation (13)). Although the α,β-diboryl ester products are hydrolytically more stable than the corresponding 1,4-addition products bearing a boron ester enolate moiety, they gradually undergo hydrolysis

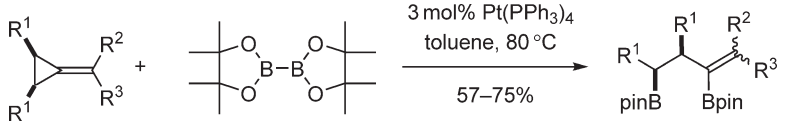
on reacting with a stoichiometric amount of water. Although the diborated product has not been confirmed, a β-boryl ester is also obtained using $Pt(PPh_3)_4$ as the catalyst.[66] A related conjugated addition of the boryl group to α,β-unsaturated esters and nitriles has also been achieved by use of the Wilkinson complex.[69]



(13)

10.16.2.1.6 Addition to methylenecyclopropanes

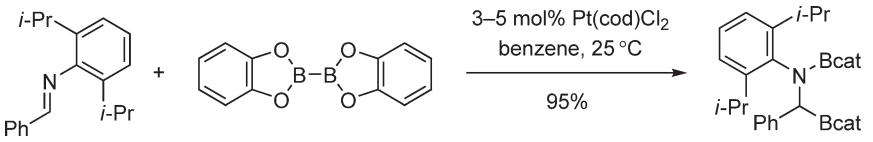
Reaction of bis(pinacolato)diboron to methylenecyclopropanes proceeds with cleavage of the proximal C–C bond of the cyclopropyl ring, giving 2,4-diboryl-1-alkenes (Equation (14)).[74]



(14)

10.16.2.1.7 Addition to Imines

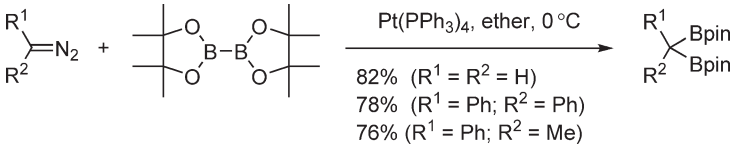
Bis(catecholato)diboron adds to aldimines in the presence of a $PtCl_2(cod)$ catalyst to give α-aminoalkylboronates, which serve as precursors of the boron analogs of α-amino acids (Equation (15)).[42]



(15)

10.16.2.1.8 Addition to diazoalkanes

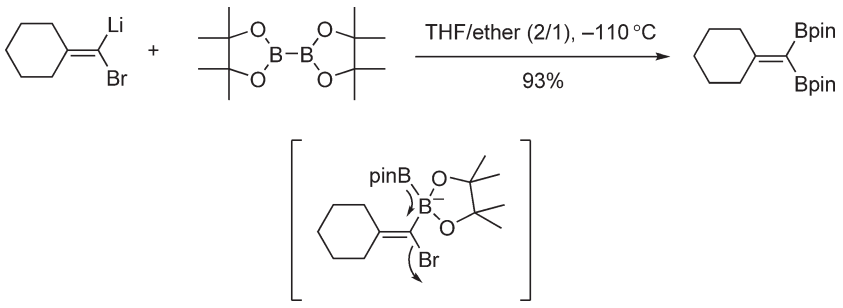
Bis(pinacolato)diboron reacts with diazomethane in the presence of $Pt(PPh_3)_4$ to give bis(pinacolatoboryl)methane in 82% yield (Equation (16)).[67] Under similar conditions, aryl-substituted diazomethanes (R^1 or $R^2 = Ar$) give the corresponding 1,1-diborylalkanes in good yields.[75]



(16)

10.16.2.1.9 Addition to carbenoids

Bis(pinacolato)diboron reacts with 1-halo-1-lithioalkenes, that is, alkylidene carbenoids, affording 1,1-diboryl-1-alkenes in good yields (Scheme 9).[76] The reaction proceeds via formation of a borate intermediate, which is followed by 1,2-migration of the boryl group with elimination of the bromo group.



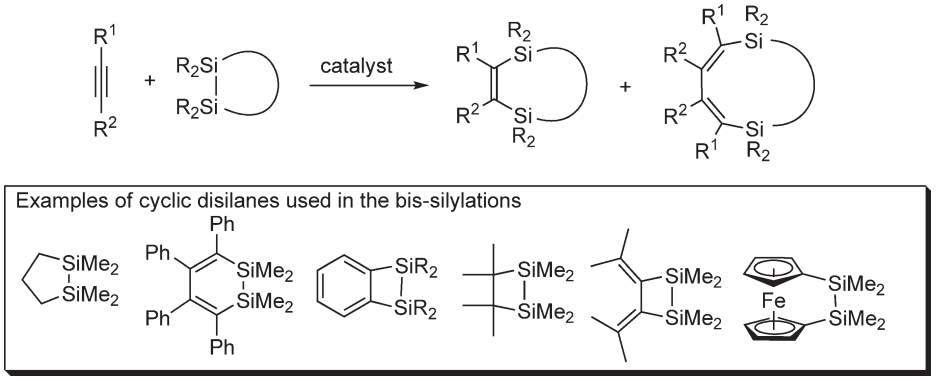
Scheme 9

10.16.2.2 Addition of Silicon–Silicon Bonds

As briefly mentioned in the introductory section, transition metal-catalyzed bis-silylation is the most extensively studied element–element addition reaction. There were many limitations in the scope of the disilanes and alkynes that could be employed in the reaction due to the rather poor activity of the catalysts found at the early stage. Around 1990, several active catalyst systems were found, opening up the new possibility of the bis-silylation in organic synthesis. First, it became possible for hexaorganodisilanes, which were regarded as the least reactive disilanes, to take part in the bis-silylation reaction of terminal alkynes by using new ligand systems, that is, *tert*-alkyl isocyanides[77] and 4-ethyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane (ETPO),[78] in combination with appropriate palladium catalyst precursors. Second, use of disilanes that are unsymmetrically substituted with electronegative groups enabled bis-silylation of poorly reactive unsaturated compounds such as internal alkynes and terminal alkenes to occur.[6] These findings boosted the synthetic applications of bis-silylation in organic synthesis.

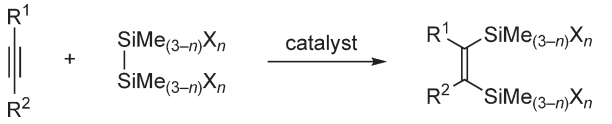
10.16.2.2.1 Addition to alkynes

Bis-silylation of terminal alkynes has been achieved with a variety of disilanes (Equation (17) and Scheme 10). Cyclic disilanes[3,79–83] and disilanes bearing electron-withdrawing substituents on the silicon atoms[3,84–86] add to terminal alkynes in the presence of conventional palladium complexes having triphenylphosphine as ligand. In the reactions of cyclic disilanes, bis-silylative dimerization of alkynes may also proceed along with the simple bis-silylation.[3,79] The formation of bis-silylative dimerization product becomes more significant when phosphine-free palladium catalysts, such as $Pd(PhCN)_2Cl_2$, are used. In addition to the palladium catalysts, nickel[87] and platinum[83] catalysts are found to be active in the reactions of cyclic disilanes with alkynes. Stereochemical course of the palladium-catalyzed bis-silylation of 1-alkynes with diastereomerically pure *cis*- and *trans*-cyclic disilanes has been investigated (Equations (18) and (19)).[88,89] The result clearly shows that the bis-silylation proceeds stereospecifically with regard to the stereochemistry at the silicon atoms. Reaction of benzodisilacyclobutene in the presence of a nickel catalyst gives an

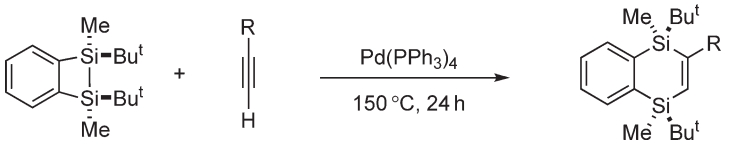


Scheme 10

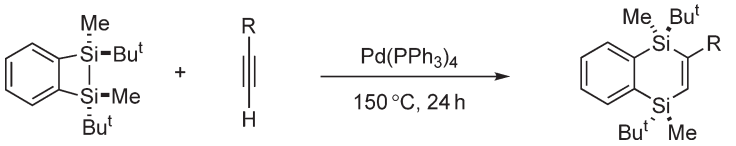
unusual product in 72% yield, which arises from the insertion of diphenylacetylene into the Si–C bond, along with the normal bis-silylation products (Equation (20)).[87]



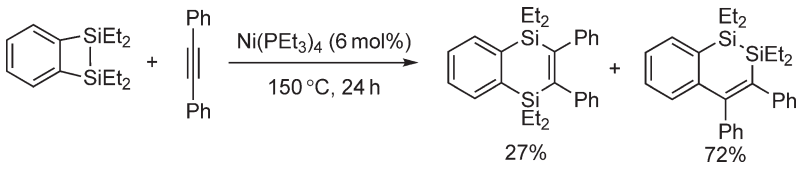
(17)



(18)

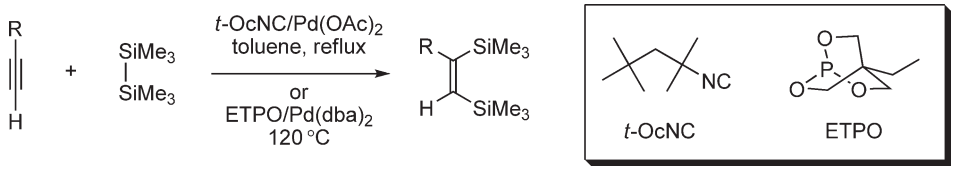


(19)

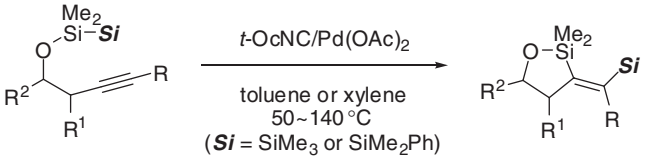


(20)

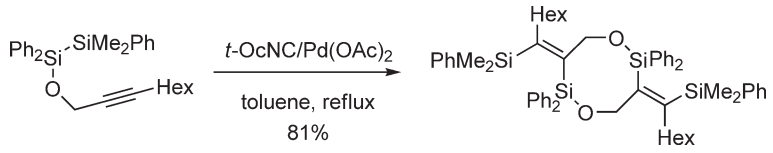
As mentioned above, the development of highly active catalyst systems allows us to use hexamethyldisilane in the bis-silylation of terminal alkynes (Equation (21)). In contrast to the terminal alkynes, bis-silylation of unactivated internal alkynes needs some modification to the reaction conditions. An intramolecular variant using the palladium–isocyanide catalyst achieves bis-silylation of internal alkynes.[77,90] Five-membered ring formation proceeds very efficiently (Equation (22)), while six-membered ring formation needs a higher reaction temperature. Four-membered ring formation also proceeds efficiently, although isolation of the four-membered ring silyl ethers has encountered difficulty in some cases.[91] In particular, the four-membered ring bis-silylation product derived from primary propargylic alcohol undergoes cyclodimerization, affording the corresponding eight-membered ring disiladioxacyclooctane (Equation (23)). Although hydrolytically unstable, the four-membered ring silyl ethers derived from secondary and tertiary propargylic alcohols are thermally stable and utilized for further synthetic transformations (Equation (24)).[91,92] Intramolecular bis-silylation of bis(silyl)acetylenes under high pressure (5–10 kbar) affords sterically congested tetrasilylalkenes in the presence of a palladium-isocyanide catalyst (Equations (25) and (26)).[93–95] The other system uses unsymmetrically substituted 1,1-difluoro-1-phenyl-2,2,2-trimethyldisilane with palladium complexes bearing trimethylphosphine or dimethylphenylphosphine.[6] Under these reaction conditions, reactions of unsymmetrical alkynes proceed regioselectively in good yields (Equation (27)).



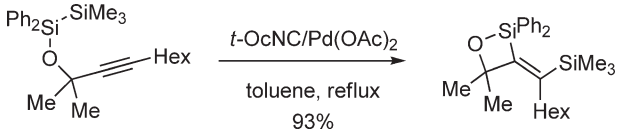
(21)



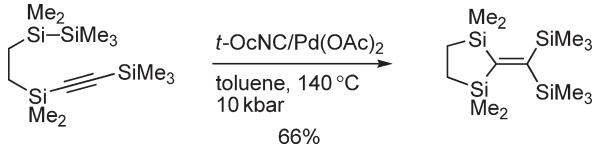
(22)



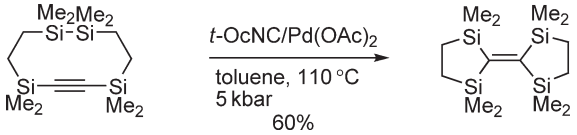
(23)



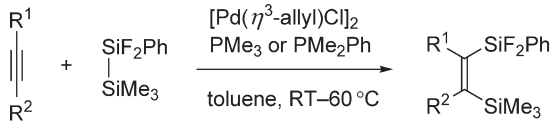
(24)



(25)



(26)

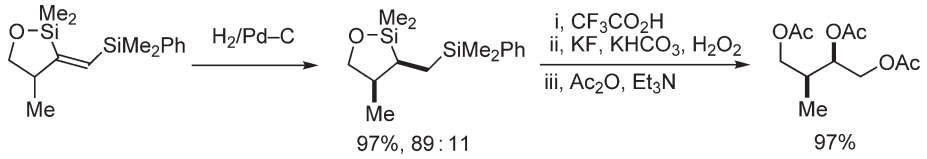


(27)

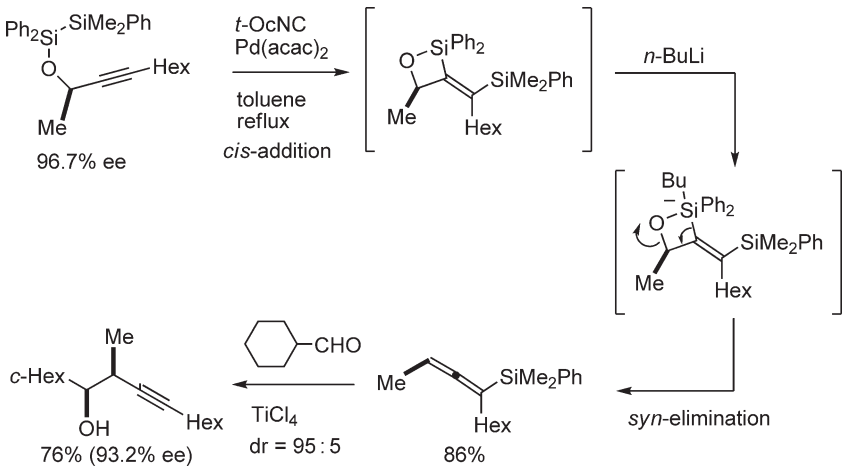
($R^1 = R^2$ = Ph: 95%; $R^1 = R^2$ = Et: 76%; R^1 = Ph, R^2 = Me: 96% (85 : 15); R^1 = Ph, R^2 = H: 94%; R^1 = *n*-Hex, R^2 = H: 94%)

Synthetic transformations of the products of the intramolecular bis-silylation have been examined. The five-membered ring products derived from homopropargylic alcohols were hydrogenated in a stereoselective manner (Scheme 11).[90] Oxidation of the products under the Tamao oxidation conditions (H_2O_2/F^-/base)[96] leads to the stereoselective synthesis of 1,2,4-triols. This method can be complementary to the one involving intramolecular bis-silylation of homoallylic alcohols (*vide infra*).

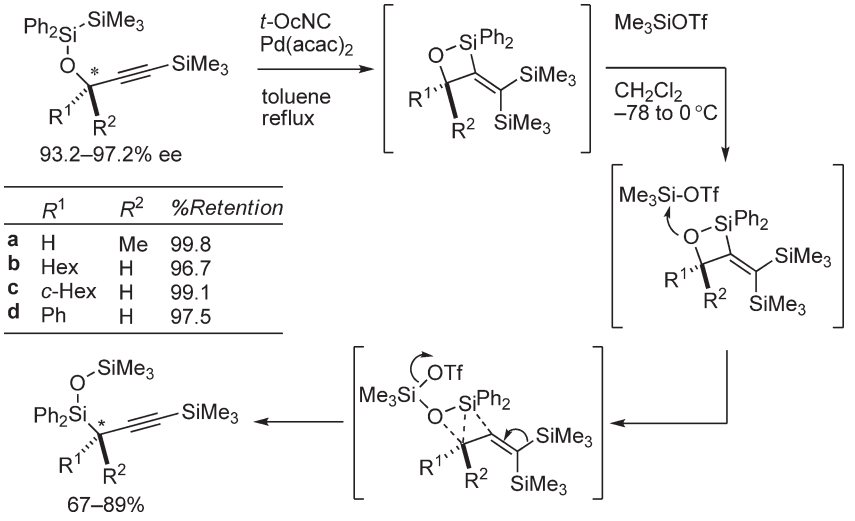
The *in situ*-generated four-membered ring ethers are treated with organolithium to give allenylsilanes in good yields via Peterson-type elimination (Scheme 12).[91] When an enantioenriched propargylic alcohol was used as a starting material, the corresponding enantioenriched allenylsilane is obtained with high degree of stereoconservation. On the other hand, treatment of the enantioenriched four-membered ring ethers with trimethylsilyl triflate results in the formation of enantioenriched propargylic silanes (Scheme 13).[92] The reaction may involve acid-catalyzed cleavage of the C–O bond, which is followed by facile 1,2-migration of the silyl group and subsequent elimination of another silyl group. A detailed study on the stereochemical course revealed that the 1,2-silyl migration takes place with almost perfect retention of configuration at the migration terminus, that is, the allylic stereogenic center.



Scheme 11



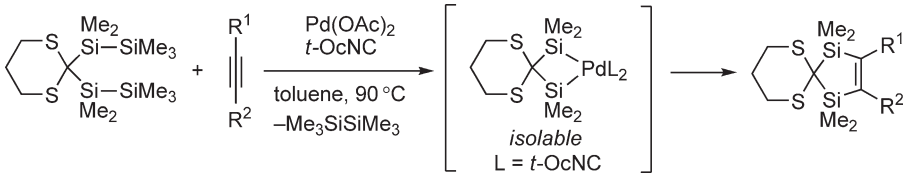
Scheme 12



	R^1	R^2	%Retention
a	H	Me	99.8
b	Hex	H	96.7
c	*c*-Hex	H	99.1
d	Ph	H	97.5

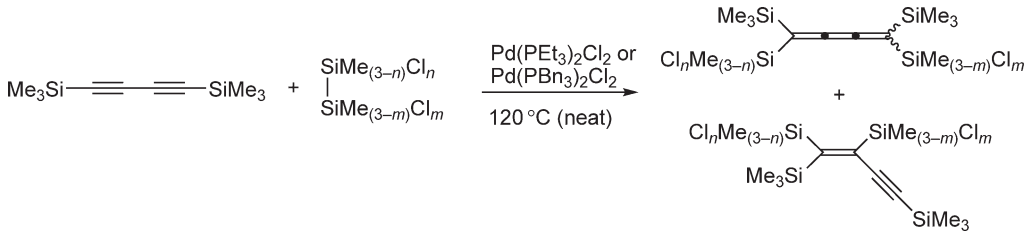
Scheme 13

A unique bis-silylation system, in which a bis(silyl)palladium intermediate is generated via recombination of two Si–Si bonds, has been developed.[8,97] A bis(disilanyl)dithiane reacts with alkynes in the presence of a palladium/isocyanide catalyst, giving five-membered ring bis-silylation products in high yield with elimination of hexamethyldisilane (Scheme 14). The recombination, that is, σ-bond metathesis, is so efficient that no product derived from direct insertion of acetylene into the Si–Si bonds of the bis(silyl)dithiane is formed at all.



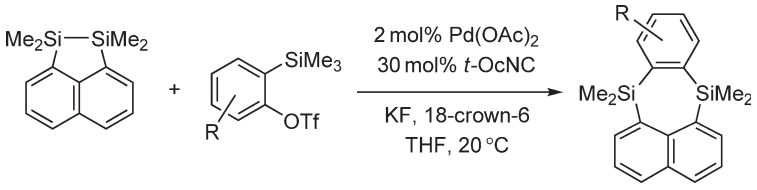
Scheme 14

Palladium-catalyzed bis-silylation of 1,4-bis(trimethylsilyl)butadiyne affords 1,2- and 1,4-addition products with varying ratios, depending on the disilanes and palladium catalysts used (Equation (28)).[98]



(28)

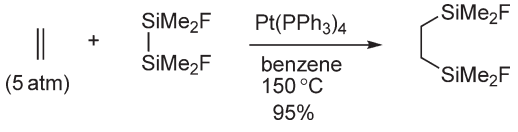
Palladium-catalyzed bis-silylation of benzynes has been achieved. Reaction of 2-trimethylsilylaryl triflates with cyclic disilanes in the presence of KF/18-crown-6 affords cyclic bis-silylation products in good yields (Equation (29)). It is crucially important to use the palladium-isocyanide catalyst.[99,100]



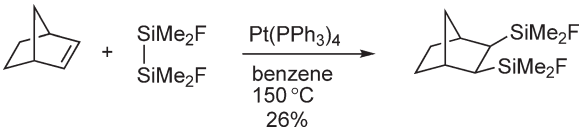
(29)

10.16.2.2.2 Addition to alkenes

Intermolecular bis-silylation of unactivated alkenes has been achieved initially with a zerovalent platinum catalyst such as $Pt(PPh_3)_4$ (Equations (30) and (31)).[101] 1,2-Difluorotetramethyldisilane undergoes addition to ethylene and norbornene in the presence of $Pt(PPh_3)_4$ catalyst at 150 °C to give the corresponding adducts in 95% and 26% yields, respectively. For the addition of 1,2-diphenyltetramethyldisilane to ethylene, $Pt(PMe_3)_4$ (33% yield) was found to be more active than $Pt(PPh_3)_4$ (4% yield).

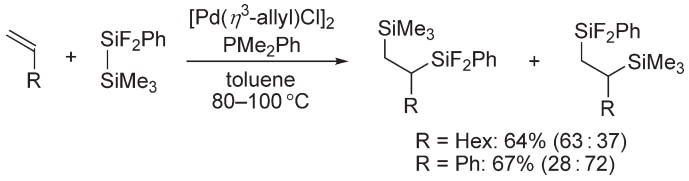


(30)

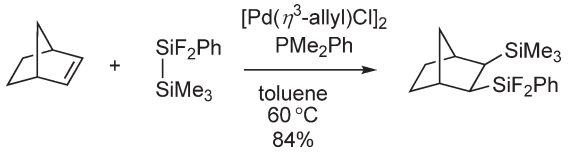


(31)

In a manner similar to that of the bis-silylation of internal alkynes shown above, the use of unsymmetrical disilanes with basic *tert*-phosphines is effective for intermolecular bis-silylation of terminal alkenes (Equations (32) and (33)).[6] Although the regioselectivities need to be improved, clean bis-silylations of 1-octene, styrene, and norbornene have been achieved in high yields.

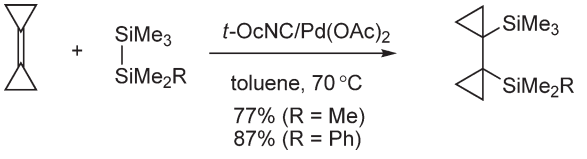


(32)



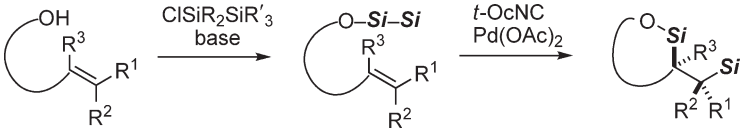
(33)

Intermolecular bis-silylation of highly strained bicyclopropylidene with hexaorganodisilanes proceeds at 70 °C in the presence of the palladium/*tert*-alkyl isocyanide catalyst (Equation (34)).[102]

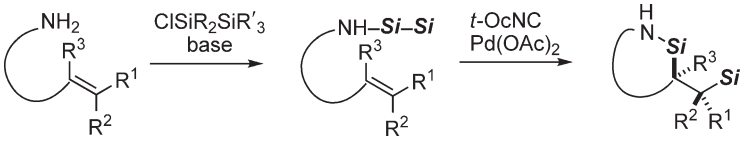


(34)

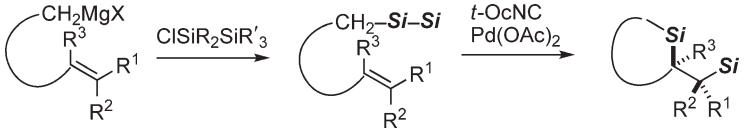
Intramolecular bis-silylation of alkenes proceeds quite efficiently in the presence of the palaldium/*tert*-alkyl isocyanide catalysts (Schemes 15–17).[103,104] There are some general aspects of the palladium-catalyzed bis-silylation that should be mentioned. First, the intramolecular bis-silylation proceeds efficiently with 4- and 5-*exo*-cyclization modes. Six-membered ring formation is possible only at elevated temperatures.[105] The substrates, in which the disilanyl group and the C═C bond are separated by tethers consisting of 2–4 atoms, are conveniently prepared from disilanyl chlorides with alkenols, aminoalkenes, or alkenyl Grignard reagents. Second, the efficiency of the intramolecular bis-silylation is largely affected by substitution pattern of the C═C bond. Thus, as exemplified by the 5-*exo*-cyclization of disilanyl ethers of homoallylic alcohols, intramolecular additions to unsubstituted vinyl group proceed even at 25–40 °C, while geminally disubstituted and vicinally disubstituted C═C bonds undergo the additions at 80 and 110 °C, respectively (Table 1).[106] No bis-silylation takes place with trisubstituted and tetrasubstituted C═C bonds even under forced reaction conditions. The only exception is the intramolecular bis-silylation of a tethered bicyclopropylidene substrate, bearing a highly reactive tetrasubstituted alkene moiety (Equation (35)). Third, the cyclizations proceed with high stereoselectivity. Regardless of the ring size formed in the intramolecular bis-silylation, alkenes that carry substituents α to the C═C bond in their tethers afford *trans*-disubstituted cyclic products. Substrates bearing β-substituents generally give *cis*-disubstituted cyclic products with high stereoselectivity.



Scheme 15

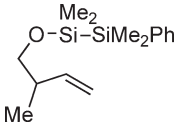
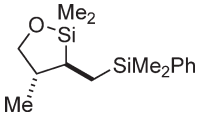
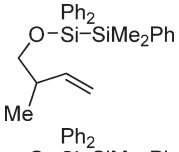
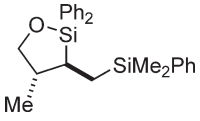
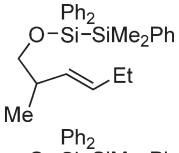
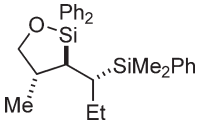
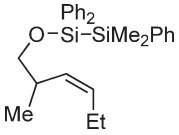
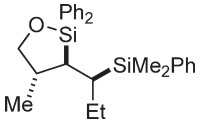
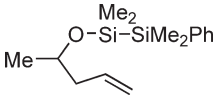
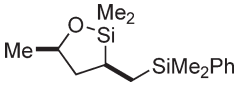
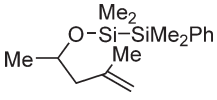
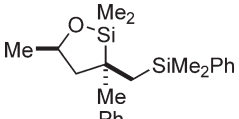
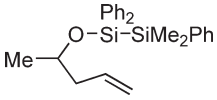
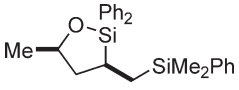
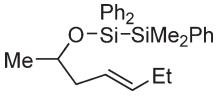
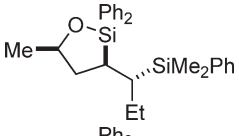
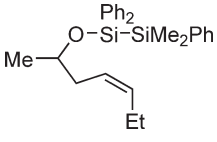
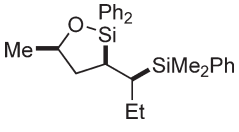


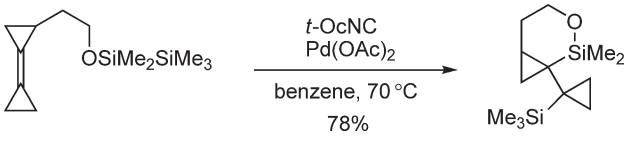
Scheme 16



Scheme 17

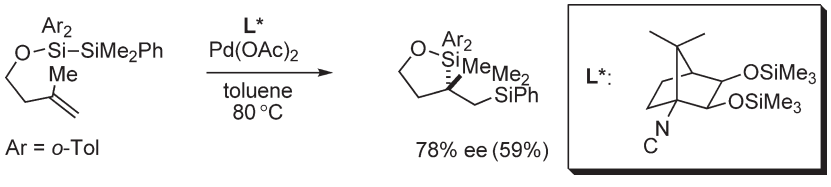
Table 1 Intramolecular bis-silylation of disilanyl ethers of substituted homoallylic alcohols in the presence of a palladium/*t*-O_cNC catalyst

Entry	*Disilanyl ether*	*Temperature*	*Product*	*Yield* (%)	*cis*:*trans*
1		RT		95	7:93
2		RT		84	3:97
3		110 °C		97	<1:>99
4		110 °C		92	<1:>99
5		RT		90	93:7
6		80 °C		97	96:4
7		RT		90	96:4
8		110 °C		99	90:10
9		110 °C		99	86:14



(35)

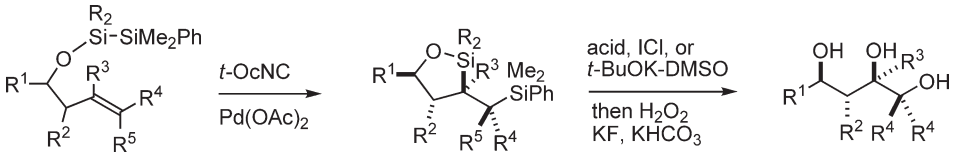
Asymmetric intramolecular bis-silylation has been achieved by using optically active isocyanide as chiral ligands on palladium (Equation (36)).[107]



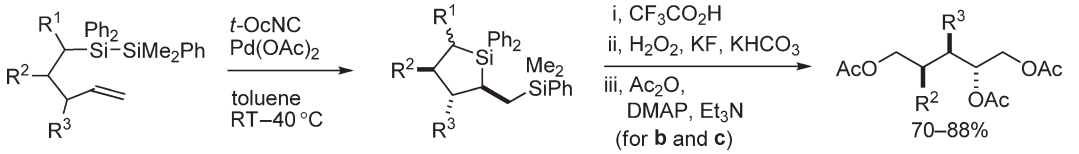
(36)

Synthetic applications of the intramolecular bis-silylation rely on its high stereoselectivities. The bis-silylation products obtained from homoallylic alcohols in stereoselective manner have been subjected to oxidative cleavage of the silicon–carbon bond under Tamao conditions using hydrogen peroxide with fluoride ion (Schemes 18–21). The Si–C oxidation proceeds with retention of configuration at the stereogenic carbon centers, giving stereo-defined 1,2,4-triols.[103,104,106] Applications of this reaction sequence to the stereoselective syntheses of other polyol systems, including 1,2,3- and 1,2,5-triols and aminodiols, have appeared.[104] The bis-silylation/oxidation sequence has also been used as the key step in the total synthesis of (–)-avenaciolide. In the bis-silylation step, effective discrimination of one of the four diastereotopic faces of the two C=C bonds of the dienol-type substrate takes place (Scheme 21).[108,109] Recently, 5-*exo*-cyclization has been applied to the synthesis of 3,4-bis(organosilyl)-1-butenes in four steps from homoallyl alcohol (Scheme 22).[110]

In a manner similar to that for the synthesis of allenylsilanes via intramolecular bis-silylation of propargylic alcohols mentioned above, combination of bis-silylation and Peterson-type elimination offers a powerful strategy for the synthesis of unsaturated organosilicon compounds.[111] Intramolecular bis-silylation of allylic alcohols has been applied to the synthesis of enantioenriched allylic silanes, which are otherwise difficult to synthesize.[112,113] Reaction of disilanyl ether **1** of the enantiopure allylic alcohol in the presence of the palladium-isocyanide catalyst at 70 °C gives eight-membered ring disiladioxacyclooctane **2** as a single stereoisomer (Scheme 23).[114] The structure and

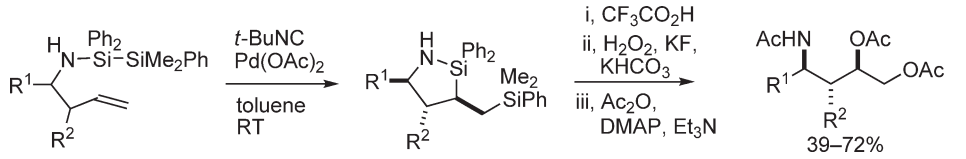


Scheme 18

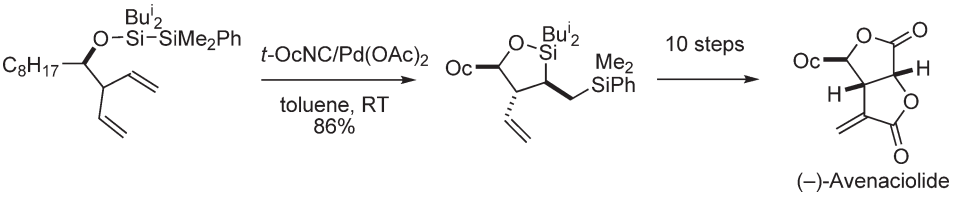


a: R^1 = Me; R^2 = R^3 = H (89%, *cis*:*trans* = 40:60)
b: R^2 = Me; R^1 = R^3 = H (92%, *cis*:*trans* = 96:4)
c: R^3 = Me; R^1 = R^2 = H (99%, *cis*:*trans* = 1:>99)

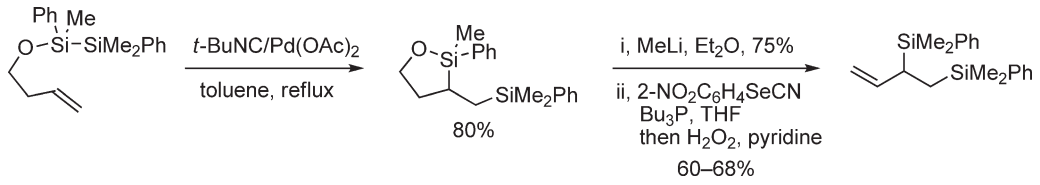
Scheme 19



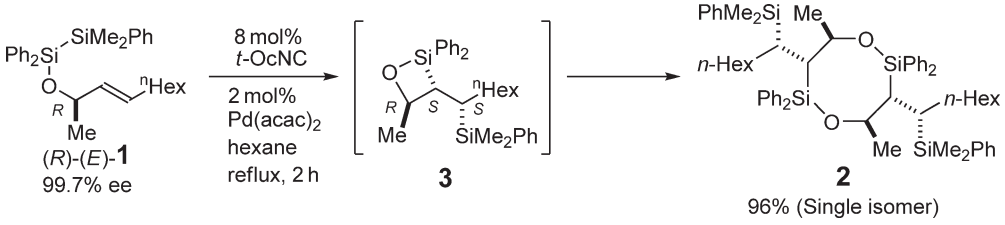
Scheme 20



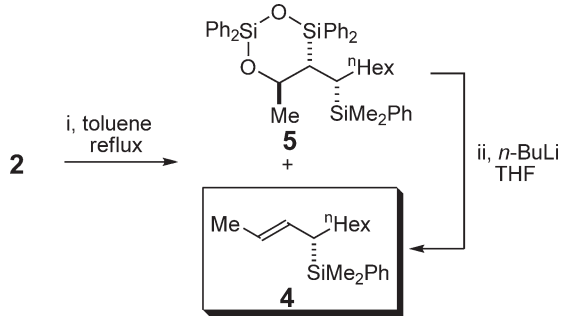
Scheme 21



Scheme 22

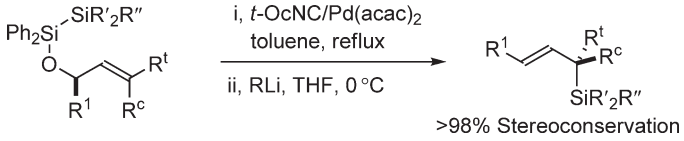


Scheme 23

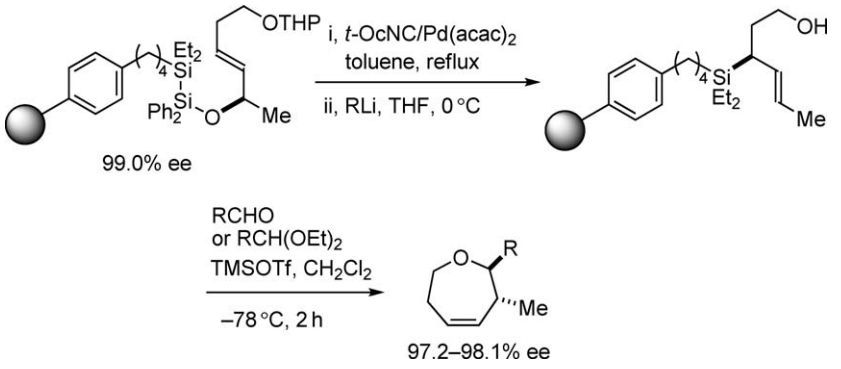


Scheme 24

stereochemistry of **2** has been determined by single crystal X-ray analysis. The formation of **2** is attributed to stereoselective 4-*exo*-cyclization, which gives *trans*-four-membered ring silyl ether **3** and subsequent dimerization. The dimer **2** then undergoes thermal ring contraction with extrusion of allylic silane **4**, giving six-membered ring disiladioxane **5** (Scheme 24). Treatment of **5** with organolithium reagents induces Peterson-type elimination, leading to the formation of the second crop of the allylic silane **4**. It is interesting to note that both crops of the allylic silane exhibited high enantiopurity with excellent purity for the *trans*-C═C bond. The reaction sequence, involving bis-silylation, thermal ring contraction, and Peterson-type elimination, can be carried out in a single reaction vessel (Equation (37)). Using this one-pot procedure, various highly enantioenriched allylic silanes have been prepared with high degree of chirality transfer from the starting allylic alcohol to the product. This method has also been applied to the synthesis of highly enantioenrichd allylic silanes bearing functional groups, which are further utilized for Prins-type allylsilane cyclizations.[115–117] Furthermore, the intramolecular bis-silylation can be carried out on solid support, leading to the solid-phase synthesis using highly enantioenriched, functionalized allylic silanes (Scheme 25).[118]



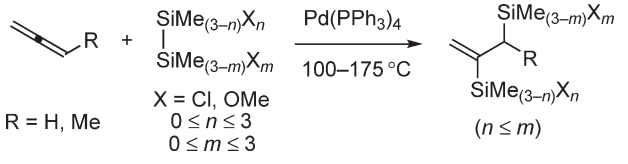
(37)



Scheme 25

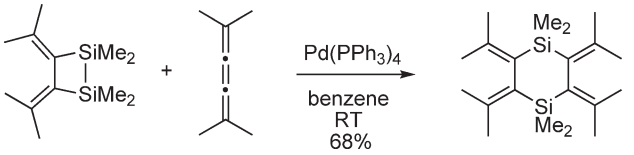
10.16.2.2.3 Addition to allenes

Bis-silylation of terminal allenes is catalyzed by palladium complexes, giving internal addition products regioselectively (Equation (38)).[119] Although rather high temperature (100–175 °C) is needed, a wide variety of disilanes including unreactive hexamethyldisilane can take part in the reaction. Notably, bis-silylation of allenes with unsymmetrically substituted disilane proceeds regioselectively, giving *β*-silylallylsilanes, in which the allylic silicon atom has more electronegative substituents.



(38)

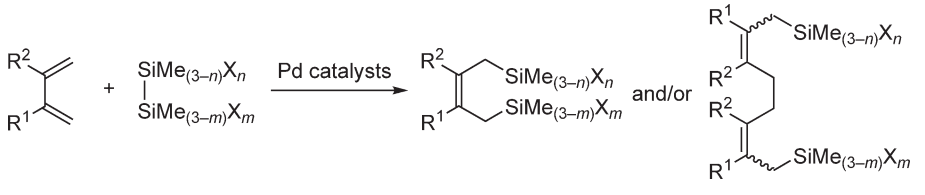
Highly strained four-membered cyclic disilane adds to the central C═C bond of a cumulated triene in the presence of $Pd(PPh_3)_4$ in a regioselective manner (Equation (39)).[82,83]



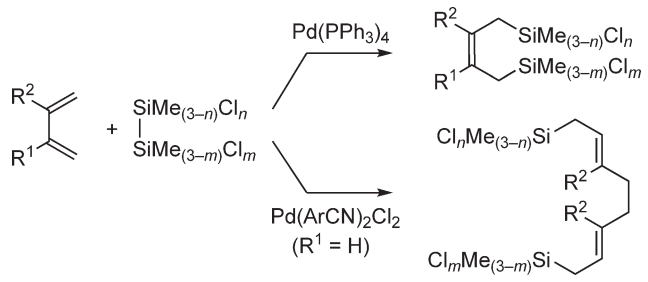
(39)

10.16.2.2.4 Addition to 1,3-dienes

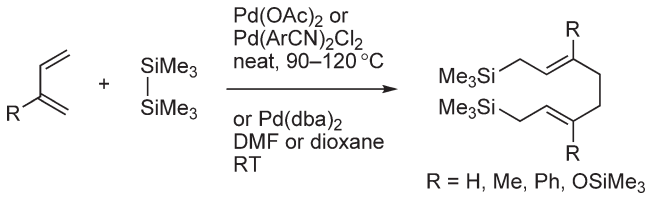
Bis-silylation of 1,3-dienes has been studied extensively, showing that 1,4-addition occurs selectively in the presence of palladium catalysts (Equation (40)).[120,1,121] Not only the simple 1 : 1 addition, but also bis-silylative dimerization of 1,3-dienes can take place under certain reaction conditions. Generally, palladium catalysts without strongly coordinating ligands tend to catalyze bis-silylative dimerization rather than the simple 1,4-addition reaction. For instance, $Pd(PPh_3)_4$-catalyzed reactions of disilanes with 1,3-dienes afford 1,4-addition products,[122] whereas the use of $Pd(ArCN)_2Cl_2$[123] or $Pd(dba)_2$[124] as catalysts leads to the formation of bis-silylative dimerization products (Scheme 26). It should be noted that the bis-silylative dimerization of unsymmetrical 2-substituted 1,3-dienes proceeds regioselectively (Equation (41)).



(40)

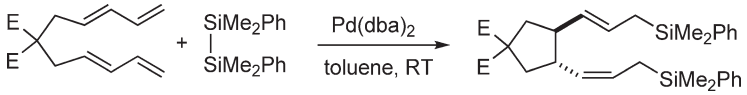


Scheme 26



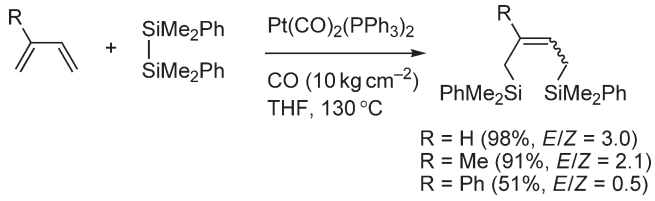
(41)

The dimerization reaction has been applied to intramolecular cyclization of bis(diene)s, leading to the formation of five- and six-membered ring products bearing two allylic silane moieties (Equation (42)).[125] Although stereoselectivity depends on the substrate structure, *trans*-(*E*,*Z*) isomers are generally favored in the five-membered ring formations.

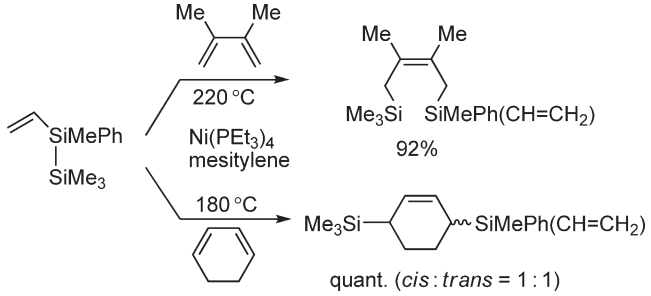


(42)

Although palladium complexes are most extensively examined as catalysts, nickel[126] and platinum[127] complexes also exhibit catalytic activity in the bis-silylation of 1,3-dienes (Equation (43) and Scheme 27).



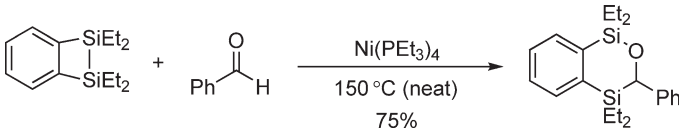
(43)



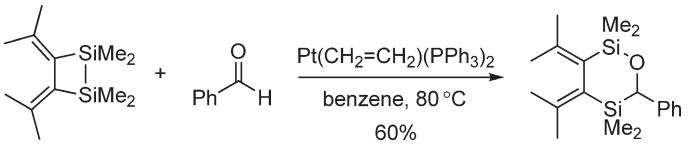
Scheme 27

10.16.2.2.5 Addition to carbonyl compounds including enones and quinones

Although no efficient bis-silylation reaction for aldehydes and ketones with acyclic disilanes has been established, highly strained cyclic disilanes add to C=O bond in a 1,2-fashion in the presence of nickel and platinum catalysts (Equations (44) and (45)).[83,128]

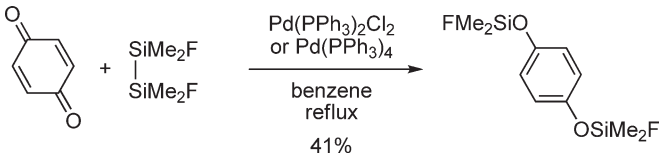


(44)



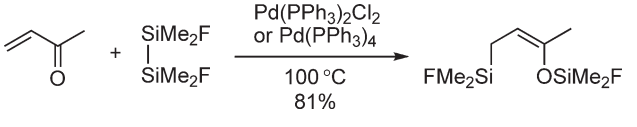
(45)

p-Benzoquinone undergoes 1,6-addition of 1,2-difluorotetramethyldisilane in the presence of palladium catalysts, giving a bis(siloxy)benzene in moderate yield (Equation (46)).[121]

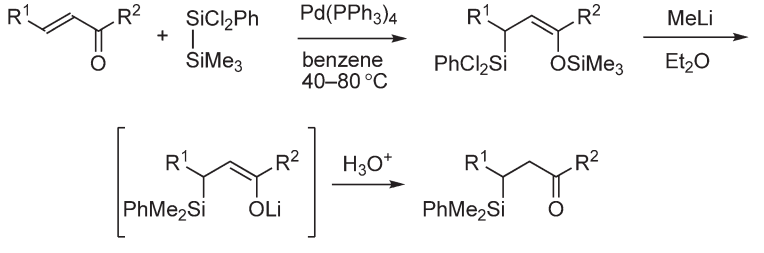


(46)

Palladium-catalyzed bis-silylation of methyl vinyl ketone proceeds in a 1,4-fashion, leading to the formation of a silyl enol ether (Equation (47)).[121] 1,4-Bis-silylation of a wide variety of enones bearing β-substituents has become possible by the use of unsymmetrical disilanes, such as 1,1-dichloro-1-phenyltrimethyldisilane and 1,1,1-trichlorotrimethyldisilane (Scheme 28).[129] The trimethylsilyl enol ethers obtained by the 1,4-bis-silylation are treated with methyllithium, generating lithium enolates, which in turn are reacted with electrophiles. The α-substituted-β-silyl ketones, thus obtained, are subjected to Tamao oxidation conditions, leading to the formation of β-hydroxy ketones. This 1,4-bis-silylation reaction has been extended to the asymmetric synthesis of optically active β-hydroxy ketones (Scheme 29).[130] The key to the success of the asymmetric bis-silylation is to use BINAP as the chiral ligand on palladium. Enantiomeric excesses ranging from 74% to 92% have been attained in the 1,4-bis-silylation.

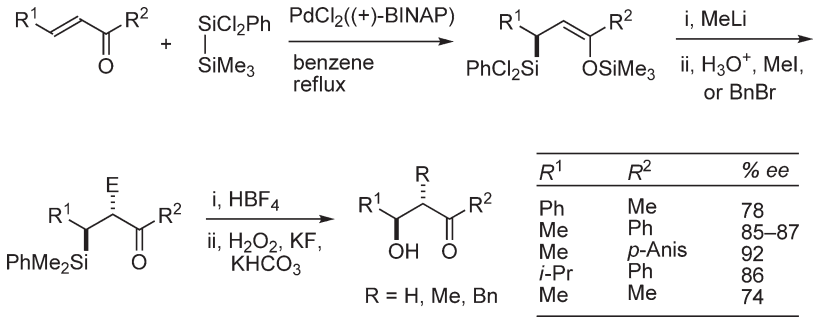


(47)



R^1 = Ph, R^2 = Me (78%); R^1 = Me, R^2 = Ph (68%); R^1 = R^2 = Ph (80%); R^1 = R^2 = Me (64%)

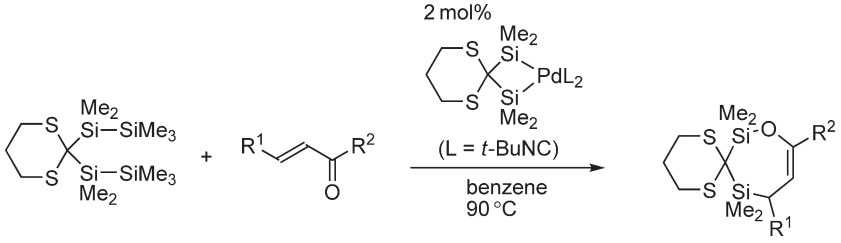
Scheme 28



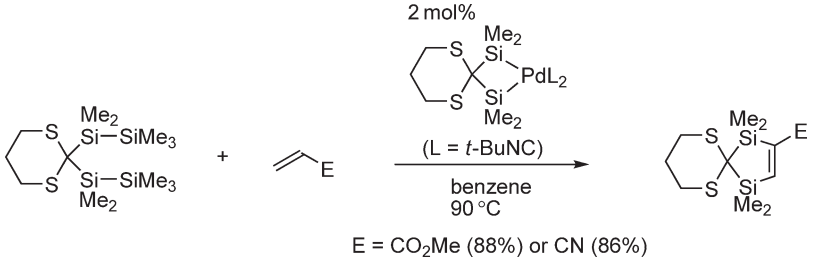
R^1	R^2	% *ee*
Ph	Me	78
Me	Ph	85–87
Me	*p*-Anis	92
i-Pr	Ph	86
Me	Me	74

Scheme 29

Palladium-catalyzed bis-silylation of α,β-unsaturated ketones using bis(disilanyl)dithiane affords seven-membered ring silyl enol ethers in high yields via 1,4-addition (Equation (48)).[8,97] Application of this reaction to α,β-unsaturated esters and nitriles gives five-membered ring 1,2-addition products in good yields (Equation (49)).

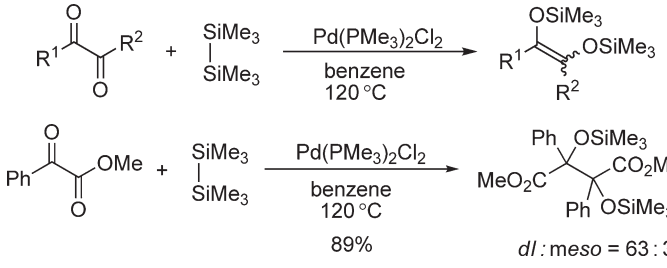


(48)



(49)

α-Diketones undergo palladium-catalyzed bis-silylation, affording 1,2-bis(siloxy)ethylene derivatives (Equation (50)).[131] In contrast, benzil, an α-keto ester, affords bis-silylative dimerization product in the presence of a palladium catalyst (Equation (51)).



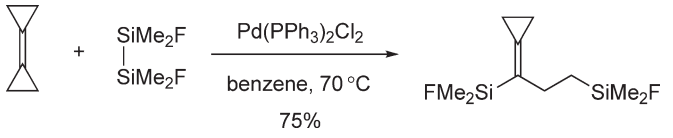
(50)

(51)

10.16.2.2.6 Addition to methylenecylopropanes

Bis-silylation of bicyclopropylidene in the presence of the palladium-isocyanide catalyst with hexamethyldisilane and phenylpentamethyldisilane gives 1,2-addition products in good yields at 70 °C (*vide supra*). No C–C bond cleavage takes place with the bis-silylation reaction. In contrast to this example, in which both the cyclopropane rings are

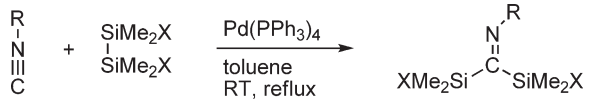
retained in the product, the reaction of 1,2-difluorotetramethyldisilane affords bis-silylative C–C bond cleavage product in good yield at 70 °C in the presence of a palladium/phosphine catalyst (Equation (52)).[102]



(52)

10.16.2.2.7 Addition to isocyanides

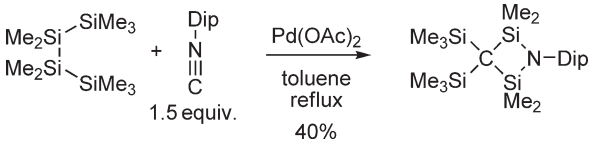
1,1-Addition of disilanes to isocyanides is catalyzed by palladium complexes, giving *N*-substituted bis(silyl)iminomethanes (Equation (53)).[132] A wide range of isocyanides including aryl isocyanides and alkyl isocyanides can take part in the reaction. However, it is important to note that *tert*-alkyl isocyanides hardly undergo the bis-silylation reaction. This low reactivity of *tert*-alkyl isocyanides allows their use as spectator ligands in the catalytic bis-silylations.



(53)

Insertion of isocyanides into Si–Si bonds of oligosilanes has been examined. For instance, 2,6-xylyl isocyanide inserts into every Si–Si bond of decamethyltetrasilane in the presence of palladium(II) acetate, whereas the use of a more bulky 2,6-diisopropylphenyl isocyanide leaves the central Si–Si bond intact (Scheme 30).[133,134]

Reaction of the tetrasilanes with 1.5 equiv. of aryl isocyanide affords a four-membered ring product, in which all the Si–Si bonds and the carbon–nitrogen bond of the isocyano group are cleaved and reorganized (Equation (54)).[135]



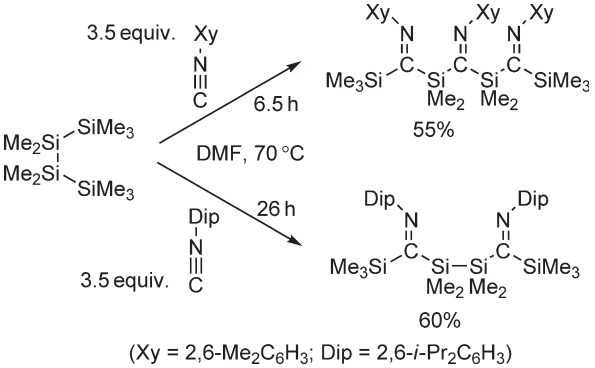
(54)

Use of strained cyclic disilane enables thermal insertion of isocyanide into the Si–Si bond.[136]

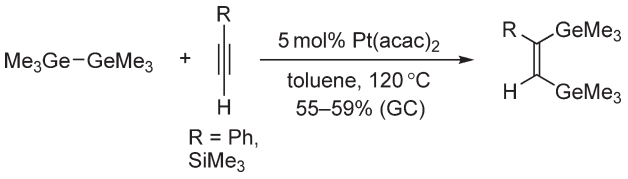
10.16.2.3 Germanium–Germanium

10.16.2.3.1 Addition to alkynes

Hexamethyldigermane reacts with terminal alkynes at 120 °C in the presence of $Pt(acac)_2$ to give (*Z*)-1,2-bis(germyl) ethenes in moderate yield (Equation (55)).[137]

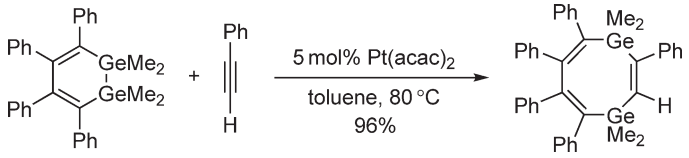


Scheme 30



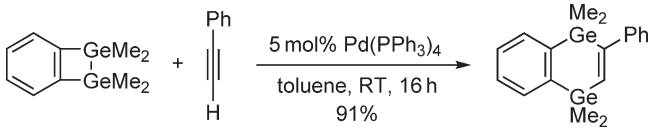
(55)

Phenylacetylene inserts into the Ge–Ge bond of 1,2-digermacyclohexa-3,5-diene under similar conditions to provide the eight-membered ring product in 96% yield (Equation (56)).



(56)

A palladium(0)–phosphine complex also catalyzes insertion of phenylacetylene into the Ge–Ge bond of a benzodigermacyclobutene (Equation (57)).[138] Reaction of a cyclotetragermane with alkynes was also reported.[139]



(57)

A tetragermylethene derivative has been synthesized through intramolecular digermation using the palladium-isocyanide catalyst under high pressure (5 kbar).[95]

10.16.2.3.2 Addition to Fullerene[60]

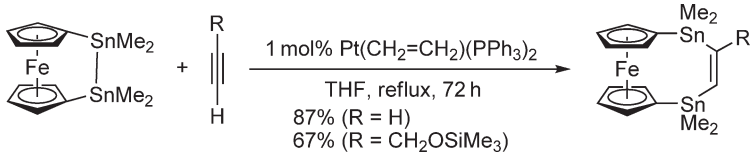
Photochemical digermation reactions of fullerene[60] with a tetragermacyclobutane[140,141] and a digermacyclopropane[142] have been reported.

10.16.2.4 Tin–Tin

10.16.2.4.1 Addition to alkynes

Since the first report on the addition of hexamethyldistannane to alkynes appearing in 1986,[143] a number of modified procedures have been developed for the distannation (Table 2).[144–154] A palladium–isocyanide complex efficiently catalyzes distannation of propargylic alkynes and methyl propiolate with $(Bu_3Sn)_2$. *N*-benzyl ynamides undergo distannation with $(Me_3Sn)_2$ in the presence of as low as 0.1 mol% Pd catalyst to give the corresponding (*Z*)-adducts in high yield. For internal alkynes, only limited examples which utilize electronically activated alkynes have been reported.

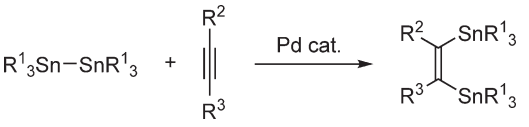
1,2-Distanna-[2]ferrocenophane adds to terminal alkynes in the presence of a platinum catalyst to give 1,4-distanna-[4]ferrocenophanes in good yield (Equation (58)).[155,156] Cyclooctyne, which is an extremely reactive internal alkyne, affords the corresponding adduct in 97% yield.



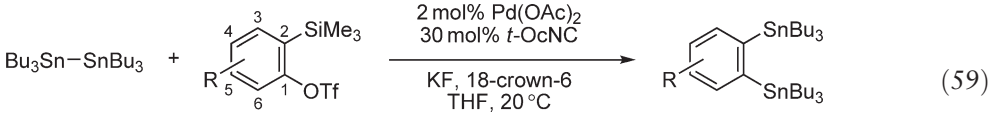
(58)

Benzyne, which is generated *in situ* from 2-(trimethylsilyl)phenyl triflate and KF, acts as an alkyne congener in distannation in the presence of palladium–*tert*-alkyl isocyanide complex.[157] A variety of substituted benzyne derivatives inserts into the Sn–Sn bond to give 1,2-bis(stannyl)benzenes (Equation (59)). The reaction fails to occur in the presence of other palladium catalysts such as $Pd(PPh_3)_4$.

Table 2 Palladium-catalyzed distannation of alkynes



R^1	R^2	R^3	*Conditions*	*Yield (%)*	*References*
Me	H	CH_2OSiMe_3, CH_2OTHP, CH_2OCOPh	4 mol% $Pd_2(dba)_3$, RT	91–94	107
Bu	H	CH_2OMe, CH_2NHBoc, CH_2NMe_2	2.5 mol% $PdCl_2(Bu^tNC)_2$, toluene, RT, 12–16 h	76–83	108
Bu	H	CO_2Me	2.5 mol% $PdCl_2(Bu^tNC)_2$, toluene, RT, 12–16 h	75	108
Me	H	N(COPh)CH_2Ph, N(Ts)CH_2Ph	0.05–0.1 mol% $Pd(PPh_3)_4$, THF, 50–60 °C	86–92	109–110
Bu	CO_2Me	CO_2Me	2.5 mol% $PdCl_2(Bu^tNC)_2$, toluene, RT, 12–16 h	53	108
Me	Et, Pr^i, $(CH_2)_3OTHP$	CO_2Me	0.01–0.02 mol% $Pd(PPh_3)_4$, THF, RT, 15–36 h	83–90	111
Bu	CH_2OTBS, CH_2OTHP	CO_2Me	0.2 mol% $PdCl_2(PPh_3)_2$, THF, RT, 42 h	75–98	112,113
Me	$(CH_2)_2OTBS$	CHO, COMe, $COPr^i$	5 mol% $Pd(PPh_3)_4$, THF, reflux, 2–5 h	87–94	114
Bu	CH_2OH	CH_2OH	$PdCl_2(PhCN)_2$, THF, RT, 48 h	85	115,116
Me	*n*-C_6H_{13}	OEt	2 mol% $Pd(PPh_3)_4$, cat. galvinoxyl, benzene, RT	88	117

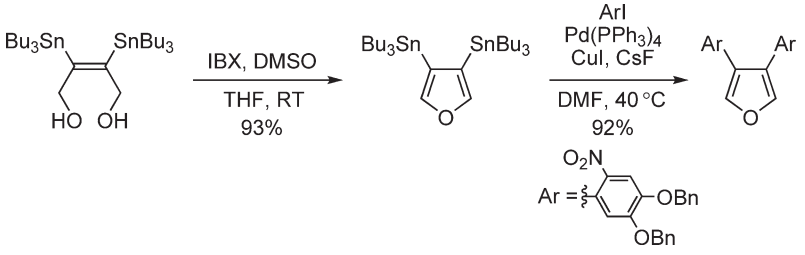


(59)

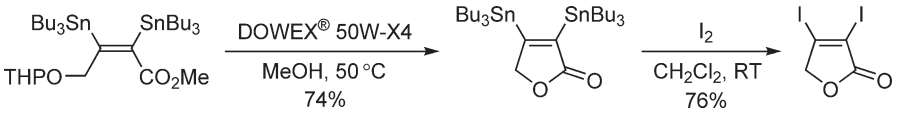
R = H (73%), 4-Me (71%), 4,5-Me_2 (73%), 3,6-$(OMe)_2$ (63%), 6-Me (55%), 3-OMe (59%)

A distannation product of 2-butyne-1,4-diol oxidatively cyclizes to provide 3,4-bis(stannyl)furan, which then undergoes palladium-catalyzed cross-coupling with an aryl iodide to give 3,4-diarylfuran (Scheme 31).[152,153]

A 1,2-distannated product cyclizes to a distannyllactone under acidic conditions (Scheme 32). The subsequent reaction with I_2 (2 equiv.) affords the corresponding diiodolactone.[149,150]



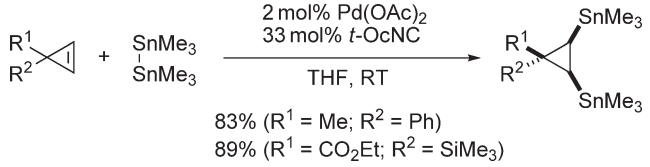
Scheme 31



Scheme 32

10.16.2.4.2 Addition to alkenes

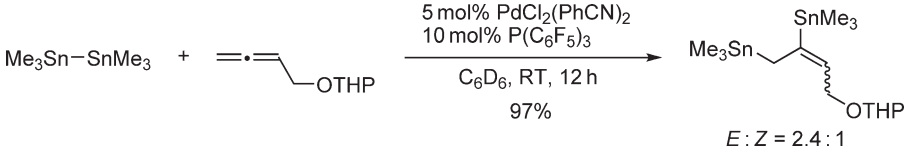
Addition of distannane to alkenes has been achieved only with strained cyclopropenes (Equation (60)).[158] 3,3-Disubstituted cyclopropenes undergo highly face-selective distannation in the presence of the palladium–isocyanide complex to afford *cis*-adducts.



(60)

10.16.2.4.3 Addition to allenes

Addition of the Sn–Sn bond to allenes in the presence of a Pd–$P(C_6F_5)_3$ catalyst occurs selectively at the terminal C═C bond of allenes to give β-stannylallylstannanes (Equation (61)).[159]

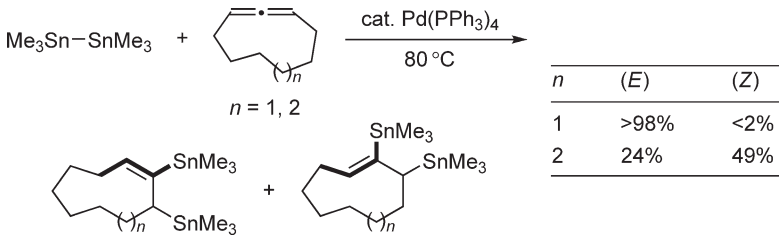


(61)

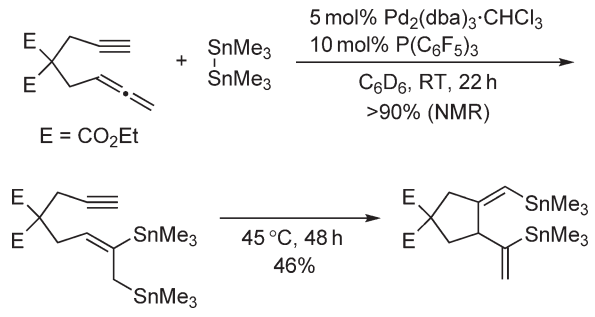
While distannation of 1,2-cyclononadiene gives (*E*)-1,2-adduct in excellent yield, the corresponding reaction of 1,2-cyclodecadiene affords a 2 : 1 mixture of (*Z*)- and (*E*)-isomers (Scheme 33).[160]

Distannation of allenynes initially takes place at the allene moiety (Scheme 34).[159,161] Upon heating, the produced allylstannane moiety further undergoes palladium-catalyzed intramolecular allylstannation of the alkyne moiety, affording the corresponding cyclized product.

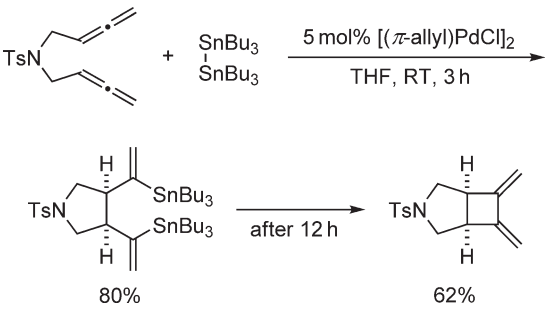
Distannative cyclization of bis(allene)s is catalyzed by $[(\pi\text{-allyl})PdCl]_2$ at RT. The reaction affords cyclopentanes having two 1-stannylvinyl groups with a *cis*-arrangement in 80% yield (Scheme 35).[162] After a prolonged reaction



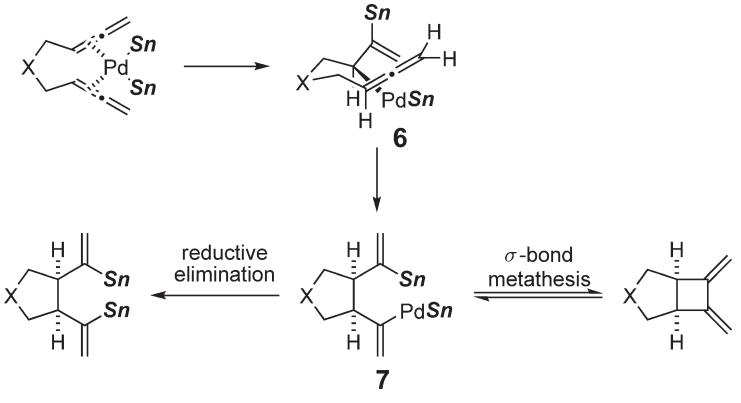
Scheme 33



Scheme 34



Scheme 35



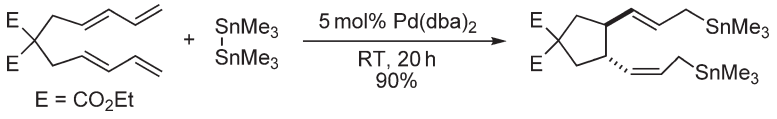
Scheme 36

(12 h), the initial product is transformed to *cis*-fused bicyclic dienes through the palladium-catalyzed homocoupling of the vinylstannane moieties.

A proposed mechanism of the bis(allene) cyclization involves the formation of the σ-allyl(stannyl)palladium species **6**, which undergoes carbocyclization to give vinyl(stannyl)palladium intermediate **7** (Scheme 36). Reductive elimination and σ-bond metathesis may lead to the formation of the *cis*-pentane derivative and the bicyclic product, respectively. The cyclization of allenic aldehydes catalyzed by a palladium complex was also reported.[163]

10.16.2.4.4 Addition to 1,3-dienes

Diastereoselective intramolecular cyclization of bis(diene)s in the presence of a palladium catalyst has been reported, providing cyclopentane derivative stereoselectively (Equation (62)).[125]

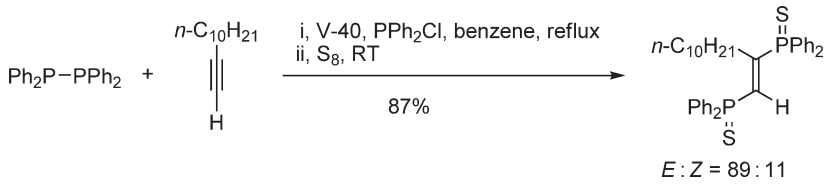


(62)

10.16.2.5 Phosphorus–Phosphorus

10.16.2.5.1 Addition to alkynes

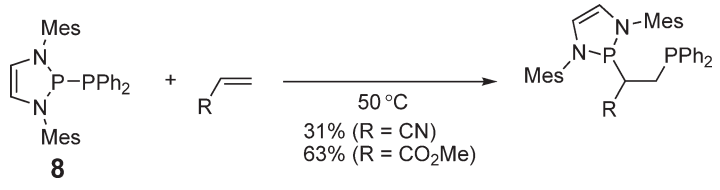
Commercially available tetraphenyldiphosphine adds to terminal alkynes in the presence of a radical initiator (V-40) and Ph_2PCl in refluxing benzene (Equation (63)).[164] After treatment of the reaction mixture with sulfur, phosphine sulfides are obtained as a mixture of stereoisomers.



(63)

10.16.2.5.2 Addition to alkenes

Relatively polar diphosphine 8 has an elongated P–P bond, and thus exhibits unusual reactivity. The reaction of 8 with acrylonitrile or methyl acrylate proceeds at 50 °C in a chemo- and regioselective manner to afford the 1,2-addition product with the PPh_2 group attached at the terminal position (Equation (64)).[165] Tetrachlorodiphosphine reacts with cyclohexene to give *trans*-adduct presumably via an ionic pathway.[166]

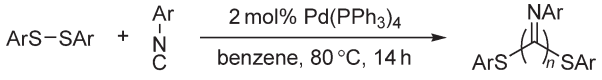


(64)

10.16.2.6 Bonds between Chalcogen Elements (S, Se, and Te)

10.16.2.6.1 Addition to isocyanide

Successive multiple insertions of an aryl isocyanide (ArNC) into the S–S bond of a diaryl disulfide $(ArS)_2$ occurs in the presence of $Pd(PPh_3)_4$ to produce the corresponding poly(imino)alkane endcapped with an arylthio group (Equation (65)).[167] Products of higher molecular weights are formed when isolated poly(imino)alkanes are again subjected to the conditions of the insertion reaction (up to $n = 9$).



ArNC (equiv.)	*n* = 1	*n* = 2	*n* = 3
1	41	23	4
4	3	81	10

(65)

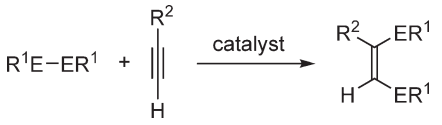
10.16.2.6.2 Addition to alkynes

Addition of diphenyl disulfide $(PhS)_2$ to terminal alkynes is catalyzed by palladium complexes to give 1,2-bis(phenylthio)alkenes (Table 3).[168–172] The reaction is stereoselective, affording the (*Z*)-adducts as the major isomer. A rhodium(I) catalyst system works well for less reactive aliphatic disulfides.[173] Bis(triisopropylsilyl) disulfide adds to alkynes to give (*Z*)-1,2-bis(silylsulfanyl)alkenes, which allows further transformations of the silyl group to occur with various electrophiles.[174,175] Diphenyl diselenide also undergoes the 1,2-addition to terminal alkynes in the presence of palladium catalysts.[176]

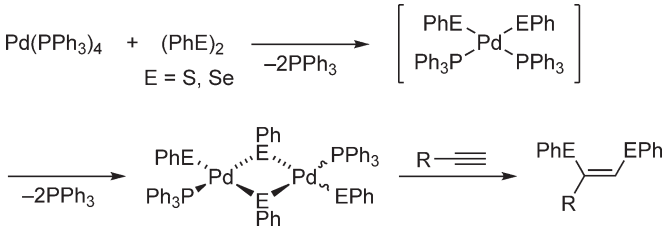
A stoichiometric reaction between $Pd(PPh_3)_4$ and $(PhE)_2$ (E = S or Se) results in the formation of dinuclear complexes, *cis*- and *trans*-$[Pd_2(EPh)_4(PPh_3)_2]$, which react with alkynes to give (*Z*)-adducts (Scheme 37).[177–180]

The addition of organodichalcogenides to alkynes does not necessarily require the aid of transition metal catalysts. Indeed, the reaction proceeds via different mechanisms under various conditions (radical,[181,181a] In,[182] CsOH,[183] $SnCl_4$,[184] and phase-transfer catalysts[185]). Treatment of a mixture of $(PhS)_2$ and terminal alkynes with $GaCl_3$ affords (*E*)-products ($E : Z = > 20 : 1$).[186] The reaction is assumed to involve a thiirenium ion as the intermediate (Scheme 38).

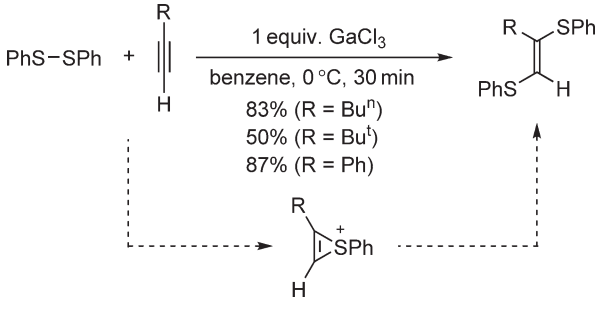
Table 3 Palladium-catalyzed reactions of disulfide and diselenide with alkynes



ER^1	R^2	*Conditions*	*Yield* (%)	*Z* : *E*	*References*
SPh	n-C_8H_{17}	1 mol% $Pd(PPh_3)_4$, benzene, 80 °C, 12 h	91	Z	131
SPh,	Bu^n, CH_2OMe	1.5 mol% $Pd_2(dba)_3$, 30 mol% $P(OPr^i)_3$, toluene, 100 °C, 3 h	87–91	>97 : 3	132
SPh	Ph		91	>10 : 1	132
SPh	n-C_5H_{11}, CH_2NMe_2, $(CH_2)_2OH$	1 mol% $Pd(PPh_3)_4$, 15 mol% PPh_3, 100 °C, 2 h	80–90	>97 : 3	133,134
SBu^n	Ph, n-C_6H_{13}, Bu^t, $SiMe_3$, $(CH_2)_4OH$	3 mol% $RhH(PPh_3)_4$, 12 mol% $P(C_6H_4OMe\text{-}p)_3$, 3 mol% CF_3SO_3H, acetone, reflux, 10 h	62–100	Z	136
$SSi(Pr^i)_3$	n-C_8H_{17}, CH_2Ph, *cyclo*-C_6H_{11}, Bu^t	5 mol% $Pd(PPh_3)_4$, toluene, 90 °C, 15 h	67–96	Z	137,138
SePh	Bu^n	1.5 mol% $Pd_2(dba)_3$, 30 mol% $P(OPr^i)_3$, toluene, 100 °C, 3 h	91	>97 : 3	132
SePh	Ph		96	>10 : 1	132
SePh	$(CH_2)_2OH$, CH_2NMe_2	1 mol% $Pd(PPh_3)_4$, 15 mol% PPh_3, 100 °C, 2 h	80–87	>97 : 3	133,134

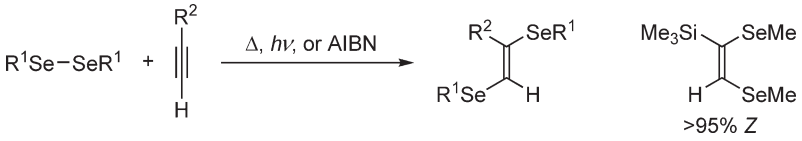


Scheme 37



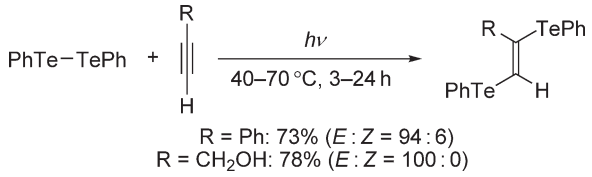
Scheme 38

Dialkyl diselenides add to terminal alkynes to give (*E*)-1,2-bis(alkylseleno)alkenes predominantly (Equation (66)).[187–189] In the reaction of trimethylsilylacetylene, the (*Z*)-isomer is selectively produced (>95% *Z*), presumably due to steric reasons.[190,190a] The reactivity of the diselenides (R in $(RSe)_2$) was found to be in the order $Ph \approx Me \geq Et > Pr^i >> Bu^t$.



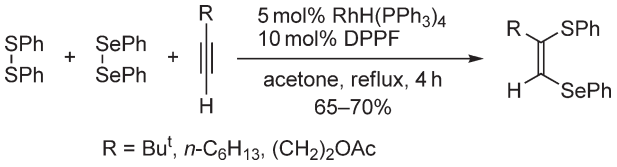
(66)

Diphenyl ditelluride adds to alkynes upon irradiation with a tungsten lamp in the absence of solvent to give 1,2-bis(phenyltelluro)alkenes (Equation (67)).[191] The (*E*)-isomers are obtained as the major product through a radical chain mechanism. Functionalized internal alkynes such as dimethyl acetylenedicarboxylate and dihaloalkynes XCCX (X = Cl or Br) are able to participate in the reaction.[192]



(67)

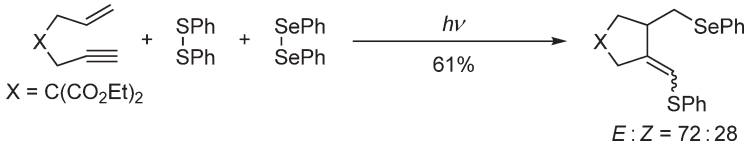
Introduction of two different chalcogen elements to the C–C unsaturated bond is of particular interest from both synthetic and mechanistic viewpoints. Therefore, extensive studies have been carried out on the development of the $(RE)_2/(R'E')_2$ binary system without using RE–E′R′ compounds, which are difficult to prepare. (*Z*)-1-Seleno-2-thio-1-alkenes are produced regio- and stereoselectively when a mixture of diaryl disulfides and diaryl diselenides is subjected to a rhodium-catalyzed reaction with alkynes (Equation (68)).[193]



(68)

The thioselenation is achieved also by a radical mechanism under photo-irradiation. The adduct has the regiochemistry opposite to that observed in the rhodium-catalyzed reaction (Scheme 39).[194,196]

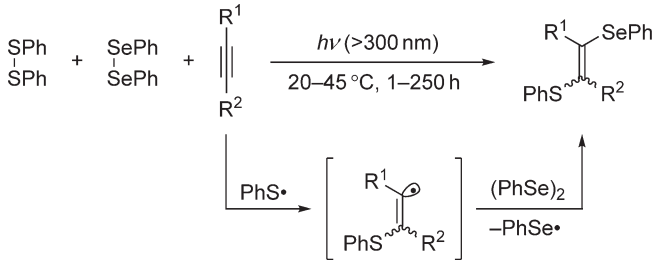
The reaction of 1,6-enynes with $(PhS)_2$ and $(PhSe)_2$ undergoes 5-*exo*-radical cyclization (Equation (69)).[194]



(69)

The $(PhE)_2/(PhTe)_2$ (E = S or Se) binary system also works well for the photo-induced reactions with terminal alkynes giving *vic*-RCH(TePh)=CH(EPh) (Table 4).[197]

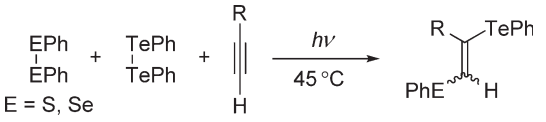
Even the three-component coupling reaction of diphenyl diselenide, ethyl propiolate, and unsaturated compounds occurs under photo-irradiation (Table 5). Alkenes,[198,199] 1,3-dienes,[198,199] vinylcyclopropanes,[200] and isocyanides[199,201] serve as the unsaturated coupling partner to afford the corresponding coupling products with high regioselectivity.



R^1	R^2	*Yield* (%)	*E* : *Z*
Ph	H	96	100 : 0
n-C_6H_{13}	H	74	73 : 27
Ph	Pr	87	86 : 14
Pr	Pr	76	95 : 5

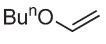
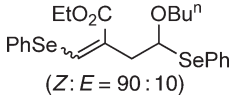
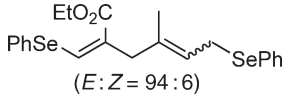
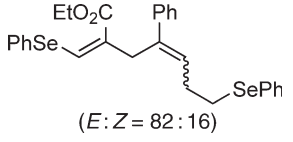
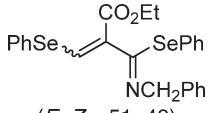
Scheme 39

Table 4 Photo-induced reactions of terminal alkynes with $(PhE)_2/(PhTe)_2$ (E = S or Se) binary system



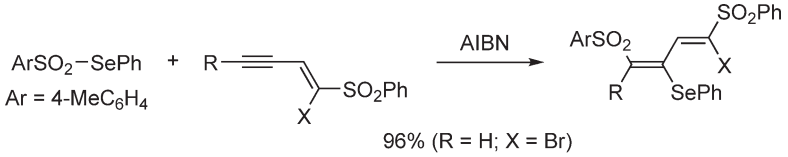
E	*R*	*Conditions*	*Yield* (%)	*E* : *Z*
S	Ph	>400 nm, 1 h	80	100 : 0
S	*n*-C_6H_{13}	>400 nm, 32 h	60	55 : 45
Se	Ph	>400 nm, 2 h	95	90 : 10
Se	*n*-C_6H_{13}	>500 nm, 114 h	29	100 : 0

Table 5 Photo-induced three-component coupling reaction of diphenyl diselenide, ethyl propiolate, and unsaturated compounds

Unsaturated compound	*Product*	*Yield* (%)	*References*
	 ($Z:E = 90:10$)	78	161,162
	 ($E:Z = 94:6$)	55	161,162
	 ($E:Z = 82:16$)	72	163
$PhCH_2NC$	 ($E:Z = 51:49$)	85	162,164

A four-component coupling reaction proceeds, forming a cyclopentane ring through sequential selective addition and cyclization, although the product is obtained as a mixture of stereoisomers (Scheme 40).[202]

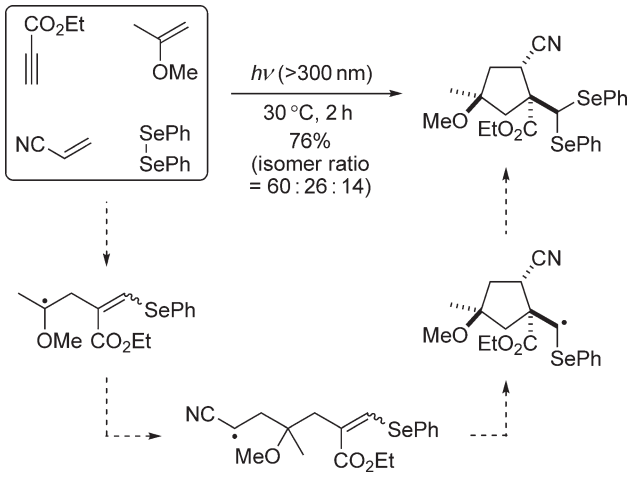
Radical-induced addition of 4-$MeC_6H_4SO_2$–SePh to conjugated ynenyl sulfones occurs in a *trans*-fashion with high regioselectivity (Equation (70)).[203]



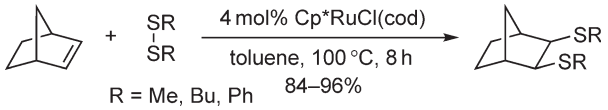
(70)

10.16.2.6.3 Addition to alkenes

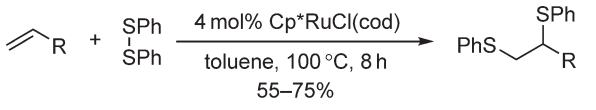
Addition of disulfides to carbon–carbon double bonds is catalyzed by ruthenium complexes (Equation (71)).[204] Even relatively less reactive dialkyl disulfides add to norbornene with high stereoselectivity in the presence of a catalytic amount of $Cp^*RuCl(cod)$. Diphenyl disulfide adds to ethylene and terminal alkenes under identical conditions (Equation (72)).



Scheme 40



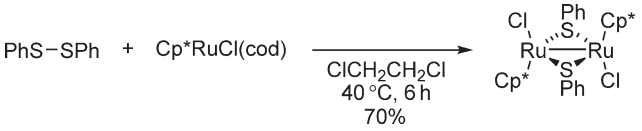
(71)



(72)

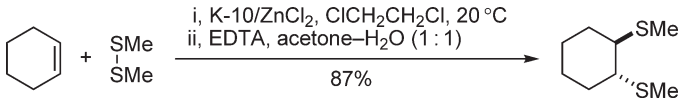
R = H, $SiMe_3$, CO_2Me, CH_2OH, Ph

The stoichiometric reaction of $(PhS)_2$ with $Cp^*RuCl(cod)$ gives a thiolate-bridged diruthenium complex, which also shows a high catalytic activity for the addition to alkenes (Equation (73)).



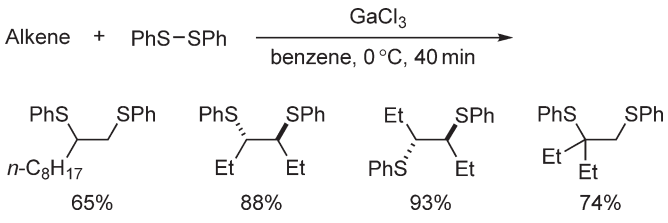
(73)

Montmorillonite (K-10) impregnated with $ZnCl_2$ works as the catalyst for the *trans*-addition of dimethyl disulfide to alkenes (Equation (74)).[205] Catalysts comprising K-10 impregnated with either $CuCl_2$, $FeCl_2$, or $FeCl_3$ exhibit a comparable activity.

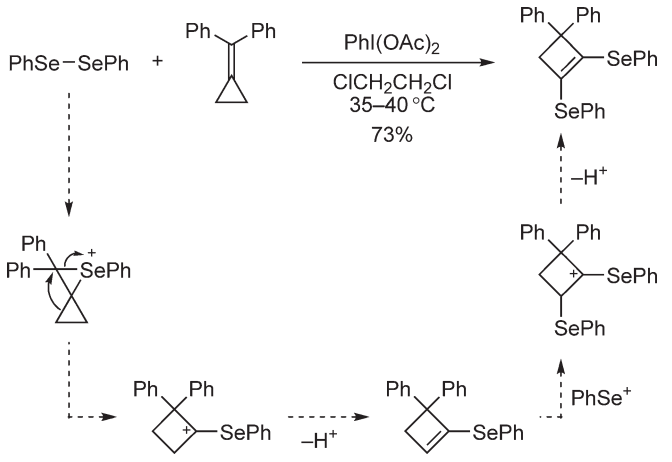


(74)

Addition of diphenyl disulfide to various alkenes is promoted also by $GaCl_3$ at 0 °C (Equation (75)).[186]



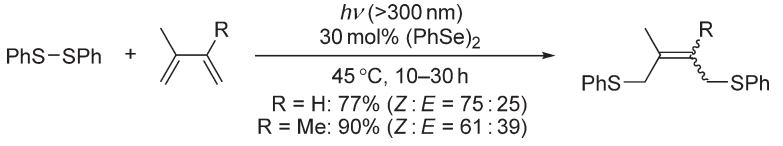
(75)



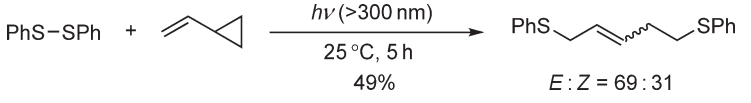
Scheme 41

Reaction of diaryl diselenides with methylenecyclopropanes in the presence of $PhI(OAc)_2$ (2.2 equiv.) results in ring expansion to afford 1,2-diselenylcyclobutenes (Scheme 41).[206]

Under photo-irradiation, $(PhS)_2$ reacts with 1,3-dienes (Equation (76))[207,208] and vinylcyclopropanes (Equation (77))[197] to give the 1,4- and 1,5-adducts, respectively.



(76)

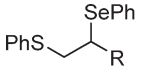
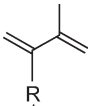
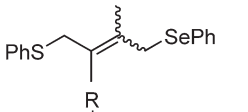
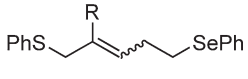


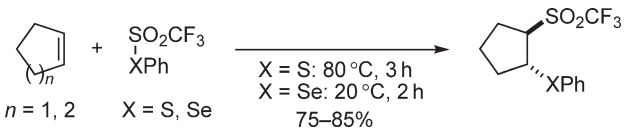
(77)

Thioselenation of alkenes,[209,210] 1,3-dienes,[207] and vinylcyclopropanes[197] occurs by using the binary system of $(PhS)_2/(PhSe)_2$ to afford the adducts regioselectively in good yield (Table 6). Addition of a disulfide to fullerene[60] is achieved using this binary system.[211]

Addition of CF_3SO_2–XPh (X = S or Se) to alkenes occurs thermally to give *trans*-adducts via an ionic pathway (Equation (78)).[212] The reaction of 2,3-dimethyl-1,3-butadiene gives a 1,4-adduct (80%, $Z:E = 60:40$).

Table 6 Photo-induced thioselenation of unsaturated compounds by using $(PhS)_2/(PhSe)_2$ binary System

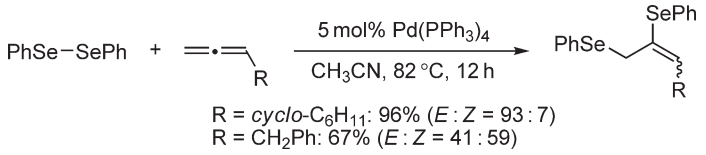
Substrate	*Product*	*Yield (%)*	*References*
		$R = Bu^n$: 74 $R = CO_2Et$: 83	172
		68	170
		R = Me: 86 ($E:Z = 67:33$) R = Ph: 90 ($E:Z = 40:60$)	160



(78)

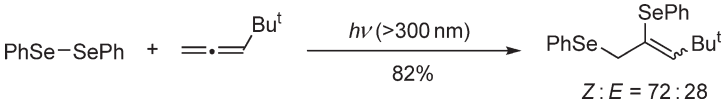
10.16.2.6.4 Addition to allenes

Addition of diselenide to allenes is efficiently catalyzed by $Pd(PPh_3)_4$. The addition occurs exclusively at the less substituted terminal C═C bond (Equation (79)).[213] The addition to vinylidenecyclopropanes is catalyzed by iodosobenzene diacetate.[214]

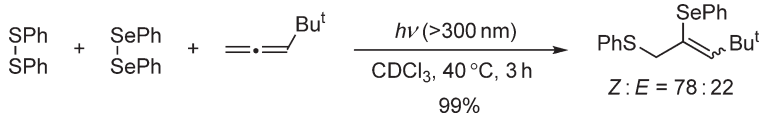


(79)

tert-Butylallene, which fails to react with $(PhSe)_2$ under palladium catalysis, undergoes the diselenide addition upon photo-irradiation (Equation (80)).[215] Using the $(PhS)_2/(PhSe)_2$ binary system, introduction of two different chalcogen elements into allenic C═C bond is also viable (Equation (81)).



(80)



(81)

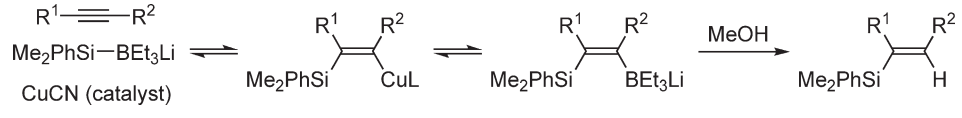
10.16.3 Heteronuclear Element–Element Bonds

10.16.3.1 Addition of Boron–Silicon and Boron–Germanium Bonds

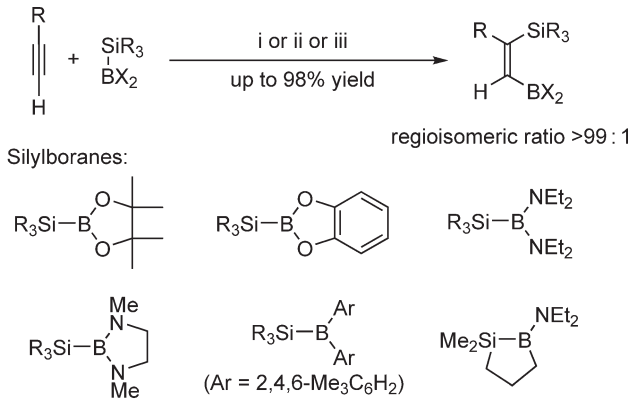
10.16.3.1.1 Silaboration and germaboration of alkynes

The first report on the addition of boron–silicon bonds to carbon–carbon triple bonds appeared in 1986.[216] In this reaction, silylborate ($R_3SiBEt_3{\cdot}Li$) reversibly added to carbon–carbon triple bonds in the presence of a copper or cobalt catalyst in methanol, leading to the formation of formal hydrosilylation products via protodeboration, which shifted the equilibrium to the adducts (Scheme 42).

The addition of the neutral silylborane to carbon–carbon triple bonds, in which both the boron and silicon groups were retained in the products, was achieved in 1996 by using palladium catalysts.[217] Although, in the preliminary report, *tert*-alkyl isocyanide was used as the ligand on palladium, it was later reported that conventional phosphine ligands were as effective as isocyanides.[218,219] It is noteworthy that the silaboration of terminal alkynes proceeds with high regioselectivity with the boryl group attached to the terminal position. In addition to the pinacol, catechol, and diamino derivatives, silyldiarylboranes were found to add to carbon–carbon triple bonds in the presence of palladium catalysts (Scheme 43).[220] Addition of five-membered ring silylborane to alkynes is carried out using the palladium–isocyanide catalyst, leading to a regioselective formation of seven-membered ring alkenes in high yields.[221]

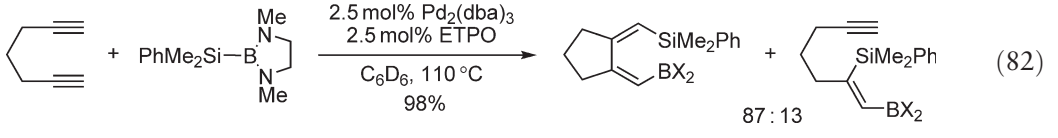


Scheme 42

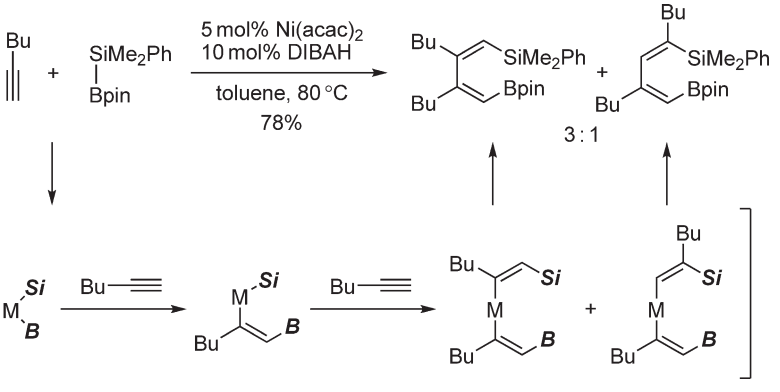


Scheme 43

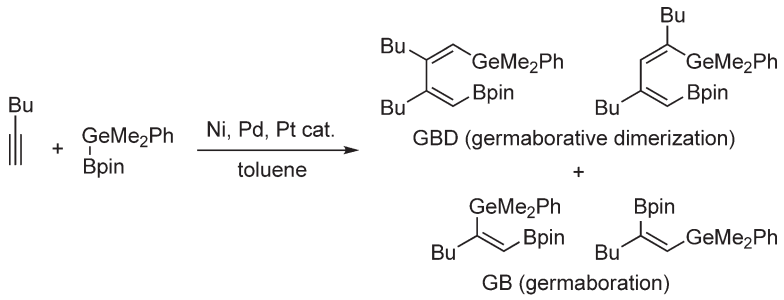
Silaborative dimerization of alkynes has also been reported. On reacting 1,6-diyne with silylborane in the presence of a palladium catalyst,[218] intramolecular coupling of the triple bonds takes place to give 1,2-dialkylidene cycloalkane (Equation (82)). On the other hand, the use of nickel catalysts in the reaction of alkynes leads to silaborative dimerization of alkynes (Scheme 44).[222] It is interesting to note that the dimerization of terminal alkynes proceeds regioselectively. Among the four possible regioisomers, only two isomers which carry boryl groups at the terminal positions are obtained in a 3 : 1 ratio. It seems likely that the reaction mechanism involves bis(alkenyl)nickel intermediates, which are formed via insertion of two alkyne molecules into the B–Ni and Si–Ni bonds, respectively, in regioselective manners. The mechanistic similarity of the nickel-catalyzed process to the palladium-catalyzed one has been proposed on the basis of the analogous results observed in the reaction of a germylborane with alkynes (Scheme 45).[222]



(82)

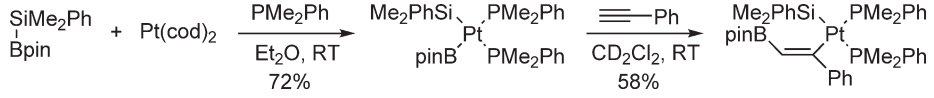


Scheme 44



Catalyst	*GBD*	*GB*
$Ni(acac)_2$/DIBAH	74% (74 : 26)	trace
$Pd(acac)_2$/*t*-OcNC	39% (96 : 4)	46% (>99 : 1)
$Pt(CH_2{=}CH_2)(PPh_3)_2$	0%	87% (91 : 9)

Scheme 45



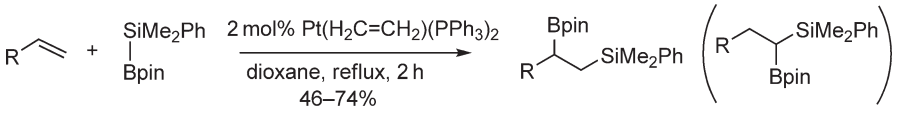
Scheme 46

In relation to the mechanistic proposal, an interesting reactivity of (boryl)(silyl)platinum(II) complex has been reported.[223] The complex is prepared by the reaction of silylborane with $Pt(cod)_2$ complex via oxidative addition (Scheme 46). The (boryl)(silyl)platinum complex undergoes insertion of alkynes at the B–Pt bond to give (*β*-borylalkenyl)(silyl)platinum(II) complex in high yield. Importantly, the insertion takes place regioselectively, with Pt–C bond formation at the internal *sp*-carbon atom. This result may indicate that the boron–transition metal bond is more prone to undergo insertion of unsaturated molecules.

Theoretical studies on the catalytic process have also been reported.[224]

10.16.3.1.2 Addition to alkenes

Addition of silylpinacolborane to alkenes has been achieved with platinum catalysts (Equation (83)).[225] The reaction proceeds regioselectively to provide products in which the silyl groups are attached to the terminal carbon atoms contrary to the silaboration of alkynes. Although no regioisomers are detected, 1-boryl-1-silylalkenes are formed as major byproducts.

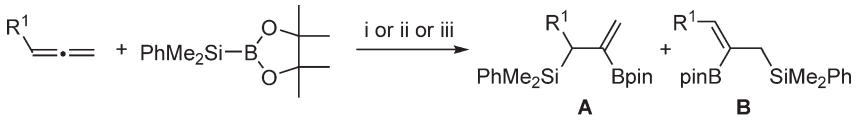


(83)

R = Hex, $AcOCH_2CH_2$, $CH_3C(=O)CH_2CH_2$, Ph, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$, H

10.16.3.1.3 Silaboration of allenes

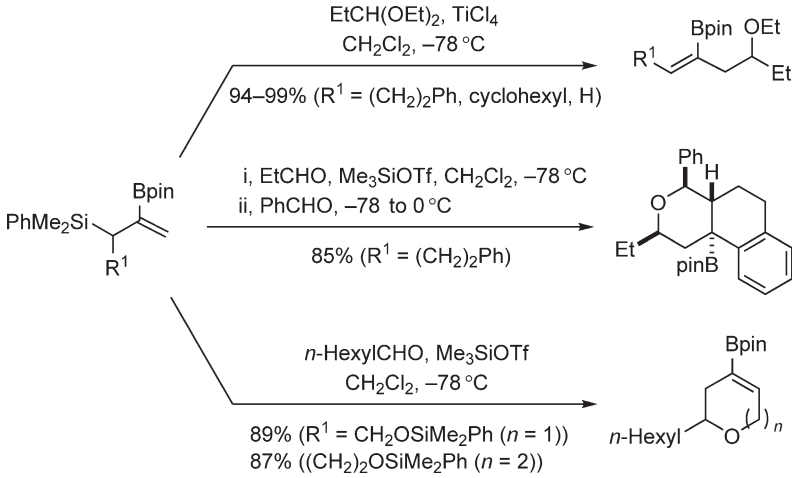
Allenes undergo silaboration with silylpinacolborane in the presence of palladium catalysts (Scheme 47). Although catalyst systems initially reported using isocyanides[226] and the cyclic phosphite ETPO[227] as the ligands on palladium, more recent reports have shown that conventional *tert*-phosphines and phosphites are also effective.[228,229] The palladium-catalyzed addition of a silylborane to the C=C bond of monosubstituted terminal allenes takes place selectively at the internal C=C bond with B–C bond formation at the central *sp*-carbon of the allene. The regioselective silaboration affords allylsilanes bearing *β*-boryl substituents, which serve as useful synthetic



i, 2 mol% $Pd(acac)_2$, 8 mol% 2,6-xylyl isocyanide, octane, 120 °C, 2 h;
ii, 2.5 mol% $Pd_2(dba)_3$, 10 mol% ETPO, THF, 80 °C, 9 h;
iii, 2 mol% CpPd(η^3-allyl), 4–8 mol% *tert*-phosphine or phosphite, 80–120 °C

R^1 = H; R^2 = H, Me, Bu^n, $(CH_2)_2Ph$, CH_2CO_2Et, cyclohexyl, Bu^t, OMe
Yield = up to 99% (**A** : **B** = >99 : 1)
R^1 = H; R^2 = Ph (**A** : **B** = 90 : 10), 4-$MeOC_6H_4$ (**A** : **B** = 94 : 6), 4-$CF_3C_6H_4$ (**A** : **B** = 36 : 64)
Yield = up to 99%

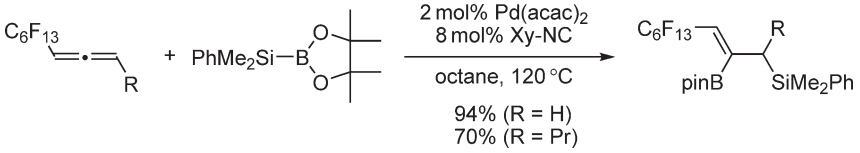
Scheme 47



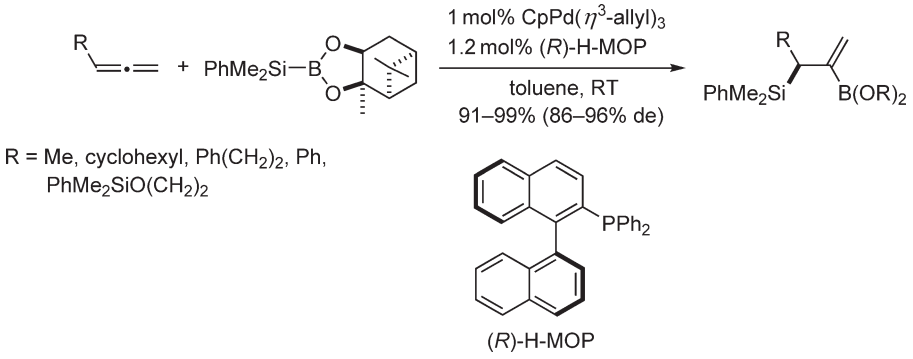
Scheme 48

intermediates for the synthesis of functionalized organoboron compounds. Tolerability of the boryl groups in the Lewis acid-mediated allylation has been demonstrated in the reaction with acetals and aldehydes (Scheme 48).[229] β-Borylallylsilanes bearing a terminal siloxy group are prepared by silaboration and used for six- and seven-membered ring formations to give cyclic alkenylboranes, which are otherwise inaccessible.[229] As an extension of the allylation, one-pot synthesis of tricyclic skeleton has also been achieved.[230]

Reactions of allenes bearing a perfluoroalkyl group afford silaboration products in which the silyl group is attached to the perfluoroalkyl group (Equation (84)).[228] The reaction has been extended to catalytic asymmetric synthesis, in which chiral monodentate ligands are used (Equation (85)).[231] Enantiofacial selectivity of up to 96% de has been achieved in the silaboration of terminal allenes with a silylborane bearing an optically active pinanedioxy group using an enantiopure diphenylphosphino-1,1′-binaphthyl ligand on palladium. It is crucially important to use the matched combination of the chiral silylborane and ligand in the double asymmetric induction system.



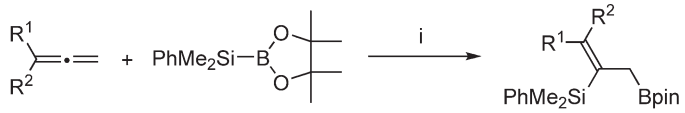
(84)



(85)

On the other hand, platinum-catalyzed silaboration of allenes results in an opposite regiochemical preference. Silaboration of a 1,1-disubstituted allene affords terminal addition product regioselectively in the presence of a platinum catalyst, whereas the internal addition product is obtained with a $Pd_2(dba)_3$–PPh_3 catalyst (Scheme 49).[227]

A unique system for catalytic silaboration of allenes, in which a catalytic amount of organic halide is used as a crucial additive, has been reported (Equation (86)).[232] In the presence of $Pd_2(dba)_3$ (5 mol%) with 3-iodo-2-methyl-2-cyclohexen-1-one (10 mol%), reactions of terminal allenes with a silylborane afford β-silylallylboranes in good yields with excellent regioselectivity. It is worth noting that the addition takes place at the terminal C═C bond in contrast to the above-mentioned palladium-catalyzed silaboration. The alkenyl iodide can be replaced with iodine or trimethylsilyl iodide. The key reaction intermediate seems to be silylpalladium(II) iodide, which promotes the insertion of allenes with Si–C bond formation at the central *sp*-carbon.



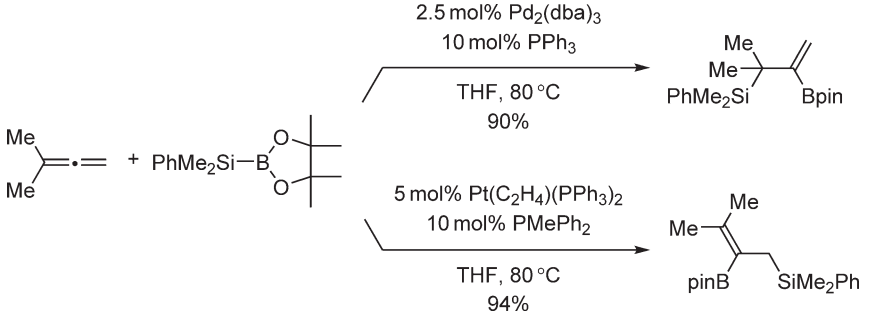
(86)

i, 5 mol% $Pd(dba)_2$, 5 mol% 3-iodo-2-methyl-2-cyclohexen-1-one, EtOAc, 80 °C, 5 h

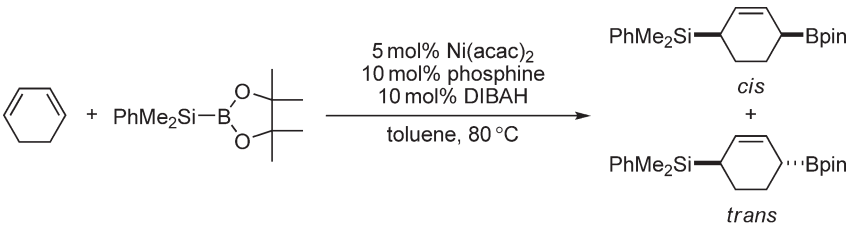
R^1 = H; R^2 = Ph, 1-naphthyl, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-XC_6H_4 (X = Me, Cl, Br, MeC(O), EtO_2C), Bu^n, cyclopentyl, cyclooctyl: 44–93% (*E* : *Z* = >99 : 1–93 : 7)
R^1 = R^2 = Me: 62%

10.16.3.1.4 Silaboration of 1,3-dienes

Silylpinacolborane adds to 1,3-dienes in the presence of nickel catalysts in a 1,4-fashion, giving (*Z*)-alkenes bearing α-boryl and α'-silyl groups.[233] Besides the acyclic 1,3-dienes, cyclic 1,3-dienes undergo the 1,4-silaboration in good yields (Scheme 50). It should be noted that a significant ligand effect on the stereoselectivities is observed in the silaboration of 1,3-cyclohexadiene. Use of cyclohexyldiphenylphosphine leads to the exclusive formation of *cis*-3-silyl-6-borylcyclohexene with high stereoselectivity, whereas trialkylphosphines and aryldialkylphosphine result in the formation of mixtures of *cis*- and *trans*-isomers.



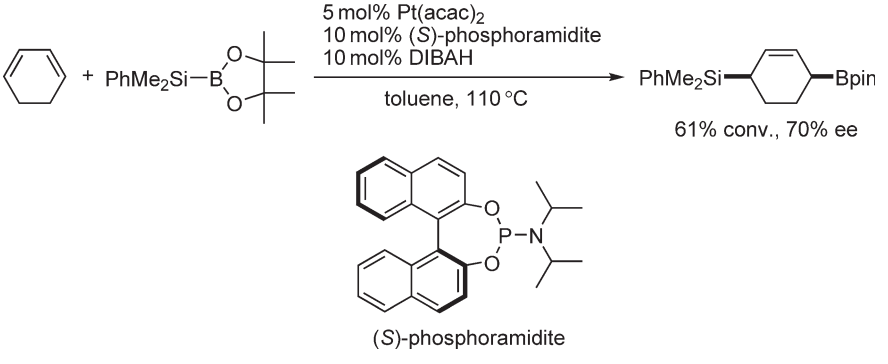
Scheme 49



Phosphine	*Yield* (%)	*cis/trans*
PBu^n_3	39	94/6
PMe_2Ph	92	60/40
$PMePh_2$	97	93/7
$PCyPh_2$	99	>99/1
PPh_3	0	

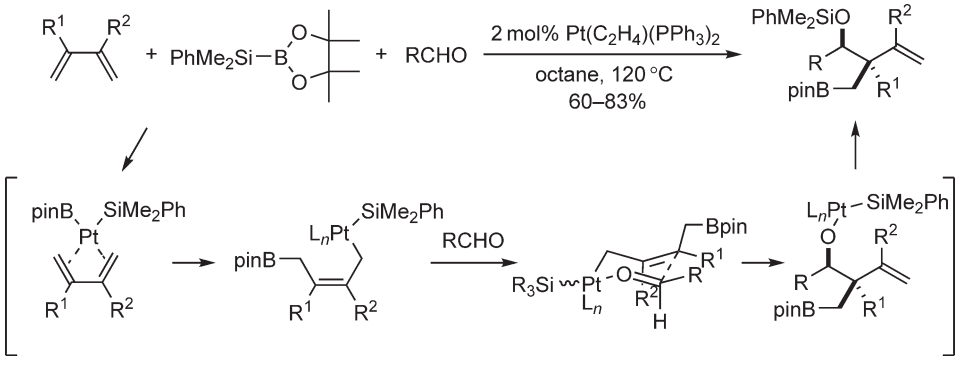
Scheme 50

Platinum catalysts are also effective for the silaboration of 1,3-dienes.[234] Although almost no stereoselectivitiy is observed in the silaboration of acyclic 1,3-dienes, 1,3-cyclohexadiene undergoes the stereoselective silaboration in fair yields (Equation (87)). Enantioselective silaboration of 1,3-cyclohexadiene has been achieved with 70% ee by using a platinum catalyst bearing a binol-based optically active phosphoramidite ligand.[235]



(87)

Using platinum catalysts, silaborative C–C bond forming reaction has been achieved. 1,3-Dienes, aldehydes, and silylborane are coupled in the presence of platinum catalysts, to give organoboron products via formation of Si–O, C–C, and B–C bonds in a single step (Scheme 51). The C–C bond formation is likely to be the result of the catalysis of the platinum complex, because the isolated silaboration product gives organosilicon products via



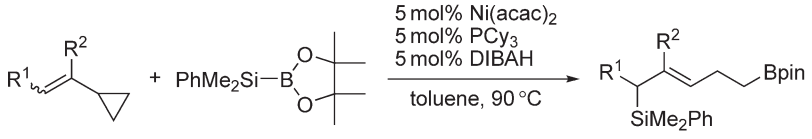
Scheme 51

thermal allylboration. An interesting feature of the reaction is the high stereoselectivity for the formation of the organoboron compounds. It is presumed that the silaborative coupling reaction proceeds via allylplatinum(II) species, which reacts with aldehydes via chair-like cyclic transition state, giving the organoboron product in a stereoselective manner.

10.16.3.1.5 Silaboration of vinylcyclopropanes and methylenecylopropanes

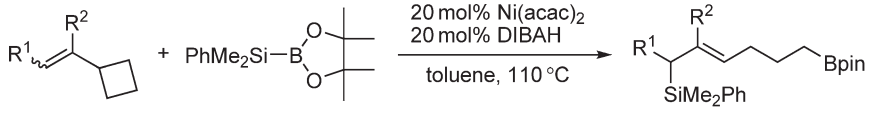
Unsaturated organic molecules bearing a C=C bond and a small ring in close proximity may undergo addition of a silicon–boron bond with cleavage of the C–C bond of the small ring. Vinylcyclopropanes bearing various substituents at their C=C bonds undergo silaboration in the presence of phosphine/nickel catalysts to give acyclic boron-substituted allylic silanes (Scheme 52).[236] The reactions proceed with high regio- and stereoselectivity, furnishing *trans* C=C bonds through introduction of the silyl groups to the allylic positions. It is interesting to note that the reaction system has been successfully extended to vinylcyclobutanes (Scheme 53). Homologous boryl-substituted allylic silanes are obtained in the silaboration of vinylcyclobutanes in the presence of a nickel catalyst without phosphine ligands.

Silaboration of methylenecyclopropanes proceeds in the presence of palladium or platinum catalysts.[237] Interestingly, Pd- and Pt-catalyzed reactions provide complementary products in certain cases. In the reaction of benzylidenecyclopropane, (*E*) and (*Z*) products are obtained in the presence of palladium and platinum catalysts, respectively, via cleavage of the proximal C–C bond (Scheme 54). The boryl group and silyl group are introduced to sp^2- and sp^3-carbons, respectively, in a highly regioselective manner. Palladium- and platinum-catalyzed silaborations of cyclohexylidenecyclopropane proceed through highly selective cleavage of either distal or proximal C–C bond,



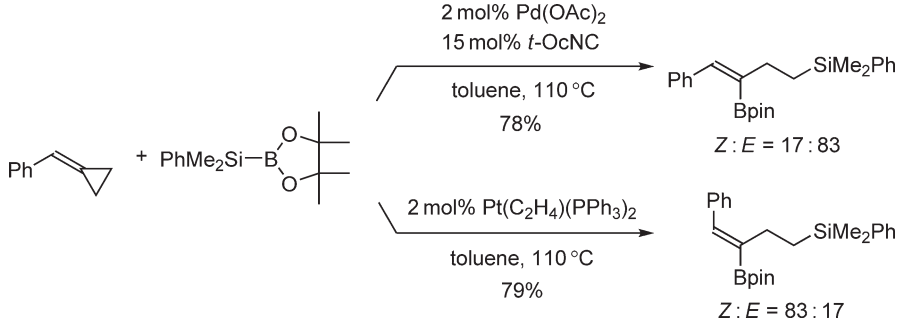
R^1	R^2	*Yield* (%)
H	Ph	89
Ph	H	82
Ph	Me	56

Scheme 52

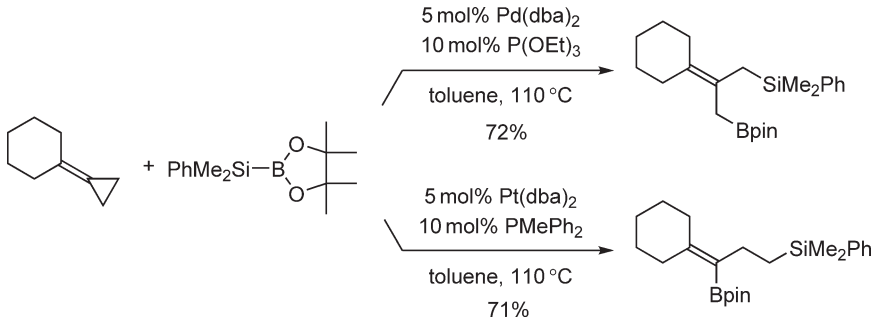


R^1	R^2	*Yield* (%)
H	Ph	65
Ph	Ph	77

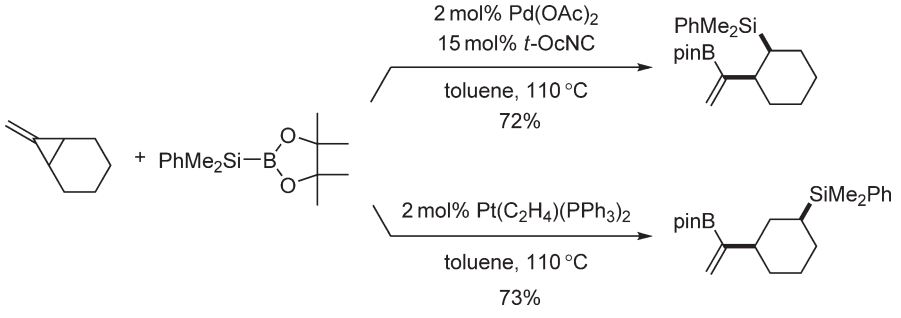
Scheme 53



Scheme 54



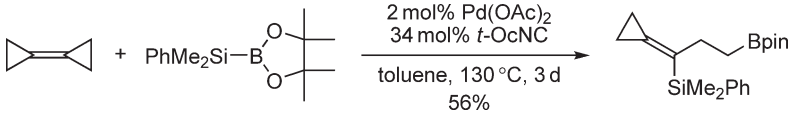
Scheme 55



Scheme 56

respectively, giving two different products in good yields (Scheme 55). An additional example is the reaction of cyclohexane-fused methylenecyclopropane (Scheme 56). The reaction of a bicyclic *exo*-methylenecyclopropane affords *cis*-1,2-disubstituted cyclohexane and *cis*-1,3-disubstituted cyclohexane derivatives selectively in the presence of palladium and platinum catalysts, respectively. The formation of the 1,3-disubstituted product may be due to the β-hydride elimination of an intermediary platinum complex followed by readdition of the eliminated hydrosilane with opposite regioselectivity.

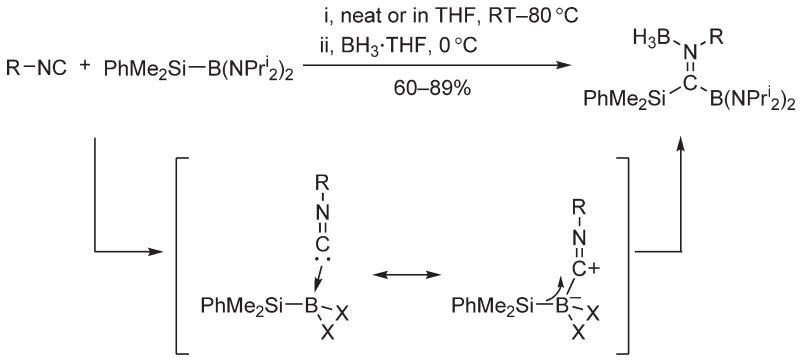
Silaboration of bicyclopropylidene proceeds via proximal C–C bond cleavage at 130 °C in the presence of the palladium/*tert*-alkyl isocyanide catalyst (Equation (88)). In contrast to the aforementioned silaboration of methylene cyclopropanes, vinylsilane products are obtained with high regioselectivity.[102]



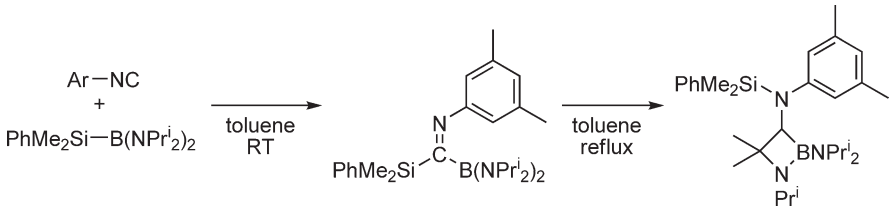
(88)

10.16.3.1.6 Silaboration of isocyanides

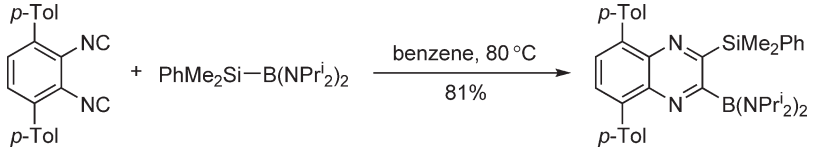
1,1-Addition of silylboranes to isocycanides proceeds in the absence of catalyst (Scheme 57).[238] The products, (boryl)(silyl)iminomethanes, are moisture sensitive, suffering from decomposition on silica gel. The imine can be converted into the corresponding imine–borane (BH_3) complexes, which are stable enough to be isolated by silica gel column chromatography. Primary, secondary, and tertiary alkyl isocyanides and aryl isocyanides can take part in the reaction. The reaction mechanism may involve coordination of isocyanide to the boron atom followed by 1,2-migration of the silyl group from boron to carbon. The (boryl)(silyl)iminomethanes undergo unusual four-membered ring formation at higher temperature (Scheme 58). Reaction of a 1,2-diisocyanobenzene derivative with silylborane affords 2-silyl-3-borylquinoxaline in good yield via successive insertions of the two isocyano groups into the boron–silicon bond (Equation (89)).[239]



Scheme 57



Scheme 58



(89)

10.16.3.1.7 Silaboration of carbenoids

The reaction of silylborane with 1-halo-1-lithio-1-alkenes yields 1-boryl-1-silyl-1-alkenes via borate formation followed by 1,2-migration of silyl group (Equation (90)).[76,240] The mechanism seems to be closely related to that proposed for the silaboration of isocyanide (Figure 2). Vinyl-substituted carbenoids, 1-chloro-1-lithio-2-alkenes, react with silylpinacolborane to give 1-boryl-1-silyl-2-alkanes in good yield (Equation (91)).[241] This methodology is applied to the synthesis of 1-boryl-1-silyl-2-cyclobutene.[242] Similar reactions are carried out with other carbenoid

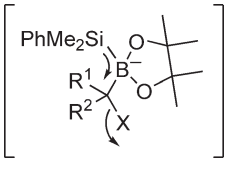
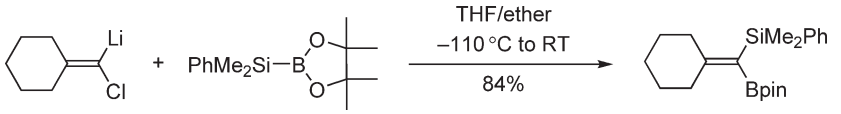
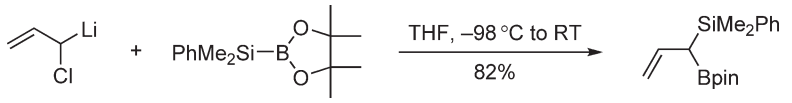


Figure 2 Plausible mechanism of the silyl group migration in the reaction of silylborane with carbenoid.

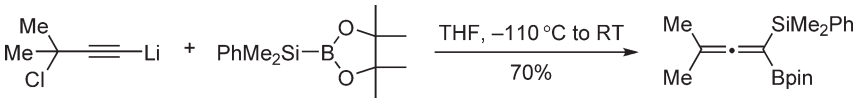
precursors such as 3-chloro-1-lithio-1-alkynes[243] and di- or trihalolithiomethanes,[244] affording 1-boryl-1-silylallenes and mono- or dihalo(boryl)(silyl)methanes, respectively (Equations (92) and (93)).



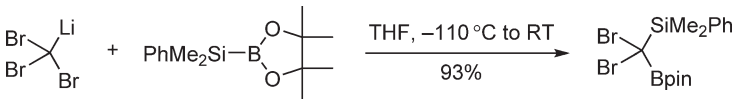
(90)



(91)



(92)

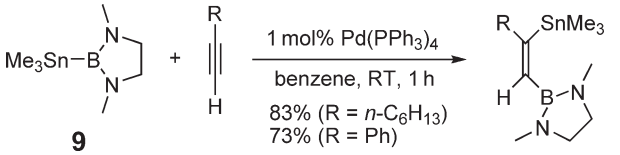


(93)

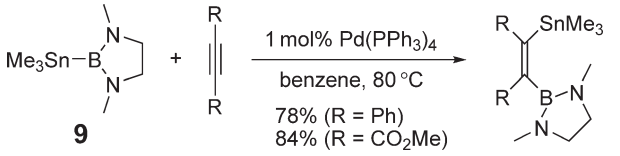
10.16.3.2 Addition of Tin–Boron Bond

10.16.3.2.1 Addition to alkynes

Addition of stannylboranes to alkynes is efficiently catalyzed by palladium(0) complexes. The tin–boron bond of stannylborane **9** adds to terminal alkynes in the presence of 1 mol% of $Pd(PPh_3)_4$ at RT to afford (*Z*)-*β*-stannylalkenylboranes in good yield (Equation (94)).[245] The reaction is highly regioselective; the boryl group is exclusively attached to the terminal carbon. $Pd(dba)_2$ and $PdCl_2(PPh_3)_4$ also exhibit catalytic activities. However, platinum(0) complex $Pt(PPh_3)_4$, which is effective for the addition of B–B and Si–B bonds, is totally ineffective. Internal alkynes are less reactive, and require heating at 80 °C (Equation (95)).

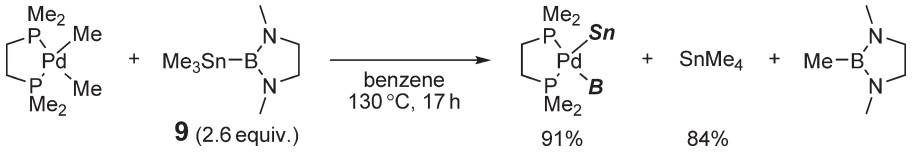


(94)



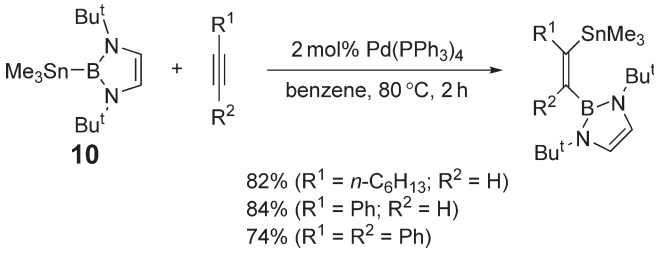
(95)

(Boryl)(stannyl)palladium(II) complex, which is a putative intermediate of the stannaboration, is in fact formed by heating $PdMe_2$(dmpe) and the stannylborane **9** (Equation (96)). The complex reacts with 1-octyne at 80 °C to afford the stannaboration product in 36% yield.



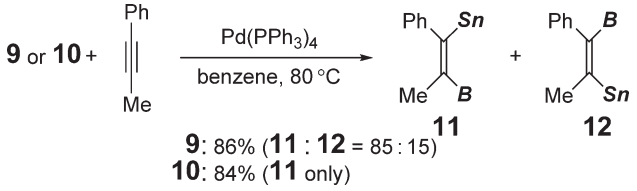
(96)

Diazaboroline **10** has also been used for the stannaboration reaction of alkynes (Equation (97)).[246]



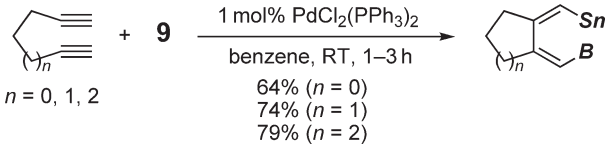
(97)

The reaction of diazaboroline **10** selectively furnishes only the regioisomer **11**,[245] whereas that of diazaborolidine **9** with 1-phenyl-1-propyne results in the formation of a mixture of regioisomers **11** and **12** (85 : 15) (Equation (98)).[246]



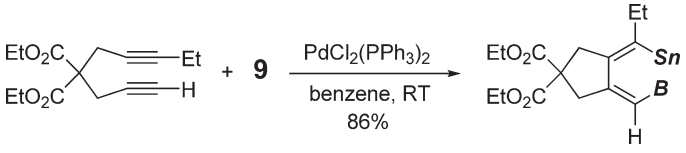
(98)

Stannaboration of diynes and enyne provide cycloalkanes incorporating both stannyl and boryl groups, which are otherwise difficult to synthesize. Palladium-catalyzed reactions of 1,4-, 1,5-, and 1,6-diynes with **9** give the corresponding cyclization products in good yields (Equation (99)).[247] The reaction is so efficient that even a strained four-membered ring is readily formed.



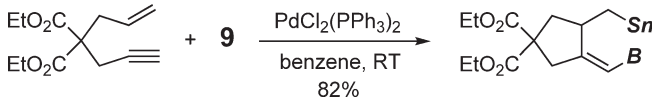
(99)

In the reaction of an unsymmetrical diyne with **9**, the boryl group is introduced regioselectively to the terminal acetylenic bond (Equation (100)).



(100)

An enyne undergoes the stannaborative cyclization with **9** in a completely regioselective fashion (Equation (101)). The boryl group is introduced exclusively to the acetylenic bond to give an isomerically pure product. These results obtained with the unsymmetrical substrates suggest that the more reactive unsaturated bond initially inserts into the Pd–B bond.

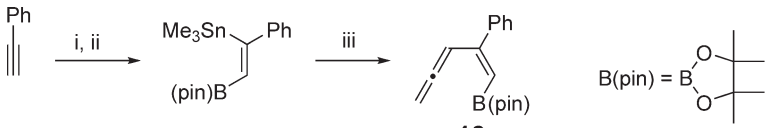


(101)

In the study of substituent effect on the thermal electrocyclic ring-closing reactions of vinylallenes, two stereoisomeric boryl-substituted vinylallenes **13** and **14** are synthesized by means of the palladium-catalyzed stannaboration of alkynes (Schemes 59 and 60).[248]

10.16.3.2.2 Addition to 1,3-dienes

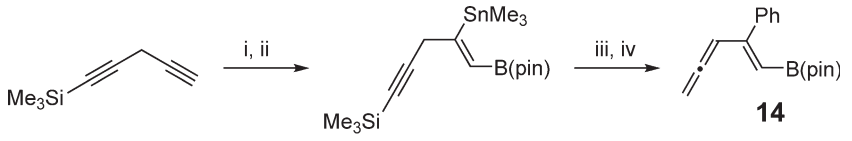
Stereoselective 1,4-addition of the tin–boron bond to 1,3-diene occurs in the presence of a palladium catalyst, which is prepared *in situ* from Pd(dba)$_2$ and ETPO, at 80 °C in THF to give (*Z*)-1-boryl-4-stannyl-2-butenes (Equation (102)).[249] For unsymmetrical 1,3-diene like isoprene, highly regioselective 1,4-stannaboration is observed.



13

i, Me_3Sn-$B(NEt_2)_2$, $Pd(PPh_3)_4$, benzene, 60 °C; ii, pinacol, RT (90%, two steps);
iii, propargyl bromide, $BnPdCl(PPh_3)_2$, CuI, DMF, RT–35 °C (45%)

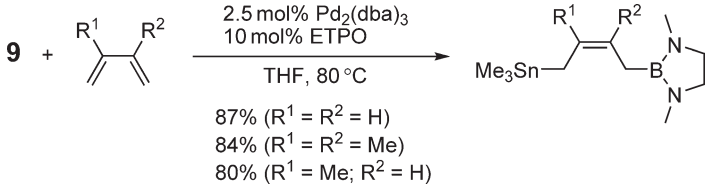
Scheme 59



14

i, Me_3Sn-$B(NEt_2)_2$, $Pd(PPh_3)_4$, toluene, RT; ii, pinacol, RT (52%, two steps);
iii, iodobenzene, $BnPdCl(PPh_3)_2$, CuI, DMF, 90 °C (24%); iv, NaOH, MeOH (16%)

Scheme 60

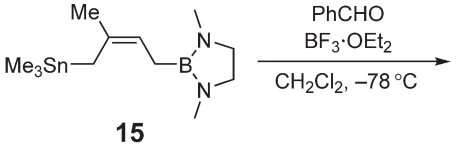


(102)

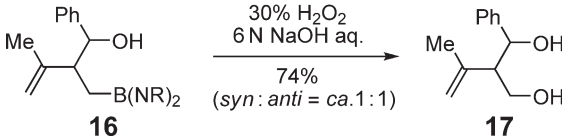
Stepwise utilization of both elements is achieved with a stannaboration product of isoprene (Scheme 61). Reaction of **15** with benzaldehyde in the presence of $BF_3{\cdot}OEt_2$ occurs selectively at the allylstannane moiety to give **16**. Oxidation of the resulting C–B bond with H_2O_2 under basic conditions affords diol **17** as a mixture of diastereomers.

10.16.3.2.3 Addition to allenes

Reaction of an allene with stannylborane **9** in the presence of a palladium catalyst results in the double insertion of 1,1-dimethylallene into the tin–boron bond, affording the 1 : 2 adduct **18** (74% GC yield) along with the 1 : 1 adduct (18% GC yield) (Equation (103)).[227]

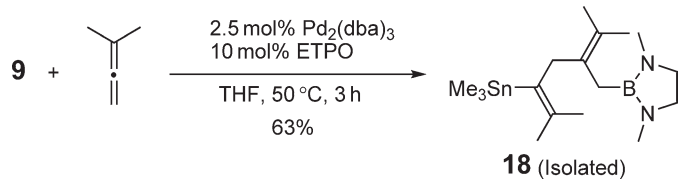


15



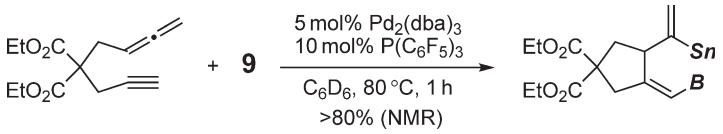
16 **17**

Scheme 61



(103)

Reaction of the stannylborane **9** with an allenyne gives a cyclization product, in which the boryl and stannyl groups are introduced to the acetylenic terminus and the allenic central carbon, respectively (Equation (104)).[159] Based on the assumption that an unsaturated functionality initially inserts into the Pd–B bond of (boryl)(stannyl)palladium(II) species, it seems likely that the alkyne moiety is more reactive than the allene moiety in this reaction.

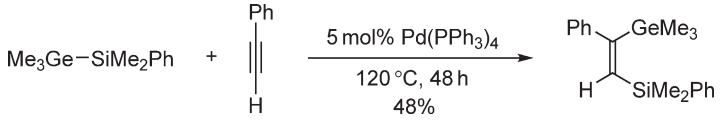


(104)

10.16.3.3 Silicon–Germanium

10.16.3.3.1 Addition to alkynes

Addition of a silylgermane to phenylacetylene is catalyzed by $Pd(PPh_3)_4$ at 120 °C to give (*Z*)-α-germyl-β-silylstyrene in 48% yield (Equation (105)).[250]



(105)

10.16.3.4 Silicon–Tin

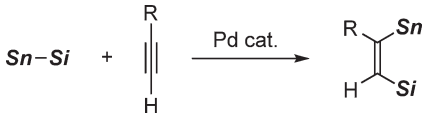
10.16.3.4.1 Addition to alkynes

Palladium-catalyzed addition of a silicon–tin linkage across a carbon–carbon triple bond was first reported in 1985 by the Mitchell group and the Chenard group independently.[251,252] Since then, the silastannation reaction of alkynes has been studied extensively (Table 7).[253–261]

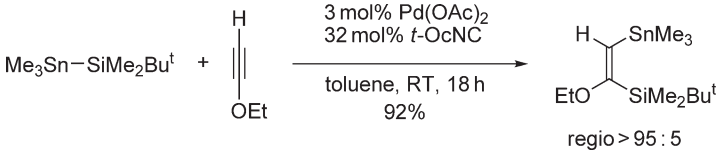
Palladium(0)–*tert*-alkyl isocyanide complex, which is effective for the activation of silicon–silicon linkage, also catalyzes addition of silylstannanes to alkynes efficiently. The silastannation proceeds at RT with high regio- and stereoselectivities to give (*Z*)-β-stannylalkenylsilanes in high yields. It is of note that no reaction occurs at RT with $Pd(PPh_3)_4$. Arylacetylenes, relatively reactive alkynes, can be silastannated at RT by using palladium(0)–phosphite catalysts. Whereas an *N*-benzyl *N*-tosyl ynamine undergoes regio- and stereoselective silastannation with Bu_3Sn–$SiMe_3$ in the presence of $Pd(PPh_3)_4$, an *N*-benzoyl *N*-tosyl ynamine leads to the formation of a mixture of the regioisomers (α-Sn : β-Sn = 55 : 45). The silastannation in ionic liquids has also been reported. The immobilized catalyst can be recycled up to 10 times without loss of activity. Silastannation using (tributylstannyl)(5-methyl-2-furyl)dimethylsilane was employed in a synthesis of the C23–C32 fragment of rapamycin.[262] A marked contrast is observed between $Pd(PPh_3)_4$ and palladium–isocyanide catalyst in the silastannation reaction of ethyne. A mixture of (*Z*)- and (*E*)-isomers (1 : 4) is produced with $Pd(PPh_3)_4$, whereas the (*Z*)-isomer is stereoselectively obtained with palladium–isocyanide catalyst.

The palladium–isocyanide complex is effective for silastannation of ethoxyethyne, a labile alkyne, to produce (*Z*)-1-ethoxy-1-silyl-2-stannylethene with high regioselectivity (Equation (106)).[253] The regioselectivity observed has also been studied by computation.[263]

Table 7 Palladium-catalyzed silastannation of alkynes



Sn–Si	*R*	*Pd cat.* (mol%)	*Conditions*	*Yield* (%)	*References*
Me_3Sn–$SiMe_2Bu^t$	Bu	$Pd(OAc)_2$ (4), t-OcNC (30)	Toluene, RT, 24 h	89	217
Bu_3Sn–$SiMe_3$	C_6H_4X-*p*(X = H, F, Cl, CO_2Et, NO_2, CN)	$Pd(dba)_2$ (1), $P(OEt)_3$ (2)	THF, RT, 1–5 h	70–96	218
Bu_3Sn–$SiMe_3$	$N(CH_2Ph)(Ts)$	$Pd(PPh_3)_4$ (0.05)	THF, 50 °C, 2–3 h	91	219
Bu_3Sn–$SiMe_3$	$CH_2CO_2SnBu_3$	$Pd(PPh_3)_4$ (2)	Galvinoxyl, THF, reflux, 6 h	80	220,221
Bu_3Sn–$SiMe_3$	CH_2OH, CH(OH)Ph, $CH(OH)Bu^t$, CH(OTBS)Ph, CH(OMEM)Ph	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5), PPh_3 (10)	THF, reflux	80–88	222
Bu_3Sn–$SiMe_3$	Ph, n-C_8H_{17}, $(CH_2)_4OH$	$Pd(PPh_3)_4$ (5)	[bmim]PF_6–Et_2O, 70 °C, reflux, 15–36 h	89–100	223,224
Bu_3Sn–$SiMe_3$	H	$Pd(OAc)_2$ (2), t-OcNC (8)	Toluene, 35 °C	86	225
Bu_3Sn–$SiMe_2(OPr^i)$	H	$Pd(OAc)_2$ (2), t-OcNC (8)	Toluene, 35 °C	81	225

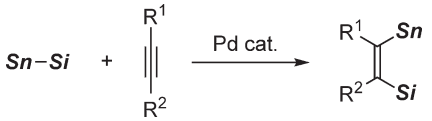


(106)

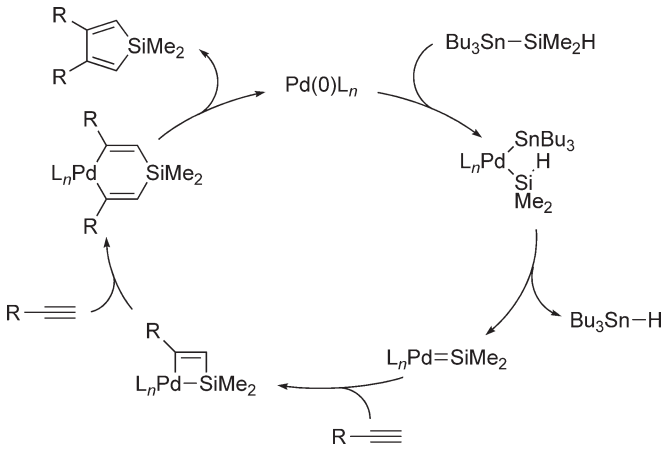
Both the palladium–isocyanide complex and $Pd(PPh_3)_4$ catalyze the silastannation of internal 1-alkoxy-1-alkynes (Table 8) Interestingly, the regiochemistry of the products obtained with $Pd(PPh_3)_4$ is opposite to that obtained with palladium–isocyanide complex.[264] Addition of Me_3Sn–$SiMe_3$ to 1-phenylthio-1-alkynes is performed with a Pd–trifurylphosphine catalyst. Silastannation of alkynoate esters lacks regioselectivity.[265] Silastannation of ordinary internal alkynes like 4-octyne and diphenylacetylene has been unsuccessful so far.

3,4-Disubstituted silole derivatives are synthesized by the palladium-catalyzed reaction of (trialkylstannyl)dimethylsilane with terminal alkynes (Equation (107)).[266] The mechanism is supposed to involve a palladium silylene complex, which is generated via β-hydride elimination from $L_nPd(SiMe_2H)(SnBu_3)$ (Scheme 62). Successive incorporation of two alkyne molecules into the complex followed by reductive elimination gives rise to the silole products.

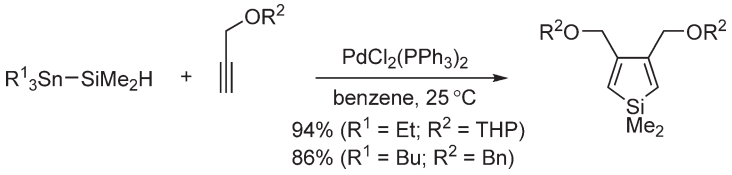
Table 8 Palladium-catalyzed silastannation of alkoxy- and thioalkanes



Sn–Si	R^1	R^2	*Pd cat.*	*Yield* (%)	*References*
Me_3Sn–$SiMe_2Bu^t$	Me	OEt	$Pd(OAc)_2$–t-OcNC	99 (>95 : 5)	217
Me_3Sn–$SiMe_3$	OCH_2OCH_2Ph	Bu	$Pd(PPh_3)_4$	58	227
Me_3Sn–$SiMe_3$	OEt	n-C_6H_{13}	$Pd(PPh_3)_4$	90	227
Me_3Sn–$SiMe_3$	SPh	CH_2OP (P = H, Me, THP)	$Pd_2(dba)_3$–TFP	77–80	227
Bu_3Sn–$SiMe_3$	CO_2Me	CH_2OTHP	$PdCl_2(PPh_3)_2$	62 (1 : 1)	228



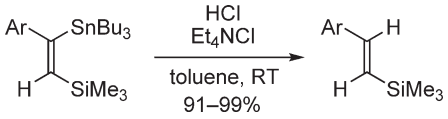
Scheme 62



(107)

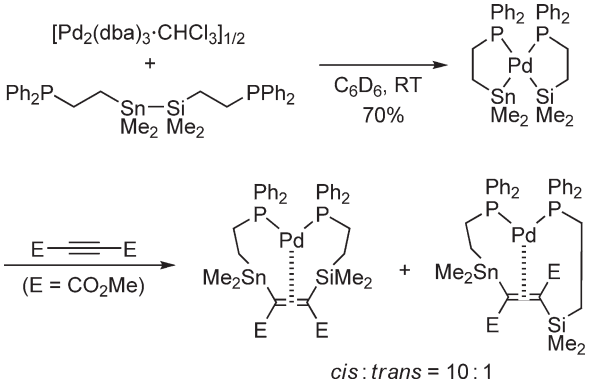
A thermodynamically stable (silyl)(stannyl)palladium(II) complex is synthesized by an oxidative addition of the Si–Sn linkage to palladium(0) (Scheme 63).[267] The complex has the square-planar geometry with a *cis*-arrangement of the silicon and tin atoms. An alkyne reacts with the complex to afford a silastannated product as a mixture of *cis*/*trans* stereoisomers (10 : 1).

The silastannation products serve as useful building blocks. Treatment of (*Z*)-α-stannyl-β-silylstyrenes with HCl in the presence of Et_4NCl results in protodestannation with retention of stereochemistry to give the corresponding (*E*)-β-silylstyrenes in high yield (Equation (108)).[254]

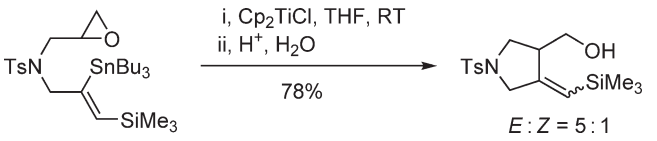


(108)

A silastannation product bearing an epoxide moiety undergoes titanium(III)-mediated cyclization with the vinylstannane moiety (Equation (109)).[268]



Scheme 63

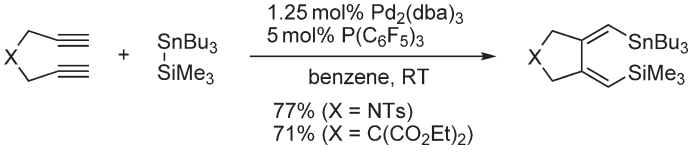


(109)

Palladium-catalyzed cross-coupling of **19** with allyl bromide occurs exclusively at the vinylstannane moiety to give 1-ethoxy-1-silyl-1,4-diene **20**. The following ether exchange with allyl alcohol causes the Claisen rearrangement to give an acylsilane derivative **21** (Scheme 64).[253]

Lithiation of the vinylstannane moiety of **22** with Bu^nLi followed by the reaction with PhCHO gives (*Z*)-γ-silyl allylic alcohol **23** (Scheme 65).[261] The subsequent Cu(I)-mediated cross-coupling with allyl chloride affords (*Z*)-allylic alcohol **24** with the (*Z*)-stereochemistry retained.

The palladium-catalyzed addition of silylstannanes to 1,6-diynes invokes intramolecular cyclization, giving rise to 1,2-dialkylidene cyclopentanes (Equation (110)).[269] The resulting *Z,Z*-1-silyl-4-stannyl-1,3-diene moiety fixed in an *s-cis*-conformation makes the molecule axially chiral. Rapid equilibrium between the two helical forms is observed by NMR spectroscopy.[270,161]

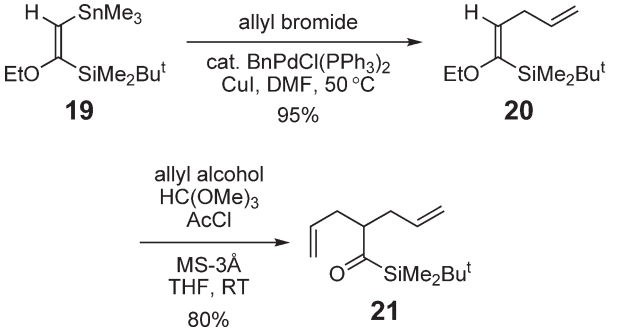


(110)

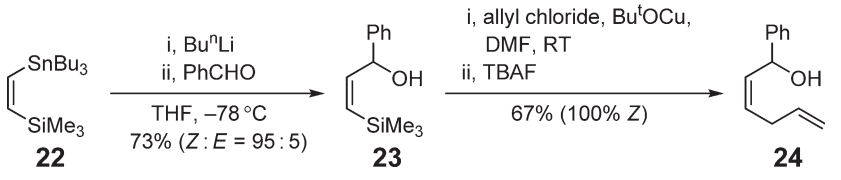
A similar silastannative cyclization reaction has been extensively studied with 1,6-enynes (Table 9).[271–274] Several palladium catalysts including palladium(0)–DBA complex and even a heterogeneous catalyst are effective, whereas $Pd(PPh_3)_4$ gives an uncyclized simple adduct predominantly.

Mechanistically, a (silyl)(stannyl)palladium initially formed undergoes regioselective silylpalladation to the alkyne moiety of the enyne (Scheme 66). Then, two possible pathways are conceivable for addition to the alkene moiety, that is, stannylpalladation and carbopalladation. It has not been established that which pathway operates.

The reactions catalyzed by cationic palladium complexes are believed to proceed via a different mechanism (Scheme 67).[273] Initially, a cationic silylpalladium(II) species is generated by σ-bond metathesis of the Br–Pd^+ with a silylstannane. Subsequently, the alkyne and alkene moieties of the 1,6-diyne successively insert into the Pd–Si bond to form a cationic alkylpalladium(II), which then undergoes σ-bond metathesis with silylstannane to liberate the product and regenerate the active catalyst species, ***Si***–Pd^+.

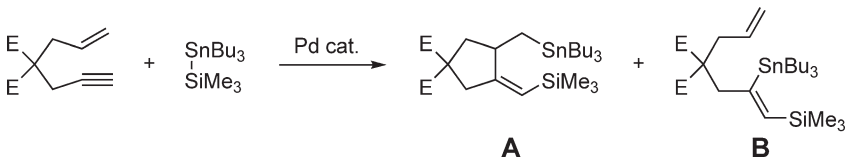


Scheme 64

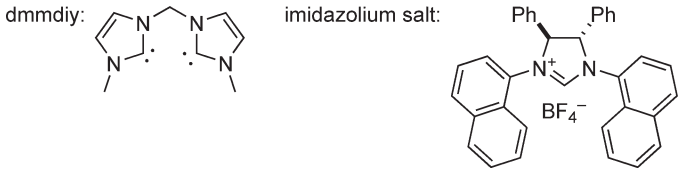


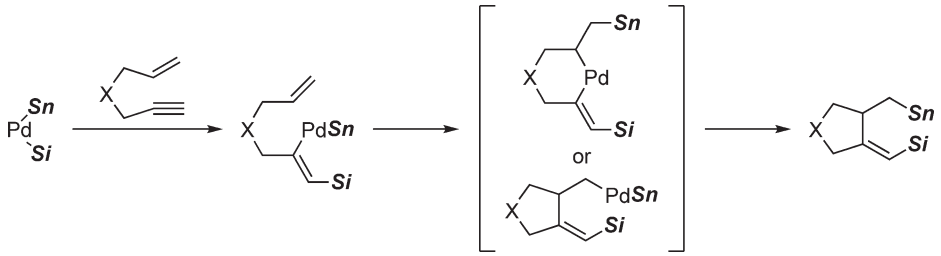
Scheme 65

Table 9 Palladium-catalyzed silastannative cyclization of enyne derived from diethyl malonate

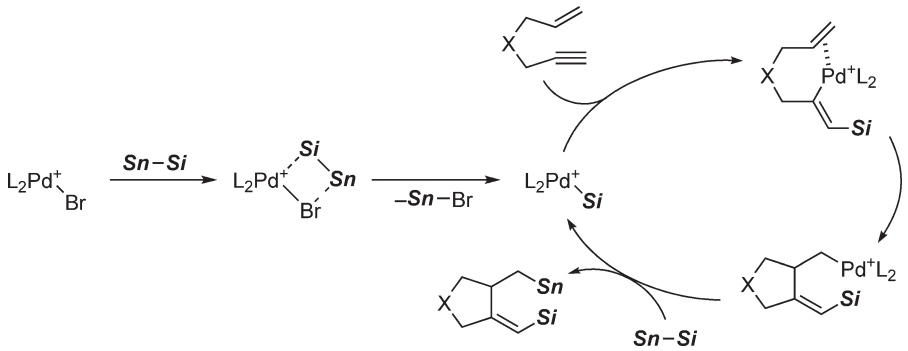


Pd cat. (mol%)	*Conditions*	*A* (%)	*B* (%)	*References*
$Pd(PPh_3)_4$ (3)	THF, 50 °C, 4 h	14	80	235,236
$Pd_2(dba)_3{\cdot}CHCl_3$ (3)	THF, RT, 16 h	63		235,236
$Pd(OH)_2/C$ (10)	THF, RT, 20 h	90	2	235,236
$Pd_2(dba)_3$ (5), P(*cyclo*-$C_6H_{11})_2$(*o*-biphenyl) (20)	Toluene, 60 °C, 21 h	71		237
$PdBr_2$(dmmdiy) (5), $NaB[3,5\text{-}(CF_3)_2C_6H_3]_4$	Toluene, 45 °C, 42 h	81		237
$Pd_2(dba)_3{\cdot}CHCl_3$ (3), imidazolium salt (6), Cs_2CO_3 (12)	$ClCH_2CH_2Cl$, 40 °C, 11 h	68		238





Scheme 66

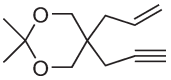
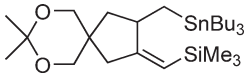
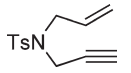
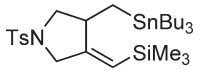
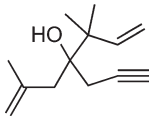
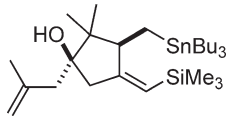


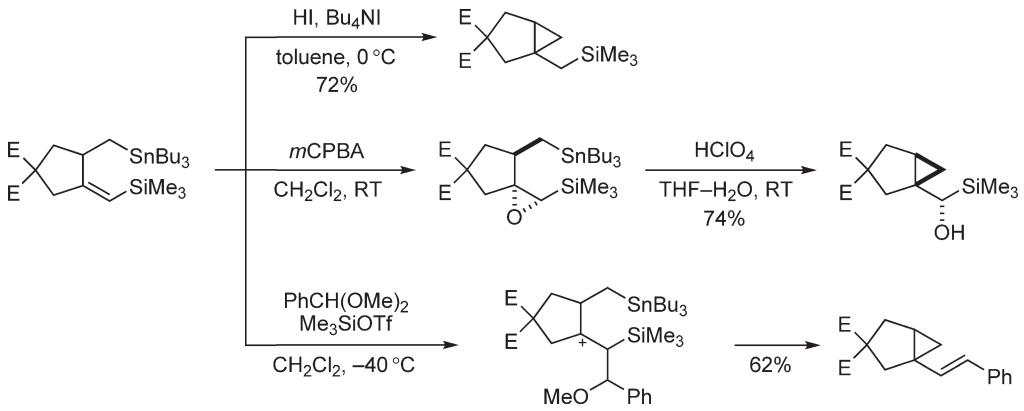
Scheme 67

The regioselective silastannation is applicable to other 1,6-enynes in the presence of various palladium catalysts (Table 10).[275]

The product possesses a homoallylic stannane moiety, which can be utilized as a useful synthon for cyclopropane formation (Scheme 68). Upon treatment of the homoallylstannane with HI, destannative cyclization takes place to give cyclopropylmethylsilane.[271,272] A Lewis acid-catalyzed reaction with benzaldehyde dimethyl acetal affords vinylcyclopropane.[273]

Table 10 Palladium-catalyzed silastannative cyclization of enynes

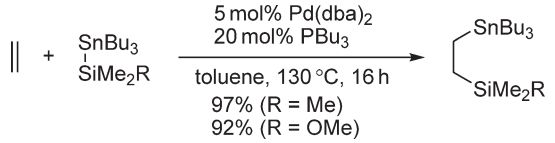
Enyne	*Pd cat.* (mol%)	*Product*	*Yield* (%)	*References*
	$Pd(OH)_2/C$ (10)		65	235,236
	$Pd_2(dba)_3$ (5), P(*cyclo*-C_6H_{11})$_2$(*o*-biphenyl) (20)		76	237
	$Pd(OH)_2/C$ (10)		82	235,236
	$PdBr_2$(dmmdiy) (5), NaB[3,5-$(CF_3)_2C_6H_4]_4$		80	237
	$Pd_2(dba)_3$·$CHCl_3$ (3), imidazolium salt (6), Cs_2CO_3 (12)		62	236,238
	$PdCl_2$ (6)		70	239



Scheme 68

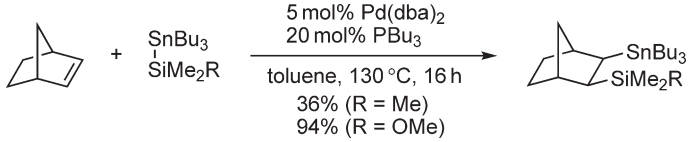
10.16.3.4.2 Addition to alkenes

Silylstannanes add to ethylene in the presence of palladium catalysts (Equation (111)). A trialkylphosphine with moderate steric bulkiness is suitable as the ligand for the reaction.[276]



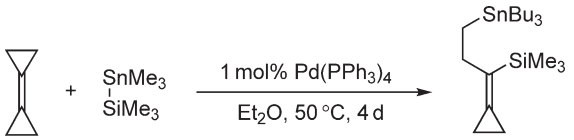
(111)

Norbornene also undergoes silastannation from the *exo*-side under identical conditions (Equation (112)). However, ordinary alkenes such as 1-hexene, styrene, and cyclohexene fail to react with silylstannanes.

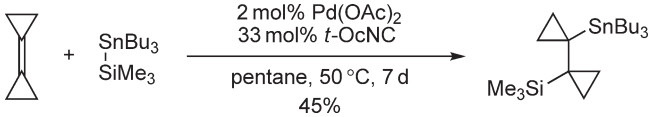


(112)

Bicyclopropylidene, a particularly reactive tetrasubstituted alkene, reacts with Me_3Sn–$SiMe_3$ in the presence of $Pd(PPh_3)_4$ to give 1-cyclopropylidene-1-silyl-3-stannylpropane in high yield (Equation (113)).[102] In contrast, the reaction with Bu_3Sn–$SiMe_3$ in the presence of palladium(0)–*tert*-alkyl isocyanide catalyst affords 1-silyl-1′-stannylbicyclopropyl (Equation (114)).

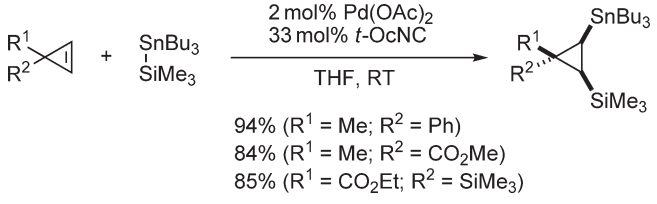


(113)



(114)

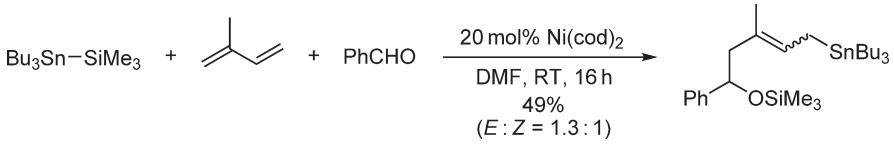
The palladium–isocyanide catalyst is also effective for the silastannation of cyclopropenes (Equation (115)).[158] The reaction proceeds smoothly under mild conditions (RT, 10–30 min) with high face selectivity to give tetrasubstituted cyclopropanes in good yield.



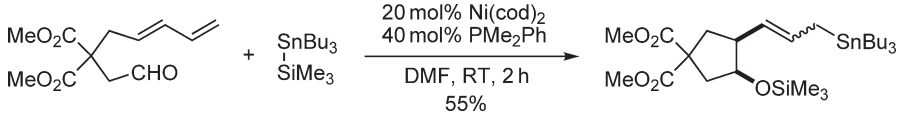
(115)

10.16.3.4.3 Addition to 1,3-dienes

Silastannative coupling of 1,3-diene and aldehydes is achieved both in inter- and intramolecular fashions (Equations (116) and (117)).[277] Interestingly, the reaction is catalyzed by nickel(0) complexes, whereas a platinum complex is used for simple 1,4-silastannation of 1,3-diene.[278]



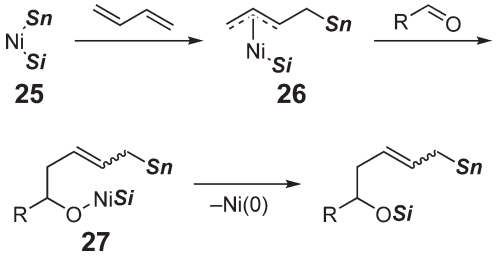
(116)



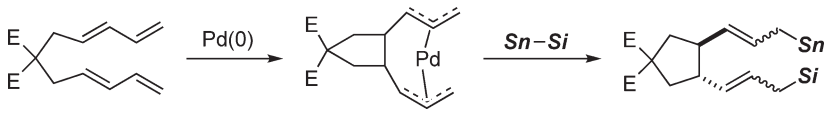
(117)

It is proposed that the reaction proceeds through (i) oxidative addition of a silylstannane to Ni(0) generating (silyl)(stannyl)nickel(II) complex **25**, (ii) insertion of 1,3-diene into the nickel–tin bond of **25** giving π-allylnickel intermediate **26**, (iii) inter- or intramolecular allylation of aldehydic carbonyl group forming alkoxy(silyl)nickel intermediate **27**, and (iv) reductive elimination releasing the coupling product (Scheme 69).

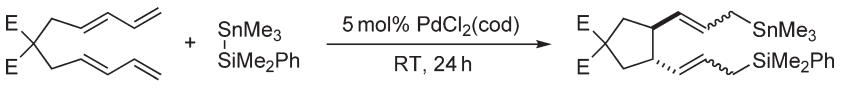
Silastannative cyclization of bis(diene) catalyzed by $PdCl_2$(cod) achieves formal 1,8-silastannative C–C bond formation (Equation (118)).[125] Poor stereoselectivity at the allylic metal moieties (*E*/*Z*) is observed.



Scheme 69



Scheme 70

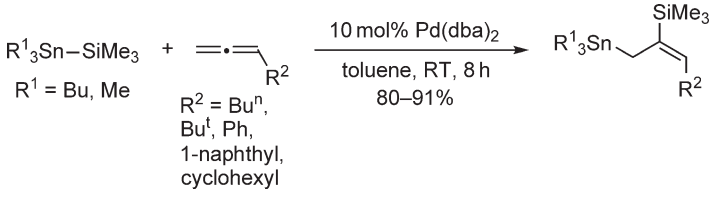


E = CO_2Et: 77% (*trans* : *cis* = 96 : 4)
E = $SO_2C_6H_4Me$-*p*: 97% (*trans* : *cis* = 92 : 8) (118)

The reaction is believed to involve a *trans*-(*anti*-η^3)-(*syn*-η^3)-bisallylpalladium(II) species as an active intermediate (Scheme 70).

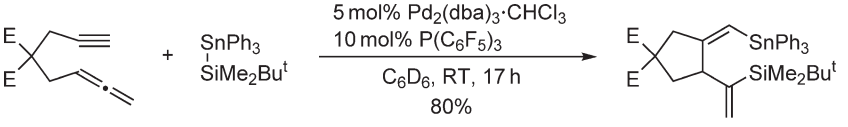
10.16.3.4.4 Addition to allenes

Highly regio- and stereoselective silastannation is achieved by employing phosphine-free $Pd(dba)_2$ as the catalyst (Equation (119)).[279] The addition takes place at the less substituted allenic C=C bond to afford β-silyl (*E*)-allylstannanes. In contrast, the reaction in the presence of $Pd(PPh_3)_4$ gives three isomers.[280–281]



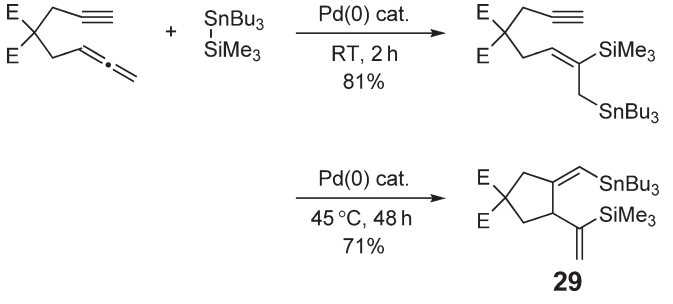
(119)

Addition of $Ph_3Sn–SiMe_2Bu^t$ to an allenyne occurs with concomitant cyclization in the presence of a palladium(0) catalyst at RT (Equation (120)).[159] The silyl group is introduced at the central allenic carbon and the stannyl group at the terminal acetylenic carbon to furnish cyclopentane **28**. Unlike stannaboration, the allene moiety initially reacts. Use of a less reactive silylstannane enables isolation of a simple 1,2-adduct (Scheme 71). Upon heating in the presence of the Pd catalyst, the isolated 1,2-adduct undergoes intramolecular allylstannation to give cyclized product **29**.



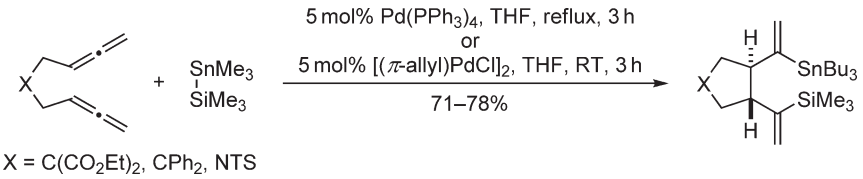
28 (120)

The palladium-catalyzed silastannation of bis(allene)s gives *trans*-cyclized product stereoselectively (Equation (121)).[162] This stereochemical outcome stands in contrast to the distannation of the bis(allene)s, which affords *cis*-cyclized product.



29

Scheme 71



(121)

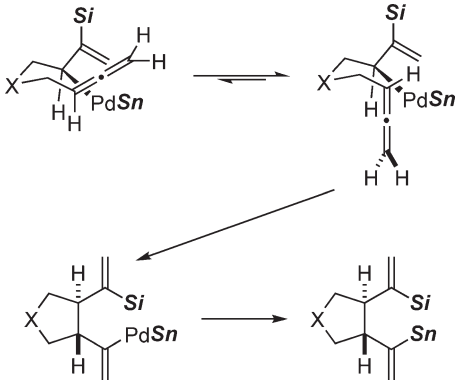
The observed *trans*-stereoselectivity is accounted for by assuming unfavorable interaction between the trimethylsilyl group and the allenyl group (Scheme 72).

Allenes having a remote carbonyl group react with a silylstannane in the presence of $[(\pi\text{-allyl})PdCl]_2$ at RT to give *cis*-2-(1-silylvinyl)cycloalkan-1-ols (Table 11).[282] Five- and six-membered rings are constructed through the silastannative coupling.

10.16.3.5 Boron–Sulfur

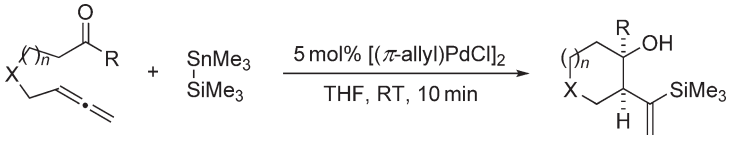
10.16.3.5.1 Addition to alkynes

Regio- and stereoselective addition of 9-(phenylthio)-9-BBN to terminal alkynes is catalyzed by $Pd(PPh_3)_4$ to produce 9-[(*Z*)-*β*-(phenylthio)alkyenyl]-9-BBN (Scheme 73).[283] Addition of styrene avoids catalyst deactivation by trapping free thiophenol generated in the reaction mixture. The produced alkenylboranes exhibit high reactivities for protonolysis with MeOH to produce 2-phenylthio-1-alkenes.

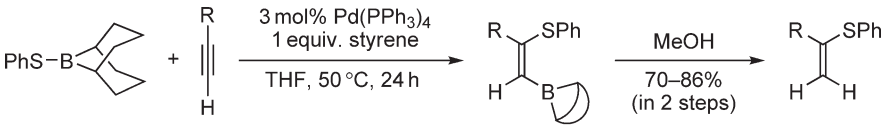


Scheme 72

Table 11 Palladium-catalyzed silastannative cyclization of allenyl ketones

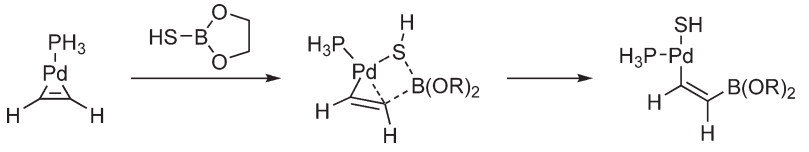


X	*n*	*R*	*Yield* (%)
NTs	0	H	71
$C(CO_2Et)_2$	0	H	63
NTs	1	H	62
O	1	H	68
NTs	0	Me	67
NTs	1	Me	67



R = $(CH_2)_5CH{=}CH_2$, $(CH_2)_4CO_2Me$, $(CH_2)_3Cl$, $(CH_2)_3CN$, CH_2OTHP

Scheme 73



Scheme 74

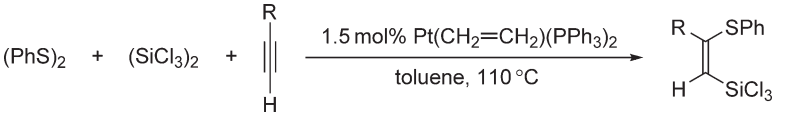
A DFT study reveals that the thioboration reaction proceeds via a metathesis-like pathway between Pd–C and S–B bonds forming Pd–S and C–B bonds, rather than an oxidative addition of the B–S bond to the Pd(0) complex (Scheme 74).[284]

10.16.3.6 Silicon–Sulfur

10.16.3.6.1 Addition to alkynes

A highly air and moisture sensitive thiosilane PhS–$SiCl_3$, which is prepared by the reaction of PhSLi with excess $SiCl_4$, adds to terminal alkynes in the presence of $Pt(CH_2{=}CH_2)(PPh_3)_2$ at 110 °C (Scheme 75).[285] After treatment of the reaction mixture with MeLi, [(*Z*)-*β*-(phenylthio)alkenyl]trimethylsilanes are obtained with high regio- and stereoselectivity.

Heating a mixture of diaryl disulfide $(ArS)_2$, hexachlorodisilane $(SiCl_3)_2$, and alkynes under identical conditions provides a more convenient way to obtain thiosilylation products (Equation (122)).

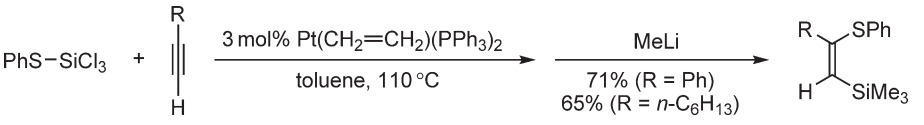


(122)

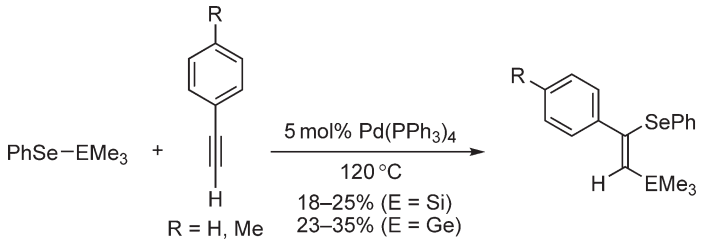
10.16.3.7 Selenium–Silicon and Selenium–Germanium

10.16.3.7.1 Addition to alkynes

Palladium-catalyzed addition of the selenium–silicon bond of PhSe–$SiMe_3$ to arylacetylenes proceeds in a regio- and stereoselective manner to afford (*Z*)-*α*-(phenylseleno)-*β*-(trimethylsilyl)styrenes (Equation (123)).[250] Aliphatic alkynes fails to undergo the addition reaction. Analogous addition of the Se–Ge bond to alkynes occurs under similar conditions.



Scheme 75

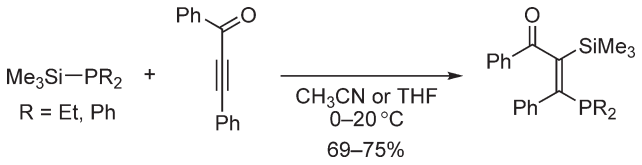


(123)

10.16.3.8 Silicon–Phosphorus

10.16.3.8.1 Addition to alkynes

Silylphosphines add thermally to the carbon–carbon triple bond of acetylenic ketones. The reaction affords (*Z*)-α-silyl-β-phosphino-α,β-unsaturated ketones via regioselective *cis*-1,2-addition (Equation (124)).[286]



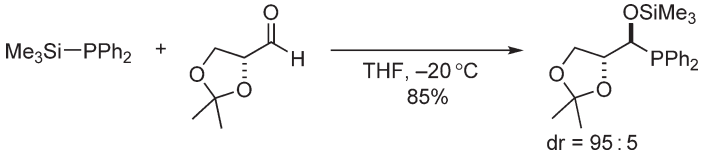
(124)

10.16.3.8.2 Addition to alkenes

Dialkyl(trimethylsilyl)phosphines undergo 1,4-addition to α,β-unsaturated ketones[287–288] and esters[289] to give phosphine-substituted silyl enol ethers and silyl ketene acetals, respectively. A three-component coupling reaction of a silylphosphine, activated alkenes, and aldehydes in the presence of a catalytic amount of CsF affords an aldol product (Scheme 76).[290,291]

10.16.3.8.3 Addition to aldehydes

Silylphosphines are known to add to aldehydic carbonyl groups.[292] The reaction between $Me_3Si–PPh_2$ and chiral aldehydes proceeds with a high diastereoselectivity to afford α-siloxyalkylphosphines (Equation (125)).[293]

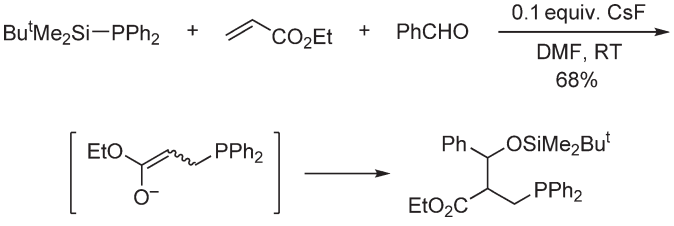


(125)

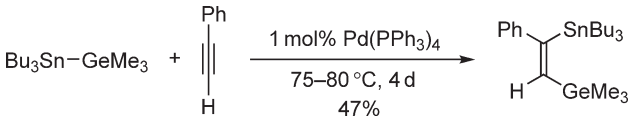
10.16.3.9 Germanium–Tin

10.16.3.9.1 Addition to alkynes

A protocol originally reported for the addition of Ge–Sn bond to phenylacetylene employed $Bu_3Sn–GeMe_3$.[294] The reaction is highly regio- and stereoselective, although the yield is moderate up to 50% (Equation (126)).

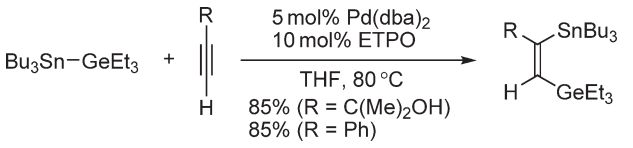


Scheme 76



(126)

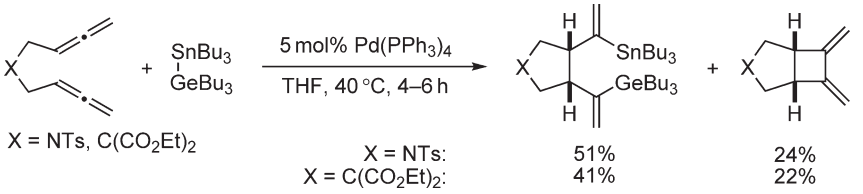
The use of a less reactive triethylgermyl derivative with a Pd(0)–phosphite catalyst achieves high yield germastannation of alkynes (Equation (127)).[295,296] With this system, a propargylic alcohol as well as phenylacetylene is successfully transformed to the corresponding 1,2-adducts in good yield.



(127)

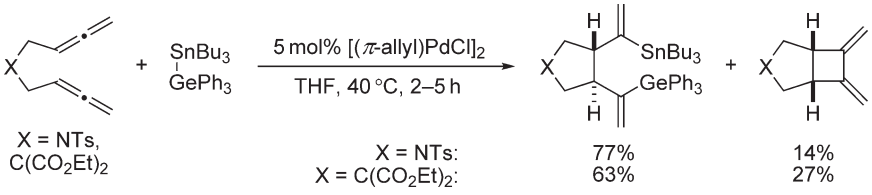
10.16.3.9.2 Addition to allenes

Addition of $Bu_3Sn–GeBu_3$ to bis(allene)s occurs diastereoselectively in the presence of $Pd(PPh_3)_4$ to give *cis*-germastannative cyclization products along with *cis*-fused bicyclic dienes (Equation (128)).[297]



(128)

On the other hand, the corresponding *trans*-isomers are formed as the major product when the germylstannane $Bu_3Sn–GePh_3$ is used in the presence of $[(\pi\text{-allyl})PdCl]_2$ (Equation (129)).

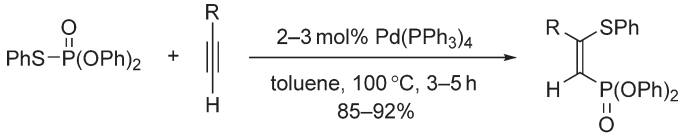


(129)

10.16.3.10 Phosphorus–Sulfur

10.16.3.10.1 Addition to alkynes

1,2-Addition of a phosphorus–sulfur bond to a carbon–carbon triple bond is catalyzed by a palladium(0) complex (Equation (130)).[298] Terminal aliphatic alkynes having various functional groups undergo the addition with PhS–$P(O)(OPh)_2$ to afford (*Z*)-adducts in high yield. In contrast to aliphatic alkynes, phenylacetylene gives a mixture of *E*/*Z* adducts. Internal alkynes and alkenes are unreactive.



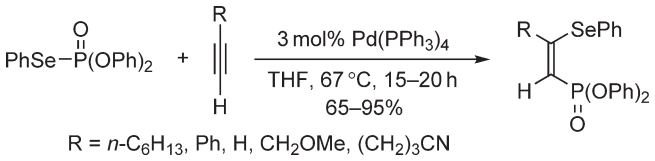
(130)

R = *n*-C_6H_{13}, $(CH_2)_3Cl$, CH_2OMe, $(CH_2)_2OH$

10.16.3.11 Phosphorus–Selenium

10.16.3.11.1 Addition to alkynes

Facile 1,2-addition of the P–Se bond to alkynes occurs in a manner analogous to the addition of the P–S bond (Equation (131)).[299] High regio- and stereoselectivies are observed with phenylacetylene as well as aliphatic alkynes.

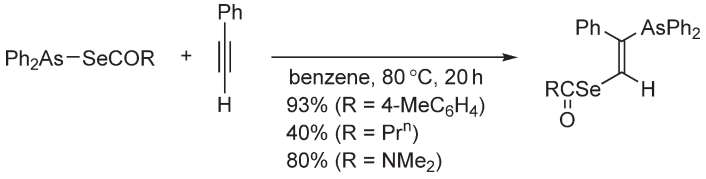


R = *n*-C_6H_{13}, Ph, H, CH_2OMe, $(CH_2)_3CN$ (131)

10.16.3.12 Arsenic–Selenium

10.16.3.12.1 Addition to alkynes

Compounds having an As–Se bond undergo thermal addition to phenylacetylene at 80 °C to give (*E*)-adducts, with the Se group attached at the terminal carbon (Equation (132)).[300]



(132)

10.16.4 Conclusive Remarks

Additions of a variety of element–element bonds, which consist of non-hydrogen elements such as silicon, germanium, tin, boron, sulfur, selenium, and phosphorous, to unsaturated organic molecules have been explored. For further development of this class of reactions, it is critically important to introduce new catalysts and new element–element reagents. Since there is an increasing demand for the efficient and selective synthesis of new organic molecules possessing those elements, development of new element–element addition reactions seems to be highly important and useful. Further efforts devoted to the stereochemical control of the element–element addition reactions would lead to the development of enantioselective and diastereoselective organic synthesis. In addition, exploration of new reactions for the utilizationy of the products of the element–element addition reactions in organic synthesis also seems to be an important subject in organic synthesis.

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10.17 C–E Bond Formation through Hydrosilylation of Alkynes and Related Reactions

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10.17.1 Introduction

Organosilicon compounds play an increasingly important role in organic chemistry. Although silicon is best known for its use as an oxygenation protecting group, carbosilanes have a long and rich history, and their use has only increased in recent years. Carbosilanes find use as temporary tethers,[1,2,2a,3,3a] as weak nucleophiles,[3,3a,4,4a] as stereochemical directing groups,[5,6] as placeholders for oxygenation through Tamao–Fleming oxidation,[7] and as organometallics in various transition metal-catalyzed coupling reactions.[8,8a,9,9a–9c] The advantages of employing silicon in synthetic routes include low cost and toxicity, chemical stability, orthogonal activation with fluoride, functional group tolerance, ease of byproduct removal, and finally the ability to modulate stability, reactivity, and other properties by varying the substituents at silicon. In addition, poly(siloxane)s and poly(vinylsiloxane)s are important materials whose properties can be tuned by the silane structure.

Where vinylsilanes are called for, the traditional approach is lithiation of an analogous vinyl halide, followed by trapping with a chlorosilane. This method requires the initial synthesis of a stereodefined halide, and may prevent taking advantage of the broad functional group compatibility of silicon chemistry. In contrast, hydrosilylation of alkynes represents probably the most straightforward, atom-economical access to vinylsilanes. Metal-catalyzed reactions play a special role in the case of alkyne hydrosilylation because, while many important organometallics can be formed by the uncatalyzed addition of a metal hydride to an alkyne (B, Zr, Al), or by a radical process (Sn), hydridosilanes are generally unreactive without catalysis, and relatively little selective radical chemistry is known.[10,10a–10d]

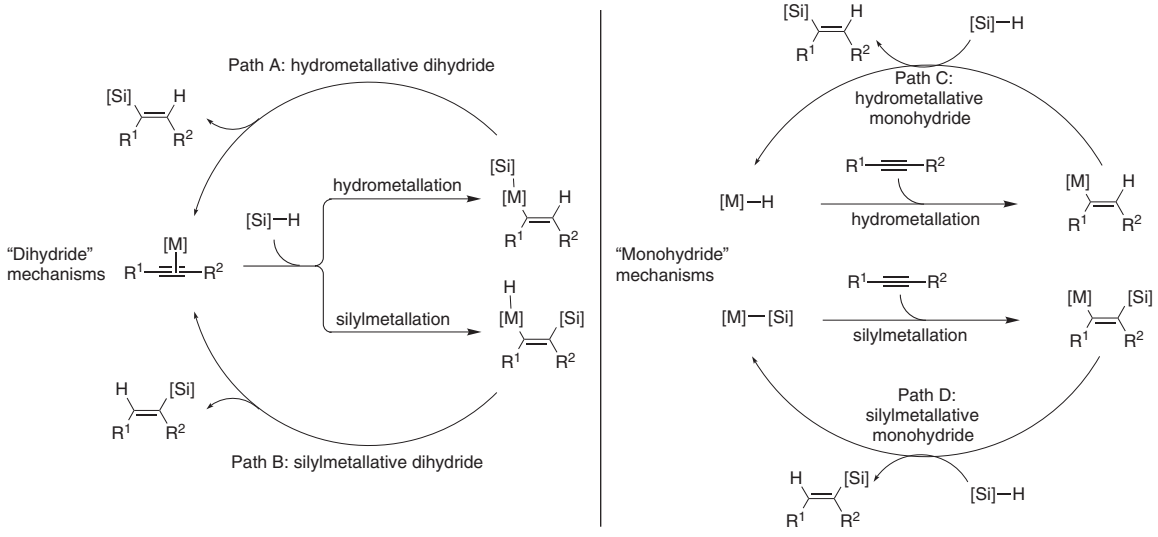
Alkyne hydrosilylation continues as a focus of current research. Despite the relative simplicity of the transformation, it is becoming increasingly clear that different catalysts often utilize unique mechanisms. In addition, the demands placed by the need to access vinylsilanes of differing substitution patterns, stereochemistries, and functional groups require a diverse, complementary set of methodologies. This discussion covers hydrosilylation reactions

catalyzed by transition metals.[11–13] This article focuses on more recent developments in the field and on important methodological advances for the use of vinylsilanes in synthesis. The discussion begins with an overview of the mechanism of alkyne hydrosilylation and discusses the hydrosilylation of terminal and internal alkynes, then closes with tandem reductive C–C bond-forming reactions of alkynes producing vinylsilane products and some additional applications which do not fit naturally within a specific hydrosilylation class. Since addition of a silyl hydride to the same face of a triple bond (*cis*-addition process) typically results in the formation of the (*E*)-olefin product (*trans*-olefin), in order to minimize confusion, *E*/*Z* nomenclature is used to describe product stereochemistry and the terms *cis* and *trans* are reserved to describe the orientation of the hydrogen and silicon groups in the addition process.

In addition to transition metals, recent work has demonstrated that strong Lewis acids will catalyze the addition of silanes to alkynes in both an intra- and an intermolecular fashion.[14,14a–14c] The formation of vinylsilanes from alkynes is possible by other means as well, such as the synthetically important and useful silylcupration[15,15a] of alkynes followed by cuprate protonation to afford vinylsilanes. These reactions provide products which can be complementary in nature to direct hydrometallation. Alternatively, modern metathesis catalysts have made possible direct vinylsilane synthesis from terminal olefins.[16,16a]

10.17.2 Mechanistic Aspects of Hydrosilylation

Catalysis of the hydrosilylation reaction by metal catalysts allows reaction of normally inert silanes. Variation of the catalyst system can achieve different regio-, and stereo-, and chemoselectivities. Though selectivities can be altered by steric tuning of the catalyst or by the sterics and electronics of the silane, changes in reaction mechanism have most often formed the basis for the development of complementary methods. Catalyzed hydrosilylation occurs by an ever increasing array of known mechanisms, but as with many important methods in transition metal catalysis, the mechanism for many known reactions is poorly understood. The mechanisms of alkyne hydrosilylation share common facets with alkyne hydrometallation in general,[13,17,18] and with olefin hydrometallation.[17,18] Historically, one of the four general pathways explained the results of many different hydrosilylation catalysts (Scheme 1). Divisions are based on the timing of the bond formation; initial bond formation occurs either for the H–C bond (hydrometallative, paths A and C) or for the Si–C bond (silylmetallative, paths B and D). Further division is possible based on catalyst structure. By analogy to homogeneous hydrogenation, a "dihydride" mechanism adds to an alkyne a hydride and a silicon species from the same silicon species hydride molecule (paths A and B), while a "monohydride" mechanism adds a hydrogen and a metalloid from different molecules (paths C and D). In many cases, all four mechanisms could, in principle, produce the same products, and uncertainty about the nature of the active catalyst can make the distinction between monohydride- and dihydride-type catalysis difficult. This uncertainty makes identification of the factors controlling product outcome difficult. This is not an exhaustive set of catalyzed hydrosilylation classes, and

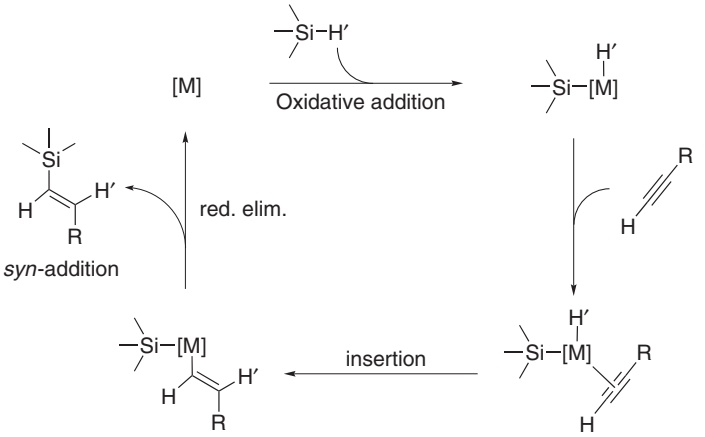


Scheme 1

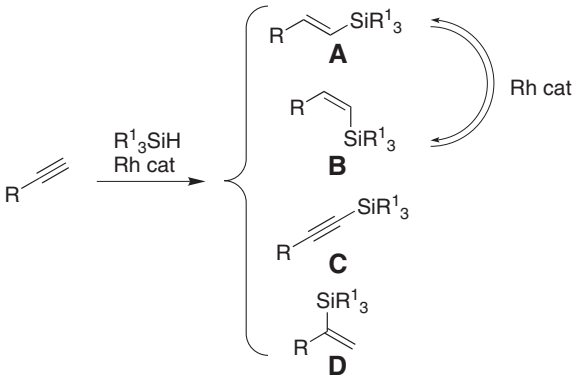
any broad classification system risks missing the devil in the details. All generalizations into broad mechanistic classes must be approached with care, and certainly the reader should be aware that our understanding of catalyzed hydrometallation is far from complete.

The Chalk–Harrod mechanism first proposed a pathway based on oxidative addition, migratory insertion, and reductive elimination (Scheme 2).[19,19a,19b] Though it arose from studies of cobalt-catalyzed olefin hydrosilylation, the Chalk–Harrod model was successfully applied to platinum-catalyzed hydrosilylation of alkenes and alkynes. This proposal correctly predicts terminal (β)-silane products from placement of the bulky M–SiR^1_3 fragment distal to the alkyne substituent. There has been some discussion through the years about the catalytic activity of platinum aggregates and colloids relative to monoatomic species.[20,20a–20d] More recent evidence points to a monoatomic platinum complex as the active catalyst despite the occasional appearance of platinum(0) colloids during the reaction course.[21] The mechanism has received several refinements and challenges, largely to address the observation of unusual products from hydrosilylation reactions. These include (*Z*)-vinylsilanes from *trans*-addition, the predominance of α-silyl products, and silylalkynes from dehydrogenative silylation.

Quickly, it became clear that iridium and rhodium do not cleanly fit the Chalk–Harrod mechanism as does platinum. For electron-rich silanes and relatively unhindered terminal alkynes, the major product is the (*Z*)-vinylsilane (Scheme 3, **B**) from apparent unusual *trans*-addition to the alkyne.[22] This observation was followed by important and confusing discoveries. First, rhodium, under appropriate conditions, will catalyze the isomerization of the (*Z*)-vinylsilane product **B** to the (*E*)-vinylsilane product **A**.[23] Second, rhodium can also catalyze the reverse, contra-thermodynamic reaction of the (*E*)-vinylsilane **A** to the (*Z*)-vinylsilane **B**.[24]



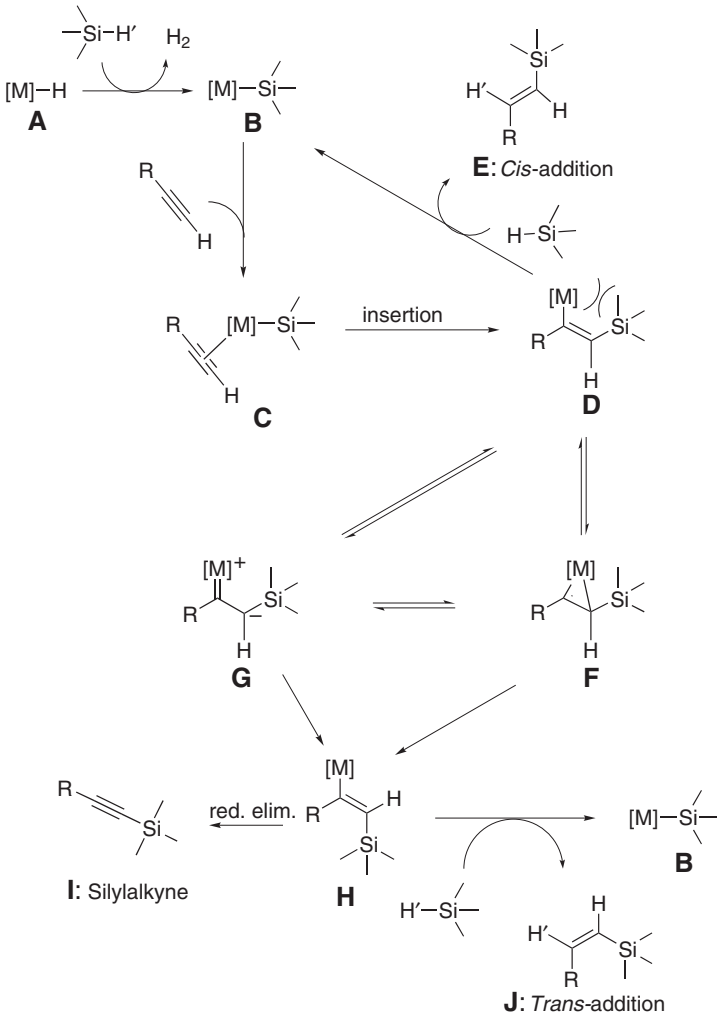
Scheme 2



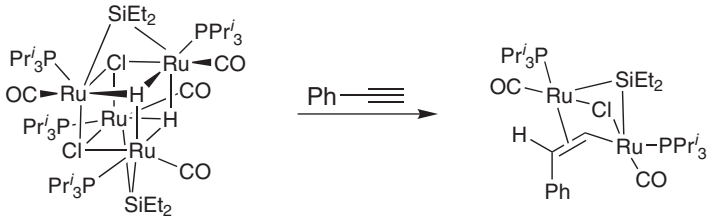
Scheme 3

To account for the predominant appearance of *trans*-addition products (Scheme 3, **B**) with terminal alkynes, as well as smaller amounts of silylalkynes **C** from dehydrogenative silylation, Crabtree[25] (and similarly Ojima[26]) proposed a mechanism based on silylmetallation in the migratory insertion step and subsequent (*E*)–(*Z*) isomerization through either a metal carbene or metallocyclopropene intermediate. Noteworthy is the proposed "monohydride"-type mechanism[25] (by analogy to homogeneous hydrogenation) that permits (*E*)–(*Z*) isomerization to out-compete reductive elimination, which must occur via intermolecular reaction with a molecule of silane. Indeed, there is some evidence that a "monohydride" mechanism may be active even in processes selective for trans addition where it is not readily apparent from the precatalyst structure.[27] Focusing predominantly on the course of hydrosilylation reactions with a single metal, Crabtree (iridium) and Ojima (rhodium) sought answers to longstanding fundamental mechanistic questions in catalyzed simple addition reaction to alkynes, and significant overlap of the mechanism for the two metals is assumed.

The mechanistic proposal fits well with data available. Electron-rich silanes (e.g., Et_3SiH) provide good selectivity for the *trans*-addition process to give (*Z*)-vinylsilane products, while electron-poor silanes (e.g., $(MeO)_3SiH$) generally provide more (*E*)-vinylsilane product.[11,25,26] Electron-poor silanes are not as able to stabilize positive charge at the β-position present in the isomerization intermediates **F** or **G** (Scheme 4), and so oxidative addition or transmetallation occurs prior to isomerization. It is argued that α-anion stabilization is not as dependent on the substituents at silicon.[26,28] The dehydrogenative product **I** is formed most readily for hindered terminal alkynes, where a large R-group should favor strain release in the elimination step.[25]



Scheme 4



A B

Scheme 5

Cationic ruthenium complexes of the type $[Cp^*Ru(MeCN)_3]PF_6$ have been shown to provide unique selectivities for inter- and intramolecular reactions that are difficult to reconcile with previously proposed mechanistic routes.[29–31] These observations led to a computational study and a new mechanistic proposal based on concerted oxidative addition and alkyne insertion to a stable ruthenacyclopropene intermediate.[32] This proposal seems to best explain the unique selectivities. A similar mechanism in the context of C–H activation has recently been proposed from a computational study of a related ruthenium(II) catalyst.[33]

Recently, a proposal has been put forth that a *trans*-addition process may be possible through dinuclear ruthenium intermediates.[34] As shown in Scheme 5, reaction of tetraruthenium aggregate **A** with phenylacetylene results in the fully characterized bridging dinuclear alkenyl complex **B**. The authors propose a direct *trans*-delivery of hydride through a dinuclear intermediate may be active in the hydrosilylation catalyzed by **A**, though compound **B** itself is unreactive to Et_3SiH.

10.17.3 Hydrosilylation of Terminal Alkynes

10.17.3.1 Catalysis by Late Transition Metals: Groups 10 and 11

Of the transition metals, platinum has probably the longest history as an alkyne hydrosilylation catalyst. Speier's catalyst (H_2PtCl_6) has been used extensively for alkene hydrosilylation, and also functions in alkyne hydrosilylation.[11] H_2PtCl_6 and platinum(0) catalysts have the advantages of excellent turnover numbers (often >10,000), clean *cis*-hydrometallation leading only to (*E*)-vinylsilanes and the regioisomeric α-vinylsilane, and tolerance of a wide range of carbon and heteroatom substituents on the silane.[35] Despite the long history of platinum catalysts in alkyne hydrosilylation, the issue of controlling regioselectivity was not satisfactorily addressed until relatively recently.

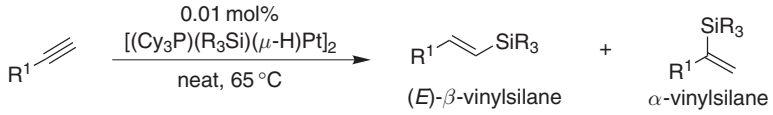
Speier's catalyst itself is quite non-selective in silane additions to typical alkynes (see Table 1, entry 1).[36] Platinum complexes with bulky trialkyl phosphines show improved steric discrimination. Complexes of the type $Pt(Cy_3P)(ethylene)_2$ or their silane adducts $[(Cy_3P)(R_3Si)(\mu\text{-}H)Pt]_2$ provide very useful regiochemical selectivity while retaining impressive catalyst loadings of about 0.01 mol.% (Table 1, entries 2–8).[37,37a] Also notably, phosphine complexes allow the use of phenyl-, alkoxy-, and chlorosilanes. However, for the important alkoxysilane substrates, there is a significant drop in regioselectivity (to 82 : 18, see entry 5) which is not explained solely on the basis of electronegativity or lack of steric bulk, given the excellent selectivity with Cl_3SiH (96 : 4, entries 4 and 6).

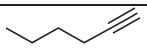
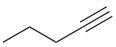
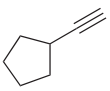
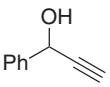
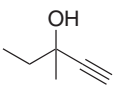
The use of tri-*tert*-butylphosphine has produced still higher selectivities, allowing near total control in the synthesis of (*E*)-vinylsilanes, including alkoxysilanes and disiloxanes.[38,39] In the context of a total synthesis of an HMG-CoA reductase inhibitor, hydrosilylation with a chlorosilane catalyzed by a platinum(0) olefin complex, $Pt_2\{[(CH_2{=}CH)Me_2Si]_2O\}_3$ (also known as Karstadt's catalyst), followed by coupling with a 2,6-disubstituted aryl iodide forged a key intermediate shown in Scheme 6.[38]

A separate, quite thorough study of terminal alkyne hydrosilylation with platinum arrived at a similar set of conditions.[39] This work utilized a one-pot hydrosilylation with the preformed platinum(0) complex $(t\text{-}Bu_3P)Pt[(CH_2{=}CH)Me_2Si]_2O$ ($[(CH_2{=}CH)Me_2Si]_2O$ = DVDS) and subsequent palladium-catalyzed coupling reaction to demonstrate that the platinum catalyst is compatible with cross-coupling conditions, providing a convenient "hydrocarbation" of terminal alkynes (Table 2).

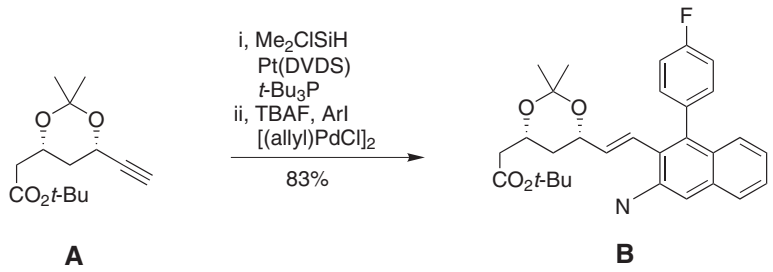
Other ligands have been examined to improve the performance of platinum-catalyzed reactions,[40] and bicyclic aminophosphines (Scheme 7, **C**) are a sterically demanding structural class that has been employed to afford very high regioselectivities[41]

Table 1 Hydrosilylation of terminal alkynes with platinum–phosphine complexes



Entry	*Alkyne*	*Silane*	*Yield*	*β*:*α* *ratio*[a]
1[b]		Et_3SiH	78	42:58[b]
2		Et_3SiH	92	96:4
3		Cl_2MeSiH	86	95:5
4		Cl_3SiH	88	96:4
5		$(EtO)_3SiH$	83	82:18
6		Cl_3SiH	93	96:4
7		Et_3SiH	81	84:16
8		Et_3SiH	90	93:7

[a]In all cases, no (*Z*)-vinylsilane was produced.
[b]Reaction performed with Speier's catalyst, H_2PtCl_6.



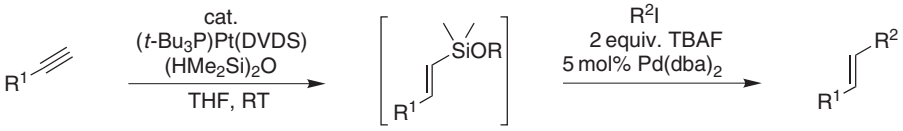
Scheme 6

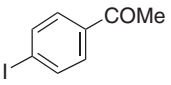
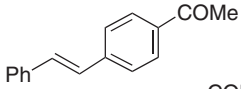
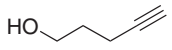
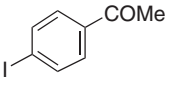
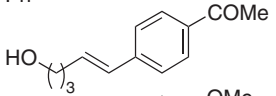
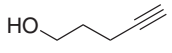
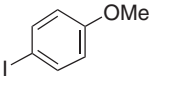
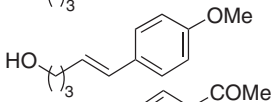
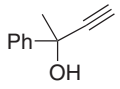
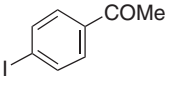
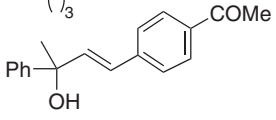
Combining two different hydrosilylation catalysts in sequence with chlorodimethylsilane has allowed the construction of complex dye assemblies and conducting polymers. In the example shown (Scheme 8), Karstedt's catalyst was chosen after a brief screen for the hydrosilylation of an aromatic diyne with chlorodimethylsilane. After reduction of the chlorosilane, an equimolar mixture of disilane **B** and diyne **A** was treated with a catalytic amount of Wilkinson's catalyst, resulting in the formation of polymer C.[42] Hydrosilylation of alkynes has also been studied as a means of synthesizing oligo(phenylenevinylene) units with pendant alkoxysilanes to create curable, hole-transporting films.[43,43a]

The robustness and excellent turnover numbers of platinum complexes with terminal alkynes have made it the catalyst of choice for the synthesis of polymers and other macromolecular architechtures. Alkyne hydrosilylation with platinum has also served as a key element in the synthesis of dendrimers. Sequential reaction of an alkyne with $HSiMeCl_2$ and lithiated phenylacetylene afforded the branching unit of a dendrimer synthesis which has been used to afford a large variety of structures at high generation.[44,44a,44b]

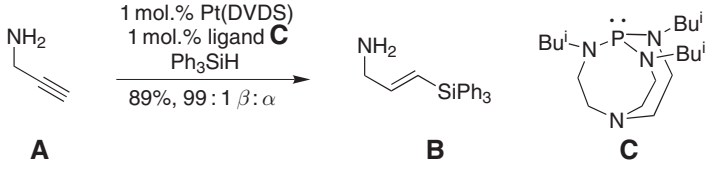
Recently, a palladium-catalyzed reaction has been reported which provides exclusive *cis*-addition and good selectivity for the terminal silane similar to platinum-based catalysts. The catalyst system, $Pd_2(dba)_3 + 4PCy_3$, is unreactive to internal alkynes and succeeds with a range of aryl and akyl terminal alkynes.[45]

Table 2 A tandem hydrosilylation cross-coupling approach to aryl olefins

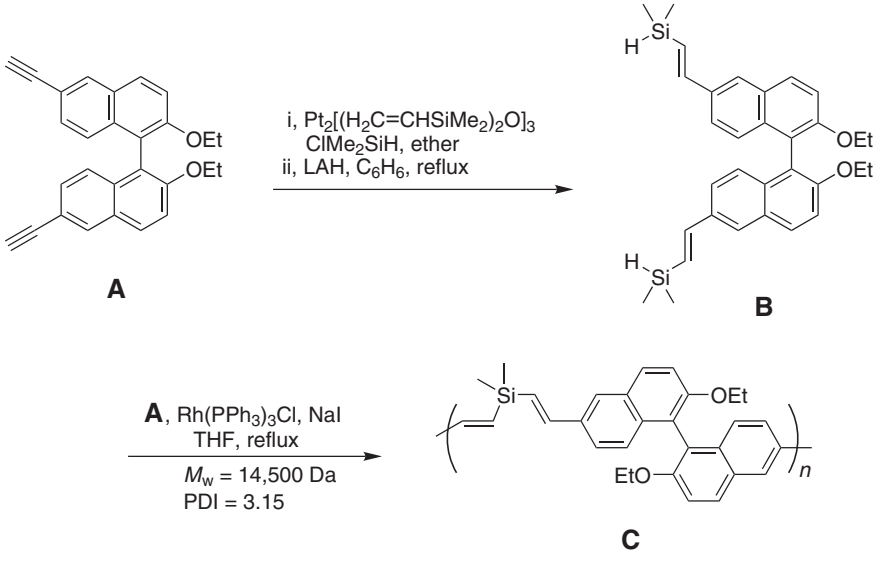


Entry	*Alkyne*	*Iodide*	*Product*[b]	*Yield*[a]
1[b]				89
2				82
3				89
4				72

[a]Reaction time for hydrosilylation: 30 min. For coupling: 10 min to 24 h.
[b]In all cases, 2% regioisomeric products detected.



Scheme 7



Scheme 8

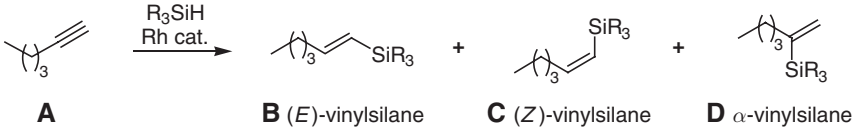
Though most of the catalysts discussed here are homogeneous, monoatomic species, it is possible to catalyze alkyne hydrosilylation by nanoparticles and polyatomic clusters.[46,47] Recently, a report on this topic demonstrated the feasibility of using gold nanoclusters supported on alumina as a catalyst for alkyne hydrosilylation.[48]

10.17.3.2 Hydrosilylation with Group 9 Transition Metals

The mechanistic and synthetic puzzle of alkyne hydrosilylation opened more fully with the discovery that rhodium will catalyze the *trans*-hydrosilylation of terminal alkynes.[22] There is much work extant in this area, and good summaries of the various catalytic systems exist.[11] A *trans*-addition process to give (*Z*)-β-silane products **C** is well precedented with trialkylsilanes (Table 3), for both rhodium and mixed rhodium–cobalt complexes (entry 4).[22,26] However, the selectivity erodes significantly upon switching to Me_2PhSiH (entry 5), and, due to the mechanistic requirements for equilibration of the β-silyl vinylrhodium intermediate, electron-poor silanes react exclusively to give (*E*)-β-silane products **B** (see entries 6 and 7).

Efforts to tune the reactivity of rhodium catalysts by altering structure, solvent, and other factors have been pursued.[49,49a,50] Although there is (justifiably) much attention given to catalysts which provide *trans*-addition processes, it is probably underappreciated that appropriate rhodium complexes, especially cationic phosphine complexes, can be very good and reliable catalysts for the formation of (*E*)-β-silane products from a *cis*-addition process. The possibilities and range of substrate tolerance are demonstrated by the two examples in Scheme 9. A very bulky tertiary propargylic alcohol as well as a simple linear alkyne provide excellent access to the (*E*)-β-vinylsilane products.[49,49a,51] In order to achieve clean *cis*-addition, cationic complexes have provided consistent results, since vinylmetal isomerization becomes less competitive for a cationic intermediate. Thus, halide-free systems with

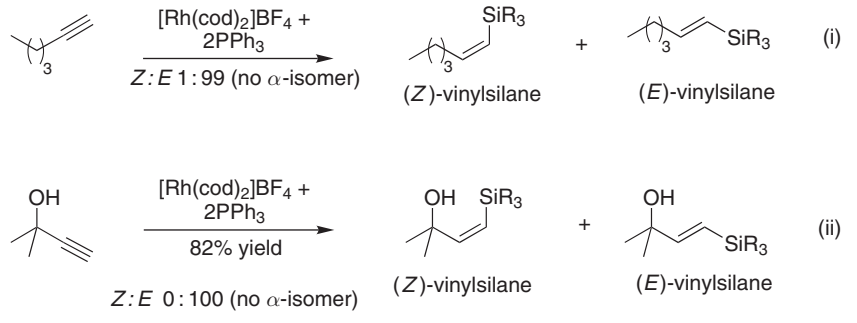
Table 3 Access to (*Z*)-vinylsilanes with rhodium complexes



A **B** (*E*)-vinylsilane **C** (*Z*)-vinylsilane **D** α-vinylsilane

Entry[a]	*Silane*	*Temp* (°C)	*Catalyst*	*Product ratio* B	C	D	*Yield*[b]
1	Et_3SiH	40	0.1% $Rh(PPh_3)_3Cl$	3	94	3	100
2	Et_3SiH	20	0.1% $Rh(PPh_3)_3Cl$	7	79	14	84
3	Et_3SiH	20	0.05% $Rh_4(CO)_{12}$	5	89	6	96
4	Et_3SiH	20	0.1% $Co_2Rh_2(CO)_{12}$	3	95	3	100
5	Me_2PhSiH	25	0.1% $Rh_4(CO)_{12}$	27	60	13	100
6	$(MeO)_3SiH$	0	0.1% $Rh_4(CO)_{12}$	95	0	5	98
7	$ClMe_2SiH$	0	0.1% $Rh_4(CO)_{12}$	74	0	26	85

[a]Reactions generally 12–68 h.
[b]Yield determined by GC analysis.



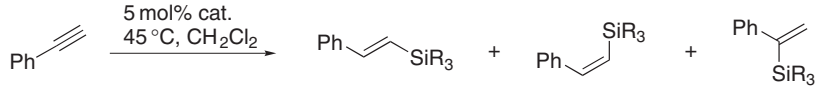
Scheme 9

non-coordinating counterions have typically been employed. Another approach to the problem of selective *cis*-addition processes is the use of surfactant micelles in aqueous solution, which presumably encourage ionic dissociation to an active cationic rhodium species.[52] Although selectivities reported are modest, the approach has the benefits of employing more stable neutral rhodium precursors in a low waste, green chemistry aqueous process.

However, the need for synthetically useful substituents on silicon limits the synthetic utility of most rhodium catalysts. The variable results with rhodium complexes were used to advantage by Faller, who showed that the complexes $[Cp^*Rh(BINAP)](SbF_6)_2$ (where BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) and $[Cp^*RhCl_2]_2$ give opposite geometrical selectivities, with the cationic system presumably following a Chalk–Harrod mechanism, while the neutral $(Cp^*RhCl_2)_2$ may be a precatalyst for a monohydride-type active catalyst such as $[Cp^*Rh(SiR_3)]^+$.[27] The significant success with $(EtO)_3SiH$ is noteworthy, and further analysis of substrate scope might lead to an extremely useful process (Scheme 10).

The other well-characterized metal (i.e., iridium) for *trans*-addition processes to terminal alkynes suffers from similar limitations.[53,53a–53f] While iridium provides good selectivity for (*Z*)-β-vinylsilanes (Table 4, **C**) with $MePh_2SiH$ (Table 4, entry 1), silanes with electron withdrawing groups (entry 6) and bulky alkynes (entry 4) exhibit significant deterioration in selectivity.[25]

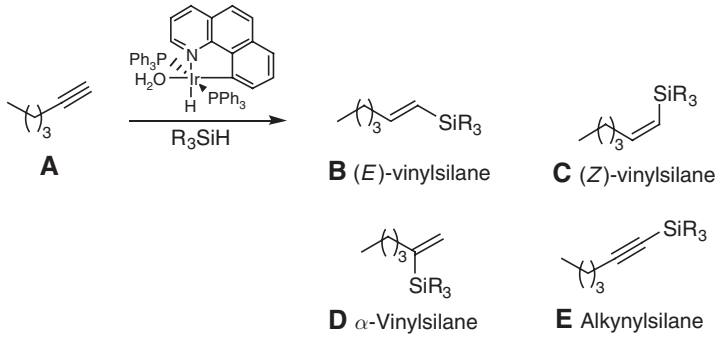
In contrast to rhodium and iridium, monoatomic cobalt has not been investigated extensively as a hydrosilylation catalyst, though one report discusses the use of cobalt phosphine complexes.[54]

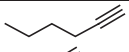


Catalyst:	silane:			
$[Cp^*Rh(BINAP)](SbF_6)_2$	Et_3SiH	97.4	0	2.6
	$(EtO)_3SiH$	81.2	0	18.8
$(Cp^*RhCl_2)_2$	Et_3SiH	5.5	92.9	1.5
	$(EtO)_3SiH$	3.5	96.5	0

Scheme 10

Table 4 Iridium-catalyzed alkyne hydrosilylation



				Product ratio			*Yield*	
Entry	*Silane*	*Temp*	*Alkyne*[a]	**B**	**C**	**D**	**B + C + D**	**E**
1	$MePh_2SiH$	rt		2	97	1	87	2
2	$MePh_2SiH$	rt		4	74	22	81	6
3	$MePh_2SiH$	65 °C		45	44	11	75	13
4	$MePh_2SiH$	65 °C		58	29	15	28	32
5	Et_3SiH	rt		5.5	91	3.5	81	4
6	$(MeO)_3SiH$	rt		39	57	4	19	1

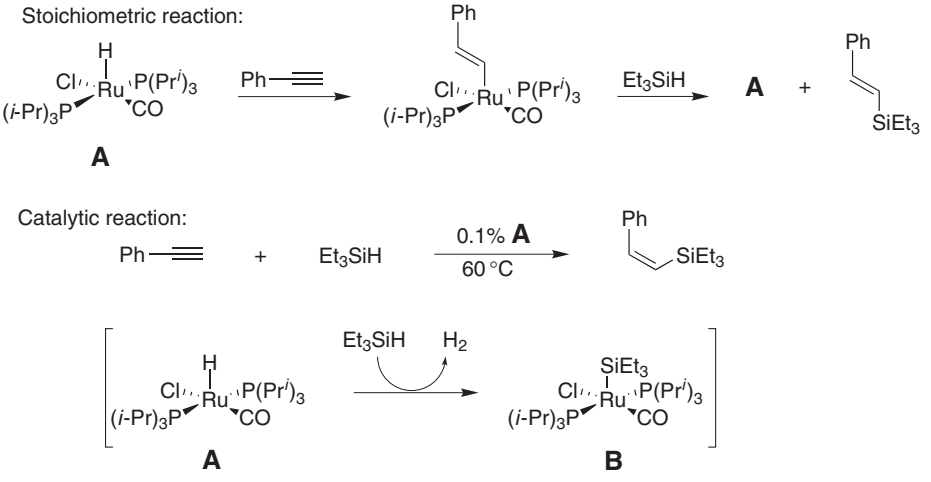
[a]Cy = cyclohexyl.

10.17.3.3 Ruthenium and Iron Catalysis

Ruthenium complexes do not have an extensive history as alkyne hydrosilylation catalysts. Oro noted that a ruthenium(II) hydride (Scheme 11, **A**) will perform stepwise alkyne insertion, and that the resulting vinylruthenium will undergo transmetallation upon treatment with triethylsilane to regenerate the ruthenium(II) hydride and produce the (*E*)-β-vinylsilane in a stoichiometric reaction. However, when the same complex is used to catalyze the hydrosilylation reaction, exclusive formation of the (*Z*)-β-vinylsilane is observed.[55] In the catalytic case, the active ruthenium species is likely not the hydride **A** but the Ru–Si species **B**. This leads to a monohydride silylmetallation mechanism (see Scheme 1). More recently, small changes in catalyst structure have been shown to provide remarkable changes in stereoselectivity (Scheme 11).[56]

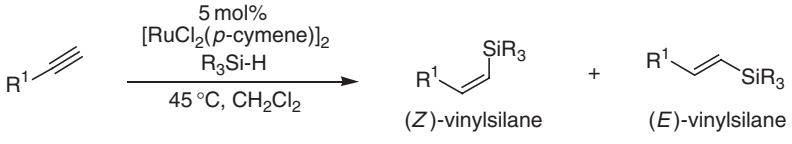
Recently, the dissimilar complex $[RuCl_2(p\text{-cymene})]_2$ has also demonstrated excellent selectivity for the (*Z*)-vinylsilane products for a variety of substrates (see Table 5). Whether or not this complex also acts as a monohydride-type hydrosilylation catalyst—as do the vast majority of well understood systems—is an open question. The selectivities for (*Z*)-β-vinylsilane products are some of the best yet reported, especially for α-branched substrates (entry 4). From a synthetic point of view, the catalyst is exciting, but at present is limited to trialkyl- and triphenylsilanes in intermolecular applications (see Scheme 21), presenting problems for some applications.

Interestingly, the $[RuCl_2(p\text{-cymene})]_2$ catalyst used for selective synthesis of (*Z*)-vinylsilanes produces instead the α-vinylsilanes with appropriately positioned hydroxyl groups.[57] For the homopropargylic system shown (Scheme 12), the selectivity is 98 : 2. For propargylic or bishomopropargylic systems, only small amounts (2–13%) of the α-product



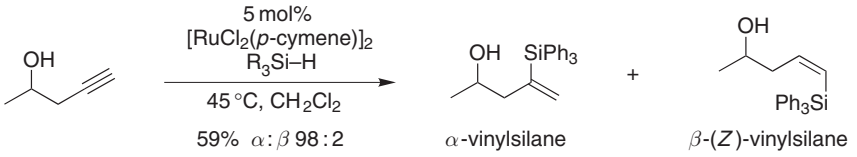
Scheme 11

Table 5 Ruthenium-catalyzed *trans*-hydrosilylation



Entry	*Alkyne*	*Silane*	*Yield*	*(Z)/(E) ratio*[a]
1	Ph—	Et_3SiH	81	96 : 4
2		Ph_3SiH	94	96 : 4
3	Cl	Ph_3SiH	87	96 : 4
4	OBn	Ph_3SiH	89	96 : 4
5	BnO_2C	Ph_3SiH	85	96 : 4

[a]In all cases, 1% of the α-silane was observed.



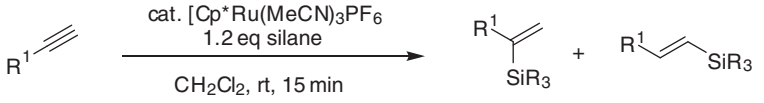
Scheme 12

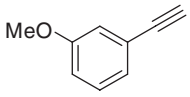
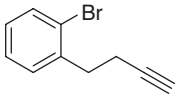
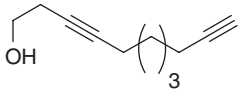
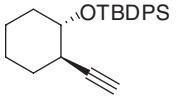
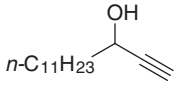
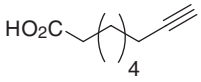
are formed. Mechanistically, this result would seem to imply an initial hydroruthenation directed by ruthenium–hydroxyl interactions. Only recently has a proposal for achieving selectivity for a *trans*-addition process by a hydrometallation mechanism appeared,[32] and the overall mechanism as well as the nature of the hydroxyl direction with $[RuCl_2(p\text{-cymene})]_2$ remain obscure.

While functional group direction is one strategy for the formation of α-vinylsilanes, recently cationic cyclopentadienylruthenium complexes have been shown to give selective α-vinylsilane formation without a directing group (Table 6).[30] The catalyst is compatible with alcohol, acid, protected amine, and internal alkyne functionality, and importantly succeeds with alkyl-, aryl-, halide-, and alkoxy-substituted silanes. Cyclopentadienylruthenium catalysts remain the only general method for accessing α-vinylmetal species by hydrometallation without the need for neighboring functional groups.[30a]

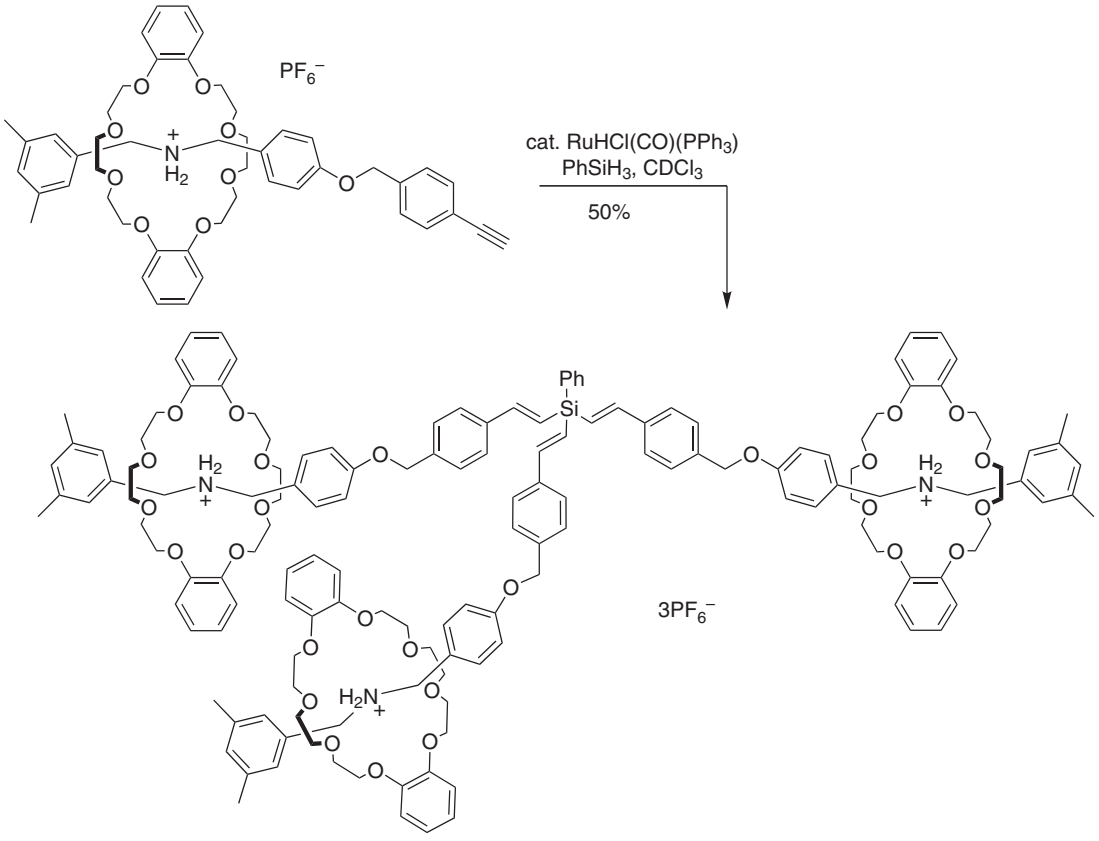
The large bulk of silyl groups means that they are potentially useful for the formation of the mechanical bonds of rotaxanes and related structures.[58,58a] The ruthenium(II) complex $RuHCl(CO)(PPh_3)$—originally developed for the *cis*-addition of silanes to phenylacetylene[56]—was shown to provide superior rotaxane yield as well as olefin selectivity, and allowed the synthesis of a higher-order *tris*-rotaxane (Scheme 13).[59] Yields of the threaded rotaxanes varied significantly across different catalysts, and the evidence indicates that the crown ether and ammonium moieties have significant impact on reactivity and stereoselectivity.

Table 6 Selective synthesis of α-vinylsilanes with a cationic ruthenium complex



Entry	*Alkyne*	*Silane*	*mol% catalyst*	*Ratio* (α:β)	*Yield*
1		$(EtO)_2MeSiH$	1	9:1	86
2		$(EtO)_3SiH$	1	13:1	92
3		$(EtO)_3SiH$	1	9:1	71[a]
4		$(EtO)_3SiH$	5	20:1	87
5		$(EtO)_3SiH$	1	13:1	58
6[b]		Et_3SiH	1	20:1	89

[a]No reaction at the internal alkyne was observed with 1.05 eq. silane.
[b]$[CpRu(MeCN)_3]PF_6$ was used as catalyst.



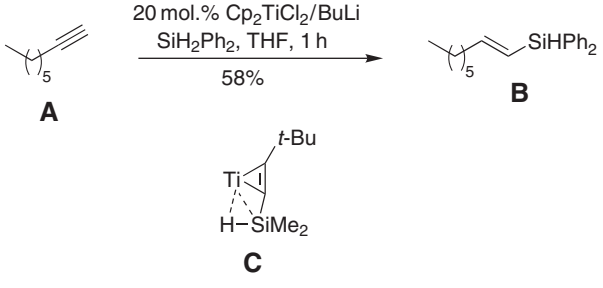
Scheme 13

Within group 8, a bis-dinitrogen complex of an iron(0) tridentate pyridinediimine structure has also recently been shown to catalyze the hydrosilylation of alkyne.[60] This discovery is a new example of the utility of low-valent iron in catalysis.[61]

10.17.3.4 Early Transition Metals as Catalysts

The history of alkyne hydrosilylation is dominated by late transition metals with facile redox cycles to catalyze what is generally thought of as a reductive process. However, metals without clear redox cycles prove that polar chemistry can operate on alkynes in the presence of functionalized substrates.[62,62a] The use of actinide catalysts of uranium and thorium has recently appeared. Complexes of the type $Cp^*_2UMe_2$ and $(Me_2SiCp^*_2)ThBu_2$ catalyze the hydrosilylation of terminal alkynes. The authors propose an unusual mechanism based on alkynylactinide intermediates.[63,63a]

Group 4 metal catalysts have been little used in alkyne hydrosilylation. Cp_2Ti(formed *in situ*) has been shown to catalyze the hydrosilylation of simple terminal and symmetrical internal alkynes in modest yield (see Scheme 14).[64] The authors postulate that the requirement for a silyl dihydride (or trihydride) may derive from a stabilizing agnostic



Scheme 14

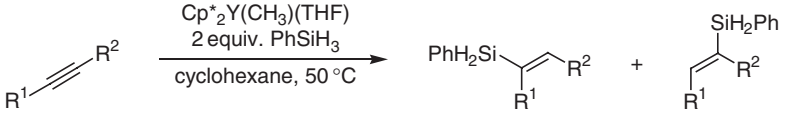
interaction akin to that observed in a silyl–alkyne complex C.[65,65a] Other explanations are possible, including that the requirement for dihydridosilanes indicates a titanium silylene intermediate.[66,66a]

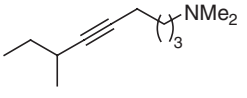
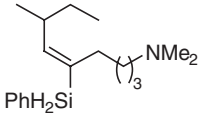
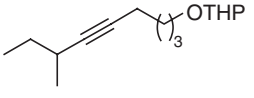
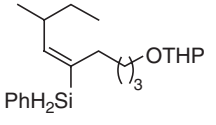
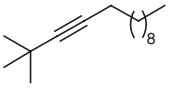
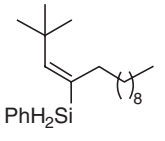
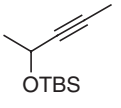
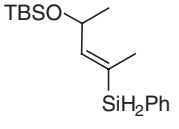
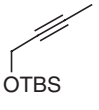
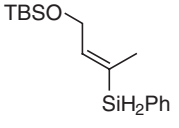
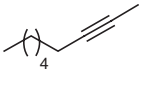
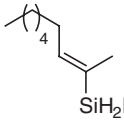
10.17.3.5 Intermolecular Hydrosilylation of Internal Alkynes

10.17.3.5.1 Yttrium catalysts for regiocontrol based on sterics

Probably the only very successful, broad method of steric differentiation of internal alkynes employs an yttrium catalyst.[67] As shown in Table 7, exceptional regioselectivity is observed for alkynes bearing an α-branch point on one side (entries 1 and 2). Even the discrimination of methyl for straight-chain alkyl is possible, providing a 7.2 : 1 mixture of regioisomers when the more discriminating catalyst $Cp^*_2Y(CH(TMS)_2)$ is used (entry 7). A secondary propargylic silyl ether (entry 4) provides complete selectivity for the β-silyl product, though similar selectivity with a primary propargylic silyl ether (entry 5) indicates that factors other than sterics—such as electronic or catalyst coordination—must also be involved. Noteworthy is the tolerance of the reaction for an unprotected teriary amine (entry 1) and the acid-sensitive

Table 7 Steric differentiation as a regiocontrol element in the hydrosilylation of internal alkynes



Entry	*Alkyne*	*Major product*	*Yield*	*Ratio*[a]
1			73	100 : 0
2			84	100 : 0
3			28	100 : 0
4[b]			82[b]	100 : 0
5[b]			23[b]	100 : 0
6			81	4.1 : 1
7[c]			ND	7.2 : 1

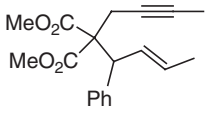
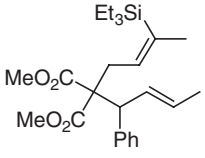
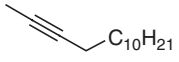
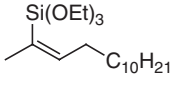
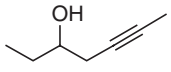
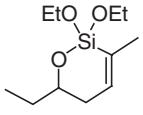
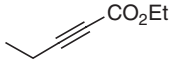
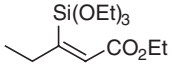
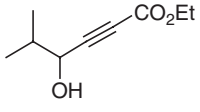
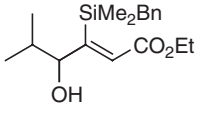
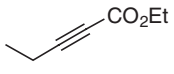
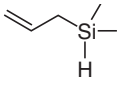
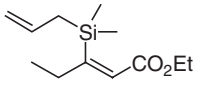
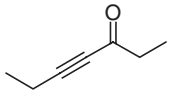
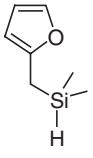
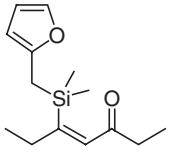
[a]Regioselectivity of (*E*)-vinylsilane isomers. No (*Z*) isomers observed.
[b]Reaction temp 90 °C.
[c]Catalyst used was $Cp^*_2Y(CH(TMS)_2)$.

tetrahydropyranyl ether (entry 2). The catalyst system does have limitations, however. Severely hindered substrates (entry 3) suffer from poor turnover, as do even modestly electron-poor alkynes (entry 5). Perhaps the most important limitation is that of the silane. Only $PhSiH_3$ was reported in the study, limiting the adaptability and utility of the system for some applications. However, the phenylsilane dihydride products of the yttrium process are stable to chromatography, and hydridosilanes have been employed in a host of subsequent transformations.[7,68]

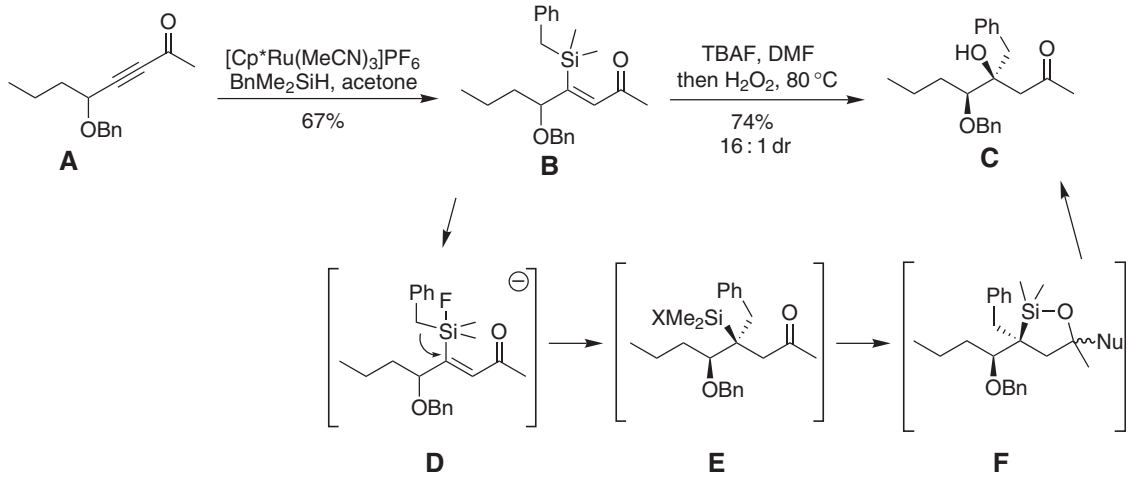
10.17.3.5.2 Ruthenium catalysis

One of the few other studies of internal alkynes involves the ruthenium catalyst $[Cp^*Ru(MeCN)_3]PF_6$. This complex provides exclusively *trans*-addition to give (*Z*)-vinylsilane products (Table 8). Although *trans*-addition processes to terminal alkynes are well known, such catalysts generally provide *cis*-addition processes for internal alkynes,[69] and Table 8 illustrates the only reported transition metal catalyst affording a clean *trans*-addition process with internal alkynes. For unconjugated alkynes, some selectivity can be obtained (entries 1–3). Substrates with nearby olefins (entry 1) or alcohols (entry 3) may indicate the presence of directing effects. In general, however, the selectivity is modest and predictive ability is low. A substrate class with clean, predictable selectivity is α,β-alkynyl ketones and carboxylic acid derivatives. Here, strong preference for the (*Z*)-β-silyl ester or ketone is observed, especially for silanes without an alkoxy substituent (entries 4–7).[6,30]

Table 8 *Trans*-hydrosilylation of internal alkynes catalyzed by $[Cp^*Ru(MeCN)_3]PF_6$

Entry	*Alkyne*	*Silane*	*Major product*	*Ratio*[a]	*Total yield*
1		Et_3SiH		>20 : 1	70[b]
2		$(EtO)_3SiH$		2.4 : 1	100
3		$(EtO)_3SiH$		5 : 1	71[b,c]
4		$(EtO)_3SiH$		5 : 1	99
5		$BnMe_2SiH$		8 : 1	83
6				>20 : 1	85[b]
7				>20 : 1	89[b]

[a]Ratio of two regioisomeric (*Z*)-vinylsilanes. No evidence of cis addition process is observed.
[b]Yield is given for pure major product.
[c]Product isolated as the cyclic compound due to cyclization after hydrosilylation.



Scheme 15

The preference for the β-silyl isomer product complements methods available for hydrostannation of alkynes, for which the α-stannyl regioisomer is formed preferentially.[70,70a–70e] In addition, the β-silyl products serve as the platform for a tertiary alcohol synthesis (Scheme 15). Upon treatment of vinylsilanes such as **B** with tetrabutylammonium fluoride (TBAF) in DMF at 0 °C, a 1,2 carbon-to-silicon migration occurs, affording the tertiary heterosilane **E**. Oxidation of the C–Si bond then provides the tertiary alcohol. Good 1,2-diastereocontrol has been demonstrated for γ-alkoxy substrates, as in the example shown. The studies suggest that the oxidation of the sterically demanding silane intermediate is facilitated by the intramolecular formation of a silyl hemiketal or silyllactone for ketone or ester substrates, respectively.[71]

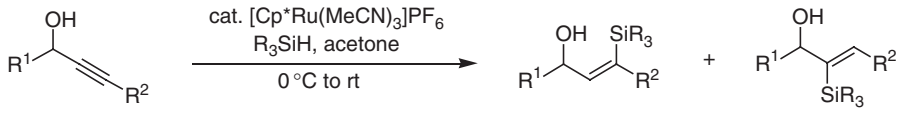
It has also recently been shown that β-trimethylsilylacrylic acids (produced in the work by circuitous means but accessible by ruthenium-catalyzed hydrosilylation[71]) serve as competent partners for palladium-catalyzed cross-coupling in the absence of fluoride. The authors invoke an intramolecular activation by the carboxylate similar to that in Scheme 15.[72]

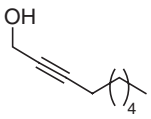
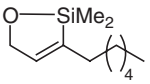
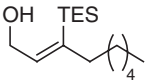
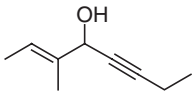
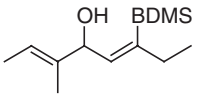
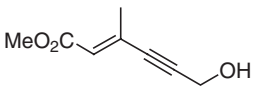
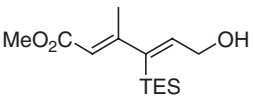
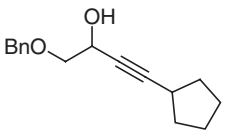
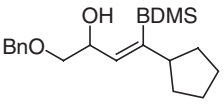
Propargylic alcohols are a substrate class that has also shown regioselectivity with the $[Cp^*Ru(MeCN)_3]PF_6$ catalyst (Table 9). The complex provides exclusive *trans*-addition for all alkynes, and in this context provides the distal, (*Z*)-β-vinylsilane product. Propargylic alcohols provide increased reactivity, affording good yields even for alkynes with sterically demanding α-branching at both termini.[6,73] The use of alkoxysilanes provides products that cyclize under the reaction conditions to give cyclic siloxanes, which are only marginally stable. Trialkylsilanes generally provide better regioselectivity, and the use of benzyldimethylsilanes (BDMS) provides more robust vinylsilane products useful in subsequent oxidative[6] and cross-coupling pathways.[74] An enyne (entry 5) provides very good regioselectivity for a vinylmetal product with complementary stereochemistry to that obtained for similar substrates in palladium-catalyzed hydrostannation.[75,75a]

The use of vinylsilanes as precursors to ketone functionality is an established method for the synthesis of β-hydroxy ketones. Intramolecular hydrosilylation of homopropargylic alcohols (see Section 10.17.3.6.1) offers one solution. The success of direct, intermolecular hydrosilylation of propargylic alcohols, together with efficient methods of accessing stereodefined propargylic alcohols, makes such an approach attractive.[6] Both substrate-controlled[76,76a] and reagent-controlled[77,77a] approaches to propargylic alcohols serve as a platform for further oxidative elaboration through hydrosilylation processes. The propargylic alcohol approach allows for the introduction of additional complexity at the α-carbon, with excellent diastereocontrol due to the (*Z*)-vinylsilane geometry (Scheme 16).[5]

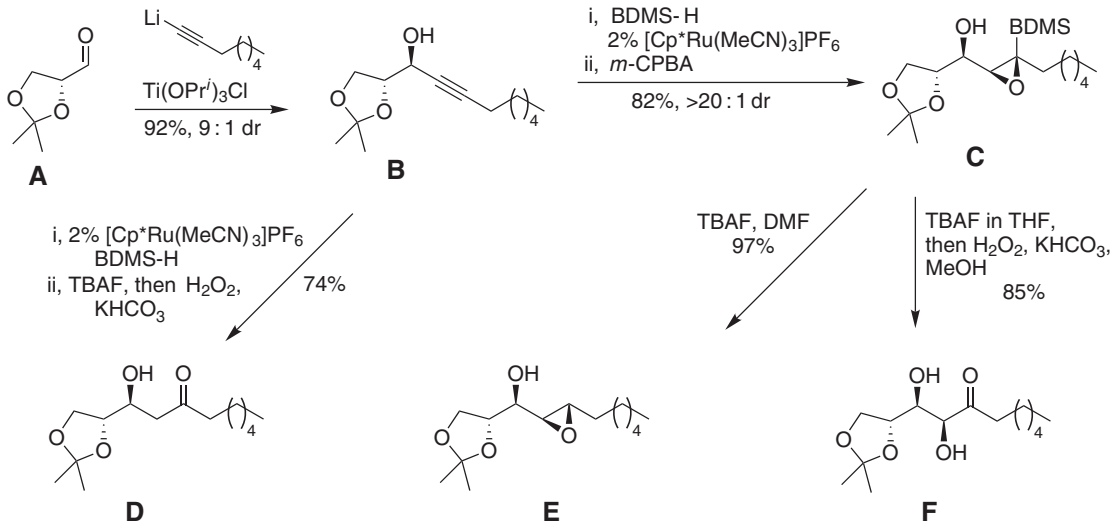
Another recent disclosure examined silicon-to-copper transmetallation as a mild means of synthesizing alkenylcopper reagents from stable precursors. The method requires activation of the silyl group by an allylic alcohol. Again, the silanes in this work are produced by circuitous means but should be accessible by ruthenium-catalyzed hydrosilylation. Treatment of the silyl alcohol with a stoichiometric amount of copper(I) *tert*-butoxide results in the C-to-O migration of the silyl group to produce a vinylcuprate shown to be competent for subsequent allylation to produce 1,4-diene products (Scheme 17).

Table 9 Selective *trans*-hydrosilylation of propargylic alcohols

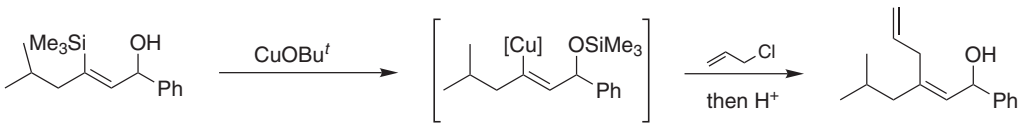


Entry	*Alkyne*	*Silane*[b]	*Cat.* (mol%)	*Major product*	*Yield/selectivity*[d]
1[c]		$Me_2(EtO)SiH$	2.5		30% ND
2		Et_3SiH	1.0		99% 13 : 1
3		BDMS-H	2.0		58%[a] 5 : 1
4		Et_3SiH	5.0		63%[a] >20 : 1
5		BDMS-H	3.0		91% 9 : 1

[a]Isolated yield of pure major isomer.



Scheme 16



Scheme 17

Quite recently, ruthenium carbene complexes more typically known as olefin metathesis catalysts have been shown to act as alkyne hydrosilylation catalysts.[78,79] *Trans*-addition is the major product with trialkylsilanes, even in a single example with an internal alkyne.[78] This result represents one of the very few examples of *trans*-hydrosilylation of internal alkynes.

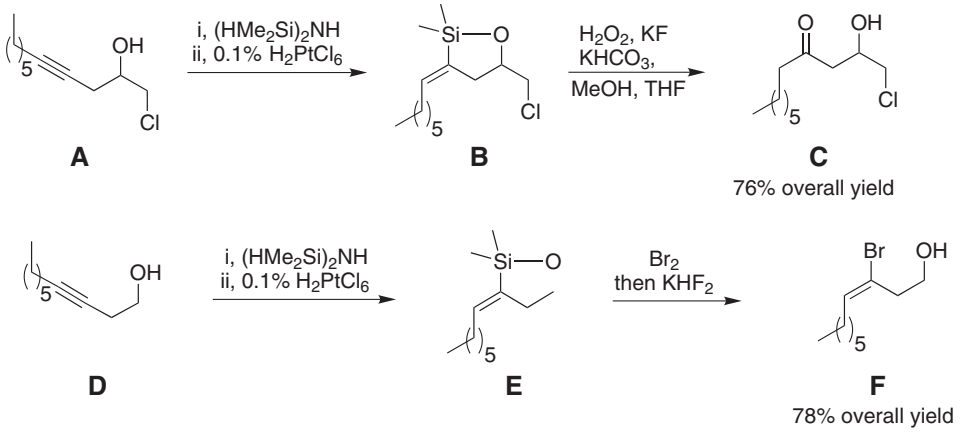
10.17.3.6 Intramolecular Hydrosilylation

10.17.3.6.1 Intramolecular *cis*-addition processes with platinum catalysts

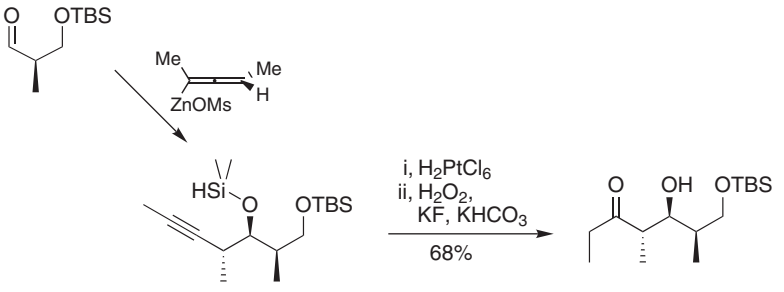
An important means of obtaining regioselectivity for intramolecular alkynes is tethering a silane to the alkyne, creating an intramolecular hydrosilylation which is often very regio- and stereoselective. Pioneering studies established that platinum catalysis (H_2PtCl_6) allows clean 5-*exo-dig* cyclization of silylated homopropargylic alcohols (Scheme 18).[80] The resulting cyclic vinylsiloxanes were elaborated through bromination and oxidation[7] reactions. Alcohol silylation in intramolecular hydrosilylation reactions is typically performed through mild heating (40–80 °C) of the substrate alkynyl alcohol in neat 1,1,3,3-tetramethyldisilazane (TMDS).[80,81]

More recent applications of the intramolecular hydrosilylation of homopropargylic alcohols with platinum catalysis have expanded the utility of this reaction. Marshall has linked stereoselective aldehyde propargylation with hydrosilylation/oxidation sequences, providing access to stereodefined, highly substituted polyketide fragments (Scheme 19).[81] The work provides important validation for the use of alkyne oxidation strategies in the synthesis of highly functionalized molecules.[82] Importantly, the strained five-membered siloxacycle intermediate permits oxidation in the presence of fluoride-sensitive primary *tert*-butyldimethylsilyl (TBS) ethers, which is not generally true of silane oxidations.[7]

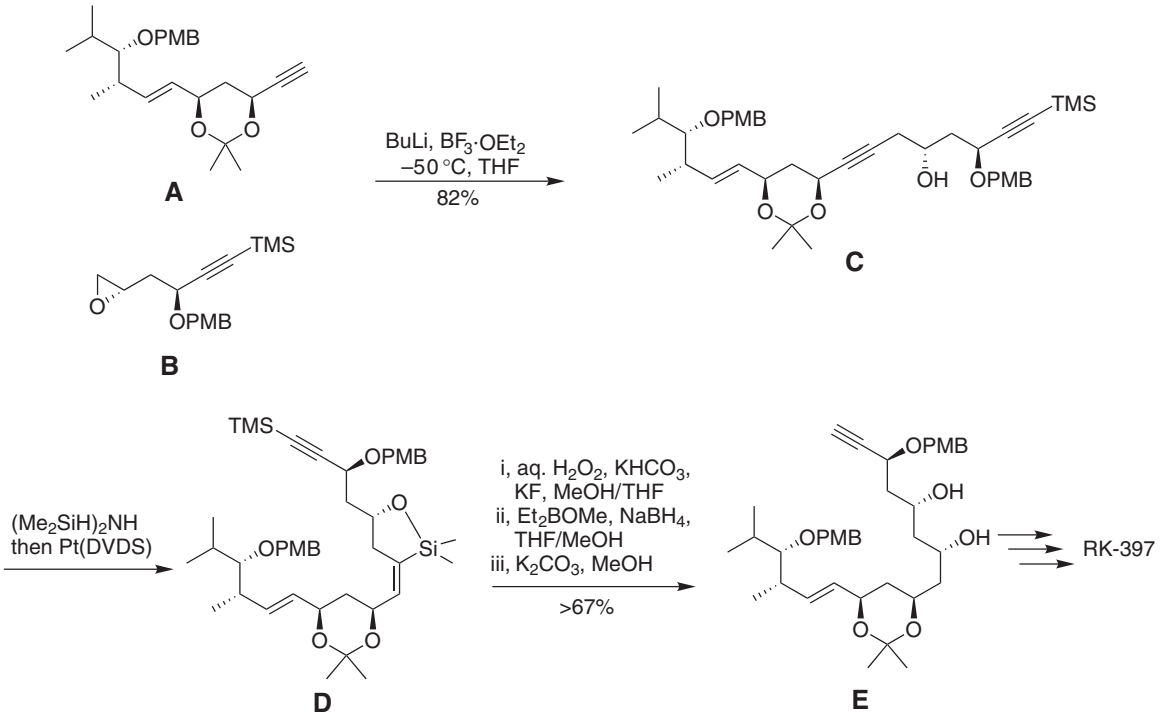
An alternative disconnection of homopropargylic alcohols substrates for intramolecular hydrosilylation is the opening of an epoxide with an alkynyl anion. This strategy was employed in a total synthesis of the macrolide RK-397 (Scheme 20). Epoxide ring opening serves to establish homopropargylic alcohol **C** with the appropriate stereochemistry. A hydrosilylation/oxidation protocol affords the diol **E** after liberation of the terminal alkyne. The



Scheme 18



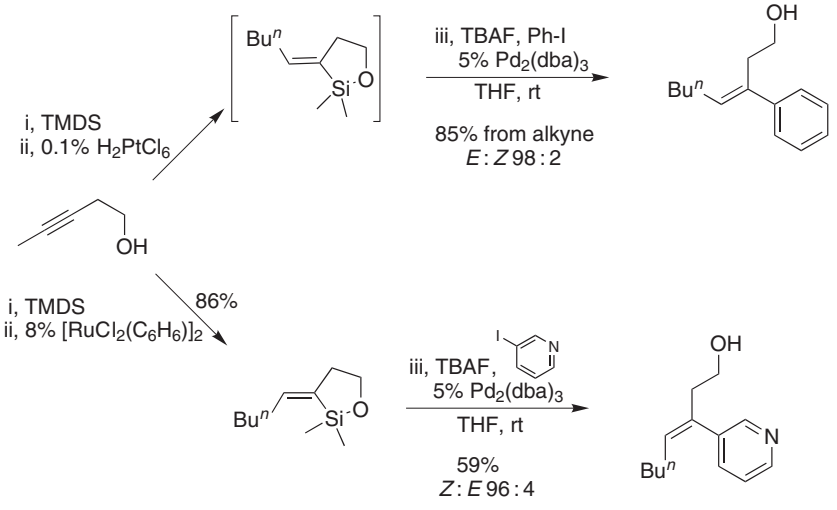
Scheme 19



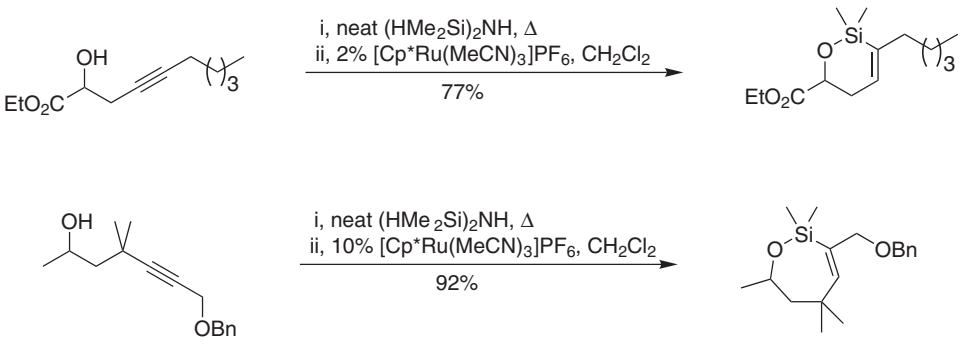
Scheme 20

success of the hydrosilylation/oxidation protocol in the presence of a TMS-protected terminal alkyne and an oxidation-sensitive paramethoxybenzyl group is noteworthy.[83]

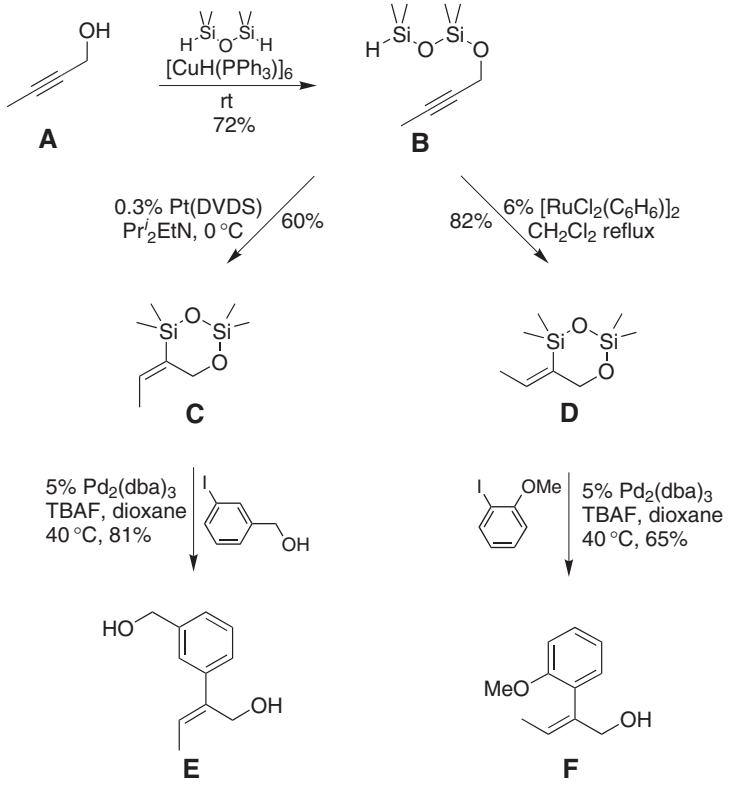
Denmark pursued intramolecular alkyne hydrosilylation in the context of generating stereodefined vinylsilanes for cross-coupling chemistry (Scheme 21). Cyclic siloxanes from platinum-catalyzed hydrosilylation were used in a coupling reaction, affording good yields with a variety of aryl iodides.[84] The three steps are mutually compatible and can be carried out as a one-pot "hydro-arylation" of propargylic alcohols. The isomeric *trans-exo-dig* addition was also achieved. Despite the fact that many catalysts for terminal alkyne hydrosilylation react poorly with internal alkynes, the group found that ruthenium(II) chloride arene complexes—which provide complete selectivity for *trans-*



Scheme 21



Scheme 22



Scheme 23

addition in terminal alkynes[57] (see Table 5)—facilitate a *trans*-addition for intramolecular hydrosilylation with silylated homopropargylic alcohols as well.[85]

10.17.3.6.2 Intramolecular hydrosilylation catalyzed by ruthenium

The final cyclization manifold has been realized with a different ruthenium catalyst (Scheme 22). The cationic $[Cp^*Ru(MeCN)_3]PF_6$ induces exclusive *endo-dig* cyclization of both homopropargylic and bis-homopropargylic alcohols.[29,73] The clean reaction to form a seven-membered ring is noteworthy for several reasons: intramolecular *exo-dig* cyclization with bis-homopropargylic alcohols is not well established, the platinum-catalyzed case has been reported to be problematic,[80] and the selectivity for seven-membered ring formation over the *exo-dig* cyclization to form a six-membered ring is likely not thermodynamic. The *endo-dig* cyclization manifold was thus significant evidence that a re-examination of alkyne hydrosilylation mechanisms is necessary (see Section 10.17.2).

While homopropargylic and bis-homopropargylic silyl ethers can provide clean intramolecular reactivity, propargylic ethers have been unsuccessful in intramolecular hydrosilylation due to the strain of small-ring intermediates.[86] A successful approach to this problem using a disiloxane tether has recently appeared (Scheme 23). Tackling rather formidable technical obstacles, an O–Si–O–Si–H linkage was shown to allow *exo-dig* cyclization to the six-membered ring product, despite the fact that such cyclizations are known to be difficult in the analogous case of bis-homopropargylic silyl ethers. The approach relies on a copper-catalyzed dehydrogenative silylation to produce the requisite, rather sensitive tetramethyldisiloxane **B** (Scheme 23).[87] This substrate then participates in both a *cis*-addition process with a platinum catalyst and a *trans*-addition process catalyzed by $[RuCl_2(C_6H_6)]_2$ to afford vinylsilanes **C** and **D**, respectively. The approach showcases the result in the synthesis of the trisubstituted olefins **E** and **F** through palladium-coupling reactions to access either olefin stereoisomer through choice of hydrosilylation catalyst.[88]

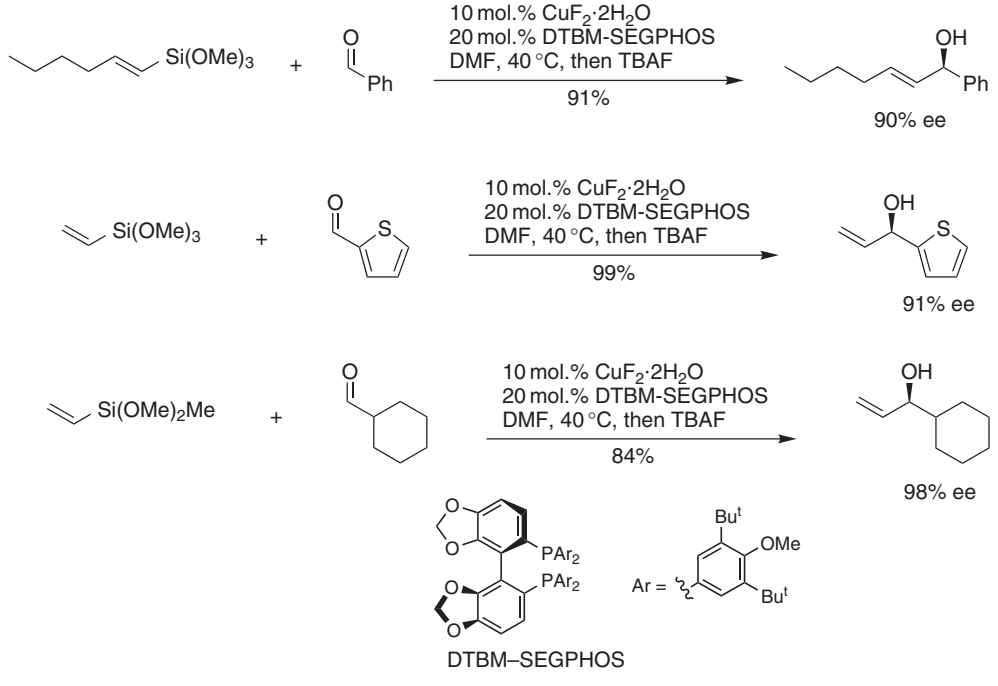
10.17.4 Additional Applications of Vinylsilanes

Numerous applications of vinylsilanes have appeared in the literature in which alkyne hydrosilylation is not the basis of the vinylsilane synthesis. In some cases, more direct routes exist for the synthesis of the required vinylsilanes. However, in many cases advances in alkyne hydrosilylation might provide more efficient access to the vinylsilane starting materials. Some noteworthy applications of vinylsilanes in contexts where the vinylsilanes were not produced by alkyne hydrosilylation are presented here, with an emphasis on those employing vinylsilanes which may themselves be accessible by alkyne hydrosilylation.

Classically, vinylsilanes have served as nucleophiles in Friedel–Crafts acylation and related reactions with strong electrophiles.[4,4a,89] These strategies have been employed in the synthesis of natural products.[90,90a]

Palladium-catalyzed cross-coupling of vinylsilanes has become a widely developed synthetic method, with the advantages of stable organometallic reagents, environmentally benign byproducts, and facile separation of the organometallic byproduct. However, silicon-based cross-coupling strategies remain the exception rather than the norm in total synthesis because of the established reliability of other methods and the dearth of examples employing less activated cross-coupling partners such as aryl chlorides. Good reviews of this topic exist.[8,8a,11,91]

Selective vinylation of aldehydes lags far behind allylation as a synthetic method despite importance of chiral allylic alcohols in synthesis. Vinylmetal species are generally much less nucleophilic that their allyl counterparts, and some vinylmetallic species, such as organotitanium, run into stability issues not encountered in alkylmetals.[92]



Scheme 24

Vinylsilane to copper transmetallation has entered the literature,[93,93a,93b] and a system suitable for catalytic asymmetric addition of vinylsilanes to aldehydes was developed (Scheme 24).[94] A copper(I) fluoride or alkoxide is necessary to initiate transmetallation, and the work employs a copper(II) fluoride salt as a pre-catalyst, presumably reduced *in situ* by excess phosphine ligand. The use of a bis-phosphine was found crucial for reactivity of the vinylcopper species, which ordinarily would not be regarded as good nucleophiles for addition to aldehydes. The highly tailored 5,5′-bis(di(3,5-di-tert-butyl-4-methoxyphenyl)phosphino-4,4′-bis(benzodioxolyl) (DTBM–SEGPHOS) (see Scheme 24) was found to provide the best results, and the use of alkoxysilanes is required. Functional group tolerance has not been adequately addressed, but the method does appear encouraging as a way to activate vinylsilanes for use as nucleophiles.

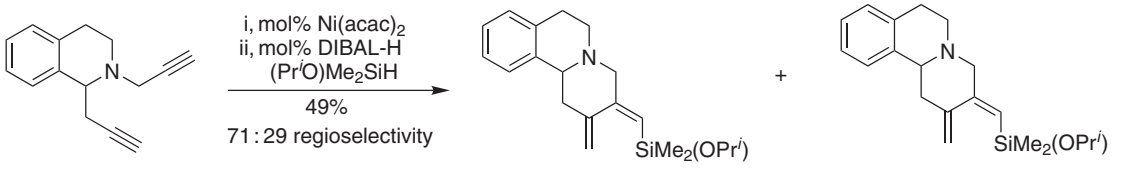
10.17.5 Tandem Reductive Alkyne Silylation/C–C Bond Formation

The vinylsilane C–Si bond can also be formed from a silane by reductive cyclization/hydrosilylation of a 1,6- or 1,7-diyne. Reductive cyclization of diynes is an important ring-forming method catalyzed by transition metals, and silanes are common reductants in this process. However, in many cases the silane serves only as a hydride source, and the silyl group is not retained in the isolated product.[95] Here, the focus is on the more rare methods which allow simultaneous C–C bond formation and vinylsilane installation.

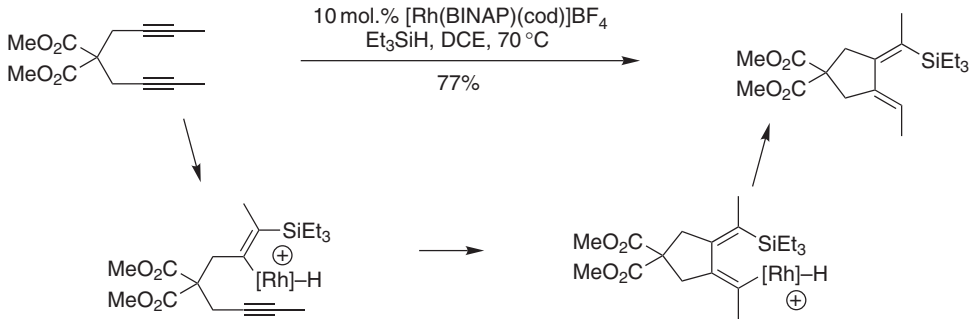
The first reported diyne hydrosilylation/cyclization was reported with a nickel catalyst,[96,97] perhaps surprising given that nickel has not proved to be particularly successful as a simple alkyne hydrosilylation catalyst.[98] Though the reaction has subsequently been reported for the intermolecular silylative dimerization of alkynes,[99] most work has focused on the intramolecular reaction for reasons of regio- and chemoselectivity. Treatment of 1,7-diynes with a silane and 1 mol% of an $Ni(acac)_2$ precatalyst and 2 mol% of diisobutylaluminum hydride results in the formation of exocyclic 1,3-dienes (Scheme 25). The best results were obtained with bis-terminal alkynes—internal alkynes react in low yield—and some regioselectivity is demonstrated with an unsymmetrical substrate (Scheme 25). The diene products thus obtained are useful substrates for Diels–Alder cycloaddition reactions, and the silyl group can serve as a functional handle to build, for instance, silyl-tethered intramolecular cycloaddition substrates.[96] Importantly, and unlike much of the rhodium work to follow, nickel catalysis functions well with heteroatom-substituted silanes, allowing more facile oxidation or palladium-catalyzed cross-coupling in subsequent reactions.

While nickel catalysis was reported only for 1,7-diynes, rhodium catalysis expands the scope of this reaction to 1,6-diynes.[100,100a,100b,100c,101] Most recently, Widenhoefer has demonstrated a robust rhodium catalyst, $[Rh(BINAP)(cod)]BF_4$, which provides modest yields for a large variety of substrates.[102] The same group had previously studied platinum complexes, which provide hydrosilylation/cyclization solely with terminal alkynes.[103,103a,103b] The rhodium catalyst provides complementary reactivity with internal alkynes.[101] Unfortunately, a general, high-yielding catalyst for mixed terminal-internal alkynes systems, where the prospects for a regioselective reaction seem most favorable, is yet to appear (Scheme 26).[96]

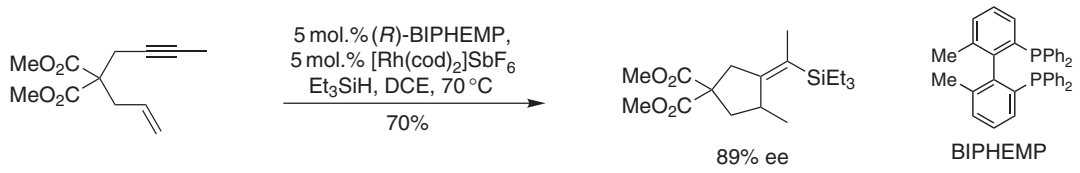
A hydrosilylation/cyclization process forming a vinylsilane product need not begin with a diyne, and other unsaturation has been examined in a similar reaction. Alkynyl olefins and dienes have been employed,[97] and since unlike diynes, enyne substrates generally produce a chiral center, these substrates have recently proved amenable to asymmetric synthesis (Scheme 27). The BINAP-based catalyst employed in the diyne work did not function in enyne systems, but the close relative 6,6′-dimethylbiphenyl-2,2′-diyl-bis(diphenylphosphine) (BIPHEMP) afforded modest yields of enantio-enriched methylene cyclopentane products.[104] Other reported catalysts for silylative cyclization include cationic palladium complexes.[105,105a] A report has also appeared employing cobalt–rhodium nanoparticles for a similar reaction to produce racemic product.[46]



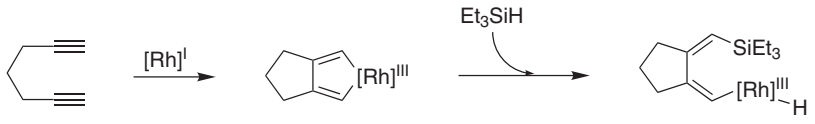
Scheme 25



Scheme 26



Scheme 27



Scheme 28

The current mechanistic understanding of these reductive cyclization processes is largely conjecture. Stepwise oxidative addition, migratory insertion, and reductive elimination (see Scheme 26) is a widely proposed mechanism. However, other mechanisms – such as initial cyclometallation – are to afford a rhodacyclopentadiene followed by either oxidative addition to a rhodium(V) intermediate or (perhaps more likely) σ-bond metathesis with an additional molecule of silane (Scheme 28).

10.17.6 Conclusion

Organosilicon reagents continue to play a major role in the elaboration of olefins in organic synthesis. The benefits of silicon-based methods—low cost, low toxicity, intermediate stability, ease of purification—ensure that their importance in organic chemistry will continue to increase. Silanes as placeholders for oxidation and as "traceless" tethers are established methods that continue to be advanced and refined. The utility of vinylsilanes in subsequent metal-catalyzed reactions has come to the fore coincident with the tremendous impact of transition metal catalysis on organic chemistry. The most prominent example clearly has been palladium-catalyzed cross-coupling of vinylsilanes. However, recent work indicates that the future will bring the use of vinylsilanes in a broad array of new reactions. The advance of a broad array of transition metal-catalyzed reactions into the synthesis of materials lagged behind the adoption of complex catalysis in target-oriented synthesis; however, their use clearly continues to develop, as demonstrated by hydrosilylative approaches to complex polymers, dendrimers, and supramolecular structures.

Due to this increasing utility, the facile synthesis of vinylsilanes becomes a crucial development for the widespread incorporation of organosilicon methodology. A main goal of hydrosilylation methods is to supplant often circuitous vinyl halide routes with efficient reactions that provide more atom economical access to similar organometallics. The goal of achieving methods to synthesize any given geometrical isomer by hydrosilylation is not necessarily unachievable. Recent reports employ hydrosilylation for the synthesis of vinylsilane isomers not possible to imagine based on

previous methods—notably clean *trans*-addition processes and a small number of selective reactions with internal alkynes. It is apparent from even a cursory read that there remain gaps in the ability of synthetic chemists to employ hydrometallation for the synthesis of vinylsilane structures. As a whole, the hydrosilylation of internal alkynes is a little-studied field and presents many unsolved problems.

Another important contribution of transition metal-catalyzed alkyne hydrosilylation continues to be the mechanistic analysis of catalysis. As a relatively simple addition process, hydrosilylation has lent itself to extensive and thorough mechanistic analysis; yet, numerous reaction pathways have now been postulated, and it is clear that many paths are possible. Importantly, principles from hydrosilylation reactions often are of use in the understanding of related, more complex transformations. Despite past achievements, much current thinking is based as much on speculation as on solid data. It is likely that continued, detailed exploration of the mechanistic underpinnings of hydrosilylation reactions will lead to new understanding and better reactions.

Acknowledgment

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10.18 C–E Bond Formation through Asymmetric Hydrosilylation of Alkenes

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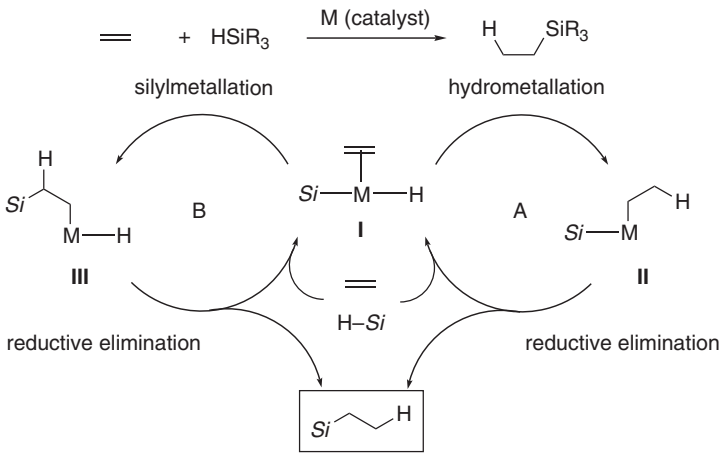
10.18.1 Introduction

Hydrosilylation is the reaction where hydrosilanes add to unsaturated substrates.[1,2] From the viewpoint of asymmetric heterofunctionalization, it generally refers to the addition of silicon–hydrogen bond across carbon–carbon double bond by the catalysis of transition metal complexes forming both valid hydrogen–carbon and silicon–carbon bonds. On this subject, there have been several pertinent reviews which have made a comprehensive survey.[3–8] Like other catalytic asymmetric reactions, asymmetric hydrosilylation is realized by incorporation of a chiral ligand on the metal catalyst. The optically active hydrosilylation products are versatile intermediates in organic synthesis via some efficient transformations. One useful transformation is the oxidative cleavage of a carbon–silicon bond forming a carbon–oxygen bond with retention of configuration, which provides a method of preparing enantiomerically enriched alcohols by way of the organosilicon compounds.[9,10] Another is the diastereoselective reactions of chiral allyl- and allenylsilanes with C═O and C═N bonds[11–12a] where more than one chiral centers can be constructed in sophisticated molecules. The challenge of asymmetric hydrosilylation, in many cases, concerns design of efficient catalytic systems for the achievement of not only the enantioselectivity but also the regioselectivity. Much effort has been dedicated to this purpose and some efficient approaches have been established including palladium/MOP system for hydrosilylation of 1-alkenes, styrenes, and 1,3-dienes giving allylic silanes, which demonstrates the utility of asymmetric hydrosilylation for the synthesis of key building blocks not available using other methodologies. Asymmetric hydrosilylation has been extended to rhodium-catalyzed intramolecular hydrosilylation and cyclization/hydrosilylation of 1,6-dienes and -enynes giving a five-membered cyclic silylated product. This chapter is a comprehensive review on all of these fruitful successes reported for the catalytic asymmetric hydrosilylation.

10.18.2 Mechanism of Transition Metal-Catalyzed Hydrosilylation of Alkenes

The early research of catalytic hydrosilylation was concentrated on platinum-catalyzed reaction with a wide variety of hydrosilanes and alkenes.[1,13] A transition metal complex ML*n* (L = ligand), especially an electron-rich complex of a late transition metal such as Co(I), Rh(I), Ni(0), Pd(0), and Pt(0) as a pre-catalyst, activates both hydrosilanes, $HSiR_3$, and a variety of substrates, typically alkenes. A catalytic cycle is considered to involve two successive steps as depicted in Scheme 1. The hydrosilylation of alkenes catalyzed by $H_2PtCl_6{\cdot}6H_2O$/*i*-PrOH (called the Speier catalyst) generally proceeds by Chalk–Harrod mechanism (Scheme 1, cycle A).[14,15] Reversible oxidative addition of a hydrosilane to the metal–alkene complex gives a hydrido–silyl complex **I**. The complex **I** undergoes rapid reversible migratory insertion of the alkene into the M–H bond (hydrometallation) to give the alkyl–silyl species **II**. Irreversible reductive elimination of the alkyl

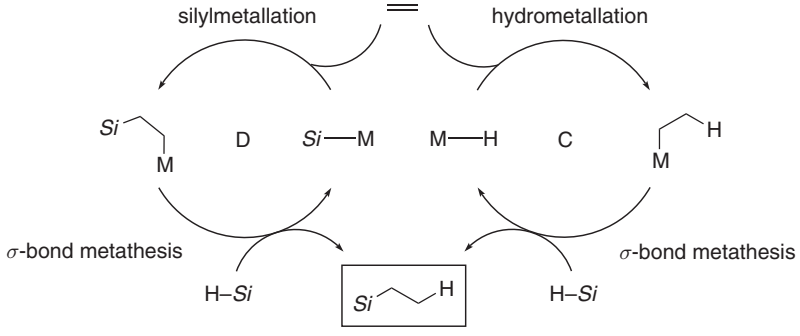


Scheme 1

and silyl ligands from **II** forms the hydrosilylation product. The plausibility of each step has been well established by many model reactions.[16]

Although the Chalk–Harrod mechanism can account for an alkene isomerization, an H–D exchange between deuteriosilanes and alkenes, as well as the observed regioselectivity always associated with the catalytic hydrosilylation, an alternative mechanism has been proposed which involves preferentially an alkene insertion into the M–Si bond (silylmetallation) in order to account for the formation of a vinylsilane observed in the hydrosilylation of ethylene with triethylsilane catalyzed by $Fe(CO)_5$. The reaction with a high molar ratio of alkene to silane gives triethylvinylsilane almost quantitatively. In this case, silylmetallation was suggested to give β-silylalkyl–hydrido intermediate **III**, followed by reductive elimination to complete the hydrosilylation[17–19] or subsequent β-hydride elimination from the insertion product **III** to generate the vinysilane (Scheme 1, cycle B). Recently, it has become evident that the silylmetallation is a fairly common process with a number of other catalyst systems of rhodium, cobalt, and palladium. Some of them will be discussed in the following sections. It is worth mentioning that hydrosilylation exhibits a wide spectrum of reactivities in the oxidative addition step depending on the substituents on the silicon atom and the nature of the metal catalyst. Thus, Pt complexes tolerate any hydrosilane, such as $HSiCl_nMe_{3-n}$ ($n = 1$–3), $HSi(OR)_3$, and H_nSiR_{4-n} ($n = 1-3$; R = alkyl or Ph) in the hydrosilylation, while Pd complexes are applicable mostly to $HSiCl_nR_{3-n}$ ($n = 2$, 3) and Rh complexes, preferably $HSiR_3$.[2]

Recently, another type of catalytic cycle for the hydrosilylation has been reported, which does not involve the oxidative addition of a hydrosilane to a low-valent metal. Instead, it involves σ-bond metathesis step to release the hydrosilylation product from the catalyst (Scheme 2). In the cycle C, alkylmetal intermediate generated by hydrometallation of alkene undergoes the metathesis with hydrosilane to give the hydrosilylation product and to regenerate the metal hydride. This catalytic cycle is proposed for the reaction catalyzed by lanthanide or a group 3 metal.[20] In the hydrosilylation with a trialkylsilane and a cationic palladium complex, the catalytic cycle involves silylmetallation of an alkene and metathesis between the resulting β-silylalkyl intermediate and hydrosilane (cycle D).[21]



Scheme 2

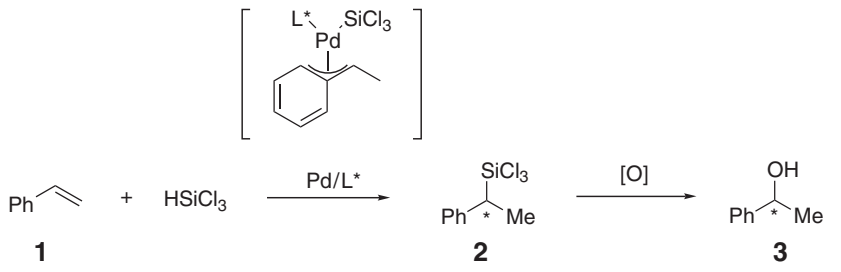
10.18.3 Asymmetric Hydrosilylation of Styrene and its Derivatives

The asymmetric hydrosilylation that has been most extensively studied so far is the palladium-catalyzed hydrosilylation of styrene derivatives with trichlorosilane. This is mainly due to the easy manipulation of this reaction, which usually proceeds with perfect regioselectivity in giving benzylic silanes, 1-aryl-1-silylethanes. This regioselectivity is ascribed to the formation of stable π-benzylpalladium intermediates (Scheme 3).[1,5,5a] It is known that bisphosphine–palladium complexes are catalytically much less active than monophosphine–palladium complexes, and, hence, asymmetric synthesis has been attempted by use of chiral monodentate phosphine ligands. In the first report published in 1972, menthyldiphenylphosphine **4a** and neomenthyldiphenylphosphine **4b** have been used for the palladium-catalyzed reaction of styrene **1** with trichlorosilane. The reactions gave 1-(trichlorosilyl)-1-phenylethane **2** with 34% and 22% ee, respectively (entries 1 and 2 in Table 1).[22,23]

Use of ferrocenylmonophosphine (*R*)-(*S*)-PPFA **5a** for the same reaction improved the enantioselectivity.[24,25,26] Here, the hydrosilylation product was oxidized into (*S*)-1-phenylethanol **3** with 52% ee (entry 3). The ferrocenylmonophosphine **6** supported on Merrifield polystyrene resin has been also used for the hydrosilylation of styrene, though the enantioselectivity was lower (15% ee) (entry 4).[27] Several chiral (β-*N*-sulfonylaminoalkyl)phosphines **7** were prepared from (*S*)-valinol and used for the asymmetric hydrosilylation of styrene.[28] For styrene, phosphine **7a** which contains methanesulfonyl group was most effective giving (*S*)-1-phenylethanol **3** with 65% ee (entry 5). Other amidophosphines **7b–7e** are also fairly effective for this asymmetric hydrosilylation (entries 6–9).[29,29a]

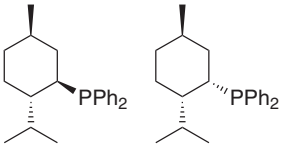
A substantial improvement in enantioselectivity was observed in the asymmetric hydrosilylation using axially chiral monophosphine ligands, MOPs, whose chirality is due to 1,1′-binaphthyl axial chirality.[30,30a] Initial studies using MeO-MOP, which is a standard MOP ligand substituted with methoxy group at its 2′-position, showed that the MOP ligand is not particularly effective for styrene.[31] Thus, the palladium-catalyzed hydrosilylation of styrene **1** with trichlorosilane in the presence of (*R*)-MeO-MOP **9** ligand under standard conditions (without solvent) followed by oxidation gave (*R*)-1-phenylethanol **3** with only 14% ee (entry 13 in Table 1). Use of benzene as solvent for the hydrosilylation improved the enantioselectivity to 71% (entry 12). The substituents at the 2′-position in MOP ligands strongly affected the enantioselectivity.[32] Ligand H-MOP **10a**, which has the same 1,1′-binaphthyl skeleton as MeO-MOP but lacks the methoxy group, is particularly effective for the palladium-catalyzed hydrosilylation of styrene giving (*R*)-**3** with 94% ee (entry 14). On the other hand, the enantiomeric purities of alcohol **3** obtained with CN-MOP **10d** and Et-MOP **10e** were much lower, 26% ee (*R*) and 18% ee (*R*), respectively (entries 17 and 18). The monophosphine (*S*)-**11**, which was prepared through the catalytic asymmetric cross-coupling,[33] was as effective as (*S*)-H-MOP **10a** for the hydrosilylation of styrene giving (*R*)-**3** with 91% ee (entry 19). These results suggest that the small size of the hydrogen at the 2′-position in H-MOP **10a** is important for high enantioselectivity.

Introduction of two trifluoromethyl groups onto the phenyl rings of the diphenylphosphino group on H-MOP ligand greatly enhanced the enantioselectivity and catalytic activity of its palladium complex.[34,34a] Thus, the hydrosilylation of styrene with trichlorosilane in the presence of 0.1 mol% of the palladium catalyst coordinated with (*R*)-H-MOP-2(CF_3) **12f** was completed within 1 h at 0 °C to give a quantitative yield of 1-phenyl-1-(trichlorosilyl)ethane, whose enantiomeric purity was determined to be 97% ee by oxidation into (*S*)-1-phenylethanol (entry 25). Deuterium-labeling studies on the hydrosilylation of regiospecifically deuteriated styrene revealed that β-hydrogen elimination from 1-phenylethyl(silyl)palladium intermediate is very fast compared with reductive elimination giving hydrosilylation product when ligand H-MOP-2(CF_3) is used. The catalytic cycle involving a hydropalladation step is supported by the results obtained for the reaction of *o*-allylstyrene **22**

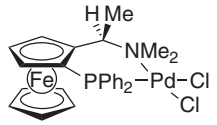


Scheme 3

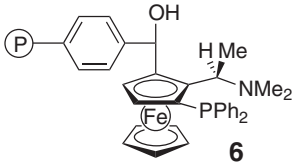
with trichlorosilane, which gives hydrosilylation products at the styrene double bond **23** and cyclized product **24**. The silylpalladation mechanism is denied by the absence of side-products which would result from the intermediate of silylpalladation process (Scheme 4).[35]



4a **4b**



PdCl$_2$[(*R*)-(*S*)-PPFA **5a**]



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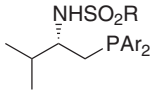
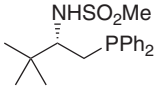
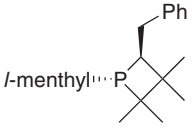


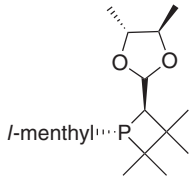
7a: R = Me, Ar = Ph
7b: R = Me, Ar = 4-MeOC$_6$H$_4$
7c: R = Me, Ar = 4-ClC$_6$H$_4$
7d: R = Ph, Ar = Ph
7e: R = CF$_3$, Ar = Ph



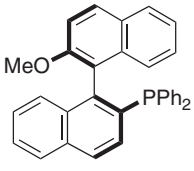
7f



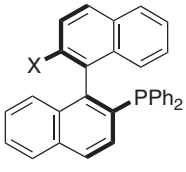
8a



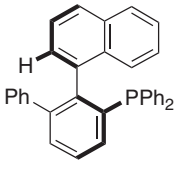
8b



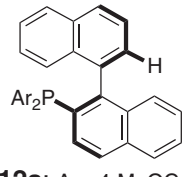
9: (*R*)-MeO-MOP



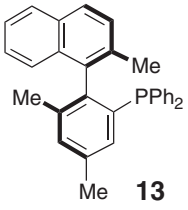
10a: (*S*)-H-MOP, X = H
10b: (*R*)-HO-MOP, X = OH
10c: (*R*)-CO$_2$Me-MOP, X = CO$_2$Me
10d: (*R*)-CN-MOP, X = CN
10e: (*S*)-Et-MOP, X = Et



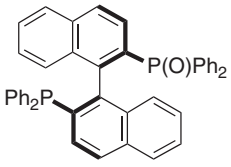
(*S*)-**11**



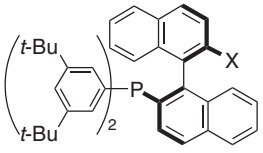
12a: Ar = 4-MeOC$_6$H$_4$
12b: Ar = 4-CF$_3$C$_6$H$_4$
12c: Ar = 3-CF$_3$C$_6$H$_4$
12d: Ar = 3,5-Me$_2$C$_6$H$_3$
12e: Ar = 3,5-Cl$_2$C$_6$H$_3$
12f: Ar = 3,5-(CF$_3$)$_2$C$_6$H$_3$



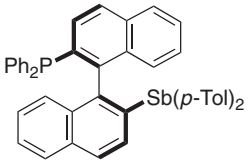
13



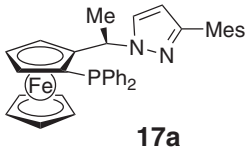
(*S*)-**14**



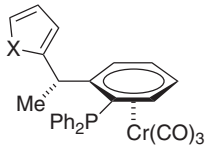
15a: X = H
15b: X = MeO
15c: X = CN



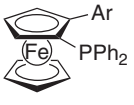
16



17a

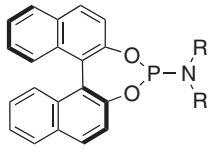


18a: X = O
18b: X = S
18c: X = NMe

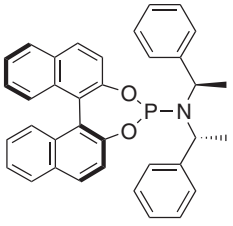


(*S*)-MOPF

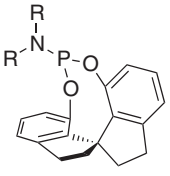
19a: Ar = Ph
19b: Ar = 2-MeOC$_6$H$_4$
19c: Ar = 3,5-(CF$_3$)$_2$C$_6$H$_3$
19d: Ar = 4-MeOC$_6$H$_4$
19e: Ar = 1-Naphthyl



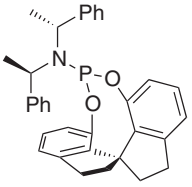
20a: R = Me
20b: R = *i*-Pr



20c



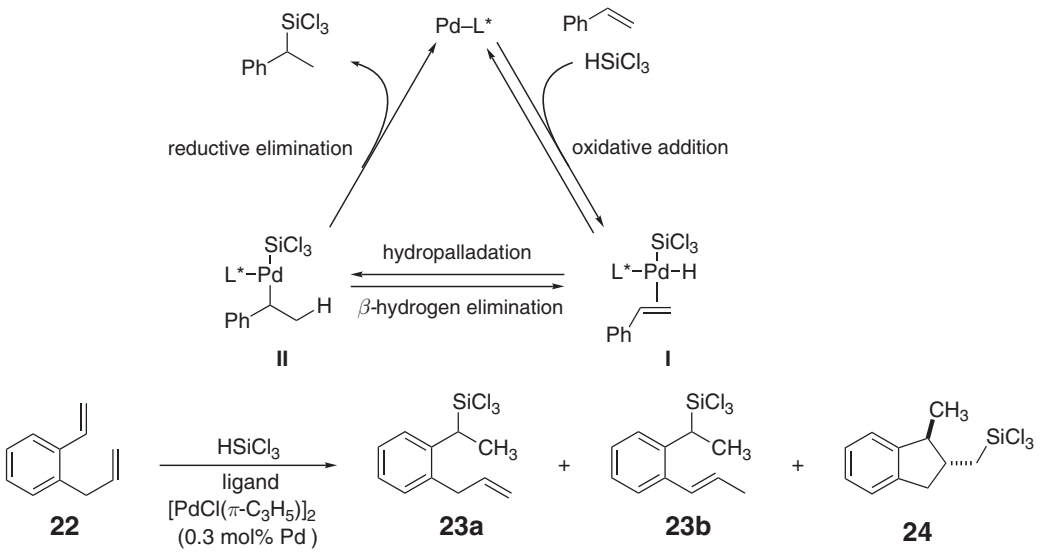
21a: R = Me
21b: R = –(CH$_2$)$_4$–
21c: R = i-Pr



21d

Table 1 Palladium-catalyzed asymmetric hydrosilylation of styrene **1** with trichlorosilane

Entry	*Ligand L**	*Catalyst* (mol%)	*Pd/L**	*Solvent*	*Temp.* (°C)	*Time* (h)	*Yield* (%)	*ee* (%)	*References*
1	**4a**	0.2	1/2		RT	5	87	34 (*S*)	22,23
2	**4b**	0.2	1/2		RT	5	87	22 (*R*)	22,23
3	(*R*)-(*S*)-PPFA **5a**	0.01			70	40	95	52 (*S*)	26
4	**6**	0.1			70	48	(100)	15 (*R*)	27
5	(*S*)-**7a**	0.1			RT	24	57	65 (*S*)	28
6	(*S*)-**7b**	0.1			RT	24	60	52 (*S*)	28
7	(*S*)-**7c**	0.1			RT	24	88	59 (*S*)	28
8	(*S*)-**7d**	0.1			RT	24	81	51 (*S*)	28
9	(*S*)-**7e**	0.1			RT	24	90	63 (*S*)	28
10	(R_P,S_C)-**8a**	0.03	1/1		50	24	>90	18 (*R*)	29,29a
11	(R_P,R_C,(*R*,*R*))-**8b**	0.03	1/1		50	24	>90	24 (*R*)	29,29a
12	(*R*)-MeO-MOP **9**	0.1	1/2	Benzene	5	44	100	71 (*R*)	31
13	(*R*)-MeO-MOP **9**	0.1	1/2		0	24	100	14 (*R*)	32
14	(*S*)-H-MOP **10a**	0.1	1/2		−10	32	92	94 (*R*)	32
15	(*R*)-HO-MOP **10b**	0.1	1/2		0	22	84	34 (*S*)	32
16	(*R*)-CO_2Me-MOP **10c**	0.1	1/2		0	12	100	30 (*S*)	32
17	(*R*)-CN-MOP **10d**	0.1	1/2		0	24	100	26 (*R*)	32
18	(*S*)-Et-MOP **10e**	0.1	1/2		0	12	100	18 (*R*)	32
19	(*S*)-**11**	0.1	1/2		0	24		91 (*R*)	33
20	(*R*)-**12a** (*p*-OMe)	0.1	1/2		0	24	89	92 (*S*)	34,34a
21	(*R*)-**12b** (*p*-CF_3)	0.1	1/2		0	11	92	93 (*S*)	34,34a
22	(*R*)-**12c** (*m*-CF_3)	0.1	1/2		0	15	81	95 (*S*)	34,34a
23	(*R*)-**12d** (3,5-Me_2)	0.1	1/2		0	16	95	92 (*S*)	34,34a
24	(*R*)-**12e** (3,5-Cl_2)	0.1	1/2		0	20	89	94 (*S*)	34,34a
25	(*R*)-**12f** (3,5-$(CF_3)_2$)	0.1	1/2	Benzene	0	1	93	97 (*S*)	34,34a
26	(*R*)-**12f** (3,5-$(CF_3)_2$)	0.1	1/2		−20	24	85	98 (*S*)	34,34a
27	**13**	0.2	1/1		0	24	86	36 (*S*)	36
28	(*S*)-BINAPO **14**	0.1	1/2	Benzene	RT	70	(100)	72 (*S*)	37
29	(*R*)-**15a**	0.1	1/2		5	16	(100)	88 (*R*)	38
30	(*R*)-**15b**	0.1	1/2		5	43	(100)	57 (*R*)	38
31	(*R*)-**15c**	0.1	1/2		5	2	(100)	81 (*S*)	38
32	(*R*)-BINAPSb **16**	0.2	1/2		0	10	78	95 (*R*)	39
33	(*R*)-(*S*)-**17**	0.2		Benzene	RT		63	63 (*S*)	40,40a
34	**18a**	0.25		CH_2Cl_2	−40	48	>85	87 (*S*)	41
35	**18b**	0.25		CH_2Cl_2	−50	48	>85	92 (*S*)	41
36	**18c**	0.05		CH_2Cl_2	−40	48	>85	65 (*S*)	41
37	**19a**	1.0	1/2	Benzene	RT	36	73	70 (*S*)	43,43a
38	**19b**	1.0	1/2	Benzene	RT	36	49	60 (*S*)	43,43a
39	**19a**	1.0	1/2		RT	1.5	(100)	76 (*S*)	43,43a
40	**19b**	1.0	1/2		RT	0.5	(100)	68 (*S*)	43,43a
41	**19c**	1.0	1/2		RT	8	(100)	25 (*S*)	43,43a
42	**19d**	0.1	1/2		RT	5.5	(100)	90 (*S*)	43,43a
43	**19e**	0.1	1/2		RT	3.5	(100)	85 (*S*)	43,43a
44	(*R*)-**20a**	1.0	1/2		RT	24	(100)	55 (*S*)	44
45	(*R*)-**20b**	1.0	1/2		RT	24	(100)	20 (*R*)	44
46	(S_A,R_C,R_C)-**20c**	0.25	1/2		20	14	87	99 (*R*)	44
47	(*R*)-**21a**	0.25	1/2		RT	20	91	62 (*R*)	45
48	(*R*)-**21b**	0.25	1/2		RT	45	61	46 (*R*)	45
49	(*R*)-**21c**	0.25	1/2		RT	30	42	51 (*S*)	45
50	(*R*,*R*,*R*)-**21d**	0.25	1/2		RT	2	99	97 (*R*)	45

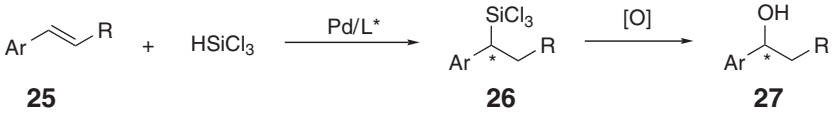


Ligand	*Temp.* (°C)	*Time* (h)	*Yield* (%)	**23a/23b/24**
PPh_3	50	2	90	50/37/13
(*R*)-H-MOP-2(CF_3) **12d**	−20	120	74	42/11/47

Scheme 4

Other chiral monophosphine ligands **14**, **15**, and **16**, which are similar to the MOP ligands in that they have diphenylphosphino group at the 2-position of the 1,1′-binaphthyl skeleton, have been also examined for their enantioselectivity in the palladium-catalyzed asymmetric hydrosilylation of styrene (entries 28–32).[36–39] Of these binaphthyl-monophosphines, **16**, which is substituted with a stibano group at the 2′-position, is most enantioselective giving **3** with 95% ee. Moderate to high enantioselectivity has been reported with monophosphine ligands on a planar chiral ferrocene **17** (entry 33)[40,40a] and η^6-arene(tricarbonyl)chromium **18** (entries 34–36).[41] For the hydrosilylation catalyzed by palladium/**17a**, a mechanism involving the hydropalladation step is proposed based on an *ab initio* calculation.[42] Planar chiral 2-aryl-1-diphenylphosphinoferrocenes **19** which are a new type of chiral ferrocenylmonophosphines were also used for the asymmetric hydrosilylation of styrene (entries 37–43).[43,43a] The enantioselectivity was dependent on the aryl substituents, the highest (90% ee) being observed with **19d** where the aryl is 4-methoxyphenyl. The hydrosilylation is very fast, completed within 15 min in the presence of 0.1 mol% of the palladium catalyst. Recently, it was reported that very high enantioselectivity is realized by use of one of the chiral phosphoramidite ligands **20** which are readily accessible from (*S*)-1,1′-binaphthol (entries 44–46).[44] The most enantioselective is that substituted with bis((*R*)-1-phenylethyl)amino group on the phosphorus atom, which gave (*R*)-1-phenylethanol with 99% ee. Another type of chiral phosphoramidite ligands **21**, which are based on a *spiro*-diol, were also enantioselective (up to 97% ee) for the hydrosilylation of styrene (entries 47–50).[45]

Some of the chiral phosphorus ligands shown above have been examined for their enantioselectivity in the asymmetric hydrosilylation of substituted styrenes on the phenyl ring or at the β-position (Scheme 5, Table 2). In general, the high enantioselectivity observed for non-substituted styrene **1** was also observed in the reaction of substituted styrenes **25**. For example, (*R*)-H-MOP-2(CF_3) **12f**, which is one of the most enantioselective ligands for styrene, showed uniformly high enantioselectivity (91–98% ee) for the styrenes substituted with methyl, chloro, bromo, methoxy, or nitro group on the phenyl ring (entries 12–21). The styrenes substituted with methyl or alkoxymethyl groups at the β-position also underwent the hydrosilylation in the presence of a palladium/**12f** catalyst



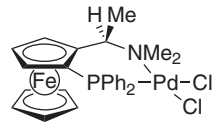
Scheme 5

to give the corresponding benzylic silanes **26** of high (97–98% ee) enantiomeric purity (entries 22–24). The high enantioselectivity for substituted styrenes has been also reported with chiral phosphoramidite ligands **20c** (entries 42–50) and **21d** (entries 51–60). It is remarkable that the regioselectivity in giving benzylic silanes is always perfect in the palladium-catalyzed hydrosilylation of styrene derivatives with trichlorosilane.

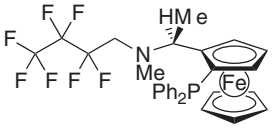
The palladium-catalyzed asymmetric hydrosilylation of styrenes has been applied to the catalytic asymmetric synthesis of 1-aryl-1,2-diols from arylacetylenes (Scheme 6).[46] Thus, (*E*)-1-aryl-2-(trichlorosilyl)ethenes, which are readily generated by platinum-catalyzed hydrosilylation of arylacetylenes, were treated with trichlorosilane and the palladium catalyst coordinated with MOP ligand **12f** to give 1-aryl-1,2-bis(silyl)ethanes, oxidation of which produced the enantiomerically enriched (95–98% ee) 1,2-diols.

A chiral bis(oxazolinyl)phenylrhodium complex was found to catalyze the asymmetric hydrosilylation of styrenes with hydro(alkoxy)silanes such as $HSiMe(OEt)_2$ (Scheme 7).[47] Although the regioselectivity in forming branched product **27** is modest, the enantiomeric purity of the branched product **27** is excellent for styrene and its derivatives substituted on the phenyl group. The hydrosilylation products were readily converted into the corresponding benzylic alcohols **29** (up to 95% ee) by the Tamao oxidation.

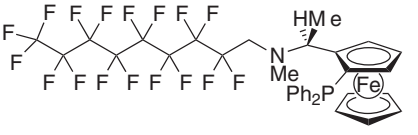
Organolanthanide and group 3 metallocene complexes, which have been originally developed as olefin polymerization catalysts, show distinctive characteristics for olefin hydrosilylation.[48,20] Organolanthanide-catalyzed hydrosilylation of α-substituted styrenes gave the corresponding benzylic *tert*-alkylsilanes because of an interaction of the electrophilic lanthanide center with the arene π-system (Scheme 8). It was demonstrated that a chiral organosamarium pre-catalyst coordinated with a menthylcyclopentadienyl ligand **30** (70% enantiopure) effects the hydrosilylation of 2-phenyl-1-butene **31** with high enantioselectivity.[20] The catalytic cycle of the lanthanide-catalyzed hydrosilylation is classified into the type C in Scheme 2, which involves an olefin insertion into metal-hydride bond followed by metathesis between metal–carbon and hydrogen–silicon bonds.[20]



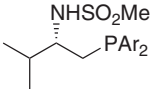
$PdCl_2$[(*R*)-(*S*)-PPFA **5a**]



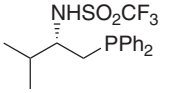
(*S*)-(*R*)-**5b**: R = $CH_2C_3F_7$-*n*



(*S*)-(*R*)-**5c**: R = $CH_2C_8F_{17}$-*n*



7a: Ar = Ph
7b: Ar = 4-$MeOC_6H_4$



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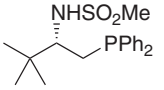

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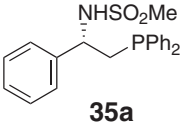

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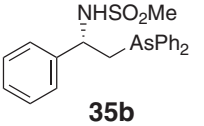

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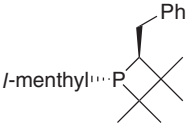

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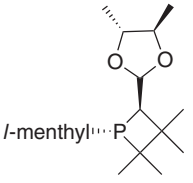

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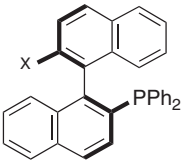
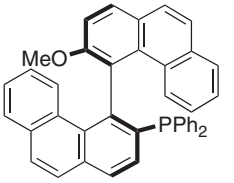
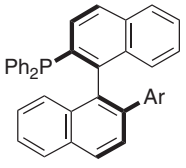


9: (*R*)-MeO-MOP, X = OMe
10a: (*S*)-H-MOP, X = H
10f: (*R*)-TBSO-MOP, X = $OSiMe_2Bu$-*t*

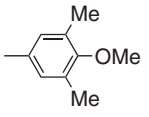


36: (*R*)-MOP-phen

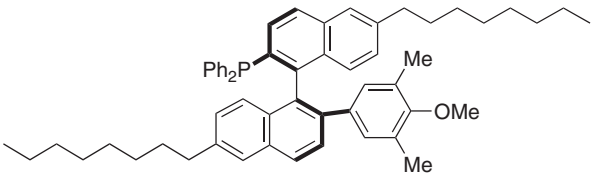


(*R*)-Ar-MOP

37a: Ar = Ph
37b: Ar = 4-$MeOC_6H_4$
37c: Ar = 4-$CF_3C_6H_4$
37d: Ar = 3-MeC_6H_4
37e: Ar = 3,5-$Me_2C_6H_3$



37f: Ar =



37g

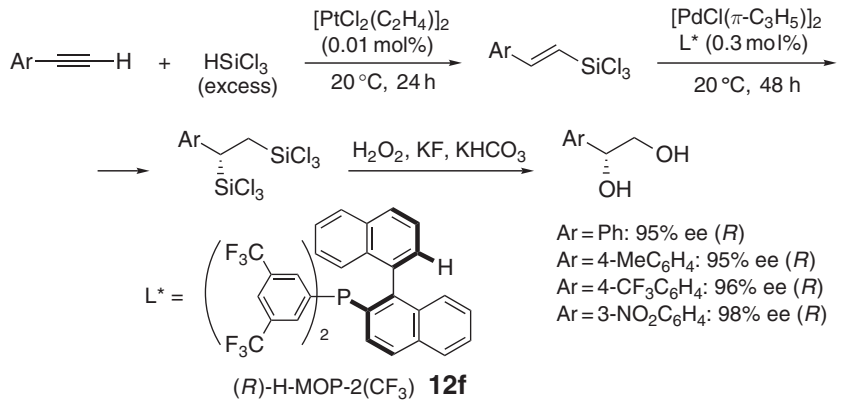
Table 2 Palladium-catalyzed asymmetric hydrosilylation of substituted styrenes **25** with trichlorosilane

	Substrate **25**									
Entry	*Ar*	*R*	*Ligand L**	*Catalyst* (mol%)	*Solvent*	*Temp* (°C)	*Time*	*Yield* (%)	*ee* (%)	*References*
1	Ph	Me	(*R*)-**9**	0.1	Toluene	40	48 h	89	82 (*R*)	31
2	Ph	CH_2OMe	(*R*)-**9**	0.1	Benzene	40	72 h	94	80 (*R*)	31
3	Ph	CH_2OCH_2Ph	(*R*)-**9**	0.1	Toluene	40	7 d	91	80 (*R*)	31
4	indene		(*R*)-**9**	0.1		5	72 h	88	85 (*R*)	31
5	2-ClC_6H_4	H	(*R*)-**9**	0.1		5	13 h	99	81 (*R*)	31
6	4-MeC_6H_4	H	(*S*)-**10a**	0.1		0	15 h	94	89 (*R*)	32
7	4-$CF_3C_6H_4$	H	(*S*)-**10a**	0.1		0	5 d	98	96 (*R*)	32
8	3-ClC_6H_4	H	(*S*)-**10a**	0.1		0	36 h	68	95 (*R*)	32
9	4-ClC_6H_4	H	(*S*)-**10a**	0.1		0	5 d	80	94 (*R*)	32
10	Ph	Me	(*S*)-**10a**	0.1		20	7 d	95	89 (*R*)	32
11	Ph	*n*-Bu	(*S*)-**10a**	0.1		20	4 d	89	92 (*R*)	32
12	2-MeC_6H_4	H	**12f**	0.1	Toluene	0	10 h	83	97 (*S*)	34,34a
13	3-MeC_6H_4	H	**12f**	0.1	Toluene	0	4 h	91	97 (*S*)	34,34a
14	4-MeC_6H_4	H	**12f**	0.1	Toluene	0	0.5 h	90	95 (*S*)	34,34a
15	2-ClC_6H_4	H	**12f**	0.1	Toluene	0	15 h	88	91 (*S*)	34,34a
16	3-ClC_6H_4	H	**12f**	0.1	Toluene	0	4 h	93	96 (*S*)	34,34a
17	4-ClC_6H_4	H	**12f**	0.1	Toluene	0	4 h	92	98 (*S*)	34,34a
18	3-BrC_6H_4	H	**12f**	0.1		0	6 d	90	94 (*S*)	34,34a
19	4-BrC_6H_4	H	**12f**	0.1	Toluene	−10	15 h	95	97 (*S*)	34,34a
20	4-$MeOC_6H_4$	H	**12f**	0.1	Toluene	−10	20 h	90	97 (*S*)	34,34a
21	3-$NO_2C_6H_4$	H	**12f**	0.1	Toluene	0	6 d	89	98 (*S*)	34,34a
22	Ph	Me	**12f**	0.1	Toluene	0	48 h	81	98 (*S*)	34,34a
23	Ph	CH_2OMe	**12f**	0.1		0	30 h	85	97	34,34a
24	Ph	CH_2OCH_2Ph	**12f**	0.1		20	16 h	87	97 (*S*)	34,34a
25	4-MeC_6H_4	H	**13**	0.2		0	24 h	99	28 (*S*)	36
26	4-ClC_6H_4	H	**13**	0.2		0	96 h	87	50 (*S*)	36
27	Ph	Me	**13**	0.2		0	144 h	88	30 (*S*)	36
28	2-naphthyl	H	**15a**	0.4	Toluene	5	88 h	(100)	55 (*R*)	38
29	2-naphthyl	H	**12d**	0.4	Toluene	5	138 h	(95)	80 (*R*)	38
30	2-naphthyl	H	**15c**	0.4	Toluene	5	68 h	(100)	66 (*S*)	38
31	4-$MeOC_6H_4$	H	**12d**	0.1	Toluene	5	65 h	(100)	80 (*R*)	38
32	4-MeC_6H_4	H	**17**	0.2	Benzene	RT		71	47 (*S*)	40,40a
33	4-$MeOC_6H_4$	H	**17**	0.2	Benzene	RT		59	6 (*R*)	40,40a
34	4-$NMe_2C_6H_4$	H	**17**	0.2	Benzene	RT		49	64 (*R*)	40,40a
35	4-ClC_6H_4	H	**17**	0.2	Benzene	RT		61	67 (*S*)	40,40a
36	4-$CF_3C_6H_4$	H	**17**	0.2	Benzene	RT		39	59 (*S*)	40,40a
37	4-MeC_6H_4	H	**18a**	0.15	CH_2Cl_2	−25	48 h	>85	83 (*S*)	41
38	4-$MeOC_6H_4$	H	**18a**	0.10	CH_2Cl_2	−25	48 h	>85	77 (*S*)	41
39	4-FC_6H_4	H	**18a**	0.05	CH_2Cl_2	−25	48 h	>85	82 (*S*)	41
40	4-ClC_6H_4	H	**18a**	0.05	CH_2Cl_2	−25	48 h	>85	83 (*S*)	41
41	4-$CF_3C_6H_4$	H	**18a**	0.25	CH_2Cl_2	−25	48 h	>85	71 (*S*)	41
42	3-$NO_2C_6H_4$	H	**20c**	0.25	–	40	144 h	94	95 (*R*)	44
43	2-ClC_6H_4	H	**20c**	0.25	–	20	40 h	89	96 (*R*)	44
44	3-ClC_6H_4	H	**20c**	0.25	–	20	60 h	91	98 (*R*)	44
45	2-$CF_3C_6H_4$	H	**20c**	0.25	–	20	40 h	74	95 (*R*)	44
46	3-$CF_3C_6H_4$	H	**20c**	0.25	–	40	60 h	88	98 (*R*)	44
47	2-MeC_6H_4	H	**20c**	0.25	–	20	40 h	75	97 (*R*)	44
48	3-MeC_6H_4	H	**20c**	0.25	–	20	40 h	95	86 (*R*)	44
49	2,4-$Me_2C_6H_4$	H	**20c**	0.25	–	20	40 h	80	96 (*R*)	44
50	Ph	Me	**20c**	0.25	–	40	40 h	91	98 (*R*)	44
51	3-MeC_6H_4	H	**21d**	0.25	–	RT	3 h	90	97 (*R*)	45
52	4-MeC_6H_4	H	**21d**	0.25	–	RT	4 h	91	98 (*R*)	45
53	2-ClC_6H_4	H	**21d**	0.25	–	RT	7 h	88	99 (*R*)	45
54	3-ClC_6H_4	H	**21d**	0.25	–	RT	9 h	86	95 (*R*)	45
55	4-ClC_6H_4	H	**21d**	0.25	–	RT	3 h	90	96 (*R*)	45
56	4-$MeOC_6H_4$	H	**21d**	0.25	–	0	3 h	84	82 (*R*)	45
57	4-$CF_3C_6H_4$	H	**21d**	0.25	–	RT	4 h	94	96 (*R*)	45

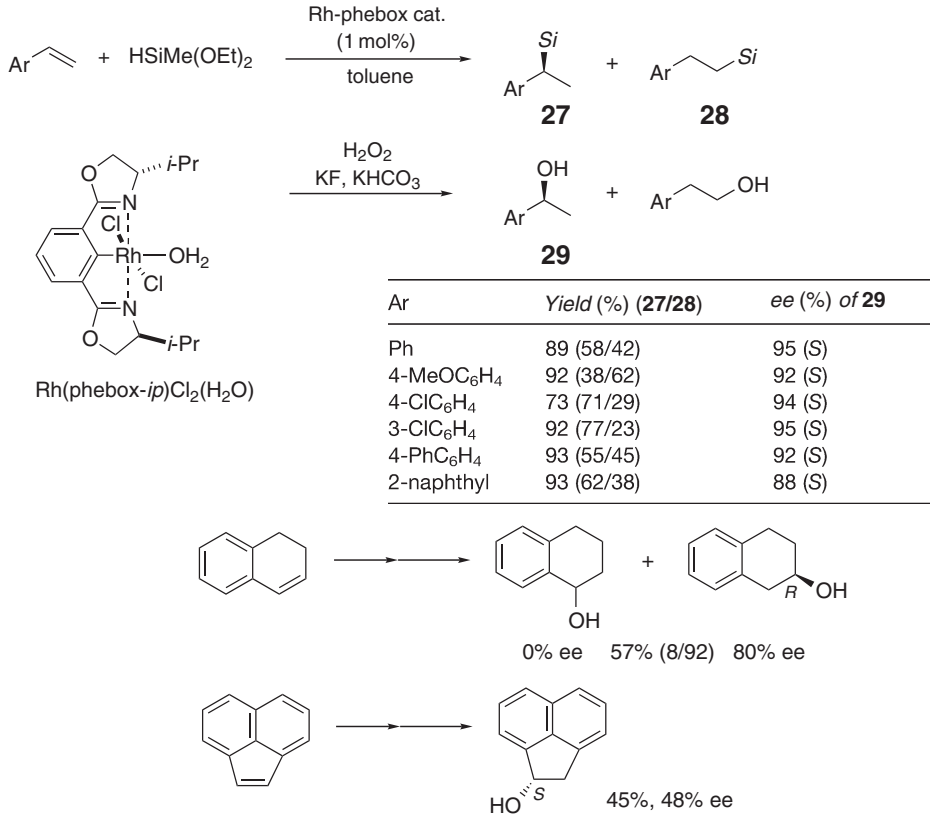
(*Continued*)

Table 2 (Continued)

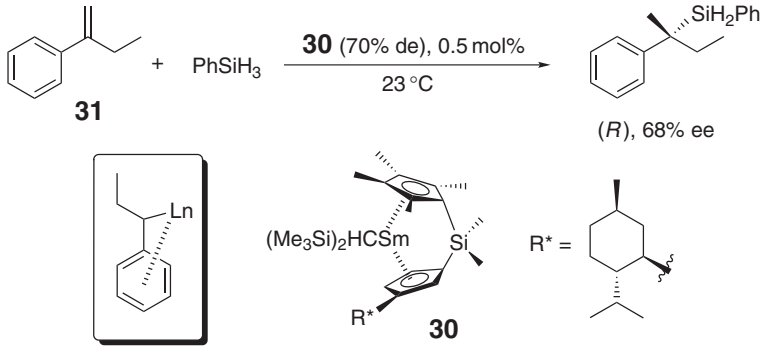
	Substrate **25**								
Entry	*Ar*	*R*	*Ligand L**	*Catalyst* (mol%)	*Solvent*	*Temp* (°C)	*Time*	*Yield* (%)	*ee* (%)	*References*
58	3-BrC_6H_4	H	**21d**	0.25	–	RT	45 h	75	97 (*R*)	45
59	4-BrC_6H_4	H	**21d**	0.25	–	RT	7 h	93	95 (*R*)	45
60	Ph	Me	**21d**	0.25	–	RT	36 h	86	95 (*R*)	45
61	1,2-Dihydro-naphthalene		**21d**	5.0	–	RT	5 d	80	88 (*R*)	45



Scheme 6



Scheme 7

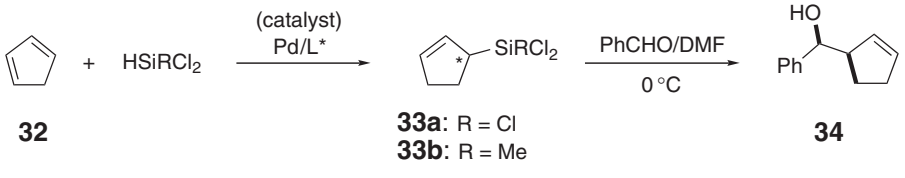


Scheme 8

10.18.4 Asymmetric Hydrosilylation of 1,3-Dienes

Palladium-catalyzed asymmetric hydrosilylation of 1,3-dienes with trichlorosilane is another synthetically useful asymmetric reaction because the reaction produces enantiomerically enriched allylsilanes, which are chiral reagents, giving, for example, homoallyl alcohols on reaction with the aldehydes.[11–12a] Similarly to the palladium-catalyzed hydrosilylation of styrenes, monodentate phosphine ligands are used because the palladium complexes coordinated with chelating bisphosphine ligands are much less active than those of monophosphine ligands for 1,3-dienes. The palladium-catalyzed hydrosilylation proceeds smoothly in a 1,4-fashion giving allylic silanes with hydrosilanes containing electron-withdrawing heteroatoms or substituents on the silicon.[49,50] Asymmetric hydrosilylation of cyclopentadiene **32** forming optically active 3-silylcyclopentene **33** has been most extensively studied (Scheme 9, Table 3). In the first report, hydrosilylation of cyclopentadiene **32** with methyldichlorosilane in the presence of 0.01 mol% of palladium–(*R*)-(*S*)-PPFA **5a** as a catalyst gave allylsilane (*S*)-**33a** with 25% ee (entry 1).[51] Use of ferrocenylphosphines **5b** and **5c** containing perfluoroalkyl groups on the side chain for the reaction of **32** with trichlorosilane increased the enantioselectivity (up to 60% ee).[52] Some of (*β*-*N*-sulfonylaminoalkyl)phosphines **7**[28] and **35**[53] are also useful for the asymmetric hydrosilylation of **32**, which gave **33b** with 71% ee (entry 6). A phosphetane ligand **8** has been also used for this asymmetric hydrosilylation.[54,54a] Although the MOP ligand, MeO-MOP **9** or H-MOP **10a**, is not enantioselective for cyclopentadiene, its biphenanthryl analog (MOP-phen, **36**) gave allylsilane **33a** with 80% ee in the reaction at 20 °C (entry 17).[55] The enantiomeric purity of the allylsilane was determined by transformation into homoallylic alcohol **34** obtained by the reaction with benzaldehyde. New MOP ligands **37**, which are substituted with aryl groups at the 2′-position of the MOP skeleton, were found to be more enantioselective than other MOP ligands.[56] Of the aryl groups at the 2′-position examined, 3,5-dimethyl-4-methoxyphenyl was most enantioselective, giving allylsilane **33** with 90% ee (entry 25). The Ar-MOP ligand **37g** containing *n*-octyl group at the 6- and 6′-positions showed higher enantioselectivity than that lacking the long-chain alkyl group (entry 26).[57,57a] The higher solubility of the dioctylated ligand in the reaction system realized high catalytic activity at a low reaction temperature.

In the asymmetric hydrosilylation of 1,3-cyclohexadiene **38** (Scheme 10, Table 4), catalyzed by chiral ferrocenylphosphines **5** and **40**, the enantioselectivity is higher with phenyldifluorosilane than that with trichlorosilane or methyldichlorosilane (entries 1–4). The reaction of **38** with phenyldifluorosilane in the presence of a palladium catalyst coordinated with ferrocenylphosphine **40b** gave allylsilane (*S*)-**39c** with 77% ee.[58,59] The use of (*β*-*N*-sulfonylaminoalkyl)phosphine **35a** for the reaction of **38** with methyldichlorosilane exhibited the same level of asymmetric induction (entries 5–6).[53] In this asymmetric hydrosilylation, combination of trichlorosilane and

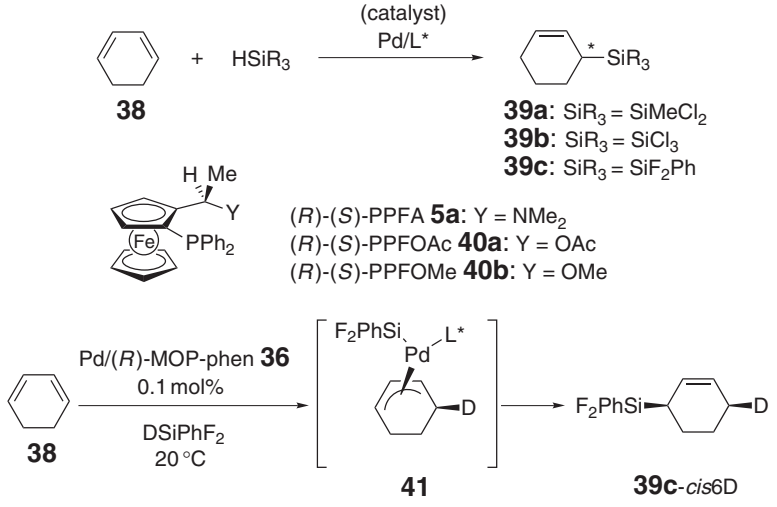


Scheme 9

Table 3 Palladium-catalyzed asymmetric hydrosilylation of cyclopentadiene **32**

Entry	*Ligand L**	*Catalyst* (mol% Pd)	*$HSiX_3$*	*Solvent*	*Temp.* (°C)	*Time* (h)	*Yield* (%)	*ee* (%)	*References*
1	(*R*)-(*S*)-PPFA **5a**	0.01	$HSiMeCl_2$		30	20	87	25 (*S*)	51
2	(*S*)-(*R*)-**5b**	0.02	$HSiCl_3$		25	90	73	57 (*R*)	52
3	(*S*)-(*R*)-**5b**	0.02	$HSiCl_3$		0	20	7	60 (*R*)	52
4	(*S*)-(*R*)-**5c**	0.02	$HSiCl_3$		25	90	41	55 (*R*)	52
5	(*S*)-**7a**	0.1	$HSiMeCl_2$		0	40	82	61 (*S*)	28
6	(*S*)-**7a**	0.1	$HSiMeCl_2$		−20	40	35	71 (*S*)	28
7	(*S*)-**7b**	0.1	$HSiMeCl_2$		0	40	74	62 (*S*)	28
8	(*S*)-**7e**	0.1	$HSiMeCl_2$		0	40	84	72 (*S*)	28
9	(*S*)-**7f**	0.1	$HSiMeCl_2$		0	40	84	68 (*S*)	28
10	(*S*)-**35a**	2.0	$HSiMeCl_2$	CH_2Cl_2	0	40	>85	37 (*S*)	53
11	(*S*)-**35b**	2.0	$HSiMeCl_2$	CH_2Cl_2	0	40	>85	28 (*S*)	53
12	(R_P,S_C)-**8a**	0.03	$HSiCl_3$		28	2	70	54 (*S*)	54,54a
13	(R_P,R_C,(*R*,*R*))-**8b**	0.03	$HSiCl_3$		40	20	60	65 (*S*)	54,54a
14	(*R*)-MeO-MOP **9**	0.1	$HSiCl_3$		20	14	100	39 (*R*)	55
15	(*R*)-H-MOP **10a**	0.1	$HSiCl_3$		20	3	91	28 (*R*)	55
16	(*R*)-TBSO-MOP **10f**	0.1	$HSiCl_3$		20	9	100	49 (*R*)	55
17	(*R*)-MOP-phen **36**	0.1	$HSiCl_3$		20	120	99	80 (*R*)	55
18	(*R*)-MOP-phen **36**	0.1	$HSiCl_3$		40	45	85	72 (*R*)	55
19	(*R*)-Ar-MOP **37a**	0.25	$HSiCl_3$		0	24	84	69 (*S*)	56
20	(*R*)-Ar-MOP **37b**	0.25	$HSiCl_3$		0	24	84	76 (*S*)	56
21	(*R*)-Ar-MOP **37c**	0.25	$HSiCl_3$		0	24	83	47 (*S*)	56
22	(*R*)-Ar-MOP **37d**	0.25	$HSiCl_3$		0	24	85	76 (*S*)	56
23	(*R*)-Ar-MOP **37e**	0.25	$HSiCl_3$		0	24	83	79 (*S*)	56
24	(*R*)-Ar-MOP **37f**	0.25	$HSiCl_3$		0	24	79	88 (*S*)	56
25	(*R*)-Ar-MOP **37f**	0.25	$HSiCl_3$		−20	72	89	90 (*S*)	56
26	(*R*)-**37g**	0.25	$HSiCl_3$		−30	168	75	91 (*S*)	57,57a

MOP-phen was not so enantioselective, giving the allylsilane **39b** with 51% ee under optimized conditions (entry 7).[55] The use of phenyldifluorosilane in place of trichlorosilane for the Pd/MOP-phen system did not improve the enantioselectivity, but the reaction with deuterium–labeled silane ($DSiF_2Ph$) gave significant insight into the mechanism of palladium-catalyzed hydrosilylation of 1,3-dienes. Thus, the reaction of 1,3-cyclohexadiene with $DSiF_2Ph$ gave *cis*-3-(phenyldifluorosilyl)-6-deuteriocyclohexene as a single isomer without any diastereo- or regioisomers, demonstrating that 1,4-*cis*-addition is an exclusive pathway. The π-allylpalladium intermediate, which is



Scheme 10

Table 4 Palladium-catalyzed asymmetric hydrosilylation of cyclohexadiene **38**

Entry	*Ligand L**	*Catalyst* (mol% Pd)	*$HSiX_3$*	*Solvent*	*Temp.* (°C)	*Time* (h)	*Yield* (%)	*ee* (%)	*References*
1	(*R*)-(*S*)-PPFA **5a**	0.01	$HSiMeCl_2$		30	20	95	2 (*S*)	51
2	(*R*)-(*S*)-PPFOAc **40a**	1	$HSiCl_3$		RT	39	44	38 (*S*)	58,59
3	(*R*)-(*S*)-PPFOAc **40a**	1	$HSiPhF_2$		RT	20	58	77 (*S*)	58,59
4	(*R*)-(*S*)-PPFOMe **40b**	1	$HSiPhF_2$		RT	20	50	54 (*S*)	58,59
5	(*S*)-**35a**	2.0	$HSiMe_2Cl$		0	40	<25	84 (*S*)	53
6	(*S*)-**35a**	2.0	$HSiMeCl_2$		0	40	>80	72 (*S*)	53
7	(*R*)-MOP-phen **36**	0.1	$HSiCl_3$		20	150	99	51 (*R*)	55
8	(*R*)-Ar-MOP **37f**	0.25	$HSiCl_3$		0	72	75	79 (*S*)	56
9	(*R*)-**37g**	0.25	$HSiCl_3$		−10	168	70	83 (*S*)	57,57a

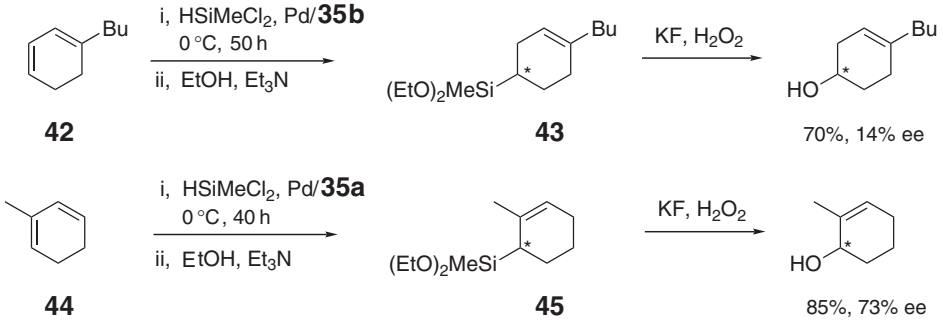
formed by the addition of PdD(Si)L* species to the diene, has the silyl group located at the *trans*-position to the π-allyl carbon next to the deuterated carbon, rapidly undergoes reductive elimination to form compound **41** before *trans–cis* isomerization of intermediate can occur (Scheme 10). The Ar-MOP ligand **37f** can be also used for the asymmetric hydrosilylation of cyclohexadiene **38**, although the enantioselectivity is not high (79% ee) compared with that observed for cyclopentadiene **32** (entry 8).[56] The enantioselectivity was improved up to 83% ee by use of the dioctylated Ar-MOP ligand **37g** (entry 9).[57,57a]

The (*β*-*N*-sulfonylaminoalkyl)phosphine **35a** and its arsine analog **35b** were examined for the palladium-catalyzed hydrosilylation of substituted cyclohexadienes (Scheme 11).[53] The hydrosilylation of 1-butylcyclohexa-1,3-diene **42** with methyldichlorosilane did not proceed with the phosphine ligand **35a**, but it proceeded smoothly with the arsine ligand **35b** to give homoallylic silane **43**, although the enantioselectivity is low (14% ee). In the reaction of 2-methylclohexa-1,3-diene **44**, regioselective 1,4-addition giving allylsilane **45** (73% ee) was observed.

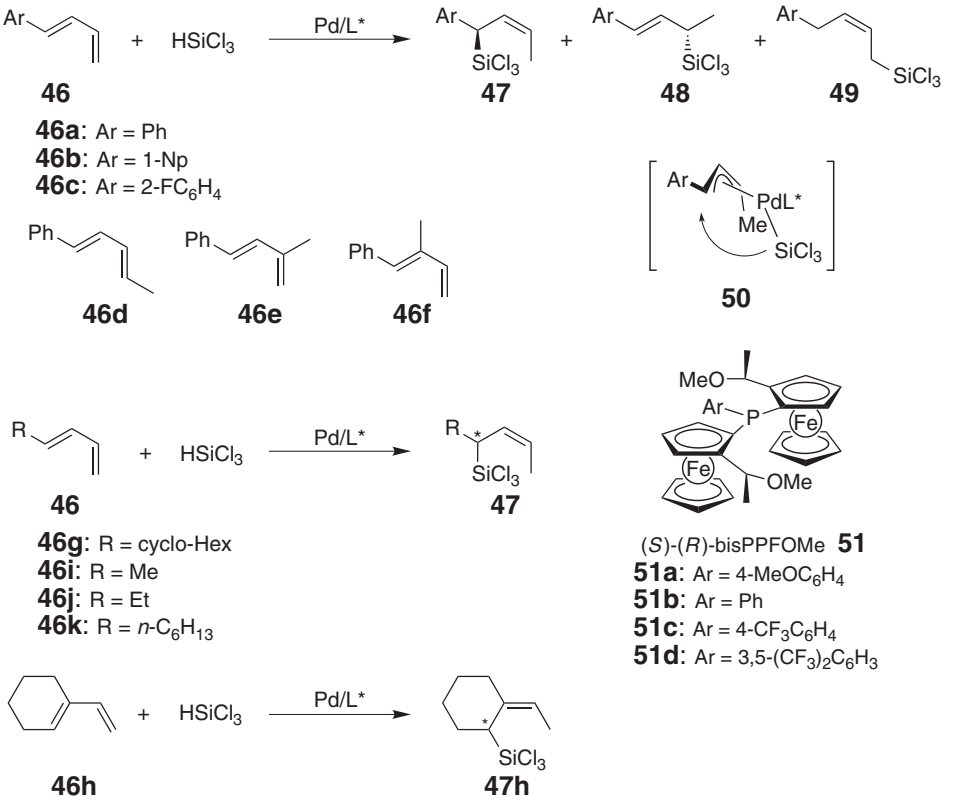
Linear 1,3-dienes have also been subjected to the palladium-catalyzed asymmetric hydrosilylation (Scheme 12, Table 5). Reaction of 1-phenyl-1,3-butadiene **46a** with $HSiCl_3$ catalyzed by palladium–(*R*)-(*S*)-PPFA **5a** gave a mixture of regioisomeric allysilanes **47**, and **48** and **49**, in a ratio of 94 to 6, the major isomer **47** and the minor isomer **48** being 64% ee (*S*) and 30% ee (*R*), respectively (entry 1).[60] π-Allylpalladium intermediate **50** was proposed for this hydrosilylation. Use of phenyldifluorosilane in place of trichlorosilane slightly improved the enantioselectivity (entry 8).[58,61] Similar level of enantioselectivity (71–72% ee) was reported for the reaction using Ar-MOP ligand **37f** (entry 11) and its dioctylated derivative **37g** (entry 12).[57a]

Hydrosilylation of alkyl-substituted 1,3-dienes **46g–46j** in the presence of a ferrocenylmonophosphine–palladium catalyst also proceeded with high regioselectivity to give the corresponding 1,4-addition products with moderate enantioselectivity (entries 13–16).[52,62] Enantioselectivity was improved by using ligands **37f** and **37g** (entries 17 and 18).[57a]

A new type of chiral ferrocenylphosphine ligands were examined for their enantioselectivity in the asymmetric hydrosilylation of 1,3-decadiene **46k**. One of the bis(ferrocenyl)monophosphine ligands **51**, which has two planar chiral ferrocenyl groups on the phosphorus atom, is more effective than the MOP-type ligands, including **37f** and **37g**. The ferrocenylphosphine (*S*)-(*R*)-bisPPFOMe-Ar **51d**, where the aryl group is 3,5-$(CF_3)_2C_6H_3$, gave the corresponding



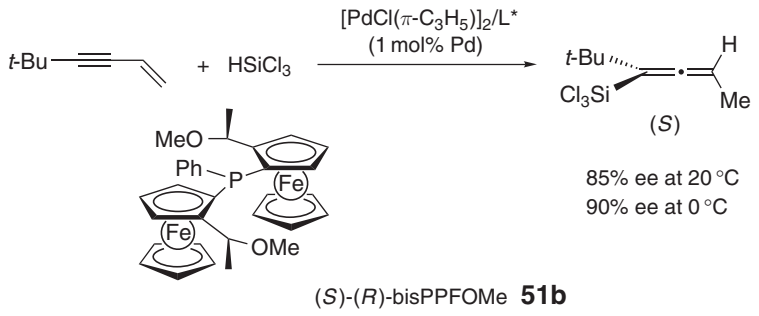
Scheme 11



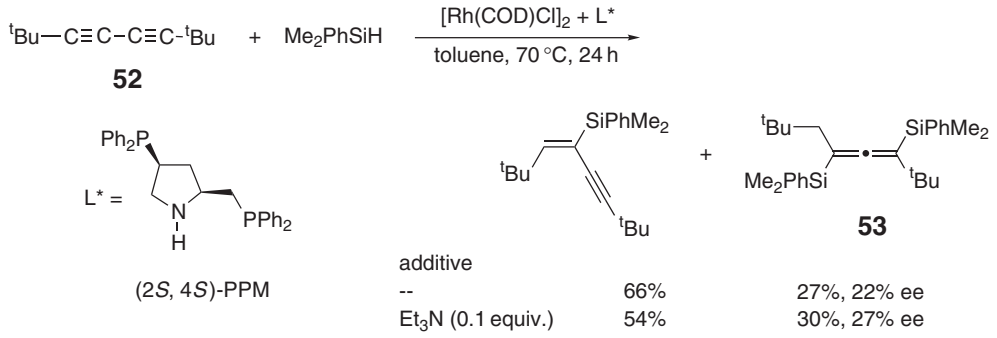
Scheme 12

Table 5 Palladium-catalyzed asymmetric hydrosilylation of linear 1,3-dienes **46**

Entry	*Diene*	*Ligand L**	*Catalyst* (mol% Pd)	*HSiX*$_3$	*Temp.* (°C)	*Time* (h)	*Yield* (%) (**47**/(**48** + **49**))	*ee* % *of* **47**	*References*
1	**46a**	(*R*)-(*S*)-PPFA **5a**	0.01	$HSiCl_3$	80	16	62 (94/6)	64 (*S*)	60
2	**46b**	(*R*)-(*S*)-PPFA **5a**	0.01	$HSiCl_3$	80	16	66 (49/51)	29 (*S*)	60
3	**46a**	(*S*)-(*R*)-**5c**	0.02	$HSiCl_3$	80	20	64 (81/19)	66 (*R*)	52
4	**46c**	(*S*)-(*R*)-**5c**	0.02	$HSiCl_3$	50	90	78 (91/9)	56	52
5	**46d**	(*R*)-(*S*)-PPFA **5a**	0.01	$HSiCl_3$	80	16	56 (93/7)	31 (*S*)	60
6	**46e**	(*R*)-(*S*)-PPFA **5a**	0.01	$HSiCl_3$	80	16	66 (100/0)	50 (*S*)	60
7	**46f**	(*R*)-(*S*)-PPFA **5a**	0.01	$HSiCl_3$	80	16	74 (99/1)	39 (*S*)	60
8	**46a**	(*R*)-(*S*)-PPFA **5a**	0.4	$HSiF_2Ph$	RT	22	53	69 (*S*)	58
9	**46a**	(*R*)-HO-MOP **10b**	0.3	$HSiFPh_2$	20	12	96	66 (*S*)	61
10	**46a**	(*R*)-TBSO-MOP **10f**	0.3	$HSiClPh_2$	20	3	94	56 (*R*)	61
11	**46a**	(*R*)-Ar-MOP **37f**	0.25	$HSiCl_3$	0	168	14 (100/0)	71 (*S*)	57a
12	**46a**	(*R*)-**37g**	0.25	$HSiCl_3$	0	168	52 (100/0)	72 (*S*)	57a
13	**46g**	(*S*)-(*R*)-**5b**	0.02	$HSiCl_3$	50	140	92 (92/8)	52	52
14	**46h**	(*S*)-(*R*)-**5b**	0.2	$HSiCl_3$	50	80	81 (98/2)	43	62
15	**46i**	(*R*)-(*S*)-PPFA **5a**	0.01	$HSiF_2Ph$	RT	9	82	69 (*R*)	58
16	**46j**	(*R*)-(*S*)-PPFA **5a**	0.5	$HSiF_2Ph$	RT	9	75	69 (*R*)	58
17	**46k**	(*R*)-Ar-MOP **37f**	0.25	$HSiCl_3$	−10	168	9 (100/0)	77 (*R*)	57a
18	**46k**	(*R*)-**37g**	0.25	$HSiCl_3$	−10	168	76 (100/0)	77 (*R*)	57a
19	**46k**	(*S*)-(*R*)-**51a**	1.0	$HSiCl_3$	20	96	43 (82/18)	68 (*S*)	63
20	**46k**	(*S*)-(*R*)-**51b**	1.0	$HSiCl_3$	20	29	78 (90/10)	76 (*S*)	63
21	**46k**	(*S*)-(*R*)-**51c**	1.0	$HSiCl_3$	20	8	89 (90/10)	78 (*S*)	63
22	**46k**	(*S*)-(*R*)-**51d**	1.0	$HSiCl_3$	20	25	91 (87/13)	87 (*S*)	63
23	**46k**	(*S*)-(*R*)-**51d**	1.0	$HSiCl_3$	−5	168	81 (89/11)	93 (*S*)	63
24	**46g**	(*S*)-(*R*)-**51d**	1.0	$HSiCl_3$	−5	168	81 (93/7)	90 (*S*)	63



Scheme 13



Scheme 14

allylic silanes of highest enantioselectivity in the palladium-catalyzed hydrosilylation of 1,3-decadienes (93% ee) (entry 23).[63] The high selectivity (90% ee) for the formation of **47** was also observed in the reaction of diene **46g** (entry 24).

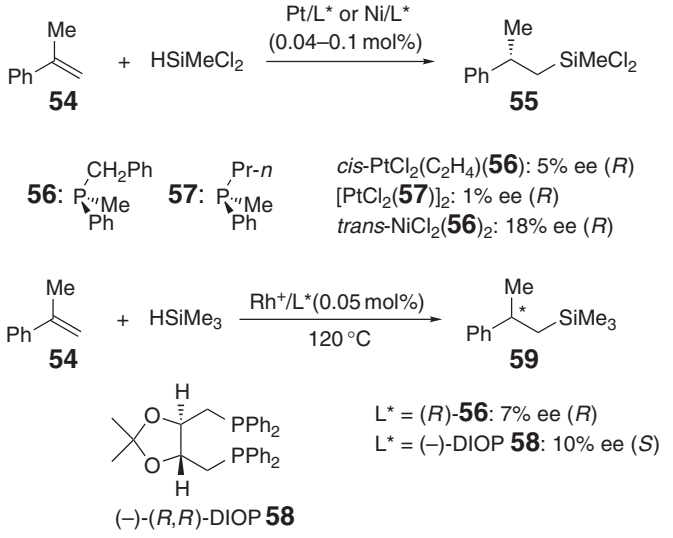
A new type of asymmetric hydrosilylation which produces axially chiral allenylsilanes has been reported by use of a palladium catalyst coordinated with the bisPPFOMe ligand **51b**.[64] The hydrosilylation of 1-buten-3-ynes substituted with bulky groups such as *tert*-butyl at the acetylene terminus took place in a 1,4-fashion to give allenyl(trichloro)-silanes with high selectivity. The highest enantioselectivity (90% ee) was observed in the reaction of 5,5-dimethyl-1-hexen-3-yne with trichlorosilane catalyzed by the bisPPFOMe-palladium complex (Scheme 13).

The catalytic reaction giving allenes by the addition of a hydrosilane twice to 1,3-diynes[65] has been applied to the asymmetric synthesis of axially chiral allenylsilanes although the selectivity and scope of this reaction are relatively low. A chiral rhodium complex coordinated with (2*S*,4*S*)-PPM is the best catalyst for the addition of phenyldimethyl-silane to diyne **52** giving allene **53** with 22% ee (Scheme 14).[66,66a]

10.18.5 Asymmetric Hydrosilylation of Alkyl-Substituted Acyclic Alkenes

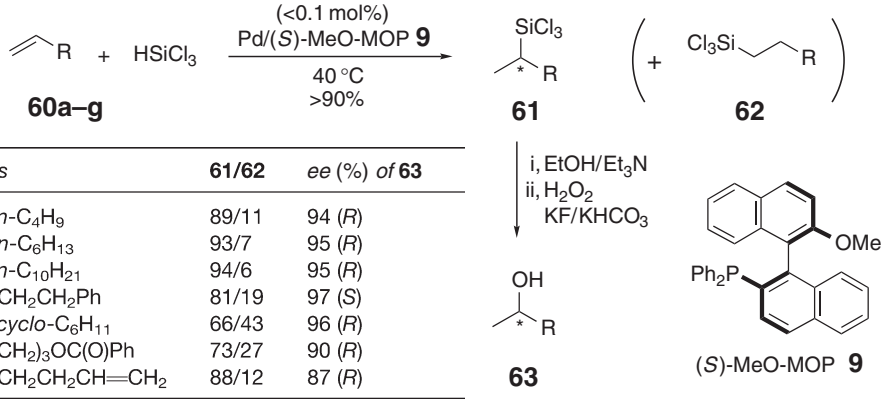
The first example of catalytic asymmetric hydrosilylation is the addition of methyldichlorosilane to 2-phenylpropene **54** in the presence of a platinum catalyst coordinated with (*R*)-benzylmethylphenylphosphine **56**, which was reported by Yamamoto, Hayashi, and Kumada in 1971. The reaction catalyzed by 0.07 mol% of *cis*-$PtCl_2(C_2H_4)$(**56**) proceeded at 40 °C to give (*R*)-1-(methyldichlorosilyl)-3-phenylpropane **55** with 5% ee (Scheme 15).[67,67a] Using a platinum catalyst with (*R*)-methylphenylpropylphosphine **57**, the enantioselectivity was lower (1% ee). Use of *trans*-$NiCl_2$(**56**)$_2$ catalyst bearing the phosphorus chiral ligand **56** for the hydrosilylation of **54** improved the enantioselectivity up to 18% ee.[68,68a] Cationic rhodium complexes coordinated with (*R*)-benzylmethylphenylphosphine **56** or (−)-DIOP **58** as a ligand catalyzed the hydrosilylation of 2-phenylpropene **54** with trimethylsilane to give 1-(trimethylsilyl)-3-phenylpropane **59** with 7% and 10% ee, respectively.[68a]

It is well documented that hydrosilylation of alkyl-substituted terminal olefins catalyzed by transition metal complexes proceeds with high regioselectivity in giving linear hydrosilylation products which do not possess a stereogenic carbon center.[2] It follows that the asymmetric synthesis by use of the hydrosilylation of alkyl-substituted



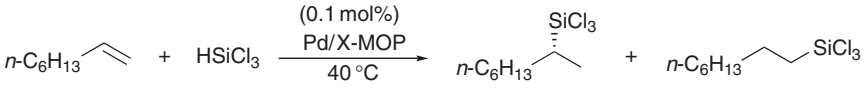
Scheme 15

terminal olefins is not straightforward. An exceptional system consisting of palladium catalyst and an axially chiral monodentate phosphine ligand, MeO-MOP **9** or its analogs,[30,30a] has been reported to effect the asymmetric hydrosilylation of alkyl-substituted terminal olefins to give branch products with high regioselectivity and with high enantioselectivity (Scheme 16).[69,69a] Simple terminal olefins **60** were transformed efficiently into the corresponding optically active 2-alkanols **61** with enantioselectivities ranging between 94% and 97% ee by the catalytic hydrosilylation–oxidation procedure. For example, the reaction of 1-octene **60b** with trichlorosilane in the presence of 0.1 mol% of palladium catalyst generated from $[PdCl(\pi\text{-}C_3H_5)]_2$ and (*S*)-MeO-MOP **9** at 40 °C for 24 h gave 2-octylsilane **61b** and 1-octylsilane **62b** in a ratio of 93 to 7. The branched isomer was oxidized into (*R*)-2-octanol **63b** with 95% ee. Asymmetric hydrosilylation of 4-pentenyl benzoate and 1,5-heptadiene gave the corresponding 2-alkanols with 90% and 87% ee, respectively. The ester carbonyl and the internal double bond remained intact.[69,69a] The high selectivity was also observed with MOP ligands **10f**, **10g**, and **10e**, which have other substituents than methoxy at the 2′-position (Scheme 17).[69,69a] Thus, the hydrosilylation of 1-octene **60b** with MOP ligands substituted with benzyloxy or isopropoxy gave over 91% enantioselectivity and over 80% branched selectivity, suggesting that the steric bulkiness of the 2′-substituents has little influence on this asymmetric hydrosilylation. The presence of an alkoxy group at the 2′-position is not essential for the high selectivity because replacement of the alkoxy group by an alkyl group did not affect the selectivity.

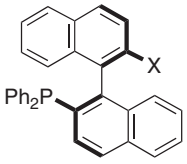


Structures	**61/62**	*ee* (%) *of* **63**
60a: R = *n*-C_4H_9	89/11	94 (*R*)
60b: R = *n*-C_6H_{13}	93/7	95 (*R*)
60c: R = *n*-$C_{10}H_{21}$	94/6	95 (*R*)
60d: R = CH_2CH_2Ph	81/19	97 (*S*)
60e: R = *cyclo*-C_6H_{11}	66/43	96 (*R*)
60f: R = $(CH_2)_3OC(O)Ph$	73/27	90 (*R*)
60g: R = $CH_2CH_2CH{=}CH_2$	88/12	87 (*R*)

Scheme 16



60b (*R*)-**61b** **62b**



X-MOP **10**

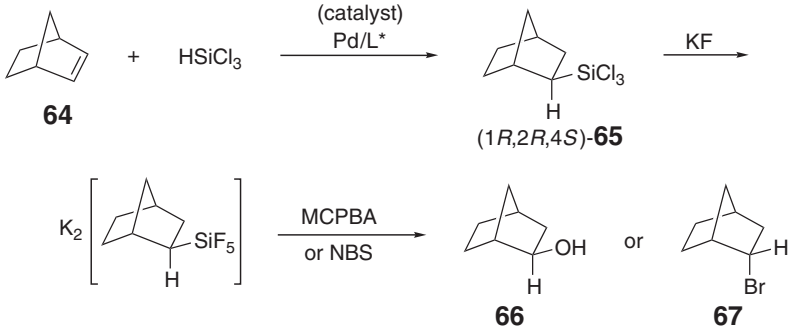
X-MOP	*Yield* (%)	**61b : 62b**	*ee* (%)
(*S*)-MeO-MOP **9**	83	93 : 7	95 (*R*)
(*S*)-PhCH$_2$O-MOP **10f**	85	80 : 20	95 (*R*)
(*S*)-*i*-PrO-MOP **10g**	88	90 : 10	91 (*R*)
(*R*)-Et-MOP **10e**	80	90 : 10	93 (*R*)

Scheme 17

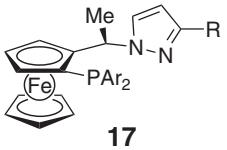
Another example of the palladium-catalyzed asymmetric hydrosilylation of simple terminal alkene, 1-hexene, was reported recently where *spiro*-phosphoramidite **21d** gave 35% yield of (*R*)-2-hexanol with 68% ee.[45]

10.18.6 Asymmetric Hydrosilylation of Cyclic Alkenes

Asymmetric hydrosilylation of norbornene **64** was first attempted by use of palladium catalyst coordinated with ferrocenylmonophosphine, (*R*)-(*S*)-PPFA **5a**.[26] The hydrosilylation of **64** with trichlorosilane gave (1*R*,2*R*,4*S*)-*exo*-2-(trichlorosilyl)norbornane **65** with 53% ee (Scheme 18). Treatment of **65** with potassium fluoride followed by oxidation of the resulting pentafluorosilicate with MCPBA or NBS gave *exo*-2-norbornanol **66** or *endo*-2-bromonorbornane **67**, respectively. A fine-tuning of chiral ferrocenylphosphine ligand by introduction of 3,5-bis(trifluoromethyl)phenyl group and a pyrazole **17d** gave the corresponding product with up to 99% ee (Table 6, entry 5).[40,40a] The palladium–MeO-MOP **9** complex shows high enantioselectivity and catalytic activity in most cases.[70] The hydrosilylation of norbornene **64** with trichlorosilane took place at 0 °C in the presence of 0.01 mol% of the MOP/palladium catalyst to give a quantitative yield of *exo*-2-(trichlorosilyl)norbornane **65** as a single product (Scheme 19). Direct oxidation of **65** with hydrogen peroxide in the presence of a large excess of potassium fluoride and potassium bicarbonate gave (1*S*,2*S*,4*R*)-*exo*-2-norbornanol **66** with 93% ee in a high yield (entry 6). The hydrosilylation carried out at −20 °C raised the enantioselectivity to 96% ee (entry 7). Bicyclo[2.2.2]octene, a diester of norbornenedicarboxylic acid, and 2,5-dihydrofuran derivatives were also successfully subjected to the asymmetric hydrosilylation–oxidation under similar reaction conditions to give the corresponding optically active alcohols with enantioselectivity in excess of 92%.[70,71]



64 (1*R*,2*R*,4*S*)-**65** **66** **67**



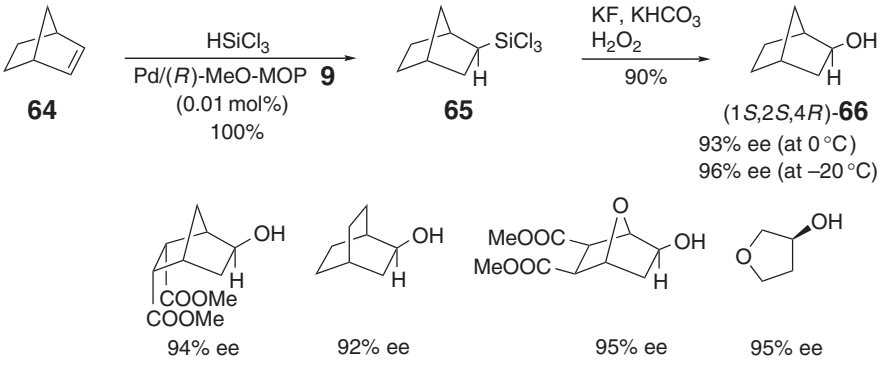
17

17a: R = Mes, Ar = Ph
17b: R = 9-Anthryl, Ar = Ph
17c: R = 2,4,6-(MeO)$_3$C$_6$H$_4$, Ar = Ph
17d: R = Mes, Ar = 3,5-(CF$_3$)$_2$C$_6$H$_4$

Scheme 18

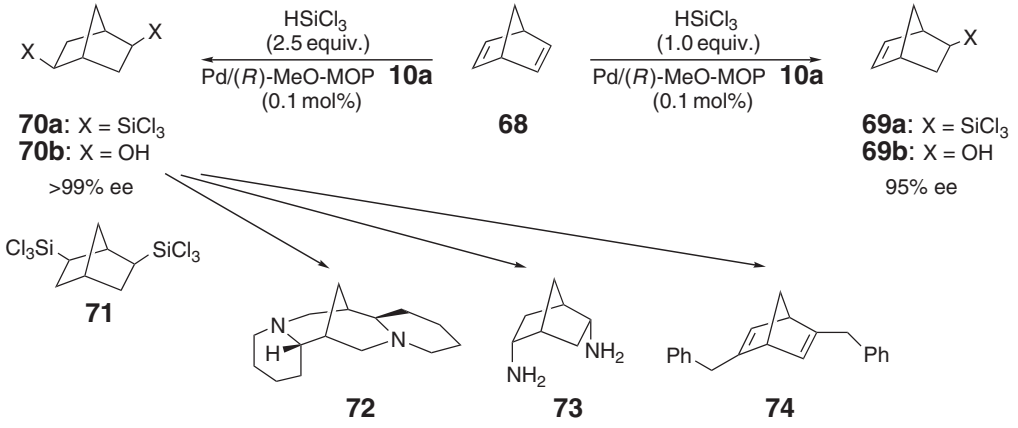
Table 6 Palladium-catalyzed asymmetric hydrosilylation of norbornene **64**

Entry	*Ligand L**	*Catalyst* (mol% Pd)	$HSiX_3$	*Solvent*	*Temp.* (°C)	*Time*	*Yield* (%)	*ee* (%)	*References*
1	(*R*)-(*S*)-PPFA **5a**	0.01	$HSiCl_3$		70	40 h	53	53	26
2	(*R*)-(*S*)-**17a**	0.1	$HSiCl_3$		0		56	91	40,40a
3	(*R*)-(*S*)-**17b**	0.1	$HSiCl_3$		25		54	81	40,40a
4	(*R*)-(*S*)-**17c**	0.1	$HSiCl_3$		0		30	82	40,40a
5	(*R*)-(*S*)-**17d**	0.1	$HSiCl_3$		0		59	99.5	40,40a
6	(*R*)-MeO-MOP **9**	0.01	$HSiCl_3$		0	24 h	100	93	70
7	(*R*)-MeO-MOP **9**	0.01	$HSiCl_3$		−20	3 d	99	96	70

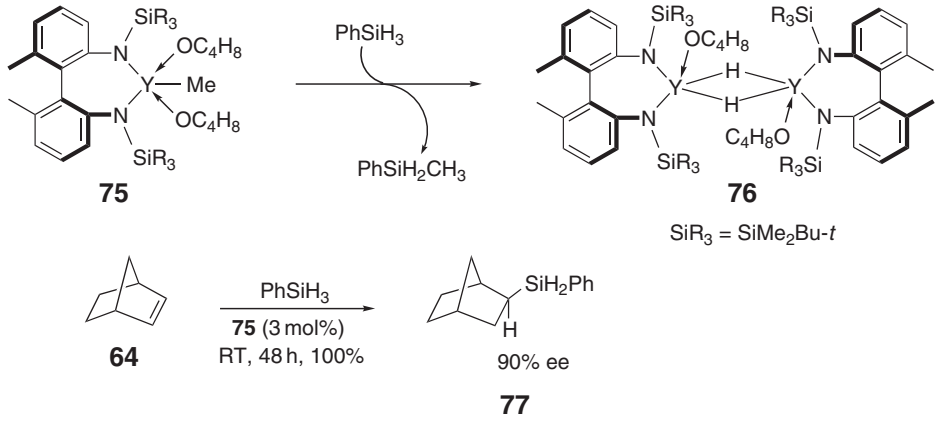


Scheme 19

It is remarkable that the monofunctionalization of norbornadiene **68** giving *exo*-5-trichlorosilyl-2-norbornene **69a** is effected by the palladium–MeO-MOP catalyst with high chemo- and enantioselectivity (Scheme 20).[70] Thus, the reaction of **68** with 1.0 equiv. of trichlorosilane and the palladium–MeO-MOP catalyst followed by the hydrogen peroxide oxidation gave (1*R*,4*R*,5*S*)-*exo*-5-hydroxy-2-norbornene **69b** with 95% ee. Reacting **68** with 2.5 equiv. of trichlorosilane induced enantioselective hydrosilylation in both double bonds, thus giving a 78% yield of chiral disilylnorbornane **70a** and the *meso*-isomer **71** in a ratio of 18 : 1. The oxidation of **70a** gave the diol (1*R*,2*S*,4*R*,5*S*)-**70b** with higher than 99% ee, the high enantiomeric purity being due to the expected double stereoselection. The diol **70b** obtained by this method has been used as a key intermediate for the asymmetric synthesis of (+)-sparteine **72**,[72] chiral diamine **73**,[73] and chiral norbornadiene ligand **74**.[74]



Scheme 20



Scheme 21

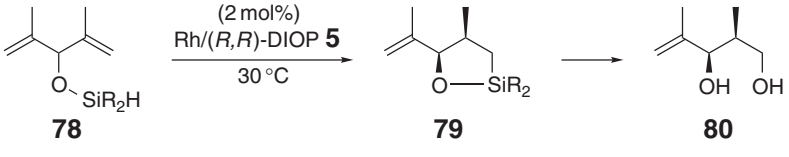
The yttrium hydride {[2,2′-bis(*tert*-butyldimethylsilylamido)-6,6′-dimethylbiphenyl]YH(THF)}$_2$ **76**, conveniently generated *in situ* from [2,2′-bis(*tert*-butyldimethylsilylamido)-6,6′-dimethylbiphenyl]YMe(THF)$_2$ **75**, demonstrated its high catalytic activity in the asymmetric hydrosilylation. This system represents the first use of a d^0 metal complex with non-Cp ligands for the catalytic hydrosilylation of olefins. Hydrosilylation of norbornene with $PhSiH_3$ gave the corresponding product **77** with 90% ee (Scheme 21).[75]

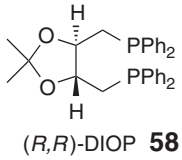
Although it is not a catalytic asymmetric hydrosilylation, chirality transfer was reported in the palladium-catalyzed addition of an enantiomerically enriched hydrosilane to norbornene.[76]

10.18.7 Asymmetric Intramolecular Hydrosilylation

Intramolecular asymmetric hydrosilylation–oxidation of (alkenyloxy)hydrosilanes provides an efficient method for the preparation of optically active polyols from allylic alcohols. Cyclization of silyl ethers **78** of a *meso*-type allylic alcohol in the presence of rhodium–DIOP **58** as a catalyst proceeded with high diastereoselectivity and high enantiotopos selectivity. Oxidation of carbon–silicon bond in the resulting oxasila-cyclopentane derivatives **79** gave *syn*-2,4-dimethyl-4-pentene-1,3-diol **80** with high ee (Scheme 22).[77] The enantioselectivity was dependent on the alkyl groups on the silicon, and sterically hindered 3,5-dimethylphenyl group gives the highest selectivity (93% ee).

Asymmetric cyclization was also successful in the rhodium-catalyzed hydrosilylation of silyl ethers **81** derived from allyl alcohols. High enantioselectivity (up to 97% ee) was observed in the reaction of silyl ethers containing a bulky group on the silicon atom in the presence of a rhodium–BINAP catalyst (Scheme 23).[78] The cyclization products **82** were readily converted into 1,3-diols **83** by the oxidation. During studies on this asymmetric hydrosilylation, silylrhodation pathway in the catalytic cycle was demonstrated by a deuterium-labeling experiment.[79]

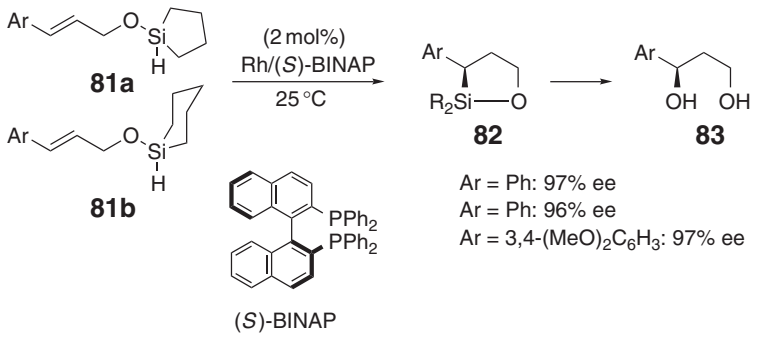




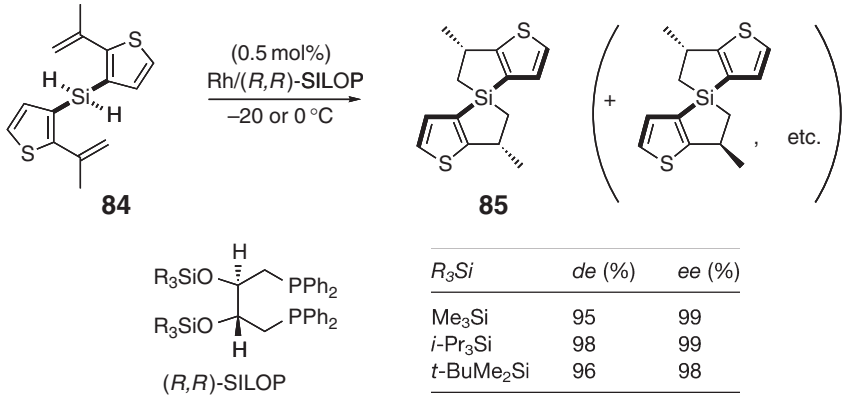
(*R,R*)-DIOP **58**

R	*syn/anti*	*ee* (%)
Me	95/5	80
Ph	99/1	83
3,5-$Me_2C_6H_3$	>99/1	93

Scheme 22



Scheme 23



R_3Si	*de* (%)	*ee* (%)
Me_3Si	95	99
i-Pr_3Si	98	99
t-$BuMe_2Si$	96	98

Scheme 24

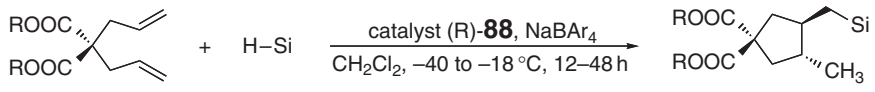
Axially chiral spirosilane **85** was efficiently prepared by double intramolecular hydrosilylation of bis(alkenyl)dihydrosilane **84**. By use of SILOP ligand, a C_2-symmetric spirosilane which is almost enantiomerically pure was obtained with high diastereoselectivity (Scheme 24).[80] SILOP ligand is much more stereoselective for this asymmetric hydrosilylation than DIOP **58** though they have similar structures.

10.18.8 Asymmetric Cyclization-Hydrosilylation

Hydrosilylation of 1,6-dienes accompanied by cyclization giving a five-membered ring system is emerging as a potential route to the synthesis of functionalized carbocycles.[81,81a,81b,82] As its asymmetric version, diallylmalonates **86** were treated with trialkylsilane in the presence of a cationic palladium catalyst **88**, which is coordinated with a chiral pyridine–oxazoline ligand. As the cyclization–hydrosilylation products, *trans*-disubstituted cyclopentanes **87** were obtained with high diastereoselectivity (>95%), whose enantioselectivity ranged between 87% and 90% (Scheme 25).[83,83a]

The catalytic cycle proposed for the cyclization–hydrosilylation with the cationic palladium catalyst is classified into the type D in Scheme 2. The reaction consists of an olefin insertion into palladium–silicon bond and the metathesis between palladium–carbon and hydrogen–silicon bond, regenerating the silylpalladium intermediate and releasing the product where migratory insertion of the pendant olefin into the alkylpalladium is involved before the metathesis (Scheme 26).[83a]

For the conversion of silyl-carbon bond in the cyclization products into hydroxy-carbon bond, several functionalized hydrosilanes were examined (Scheme 27).[84,84a,84b] Of the hydrosilanes examined, benzhydryldimethylsilane ($HSiMe_2CHPh_2$) was found to be most enantioselective in the reaction of diene **86a** to give the cyclization product **87a** with 93% ee. The second highest enantioselectivity (91% ee) was observed with hydrosiloxane $HSiMe_2OSiPh_2Bu$-*t*. The cyclization–hydrosilylation with the $HSiMe_2CHPh_2$ and catalyst **88** was very successful

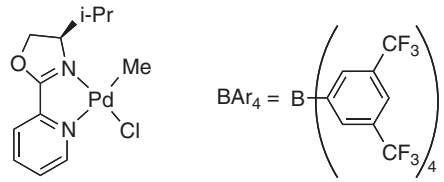


86

86a: R = Me
86b: R = *t*-Bu

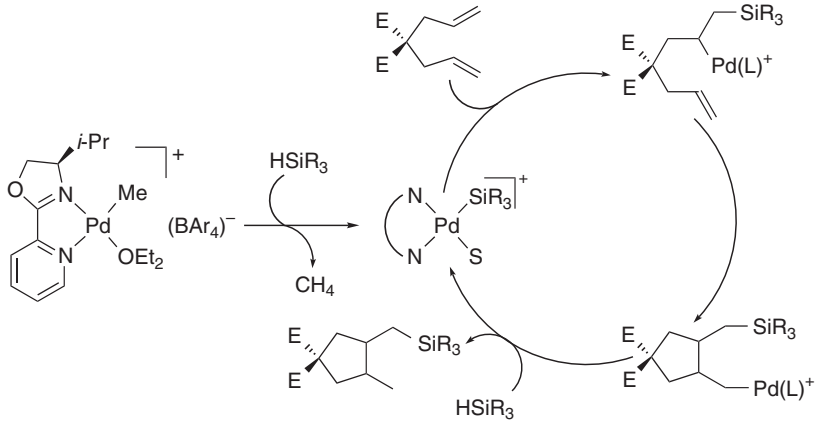
87

Diene	*Silane*	*Yield* (%)	*de* (%)	*ee* (%)
86a	$HSiMe_2t$-Bu	87	97	89
86b	$HSiMe_2Ph$	59	≥95	87
86b	$HSiEt_3$	79	≥98	90

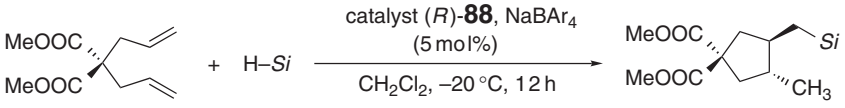


88

Scheme 25



Scheme 26

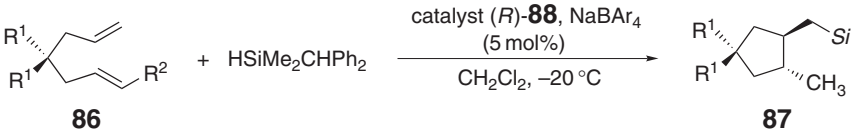


86a

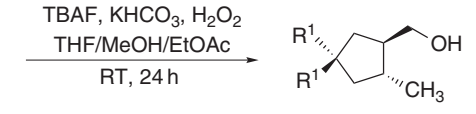
87a

Silane	*ee* (%)
$HSiMe_2OSiMe_3$	75
$HSiMe_2OSiMe_2t$-Bu	80
$HSi(i\text{-Pr})_2OSiMe_3$	87
$HSiMe_2OSi(i\text{-Pr})_3$	89
$HSiMe_2OSiPh_2t$-Bu	91
$HSiMe_2CHPh_2$	93
$HSiMe_2CH_2Ph$	86

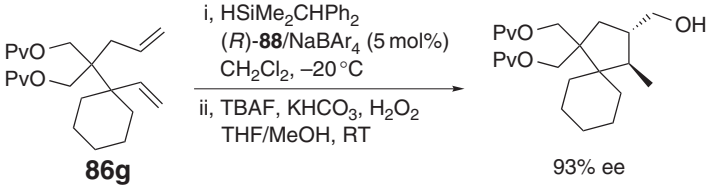
Scheme 27



86c: $R_1 = CO_2Bn$, $R^2 = H$
86d: $R_1 = CH_2OPv$, $R^2 = H$
86e: $R_1 = CH_2OBn$, $R^2 = H$
86f: $R_1 = CO_2Me$, $R^2 = Me$



Diene	*Yield silylation* (%)	*Yield oxidation* (%)	*ee* (%)
86c	87	88	94
86d	96	87	95
86e	89	73	95
86f	87	76	90



Scheme 28

for the dienes **86c–86g** (Scheme 28).[84b] The oxidation of the benzhydryldimethylsilyl group in **87** into hydroxy group proceeded in high yield by treatment with TBAF, $KHCO_3$, and 50% H_2O_2.

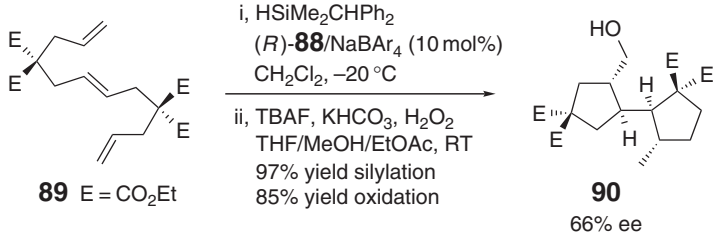
The asymmetric cascade cyclization–hydrosilylation of triene **89** under similar conditions gave bicyclopentane derivative **90** in a high yield, although the enantioselectivity was diminished (Scheme 29).[84b]

Asymmetric cyclization–hydrosilylation of 1,6-enyne **91** has been reported with a cationic rhodium catalyst of chiral bisphosphine ligand, biphemp (Scheme 30).[85] The reaction gave silylated alkylidenecyclopentanes with up to 92% ee. A mechanism involving silylrhodation of alkyne followed by insertion of alkene into the resulting alkenylrhodium bond was proposed for this cyclization.

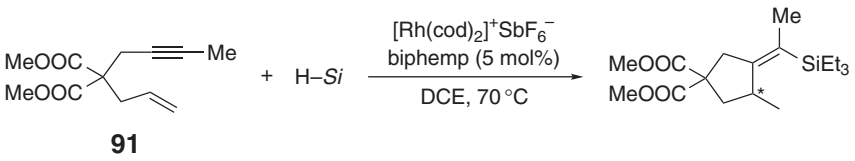
Under a pressure (20 bar) of carbon monoxide, carbonylative silylcarbocyclization of enyne **92** was examined in the presence of a cationic rhodium–BINAP catalyst (Scheme 31).[86] Although the enantioselectivity is low, the five-membered carbocycle functionalized with an alkenylsilane moiety and a formyl group was obtained with high selectivity.

The asymmetric cyclization–hydrosilylation of 1,5-dienes has been also reported by use of a chiral yttrocene complex (Scheme 32).[87] Highest enantioselectivity (50% ee) was observed for 3,3-dimethyl-1,5-hexadiene with diphenylsilane.

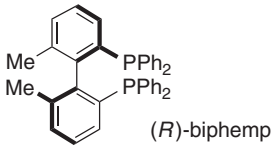
In conclusion, catalytic asymmetric hydrosilylation has been developed as one of the most efficient methods of asymmetric functionalization of carbon–carbon double bonds. The asymmetric hydrosilylation is reaching very high level in terms of both catalytic activity and enantioselectivity, and it is expected to be applied to industrial production of useful chiral molecules in the near future.



Scheme 29



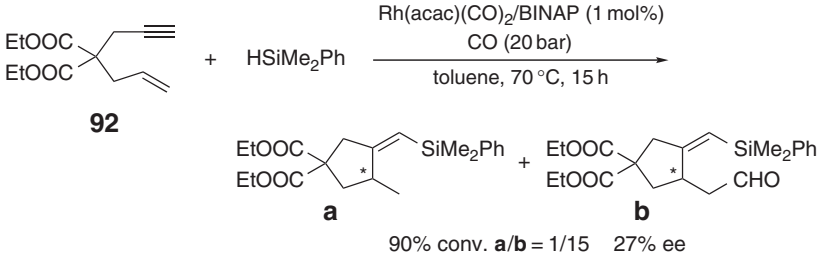
91



(*R*)-biphemp

Silane	*Yield* (%)	*ee* (%)
$HSiMeEt_2$	76	88
$HSiEt_3$	81	92

Scheme 30

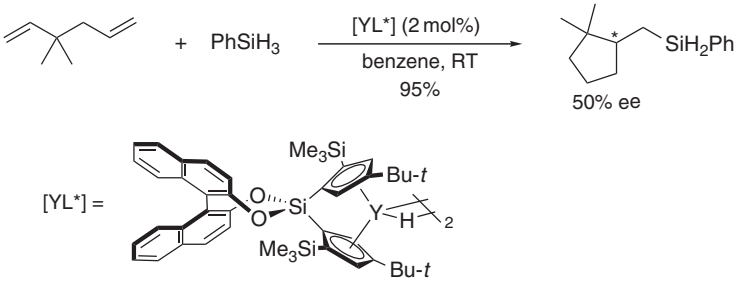


92

a **b**

90% conv. **a**/**b** = 1/15 27% ee

Scheme 31



Scheme 32

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10.19 C–E Bond Formation through Hydroboration and Hydroalumination

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10.19.1 Introduction

This chapter aims to update applications of hydroboration and hydroalumination in organic synthesis covered in both COMC(1982)[1,1a–1g] and COMC(1995),[2,2a] and we now review the literature for the period 1993–2004. Since 1993, the use of hydroboration in organic synthesis has been rapidly increasing and this is especially true of the enantioselective variant. The application of hydroaluminations in organic synthesis, while not as widely used as hydroborations, has also undergone significant development within the last decade.

This chapter has been organized into three sections. The first section deals with transition metal-catalyzed hydroboration in organic synthesis and this is divided into three subsections – mechanism, chemoselectivity, and stereoselectivity. The second section deals with the application of transition metal-catalyzed hydroalumination reactions in organic synthesis, and this is also divided into three subsections – mechanism, chemoselectivity, and stereoselectivity. The third section examines the application of both hydroborations and hydroaluminations in total synthesis.

10.19.2 Hydroboration

Hydroboration, the addition of a boron–hydrogen bond across an unsaturated moiety, was first discovered by H. C. Brown in 1956.[3] Usually, the reaction does not require a catalyst, and the borane reagent, most commonly diborane (B_2H_6) or a borane adduct (BH_3·THF), reacts rapidly at room temperature to afford, after oxidation, the *anti*-Markovnikov alkene hydration product. However, when the boron of the hydroborating agent is bonded to heteroatoms which lower the electron deficiency, as is the case in catecholborane (1,3,2-benzodioxaborole) **1** (Scheme 1), elevated temperatures are needed for hydroboration to occur.[4,5]

The development of a catalytic hydroboration process was aided by the observation of Kono and Ito in 1975 that Wilkinson's catalyst [$Rh(PPh_3)_3Cl$] **2** undergoes oxidative addition when treated with catecholborane **1** (Scheme 1).[6]

1 2 3

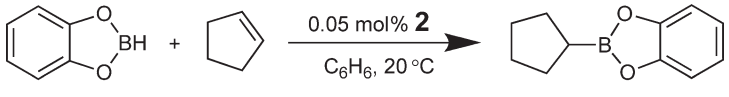
Scheme 1

Subsequently, Westcott *et al*. reported the isolation of the oxidative addition adduct with the triisopropylphosphine derivative and its characterization by X-ray crystallography.[7]

It took another decade however before the idea of developing a rhodium-catalyzed olefin hydroboration process came to fruition. This occurred in 1985 when Männig and Nöth reported the first examples of such a process.[8] They discovered that Wilkinson's catalyst **2** was effective for the addition of catecholborane **1** to a range of alkenes and alkynes, as exemplified by cyclopentene **4** (Scheme 2).

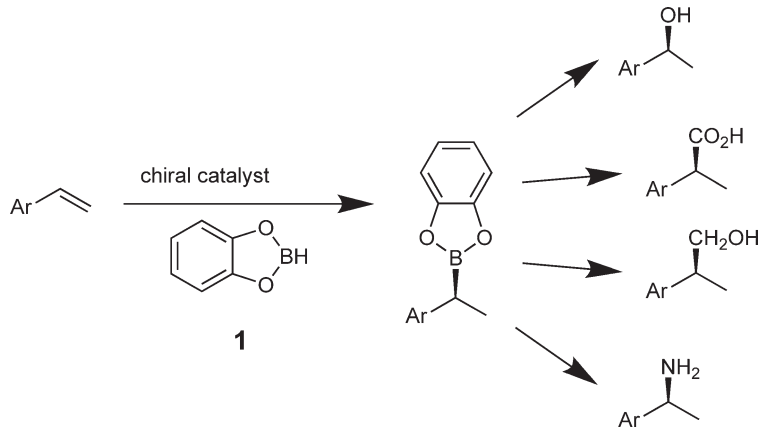
This landmark discovery paved the way for the development of transition metal-catalyzed hydroboration. The conversion of an alkene into an organoborane intermediate has made this a valuable synthetic technique, particularly since the development of enantioselective variants.[9,10] They serve as synthons for numerous functional groups[11] and are often subjected to a consecutive carbon–oxygen,[12,13] carbon–carbon,[14–21] boron–carbon,[22,23] boron–chlorine,[5] or carbon–nitrogen[24] bond-forming reaction (Scheme 3).

Attempts to expand the range of substrates to include cyclopropenes[20] and norbornene-derived meso-bicyclic hydrazines[25] have recently been reported. A further noteworthy contribution has been the development of a recyclable hydroboration process by the group of Fernández[26–28] These and other approaches toward extending the synthetic scope of catalytic asymmetric hydroboration have been the subject of recent excellent reviews.[10,29–31]



1 4 83%

Scheme 2



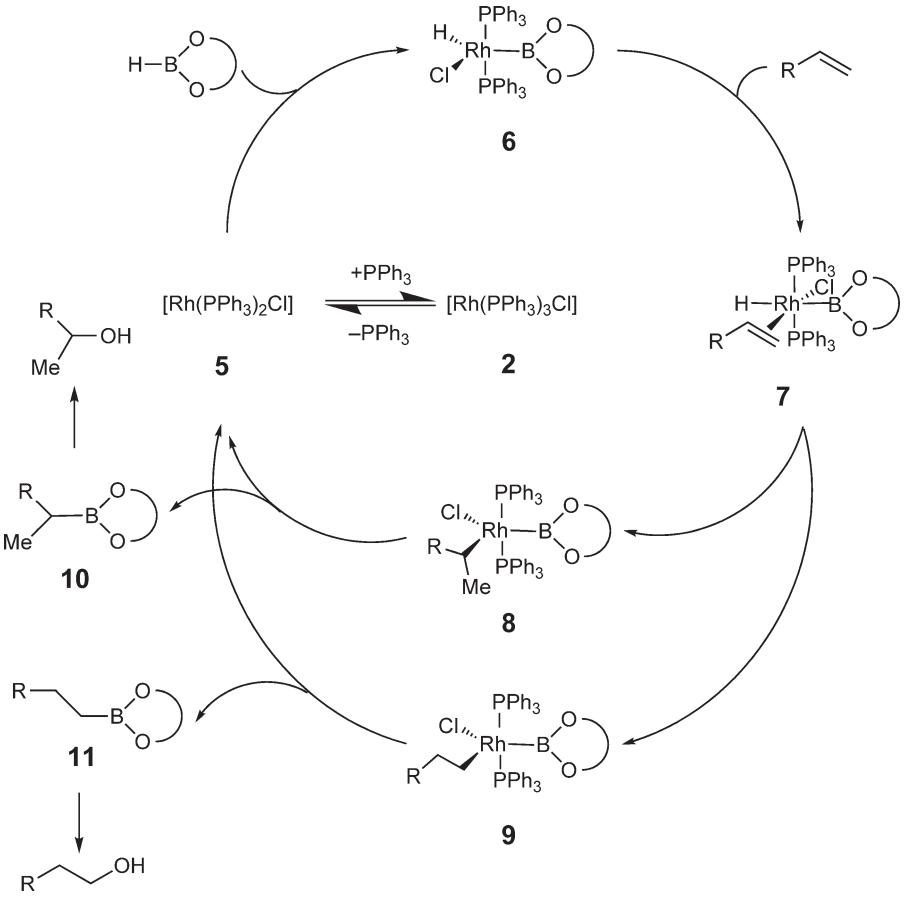
Scheme 3

10.19.2.1 Mechanism

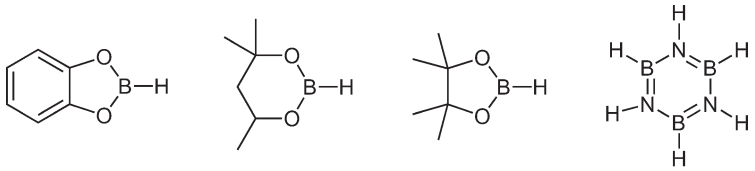
Many metals including nickel,[32,33] ruthenium,[34] iridium,[35,36] lanthanum,[37,38] titanium,[39] and zirconium[40–42] have been employed in this transformation with varying degrees of success, but rhodium has remained the metal of choice for transition metal hydroboration. The mechanism of rhodium-catalyzed hydroboration (Scheme 4), is thought to depend on the nature of the substrate, the catalyst, the ligand used and the reaction conditions employed.[43]

The dissociation of a triphenylphosphine ligand from Wilkinson's catalyst **2** generates the catalytically active species **5**, to which the B–H bond of the borane reagent oxidatively adds to give **6**. The analogous complex with $P(i\text{-Pr})_3$ rather than PPh_3 has been isolated and structurally characterized by Westcott and co-workers.[7] Coordination of the alkene *trans* to chlorine[44] generates **7**. The hydride and boryl ligands are *trans* in the reactive form of this complex.[45] Subsequent migratory insertion of the alkene into the rhodium–hydride bond produces the regioisomeric alkyl boronate esters **8** and **9**. Upon reductive elimination, these give the *anti*-Markovnikov product **10** or the Markovnikov product **11**, respectively, and the catalytic species **5** is regenerated. Supporting evidence for this last step comes from stoichiometric studies of osmium boryl complexes by Roper and Wright.[46] Theoretical studies have suggested that reductive elimination is the slowest step in the overall transformation.[45]

The original mechanism proposed by Männig and Nöth,[8] and later supported by Evans and Fu,[47] analogous to that established for the corresponding hydrogenation process, is a dissociative mechanism. After oxidative addition of the borane, coordination of the alkene (Scheme 4) takes place with simultaneous dissociation of one of the PPh_3 ligands. Burgess and co-workers favored an alternative associative mechanism[43] where the olefin and both PPh_3 ligands are bound to a six-coordinate Rh species (Scheme 4). Hydroboration has also been studied by theoretical methods.[45] In addition, the nature of the catalytic cycle has been addressed experimentally and by means of quantum chemistry methods, and this has been reviewed recently.[48] Dorigo and Schleyer[49] conducted an *ab initio* study of the



Scheme 4



1 12 13 14

Figure 1 Hydroborating agents.

dissociative mechanism and categorically excluded the possibility of an associative mechanism while Musaev and co-workers favored the latter process.[44]

The formation of vinylboranes and vinylboronate esters during some metal-promoted hydroboration of alkenes has led to the suggestion of an alternative mechanistic pathway. Insertion of the alkene into the metal–boron bond occurs in preference to insertion into the metal–hydride bond.[44,51,52] In a competing side-reaction to reductive elimination, β-H elimination from the resulting borylalkyl intermediate furnishes the vinylborane byproduct.[52] There remains however a substantial body of evidence, both experimental[53] and theoretical,[54] that supports the idea that transfer of hydride to the coordinated alkene precedes transfer of the boryl fragment.

Among efforts to elucidate the exact mechanism, Evans has proposed on the basis of deuterium labeling studies that certain steps in the catalytic cycle, namely olefin binding to the rhodium catalyst, as well as subsequent hydride migration, are reversible. However, the level of reversibility is highly substrate dependent.[47] Subsequent mechanistic investigations by Burgess,[43,55] Marder, and Baker[56] established that the catalytic cycle can be further complicated by the presence of degradation products of catecholborane, such as hydrogen and diborane for example. As a result, hydrogenation and uncatalyzed hydroboration can compete with the potentially useful selectivities of the metal-catalyzed variant.[39] Therefore, there have been considerable efforts to find alternative hydroborating agents. These include 4,4,6-trimethyl-1,3,2-dioxaborinane[8] **12** and pinacolborane[57–59] **13**, with emphasis on boron hydrides bearing boron–oxygen bonds,[60] as well as borazine[61] **14** (Figure 1). Despite these endeavors, catecholborane **1** is still the most useful borane and rhodium complexes the most useful catalysts for catalytic hydroboration.[62]

Shortly after the key mechanistic papers on rhodium-catalyzed hydroboration, Marks reported a hydroboration reaction catalyzed by lanthanide complexes that proceeds by a completely different mechanism.[63] Simple lanthanide salts such as SmI_3 were also shown to catalyze the hydroboration of a range of olefins.[64] The mechanism for this reaction was found to be complex and unknown. As in other reactions catalyzed by lanthanides, it is proposed that the entire catalytic cycle takes place without any changes in oxidation state on the central metal.

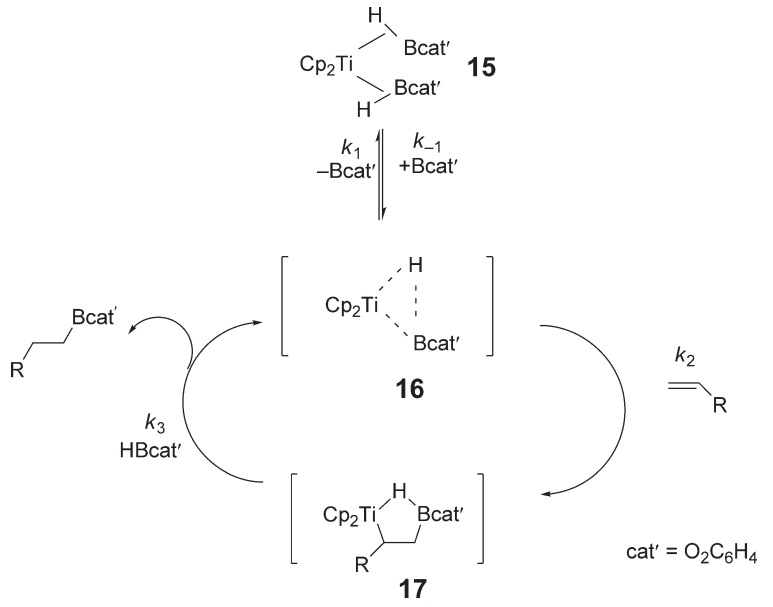
Hartwig[65] reported that dimethyltitanocene is an efficient catalyst for the hydroboration of alkenes and examined the mechanism of titanocene dicarbonyl-catalyzed the hydroboration of alkynes (Scheme 5).[66]

The mechanism involves the dissociation of the coordinated borane **15** to generate a monoborane intermediate **16**. Coordination of the alkene would generate the alkene borane complex. A β-borylalkylhydride with B–H stabilization is certainly an important resonance structure of **17**. An intramolecular reaction would extrude the alkyl boronate ester product and coordination of HBcat′ would regenerate the monoborane intermediate.

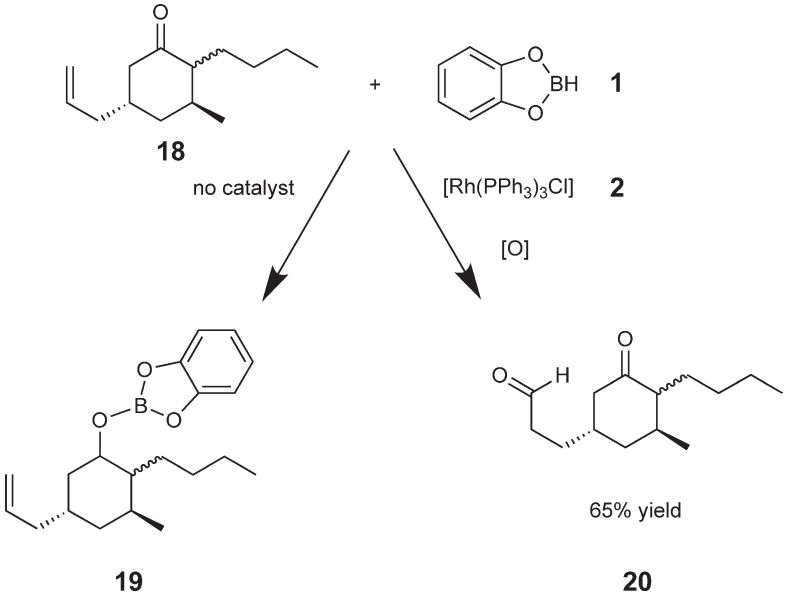
Sneddon has applied these results to the development of a process to form monoalkyldecarboranes.[67] Preliminary mechanistic investigations on the catalytic hydroboration by Cp_2TiMe_2 led to the discovery of the titanocene bis(borane) complex $Cp_2Ti(HBcat)_2$.[68]

10.19.2.2 Chemoselectivity

Männig and Nöth first demonstrated that the use of a catalyst can direct the course of the hydroboration reaction toward a different chemoselectivity than the uncatalyzed variant.[8] The functional group selectivity of hydroboration was exploited in the total synthesis of the natural product, (+)-ptilocaulin, which displays antimicrobial activity against both Gram-positive and Gram-negative bacteria as well as significant cytotoxicity toward leukemia cells.[68] In the presence of Wilkinson's catalyst **2**, the terminal olefin is preferentially hydroborated over the ketone functionality with catecholborane **1** to furnish the desired product **20** in 65% overall yield after hydrogen peroxide and PCC oxidations (Scheme 6). In the absence of catalyst, the ketone is converted to the boronate **19** leaving the olefin unreacted.



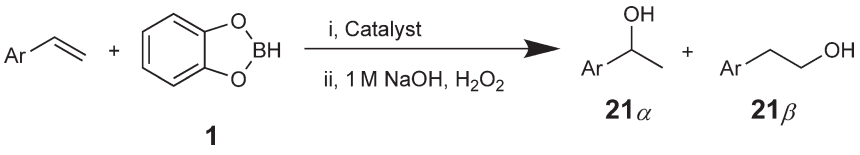
Scheme 5



Scheme 6

The uncatalyzed hydroboration–oxidation of an alkene usually affords the *anti*-Markovnikov product while the catalyzed version can be induced to produce either Markovnikov or *anti*-Markovnikov products. The regioselectivity obtained with a catalyst has been shown to depend on the ligands attached to the metal and also on the steric and electronic properties of the reacting alkene.[69] In the case of monosubstituted alkenes (except for vinylarenes), the *anti*-Markovnikov alcohol is obtained as the major product in either the presence or absence of a metal catalyst. However, the difference is that the metal-catalyzed reaction with catecholborane proceeds to completion within minutes at room temperature, while extended heating at 90 °C is required for the uncatalyzed transformation.[60] It should be noted that there is a reversal of regioselectivity from Markovnikov B–H addition in unfunctionalized terminal olefins to the *anti*-Markovnikov manner in monosubstituted perfluoroalkenes, both in the achiral and chiral versions.[70,71]

Table 1 Differences in regioselectivity between catalyzed and uncatalyzed hydroboration of vinylarenes with catecholborane



Entry	*Catalyst*	*Substrate (Ar)*	$\alpha:\beta$
1	None	Ph	8 : 92
2	$Rh(PPh_3)_3Cl$	Ph	94 : 6
3	$Rh(PPh_3)_3Cl$	4-Me–Ph	97 : 3
4	$Rh(PPh_3)_3Cl$	4-Cl–Ph	99 : 1
5	$Rh(COD)_2BF_4/PPh_3$	Ph	99 : 1
6	$Rh(COD)_2BF_4$/dppb	Ph	99 : 1
7	$Rh(COD)_2BF_4$/dppb	4-Cl–Ph	99 : 1
8	$Rh(COD)_2BF_4$/dppb	4-OMe–Ph	99 : 1
9	$Rh(COD)_2BF_4$/dppb	Mesityl	63 : 37
10	$Rh(COD)_2BF_4$/dppb	2-naphthyl	65 : 35
11	None[a]	Ph	18 : 82
12	$RhCl_3 \cdot nH_2O$[a]	Ph	17 : 83

[a]BH_3/THF as borane source.

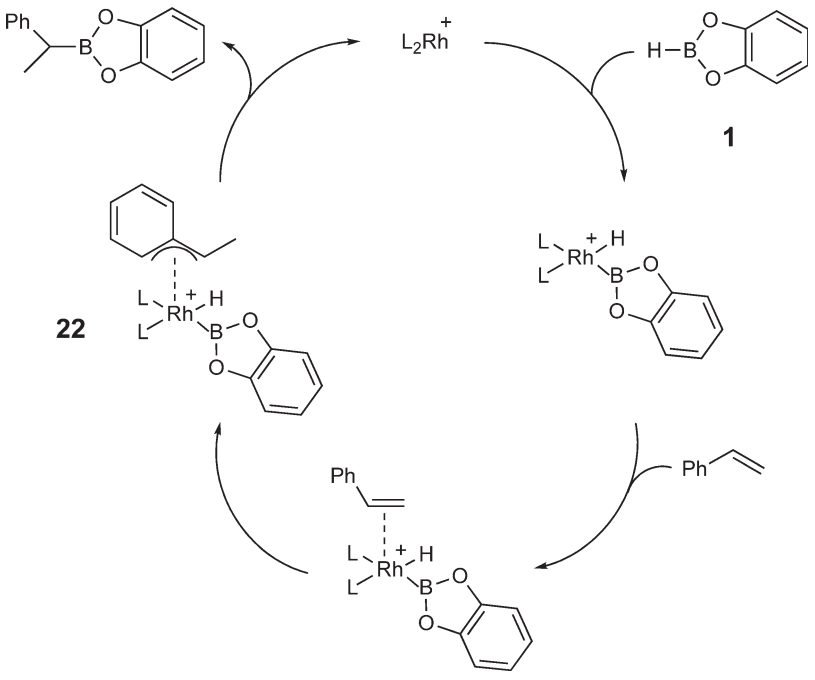
In contrast, significant differences in regioselectivity are observed between the catalyzed and uncatalyzed hydroboration of vinylarenes with catecholborane **1** (Table 1).

In the absence of a rhodium catalyst, the linear *anti*-Markovnikov or β-alcohol **21**β is formed as the major product (entry 1, Table 1).[72] However, the application of neutral or cationic rhodium complexes favored the formation of the α-alcohol **21**α, (entries 2–10), complementary to that of uncatalyzed hydroboration–oxidation. The α-alcohol **21**α was formed as the main product using Wilkinson's catalyst **2** (entries 2–4),[73] although there were inconsistencies in the literature with regard to the product distribution obtained with this catalyst system. However, this was resolved when contamination of the catalyst by oxidation was taken into account. Using cationic phosphine–rhodium(I) catalysts, Hayashi showed that the regioselectivity was relatively insensitive to the electronic effects of substitution on the aryl ring (entries 5–8) but was influenced by steric effects (entries 9–10).[12] Additionally, the choice of rhodium catalyst requires careful consideration since hydroboration with the rhodium(III) catalyst, $RhCl_3 \cdot nH_2O$, yielded the same product ratio as the uncatalyzed reaction (entries 11–12).[74]

In order to account for the high regioselectivities observed in the rhodium-catalyzed hydroboration of styrenes, Hayashi proposed a modified mechanism which proceeds through η^3-benzyl-rhodium complex **22** as a key intermediate (Scheme 7). Reductive elimination from this η^3-benzyl-rhodium complex **22** produces the secondary alkylborane regioselectively.[12] A related η^3-benzyl-palladium complex was recently isolated by Hartwig in studies of hydroamination.[75]

10.19.2.3 Stereoselectivity

The most significant growth in the last decade in the area of hydroborations has been the development of catalytic asymmetric hydroborations. The hydroboration–oxidation of substituted alkenes to give regioselectively the Markovnikov product can be used to introduce a chiral center. In fact, the vast majority of catalytic hydroborations have been applied to the formal syntheses of enantiomerically enriched alcohols by oxidation of the initial catecholborane adduct with basic hydrogen peroxide,[24] although this synthetic scope has been extended to other functionalities.[10] The attractive feature of the catecholborane hydroboration–oxidation sequence is the facile removal of the catechol byproduct by simple extraction with aqueous base. Two methods have been used to incorporate enantiodiscrimination into rhodium-catalyzed hydroboration. One such method, reported by J. M. Brown in 1990, involved the use of chiral hydroborating agents derived from ephedrine and pseudoephedrine in conjunction with an achiral catalyst.[76]



Scheme 7

However, by far the most common approach toward catalytic asymmetric hydroboration is to use a chiral catalyst and an achiral borane source. Both homobidentate *P,P* and heterobidentate *P,N* ligand classes have been employed in this transformation with varying degrees of success.

10.19.2.3.1 Chiral *P,P* ligands

The development of chiral catalysts for use in enantioselective rhodium-catalyzed hydroborations was pioneered by Burgess[9], Suzuki,[77] and Hayashi.[78] The chiral diphosphine ligands employed in their preliminary investigations **23–26** (Figures 2(a) and 2(b)), had previously been successfully applied in other catalytic asymmetric transformations.

Subsequently, Burgess[79] prepared a series of hybrid ligands (**27a–c**) (Figure 3) which were chiral not only in the carbon backbone like (*R, R*)-DIOP **25** but also at phosphorus, like DIPAMP.

The best result with these ligands was in the hydroboration–oxidation of norbornene which gave *exo*-norborneol with 84% ee. In general, modest enantioselectivities were observed and this was believed to be due to puckering of the seven-membered metal chelates away from ideal C_2-conformations. Evidence for this deviation from ideal C_2-symmetric behavior came from X-ray crystallographic analysis of molybdenum-*tetra*-carbonyl complexes. Extending the range of hydroboration–oxidation substrates to include indene and styrene gave 1-indanol and 1-phenylethanol, respectively, with the same sense of asymmetric induction irrespective of the chirality at phosphorus, showing that it was the chirality of the carbon backbone that controlled the asymmetry of the reaction (Table 2).[79] There was no correlation in these experiments between the chirality at phosphorus and that at carbon, and any attempts to produce "matched" and "mismatched" catalysts were not successful.

As a greater understanding has emerged of the control factors at play in enantioselective rhodium-catalyzed hydroborations, an increased number of novel chiral diphosphine ligands have been reported in the chemical literature (Figure 3), the majority of these within the last five years.

Of greater success were Knochel's C_2-symmetric diphosphine ligands **28–34** (Figure 4) that proved highly successful when employed in the hydroboration of styrene and substituted styrenes.[80] The corresponding 1-arylethanols was furnished with excellent regioselectivity (>99 : 1) and variable enantioselectivity after oxidation (Table 3).

The diphosphines **29–31** induced low asymmetries (8–15% ee) irrespective of the reaction conditions. The more electron-rich ligand (*R, R*)-**32** gave (*R*)-1-phenylethanol with a much-improved 65% ee (entry 1). Conversely, the application of the more electron-poor diphosphine (*R, R*)-**33** resulted in the (*S*)-enantiomer, but with the same level of enantioselection (entry 2), highlighting the importance of the electron density of the phosphorus center on the

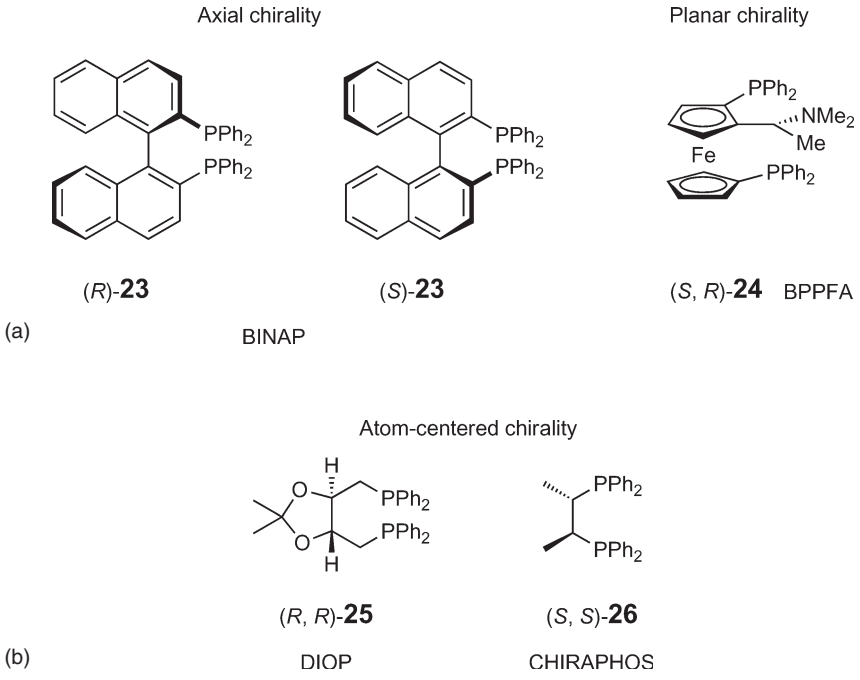


Figure 2 Chiral diphosphine ligands for asymmetric hydroboration.

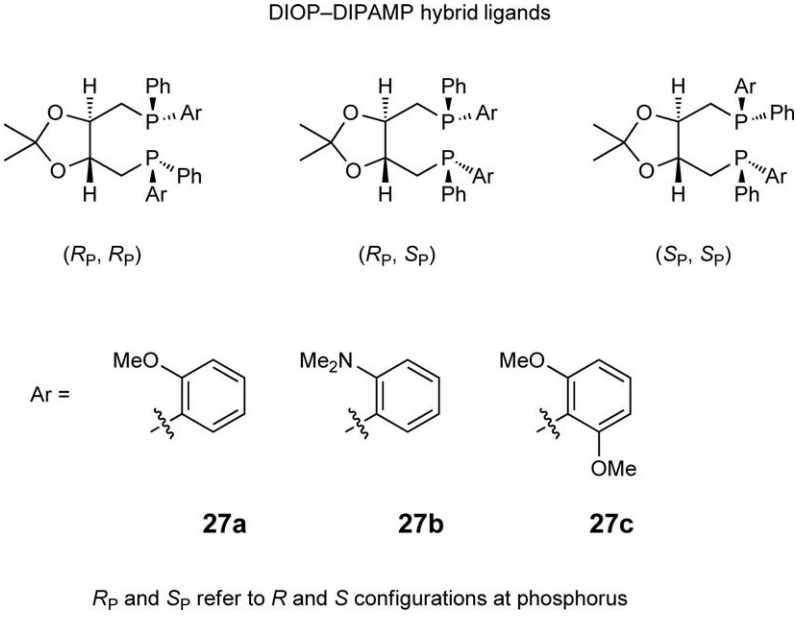


Figure 3 Chiral DIOP ligands for asymmetric hydroboration.

sense of asymmetric induction. Optimum results with styrene were achieved with the most electron-rich diphosphine (*R*, *R*)-**34**, (entry 3). With DME as solvent for 3 h at −35 °C, (*S*)-1-phenylethanol was afforded with 92% ee and near-complete regioselectivity (>99 : 1). No reaction occurred at lower temperatures while increasing the temperature resulted in both lower regio- and enantioselectivities. Under these optimum conditions, a number of *para*- and

Table 2 Hydroboration of norbornene, indene, and styrene using catecholborane

	exo-*norborneol*[a]		1-*indanol*[a]		1-*phenylethanol*[b]	
Ligand	*% ee*	*(Config.)*	*% ee*	*(Config.)*	*% ee*	*(Config.)*
(*R*, *R*)-**25**	60	1*R*	74	*S*	48	*R*
(S_P, S_P)-**27a**	84	1*R*	49	*S*	13	*R*
(R_P, S_P)-**27a**	80	1*R*	77	*S*	19	*R*
(R_P, R_P)-**27a**	60	1*R*	54	*S*	~0	*R*

[a]Typical conditions: catecholborane **1**, THF, −25 °C, 0.5 mol% 2Ligand·$[Rh(COD)Cl_2]_2$.
[b]Catalyst is 1.0 mol% $[Rh(COD)Ligand_2]BF_4$, prepared *in situ*.

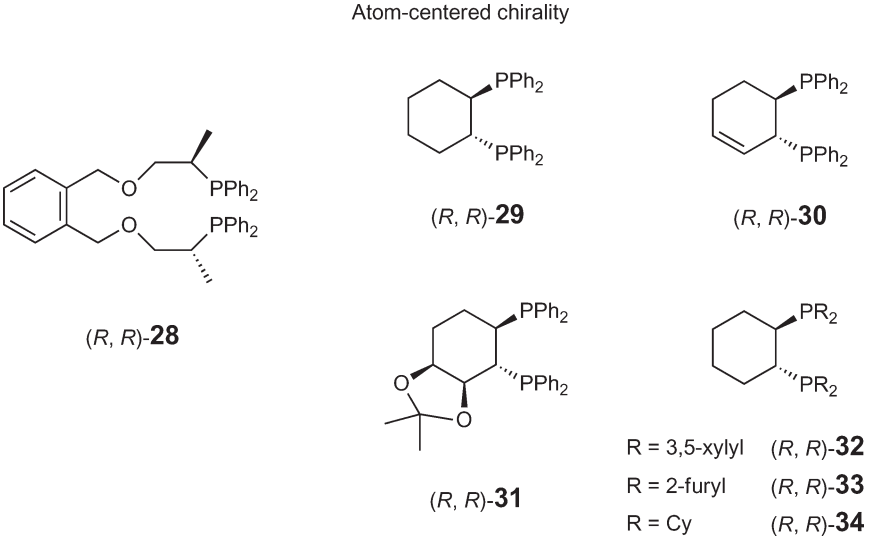


Figure 4 Chiral diphosphine ligands for hydroboration.

Table 3 Hydroboration of styrene and substituted styrene using ligands **32–34**

Entry	*Substituents*	*Ligand*	*Solvent*	*Temp.* (°C)	*% ee (Config.)*
1	R_1, R_2 = H	(*R*, *R*)-**32**	Et_2O/CH_2Cl_2[b]	−60	65 (*R*)
2	R_1, R_2 = H	(*R*, *R*)-**33**	Et_2O/CH_2Cl_2[b]	−60	65 (*S*)
3	R_1, R_2 = H	(*R*, *R*)-**34**	DME	−35	92 (*S*)
4	R_1 = H, R_2 = F	(*R*, *R*)-**34**	DME	−35	93 (*S*)
5	R_1 = H, R_2 = OMe	(*R*, *R*)-**34**	DME	−35	93 (*S*)
6	R_1 = Me, R_2 = H	(*R*, *R*)-**34**	DME	−35	91 (*S*)

[a]Regioselectivity (α/β) > 99/1 in all cases.
[b]Et_2O/CH_2Cl_2 = 4/1.

meta-substituted styrene derivatives were hydroborated with good to excellent quantitative conversion (62–100%), excellent regioselectivity (>97 : 3), and good to excellent enantioselectivity (up to 93% ee) (entries 4–6). Overall, the best result with ligand (*R*, *R*)-**34** was 93% ee and 100% conversion for the regioselective (>99 : 1) hydroboration of *para*-fluorostyrene. Using chiral diphosphine (*R*, *R*)-**33**, and a DME/toluene solvent system (3 / 2), a number of *ortho*-substituted styrene derivatives were hydroborated with relatively high levels of asymmetric induction (77–82% ee), similar regioselectivities, and surprisingly high conversions (complete conversion after 1 h at −75 °C). On the whole, rhodium complexes of these ligands are among the most efficient catalyst systems for the hydroboration of styrene derivatives.

Although the vast majority of centrally chiral diphosphine ligands to be employed in enantioselective rhodium-catalyzed hydroborations possess C_2-symmetry, there are a few examples of C_1-symmetric diphosphine ligands. Buono prepared bis(aminophosphine) ligands **35–38**,[81] while Bianchini reported (*R*, *R*)-BDPBzP **39** (Figure 5).[82]

Ligands **35–38** were applied in the hydroboration–oxidation of norbornene with catecholborane **1** (Table 4).[81] In all cases, *exo*-norborneol **40** was formed as the major product. As expected, decreasing the reaction temperature increased the enantioselectivity (entries 1 vs. 3, 7 vs. 8). Like Burgess, Buono found that the phosphine-to-rhodium ratio was a critical factor in the reaction. Increasing the amount of ligand led to an increase in ee (entries 2–4). Manipulation of the steric properties of (*R*, *R*)-**35** by increasing the steric hindrance on the amino-bound phenyl group did not improve the level of asymmetry induced; in fact, ee's were lower (entries 5 and 6). However, tuning of the electronic properties of the donor phosphorus by substitution of a phenyl ring for a cyclohexyl group simultaneously resulted in both an optimum 86% yield and 77% ee with ligand (*R*, *R*)-**38** (entry 8). Interestingly, it was with

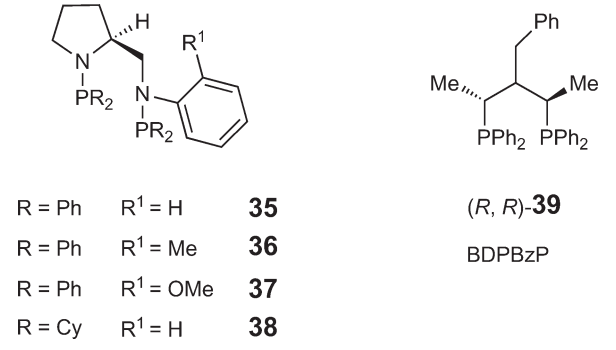
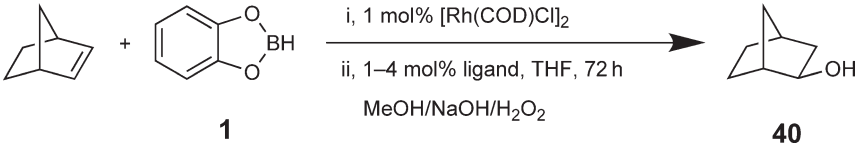


Figure 5 Phosphoramidite and phosphine ligands for hydroboration.

Table 4 Hydroboration of norbornene using phosphoramidite ligands **35–38**



1 **40**

Entry	*Ligand* (mol. %)	*Temp.* (°C)	*Yield* (%)	*% ee*
1[a]	(*R*, *R*)-**35** (2)	25	58	12
2	(*R*, *R*)-**35** (1)	−78	60	37
3	(*R*, *R*)-**35** (2)	−78	61	63
4	(*R*, *R*)-**35** (4)	−78	64	72
5	(*R*, *R*)-**36** (4)	−78	62	65
6	(*R*, *R*)-**37** (4)	−78	57	60
7[a]	(*R*, *R*)-**38** (4)	25	60	31
8	(*R*, *R*)-**38** (4)	−78	86	77

[a]Reaction time = 24 h.

the cyclohexyl-substituted diphosphine ligand (*R, R*)-**34** that Knochel also achieved the highest levels of asymmetric induction.[80]

Application of these ligands to the hydroboration–oxidation of styrene proceeded with moderate yields and much lower enantioselectivities than for norbornene. The best result was with (*R, R*)-**38**, which afforded (*S*)-1-phenylethanol in 61% yield and 42% ee. However, Bianchini's (*R, R*)-BDPBzP **39** was even less efficient for this substrate, and gave both poor yields (29%) and poor enantioselectivities (26% ee) for the hydroboration of styrene at 0 °C.[84]

The third major class of diphosphine ligands employed in catalytic asymmetric hydroboration are those possessing planar chirality (Figure 6). These ligands are chiral by virtue of the non-symmetrical disubstitution of one of the cyclopentadienyl rings.

Togni prepared the ferrocenyldiphosphine Josiphos **41**.[85] A catalyst (2 mol%) prepared *in situ* from $[Rh(NBD)_2]BF_4$ and (*R, S*)-**41** was applied to the hydroboration–oxidation of styrene with catecholborane **1**. With DME as the solvent for 10 h at −78 °C, (*R*)-1-phenylethanol was afforded in 65% yield, 92% ee, and near-perfect regioselectivity (>99 : 1), compared to 60% ee at room temperature. Unfortunately, styrene was the only substrate which reacted at low temperature. The hydroboration of more sterically demanding substrates such as indene necessitated room temperature conditions to attain complete conversion within a reasonable time. Using the same catalyst (1 mol%), (*R*)-1-indanol was formed with 42% ee after oxidation, albeit in good yield (70%). While the hydroboration–oxidation of norbornene furnished (*R*)-*exo*-norborneol **40** with complete regioselectivity, the asymmetry induced was very poor (7% ee). It was postulated that the reduced activity of Josiphos **41** in hydroborations compared to other chiral bis(diphenylphosphino) ligands reported was due to an increased basicity of the phosphine **41** compared to other ligands,[85] supporting the rationale behind Jendralla's synthesis of electron-poor biphenyl.[86]

While Josiphos **41** also possessed an element of atom-centered chirality in the side chain, Reetz reported a new class of ferrocene-derived diphosphines which had planar chirality only: ligands **42** and **43**, which have C_2- and C_1-symmetry, respectively.[87] Rhodium(I)-complexes of ligands (−)-**42** and (−)-**43** were used *in situ* as catalysts (0.75 mol%) for the hydroboration of styrene with catecholborane **1** for 12 h in toluene at −50 °C. The rhodium/C_1-symmetric (−)-**43** catalyst system was the more enantioselective of the two – (*S*)-1-phenylethanol was afforded with 52% and 77% ee with diphosphines (−)-**42** and (−)-**43**, respectively. In both cases, the regioselectivity was excellent (>99 : 1). With the same reaction time but using DME as solvent at lower temperature (−60 °C), the rhodium complex of **43** afforded the alcohol product with an optimum 84% ee.

Kang and co-workers prepared FerroPHOS ligands **44–47** (Figure 6) which are intriguingly described as possessing "cylindrical chirality" (defined as the chirality originating from the C_2-symmetricity of two identical planar chiralities).[88] The steric and electronic properties of these ligands were explored by changing the substituent in the *pseudo*-

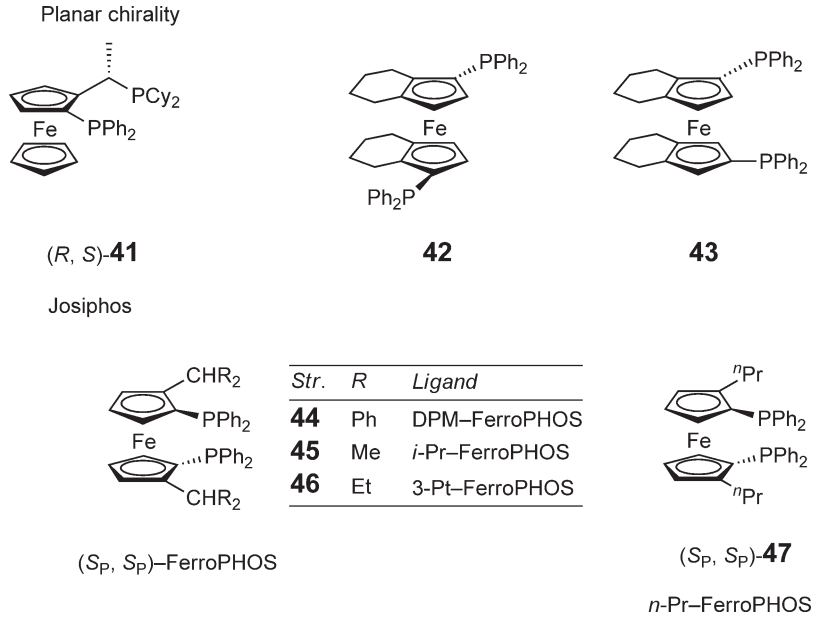


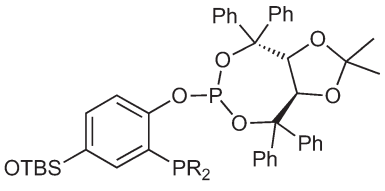
Figure 6 Planar chiral diphospine ligands for hydroboration.

benzylic position. These highly air-stable ferrocenyl diphosphines were employed in asymmetric hydroborations of styrene and indene using 2 mol% of a catalyst prepared *in situ* from the respective ligand and $Rh(COD)_2BF_4$. DPM–FerroPHOS **44** gave the best result: 85% ee, greater than 99% regioselectivity, and complete conversion for the hydroboration of styrene in DME for 11 h at −78 °C. For the hydroboration of indene, 3-Pt–FerroPHOS **46** afforded 1-indanol with an optimum 42% ee and 85% yield in THF at room temperature. In general, however, decreasing the steric bulk of the side chain in ligands **45–47** resulted in lower asymmetric induction (23–77% ee) and reduced activity (15–85%) for both substrates. Not surprisingly therefore, the least efficient ligand was *n*-Pr–FerroPHOS **47** which possessed the least sterically demanding side chain, the linear *n*-propyl group. This diphosphine showed no enantioselectivity whatsoever for the hydroboration of indene and a sluggish 15% conversion after 11 h for styrene (23% ee).[88]

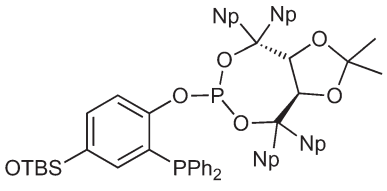
All the chelating bidentate *P,P* ligands presented thus far are chiral diphosphines. However, TADDOL-derived phosphine–phosphite ligands also represent an important subclass of *P,P* ligands. Among these are ligands **48–53** (Figure 7) identified by screening a modular 20-component ligand library. (Ligand screening found that, in general, TADDOL-derived ligands had superior activity to those derived from other chiral diols or amino alcohols.)[89]

Schmalz and co-workers tested these ligands in the rhodium-catalyzed hydroboration of styrene with catecholborane **1** (Table 5).[90] Small variations of the ligand framework led to significant and unpredictable differences in the performance of the rhodium complexes (2 mol%) generated *in situ* from $Rh(COD)_2BF_4$ and the respective ligand. For example, changing the diphenylphosphine group of ligand **48** to a bulkier, more electron-rich dicyclohexylphosphine in ligand **49**, gave rise to comparable catalytic activity, but lowered and opposite asymmetric induction (entries 1 and 2). Tuning of the other phosphorus donor atom by exchanging the phenyl-TADDOL-derived phosphite **48** with the corresponding 2-naphthyl-TADDOL-derived **50** resulted in enhanced enantioselectivity (87% ee), but significantly attenuated catalytic activity (24% yield), perhaps due to steric crowding (entry 3).

Variation of the aromatic backbone of the ligand from hydroquinone-derivatives **48–50** to the 1,5-naphthalenediol-analogs **51–53** produced all-round better performances. This was postulated to be due to stronger pre-organization arising from steric interaction between the proton in the 8-position of **51** and the phosphite core.[90] Ligand **51** gave the best overall result in terms of yield (97%) and enantioselectivity (88% ee) (entry 4). Removal of the *tert*-butyldimethylsilyl-protected alcohol to give phosphite **52** led to a lower 63% yield but slightly enhanced 91% ee



48: R = Ph
49: R = Cy



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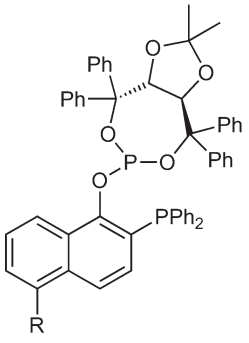
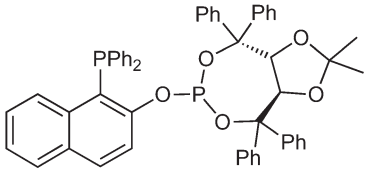


51: R = OTBS
52: R = H



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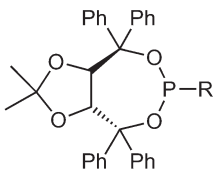
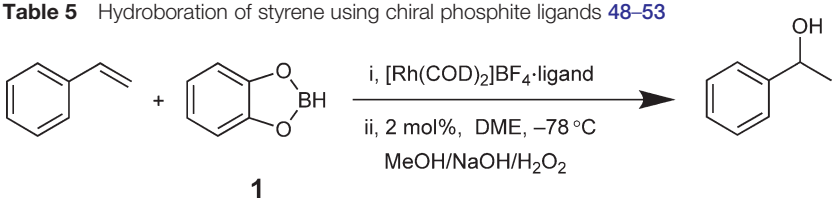


54: R = Me
55: R = Ph

Figure 7 Chiral diphosphine ligands for asymmetric hydroboration.

Table 5 Hydroboration of styrene using chiral phosphite ligands **48–53**



1

Entry	*Ligand*	*Time* (h)	*Yield* (%)[a]	*% ee (Config.)*
1	**48**	2.5	98	81 (*R*)
2	**49**	2.5	92	49 (*S*)
3	**50**	2.5	24	87 (*R*)
4	**51**	3.5	97	88 (*R*)
5	**52**	3.5	63	91 (*R*)
6	**53**	3.5	7[b]	61 (*R*)

[a]Regioselectivity (α/β) > 94/6 in all cases with the exception of entry 6.
[b]Regioselectivity (α/β) 85/15.

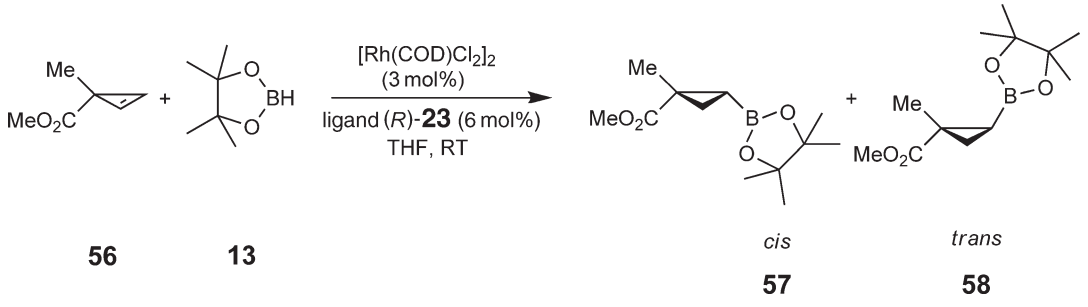
(entry 5). However, exchanging the positions of the phosphine and phosphite on the naphthalene backbone in **51** to afford the regioisomeric **53** had a significantly more deleterious effect on the selectivity (61% ee) and, in particular, the catalytic activity of this system (7% yield) (entry 6) highlighting the sensitivity of this reaction to subtle changes in ligand structure.

Finally, the group of Seebach has applied "monodentate" TADDOL-derived cyclic phosphonites **54** and **55** (Figure 7) to the hydroboration–oxidation of styrene in DME at 0 °C.[91] The methyl-phosphonite **54** regioselectively afforded (*R*)-1-phenylethanol in 64% yield and 26% ee, while the phenyl analog **55** gave the alcohol in an excellent 95% yield but with even lower – and opposite – asymmetric induction (16% (*S*)). These results illustrate that while monodentate phosphorus(III) derivatives may indeed form highly catalytically active complexes with transition metals such as rhodium, in general asymmetric hydroboration is far more effective with bidentate ligands.

More recent work employing diphosphine ligands has focused on both new substrates for hydroboration and also new hydroborating agents. Specifically, Gevorgyan has successfully employed cyclopropenes **56** as substrates, with pinacolboranes **13** as the borane source.[20] Impressive enantioselectivities were obtained with a range of diphosphines, for example, with rhodium complexes of NORPHOS (>99% ee), PHANEPHOS (97% ee), BINAP (94% ee), and Tol–BINAP (96% ee), all with near perfect *cis*-selectivity (see Scheme 8).

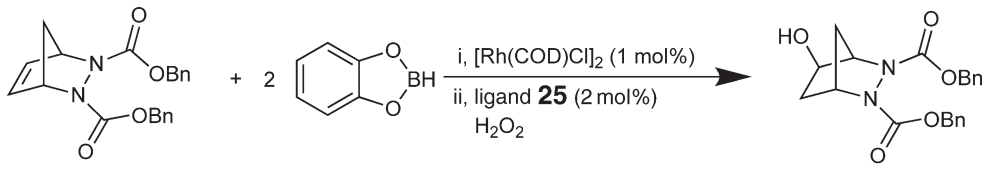
Micouin investigated rhodium-catalyzed hydroboration as a means of desymmetrizing meso hydrazines **59** in an important new application.[36] Enantiomeric excess of up to 84% was obtained after screening diphosphines such as DIOP and BDPP (Scheme 9). Interestingly, they noted an unprecedented reversal of enantioselectivity by changing from rhodium to iridium.

Nonetheless, among bidentate diphosphines and with the notable exception of BINAP **23**, there have been only sporadic examples of ligands whose rhodium complexes give enantioselectivities above 85% in hydroboration: Knochel's dicyclohexylphosphine **34**,[80] Togni's Josiphos **41**,[85] and TADDOL derivatives **48**, **50–52**.[90] Even



56 **13** **57** **58**

Scheme 8



59 **1**

Scheme 9

BINAP **23** is only effective at −78 °C. Not surprisingly, research groups began to look beyond the realm of chiral *P,P* ligands for catalytic asymmetric hydroboration and a parallel interest in the application of chiral heterobidentate chelates was generated. The phosphinamine ligand class has received the most attention. These ligands, as well as having the potential to induce asymmetry through steric factors, can also generate electronic asymmetry on the metal center due to the combination of hard and soft donor atoms and the different reactivity associated with each.[92,93]

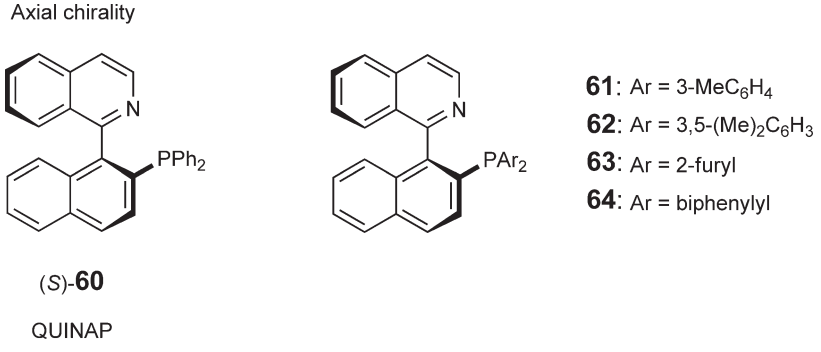
10.19.2.3.2 Chiral *P,N* ligands

The first successful axially chiral phosphinamine ligand in asymmetric catalysis was QUINAP **60** (Figure 8) reported by Brown in 1993 and the original synthesis has since been modified.[94] The donor nitrogen atom is incorporated in an isoquinoline unit to form a six-membered chelate ring.

Brown and co-workers tested cationic rhodium(I) complexes of QUINAP **60** in the enantioselective hydroboration–oxidation of vinylarenes,[95] which proceeded with excellent regioselectivities, in most of the cases >95%. QUINAP **60** is amenable to structural variation at several points. Among these are the aryl groups on phosphorus which were systematically varied to examine the effect on the efficiency and enantiodifferentiating ability of the ligand. Thus the analogs **61–64** (Figure 8) were prepared and resolved in a similar manner to QUINAP **60**.[96] Their rhodium complexes were subsequently applied in hydroboration–oxidation of vinylarenes. The key finding from this study was that the parent diphenylphosphino ligand QUINAP **60** gave superior results for electron-rich vinylarenes, whereas by making the donor phosphorus atom less electron rich, as in the difurylphosphino ligand **63**, superior results for electron-poor vinylarenes were obtained.

It became apparent during a mechanistic investigation of the allylic alkylation process with QUINAP **60**, involving both solution ^{1}H NMR and solid-state studies, that the 3-H of the isoquinoline unit takes up a position in the space near the metal that leads to critical ligand-reactant steric interactions thought to be significant for asymmetric induction.[97] This finding led to the design by Brown of the vaulted analog PHENAP **65** (Figure 9), where the donor nitrogen atom is part of a phenanthridine unit.

PHENAP **65** was prepared and resolved[98] in a similar manner to QUINAP **60** and tested in asymmetric rhodium-catalyzed hydroboration–oxidations.[99] Impressive enantioselectivities were obtained and the sterically demanding cyclic substrates were hydroborated with 64–84% ee. Compared to the corresponding results obtained with diphosphine ligands, it is clear that QUINAP **60**, and structural relatives **61–64** and PHENAP **65**, give superior results in the asymmetric rhodium-catalyzed hydroboration of several vinylarenes, and are essentially the only practical solution for β-substituted alkenes.[100] The reasons for this are not well understood, but thought to be due to the particular



(*S*)-**60**

QUINAP

Figure 8 Axially chiral *P,N* ligands for hydroboration.

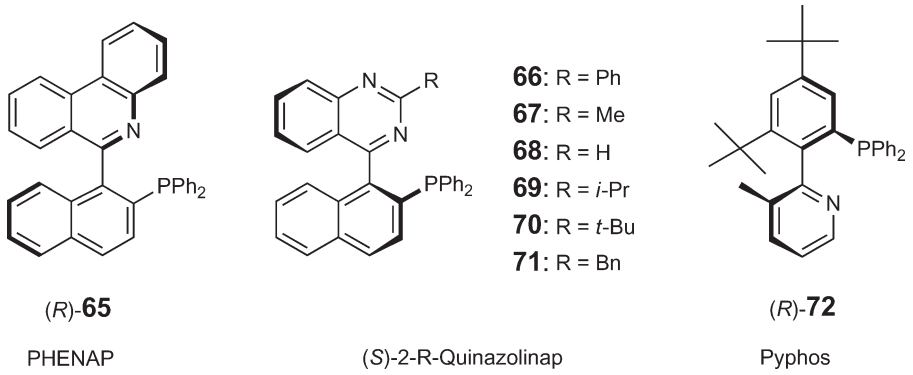


Figure 9 Axially chiral *P,N* ligands for hydroboration.

geometry of the *P,N* chelate which can accommodate the steric demand of substituents in the region of the alkene double bond. For QUINAP complexes the *P,N* chelate is a pronounced boat, and there is reduced steric demand in the region of space around the isoquinoline nitrogen, certainly when compared to the aryl residues of BINAP **23**.[95] This structural difference, coupled with the intrinsic electronic features of the *P,N* ligand, explain why the asymmetric induction is higher with chiral QUINAP **60** than with chiral BINAP **23**.[95]

The lack of characterization of reactive intermediates is a hindrance to further progress on understanding the mechanism, but recent reports from the groups of Brown and Fernandez are steps in the right direction.[100–102] In particular, Brown has identified binuclear reactive intermediates by NMR when the hydroboration pre-catalyst was examined in the presence of catecholborane at low temperatures. Fernandez has reported a theoretical study of model systems from spectroscopically postulated rhodium–BINAP and rhodium–QUINAP intermediates in the catalytic cycle, concluding that the origin of regio- and enantioselectivity in hydroboration reactions of vinylarenes is related to the coordination step of the alkene instead of the migratory insertion.

In a new departure in the quest for QUINAP-type ligands with an electron-deficient phosphorus atom, a novel QUINAP-derived triarylphosphite ligand **73** (Figure 10) was developed by Brown 10 years after the parent ligand **60** was first reported.[100]

Ligand **73** was prepared directly from a single enantiomer of the corresponding naphthol of QUINAP **60**, an early intermediate in the original synthesis, and both enantiomers of BINOL. Application in hydroboration found that, in practice, only one of the cationic rhodium complexes of the diastereomeric pair proved effective, (a*S, S*)-**73**. While (a*S, S*)-**73** gave 68% ee for the hydroboration of styrene (70% yield), the diastereomer (a*S, R*)-**73** afforded the product alcohol after oxidation with an attenuated 2% ee (55% yield) and the same trend was apparent in the hydroboration of electron-poor vinylarenes. Indeed, even with (a*S, S*)-**73**, the asymmetries induced were very modest (31–51% ee). The hydroboration pre-catalyst was examined in the presence of catecholborane **1** at low temperatures and binuclear reactive intermediates were identified. However, when similar experiments were conducted with QUINAP **60**, no intermediates of the same structural type were found.[100]

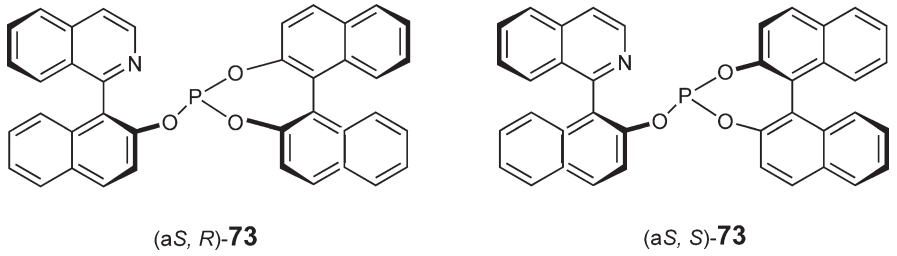


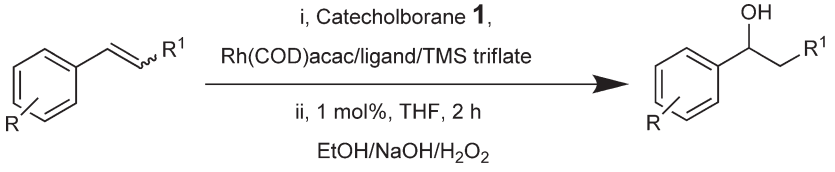
Figure 10 QUINAP-BINOL hybrid ligands.

A series of axially chiral two-substituted quinazoline-containing phosphinamine ligands, the "quinazolinaps," **66–71** (Figure 9) has been prepared and resolved by Guiry and his group.[103–106] The naphthalene–quinazoline pivot was chosen as it would be inert to racemization.[104] In light of the mechanistic observations on related ligand systems, the 2-position of the quinazoline (equivalent to the 3-position of QUINAP **60**) is believed to be important for asymmetric induction. Therefore, it was of interest to vary the substituent at the 2-position in an effort to investigate the effect of steric demand on the degree of enantioselection observed. Of interest also was the reduced basicity of the quinazolinap donor nitrogen relative to QUINAP **60** (the pK_a values of simpler heteroaromatics related to **60** and **66** are 5.1 and 3.3, respectively).[104] It was hoped that variation of this electronic desymmetrization, coupled with steric properties, would aid further understanding of the enantioselection process.

Cationic rhodium complexes of these ligands were prepared and applied in the enantioselective hydroboration–oxidation of a range of vinylarenes,[106,107] carefully chosen to highlight the effect on reactivity and enantioselectivity of different aryl substituents and β-substitution. Like QUINAP **60** and PHENAP **65**, the (*S*)-ligand gave rise to the (*S*)-secondary alcohol.

The two-substituted-Quinazolinap-derived rhodium complexes proved extremely efficient catalysts for the hydroboration–oxidation of vinylarenes (Table 6). For styrene derivatives, in most cases quantitative conversions were obtained after just 2 h at the relevant temperature (entries 1–6). Higher enantioselectivities were afforded with a 4-methoxy substituent (up to 95% ee, entry 3) compared to the 4-chloro or unsubstituted styrene analogs (entries 5 and 1), a trend also observed in hydroboration with rhodium complexes of QUINAP **60**. This highlights that both the electronic nature of the substrate combined with the inherent steric properties of the catalyst are important for high asymmetric induction. It is noteworthy that in most cases, optimum enantioselectivities were afforded by the

Table 6 Hydroboration of substituted styrene using Quinazolinap ligands **66–71**



	A	B	C	D	E	F	G
R	H	4-MeO	4-Cl	H	4-MeO	3,4-$(MeO)_2$	H
R^1	H	H	H	Me	Me	Me	Ph

H Indene
I Dihydronaphthalene

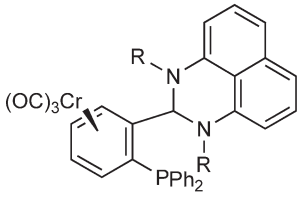
Entry	*Ligand (R group)*	*Vinylarene*	*Temp.* (°C)	*Conv.* (%)	$\alpha:\beta$	*% ee (Config.)*
1	(*S*)-**67** (Me)	**A**	20	100	88:12	90 (*S*)
2	(*S*)-**71** (Bn)	**A**	0	100	84:16	87 (*S*)
3	(*S*)-**67** (Me)	**B**	20	99	88:12	95 (*S*)
4	(*S*)-**67** (Me)	**B**	0	97	70:30	91 (*S*)
5	(*S*)-**68** (H)	**C**	20	100	83:17	81 (*S*)
6	(*S*)-**68** (H)	**C**	0	100	75:25	64 (*S*)
7	(*S*)-**67** (Me)	(*E*)-**D**	0	96	94:6	95 (*S*)
8	(*S*)-**66** (Ph)	(*E*)-**D**	20	100	91:9	94 (*S*)
9	(*S*)-**67** (Me)	(*Z*)-**D**	0	100	99:1	97 (*S*)
10	(*S*)-**69** (*i*-Pr)	(*Z*)-**D**	20	100	96:4	96 (*S*)
11	(*S*)-**67** (Me)	(*E*)-**E**	0	89	88:12	97 (*S*)
12	(*S*)-**69** (*i*-Pr)	(*E*)-**E**	20	51	77:23	93 (*S*)
13	(*S*)-**67** (Me)	(*E*)-**F**	0	75	92:8	98 (*S*)
14	(*S*)-**67** (Me)	(*E*)-**G**	20	50	na	87 (*S*)
15	(*S*)-**69** (*i*-Pr)	(*Z*)-**G**	20	84	na	99 (*S*)
16	(*S*)-**67** (Me)	(*Z*)-**G**	20	96	na	97 (*S*)
17	(*R*)-**70** (*t*-Bu)	(*Z*)-**G**	0	80	na	97 (*R*)
18	(*S*)-**68** (H)	**H**	0	39	97:3	98 (*S*)
19	(*S*)-**67** (Me)	**H**	20	100	>99:1	99.5 (*S*)
20	(*S*)-**67** (Me)	**I**	0	90	>99:1	93 (*S*)

less sterically demanding 2-methyl **62** and two-unsubstituted analogs **68**, although the steric bulk of the 2-benzyl ligand **71** proved most effective for the hydroboration of styrene at 0 °C (entry 2). In the quinazolinap series as a whole, it was found that an electron-releasing substituent, as in *p*-methoxysytrene, had an adverse effect on regioselectivity compared to styrene and *p*-chlorostyrene.[106] In general, decreasing the reaction temperature had a deleterious effect on the regio- and enantioselectivity of the hydroboration. In contrast, low temperatures (−78 °C) were necessary to obtain high enantioselectivities for these substrates with BINAP **23**. While the asymmetry observed with this modular quinazolinap series **66–71** is comparable, if not superior, to other atropisomeric systems applied, they are limited in terms of regiochemical control.

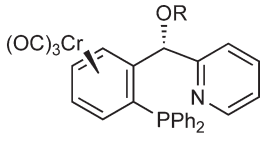
Chan and Kwong have reported the synthesis and resolution of the atropisomeric ligand pyphos **72** (Figure 9).[108,109] With the incorporation of the donor nitrogen atom in a pyridine moiety, an attractive feature of this system was the possibility of recycling the catalyst via phase separation (extraction of the ligand from the reaction mixture with hydrochloric acid). (*R*)-pyphos **72** was applied in the enantioselective hydroboration of *para*-substituted vinylarenes and regioselectivities were excellent (>98 : 2 to 99 : 1) regardless of the substituent.[110] However, the reaction is only effective at low temperatures in contrast to other *P,N* ligands such as quinap and the quinazolinaps which induce high degrees of asymmetry, even at room temperature. Although the dihedral angle of (*R*)-pyphos **72** (87°) is much larger than that of QUINAP **60**, PHENAP **65**, or the quinazolinaps **66–71**, (65–67°) comparable asymmetries were induced. However, as in rhodium-catalyzed hydroboration with these ligands, the enantioselectivity was dependent on the electronic properties of the *para*-substituent. The ee's ranged from 79% for 4-chlorostyrene, 40–94% for 4-methoxystyrene, with 90% ee for the hydroboration of styrene. It was postulated that if the vinylarene always coordinates *trans* to nitrogen,[111] then for an electron-rich substrate, there is tighter coordination to cationic rhodium than for electron-poor analogs. Hence, the electron-rich substrate is more strongly influenced by the chiral environment, which gives rise to enhanced enantioselectivity.[110]

Chung and co-workers have developed a novel class of planar chiral (1,2-disubstituted arene)chromium tricarbonyl compounds which are amenable to facile steric and electronic tuning (Figure 11). Ligands **74** and **75**, which have a diamine and a phosphorous group in the two *ortho*-benzylic positions, act as bi- and not tridentate ligands, as determined by X-ray crystallography, and form a six-membered chelate ring.[112] Another modular series within this *P,N* class are ligands **76–79** which have an additional element of atom-centered chirality. The donor nitrogen is incorporated in a pyridine ring and thus gives rise to a seven-membered chelate.[113]

Rhodium complexes of these ligands were applied to the enantioselective hydroboration of styrenes.[112,113] Regioselectivities were excellent, regardless of the electronic nature of the substituent on the styrene. Ligands **74** and **78** were the best within each series. Ligand **74** induced moderate enantioselectivities (19–81% ee) at −15 °C. As the electron-donating ability of the *para*-substituent increases (Br < H < OMe), the ee increases simultaneously (19% < 53% < 62%), a trend observed with QUINAP **60** and related *P,N* systems which also afforded higher ee's for more electron-rich substrates. Curiously, the (superior) asymmetry induced by ligand **78** was not at all sensitive to the electronic effect of the substituent on the styrene ring. Enantiomeric excesses of 82% and 84% were afforded for 4-methoxy- and 4-bromostyrene, respectively. The highest ee for both ligands was in the hydroboration of 2,4-dimethylstyrene: 81% and 86% ee for ligands **74** and **78**, respectively, where steric effects were the likely dominant factor.



74: R = H
75: R = Me



76: R = H
77: R = Me
78: R = Bn
79: R = 4-MeOC$_6$H$_4$

Figure 11 Planar chiral *P,N* ligands for hydroboration.

The application of the diphosphine Josiphos **41** to the asymmetric hydroboration–oxidation of styrene afforded 92% ee and excellent regioselectivity (>99 : 1), but this ligand was only effective at −78 °C, and only for this substrate.[85] By way of nucleophilic substitution with a pyrazole functionality at the *pseudo*-benzylic phosphine, Togni prepared a series of pyrazole-containing ferrocenyl ligands (Figure 12). These planar chiral ligands also possess an element of atom-centered chirality in the *pseudo*-benzylic position of the side chain. The simple synthetic approach allows for the preparation of a wide variety of analogs with easy modification of their stereoelectronic properties.

Rhodium complexes (1 mol%) prepared *in situ* from $[Rh(COD)_2]BF_4$ and the respective ligands **80–83** were employed in the enantioselective hydroboration–oxidation of styrene (Table 7).[114–117]

In contrast to the application of Josiphos **41** to the same transformation, these phosphinamine ligands were highly effective at ambient temperature. Ligand **80**, containing the 3,5-dimethylpyrazolyl fragment, afforded an excellent 95% ee for the hydroboration of styrene (entry 1). However, the ligands are limited in terms of regiochemical control (entries 1 and 2). Increasing the size of the pyrazole substituent from methyl to isopropyl resulted in a slightly lower 92% ee,[114] showing there was some dependence of the enantioselectivity on the steric properties of the ligand. However, the single most dominant influence was the electronic nature of the ligand. The different electronic properties of the pyrazole and phosphine moieties exert opposite influences and high asymmetries when the combination exists such that nitrogen is a good σ-donor (electron-rich pyrazole) and phosphorus is a good π-acceptor (electron-poor phosphorus).

To this end, while essentially conserving the steric bulk, replacement of the pyrazole methyl groups in **80** with the electron-withdrawing trifluoromethyl groups in **81** gave rise to a dramatic decrease in enantioselectivity, although the regioselectivity was largely unaffected (entry 2). However, when the CF_3 groups were placed on the phosphine instead in ligand **82**, thereby rendering the phosphine electron deficient, an exceptional 98.5% ee was obtained

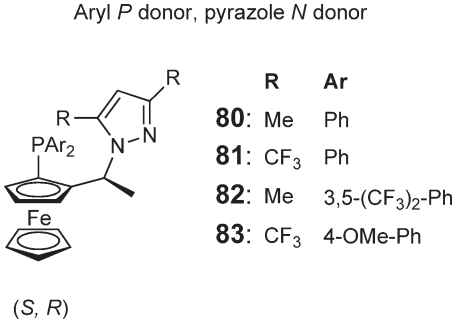
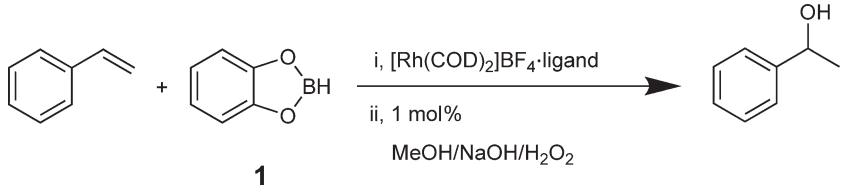


Figure 12 Planar chiral pyrazole containing *P,N* ligands.

Table 7 Hydroboration of styrene using pyrazole containing ferrocenyl ligands **80–83**

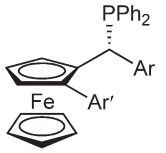


1

Entry[a]	*Ligand*	*Yield (%)*[a]	*α : β*	*% ee (Config.)*
1	(*S, R*)-**80**	91	66 : 34	95 (*R*)
2	(*S, R*)-**81**	78	61 : 39	33 (*R*)
3	(*R, S*)-**82**	63	[b]	98.5 (*S*)
4	(*R, S*)-**83**	28	[b]	5 (*S*)

[a]Typical conditions: catecholborane **1**, 1.0 mol% $[Rh(COD)_2]BF_4$·Ligand, THF, 20 °C, 3–5 h.
[b]Not quoted.

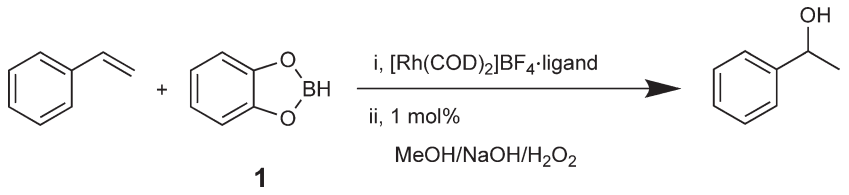
Aryl *P* donor, pyridine-type *N* donor



Ar′	Ar *Phenyl*	*o-Tolyl*	3,5-*Xylyl*
2-Pyrimidyl	**84**	**85**	**86**
2-Pyridyl	**87**	**88**	**89**
2-Quinolyl	**90**	**91**	**92**

Figure 13 Aryl *P* donor type ligands.

Table 8 Hydroboration of styrene using ferrocene type ligands



1

Entry[a]	*Ligand*	*Time* (h)	*Conv.* (%)[a]	$\alpha:\beta$	% *ee*
1	**84**	19	74	97 : 3	57[b]
2	**88**	14	54	84 : 16	80
3	**90**	16	>99	64 : 36	92

[a]Typical conditions: catecholborane **1**, THF, −45 °C, 1.0 mol% $[Rh(COD)_2]BF_4$·2Ligand.
[b]Absolute configuration (*S*) in all cases.

(entry 3). This remains the best result reported yet for the hydroboration of styrene. In a striking illustration of the interplay of electronic effects and enantioselectivity, the combination of an electron-poor pyrazole and an electron-rich phosphine as in ligand **83** only afforded 5% ee (entry 4). The possibility that the low enantioselectivities in the case of electron-poor pyrazole ligands **81** and **83** were due to partial dissociation of the ligand from rhodium during catalysis was found to be unlikely, and the pronounced effects on enantioselectivity therefore deemed largely electronic in nature.[114]

In terms of chiral ligands that incorporate both planar and atom-centered chirality, the ferrocenyl framework is unrivaled in its versatility. Moreover, the synthetic approach toward this ligand class allows for tailoring of the ligand through steric and electronic effects. The latter was in evidence in the electronic asymmetry of Togni's *P,N* ligands **80–83**. Recently, the group of Knochel has reported a set of nine new chiral ferrocenyl phosphinamine ligands **84–92** (Figure 13). These ligands were tested in the rhodium-catalyzed asymmetric hydroboration–oxidation of styrene **38**, and representative results are shown in Table 8.[117]

Ligands **84–86** with a pyrimidyl group showed excellent regioselectivity but only moderate conversion and enantioselectivity (entry 1). In contrast, rhodium complexes of ligands **90–92** bearing a quinolyl group were highly efficient catalysts, inducing excellent enantioselectivity but at the expense of the regioselectivity (entry 3). The performance of the 2-pyridyl-ligands **87–89** lay in between these two extremes (entry 2). Optimal results were obtained with ligand **90** which gave 92% ee and almost quantitative conversion for the hydroboration of styrene, although with modest regioselectivity (entry 3).

10.19.3 Hydroalumination

Among the hydrometallations reported to date, hydroboration and hydrosilylation have been the most widely investigated while hydroalumination has received less attention. The resulting organoalanes from hydroalumination are often more reactive than the organoboranes or organosilanes. While the first metal-catalyzed hydroalumination

was reported in the 1950s, the first synthetically useful enantioselective hydroalumination was described in 1995, and the synthetic utility of this reaction is just emerging.[118,119]

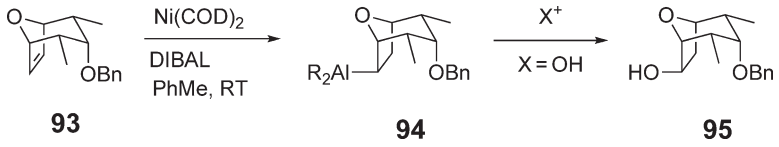
10.19.3.1 Mechanism

The mechanism of the hydroalumination is not well understood. The first mechanism proposed was by Ziegler, who suggested that some colloidal nickel species was catalyzing a displacement between an olefin and a trialkylalane.[120] Wilke suggested that the metal acted as a template to help pre-organize the olefin and the alkylaluminum, leading to an exchange reaction involving a six-membered transition state.[121] They provided evidence by showing that triethylaluminum undergoes rapid exchange with perdeuterated ethylene in the presence of tris(ethylene)nickel to generate a deuterated triethylaluminum at temperatures as low as −50 °C. In 1990, Porschke determined the crystal structure of a cyclododecatrienenickel(0)–dimethylaluminum hydride–quinuclidine complex, in which the hydride seems to bridge the nickel and aluminum with a weak nickel–aluminum bond present.[122] The uncertainty over the mechanism complicates the understanding of this reaction.

Lautens and Chiu[123] reported a reductive ring opening of oxabicyclo[*n*.2.1]alkenes **93** using DIBAL in the presence of bis(cyclooctadiene)nickel to give the racemic cycloalkanols (Scheme 10).

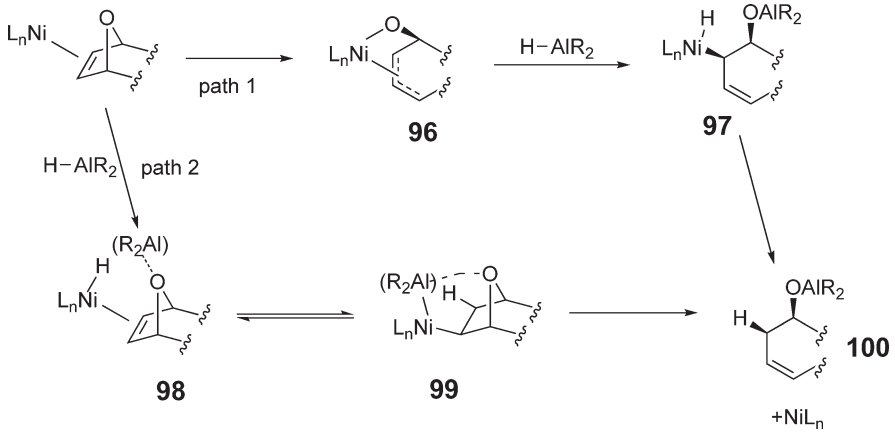
The mechanism for this nickel-catalyzed enantioselective hydroalumination was initially thought to proceed via a nickel-catalyzed hydroalumination followed by the elimination of the organoaluminum with cleavage of the oxygen bridge. However, this seems unlikely in the light of recent evidence (Scheme 11).

It is difficult to draw detailed conclusions on the location of the aluminum throughout the course of the reaction given the uncertainties associated with the first step of the reaction, namely the interaction between the aluminum hydride and nickel species. Two possible mechanisms are outlined in Scheme 11. Insertion into the allylic C–O bond to form a π-allylic nickel alkoxide is followed by reduction of the carbon–nickel bond (path 1) **96**, **97**. An alternative pathway (path 2) involves the hydronickellation of the complexed olefin followed by a β-elimination of the oxygen bridge **99**. The evidence against path 1 is that a single regioisomer is observed in all reactions with all class of substrates, which might not be expected if a π-allyl nickel was formed.



93 **94** **95**

Scheme 10



96 **97** **98** **99** **100**

Scheme 11

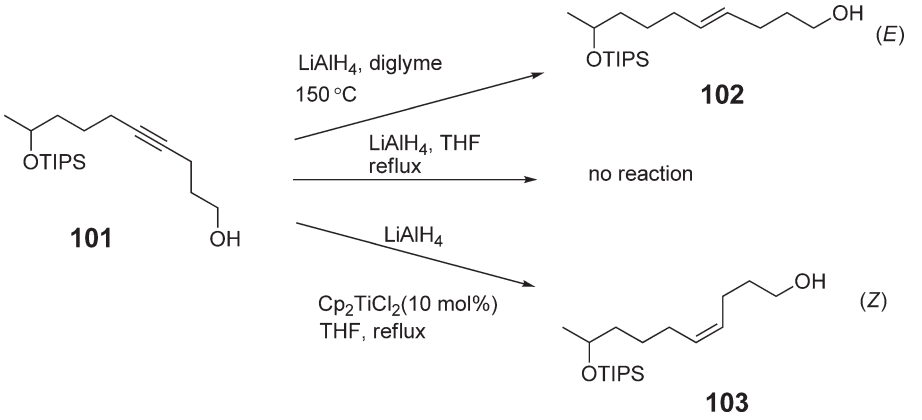
10.19.3.2 Chemoselectivity

Campagne examined the reduction of alkynols with $LiAlH_4$. In the uncatalyzed reaction, the (*E*)-alkenols **102** were obtained (Scheme 12).[124] When the reaction was carried out in refluxing THF, no reaction was observed. On using 10 mol% of the Cp_2TiCl_2 in refluxing THF, alcohol **103** was obtained in 52% yield, but surprisingly the isomeric (*Z*)-double bond was obtained in contrast to the uncatalyzed reaction.

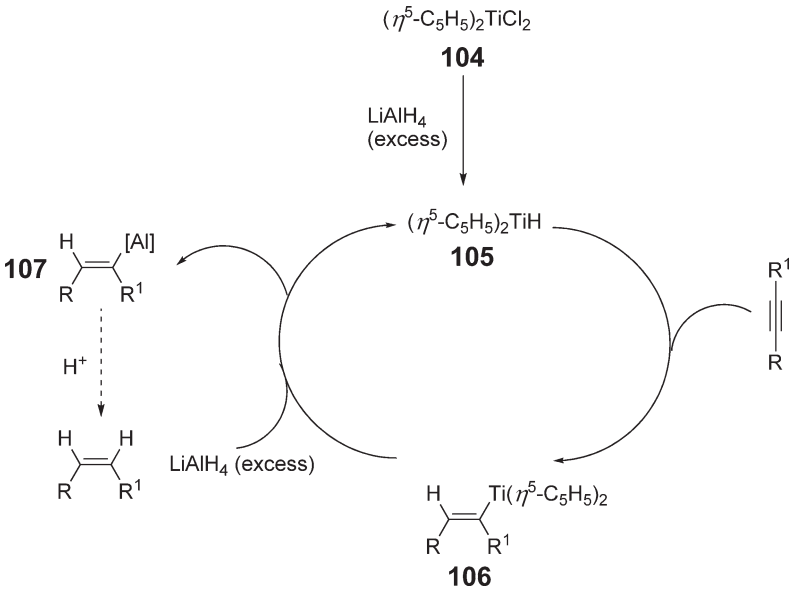
Mechanistically, the pre-catalyst Cp_2TiCl_2 **104** is reduced to a [Ti]–H **105** species which is subsequently able to hydrotitanate the triple bond **106**. A transmetallation from titanium to aluminum regenerated the [Ti]–H species to generate the (*syn*)-hydroaluminated compound **107** (Scheme 13).

Negishi reported the hydrogen transfer hydroalumination of alkenes with $(i\text{-Bu})_3Al$(TIBA) and catalytic amounts of palladium and other late transition metal complexes.[125] Although uncatalyzed hydroaluminations of alkenes with di- and trialkylalanes at elevated temperatures have long been known, their scope and limitations as well as their synthetic utility have not been extensively explored.

Negishi previously reported that a wide variety of Lewis-acidic compounds catalyzed hydrozirconation of alkenes such as 1-decene **108** with $i\text{-BuZrCp}_2Cl$.[126] It was found that the reaction of 1-decene with 1.1 molar equiv. of TIBA, in the presence of 2–5 mol% of chlorine-containing late transition metals, led to the formation of 1-iododecane **110** after treatment of the product with iodine (Table 9).



Scheme 12

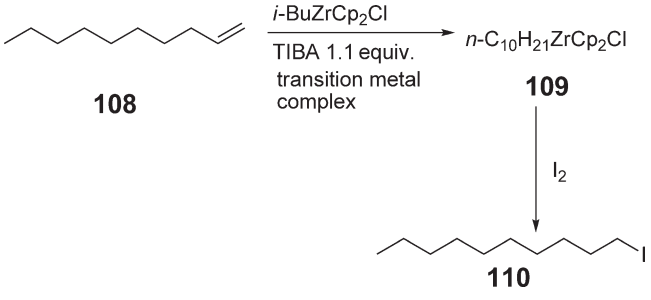


Scheme 13

The best results were obtained with palladium and platinum. The use of $Pd(OAc)_2$ in place of $Cl_2Pd(PPh_3)_2$ led to no reaction, with >90% of 1-decene remaining. This may be attributed to the absence of chloride and it is possible that bimetallic activation involving a aluminum–chloride–palladium bond is important.[127] Another finding was the use of palladium(0) complexes such as $Pd(PPh_3)_4$ or strongly reducing hydride sources such as DIBAL and $LiAlH_4$. These can readily convert palladium(II) complexes to palladium(0) complexes in place of TIBA, and this induces hydroalumination to a minor extent (<25% yield).

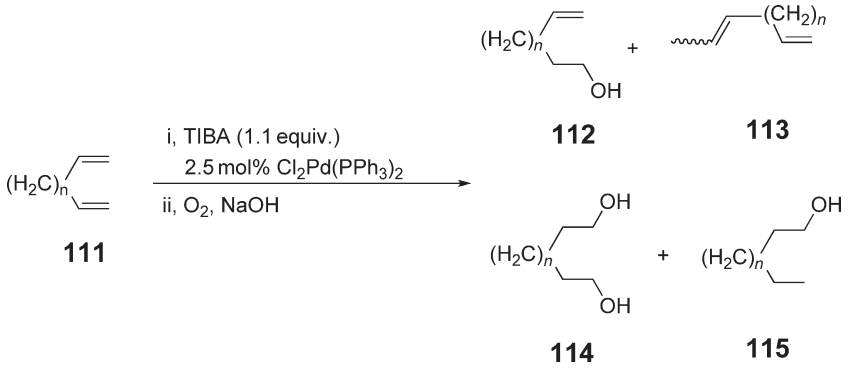
The hydroalumination of α,ω-dienes with TIBA catalyzed by $Cl_2Pd(PPh_3)_2$ was studied.[125] 1,5-Hexadiene undergoes a hydrometallation-cyclic carbometallation tandem process to give cyclopentylcarbinylalane which upon oxidation is converted to cyclopentylmethanol. However, with longer α,ω-dienes, no cyclic carbometallation has been observed. Instead, the reaction gives the expected mono- and dihydroaluminated products **112** and **114** (Table 10). The double bond-migrated **113** and fully saturated mono-aluminated **115** products are formed in varying yields.

Table 9 Hydroalumination of 1-decene using zirconium cyclopentadienyl complex



Entry	*Transition metal complex*	*Yield* (%)
1	$Cl_2Pd(PPh_3)_2$	90
2	Li_2PdCl_4	86
3	K_2PtCl_4	86
4	$Cl_2Ni(PPh_3)_2$	65
5	$ClCo(PPh_3)_3$	76
6	$ClRh(PPh_3)_3$	79

Table 10 Hydroalumination of α,ω-diene catalyzed by palladium



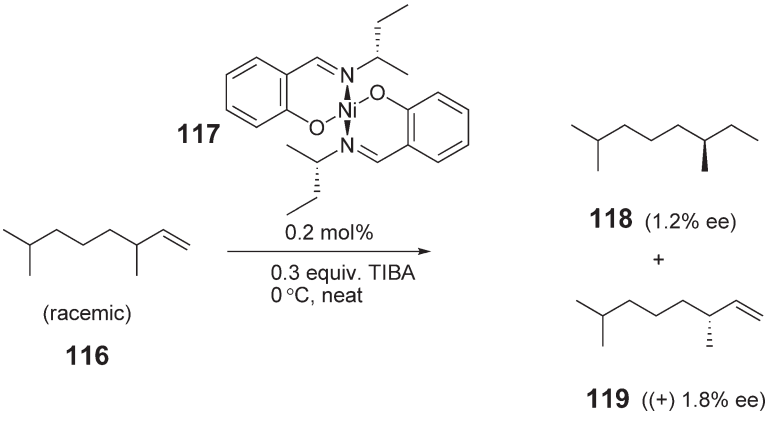
		Yield (%)					
Entry	*n of diene*	**112**	**113**	**112 + 113**	**114**	**115**	**114 + 115**
1	3	32	12	44	10	22	32
2	5	12	24	36	14	25	39
3	10	0	26	26	19	54	73

The results suggest that once hydroalumination has occurred at one end of the diene, the course of the reaction at the other double bond is significantly affected by the alkylaluminum group, possibly due to chelation in which a palladium–chloride–aluminum bond is thought to be important.

10.19.3.3 Stereoselectivity

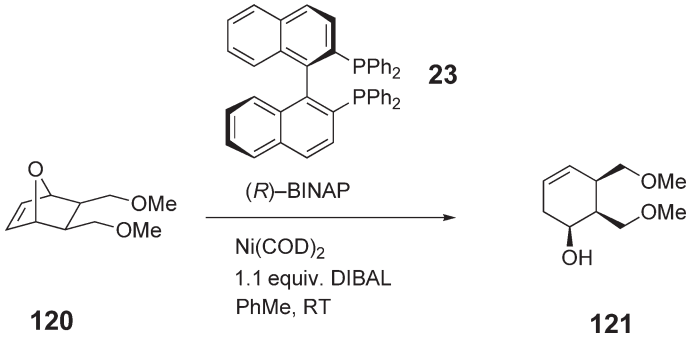
Early attempts at an asymmetric hydroalumination utilized a chiral *sec*-butylsalicylidenime complexed to a nickel(II) complex **117**.[128] When racemic 3,7-dimethyl-1-octene **116** was treated with 0.2 mol% of the nickel complex **117** and 0.3 equiv. of TIBA at 0 °C, followed by hydrolysis, the alkene **118** with 1.2% ee was obtained. The unreacted olefin **119** was recovered and found to have an ee of 1.8% (Scheme 14).

It was not until 1995 that a synthetically useful enantioselective hydroalumination was first described.[123] The early attempts to develop enantioselective hydroalumination used chiral phosphines such as prophos, chiraphos **26**, and BINAP **23** as ligands. The most successful of these was BINAP with ee's of 56% being obtained (entry 1, Table 11).



Scheme 14

Table 11 Hydroalumination of oxanorbornadienes using BINAP



Entry	*Ni(COD)$_2$* mol%	*(R)–BINAP* mol%	*Time*[a]	*ee* (%)
1	14	21	< 1 min	56
2	14	21	7 min	82
3	14	21	1 h	97
4	7	10.5	2 h	92
5	7	9	2 h	87
6	4	6	8 h	92

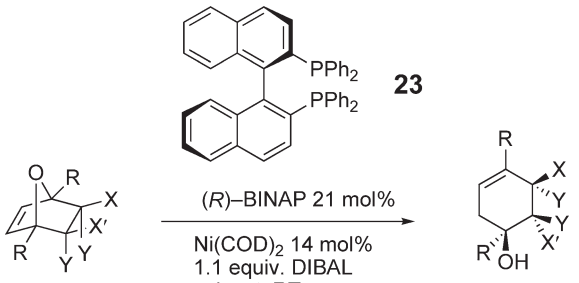
[a]Addition time of DIBAL.

Lautens and Rovis showed that the rate of addition of the reducing agent DIBAL had a significant effect on the reactions. Fast addition of the DIBAL (<1 min) gave the cyclohexenol **121** with 56% ee (entry 1, Table 11). On increasing the addition time to 7 min this raised the ee to 82% (entry 2, Table 11). The optimal addition time was found to be 1 h which gave the cyclohexenol **121** with 97% ee (entry 3, Table 11). It was possible to reduce the amount of catalyst to 1–2 mol%.

The conditions for the reaction were sufficiently mild so that a broad range of substituents was tolerated. However, steric congestion close to the reacting olefin resulted in a decrease in enantioselectivity giving the cyclohexenol **123** in 81% yield and 84% ee (Table 12).

Oxabenzonorbornadienes **124** also undergo enantioselective hydroaluminations. However, milder conditions were later developed as reactions in toluene typically resulted in the formation of naphthalene and naphthol as byproducts and the ee's were typically 60%. In the presence of THF, the reaction gave the ring-opened product in significantly better yield (88%) and ee (98%) (entry 1, Table 13). A number of oxabenzonorbornadienes were shown to undergo

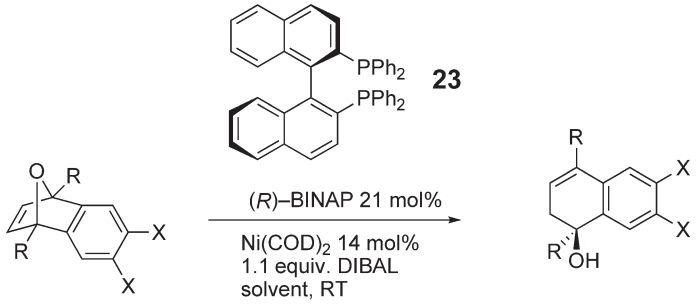
Table 12 Hydroalumination of substituted oxanorbornadienes using BINAP



122 **123**

Entry	*R*	*Y*	*X*	*X′*	*Time* (h)	*Solvent*	*Yield* (%)	*ee* (%)
1	H	H	CH_2OBn	CH_2Bn	6	PhMe	96	97
2	H	CH_2OMe	CH_2		5	THF	88	91
3	Me	H	CH_2OMe	CH_2OMe	12	PhMe	81	84
4	H	OMe	H	H	2	THF	50	86

Table 13 Hydroalumination of oxabenznorbornadienes using BINAP



124 **125**

Entry	*R*	*X*	*Time* (h)	*Yield* (%)[a]	*ee* (%)
1	H	H	1	88	98
2	H	F	3	84	96
3	H	OCH_2O	3	58	94
4	Me	H	16	66	73

[a]Reaction carried out in THF.

reductive ring openings with ee's between 73% and 96%, (entry 2–4, Table 13). Steric congestion close to the olefin had the greatest negative effect on enantioselectivity. In contrast, minimal electronic effects were noted (Table 13).

It was possible to reduce the amount of catalyst in the ring opening of oxabenzonorbornadiene using 1.9 mol% of $Ni(COD)_2$ and 3.3 mol% of BINAP to give the dihydronaphthalenol **118** in 88% yield and 91% ee (entry 2, Table 14). Recrystallization of the material gave an ee of >98%. It was possible to reduce the catalyst loading to 1.8 mol% if the temperature was increased to 40 °C (entry 3, Table 14).

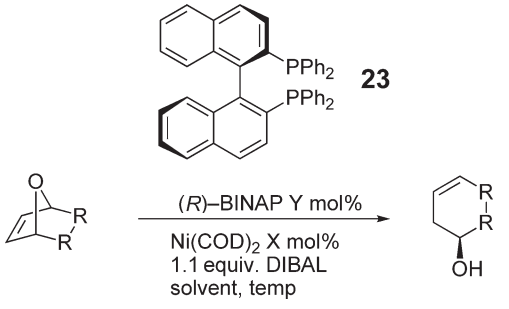
An unprotected alcohol **126** has been ring-opened using 1 mol% of $Ni(COD)_2$ and 1.9 mol% of BINAP **23** to give the diol **127** in 83% yield and 98% ee (Scheme 15).[129]

The product of the enantioselective ring opening of oxabenzonorbornadiene has been used as a key reactant in the synthesis of the antidepressant Sertraline.[130] The transition metal-catalyzed ring-opening of oxabicycles has been reviewed, with nickel-catalyzed reductive ring openings being the focus.[131]

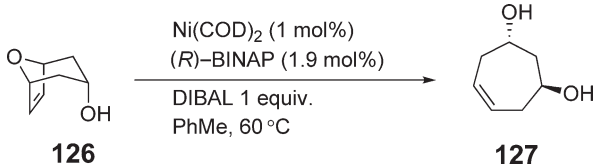
The catalyst efficiency of these hydroalumination varies from a turnover number (TON) of 20–91. It is possible that the catalyst is deactivated by the presence of oxygen and water. Examination of the ^{31}P NMR spectrum of the catalyst indicates that the phosphine monoxide and dioxide are formed in the presence of nickel prior to the addition of the substrate. Rigorous exclusion of oxygen and water is necessary in all these reactions. The enantioselective nickel-catalyzed hydroalumination route to dihydronaphthalenols may prove to be particularly important. Only one other method has been reported for the enantioselective syntheses of these compounds: microbial oxidation of dihydronaphthalene by *Pseudomonas putida* UV4 generates the dihydronaphthalenol in 60% yield and >95% ee.[132]

Negishi reported the zirconium-catalyzed enantioselective carboalumination of alkenes, which consisted of a hydroalumination/alkylalumination tandem process.[133–135] This permits the asymmetric syntheses of methyl-substituted alkanols and other derivatives, typically with >90% ee, which represents an increase in ee value by 15% from the previously obtained 70–80%.[136–138] The hydroalumination/zirconium-catalyzed enantioselective carboalumination of alkenes was carried out using (−)-bis(neomenthylindenyl)zirconium dichloride as the catalyst (Table 15).[133]

Table 14 Hydroalumination of oxabenznorbornadienes using BINAP



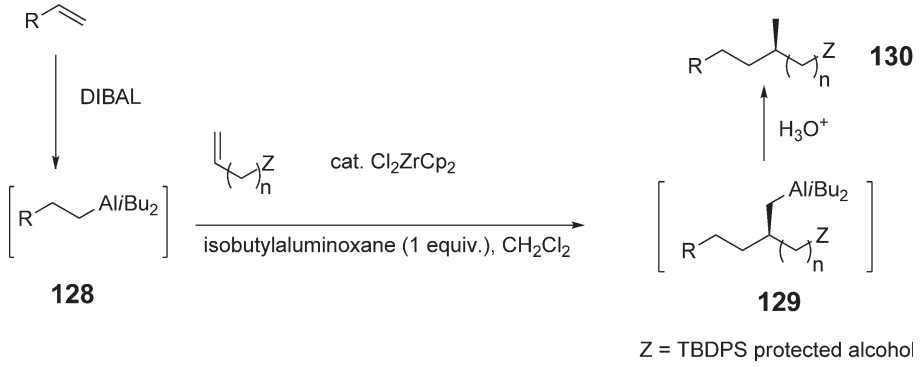
Entry	*R–R*	*X* (mol%)	*Y* (mol%)	*Time* (h)	Solv.	*Temp.* (°C)	*Yield* (%)	*ee* (%)
1	$CH(CH_2OPMB)CH(CH_2OPMB)$	1.5	2.6	16	THF	RT	99	92
2	Ph	1.9	3.3	6	THF	RT	88	91
3	Ph	1.0	1.8	5	THF	40	91	90



126 **127**

Scheme 15

Table 15 Hydroalumination zirconium catalyzed enantioselective carboalumination of alkenes



Entry	*R*	*n*	*Time* (h)	*Yield* (%)	*ee* (%)
1	*n*-pentyl	2	3	74	92
2	*n*-hexyl	2	3	77	91
3	cyclohexyl	2	3	81	91
4	$Ph_2Me_2SiCH_2$	2	3	85	90
5	*n*-hexyl	3	6	83	92
6	*n*-hexyl	4	4	76	90

The results indicate that 3-butenols and longer ω-alkenols can be alkylaluminated with a variety of alkyldiisobutylalanes **128** to produce, after hydrolysis, the corresponding methyl-substituted alkanols **130** in good yields and with 90–93% ee.

10.19.4 Applications in Total Synthesis

10.19.4.1 Hydroboration

Among recent examples that highlight the synthetic utility of transition metal-catalyzed hydroborations are its direction toward a formal syntheses of the non-steroidal anti-inflammatory agents Ibuprofen™ **131** and Naproxen™ **132**[14,15,139] as well as the anti-depressant Sertraline **133** (Figure 14).[140] In the majority of cases, rhodium-catalyzed hydroboration is utilized and the rhodium(I) source generally is Wilkinson's catalyst $RhCl(PPh_3)_3$.

Grieco in the total synthesis of (−)-epothilone B **134** used a rhodium-catalyzed hydroboration as a key step in the synthesis of the macrocyclic ring (Figure 15).[141] Completion of the synthesis of the C(3)–C(12) fragment was carried out using a rhodium-catalyzed hydroboration as the key step.

Roush used a rhodium-catalyzed hydroboration to construct a component **136** of the natural product, (−)-bafilomycin A_1 **137** (Scheme 16).[142] The hydroboration was carried out in 87% yield.

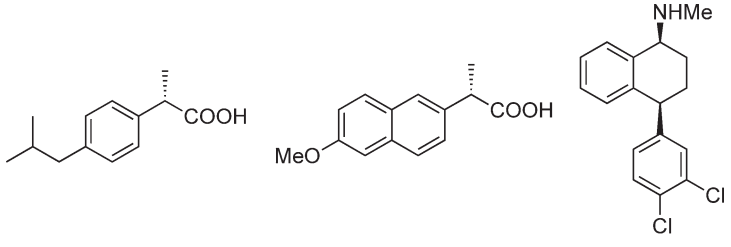
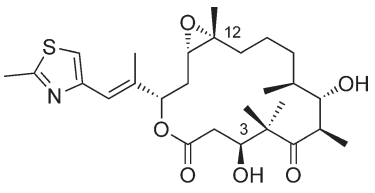


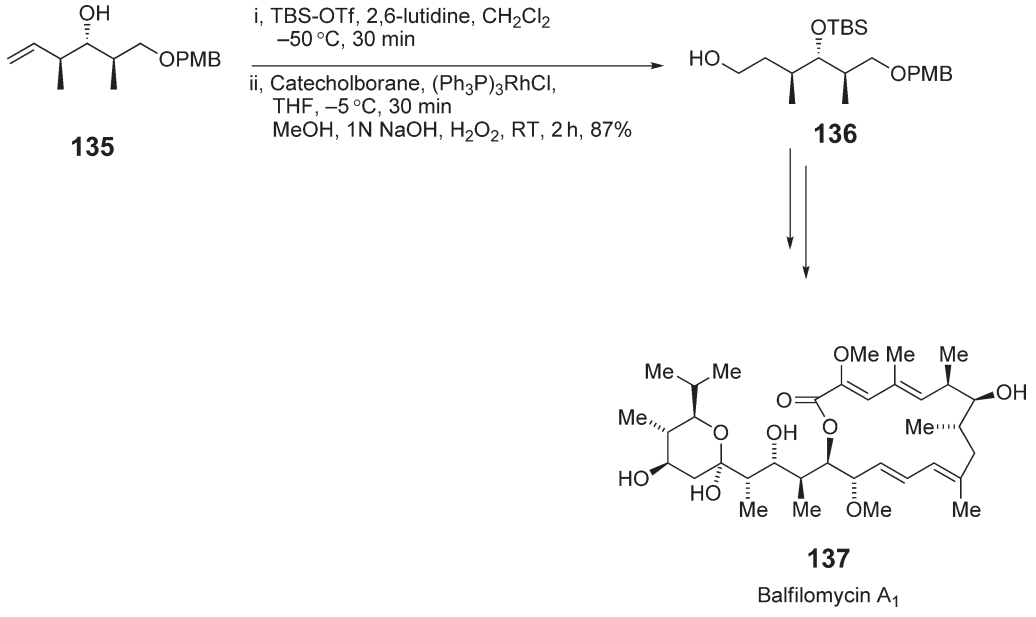
Figure 14 Common drugs potentially prepared by asymmetric hydroboration.



134

(–)-Epothilone B

Figure 15 (–)-Epothilone B.



Scheme 16

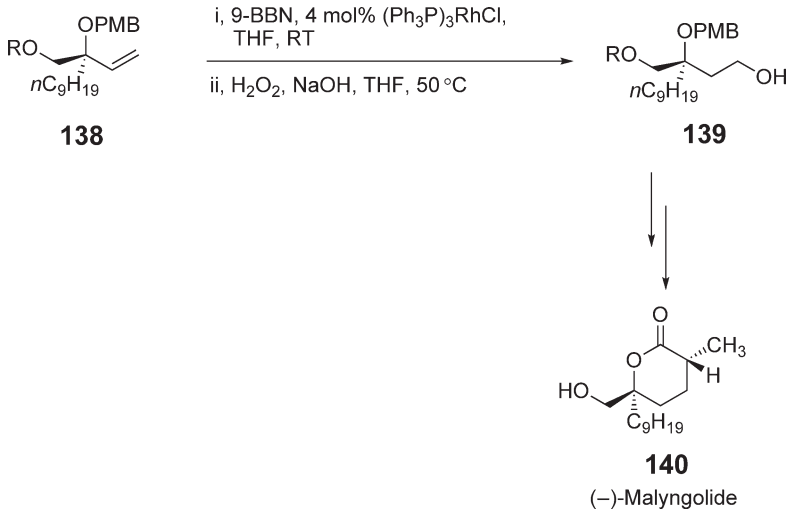
Trost used a rhodium(I)-catalyzed hydroboration to obtain a key intermediate **139** in 90% yield in the synthesis of the pyrone ring of the natural product (–)-malyngolide **140** (Scheme 17).[143]

10.19.4.2 Hydroalumination

While transition metal-catalyzed hydroboration is a well-established reaction, the same cannot be said for the transition metal-catalyzed hydroalumination. The synthetic utility of this reaction is only just beginning to emerge. Lautens has led the way in the use of hydroaluminations as the key step in the total synthesis of complex natural products. The synthesis of the anti-depressant sertraline[130] involved the formation of the tetrahydronaphthalene core, and this is best achieved using the nickel-catalyzed hydroalumination of oxabicyclic alkenes (Table 16).

The nickel-catalyzed hydroalumination of **141** in toluene gave a complex mixture of products, including the desired product **142** with 60% ee. However on changing the solvent to THF, a much better result giving a 98% ee. was obtained.

Lautens also used this nickel-catalyzed hydroalumination methodology in the total synthesis of ionomycin **145**. The starting compound was a [3.2.1]oxabicyclic alkene **143**.[144] Their rigid bicyclic structures can be used to introduce functional groups in a highly stereoselective manner. The synthesis of the key intermediate **144** involves the slow addition of DIBAL to the oxabicyclic alkene and the $Ni(COD)_2$/(*S*)-BINAP in toluene to afford **144** in 95% yield and 93–95% ee. (Scheme 18).

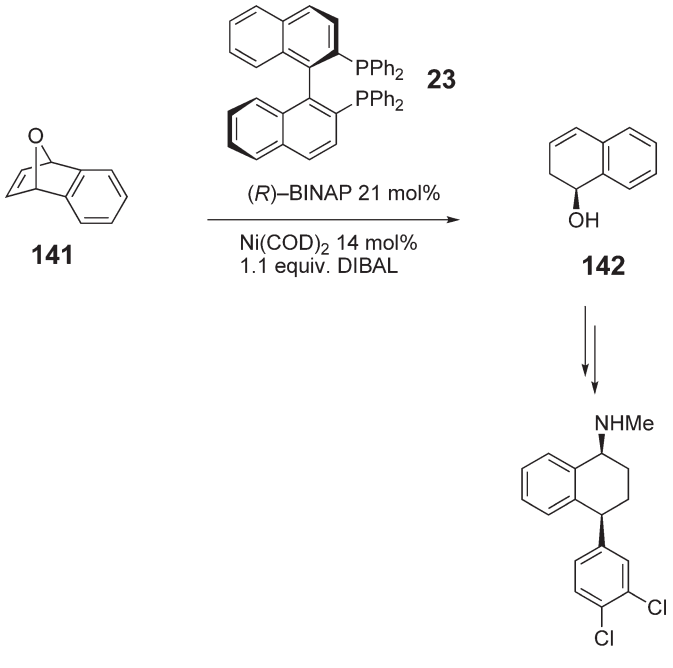


138 **139** **140**

(–)-Malyngolide

Scheme 17

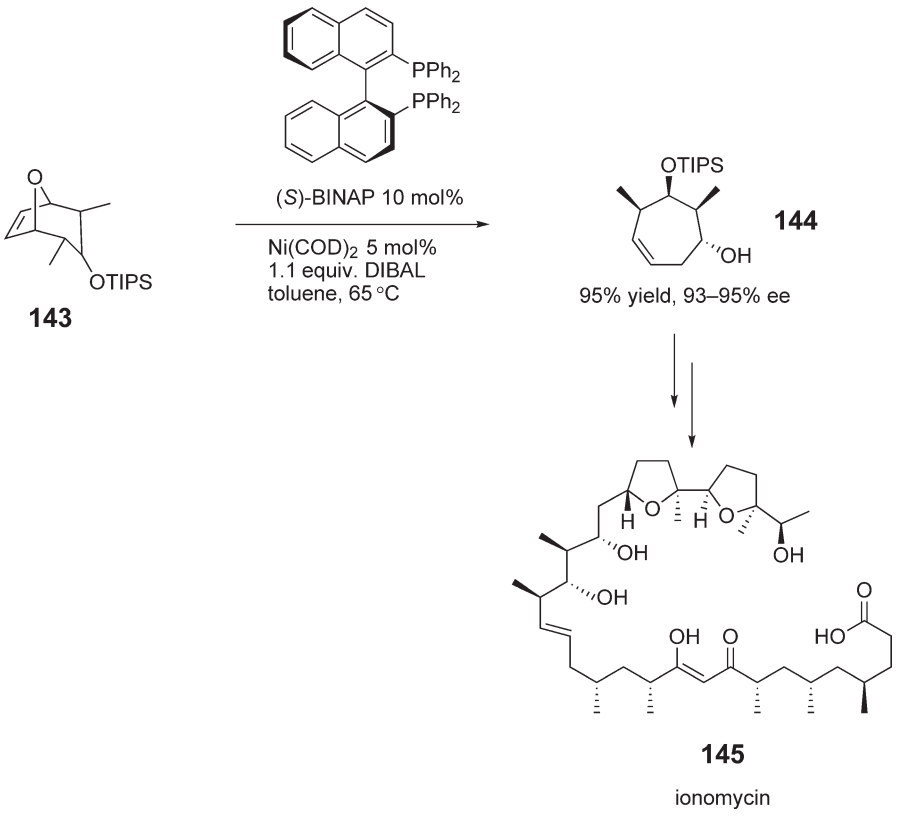
Table 16 Hydroalumination of oxabenznorbornadienes using BINAP as a key step in the synthesis of Sertraline



141 **142** **133**

Sertraline

Entry	*Solvent*	*Time* (h)	*Yield* (%)	*ee* (%)
1	PhMe	1	33	60
2	PhMe	24	70	60
3	THF	2	88	98



Scheme 18

In conclusion it is evident from the foregoing examples that transition metal-catalyzed hydroborations and hydroaluminations occupy an important role in organic synthesis. While rhodium-catalyzed hydroboration has been extensively developed, the hydroalumination is just starting to emerge as a useful reaction in organic synthesis.

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