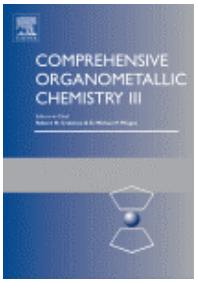

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11.01
C–C Bond Formation by Cross-coupling

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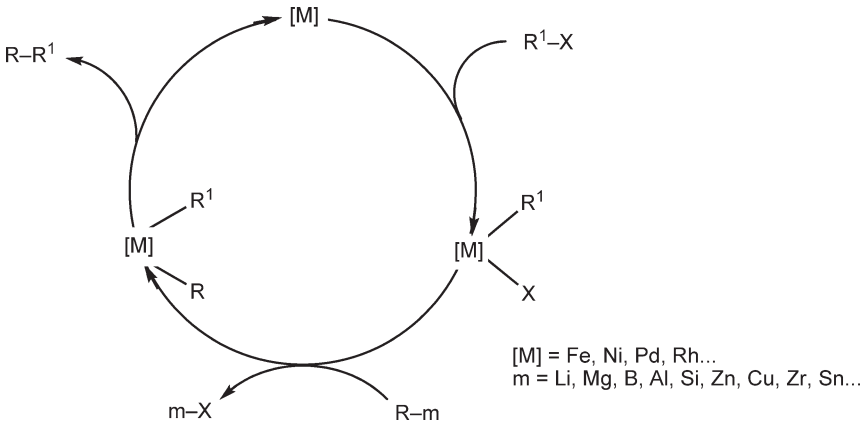
11.01.1 Introduction

The cross-coupling reactions represent a class of synthetic transformations that involve the combination of an organometallic reagent (that has a main group metal atom in most of cases) with an organic electrophile in the presence of groups 8–10 metal catalysts to achieve a C–C, C–H, C–N, C–O, C–S, C–P, or C–M bond formation (for general reviews on cross-coupling reactions see Refs: 1 and 1a–1h). Since the initial discoveries in this area in the early 1970s by Kumada, Kochi, Corriu, and Murahashi, many organometallic reagents, such as organoboron, organotin, organosilicon, and organozinc have proved to be useful for cross-coupling reactions. Many different types of



Scheme 1

electrophiles and metal complexes have been successfully employed in these reactions, resulting in a plethora of synthetic methods for molecular assemblies. For this reason, cross-coupling reactions have been used in numerous organic synthetic applications ranging from polymers and liquid crystals to pharmaceuticals and natural products.

A general catalytic cycle for cross-coupling reactions is depicted in Scheme 1. In general, the reaction occurs by a sequence of oxidative addition–transmetallation–reductive elimination. The characteristics of both the transition metal and the main group metal reagent, in addition to effects associated with other reaction conditions, will affect the catalytic performance. The oxidative addition step is often regarded as the rate-determining step in the catalytic cycle, and the strength of the C–X bond (X = halide or pseudohalide) is determinant. The relative reactivity decreases then in the order $I > OTf > Br \gg Cl$.[2]

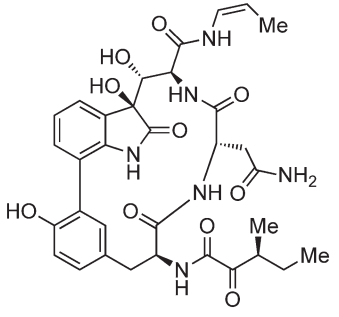
Improvements in cross-coupling reactions can be associated to two main thrusts: (i) increased activity and stability of catalytic systems; this is related to extensive research on the development of new and more efficient supporting ligands,[3] although, ligandless systems are of great importance also; and (ii) the use of new halides, pseudohalides and organometallic nucleophiles. In this chapter, we will focus on the developments in C–C bond formation by cross-coupling reactions related to the development of new and more efficient catalysts. As excellent general reviews have been published covering the literature until the end of 2001, new developments during the period from 2001 to the end of 2004 are mainly discussed here. Some developments prior to 2001 will also be discussed as leading references that contributed to major advances in the area. Each section will include a list of significant reviews.

11.01.2 Cross-Coupling Reactions

11.01.2.1 Reactions with Organoboron Reagents: The Suzuki–Miyaura Reaction

In 1979 Miyaura, Yamada, and Suzuki reported on the coupling reaction of alkenyl boronates with alkenyl bromides.[4] Nowadays, this reaction is known as the Suzuki–Miyaura reaction (for reviews, see Refs: 5 and 5a–5d); the coupling of organoboron reagents with various organic halides has broadened its scope, becoming arguably the most important transformation leading to the formation of a C–C bond, since organoboron reagents show many advantages,[6] for example: (i) ready availability of reagents by hydroboration and transmetallation, (ii) inert to water and related solvents, as well as oxygen, (iii) generally thermally stable, (iv) tolerant toward various functional groups, (v) low toxicity of starting materials and byproducts. A plethora of new catalysts, reaction conditions, organoboron reagents have been developed by a large number of research groups, and a large number of drugs,[7] polymers,[8,8a–8c] and natural products[9,9a–9g] include a Suzuki–Miyaura cross-coupling step in their synthesis. Some examples are shown in Figure 1.

As previously mentioned, the Suzuki–Miyaura reaction is generally thought to occur by a sequence of oxidative addition–transmetallation–reductive elimination. First and last steps are well understood, but the role of the base in the transmetallation step is still unclear. With the information available so far, it seems that three different processes can occur to transfer the organic group from the boron atom (Scheme 2).[6a] Although organoboronic acids do not react with R–Pd–X **i** (X = halogen), it is known that ate complexes such as Bu_4BLi,[10] $[R_3BOMe]Na$,[11] and $[ArBF_3]K$[12,12a]



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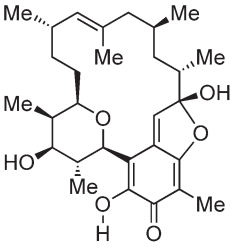
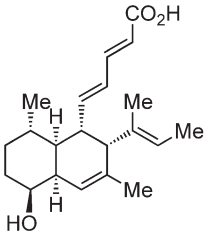
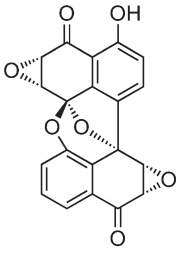


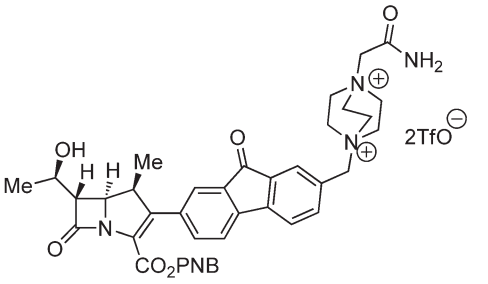
Kendomycin



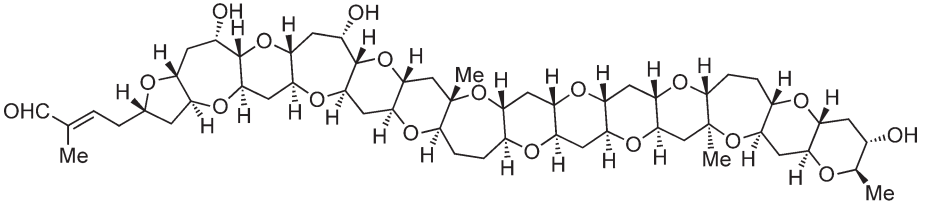
(+)-Phomopsidin



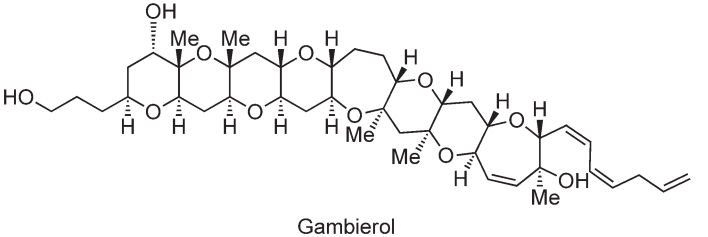
(+)-Spiroxin C



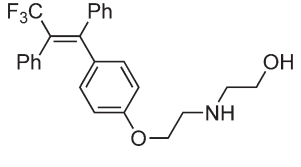
Carbapenum



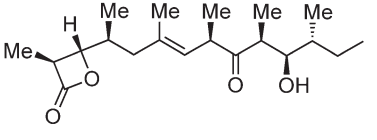
Gymnocin-A



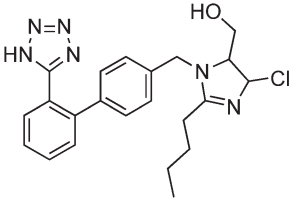
Gambierol



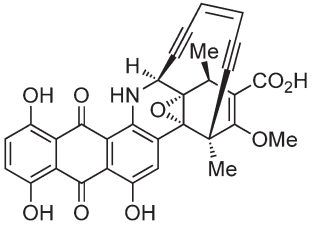
Panomifene



(–)-Ebelactone A

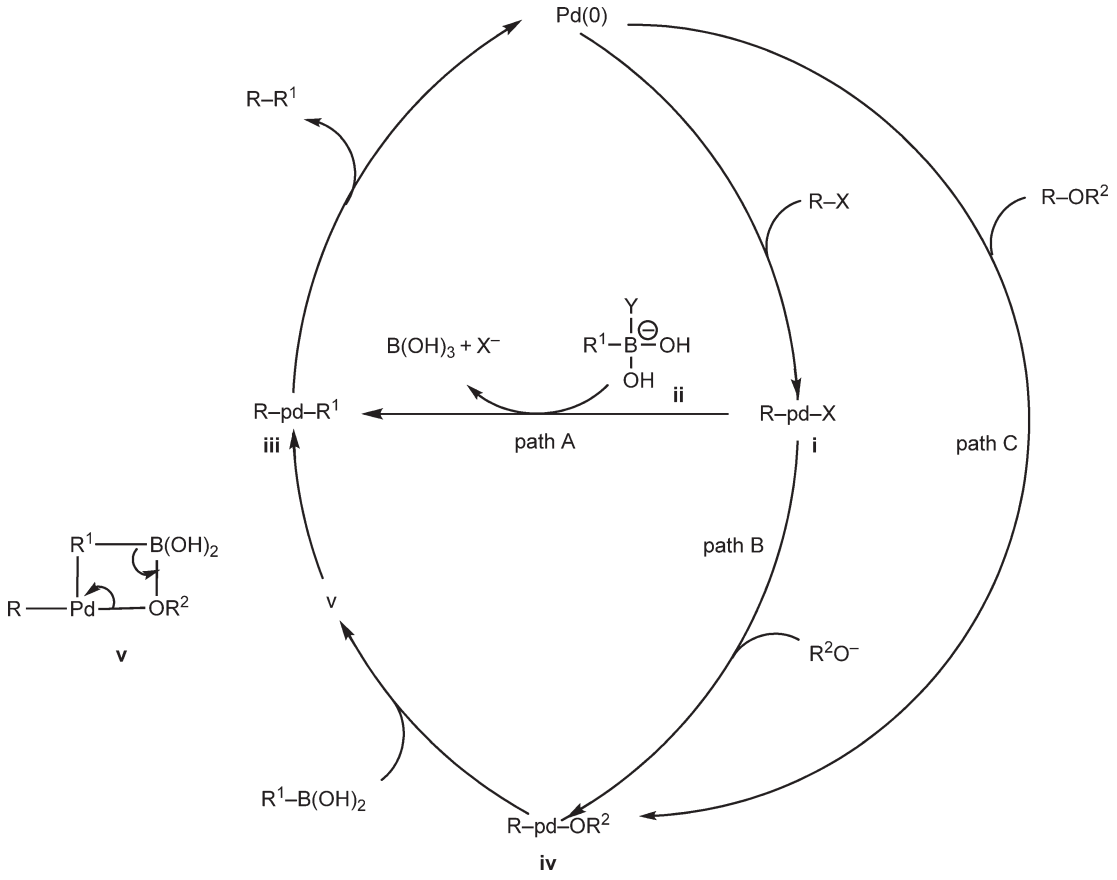


Losartan



Dynemicin A

Figure 1



Scheme 2

readily undergo cross-coupling in the absence of a base, showing how the quaternization of the boron atom with a negatively charged base enhances the nucleophilicity of the organic group on the boron atom. There is no evidence for analogous hydroxyboronate anions,[13] but species such as **ii**, which exist in alkaline solution, could similarly alkylate **i** (path A).

Path B shows the possibility of the *in situ* generation of an (alkoxo)-, (hydroxo)-, (acetyloxo)-, or (acetoxo)palladium(II) complex by exchange between **i** and a base (R^2O), forming an (alkoxo)palladium(II) intermediate **iv** that can undergo transmetallation without the aid of a base.[14] Moreover, the coupling reaction can proceed under neutral conditions for organic electrophiles yielding **iv** (path C).[15,16] Both pathways B and C may involve a rate-determining coordination of the R^2O ligand to the boron atom, as a consequence of the formation of complex **v**, which participates in the formation of **iii** by transfer of the activated organic group from boron to palladium.[16] The high reactivity of the oxo–palladium complexes can be attributed to both the high basicity of the Pd–O species (related Pt complexes are known to be more basic than NaOH)[17] and the oxophilicity of the boron center.

Since it is known that halogens and OTf ligands on **i** are easily displaced by alkoxy, hydroxyl, or acetoxy to provide a basic species **iv**,[12,12a] it seems clear that in alkaline solution both pathways A and B can occur for the cross-coupling reaction, but it is not yet clear which one is predominant.[18] Recent studies suggest that the pathway taken is highly dependent on the organoboron reagent employed.[13]

11.01.2.1.1 New coupling partners

Historically, one of the most important limitations of the Suzuki–Miyaura reaction was the poor reactivity of organic chlorides, attributed to the strength of the C–Cl bond. Aryl chlorides are very attractive halides due to their low cost and wider diversity of available compounds.[19] Prior to 1998, reports of effective palladium-catalyzed Suzuki reactions of aryl chlorides were limited to activated substrates, and generally employing very high temperatures.[20] In that year,

Fu and Buchwald independently reported on catalytic systems that overcame this limitation in good yields.[21,22] Both systems were based in the use of very electron-rich ligands (a trialkylphosphine and an arylalkylphosphine, respectively) that facilitated the cleavage of the C–Cl bond prior to the oxidative addition to the palladium center (Table 1, entries 1 and 2) and stabilize the Pd(0) species in solution to avoid its precipitation.[23,23a] Shortly after that, several research groups described systems that coupled a variety of aryl chlorides, activated and non-activated, making use of electron-rich ligands such as trialkylphosphines,[24] arylalkylphosphines,[25,26] triarylphosphines,[27,28] phosphine oxides,[29] and *N*-heterocyclic carbenes (NHC).[30,30a–30f,31]Some early examples are described in Table 1. This NHC ligand has been shown to be better donors than the best donor phosphines,[32] but without the disadvantages; most common phosphines display: (1) phosphines often are sensitive to air oxidation and therefore require air-free handling to minimize ligand oxidation, (2) when these ligands are subjected to higher temperatures, significant P–C bond degradation occurs, and then an excess of phosphine is required, and (3) they often react with Pd precursors as $Pd(OAc)_2$ in a redox process leading to the formation of $Pd(0)P_n$ and phosphine oxide.[33] Since their initial use as ligands in homogeneous catalysis,[34] NHCs have been successfully employed as an alternative for tertiary phosphines in a number of cross-coupling reactions.

In addition to the already generalized couplings of aryl iodides, bromides, and chlorides, in 2003, the coupling of activated fluorides with boronic acids was reported (Table 2, entry 1).[35,35a] The coupling with pseudohalogens has also attracted considerable attention. Aryl triflates are known as being less reactive than the corresponding iodides and bromides,[36] but have the advantage of being easily synthesized from readily available phenols.[37] Very general methods for the coupling of aryl triflates even at room temperature have been developed (Table 2, entry 2).[38,38a–38c]

Table 1

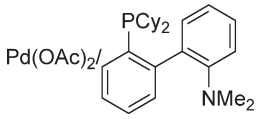
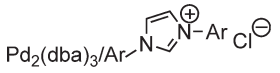
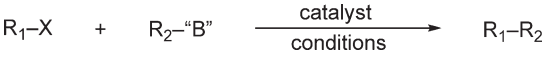
Entry	*Catalyst*	*Conditions*	*Yield* (%)	*References*
1	$Pd_2(dba)_3/PBu^t_3$	Cs_3CO_3, dioxane, 80–90 °C	82–92	21
2		CsF, dioxane, RT	92–94	22
3	$Pd(OAc)_2/n$-BuP(1-Ad)$_2$	K_3PO_4, toluene, 100 °C	55–100	24
4	 Ar = 2,4,6-$(Me)_3C_6H_2$	Cs_3CO_3, dioxane, 80 °C	88–99	31

Table 2



Entry	*X*	R_1	R_2
1	F	Aryl	Aryl
2	OTf	Aryl, alkenyl, alkyl	Aryl, alkenyl, alkyl
3	$N_2^+ BF_4^-$	Aryl	Aryl, alkenyl
4	SO_2Cl	Aryl	Aryl
5	OTs	Aryl, vinyl, alkyl	Aryl, alkyl
6	OMs	Aryl	Aryl
7	$NMe_3^+OTf^-$	Aryl	Aryl

Other pseudohalides such as aryldiazonium ions (Table 2, entry 3),[39,39a] arylsulfonyl chlorides (Table 2, entry 4),[40] aryl and alkyl tosylates (Table 2, entry 5),[41,41a–41e] aryl mesylates (Table 2, entry 6),[42,42a] and aryltrimethylammonium salts (Table 2, entry 7)[43] have also been employed.

Although boronic acids have been widely accepted as the more convenient transmetallating reagents, other boranes have been used;[3] reports have appeared regarding the use of alternative types of organoboron reagents: Batey, and more extensively Molander, have reported on the coupling of aryltrifluoroborate salts with aryl bromides,[44] iodides,[45] and triflates.[46] A variety of organoboron intermediates can be converted into the corresponding trifluoroborate salts in a very straightforward manner,[47] having the added advantage of being more air and moisture stable than boronic acids. Already some of them are commercially available. Recently, Buchwald reported on the coupling of aryltrifluoroborate salts with aryl chlorides using very mild reaction conditions.[48]

11.01.2.1.2 Palladacycle complexes as catalysts precursors

Of particular interest to large-scale synthetic processes is the development of catalysts that can operate at very low metal loadings. Palladacyclic complexes have played a significant role in this matter.[49] Pioneering work in 1995 was performed by Herrmann and co-workers using the palladacycle complex **1** for the coupling of activated chlorides with catalyst precursor loadings of 0.1 mol%.[50] Some examples in the literature are shown in Figure 2. Good activity is not limited to phosphorus-donor systems **2–4**,[51–53c] since N-donor **5** and **6**,[53,53a–53d,54] oxime-containing **7a–f**, **8a** and **8b**,[55,55a–55c] and S-donor **9**[56] palladacycles have also been described with good results. Tertiary phosphine adducts of phosphorus-, imine-, and amine-based palladacycles **10–12**[57–58b] show excellent activity at very low catalysts loadings

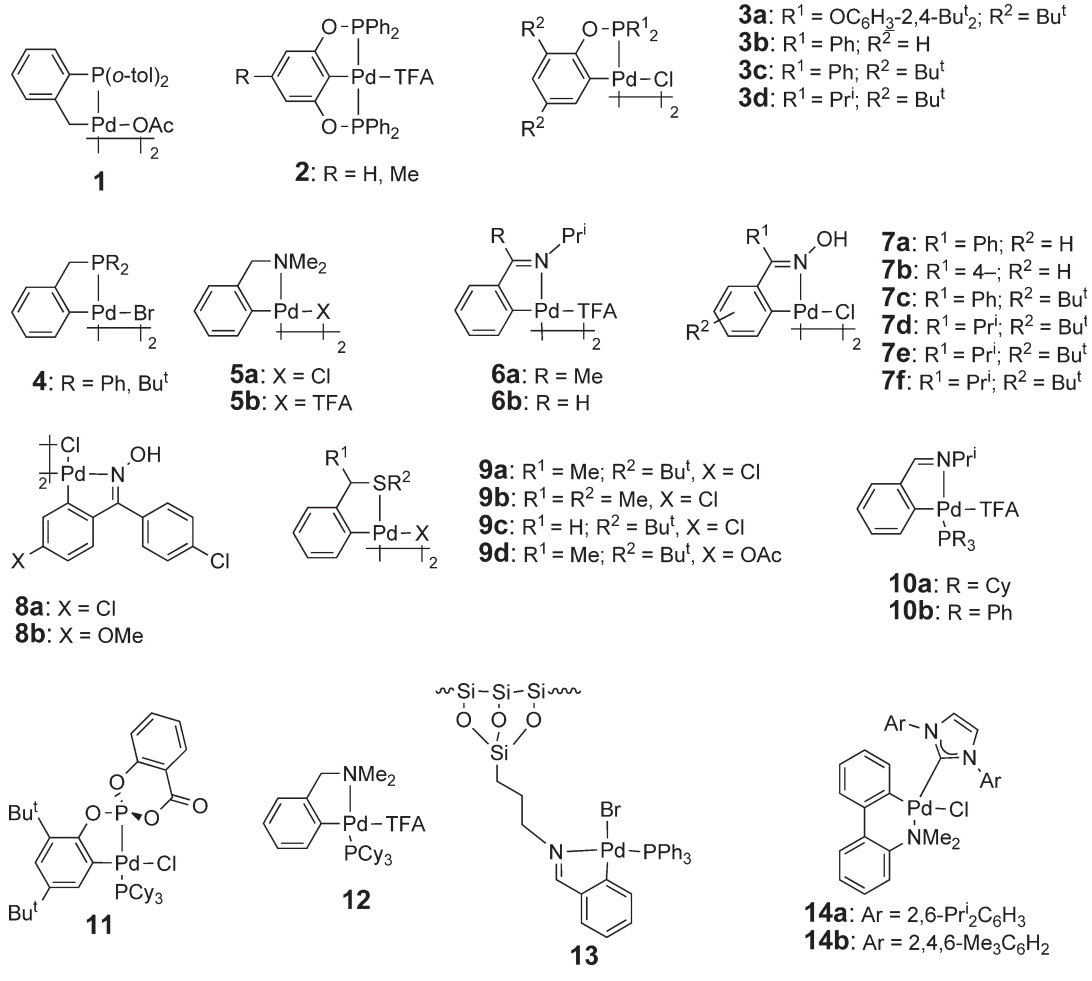


Figure 2

when aryl chlorides, both activated and unactivated, are used as substrates. Silica-supported imine-based palladacycles such as **13** show lower activity in the Suzuki–Miyaura reaction than their homogeneous counterparts.[59] Nolan and co-workers reported on the activity of an NHC-bearing palladacycle **14a** for the Suzuki–Miyaura cross-coupling of sterically hindered unactivated aryl chlorides with sterically hindered boronic acids, allowing for the synthesis in high yields of di- and tri-*ortho*-substituted biaryls at room temperature and in very short reaction times.[60]

11.01.2.1.3 Catalytic systems composed of Pd(0) or Pd(II) derivatives and phosphines

As previously mentioned, the use of electron-rich, bulky ligands (phosphines and NHCs) in combination with palladium precursors has made an impact not only on the use of the Suzuki–Miyaura reaction but in all the cross-coupling reactions. Bulky electron-rich phosphines are now by far the most used ligands to stabilize the Pd(0) intermediates, and avoid the precipitation of the metal in homogeneous catalysis (for applications of phosphine ligands in homogeneous catalysis, see Refs: 61 and 61a). Tetra-coordinated palladium–phosphine complexes such as $Pd(PPh_3)_4$ are in equilibrium with their coordinatively unsaturated species, but only the diphosphine palladium(0) or monophosphine palladium(0) species can be involved in the oxidative addition process.[62,21] Thus, bulky, electron-rich phosphines such as $P(o\text{-tolyl})_3$ and $P(Bu^t)_3$ provide highly reactive catalysts because of the formation of the coordinatively unsaturated species [Pd–L]. In addition, the electron richness imparted to the palladium by the phosphine assists in the cleavage of the Ar–X bond in the oxidative addition step, while the steric bulk of the ligand promotes the reductive elimination of the desired coupling product. The stoichiometry of phosphine to palladium, the bulkiness and the donating ability of phosphine ligands modulate the reactivity of the catalyst.

A salient example of the optimum combination of steric bulk with strong donating ability was reported in 2000 by Beller and co-workers. The use of the bulky, electron-rich bis(adamantyl)-*n*-butylphosphine in combination with$Pd(OAc)_2$ allowed for the coupling of deactivated aryl chlorides with very high turnover numbers (TONs) (10,000–20,000).[24] Another example of such effects is the use of the air-stable dimer $\{PdBr[P(1\text{-adamantyl})(Bu^t)_2]\}_2$ for the coupling of aryl bromides at room temperature.[63] In 2001, Fu and co-workers disclosed an alternative method to overcome the air-sensitivity limitation of phosphine ligands. They had previously reported on the use of $P(Bu^t)_3$/$Pd_2(dba)_3$ for the coupling of unactivated chlorides with boronic acids.[64] After this initial report, the air-sensitive and flammable $P(Bu^t)_3$ was converted into the air-stable phosphonium salt $[PH(Bu^t)_3]BF_4$ by simple quaternazition with an appropriate acid.[65] The masked phosphine can be generated by reaction with a Brönsted base. The use the phosphonium salt in combination with $Pd_2(dba)_3$ and KF as base to perform Suzuki–Miyaura couplings of arylboronic acids with activated chlorides and deactivated aryl bromides and iodides in mild reaction temperatures (20–50 °C) was reported to proceed very effectively. This same salt has been recently used for the palladium-catalyzed preparation of a variety of 2,4,5-trisubstituted 1*H*-imidazoles starting from unprotected 2,4-disubstituted 5-chloro-1*H*-imidazoles.[66] Another example of the use of these phosphonium salts, $[HP(Bu^t)_2Me]BF_4$, was reported for the coupling of alkyl bromides with β-hydrogens and alkyl boronic acids.[67] The combination of steric bulk and strong electron donation can also be obtained with *in situ* systems; the first method for achieving Suzuki–Miyaura cross-coupling of alkyl bromides that contain β-hydrogens made use of a combination of $Pd(OAc)_2$ and the very electron-donating, sterically demanding $P(^tBu)_3$ in a 1 : 2 ratio. The coupling worked under surprisingly mild conditions (room temperature).[68]

Buchwald and co-workers have described the effectiveness of tertiary phosphines as ligands in a variety of cross-coupling reactions, and provided, simultaneously as Fu,[21] the first examples of Suzuki–Miyaura cross-coupling reactions of unactivated aryl chlorides.[22] The initial system consisted of the combination of ligand **15** and $Pd(OAc)_2$. Alkyl-substituted phosphines such as **16** turned out to be more efficient, and allowed for the reaction to proceed at very low catalyst loadings (0.000,001–0.02 mol% Pd). Even hindered substrates were coupled to generate biaryls with more than one *ortho*-substituent.[69,70] Tetra-*ortho*-substituted biaryls can be synthesized in good yields using the air-stable, commercially available ligand **17**.[71] This ligand has also been employed for the coupling of aryl boronic acids with 6-halonucleosides,[72] haloquinolines,[73] and other substrates.[74,74a]

Ligand **18** (XPhos) displays an optimal performance for the coupling of unactivated aryl tosylates with boronic acids.[75] A "rational design" of the ligand, involving a fine-tuning of steric and electronic properties, led to phosphine **19**, which was used in combination with $Pd(OAc)_2$ in a 2.5 : 1 molar ratio, achieved the coupling of very sterically demanding substrates at high temperature in high yields.[76] The system also allows the coupling of *N*-heteroaryl chlorides with arylboronic acids, aryl halides with alkylboron derivates and reactions of aryl chlorides at room temperature.

Another interesting family of phosphine ligands that has been applied to this coupling reaction is the ferrocenyl-phosphines. Some air-stable examples are showed in Figure 3. Compound **20** has been used for the coupling of aryl chlorides in combination with a Pd(0) source,[77] while **21** gave excellent results for the coupling of a variety of aryl

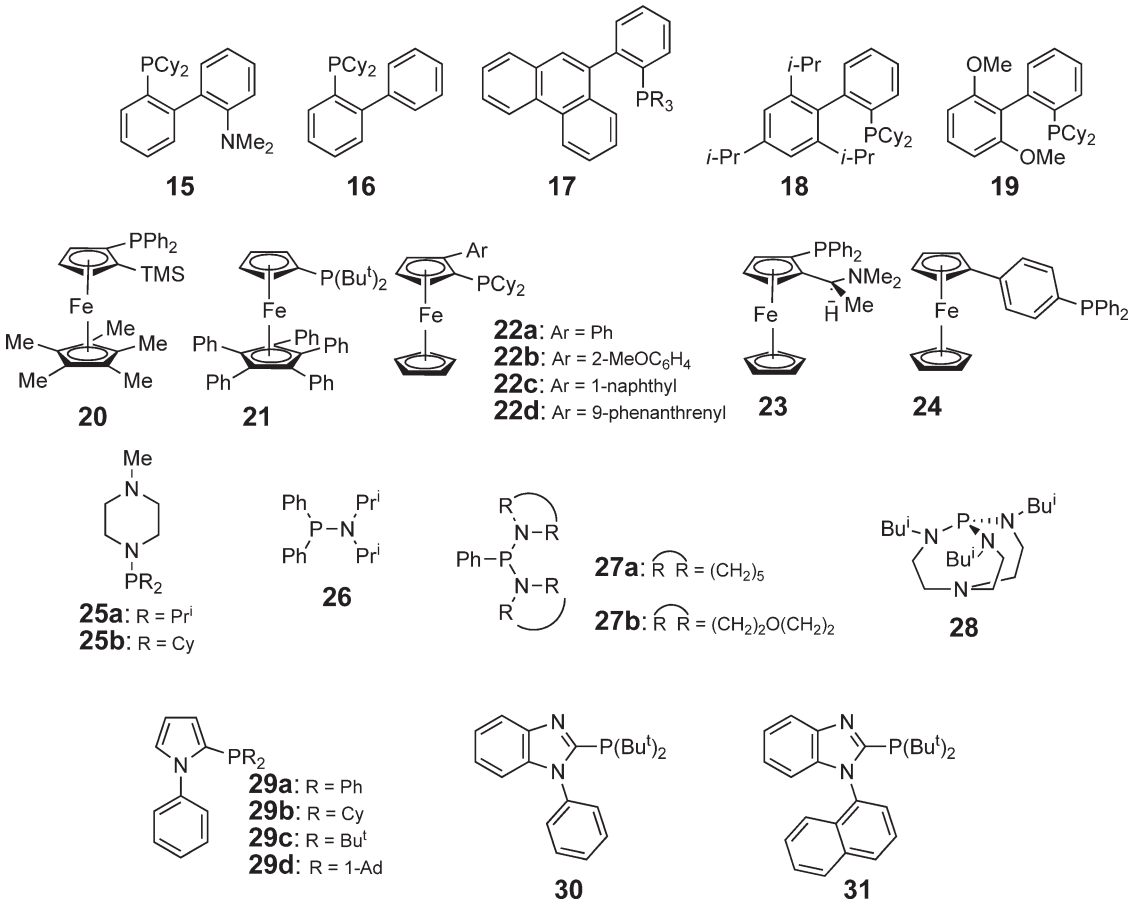


Figure 3

bromides with aryl and alkylboronic acids.[78] The series of ligands **22** was employed for the coupling of activated and unactivated aryl chlorides with arylboronic acids in high yields.[79] Chiral binaphthalenes derivatives were prepared in up to 85% ee using the chiral tertiary amine ferrocenylphosphine ligand **23** and $PdCl_2$.[80] More recently, Chan and co-workers have employed ligand **24** in combination with $Pd_2(dba)_3$ for the coupling of unactivated and activated aryl bromides or chlorides with a variety of aryl- and alkylboronic acids at 110 °C with excellent yields.[81]

Electron-rich amine-functionalized phosphines have also been investigated. Woolins *et al.* have prepared the series of ligands **25** for the coupling of aryl chlorides,[82] while a combination of $Pd(OAc)_2$ and the air-stable monoamine phosphine **26** has been used for the coupling of aryl bromides with arylboronic acids.[83] Better results were observed when ligands **27a** or **27b** were used in this system. The commercially available, very electron-rich ligand **28** has also been successfully employed to catalyze the coupling of a variety of aryl bromides and chlorides with arylboronic acids in excellent yields.[84] Beller and co-workers have shown that monodentate 2-phosphino-1-arylpyrrole ligands **29a–d**, prepared directly from *N*-aryl pyrroles, allowed highly efficient coupling reactions of electron-rich as well as electron-poor aryl chlorides with phenylboronic acid under mild conditions.[85] They have also reported on the synthesis of ligands **30** and **31**, which were used in combination with $Pd(OAc)_2$ for the coupling of aryl and heteroaryl chlorides with phenylboronic acid at 100 °C.[86]

11.01.2.1.4 Catalytic systems composed of Pd(0) or Pd(II) and *N*-heterocyclic carbenes

N-heterocyclic carbenes (NHC) have become increasingly popular in the last few years as an attractive alternative to tertiary phosphines in homogeneous catalysis, due to their strong donating ability and thermal stability.[29] Some examples are shown in Figure 4. For the Suzuki–Miyaura reaction, the first example was reported by Herrmann *et al.* in 1998.[87] Complex **32** was found to efficiently promote the reaction using unactivated aryl bromides or activated aryl

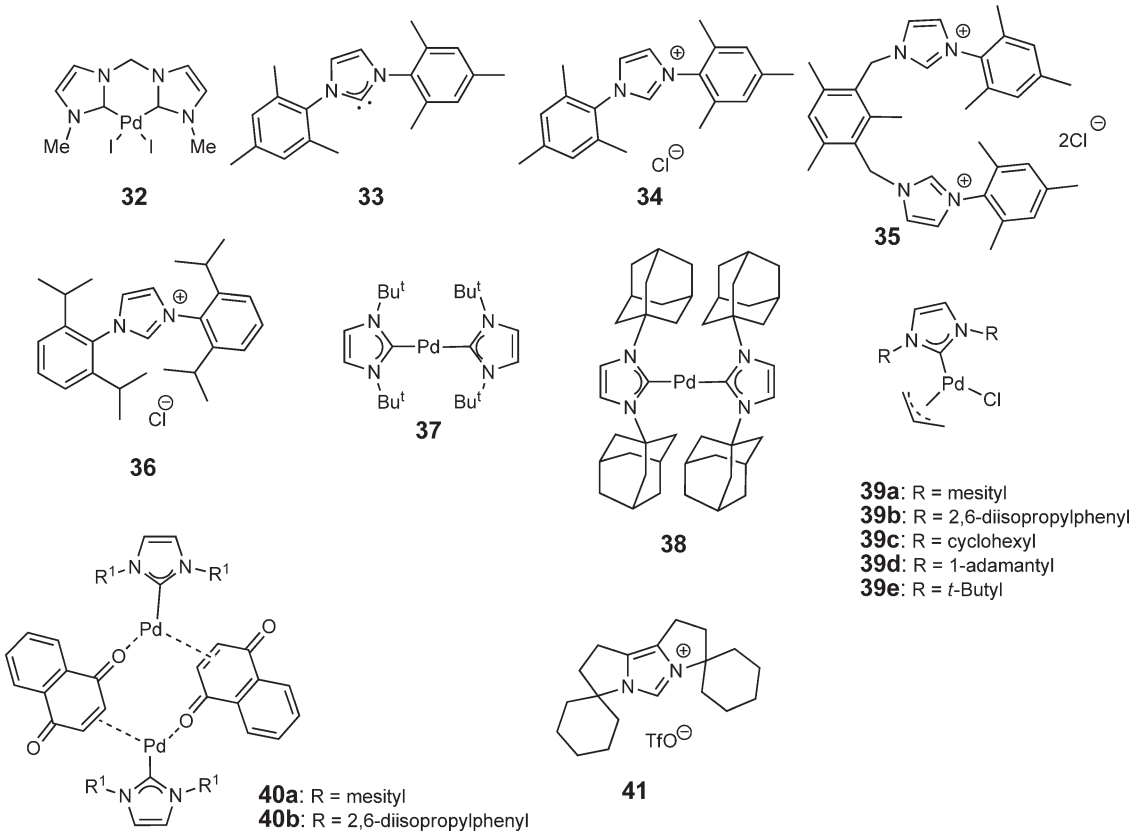


Figure 4

chlorides, in the presence of K_2CO_3 in toluene at 120 °C. Soon thereafter, the coupling of unactivated arylchlorides in high yields using ligand **33** and $Pd_2(dba)_3$ was reported by Trudell and Nolan.[31] Ligand **33** was generated *in situ* from the imidazolium chloride **34** by reaction with the base (Cs_2CO_3). Trudell also reported on the use of bisimidazolium salt **35** and $Pd(OAc)_2$ for the coupling of aryl chlorides.[88] Fürstner has reported a very versatile system for the coupling of 9-substituted borabicyclo[3.3.1]nonanes and aryl chlorides using the imidazolium salt **36** in the presence of KOMe.[89] Arentsen *et al.* recently reported on the use of this imidazolium salt in combination with $Pd(dba)_2$ for the coupling of aryl chlorides or akyl bromides with organoboranes at 40 °C.[90]

In early studies, it was observed that when the NHC was already attached to the metal center, reaction times were shortened since the time for the deprotonation of the salt and coordination to the metal center was no longer required. The use of well-defined systems also allows for a better understanding of the actual amount of stabilized palladium available in the system. Herrmann reported on two similar Pd(0) complexes bearing two carbenes, **37**[91] and **38**.[92] The latter was used in 2002 as the first example of coupling of aryl chlorides (activated and unactivated) with arylboronic acids at room temperature, in high yields, and reaction times between 2 and 24 h in the presence of CsF as base.

Following this concept of well-defined systems, Nolan has reported on the series of air- and moisture-stable NHC-bearing complexes **39**, easily prepared by reaction of $[Pd(allyl)Cl]_2$ with 2 equiv. of the corresponding carbene.[93,93a] The nature of the carbene was determinant in dictating the activity of this pre-catalyst in the Suzuki–Miyaura reaction. Later, the same group reported on the use of the commercially available **39b** for the coupling of aryl halides and with boronic acids in dioxane at 60 °C in the presence of $NaOBu^t$ requiring very short reaction times.

The system was also shown to be compatible with microwave heating.[94] Based on previous findings describing the use of technical grade isopropanol as solvent for this coupling reaction,[60] an investigation on the use of this environmentally friendly solvent employing **39a**, **39b**, **40a**, **40b**, and a variety of other NHC- and phosphine-bearing complexes was also reported.[95] In most cases, mild temperature (50 °C) and short reaction times were required for the coupling of 2,6-dimethylphenylchloride with 1-naphthaleneboronic acid leading to high yields of the desired product. In 2003, Glorius and co-workers reported the first system for the coupling of electron-rich aryl chloride for the

synthesis of di- and tri-*ortho*-substituted biaryls at room temperature making use of bioxazoline **41** and $Pd(OAc)_2$.[96] The use of this "flexible" ligand has presumably a beneficial role in the reductive elimination step by increasing the steric pressure on the palladium center. A more extended report in 2004 on this family of ligands included, for the first time, the synthesis of tetra-*ortho*-substituted biaryls with methyl and larger *ortho*-substituents from aryl chlorides using the Suzuki–Miyaura method.[97]

11.01.2.1.5 Ligandless systems

The use of expensive catalysts, sometimes difficult to prepare and recover, is a concern, especially when working in large scale. Also, as previously mentioned, the very common use of phosphine-based catalysts oftentimes brings along undesired oxidation side-reactions and formation of difficult-to-remove phosphine oxides.[33] To overcome these problems, ligandless systems are of interest for this and other cross-coupling reactions.

Commercially available $Pd(OAc)_2$ is the palladium source of choice of many of these ligandless systems. $Pd(OAc)_2$ is known to be reduced by arylboronic acids to Pd(0).[98,98a] Monteiro and co-workers reported on a system using $Pd(OAc)_2$ in combination with the salt additive tetrabutylammonium bromide (TBAB) to promote the coupling of aryl bromides and electron-deficient aryl chlorides with arylboronic acids at room temperature in very high yields.[99] The role of the additive is not clearly understood, but might stabilize anionic Pd species such as $[Br–Pdligand]^-$. A similar system was previously used by Guzzi[100] and Rehborn[101] for the coupling of aryl bromides and aryl- and 1-alkenylboronic acids in water. Marco used microwave heating for the coupling of activated aryl iodides, bromides, and chlorides under similar conditions.[102] Later, a transition metal-free system was reported for the coupling of unactivated bromides in the presence of 1 equiv. of TBAB in water, again under microwave irradiation.[103] In 2003, Bedford determined that $Pd(OAc)_2$ in a mixture of TBAB and water efficiently promote the coupling of deactivated aryl chlorides and phenylboronic acid.[104] Potassium aryl- and heteroarylflouroborates also couple with aryl- and heteroarylbromides or triflates in refluxing methanol in the presence of $Pd(OAc)_2$ and K_2CO_3.[105] Another common Pd source is $PdCl_2$; Deng *et al.* have recently reported on the use of $PdCl_2$ for the coupling of aryl and alkenyl bromides under very mild conditions,[106] while Shen *et al.* have described the use of pyridine as solvent for the coupling of aryl bromides in the presence of this Pd salt.[107]

11.01.2.1.6 Systems in aqueous media

The use of water-soluble palladium catalysts has attracted considerable attention, since these could be easily separated from the organic-soluble products and remaining starting materials, once the reaction is complete. The structures of some water-soluble pre-catalysts and ligands are shown in Figure 5. By utilizing ligand TPPS **42** in combination with $Pd(OAc)_2$, Genêt *et al.* were able to couple a wide range of arylboronic acids with aryl bromides.[108] No loss of activity was observed after reutilizing the catalyst three times. Recently, Moore and Shaughnessy were able to perform the coupling of aryl bromides using more sterically demanding modified versions of TPPTS, **43a** and **43b**.[109] Beller and co-workers reported on a very different class of ligands **44a** and **44b** bearing a hydrophilic carbohydrate that, used in combination with $Pd(OAc)_2$ and in the presence of Na_2CO_3, performed the coupling of aryl bromides with phenylboronic acid in ethanol/water/di-*n*-butylether or ethanol/water/toluene mixtures at 78 °C.[110] A similar approach was taken for the synthesis of **45** by Miyaura.[111] Shaughnessy and Booth synthesized the water-soluble alkylphosphine **46**, and found it to provide very active palladium catalysts for the reaction of aryl bromides or chlorides with boronic acids.[112] The more sterically demanding ligand **47** was shown to promote the reactions of aryl chlorides with better results than **46**. Nájera and co-workers recently reported on the synthesis of di(2-pyridyl)-methylamine–palladium dichloride complexes **48a** and **48b**, and their use in the coupling of a variety of electrophiles (aryl bromides or chlorides, allyl chlorides, acetates or carbonates) with alkyl- or arylboronic acids very low catalyst loadings at 100 °C.[113,113a] Palladium–oxime catalysts **8a** and **8b**) have also been developed. In conjunction with TBAB, these permit the coupling of aryl chlorides with phenylboronic acid in water.[55,55a–55c]

11.01.2.1.7 Supported and heterogeneous systems

Heterogeneous Pd catalysts can activate the C–Cl bond in aryl chlorides for the Suzuki–Miyaura reaction, presumably due to a synergistic anchimeric and electronic effect that occurs between the Pd surface and the aryl chlorides. Pd on carbon has been found to be a very effective pre-catalyst for a variety of substrates even under very mild reaction conditions and aqueous solvent mixtures.[114,114a–114c] In 2001, Kabalka and co-workers described that Pd powder and KF as base were useful to couple aryl iodides with arylboronic acids in methanol.[115] At the conclusion of the reaction, Pd metal could be recovered by simple decantation. The use of microwave irradiation accelerates the reaction by

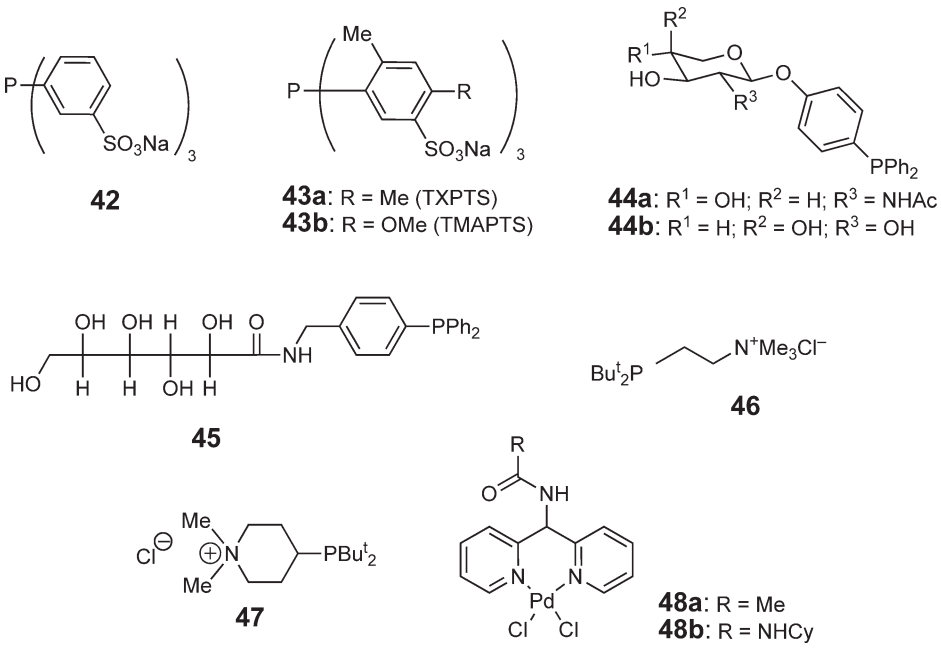


Figure 5

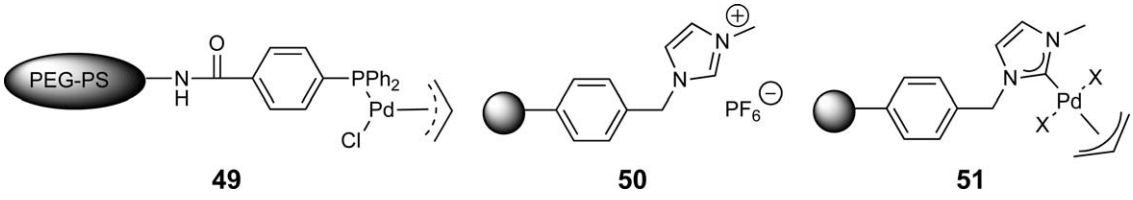


Figure 6

decreasing reaction times from hours to minutes.[116] Catalyst loadings as low as 0.005 mol% have been reported when using an air-stable Pd on activated carbon catalyst for the coupling of aryl bromides and boronic acids, with high activity for activated chlorides (TON up to 36,000).[117] In recent years, palladium nanoparticles have also been used as catalysts for Suzuki–Miyaura reactions.[118,118a,118b] The high surface/volume ratio makes them ideal for heterogeneous applications.

Recently, a Pd(0)–Y zeolite system has been reported by Artok and Bulut. In general, aryl bromides coupled with arylboronic acids at room temperature in a DMF/H_2O solvent mixture.[119] The catalyst could be recovered by filtration, but in order to obtain high yields of coupling product the temperature had to be raised to 50 °C. Regeneration of the catalyst by consecutive treatments with O_2 and H_2 was required to obtain high yields after the second use.

Another class of anchored catalysts is linked to the support through the ligand (Figure 6). Poly(ethyleneglycol)–polystyrene resin-supported palladium monophosphine complex **49** was used to catalyze the coupling of allyl acetates and aryl halides with arylboron compounds in aqueous media.[120] An *N*-heterocycle carbene analog, compound **51**, prepared from the reaction of poly(imidazoliummethyl styrene)-sg-PS resin **50** with $Pd(OAc)_2$ in a DMF/H_2O mixture at 50 °C for 2 h is also an efficient system. In DMF/H_2O mixtures 1 : 1, compound **51** efficiently catalyzed the coupling of aryl iodides with phenylboronic acid. Catalytic activity of the recovered catalyst decreased slightly in its second and third use under the same reaction conditions.

11.01.2.1.8 Non-palladium-based systems

Along with palladium, several metal-based catalysts have been used for the Suzuki–Miyaura reaction. Zhou and Fu have reported on the use of $Ni(COD)_2$ and bathophenanthroline for the coupling of unactivated secondary bromides

and arylboronic acids in the presence of KO^{t}Bu.[121] Unactivated alkyl iodides couple with aryl- or alkenylboronic acids under the same conditions. The same Ni precursor was used by Yu and Hu in combination with PCy_3 for the coupling of aryl and alkenyl arenesulfonates and arylboronic acids at room temperature.[122,123] Monteiro and co-workers have made use of $NiCl_2(PCy_3)_2$ to report the first Ni-based system for the coupling of aryl tosylates and arylboronic acids.[41f] Chang has recently reported on a heterogeneous system consisting of Ru/Al_2O_3 and NaOH in a solvent mixture DME/H_2O for the coupling of aryl iodides and arylboronate esters at 60 °C.[124] Paetzold has described the catalytic cross-coupling of aromatic carboxylic anhydrides or acid chlorides with triarylboroxines under decarbonylation, giving rise to the unsymmetrical biaryls rather than the expected diaryl ketones. This new system, which requires temperatures of 160 °C, is catalyzed by a combination $[Rh(ethylene)_2Cl]_2$/KF, and can be applied to aromatic, heteroaromatic, and vinylic carboxylic anhydrides.[125] You and co-workers have recently reported on the platinum-catalyzed Suzuki–Miyaura coupling of aryl iodides and arylboronic acids using $Pt(PPh_3)_4$ and Cs_2CO_3 in DMF at 120 °C.[126]

11.01.2.2 Reactions with Organostannane Reagents: The Migita–Kosugi–Stille Reaction

The palladium-catalyzed cross-coupling of organostannanes, discovered by the Kosugi–Migita[127,127a] and Stille[128] groups, is a very versatile and general carbon–carbon bond-forming reaction,[1] (for reviews, see Refs: 129 and 129a–129c), a special feature of which is its high chemoselectivity due to the relative inertness of the C–Sn bond. This is evidenced by the drastic reaction conditions, sometimes required for the cross-coupling. The growing availability of organostannanes and their stability to moisture and air have contributed to the widespread use of this coupling reaction. On the other hand, a disadvantage of this reaction is the toxicity of organotin reagents, which makes the coupling less attractive for large-scale processes. Tin reagents containing more alkyl groups and smaller alkyl chains show an increased toxicity.[130] This drawback is limited, owing to some recent results showing that tin derivatives of lower toxicity can be used.[131] The tolerance of the Stille reaction toward most functional groups makes it particularly effective for the synthesis of complex and functionalized molecules,[132–133l] macrocycles,[134] and polymers.[135] Some examples of compounds that include a Stille cross-coupling step in their synthesis are shown in Figure 7. Excellent publications are also available in the literature addressing mechanistic issues of this reaction.[136,136a–136f]

11.01.2.2.1 New coupling partners

In 1999, the first general method for Stille cross-couplings of aryl chlorides was reported by Fu and co-workers.[137] The reactions were catalyzed by a combination $Pd_2(dba)_3/P(^tBu)_3$ in the presence of TBAF and CsF, at 100 °C in dioxane. Phenyliodoinium dipoles have been described as suitable electrophiles for the coupling with aryltrimethylstannanes[138] and alkylstannanes.[139] Heterobenzylic sulfonium salts have also been used.[140] Recently, Dubbaka and Vogel have reported on the coupling of sulfonyl chlorides and organostannanes in good yields.[141] A combination of $Pd_2(dba)_3$, tri-(2-furyl)phosphine, and $CuBr{\cdot}Me_2S$ was used in refluxing tetrahydrofuran (THF) or toluene to carry out the reaction. In a one-step synthesis, Duchêne and co-workers have been able to prepare α-pirones from acyl chlorides with a Stille coupling,[142] while Guillaumet and co-workers recently reported on the coupling of vinyl- and arylstannanes with electron-deficient methylthioether heteroaromatics.[143] This reaction was carried out with $Pd(PPh_3)_4$ in the presence of $CuBr{\cdot}Me_2S$. New organostannanes have been employed by Rodríguez and co-workers in the *in situ* preparation and activation of monooganostannanes and their coupling with alkenyl or alkyl triflates in the presence of TBAF as a fluoride source to generate the "hypervalent" organostannanes species that undergo the transmetallation.[144,144a] By using a combination of $Pd_2(dba)_3$, PPh_3, and TBAF, Kosugi and co-workers were able to couple compounds of the general formula $ArSnBu_2Cl$ with aryl halides.[145] Osío Barcina and co-workers have recently reported on the coupling of hypervalent reagents with formula $(n\text{-}Bu_4N)^+(R^1{}_3SnF_2)^-$ (R^1 = aryl, benzyl) with vinyl and aryl triflates.[146] The hypervalent reagents are easily prepared by reaction of $R^1{}_3SnF$ and TBAF. Very recently, Kim and Yu reported on the Stille coupling of electron-deficient aryl fluorides with a variety of organostannanes in the presence of $Pd(PPh_3)_4$ in DMF at 65 °C with yields in the range 28–65%.[35]

11.01.2.2.2 Palladacycle complexes as catalysts precursors

In 1996, Louie and Hartwig demonstrated that palladacycle **1** (Figure 2) could also be used in the Stille coupling of aryl bromide substrates.[147] A turnover of 1,650 could be achieved in the reaction of 4-bromoacetophenone and $PhSnMe_3$. Complex **1** turned out to be very active for solid-phase Stille reaction of aryl bromides with polystyrene-bond stannyl components.[148] Bedford reported in 2002 that a combination of palladacycle **3a** and PCy_3 in the presence of K_3PO_4 in dioxane allowed for the coupling of unactivated aryl chlorides and aryl and vinyl stannanes at 100 °C in very high yields. Interestingly, the same results were obtained when the Pd source employed was $Pd(OAc)_2$

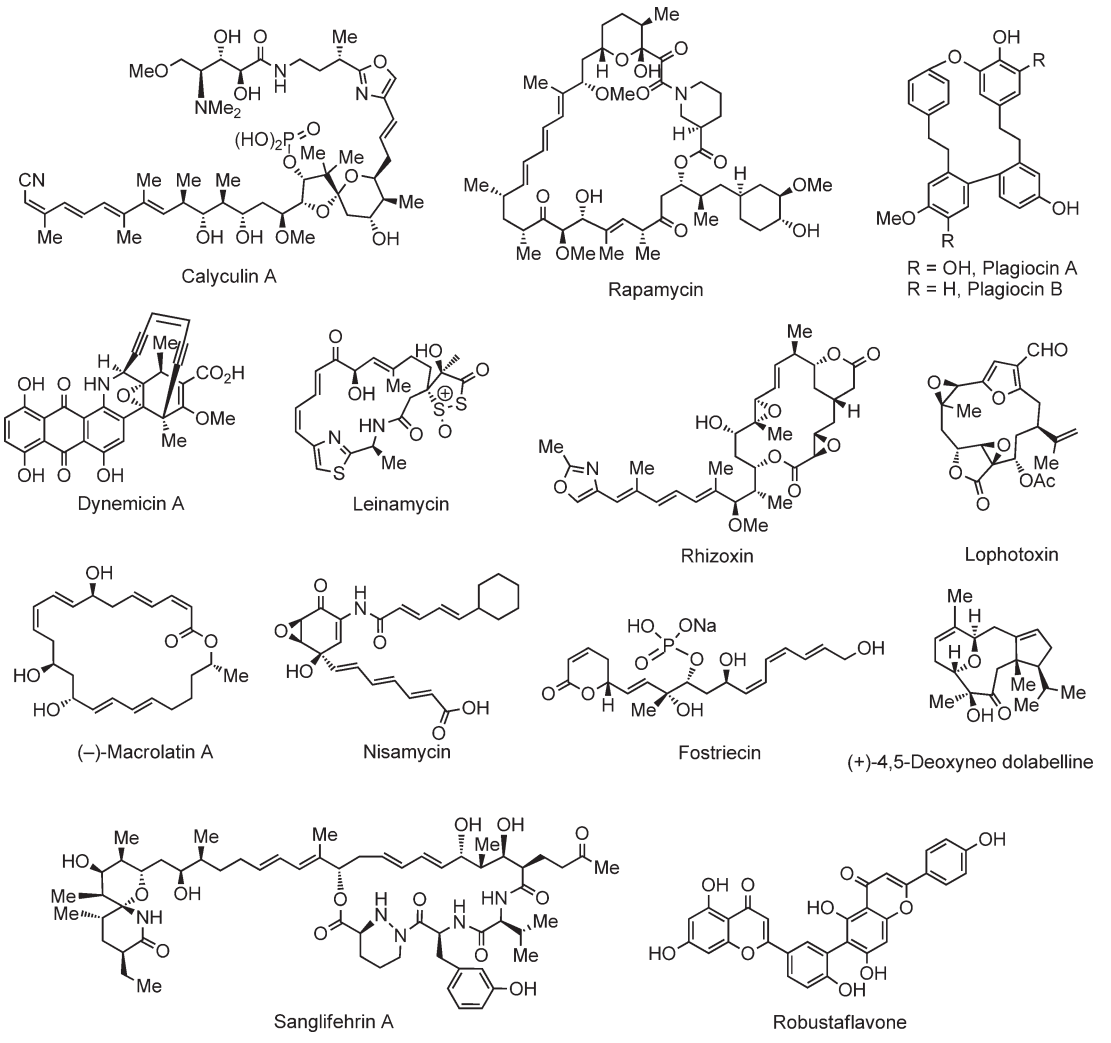


Figure 7

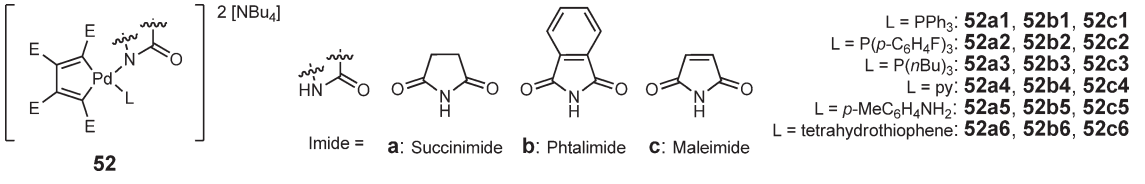


Figure 8

in the same ratios Pd : P.[149] Recently, Taylor and co-workers have reported on the synthesis of a series of palladacyclopentadiene complexes **52** (Figure 8) with mono- and didentate imidato ligands.[150] A screening for the coupling of benzyl bromide and (*Z*)-vinnylstannyl carboxylate at 60 °C showed that the tetrahydrothiophene ligand was the best for all of the imidate complexes, indicating that ligand dissociation is probably crucial for the reaction to proceed.

11.01.2.2.3 Catalytic systems composed of Pd(0) or Pd(II) and phosphines

A variety of palladium(0) or palladium(II)/phosphine systems have been used as catalyst precursors (Figure 9). Triphenylphosphine was usually the ligand of choice until Farina showed in 1991 that the use tri-(2-furyl)phosphine enhanced reaction rates.[151] The positive effects of additives such as copper salts[152,152a,152b] and diethylamine[153]

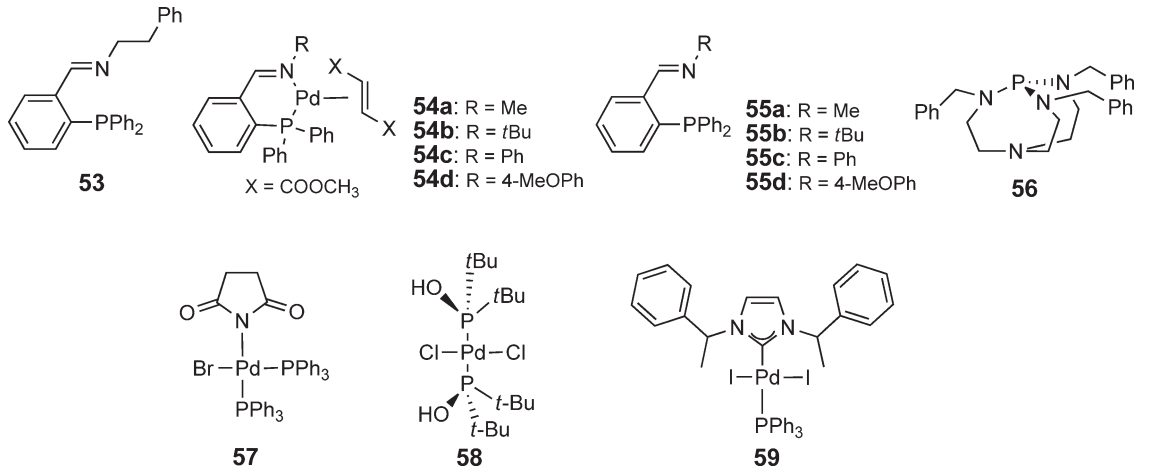


Figure 9

have been described. In 1997, Shirakawa and Hiyama reported on the use of the iminophosphine **53** in combination with $[Pd(allyl)Cl]_2$ in THF at room temperature for the coupling of aryl halides and alkynylstannanes.[154] Mechanistic studies showed that the reaction of an alkynylstannane proceeds through an unprecedent catalytic cycle, which involves an oxidative addition of the organostannanes to the Pd(0)–iminophosphine complex.

Maleczka and co-workers have performed very extensive work on systems catalytic in the organnostannane reagent.[155,155a,155b] In 2002, Scrivanti and co-workers reported on the synthesis of iminophosphine–palladium(0) complexes **54a–d** as catalysts for the Stille reaction of iodobenzene with tributylvinylstannane or tributylphenylethynylstannane.[156] In most cases, the addition of 1 equiv. of the corresponding free ligand **55a–d** to the reaction mixture increased the reaction rate. Interestingly, very similar results were obtained when combinations of $Pd(OAc)_2$ and free ligand were used. In 2004, Verkade and co-workers reported on a system for the coupling of activated and unactivated aryl chlorides and aryl and vinylstannanes: a combination $Pd_2(dba)_3$/**28** or **56** in the presence of CsF of Me_4NF in dioxane at 100–110 °C.[157]

Cheng and co-workers reported on an efficient method for the coupling allenylstannanes with aryl or alkenyl iodides for the preparation of various monosubstituted arylallenes, disubstituted allenes, and alkenylallenes.[158] The reactions were carried out in the presence of $Pd(PPh_3)_4$ and LiCl using DMF as solvent at very mild temperatures (25–50 °C). The same year, Larebours and Wolf described the use of complex **58** for the coupling of aryl bromides and chlorides and phenyltrimethylstannane in water at 135–140 °C in the presence of Cy_2NMe.[159]

One of the major breakthroughs in the Stille reaction was reported by Fu and co-workers in 2002. They used Pd/$P(^tBu)_3$ in a 1 : 2 ratio as a very reactive catalyst for Stille reactions of aryl bromides and chlorides.[160] An unprecedented array of aryl chlorides could be cross-coupled with a range of organotin reagents, including $SnBu_4$. Tetra-*ortho*-substituted biaryls could be synthesized using this system, and aryl chlorides could be coupled in the presence of aryl triflates. When the commercially available $Pd(P(^tBu)_3)_2$ was used, excellent yields were obtained. Pd/$P(^tBu)_3$ also functions as an active catalyst for Stille reactions of aryl bromides with vinyl-, alkynyl-, and arylstannanes, furnishing the first general method at room temperature for these cross-couplings. Later, these researchers established that, in the presence of PCy(pyrrolidinyl)$_2$ (pyrrolidinyl = 1-pyrrolidinyl), Stille cross-couplings of alkyl bromides and iodides not only with vinyl stannanes, but also with aryl stannanes could be accomplished.[161] Changing the phosphine to $P(^tBu)_2Me$ or to the corresponding phosphonium salt, the Stille cross-soupling of alkenyltin reagents and functionalized alkyl bromides possessing β-hydrogens at room temperature was also possible.[162]

In 2003, Fairlamb and co-workers reported on the synthesis of complex **57** as a novel catalyst for Stille reactions.[163] The complex is prepared in one step from $Pd_2dba_3{\cdot}CHCl_3$, PPh_3, and *N*-bromosuccinimide, and catalyzes the coupling of allylic and benzylic bromides with a variety of organostannanes in toluene at 60 °C.

11.01.2.2.4 Catalytic systems composed of Pd(0) or Pd(II) and *N*-heterocyclic carbenes

In 2001, Nolan described the palladium/imidazoilium salt-catalyzed coupling of aryl halides with hypervalent organostannanes.[164] The imidazolium salt **36** in combination with $Pd(OAc)_2$ and TBAF was found to be most effective for the cross-coupling of aryl bromides and electron-deficient aryl chlorides with aryl and vinyl stannanes.

The same year, Herrmann and co-workers prepared a series of mixed palladium(II) complexes bearing *N*-heterocyclic carbenes and alkyl or arylphosphines.[165] Complex **59** was identified as the most active catalyst for the coupling of aryl bromides, but failed in the case of aryl chlorides.

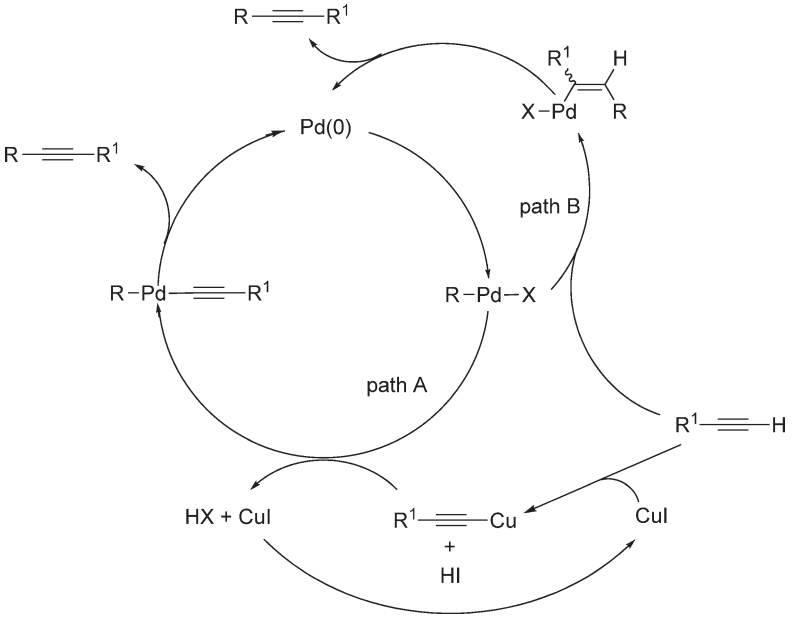
11.01.2.2.5 Other systems

Triphenylarsine is commonly used as a replacement for phosphines.[118,118a,118b] In 1995, Roth and Farina described the coupling reaction of aryl and vinyl iodides, triflates, and bromides with organostannanes using Pd on carbon in the presence of CuI and triphenylarsine.[166] Recently, Handy and Scott reported on the Stille coupling of aryl iodides and bromides with a variety of organostannanes.[167] The reaction was carried out in 1-butyl-3-methylimidazolium tetrafluoroborate, at room temperature, in an ionic liquid, in the presence of $PdCl_2(PhCN)_2$, CuI, and $AsPh_3$ at 80 °C. The facile recycling of solvent and catalyst system allowed for its use, at least five times with little loss of activity.

11.01.2.3 Reactions of Terminal Alkynes

In 1968, Stephen and Castro reported on the direct introduction of sp^2-carbon to alkynes by the reaction of Cu acetylides with aryl and alkenyl halides to arylalkynes and alkenylalynes.[168] Cassar[169] and Heck,[170] and later Sonogashira[171,171a] found that the coupling of terminal alkynes with halides can proceed smoothly by using Pd catalysts. Sonogashira and Hagihara found that the addition of CuI as co-catalyst gave better results; this is the basis for what now is known as the Sonogashira reaction.[1,172] The reaction follows the general Scheme 1; the transmetallating species, Cu–acetylide, is formed from the *in situ* reaction of CuI and the 1-alkyne (Scheme 3, path A). Alternatively, a less likely Cu-free mechanism can also be involved. In this case, carbopalladation (or insertion) of a triple bond with R–Pd–X generates an alkenylpalladium intermediate that undergoes dehydropalladation (path B).

Trialkylsilanes are commonly used as protecting groups for terminal alkynes. The low polarization of the C–Si bond makes them stable to classical Sonogashira reaction conditions. An added advantage is that many alkynylsilanes are commercially available, for example, trimethylilylacetylene (TMSA), triethylsilylacetylene (TESA) and triisopropylsilylacetylene (TIPSA).[1b] Once the coupling reaction with a haloarene is complete, the trialkylsilyl group can easily be removed *in situ* with aqueous or methanolic KOH or K_2CO_3,[173] affording a new enlarged terminal alkyne that can be coupled again if necessary. Alkynylsilanes can also be used for direct cross-coupling with haloarenes (see Section 11.01.2.3.2.1).



Scheme 3

11.01.2.3.1 The Sonogashira coupling reaction

The Sonogashira reaction has become the most widely used of the palladium-catalyzed alkynylation methods due to its generality and reliability, particularly in the context of total synthesis. Some recent examples are shown in Figure 10.[174,174a–174c]

11.01.2.3.1.(i) Palladacycle complexes and systems composed of Pd(0) or Pd(II) derivatives and *N*-heterocyclic carbenes as catalysts precursors

Herrmann reported using 0.1 mol% of palladacycle **60** (Figure 11) for the coupling of aryl bromides and terminal acetylenes at 90 °C with no added CuI.[175,175a] The Nájera group reported on two different systems for the Sonogashira reaction. The first system consisted in the use of the oxime palladacycles **7a–f** at elevated temperatures, without the aid of CuI or an amine base, for the coupling of aryl iodides and bromides.[176] They also reported on the use of complex **48b** in aqueous media for the coupling of aryl iodides and bromides and terminal acetylenes in excellent yields.[113a]

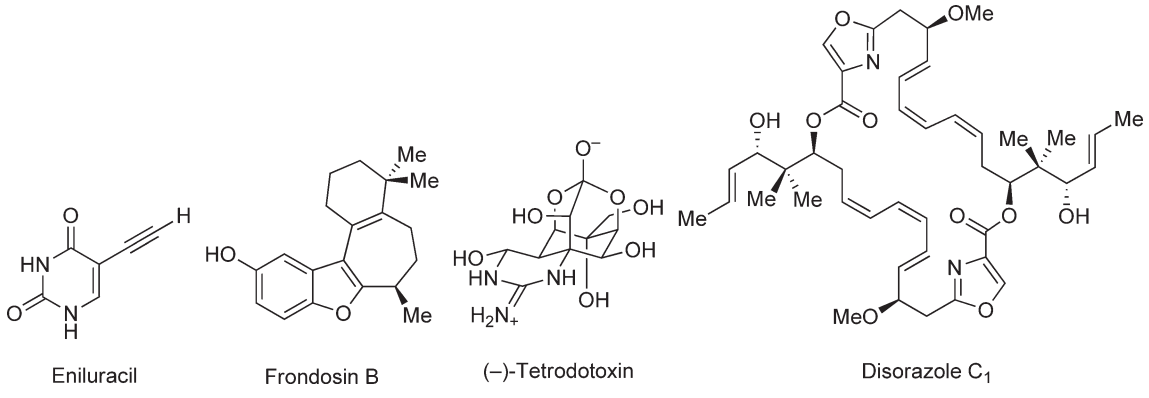


Figure 10

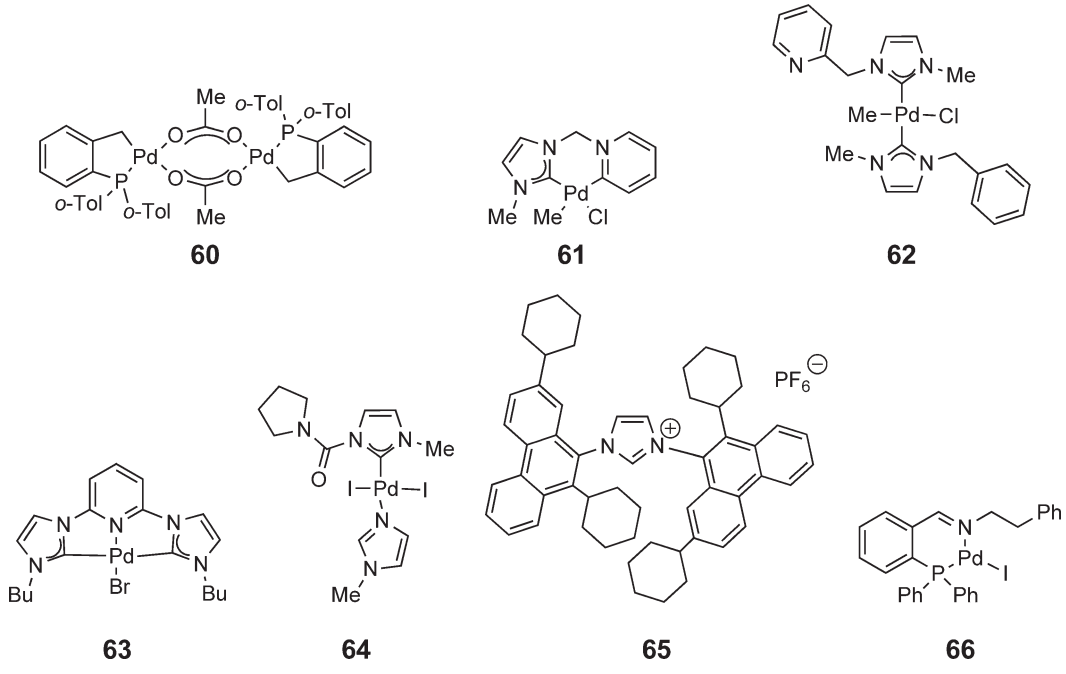


Figure 11

Regarding the use of *N*-heterocyclic carbenes, complex **32** was used by Herrmann and co-workers for the coupling of activated aryl bromides with phenylacetylene in the presence of Et_3N at 90 °C.[87] Cavell and McGuiness made use of complexes **61** and **62** for the coupling of activated aryl bromides under the same conditions.[177] Complex **61** performed better than the biscarbene **62**, presumably due to a less crowded environment around the palladium center. Complex **63** was designed by Crabtree and co-workers, and tested in combination with CuI for the coupling of aryl iodides and bromides. Iodobenzene coupled in very high yield and short reaction time, while the activated bromide 4-bromoacetophenone did not lead to any coupling product.[178] An additional example of the use of NHC-bearing complexes for the Sonogashira reaction is complex **64**, which allowed for the coupling of deactivated bromides with a variety of terminal acetylenes in the presence of CuI and PPh_3 in DMF at 80 °C.[179] The reactions could be carried out at room temperature, when coupling activated and unactivated aryl iodides. Andrus and co-workers recently reported on the coupling of unactivated aryl iodides and bromides with a variety of terminal acetylenes using a combination of phenantryl ligand **65** and $Pd(PPh_3)_2Cl_2$, in the presence of K^tOBu in refluxing THF in good yields (Figure 11).[180]

11.01.2.3.1.(ii) Catalytic systems composed of Pd(0) or Pd(II) and phosphines

The most common utilized ligands for the Sonogashira reaction are phosphines, especially PPh_3. For example, Draper and Bailey reported on the use of $Pd(PPh_3)_2Cl_2$ for the coupling of aryl iodides and phenylacetylene at room temperature in the presence of CuI and Et_3N using THF as solvent.[181] The same catalyst was used by Novák and Kotschy for the first cross-coupling reactions on chlorotetrazines to furnish a variety of alkynyl tetrazines in good to moderate yield.[182]

Due to their success in other coupling reactions, electron-rich and/or phosphines have been applied with great success. Buchwald and Fu reported on the use of $P(^tBu)_3$ in combination with $Pd(PhCN)_2Cl_2$ and CuI for the coupling of electron-rich aryl bromides and phenyl and alkylacetylenes using $^iPr_2$–NH in dioxane at room temperature,[183] and Herrmann used the same phosphine, this time simply with $Pd_2(dba)_3$, in Et_3N at room temperature, for the coupling of aryl bromides.[184] Recently, Plenio and co-workers have used the phosphonium salt $(1\text{-Ad})_2PBn{\cdot}HBr$ in toluene at 120 °C in the presence of Na_2CO_3 and CuI, with Na_2PdCl_4 as the palladium source.[185] Netherton and Fu also used a phosphonium salt in combination with CuI, $[PH(^tBu)_3]BF_4$, for the coupling of 4-bromoanisole and phenylacetylene in nearly quantitative yield at room temperature.[65]

11.01.2.3.2 Acetylene surrogates

Acetylides of other main group metals such as B (Suzuki–Miyaura coupling), Mg (Kumada–Corriu coupling), Si (Hiyama coupling), Sn (Kosugi–Migita–Stille coupling), and Zn (Negishi coupling) have been found to be suitable partners. In-,[186,186a] Ag-,[187] Al-,[188] and Ge-[189,189a] containing acetylides have also been investigated for potential cross-coupling capabilities. The coupling of these species with halides proceeds without Cu. As in most of the literature regarding the reactions of terminal alkynes, these couplings will be discussed in this section since the same products are obtained by this method and the Sonogashira reaction.

11.01.2.3.2.(i) Alkynylsilicon reagents

As previously mentioned, organosilicon reagents have been used extensively for the protection of terminal acetylenes, due to their stability to classical Sonogashira reaction conditions. On the other hand, in the presence of fluoride ions, pentacoordinate silicate intermediates are formed, which undergo transmetallation in the presence of palladium catalysts (see Section 11.01.2.5). More recently, it has been found that alkynylsilanes cross-couple with organohalides in the presence of catalytic amounts of CuCl and $Pd(PPh_3)_4$ in DMF through an organocopper intermediate as in the Sonogashira reaction. This modification is known as the "sila-Sonogashira–Hagihara" coupling, and it has been used for the coupling of aryl[190,190a] and alkynyl[191] triflates at 80 °C in modest yields. Activated chlorides can be coupled, also in modest yields, by increasing the temperature to 120 °C and using $Pd(dppb)Cl_2$ as palladium source. Under similar conditions but in the absence of palladium catalyst, the couplings of arylchloroethynes,[192] acyl chlorides,[193] and alkenyl halides[194] with alkynylsilanes have also been reported.

Nolan and co-workers reported on the coupling of arylbromides with TMS acetylenes making use of the imidazolium salt **34** in combination with $Pd(OAc)_2$ and CuI.[195] Slightly lower yields were obtained in the absence of the copper salt. Ag_2O and AgI, instead of copper salts, have also been used with $Pd(PPh_3)_4$ for the coupling of aryl iodides with bis(TMS)alkynes[196,196a] and the coupling of vinyltriflates with a variety of alkynylsilanes,[197] respectively.

11.01.2.3.2.(ii) Alkynyltin reagents

Preparation of alkynyltin reagents is typically achieved by lithiation of the corresponding terminal acetylene or by formation of the alkynylmagnesium reagent, followed by transmetallation with trialkyltin chloride.[198] The process can be performed to generate the tin species *in situ*, prior to the coupling with the organic electrophile. Alternatively, these can be prepared by reaction of the acetylene with $RSnNR^1{}_2$.[199]

Some of the most common catalysts for this coupling are $Pd(PPh_3)_4$ and $Pd(PPh_3)_2Cl_2$. The first one has been used for the coupling of alkenyl,[200,201] aryl,[202] and heteroaryl[203] iodides and alkenyl[204] and aryl triflates[205,206] with alkenyltin reagents under mild reaction conditions (50–80 °C) leading to high yields, while $Pd(PPh_3)_2Cl_2$ has been used for the coupling of alkenyl[207,208] and aryl[209] iodides at room temperature. Other palladium reagents have been used in this reaction: $Pd(MeCN)_2Cl_2$,[210,211] $Pd(PhCN)_2Cl_2$,[212] $Pd_2(dba)_3$,[213] $PdBn(PPh_3)_2Cl$,[214] and iminophosphino catalyst **66**.[215]

11.01.2.3.2.(iii) Alkynylmagnesium reagents

In addition to their use as precursors for alkynylboron, tin or zinc compounds, alkynylmagnesium reagents show a moderate reactivity toward the coupling with haloarenes and haloalkenes.[216] They are often commercially available, or easy to prepare. Their main drawback is their low chemoselectivity and high nucleophilicity, which implies incompatibilities with functional groups such as nitro and carbonyl.

Aryl and heteroaryl iodides coupling with alkynylmagnesium reagents can be performed in the presence of $Pd(PPh_3)_4$, in THF, at room temperature,[217,217a] while the coupling of aryl triflates has been reported to proceed smoothly using $Pd(alaphos)Cl_2$ as catalyst, in combination with LiBr in Et_2O in toluene achieving high yields at mild temperature (30 °C) (where alaphos = (2-dimethylamino)propyldiphenylphosphine).[218,218a,218b] With the same system, the coupling of aryl iodides can be performed with no LiBr added. Very recently, Luh and co-workers reported on a system that uses a combination of $Pd_2(dba)_3$ and PPh_3 for the coupling reactions of unactivated alkylbromides and iodides with an alkynylmagnesium reagent in THF at 65 °C.[219]

An example of a non-palladium-based system was reported by Madec *et al.* They made use of $Ni(PPh_3)_2Cl_2$ for the coupling of vinylcarbamates and alkynylmagnesium reagents in benzene at higher temperatures (70 °C), and obtained good yields of product.[220]

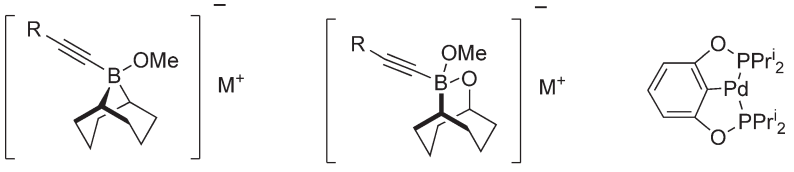
11.01.2.3.2.(iv) Alkynylboron reagents

In 1995 Soderquist[221] and Fürstner[222] independently reported that alkynylborates **67**, prepared *in situ* from 9-OMe-9-BBN and alkynylmetals, effectively cross-couple with aryl and alkyl bromides using a Pd catalyst under base-free conditions at 60 °C. Soderquist and co-workers also reported on the synthesis of alkynylborinates **68**, which are easier to isolate (Figure 12).[223]

Lithium alkynyl(trialkoxy)borates have also been found suitable partners for this reaction, and have been successfully coupled with aryl bromides,[224,225] iodides,[226] and allyl carbonates.[227] Molander recently reported on the coupling of alkynyltrifluoroborates with aryl bromides, triflates, and chlorides in moderate yields using $Pd(dppf)Cl_2$ as catalyst and Cs_2CO_3 as base, in THF or water at 60 °C.[228]

11.01.2.3.2.(v) Alkynylzinc reagents

In the late 1970s, Negishi and co-workers found that alkynylzincs gave superior yields and increased reaction rates over other alkynylmetals in cross-coupling reactions with organic electrophiles,[229] making this cross-coupling commonly referred to as the Negishi coupling (see Section 11.01.1.2.6). This protocol should be considered especially in cases involving electron-withdrawing groups conjugated to the alkyne, where it has been proved superior to the



67 **68** **69**

Figure 12

Sonogashira protocol.[230] The alkynylzinc reagent can also be prepared *in situ* form terminal alkynes by addition of $ZnCl_2$ as a co-catalyst.[231]

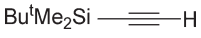
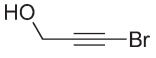
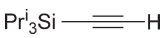
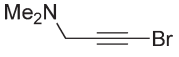
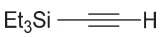
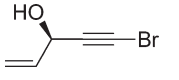
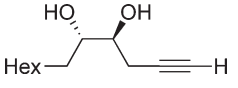
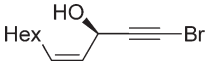
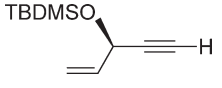
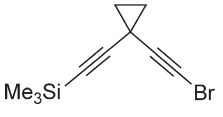
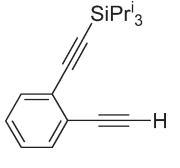
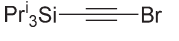
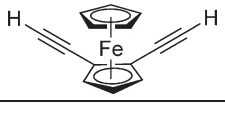
Alkenyl iodides can be coupled with organozinc reagents in moderate to good yields at room temperature using $Pd(MeCN)_2Cl_2$,[232] $Pd(PPh_3)_4$,[233] or a combination of $Pd(dba)_2$ and P(2-furyl)$_3$.[234] Alkenyl bromides can be coupled in very good yields using Pd(DPEphos)Cl_2 in THF at 0 °C,[235] and alkenyl triflates using $Pd(PPh_3)_4$ at room temperature.[236] This last example also included the coupling of heteroaryl and alkynyl iodides with alkynylzinc reagents.

Aryl iodides also couple with organozinc reagents at room temperature in the presence of $Pd(PPh_3)_4$ in THF.[212] An increase in temperature is required when multiple electron-donating groups are present.[237] Acyl chlorides also couple at room temperature using the same catalyst/solvent system.[238] As an example of an *in situ* system, Eberhard and co-workers were able to couple a variety of aryl chlorides with phenylacetylene using pincer palladacycle **69** (Figure 12) in the presence of ZnCl and Cs_2CO_3 at 160 °C, in 19–91% yield.[239] Very recently, Saá and co-workers reported on the synthesis of ynamines in high yields by Negishi coupling of terminal alkynyl amides with heteroaryl iodides in the presence of $Pd_2(dba)_3$ and PPh_3.[240]

11.01.2.3.3 The Cadiot–Chodkiewicz reaction

Haloalkynes can cross-couple with alkynylcopper species to give unsymmetrical 1,3-butadiynes, with or without the need of Pd complexes. This cross-coupling takes place in a pyridine solution at room temperature, being analogous to the Stephen–Castro coupling.[241,241a] The reaction between a terminal alkyne and a haloalkyne using a catalytic amount of Cu(I) salt in an amine base is known as the Cadiot–Chodkiewicz reaction.[242,242a,242b] Slow addition of the halide is often required to minimize homocoupling as a side-reaction, and usually $NH_2OH{\cdot}HCl$ is added as a reducing agent. A list of recent examples in the literature is shown in Table 3.[243–248] The amount of homocoupling byproducts can be reduced by introducing a palladium co-catalysts such as $Pd(OAc)_2$,[249] $Pd(PPh_3)_2Cl_2$,[250] or $Pd(PPh_3)_4$,[251] and carrying out the reactions under anaerobic conditions.

Table 3

Haloalkyne	*Terminal alkyne*	*Conditions*	*References*
		CuCl, $EtNH_2$, $NH_2OH{\cdot}HCl$, $BuNH_2$, H_2O	
		CuCl, $EtNH_2$, $NH_2OH{\cdot}HCl$, $BuNH_2$, H_2O	243
		CuCl, $EtNH_2$, $NH_2OH{\cdot}HCl$, $BuNH_2$, H_2O	
		CuCl, $EtNH_2$, $NH_2OH{\cdot}HCl$, MeOH	244
		CuCl, $EtNH_2$, $NH_2OH{\cdot}HCl$, H_2O, MeOH	244
		i, MeLi, THF, CuCl, −78 °C ii, pyridine	246
		i, BuLi, THF, −78 °C ii, CuBr, pyridine	247
		i, BuLi, THF, −78 °C ii, CuBr, $PrNH_2$	248

11.01.2.4 Reactions with Organomagnesium Reagents: The Kumada–Tamao–Corriu Reaction

The first organomagnesium reagents were prepared over a 100 years ago by Grignard, and still occupy an important place in organic chemistry.[252] Kumada[253] and Corriu[254] independently reported on their application in nickel-catalyzed cross-coupling reactions with aryl and alkenyl halides. Thus, this coupling reaction is nowadays recognized as the Kumada–Tamao–Corriu reaction.[1,255] As previously mentioned, organoboron, tin, and zinc reagents are usually prepared from organolithium or organomagnesium reagents. Therefore, the direct couplings of these reagents are more atom economical and convenient. However, the limited access to functionalized organomagnesium reagents considerably lowered the interest and development of this reaction, since no method was available for preparing polyfunctional organomagnesium reagents. The halogen–magnesium exchange reaction,[256] developed in the 1930s, has recently resurfaced as a general method for preparing a wide range of functionalized organomagnesium compounds.[257] Also, work in the late 1990s proved the compatibility of the C–Mg bond with a number of sensitive electrophilic functional groups.[258] Because of these two factors, an impressive amount of very significant contributions have appeared in the last 5 years with very exciting improvements in the Kumada–Tamao–Corriu cross-coupling reaction.

11.01.2.4.1 Nickel-based systems

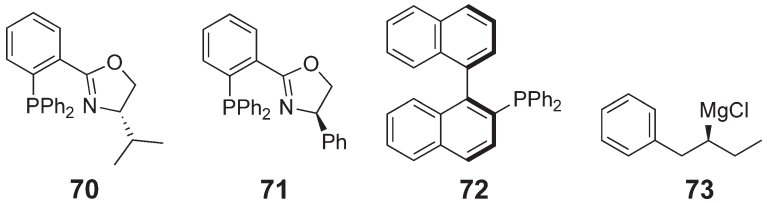
In 2000, Hermann and co-workers reported on the nickel-catalyzed cross-coupling of unactivated aryl chlorides with aryl Grignard reagents at room temperature in excellent yields.[259] The system consisted in the use of $Ni(acac)_2$ in combination with either $P(^tBu)_3$, **34**, or **36** in a 1 : 1 ratio of Ni to ligand in THF. Li and Marshall showed that air-stable phosphine sulfonides or oxides in combination with $Ni(COD)_2$ were suitable ligands to catalyze the cross-coupling of unactivated aryl chlorides with aryl Grignards.[260]

By using a variety of chiral ligands **70–72** (Figure 13), Hayashi and co-workers reported on the asymmetric cross-coupling of dinaphtothiophene with a variety of Grignard reagents to give axially chiral 1,1′-binaphthyls.[261] These reactions were carried out at room temperature using $Ni(COD)_2$ as the nickel source, with 54–97% yield and 14–95% ee. They later reported on the asymmetric synthesis of axially chiral biaryls with the same system, but this time using dibenzothiophenes as the starting materials.[262]

Grignard reagent **73** (Figure 13) in ca. 90% ee was coupled with vinyl bromide using either Ni(0) or Pd(0) catalysts in THF at −78 °C to give the corresponding product with full retention of configuration (ee = 88–89%).[263] The use of Fe- or $Co(acac)_3$ leads to considerable racemization. Also, Ni complexes allowed for higher yields than when their Pd congeners were used.

Alkyl bromides and tosylates can be efficiently coupled with a variety of R–MgBr (R = primary or secondary alkyl, aryl) in the presence of $NiCl_2$ and 1,3-butadiene as additive instead of a phosphine ligand.[264] Alkyl fluorides can couple with the same types of Grignard reagents in similar conditions, even when using $CuCl_2$ as catalyst.[265] It was shown later that the selection of the additive is critical, since the use of *N*,*N*-bis(penta-2,4-dienyl)benzylamine as additive allowed for a drastic reduction in catalyst loading for the coupling of *n*-nonylfluoride and *n*-PrMgBr.[266]

Dankwardt and Miller reported on the coupling of modified alkyl and alkenyl Grignard reagents with aryl and heteroaryl nitriles for the preparation of styrene and alkyl arene derivatives. The reactions were carried out using $NiCl_2(PMe_3)_2$ in refluxing THF.[267] Alkyl tosylates have also been reported to couple with aryl Grignards in the presence of $Ni(dppf)Cl_2$ in refluxing THF leading to moderate to good yields (43–85%).[268] Dankwardt also described the use of $NiCl_2(PCy)_2$ for the coupling of aromatic alkyl ethers with aryl organomagnesium reagents.[269] The reaction supported functionalities such as alcohols, amines, enamines, and *N*-heterocycles in the aromatic ether substrate. It was also found that alkyl and alkenyl Grignard reagents were not suitable partners for this system.



70 **71** **72** **73**

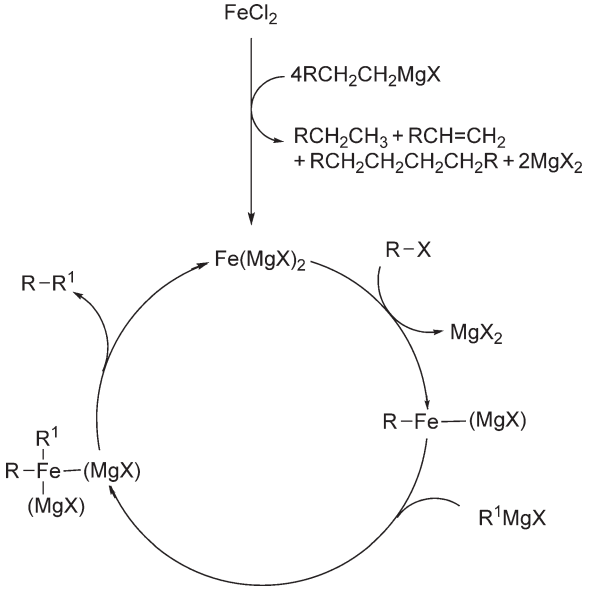
Figure 13

11.01.2.4.2 Iron-based systems

The use of iron salts as catalysts for cross-coupling reactions was already reported by Kochi and co-workers in 1971,[270] although little attention was given to this possibility in the following decades. A renewed interest has risen in the last 5 years in the use of cheap, stable, commercially available, and toxicologically benign iron salts in the Kumada–Tamao–Corriu reaction. In 1998, Cahiez showed that organomagnesium reagents readily reacted with alkenyl iodides, bromides, or chlorides in the presence of $Fe(acac)_3$ and NMP at −5 to 0 °C, with high stereo- and chemoselectivity and group tolerance.[271] The method is of special interest when functionalized arylmagnesium reagents are used, since Ni(0)- or Pd(0)-catalyzed reactions require temperatures above 20 °C, resulting in the destruction of sensitive functions either in the substrates or the product.[272]

Recently, Alami, and Figadère reported on the iron(III)-catalyzed cross-coupling of chloroenynes with alkyl Grignards to synthesize a variety of substituted quinolines, using very mild conditions, using $Fe(acac)_3$.[273] The same system was later used for the cross-coupling reaction of 1,1-dichloro-1-alkenes with Grignard reagents,[274] leading mainly to the dicoupled products in good to excellent yields. $Fe(acac)_3$ was also used by Nagano and Hayashi for the coupling of aryl organomagnesium reagents with primary and secondary alkyl bromides possessing β-hydrogens in refluxing diethyl ether.[275] Nakamura and co-workers reported on the $FeCl_3$-catalyzed coupling of primary and secondary alkyl halides with the same Grignard reagents in THF, using *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (tmeda) as additive, leading to excellent yields.[276]

Fürstner has most recently contributed to the development of iron-catalyzed Kumada–Tamao–Corriu reactions. A series of key articles have appeared addressing different aspects of the reaction: mechanism, scope, and applications. In 2002, taking recent advances in the field of "inorganic Grignard reagents" into consideration,[277] Fürstner suggested the catalytic cycle depicted in Scheme 4 (spatial distribution of the ligands is arbitrary for sake of clarity).[278] The mechanism depicts the reaction of $FeCl_2$ with 4 equiv. of RMgX to produce a new species of formal composition [$Fe(MgX_2)$], which implies that the reduction process generates Fe(II) centers, very nucleophilic, that insert into the aryl halide to initiate the cycle. The reactions carried out for the coupling of aryl chlorides, tosylates, and triflates showed to be virtually independent of the chosen iron salt, and the authors decided to use $Fe(acac)_3$ for sake of convenience. On the other hand, the system was found to be highly dependant on the nature of the nucleophile; secondary alkyl Grignards reacted better with Fe(salen)Cl complex **74** (Figure 14). In all cases, the couplings were performed in THF/*N*-methylpyrrolidone (NMP) mixtures, and the products were obtained in very good yields. A more extended report was published shortly after remarking on the compatibility of a large variety of functional groups.[279] Enol triflates, acid chlorides, and dichloroarenes are also suitable partners for the reaction.[280] This catalytic system was used in the total synthesis of the natural product latrunculin B[281] and the inmunosuppresive agent FTY720 (Figure 15).[282]



Scheme 4

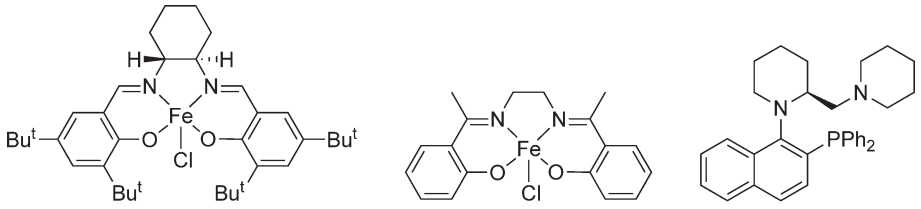


Figure 14

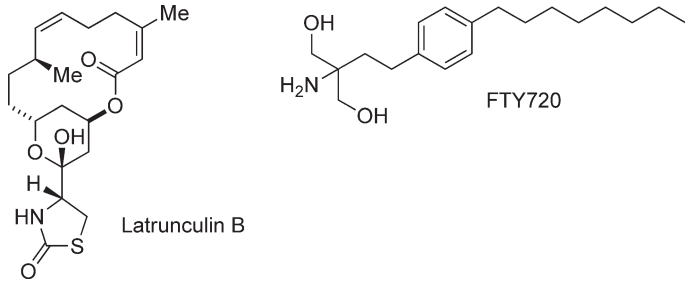


Figure 15

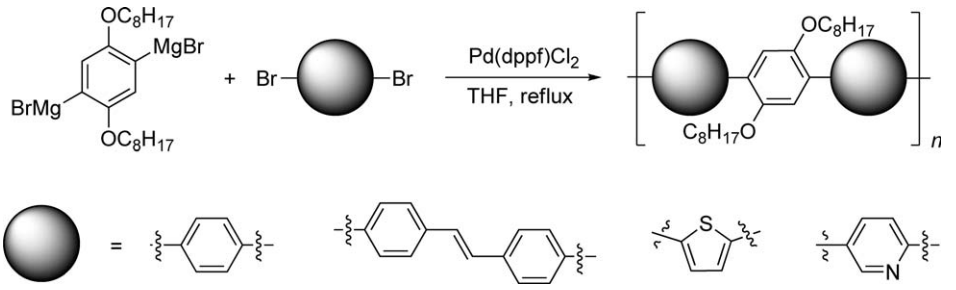
Following these results with the salen complex, Bedford reported on the synthesis of a series of Fe(III)-salen-type complexes and the use of one of them, **75** (Figure 14), for the coupling of aryl Grignard reagents with primary and secondary alkyl halides, in Et_2O at 45 °C.[283] Fürstner subsequently reported on the use of the tetrakis(ethylene)ferrate complex $[Li(tmeda)]_2[Fe(C_2H_4)_4]$ to effectively catalyze the cross-coupling of alkyl halides with a variety of aryl Grignard reagents in THF at −20 °C in excellent yields.[284]

11.01.2.4.3 Palladium-based systems

In 1999, Huang and Nolan reported the first example of cross-coupling of unactivated aryl chlorides, bromides, and iodides with aryl Grignard reagents in excellent yields. The reactions were mediated by a combination of $Pd_2(dba)_3$ and imidazolium salt **36** in a 1 : 4 ratio, in a THF/dioxane mixture at 80 °C.[285] Li reported on the use of a combination of $Pd_2(dba)_3$ and phosphine oxide $P(^tBu)_2{=}O$, generated *in situ* from the reaction of $P(Bu^t)_2Cl$ and H_2O, for the coupling of unactivated aryl chlorides with *o*-tolylmagnesium bromide at room temperature.[29] For the first time, lithium triarylmagnesates were coupled with heteroaryl bromides by Dumouchel *et al.* in the synthesis of 2-, 3-, and 4-quinolines, using $Pd(dba)_2$ and dppf in THF at room temperature.[286]

Beller and co-workers developed a novel method for the palladium-catalyzed cross-coupling of alkyl chlorides and aryl Grignard reagents with good functional group tolerance.[287] The system consisted of a combination of $Pd(OAc)_2$ and PCy_3 in a THF/NMP mixture; the reactions were carried out at room temperature in very good yields. They also reported the first Kumada reaction of alkyl chlorides catalyzed by a well-defined NHC-bearing complex, **40a**.[288] The reactions were carried out using the same conditions as the previous example.

Sato and co-workers described the site-selective coupling of 1,4-diiodo-1,3-alkadienes with Grignard reagents for the synthesis of fulvenes, catalyzed by $Pd(PPh_3)_4$.[289] The couplings proceeded selectively at the least hindered vinylic carbon. Asymmetric couplings in good yields and ee were reported by Horibe *et al.* for the reactions of 1-phenylethylmagnesium chloride and (*E*)-*β*-bromostyrene derivatives using the axially chiral ligand **76** and $Pd_2(dba)_3{\cdot}CHCl_3$.[290] Chemoselective reaction of the vinyl bromide instead of the aryl bromide, when both are present in the substrate, was also described. Naso and co-workers recently made use of the Kumada–Tamao–Corriu reaction as a general route to polymers.[291] By using a variety of dibrominated halides and bis-organomagnesium reagents in the presence of $Pd(dppf)Cl_2$ in refluxing THF, they were able to synthesize a series of polyconjugated polymers (Scheme 5).



Scheme 5

11.01.2.4.4 Other systems

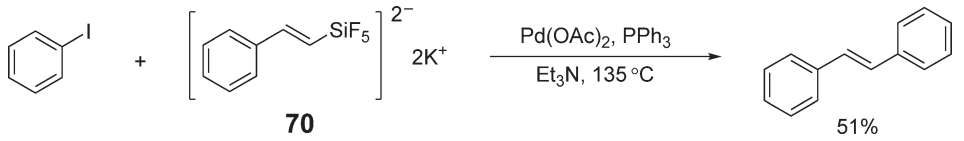
In 2001, Knochel and co-workers described the CuCN·2LiCl-mediated cross-coupling of functionalized arylmagnesium reagents with functionalized alkyl and benzylic halides.[292] Stoichiometric amounts of the copper reagent, in combination with 1.9 equiv. of $P(OMe)_3$, were required, although the reactions could be carried out with catalytic (20 mol%) amounts of copper, but in lower yields. Later, they reported on the $CoCl_2$-catalyzed cross-coupling involving a variety of arylmagnesium halides and heterocyclic chlorides, in diethyl ether and at −40 °C, achieving the desired coupling products in good yields.[293] The use of $CoBr_2$ or CoI_2 reduced the reaction times, but led to lower yields. Oshima and co-workers reported that $Co(dppp)Cl_2$ effectively catalyzes the cross-coupling reaction of primary, secondary, and teriary alkyl halides with allylic Grignard reagents in THF at room temperature.[294] A more detailed study was reported shortly after which included benzylic Grignard reagents.[295]

11.01.2.5 Reactions with Organosilicon Reagents: The Hiyama Reaction

In contrast to other organometallic compounds, organisilicon reagents are inert to normal palladium-catalyzed conditions, because of the low polarization of the carbon–silicon bond. Tetracoordinate organosilanes are not capable of transferring even one of their groups to palladium, as is possible with tetracoordinate organostannanes, although Si and Sn do not differ much in their location in the periodic table and possess similar electronegativities (1.96 for Sn, 1.90 for Si).[296] The low nucleophilic character of organosilicon compounds is important when considering tolerance toward a wide variety of functional groups.

One of the first indications that higher valent silanes could be useful donors in palladium-catalyzed cross-coupling reactions was reported by Kumada and Tamao, when they observed that the dipotassium salt of pentafluorosilicate **70** could transfer its vinylphenyl group for the palladium-catalyzed coupling with iodobenzene at high temperature (Scheme 6).[297]

The coupling of organosilicon compounds with organic electrophiles was not disclosed until 1988 by Hatanaka and Hiyama,[298] when they demonstrated that through the addition of an appropriate silicophilic nucleophile, those desired pentacoordinate species can be generated *in situ* and transfer an unsaturated group. Nucleophilic fluoride sources were found to be the additive of choice, typically TASF, TBAF, and, in some cases, KF and CsF. These are the fundamental concepts of what is nowadays called the Hiyama reaction.[1,299,299a–299f] The use of fluoride activation has some drawbacks such as the cost and corrosiveness of the fluoride ion sources and their incompatibility with common protective groups. Several fluoride-free systems have been reported that employ either other activators or other organosilicon reagents. Very recently, Denmark and co-workers have done very extensive work in this area describing mechanistic details of the fluoride-promoted and the fluoride-free cross-coupling reactions of organosilicon reagents with aryl and alkenyl iodides.[300,301]



Scheme 6

11.01.2.5.1 Coupling of arylsilanes

In 1996, Hiyama and co-workers reported on the cross-coupling of activated aryl chlorides with aryl- and alkenylchlorosilanes **71** (Figure 16).[302] The high temperatures required to activate the aryl chlorides did not affect the organosilanes; an added advantage that can be attributed to their relative inertness. The system could be catalyzed by a variety of phosphine-bearing palladium complexes in the presence of either KF or TBAF as promoters.

Mowery and DeShong reported on the use of siloxanes **72** (Figure 16) as versatile transmetallation agents for $Pd(dba)_3$-catalyzed couplings with aryl halides and allylic alcohol derivates, in the presence of TBAF and at high temperature (95 °C).[303] They later used aryl silatrane **73** (Figure 16) as a suitable partner for the fluoride-promoted cross-coupling with aryl triflates,[304] since attempts to couple siloxanes with triflates had led to hydrolysis of the aryl triflate. The system was palladium based, in the presence of a phosphine ligand and TBAF. Interestingly, the coupling with iodides and bromides led to lower yields than the analogous siloxane.

In 2000, Lee and Nolan described the use of the imidazolium salt **36** in combination with $Pd(dba)_2$ and TBAF for the coupling of aryl chlorides and bromides with phenyl or vinyltrimethoxysilane, using a solvent mixture 1,4-dioxane/THF at 80 °C, leading to good yields.[305] Lee and Fu recently reported the first method for achieving Hiyama couplings of unactivated alkyl bromides and iodides at room temperature.[306] The system worked with a combination of $PdBr_2$, $P(^tBu_2)Me$, and TBAF in THF. Fu and co-workers also reported the first metal-catalyzed cross-coupling of organosilicon reagents with secondary alkyl bromides and iodides.[307] In this case, the catalyst of choice was $NiBr_2$·diglyme, using bathophenantroline as ligand and in the presence of CsF as fluoride promoter. The system also allowed for the coupling with primary alkyl halides in good yields.

Following work by Hosomi and co-workers on the use of pentavalent bis(catechol)silicates **74** for Hiyama cross-couplings with electro-deficient aryl iodides, bromides, and triflates,[308] Seganish and DeShong reported on the palladium-catalyzed cross-coupling of a series of aryl bis(catechol)silicates with a large variety of electron-rich and electro-poor aryl iodides and triflates.[309] The reactions were carried out either in refluxing THF or refluxing dioxane.

11.01.2.5.2 Coupling of alkenylsilanes

Based on previous studies that demonstrated the ability of silacyclobutanes to access a hypercoordinate state in the presence of Lewis bases,[310,310a] Denmark and Choi investigated the coupling of alkenylsilacyclobutanes **75** with aryl and alkenyl iodides.[311] The reactions were carried out in the presence of $Pd(dba)_2$ and TBAF, at room temperature in THF, with excellent yields. They later reported on the use of 1-methyl-1-vinyl **76** and 1-methyl-1(prop-2-enyl)-silacyclobutane **77** as new class of alkene donors for the coupling with aryl and alkenyl iodides.[312] The compatibility with a variety of functionalities revealed these organosilicon compounds as very useful vinylation reagents. Vinylpolysiloxanes **78–80** (Figure 16) were found to be very useful precursors for this reaction as well.[313] Compound **78** was selected, on the basis of cost and efficiency of vinyl transfer, for coupling with a variety of aryl iodides in the presence of $Pd(dba)_2$ and TBAF, at room temperature in THF, a selection that led to product formation in good yields.

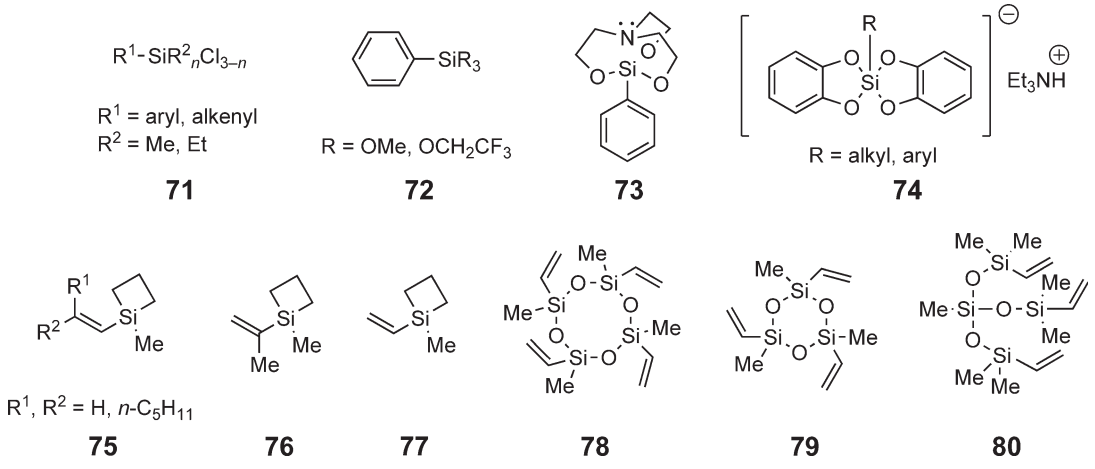
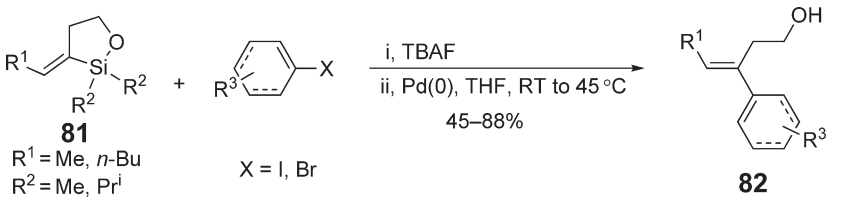


Figure 16

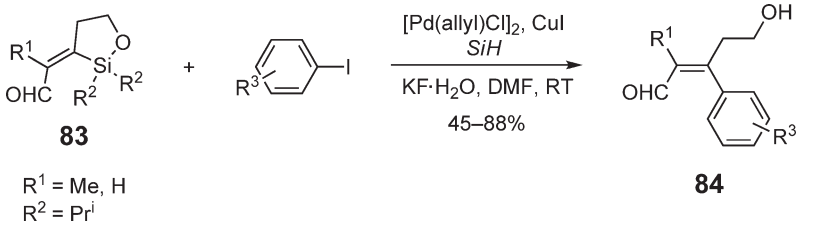


Scheme 7

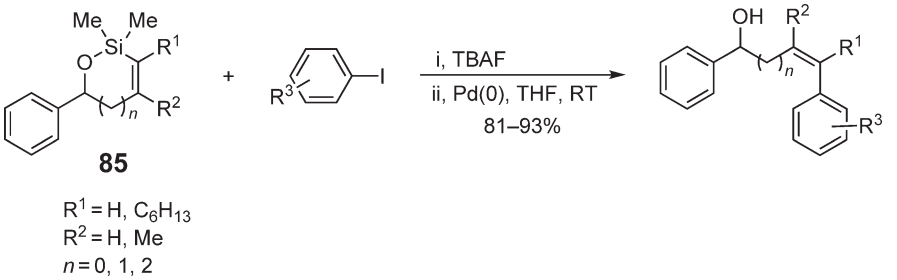
Alkylidenesilacyclopentanes **81**, formed by intramolecular hydrosilylation of homopropargyl alcohols, are proved to be efficient partners for the coupling with aryl or alkenyl iodides or bromides (Scheme 7).[314,314a] The couplings led to a series of trisubstituted homoallylic alcohols **82** in high stereoselectivities in moderate to good yields. When substrates of the type **83** are used, α,β-unsaturated aldehyde coupling products **84** can be obtained in high yields, although the coupling conditions must be reoptimized, as shown in Scheme 8, and the use of a hydrosilane SiH is required to initiate the catalytic cycle.[315] In a similar fashion, cycloalkenylsiloxanes ethers **85**, formed by ring-closing metathesis of alkenyldimethylsilylethers of ω-unsaturated alcohols, can couple with various aryl and alkenyl halides in the presence of $Pd(dba)_2$ and TBAF, at room temperature in THF, to yield highly substituted unsaturated alcohols (Scheme 9).[316]

A route to synthesize medium-sized rings with an internal 1,3-*cis*-*cis*-diene unit was also developed by Denmark in good yields and high stereospecificity.[317] Silylation of the alcohols **86** followed by ring-closing metathesis leads to substrates **87**, that undergoes an intramolecular cross-coupling reaction in the presence of $[Pd(allyl)Cl]_2$ and TBAF at room temperature. Medium-sized ring ethers **89a** and **89b** can also be prepared, using this approach, in good yields. No difference in rate or efficiency was observed for the intramolecular reaction of diasteroisomers **88a** and **88b** (Scheme 10). The system was later applied to the total synthesis of the natural product (+)-brasilenyne.[318]

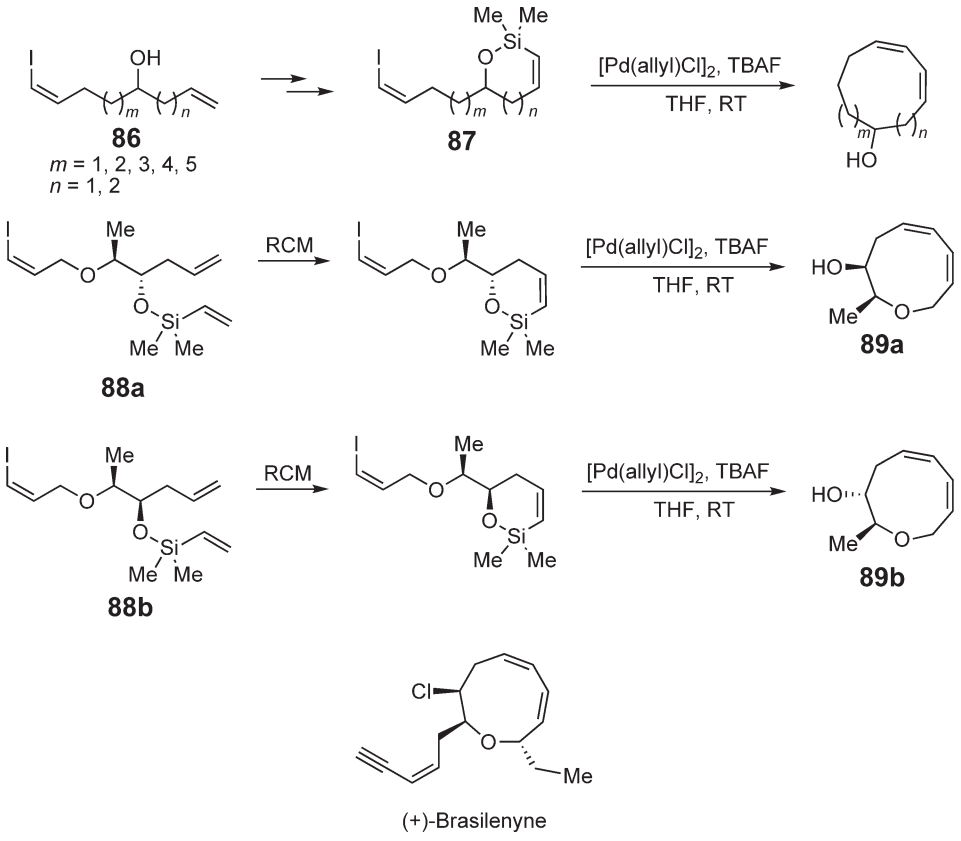
Yoshida and co-workers have reported on the use of alkenyldimethyl(2-pyridil)silanes as versatile platforms for olefin synthesis.[319,319a,319b] The combination of Mizoroki–Heck-type coupling[320] and Hiyama cross-coupling provided a diverse range of stereodefined polysubstituted olefins.



Scheme 8



Scheme 9



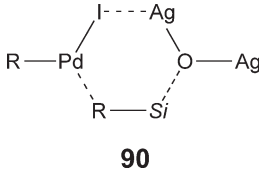
Scheme 10

11.01.2.5.3 Fluoride-free systems

Hiyama and co-workers reported on the NaOH-promoted cross-coupling reactions of aryl and alkenylchlorosilanes with organic halides (activated aryl and alkenyl bromides, iodides, and chlorides) in very good yields.[321] The reaction appeared to be very sensitive to variation of the base with LiOH, KOH, and Na_2CO_3, affording only traces of desired coupling products. The coupling reactions took place in the presence of an excess of NaOH (6 equiv. per equivalent of silane) and catalytic amounts of $Pd(OAc)_2$ and PPh_3. Phosphine-bearing palladium complexes such as $Pd(dcpe)Cl_2$ and $Pd(P^iPr_3)_2Cl_2$ also were quite effective in the coupling of alkenylchlorosilanes with aryl chlorides.

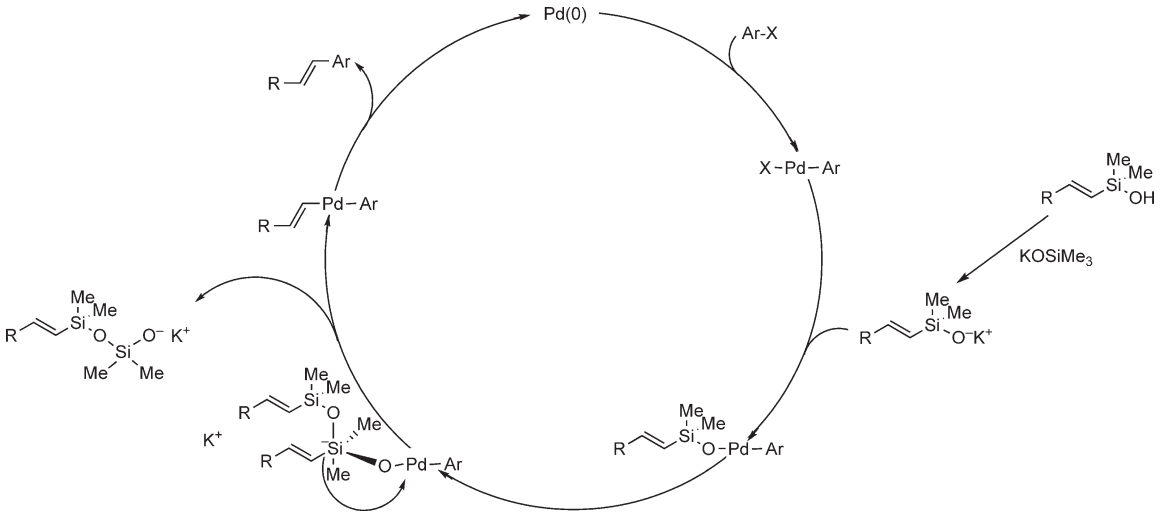
Mowery and DeShong used the commercially available hypervalent silicate complex TBAT as a phenylating agent for the cross-coupling reaction with allylic esters.[322] They later reported on the use of the same organosilane for the coupling with aryl iodides and triflates and electron-deficient aryl bromides.[323] The reactions were catalyzed by either $Pd(dba)_2$ or $[Pd(allyl)Cl]_2$ without the need of added phosphine ligands.

Silver(I) oxide has been used as promoter for the cross-coupling reactions of aryl- and alkenylsilanols, aryl- and alkenylsilanediols, and arylsilanetriols with aryl iodides.[324] Silanediols and silanetriols were, in general, more reactive than silanols. XRD analyses revealed that Ag_2O was transformed into AgI during the reaction, so the authors suggested the species **90** (Figure 17) as intermediate of the reaction after the oxidative addition of the aryl iodide



90

Figure 17



Scheme 11

to the palladium center. Yoshida and co-workers also used Ag_2O as additive for the cross-coupling of benzyl(2-pyridyl)silanes with aryl iodides, to synthesize a variety of diarylmethanes in moderate yields (34–71%).[325]

The scope of the use of the inexpensive, commercially available $KOSiMe_3$ as base was examined by Denmark and Sweis.[326] High yields and high stereospecificities were obtained for the coupling of a variety of alkenyldimethylsilanols and aryl iodides, in DME at room temperature, in very short reaction times. TBS-protected alcohols are not affected by the presence of this base. The authors proposed the formation of a silicon–oxygen–palladium linkage as a pre-association step prior to the transmetallation (Scheme 11).

Later, Denmark and Ober reported on the use of Cs_2CO_3 in combination with water for the palladium-catalyzed cross-coupling of aryl iodides and bromides with aryl silanols.[327] Although the system was not very general, since ligands, ratios, and solvents varied depending on the substrate, good yields were obtained in most cases.

11.01.2.6 Pd- or Ni-catalyzed Reactions with Organozinc Reagents: The Negishi Coupling

The cross-coupling of organozinc reagents with electrophilic halides proceeds generally with high yields and tolerates a wide range of functionalities, since organozinc reagents are inert to ketones, amino, esters, and cyano groups. The most convenient way to prepare organozinc reagents is *in situ* from organomagnesium, lithium, or aluminum reagents and $ZnCl_2$.[328] The cross-coupling reactions can be catalyzed by palladium, nickel (Negishi coupling),[1] or copper. Organozinc reagents are an excellent choice for the introduction of alkyl substituents with β-hydrogens in a substrate, since the couplings can proceed smoothly without β-elimination. Also, several reports on microwave-assisted Negishi cross-coupling have appeared in the literature.[1h,329,329a,329b] Some recent examples of compounds that include a Negishi cross-coupling step in their synthesis are shown in Figure 18.[330,330a–330n]

11.01.2.6.1 Arylzinc reagents

In 2001, Dai and Fu reported the first general method for the Negishi cross-coupling of sterically demanding vinyl and aryl chlorides with a wide range of aryl and alkylzinc reagents, using the commercially available $Pd(P(^tBu)_3)_2$ in THF/NMP mixtures at 100 °C.[331] High TONs could be obtained for the synthesis of hindered biaryls. Very recently, Milne and Buchwald used phosphine ligand **91** (Figure 19) in combination with $Pd_2(dba)_3$ to prepare tri- and tetra-*ortho*-substituted biaryls.[332] Excellent yields were obtained even at low catalyst loadings (0.1–1 mol% Pd), with a good tolerance for group functionalities.

Yang and co-workers investigated the cross-coupling of 4-tosylcoumarins and arylzinc reagents for combinatorial purposes, using $Pd(PPh_3)_4$ as catalyst in mild reaction conditions and high yields.[333] The same catalyst was used by Wei for the coupling of phenyl-, ethyl- or dibenzylzinc bromide with a variety of 4-phenylsulfinyl-2-iodo-2(*E*)-alkenols in high yields,[334] and by Bäckvall and co-workers for the cross-coupling reaction of a zinc-metallated ferrocenyl *p*-tolyl

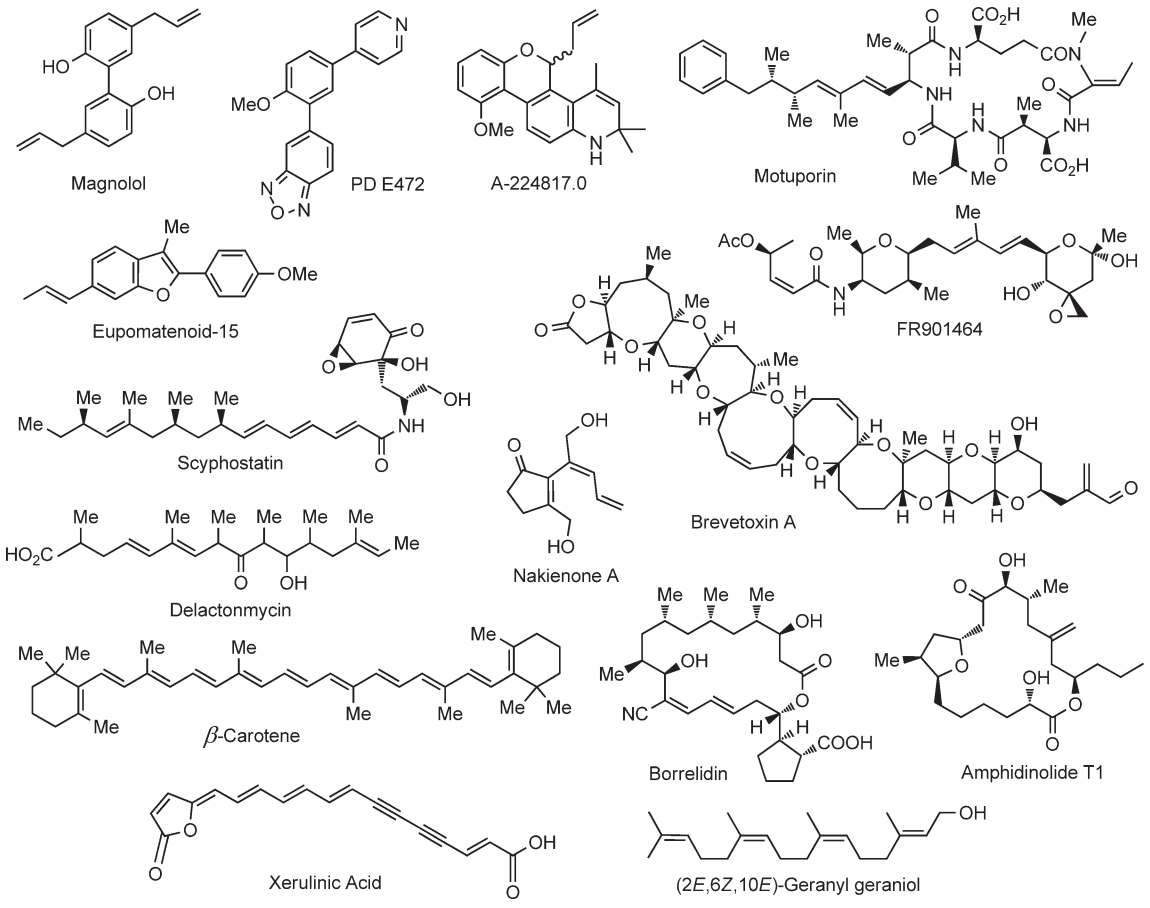


Figure 18

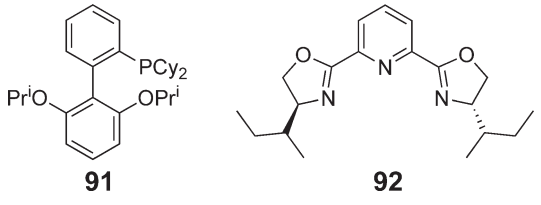


Figure 19

sulfoxide and highly substituted aryl bromides, to synthesize a series of ligands to be used in asymmetric oxidation reaction.[335] A similar system was described by Pedersen and Johannsen involving aryl iodides.[336]

A method for the synthesis of symmetrical and unsymmetrical ketones in good yields from the cross-coupling of organozinc reagents and anhydrides or mixed anhydrides, generated *in situ* from the corresponding carboxylic acids or their sodium salts and ethyl chloroformate, was developed by Wang and Zhang.[337] The reactions were catalyzed by $Pd(PPh_3)_4$ and carried out in refluxing THF.

Aryl and alkyl organozincate reagents, generated *in situ* by reaction of Grignard reagents and sub-stoichiometric amounts of $ZnCl_2$, cross-couple smoothly in refluxing THF with functionalized aryl and alkenyl as well as primary and secondary alkyl chlorides in the presence of $Pd(dppf)Cl_2$.[338]

Knochel and co-workers prepared a series of nitro-containing biphenyls in moderate to good yields by Negishi cross-coupling of various aryl iodides and nitro-substituted arylzinc reagents.[339] Heteroarylzinc chlorides can couple with vinylic and aryltellurides (R–TeBu) with in the presence of $PdCl_2$ and CuI, in THF and at room temperature, in high yields and with high stereoselectivities.[340]

11.01.2.6.2 Alkenyl- and alkylzinc reagents

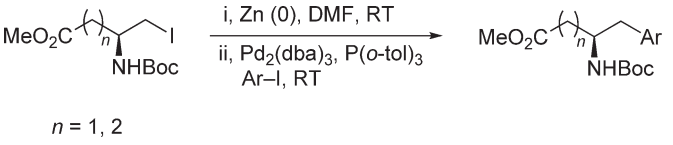
In 1997, Dunn and Jackson reported on a new approach to the synthesis of di- and tripeptides with unnatural amino acids by converting di- and tripeptides into organozinc reagents and coupling them with aryl iodides or acyl chlorides in the presence of $Pd_2(dba)_3$ and either PPh_3 or P(*o*-tol)$_3$ under mild reaction conditions, with no loss of optical purity.[341] The synthesis of β- and γ-amino acids in an analogous fashion was reported shortly after (Scheme 12).[342]

Knochel and co-workers developed the Ni(acac)$_3$-catalyzed cross-coupling reaction between polyfunctional primary iodoalkanes and a variety of primary diorganozinc compounds in the presence of *m*-trifluoromethylstyrene as a promoter.[343] The addition of this unsaturated promoter is required in order to coordinate to the nickel center and remove electron density from the metal atom, to facilitate the reductive elimination step.[344] The scope of the reaction is extended, when Ni(acac)$_2$ is used in the presence of Bu_4NI and fluorostyrene (Scheme 13).[345] With these modifications, primary and secondary alkylzinc iodides cross-couple with a variety of primary alkyl iodides or bromides in good yields. Dialkylzincs, more reactive, can couple in the absence of Bu_4NI. The same concept was used by Kambe and co-workers for the coupling of alkyl bromides and tosylates with aryl and alkyl organozinc reagents in the presence of $NiCl_2$ and N,N-bis(penta-2,4-dienyl)benzylamine.[266]

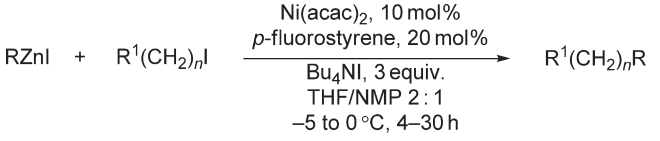
Fu and co-workers reported that unactivated secondary alkyl halides can be coupled in good yields with alkylzinc reagents at room temperature in dimethylacetamide (DMA) in the presence of Ni(COD)$_2$ and ligand **92** (Figure 19).[346] They later reported a general method for the cross-coupling of a range of β-hydrogen-containing primary alkyl iodides, bromides, chlorides, and tosylates with a large variety of alkyl-, alkenyl-, and arylzinc halides.[347] The system consisted of a combination of $Pd_2(dba)_3$, P(Cyp)$_3$/NMI in THF/NMP, allowed for the couplings to be performed at 80 °C, but required 14 h.

Herbert made use of either Pd(dppe)Cl_2 or Pd(dppf)Cl_2 for the the cross-coupling of activated and unactivated aryl bromides with dimethylzinc in refluxing dioxane, in short reaction times and high yields.[348]

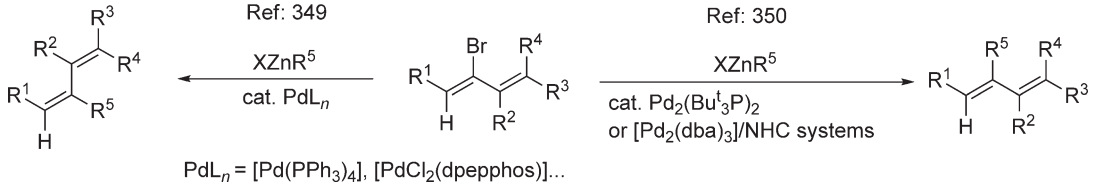
Very recently, Negishi and co-workers have reported two related systems for the synthesis of stereodefined conjugated dienes: a cross-coupling reaction of (*Z*)-2-bromo-1,3-dienes with organozinc reagents, catalyzed by a variety of phosphine-bearing palladium complexes , that proceeds with clean stereoinversion of the Br-bearing C=C bond,[349] and a stereoselective synthesis of (1*E*)-2-methyl-1,3-dienes by the palladium-catalyzed *trans*-selective cross-coupling of 1,1-dibromo-1-alkenes with alkenyl- and phenylzinc reagents, with full retention of configuration, using a combination of either $Pd_2(dba)_3$ with **36** or P(Bu^t)$_3$ (Scheme 14).[350]



Scheme 12



Scheme 13



Scheme 14

11.01.3 Closing Remarks

It should be fairly evident that more than 10 years of metal-catalyzed cross-coupling chemistry cannot be summarized in the limited number of pages allocated to this review. The amount of activity and literature in this area is still rapidly growing! One would be hard pressed to open any chemistry journal and not find at least one cross-coupling reactions, used in one form or other. We have attempted to include the most recent reviews and references.

Obviously, we owe much to the pioneers of this area and it is a testimony of the importance of their work to find cross-coupling affecting so many areas of chemistry. Much progress has been made in the last decade, and at the look of things much will emerge in the very near future to solidify the crucial importance of metal-mediated cross-coupling in modern synthetic chemistry.

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11.02 Reductive Coupling Reactions Promoted by Low-valent Early Transition Metals and Lanthanoids

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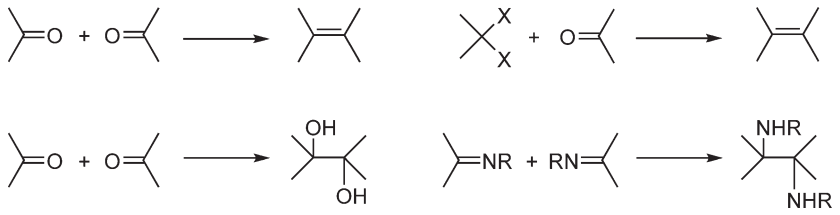
11.02.1 Introduction

Main group metals such as sodium, magnesium, and aluminum have a strong reducing potential, and thus, can be utilized in the synthesis of 1,2-diols by reductive dimerization of aldehydes or ketones.[1–3] Low-valent early transition metals and lanthanides also possess a reducing potential but mostly less than the main group metals. However, once early transition metals or lanthanides release electrons to reduce organic substrates, they start to exhibit strong Lewis acidity, especially the affinity to oxygen atoms. Therefore, reductive dimerization of aldehydes to 1,2-diols by low-valent early transition metals often occurs under mild conditions, and even deoxygenative coupling leading to alkenes takes place. In this chapter, four coupling patterns are described. The first reaction is the McMurry-type olefin synthesis by deoxygenative coupling of carbonyl compounds, which is described in Section 11.02.2.[4–6] For this transformation, low-valent titanium reagents are usually used. Prominent advancements in the McMurry-type olefin synthesis over the past decade are also described. The second topic is olefination of carbonyl compounds. Because this may be described elsewhere, only several important features are given in Section 11.02.3.[7–9] The third topic is



Scheme 1 Patterns of reductive couplings described in this chapter.

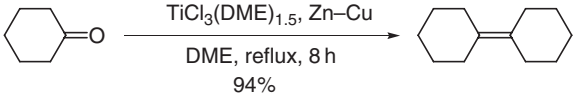
a pinacol-type coupling of aldehydes or ketones leading to 1,2-diols, which is described in Section 11.02.4.[5] Low-valent titanium and samarium(II) reagents have been usually employed for this transformation. Recently, however, low-valent group 5 and 6 metals have been employed for the coupling. Although the pinacol coupling reaction of carbonyl compounds proceeds with strong reducing agents such as magnesium, it is difficult to achieve high chemoselectivity and/or stereoselectivity using traditional methods. Enantioselective coupling reactions have been studied during the past decade. Synthesis of 1,2-diamines by reductive coupling of imines are described in Section 11.02.5 (Scheme 1).

Due to space limitations, vinylogous reactions of pinacol coupling and reductive coupling using nitriles are not described. Also, reductive coupling reactions between compounds having carbon–carbon multiple bonds and carbonyl compounds are not covered.

11.02.2 Deoxygenative Coupling of Carbonyl Compounds to Olefins: McMurry Coupling

Deoxygenative coupling reactions of carbonyl compounds with low-valent titanium are usually called McMurry coupling reactions. A number of excellent reviews have been published to date, including McMurry.[4–6,10] For the coupling reactions of aldehydes or ketones, a comprehensive review can be found in COMC (1995).[11] This section focuses on recent advances in deoxygenative coupling reactions with attention given to applications of the McMurry coupling reaction.

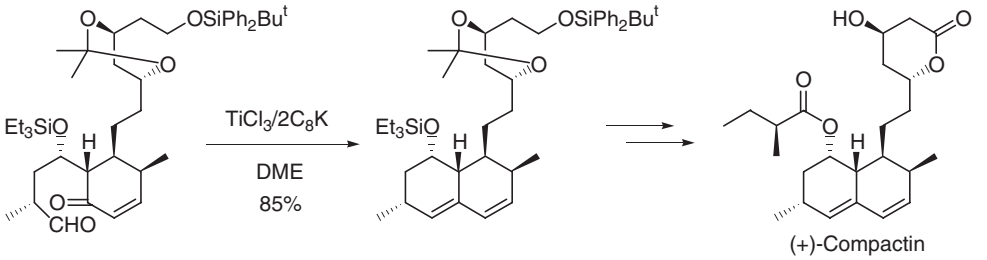
For the McMurry coupling, McMurry first proposed a combination of $TiCl_3$ and $LiAlH_4$ in 1974,[12] but then introduced several improved procedures using K, Li, and Zn–Cu couple as the reductant to overcome problems of reproducibility, handling, reactivity, and selectivity.[13–15] Many other combinations of titanium salts and reductants have also been reported in order to overcome these problems. Lectka, one of McMurry's colleagues, notes that the reproducibility problem is often attributable to one or more of the following: (i) poor-quality Zn–Cu couple, (ii) inadequately purified 1,2-dimethoxyethane (DME), (iii) poor-quality $TiCl_3$, and (iv) unintended introduction of air and/or water to the reaction mixture.[5] McMurry recommends using $TiCl_3(DME)_{1.5}$ as the titanium salt generated by heating of $TiCl_3$ in DME under reflux for 2 days to overcome the purity problem of the titanium salt,[16] and not to use LiAlH4 or K as the reductant of titanium(III) salt because of safety and efficacy reasons. In addition, although a combination of $TiCl_3(DME)_{1.5}$ and Zn–Cu couple is suitable for the McMurry coupling, Lectka recommends testing several couplings on cyclohexanone before venturing a coupling on the more complex material (Equation (1)).[5]



(1)

Fürstner has discovered that a low-valent titanium generated by pretreatment of titanium powder with Me_3SiCl or Et_3SiCl is effective for the McMurry coupling (*vide infra*).[17]

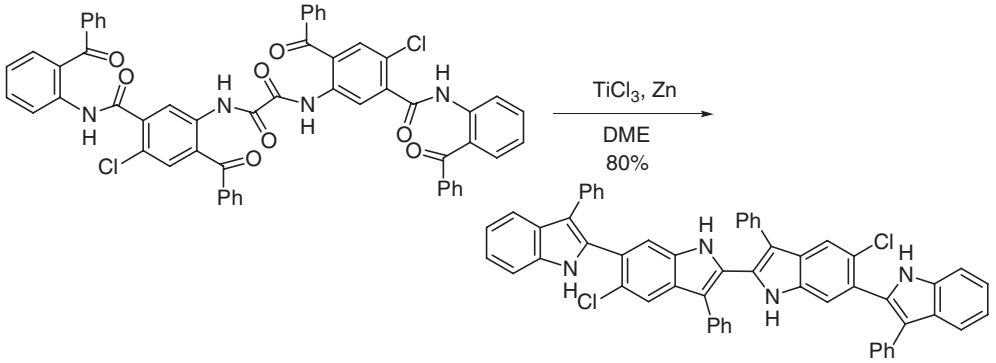
Many natural products and non-natural compounds of interesting structure are synthesized using the McMurry reaction as a key cyclization step. Several features are of particular interest: (i) Small, medium, and large ring skeletons are constructed using the McMurry coupling in good to excellent yields. Even strained double bonds can be constructed. (ii) The coupling is applicable to highly oxygenated natural products. Oxygen functionalities such as esters, carbonates, acetals, and silyl ethers remain unchanged under the McMurry coupling reaction conditions (Equation (2)).[18] (iii) Although only one case is recorded, isomerization of a double bond may occur during the coupling step.[19]



(2)

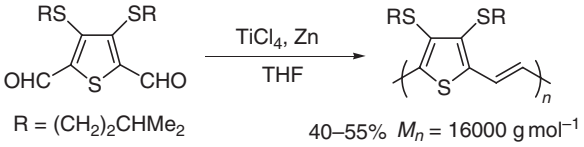
The McMurry coupling can be applied to intramolecular coupling of keto esters.[20] Because the reactivity between ketone and ester groups is so different, the reaction usually requires individualized optimization, especially in the case of large rings. A combination of $TiCl_3$ and $LiAlH_4$ in the presence of triethylamine in DME is employed for the reaction.[19,20]

One of the major advancements in the application of the McMurry coupling over the past decade is the synthesis of heterocycles, especially indoles by intramolecular coupling of keto amides. Low-valent titanium reagents prepared by reduction of $TiCl_3$ with C_8K or zinc are used for the reaction.[21–23] The amount of the titanium salt can be reduced by using Me_3SiCl as an oxide capture.[17] The titanium reagent generated from titanium powder and Me_3SiCl is also effective for the intramolecular indole synthesis (Equation (3)).[24]



(3)

The McMurry reagent can also be applied for the synthesis of polymers connected by olefinic double bonds (Equation (4)).[25–28]



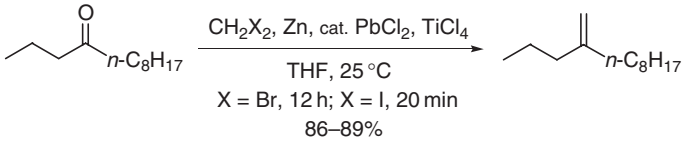
(4)

11.02.3 Olefination of Carbonyl Compounds with Polyhaloalkanes and Low-Valent Metals

It is difficult to obtain cross-coupling products of two different carbonyl compounds by an intermolecular version of the McMurry reaction. Examples that use excess amounts of one carbonyl component are few.[14] When one carbonyl component is replaced by a 1,1-dihalo compound or dithioacetal and the alternative is reduced with a low-valent metal such as low-valent titanium or chromium(II), cross-coupling products, that is, Wittig-type olefins, are produced in high yields. Because the alternative approach is described elsewhere, we concentrate on only its important features here.

First, when 1,1-dihaloalkanes are reduced with low-valent titanium derived from $TiCl_4$ and zinc, it is necessary to add a catalytic amount of $PbCl_2$ (or Pb) for reproducibility (Equations (5) and (6)).[29] Two kinds of zinc powder are available for laboratory use: electrolytic zinc derived by hydrometallurgy and distilled zinc derived by pyrometallurgy.

The electrolytic zinc is pure and free from lead; in contrast, the distilled zinc contains a catalytic amount of lead based on zinc.[29,30]



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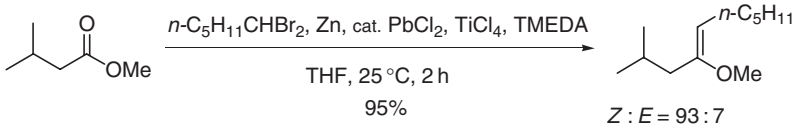
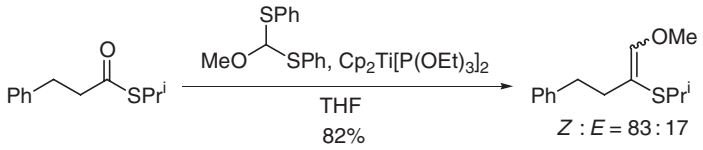


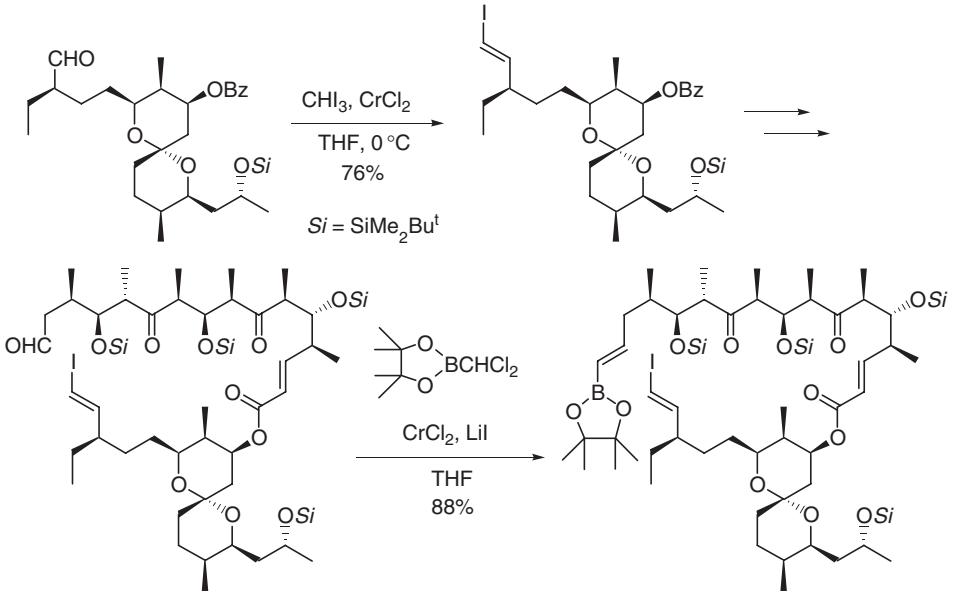
(6)

Second, titanium-based reagents are suitable for methylenation or alkylidenation of carbonyl groups of carboxylic acid derivatives such as esters and amides (Equation (7)).[31,32]



(7)

Third, chromium-based reagents prepared by reduction of 1,1-dihalo compounds with $CrCl_2$ are suitable for the transformation of aldehydes to (*E*)-iodoalkenes,[33] (*E*)-alkenylsilanes,[34] and (*E*)-alkenylboronic esters[35] with one-carbon homologation (Equation (8)).[36,37] The amount of $CrCl_2$ can be reduced to a catalytic amount by using manganese (or zinc) and Me_3SiCl.[38–40]



(8)

11.02.4 Pinacol-Type Coupling Reactions

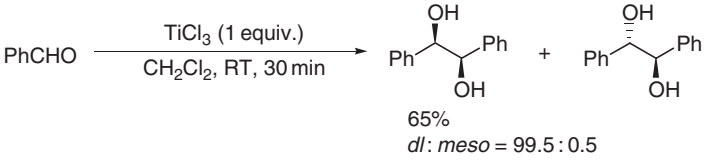
Coupling reactions of aldehydes or ketones to 1,2-diols proceed with low-valent metals such as magnesium, zinc, and aluminum.[1–3] Because it is not easy to control the stereoselectivity (diastereoselectivity and/or enantioselectivity) of the reactions with such main group metals, low-valent species of early transition metals are frequently employed with electron-donating ligands. The representative reagents are low-valent titanium and samarium species.

11.02.4.1 Titanium

Low-valent titanium is effective for pinacol coupling reactions of carbonyl compounds. Low-valent titanium reagents are produced by reduction of titanium chlorides ($TiCl_4$ or $TiCl_3$) with reductants such as potassium, lithium, magnesium, zinc, $LiAlH_4$, and BuLi, where the reactivity of the reagents depends on the methods of preparation.[4–6] For example, the McMurry coupling reaction occurs with low-valent titanium reagents upon combination with a strong reductant like potassium or $LiAlH_4$. When the McMurry reaction is conducted under milder conditions by changing the reductant of titanium chlorides and/or reaction temperature, pinacols, namely, 1,2-diols, are produced as main products.[41] Usually, the pinacol coupling is limited to homocoupling of aromatic ketones and aldehydes, because under mild conditions only aromatic ketones and aldehydes are reduced smoothly with low-valent titanium reagents. In addition, it is difficult to obtain cross-coupling products selectively in the case of intermolecular reactions. Many methods have been developed for the coupling with low-valent titanium reagents to achieve high yields and high diastereoselectivity, to reduce the amount of titanium reagents, and to enhance the applicability of the coupling. Recently, an asymmetric pinacol coupling reaction has also been attained.

11.02.4.1.1 Titanium-based reagent systems

In 1973, Mukaiyama *et al.* reported that aromatic and aliphatic carbonyl compounds gave pinacol coupling products in good to excellent yields upon treatment with a combined reagent prepared from $TiCl_4$ and zinc in tetrahydrofuran (THF; or dioxane).[42] In the same year, Tyrlik *et al.* reported that pinacol coupling of cyclohexanone proceeded well with a reagent derived from $TiCl_3$ and magnesium.[43] In addition, Tyrlik described that $TiCl_3$ did not reduce benzaldehyde in THF at room temperature but did upon heating at the reflux temperature. As a result, many stronger reducing titanium-based reagents (titanium(0) or titanium(II)) for pinacol coupling were prepared by reduction of titanium(III) or titanium(IV) salts with metals such as zinc, magnesium, and aluminum.[2,44] However, the pinacol coupling reaction of benzaldehyde was shown in 1996 to occur at room temperature with titanium(III) species (Equation (9)).[45] An isolated titanium(III) complex $TiCl_3$ (THF)(TMEDA) also promotes the pinacol coupling reaction of aromatic aldehydes in a variety of solvents in high yields (TMEDA = *N*,*N*,*N*′,*N*′,tetramethylethylenediamine[1,2-bis(dimethylamino)-ethane]).[46] Although aromatic aldehydes smoothly undergo the coupling reaction using titanium(III) species under appropriate conditions, aliphatic carbonyl compounds remain yet to be studied (*vide infra*).

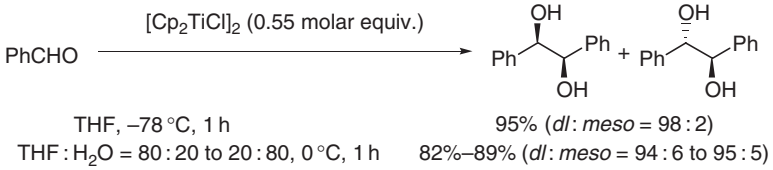


(9)

Titanium(IV) iodide[47–49] or a combination of a titanium(IV) salt and an iodide source[50] promotes pinacol coupling reactions of aromatic aldehydes. The combination of the reagents is considered to generate titanium(III) species along with I_2.

In several pinacol coupling reactions, the "titanium(II) species" is assumed to be generated by treatment of $TiCl_4$ with hexamethyldisilane.[51–54] However, the original procedure[51] was corrected in 1998 to show that the titanium species generated by this method was $TiCl_3$.[55,56]

Pinacol coupling reactions of aromatic aldehydes occur with a titanocene(III) species that was prepared by reduction of Cp_2TiCl_2 with reductants such as zinc and isoprorylmagnesium iodide in THF.[57] The reagent combinations show high *dl*-selectivities (*vide infra*). A titanocene(III) complex, $[Cp_2TiCl]_2$, also promotes pinacol coupling of aromatic aldehydes under aqueous conditions (Equation (10)).[58] The reactive species could be $[Cp_2Ti(H_2O)]Cl^+$, derived from the titanocene(III) dinuclear complex by hydrolysis. The method also provides *dl*-pinacols under high stereocontrol (*vide infra*). Cp_2TiCl_2 is frequently employed as the precursor of a titanium(III) catalyst, because it is stable and can be easily handled as a solid in the air.



(10)

Intramolecular McMurry olefination was realized by Fürstner *et al.*, who achieved synthesis of indol derivatives with a catalytic amount of $TiCl_3$.[17] They employed zinc metal as a reductant and Me_3SiCl as a deoxygenating agent

of Ti═O species. The combination of zinc (or manganese) and Me_3SiCl is applied to the pinacol coupling reaction by Gansäuer,[59] and a titanocene complex, $TiCl_3(THF)_3$, is also applicable as disclosed by Nelson and co-workers.[60,61] Catalytic pinacol coupling reactions occur with $TiCl_4$ and zinc (or aluminum) in the presence of an acylating reagent such as acetic anhydride or acetyl chloride.[62]

11.02.4.1.2 Diastereoselective coupling reactions of aromatic aldehydes

Diastereoselectivity of the pinacol coupling reaction of aromatic aldehydes (or ketones) with a combination of $TiCl_4$ (or $TiCl_3$) and a reducing agent depends on the kinds of reducing agents, molar ratio of the reagent components, co-existing metal salts, additives, and solvents. Mukaiyama's pioneering work that uses $TiCl_4$ and zinc does not discuss the diastereoselectivity of homocoupling.[42] The pinacol coupling reaction of benzaldehyde with $TiCl_4$ and zinc in a molar ratio of 1 : 1.5 : 3 in THF is later reported to produce a diastereomeric mixture of 1,2-diols in a ratio of *dl*/*meso* = 3/1.[63] When dichloromethane is used as the solvent with a molar ratio of 2 : 1, the diastereomeric ratio increases to 94/1. Upon addition of pyridine (3 equiv. of $TiCl_4$), the diastereomeric ratio decreases to 5.2/1. However, use of TMEDA in lieu of pridine gives the *dl*-diol exclusively.[63] The active species generated in the mixture of $TiCl_4$, zinc, and TMEDA has been isolated and well characterized.[46] Titanium(III) complex $TiCl_3(THF)$(TMEDA) also promotes pinacol coupling of aromatic aldehydes with a high *dl*-selectivity. The diastereoselectivity also depends on the solvent used for the coupling reaction of benzaldehyde with $TiCl_3(THF)$(TMEDA). Exclusive formation of the *dl*-pinacol is observed in THF, toluene, dichloromethane, and acetonitrile. The *dl*/*meso* ratio decreases slightly in pivalonitrile (96/4), and the ratio drops to 71/29 or 56/44 in a protic solvent such as methanol or *t*-butyl alcohol, respectively.

Treatment of benzaldehyde with $TiCl_3$ (1 equiv.) and magnesium (1.5 equiv.) in THF at 25 °C for 30 min gives a mixture of 1,2-diphenylethene (43% yield) and *dl*- and *meso*-1,2-diphenylethane-1,2-diols (29% combined yields, *dl*/*meso* = 42/58). The reaction conducted at 80 °C produces the diphenylethene in 62% yield selectively. However, when catechol (1 equiv.) is added to the reaction mixture, pinacols are produced selectively in 76% yield (*dl*/*meso* = 54/46) even at 80 °C.[64] Ultrasonic irradiation of a mixture of $TiCl_3$ (15% in dilute HCl solution, 2 equiv.) and magnesium (4 equiv.) in EtOH accelerates the pincaol formation, but the diastereomeric ratio remains at a low level (*dl*/*meso* = 68/32).[65]

Pinacol coupling reactions of aromatic aldehydes with commercially available $TiCl_3$ in a mixed solvent of THF and dichloromethane show high *dl*-selectivities.[45] Also, high *dl*-selectivities are observed with $TiCl_4$-$Bu^i{}_2Te$ in DME[66] and $TiCl_4$-Bu^nLi in Et_2O at −50 °C.[67] (see Table 1).

Diastereoselectivity of a catalytic pinacol coupling using $TiCl_4$, zinc, and acetic anhydride at room temperature for 24 h in DME is low (*dl*/*meso* = 60/40). The ratio improves a little by changing the reductant to aluminum.[62]

The pinacol coupling reaction of aromatic aldehydes mediated by a titanocene(III) species derive from Cp_2TiCl_2 and a reductant proceeds generally with high stereoselectivity. For example, a stoichiomeric reaction of benzaldehyde with Cp_2TiCl_2–zinc, –SmI_2, or –Pr^iMgI in THF at −78 °C to room temperature gives a *dl*/*meso* ratio of 92–97/8–3, 92/8, or 99/1, respectively.[57] In other experiments, coupling reactions of benzaldehyde with titanocene(III) species derived by reduction of Cp_2TiCl_2 with zinc, manganese, or an electrochemical method in THF at 20 °C show *dl*/*meso* ratios of 97/3, 97/3, or 96/4, respectively.[83] Aromatic aldehydes dimerize with $[Cp_2TiCl]_2$ in water to give the corresponding *dl*-pinacols with excellent selectivity comparable to the one obtained with Cp_2TiCl_2 and zinc.[58]

In the case of catalytic coupling reactions of aromatic aldehydes using a combination of Cp_2TiCl_2 and reductants, the stereoselectivity varies with the reagent systems although *dl*-diols are produced as major products. For example, addition of benzaldehyde and Me_3SiCl to a solution of titanocene(III) species generated from a catalytic amount of Cp_2TiCl_2 and zinc in THF at 25 °C gives 1,2-diols in 93% yield (*dl*/*meso* = 86/14).[59] The decrease in *dl*-selectivity of the catalytic reaction stems from the slow reaction step of trapping titanates of 1,2-diols with Me_3SiCl and a competitive coupling reaction of benzaldehyde with zinc and Me_3SiCl. The problem has been overcome using several methods: (i) addition of $MgBr_2$ to the reaction mixture,[59] (ii) using manganese instead of zinc,[84] and (iii) using manganese or collidine hydrochloride as a protonating agent (Equation (11)).[71,72]

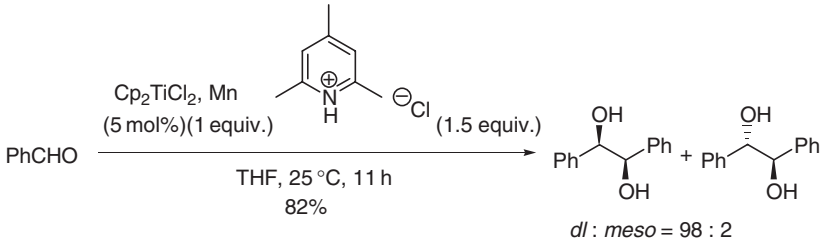


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Table 1 Pinacol coupling reactions of benzaldehyde promoted by titanium reagents

Entry	*Titanium* (equiv.)	*Additive* (equiv.)	*Solvent*	*Conditions* (°C, min or h)	*Yield* (%)	*dl*:*meso*	*References*
1	$TiCl_4$ (1.5)	Zn (3)	THF	0, 2 h	98	-	42
2	$TiCl_3$	30% aq. NaOH (pH = 10–12)	MeOH	RT, a few minutes	88[a]	57 : 43	68
3	$TiCl_4$	$TeBu^i_2$	DME	RT, 2 h	99	> 99 : < 1	66
4	Cp_2TiCl_2 (2)	Pr^iMgI (1)	THF	−78 to RT, 0.5 h	-	98.8 : 1.2	57
5	Cp_2TiCl_2 (2)	SmI_2 (1)	THF	−78 to RT, 0.5 h	-	92 : 8	57
6	$TiCl_3$ (1)		CH_2Cl_2	RT, 0.5 h	65	> 99 : < 1	45
7	$TiCl_3$ (1)	Mg (1.5), cathecol (1)	THF	80, 0.5 h	76	54 : 46	64
8	$Cp_2TiCl(THF)$ (1.1) as $[Cp_2TiCl]_2$		THF	−78, 1 h	95	98 : 2	58
9	$[Cp_2TiCl]_2$	NaCl (62)	THF/H_2O = 1/1	0, 1 h	89	95 : 5	58
10	$TiCl_3(THF)_3$ (0.1)	Zn (1.2), Me_3SiCl (1.2)	THF	0, 6 h	90	69 : 31	60
11	$TiCl_3(THF)_3$ (0.1)	Zn (1.2), Me_3SiCl (1.2), DEPU (0.3)	THF	0, 6 h	89	88 : 12	60
12	(EBTHI)$TiCl_2$ (0.03)[b]	Zn (1), Me_3SiCl (1.5), $MgBr_2$ (1.3)	THF	RT, 4 h[c]	88	97 : 3	69
13	Ti(*i*-PrO)$_4$ (1)	Sm (1.7), I_2 (1)	MeOH	−78, 1	91	91 : 9	70
14	Cp_2TiCl_2 (0.03)	Mn (1), pyridine/HCl (1.5)	THF	25, 11 h[d]	<5	-	71,72
15	Cp_2TiCl_2 (0.03)	Mn (1), 2,6-lutidine/HCl (1.5)	THF	25, 11 h[d]	75	82 : 18	71,72
16	Cp_2TiCl_2 (0.03)	Mn (1), 2,4,6-colidine/HCl (1.5)	THF	25, 11 h[d]	68	95 : 5	71,72
17	Cp_2TiCl_2 (0.05)	Mn (1), 2,4,6-colidine/HCl (1.5)	THF	25, 11 h[d]	82	98 : 2	71,72
18	Cp_2TiCl_2 (0.03)	Zn (1), 2,4,6-colidine/HCl (1.5)	THF	25, 11 h[d]	68[e]	86 : 14	71,72
19	Cp_2TiCl_2 (0.03)	Zn (1), Me_3SiCl (1.5), $MgBr_2$ (1.3)	THF	25, 3 h	90	95 : 5	73
20	$TiCl_3$ (2)	TMEDA (4)	THF	25, 4 h	86	> 99 : < 1	52
21	L_2TiCl_2 (0.03)[f]	Mn (3), Me_3SiCl (1.1)	CH_3CN	RT, 24 h	80	97 : 3	74
22	Cp_2TiPh (0.03)	Zn (1), Me_3SiCl (1.5)	THF	RT, 1.2 h	88	71 : 29	75,76
23	$TiCl_4$ (2)	Et_3N (3)	CH_2Cl_2	0–25, 5 h	71	74 : 26	77
24	$TiCl_4$ (1.5)	Zn (3)	THF	RT, –	-	67 : 33	63
25	$TiCl_4$ (1)	Zn (0.5), THF (3)	CH_2Cl_2	RT, 0.5 h	57	98.9 : 1.1	63
26	$TiCl_4$ (1)	Zn (0.5), THF (3), pyridine (3)	CH_2Cl_2	RT, –	42	84 : 16	63
27	$TiCl_4$ (1)	Zn (0.5), THF (3), DMF (1.5)	CH_2Cl_2	RT, –	55	99.1 : 0.9	63
28	$TiCl_4$ (1)	Zn (0.5), THF (3), TMEDA (1.5)	CH_2Cl_2	RT, –	77	(*dl* only)	63
29	$TiCl_3(THF)$(TMEDA) (2)		THF	25, 24 h	92	> 99 : < 1	46
30	$TiCl_3(THF)$(TMEDA) (2)		MeCN	25, 24 h	58	> 99 : < 1	46
31	$TiCl_3(THF)$(TMEDA) (2)		Bu^tCN	25, 24 h	81	96 : 4	46
32	$TiCl_3(THF)$(TMEDA) (2)		PhMe	25, 1 h	83	> 99 : < 1	46
33	$TiCl_3(THF)$(TMEDA) (2)		MeOH	25, 24 h	80	71 : 29	46
34	$TiCl_3(THF)$(TMEDA) (2)		CH_2Cl_2	25, 24 h	80	> 99 : < 1	46
35	$TiBr_2$ (1)	Cu (1), Bu^tCN (4)	CH_2Cl_2	−23, 6 h	95	97 : 3	78
36	TiI_4 (2)		EtCN	−78 to RT, –	90	> 99 : 1	47
37	TiI_4 (1)		EtCN	−78 to RT, –	22[g]	85 : 15	47
38	TiI_4 (1.3)	Cu (2.6), Bu^tCN (5.2)	CH_2Cl_2	−23, 3 h	94	> 99 : 1	79

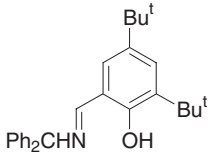
(*Continued*)

Table 1 (Continued)

Entry	*Titanium* (equiv.)	*Additive* (equiv.)	*Solvent*	*Conditions* (°C, min or h)	*Yield* (%)	*dl*:*meso*	*References*
39	$TiCl_4$ (1.5)	$Bu^n{}_4NI$ (2.2)	CH_2Cl_2, hexane	−78 to 25, 12 h	99	93:7	50
40	$TiBr_2$ (1)	Fe (1), Bu^tCN (4)	CH_2Cl_2	RT, 18 h	80	93:7	80
41	TiI_4 (1)	Cu (2), Bu^tCN (4)	CH_2Cl_2	−23, 3 h	93	>99:1	80
42	$TiCl_4(THF)_2$ (0.05)	L′ (0.05)[h], Zn (3) Me_3SiCl (1.1)	CH_3CN	RT, 5 h	99	99:1	81
43	$Ti(i\text{-}PrO)_4$ (1.5)	EtMgBr (1.1)	THF	RT, 0.3 h	95	61:39	82
44	$TiCl_3$ (2)	Mg (4)	EtOH	10–18, 0.67 h	75[i]	68:32	65

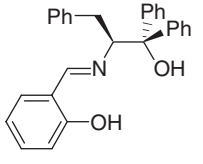
[a]Benzyl alcohol was produced in 12% yield.
[b]EBTHI = *rac*-ethylenebis(η^5-tetrahydroindenyl).
[c]Benzaldehyde was added over a period of 2 h.
[d]Benzaldehyde was added over a period of 3 h.
[e]Benzyl alcohol was produced in 7% yield.

[f]L =



[g]Benzaldehyde acetal of the desired pinacol was produced in 64% yield.

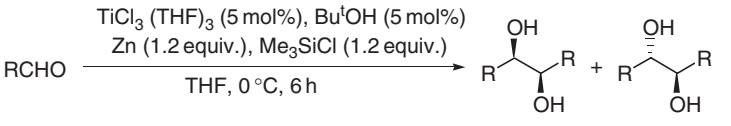
[h]L′ =



[i]Ultrasonic irradiation (25 kHz). Benzyl alcohol was produced in 10% yield.

11.02.4.1.3 Pinacol coupling reactions of aliphatic aldehydes

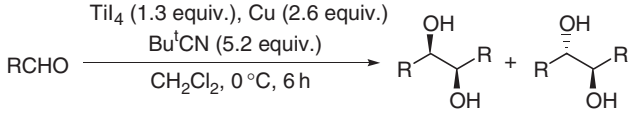
Aliphatic carbonyl compounds are less reactive than aromatic ones. To accelerate the pinacol coupling, addition of a Lewis base or proton source to the titanium reagents has been examined. However, there have been only a few methods of intermolecular dimerization having wide applicability. In addition, the diastereoselectivities of the reported methods are not high. For example, addition of *t*-butyl alcohol to a reagent made from a combination of $TiCl_3(THF)_3$, zinc, and Me_3SiCl causes aliphatic ketones to give 1,2-diols in good to excellent yields with diastereoselection (*dl*/*meso*) ranging from 1.5/1 to 3/1 (Equation (12)).[60] A reagent made from Cp_2TiCl_2, zinc (or manganese), and Me_3SiCl promotes pinacol coupling of aliphatic aldehydes.[61,84] The diastereoselectivity in these reactions remains also at a moderate level.



R	*Yield* (%)	*dl* : *meso*
c-C_6H_{11}	85	83 : 17
Me_2CHCH_2	76	67 : 33

(12)

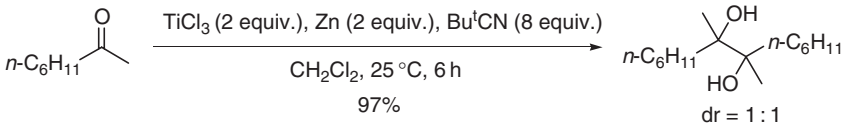
Among them, a combination of a stoichiometric amount of TiI_4 and copper (or $TiBr_2$ and copper) is effective for the pinacol coupling of aliphatic aldehydes as well as aromatic aldehydes. According to the original literature, the titanium bromide species is ascribed to $TiBr_2$. In the original literature, elemental analysis of a dark brown solid sample derived from $TiBr_4$ and $Me_3SiSiMe_3$ was carried out. The reagent combination shows moderate diastereoselectivity. As mentioned earlier, TiI_4 causes pinacol coupling of benzaldehyde at room temperature in moderate yields. However, TiI_4 does not mediate the reaction of aliphatic aldehyde. Addition of copper is indispensable for the reaction of aliphatic aldehyde (Equation (13)).[60,78–80]



R	*Yield* (%)	*dl* : *meso*
Bu^n	72	80 : 20
Bu^i	85	75 : 25
c-C_6H_{11}	98	85 : 15

(13)

Aliphatic ketones reductively dimerize upon treatment with $TiCl_3$ (reported as $TiCl_2$ in the literature (*vide supra*)) and zinc in the presence of pivalonitrile in dichloromethane (Equation (14)).[85] In the reaction, addition of pivalonitrile produces a dramatic accelerating effect.

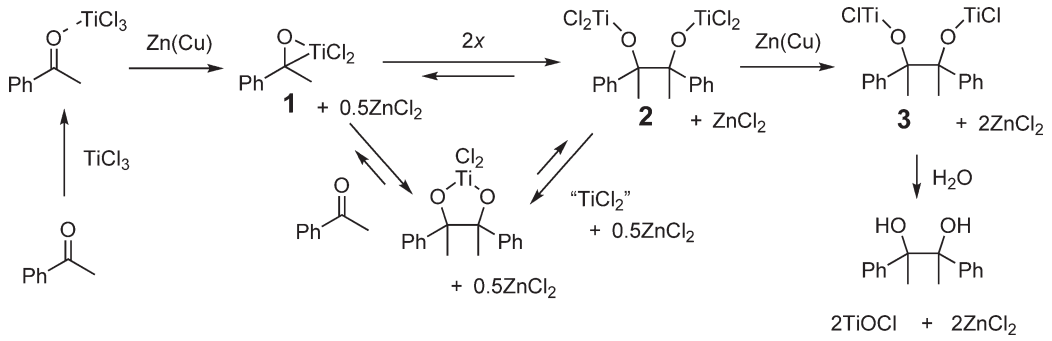


(14)

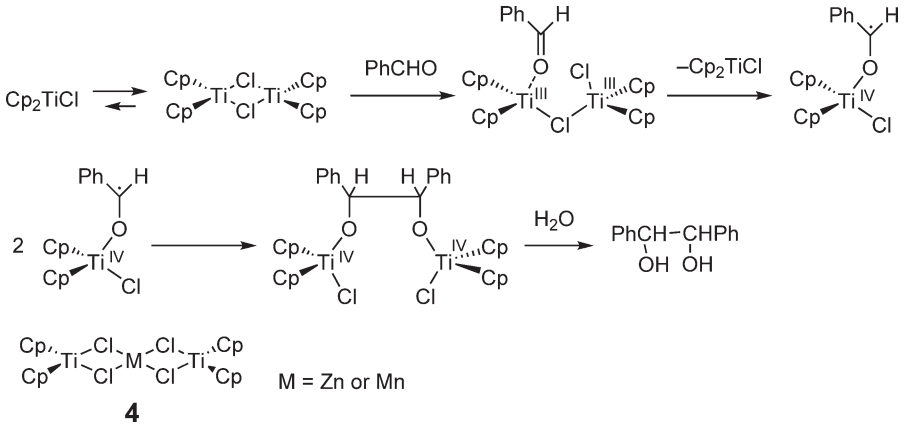
11.02.4.1.4 Mechanism of pinacol coupling with low-valent titanium

Although there are many reports on the utilization of McMurry pinacol coupling reactions with a low-valent titanium, only a few mechanistic details are known. It has been long believed that the highly dispersed Ti(0) particles are initially formed and that the carbonyl coupling proceeds heterogeneously on the particle surface via ketyl radical intermediates (radical mechanism).[86] In 1995, Bogdanović and Fürstner proposed the following reaction mechanism (nucleophilic mechanism) for the McMurry pinacol coupling with $TiCl_3(DME)_{1.5}$ and zinc–copper couple based on experimental results (Scheme 2):[87,88] (i) Pure $TiCl_3$ in DME is not reduced by a zinc–copper couple. (ii) Lewis-acidic $TiCl_3$ coordinates to a carbonyl compound, and one-electron reduction takes place to give a side-on coordinated species **1** (iii) Intermolecular dimerization of **1** or nucleophilic addition of **1** to another carbonyl compound followed by reduction gives **2**. (iv) Reduction of **2** with zinc–copper gives **3**. This nucleophilic mechanism is supported by a density functional theory (DFT) calculation, although the results of the calculation do not rule out the possibility of a radical pathway under different reaction conditions.[89]

For pinacol coupling reactions with a catalytic amount of Cp_2TiCl_2 and reductants such as zinc and manganese, high *dl*-selectivities are observed frequently. The mechanism for the stereoselectivities has been explained by a



Scheme 2



Scheme 3

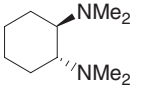
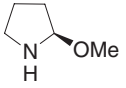
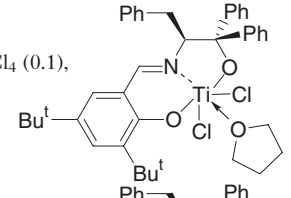
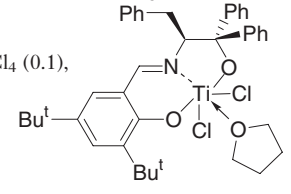
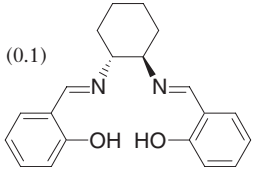
trimetallic species based on the structure of isolated trimetallic complexes **4** (Scheme 3). However, Daasbjerg, Skrydstup and co-workers recently disclosed an electrochemical study on the structure of titanocene(III) reagents prepared by reduction of Cp_2TiCl_2 with manganese or zinc in solution (Scheme 3).[83,90] The redox-active intermediate in each combination is disclosed to be and most likely is Cp_2TiCl, which is in equilibrium with its dimer, $(Cp_2TiCl)_2$, and the equilibrium lies to the dimer. Upon addition of benzaldehyde, the aldehyde is considered to coordinate to $(Cp_2TiCl)_2$, and one-electron transfer then takes place to give a ketyl radical. The diastereoselectivity is attributed to a steric interaction at the stage of ketyl radical coupling. Several transition states are suggested for the coupling which explain the high *dl*-selectivity. The remaining details are yet to be clarified.[91]

11.02.4.1.5 Asymmetric pinacol coupling reactions

Asymmetric pinacol coupling reactions with a stoichiometric amount of titanium salts have been observed using a combination of $TiCl_3$ and chiral amines such as *N*,*N*,*N*′,*N*′-tetramethyl-1,2-cyclohexanediamine and 2-methoxymethylpyrrolidine.[52–54] In these reports, the titanium salt is considered to be $TiCl_2$.[92] However, the titanium salt prepared by reduction of $TiCl_4$ with $Me_3SiSiMe_3$ has proved to be $TiCl_3$.[55,56] The enantioselectivities of the reactions using the chiral amines are modest (Table 2).

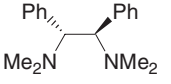
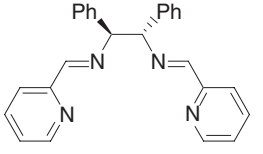
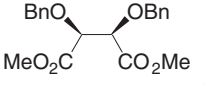
A catalytic version of the asymmetric pinacol coupling was first accomplished with chiral titanocene **5** (Equation (15)). Treatment of benzaldehyde with **5**, manganese, and Me_3SiCl in THF at 25 °C for 24 h gave 1,2-diol **6** in a ratio of *dl*:*meso* = 3.4:1 with 32% ee.[98] The enantioselectivities were improved by using chiral salen (Schiff bases) as the chiral ligands. Asymmetric pinacol coupling of aromatic aldehydes mediated and catalyzed by the chiral, air stable titanium(IV) complexes afforded the chiral 1,2-diols in high yields and enantioselectivities.[93–97]

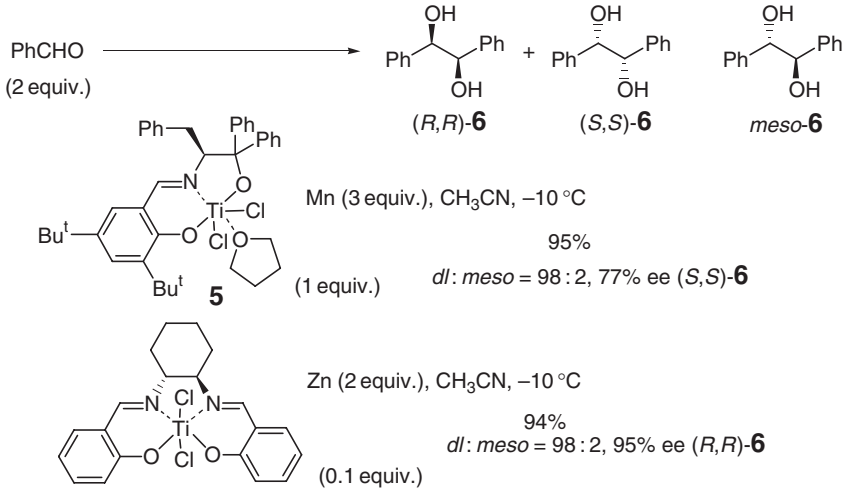
Table 2 Asymmetric pinacol coupling reactions of benzaldehyde with titanium reagents

Entry	*Titanium* (equiv.)	*Additive* (equiv.)	*Solvent*	*Conditions* (°C, min or h)	*Yield* (%)	*dl* : *meso*	*ee* (%)	*References*
1	$TiCl_3$ (2)	 (4)	THF	25, 8 h	88	14 : 1	40 (*S*,*S*)	52
2	$TiCl_3$ (2)	 (4)	THF	−78, 23 h	31	81 : 19	65 (*S*,*S*)	53
3	$TiCl_4$ (0.1),  (1)	Mn (3), Me_3SiCl (1.5)	CH_3CN	25, –	94	96 : 4	63 (*S*,*S*)	93
4	$TiCl_4$ (0.1),  (1)	Mn (3)	CH_3CN	−10, –	> 95	98 : 2	77 (*S*,*S*)	93
5	Ti(salen)Cl_2 (0.1) salen = 	Zn (2), Me_3SiCl (1.5)	CH_3CN	−10, 4 h	94	98 : 2	95	94

(*Continued*)

Table 2 (Continued)

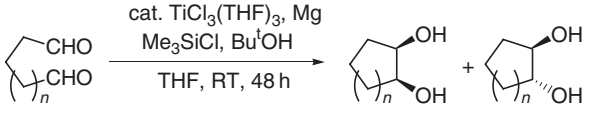
Entry	*Titanium* (equiv.)	*Additive* (equiv.)	*Solvent*	*Conditions* (°C, min or h)	*Yield* (%)	*dl*:*meso*	*ee* (%)	*References*
6	$TiCl_4$ (1)	THF (2), Zn (1),  (1)	CH_2Cl_2	–, 20 min	95	>99:<1	52 (*S*,*S*)	95
7	$TiCl_4(THF)_2$ (0.15)	Mn (3.0), Me_3SiCl (1.5),  (0.15)	CH_3CN	0, 24 h	95	93:7	88 (*S*,*S*)	96
8	$TiCl_4$ (1)	THF (2), Zn (1),  (1)	CH_2Cl_2	20, 20 min	95	>99:<1	67 (*S*,*S*)	97



(15)

11.02.4.1.6 Intramolecular coupling to cyclic 1,2-diols and its synthetic applications

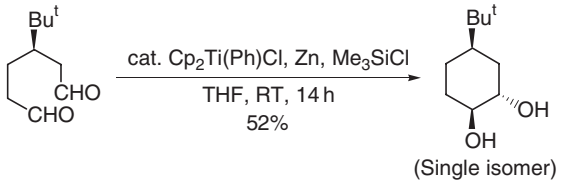
Treatment of alkanedials with the reagent for pinacol coupling causes intramolecular cyclization leading to 1,2-cycloalkanes. The diastereoselectivity depends on the ring size formed (Equation (16)).[60]



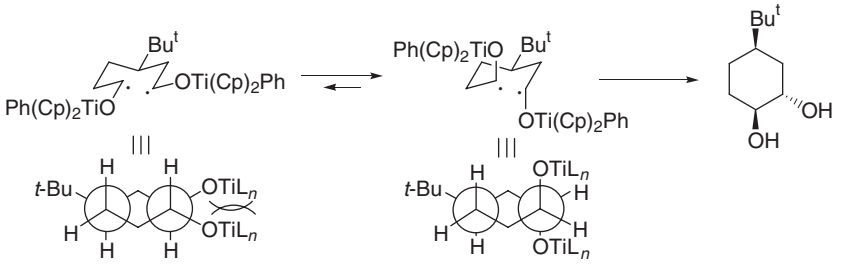
n	*Yield* (%)	*cis* : *trans*
1	74	89 : 11
2	73	52 : 48

(16)

By choosing an appropriate titanium complex, a *trans*-isomer of 1,2-cyclohexanols can be prepared selectively. Because intramolecular pinacol coupling of hexanedials with SmI_2 usually produces *cis*-isomers of cyclohexane-1,2-diols, the titanium-mediated reaction complements the samarium-mediated cyclization (Equation (17)). In addition, when a *t*-butyl group fixes the conformation of the substrate, one of the diastereomers is produced selectively (Equation (18)).[75,76]



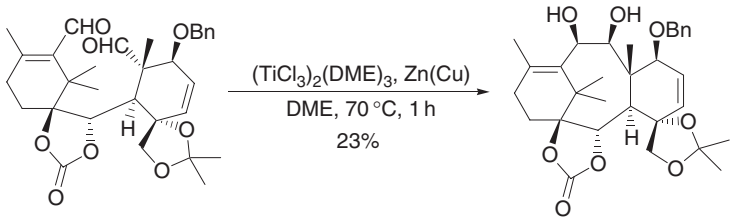
(17)



(18)

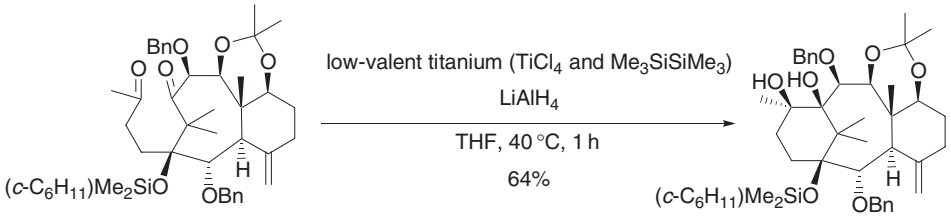
The first example of a titanium-based intramolecular pinacol coupling in a total synthesis is the construction of the D ring of gibberellic acid, as reported by Corey *et al.*[99] They used a modified McMurry reagent derived from $CpTiCl_3$ (6 equiv.) and $LiAlH_4$ (4.5 equiv.) in THF at 50 °C.[44] Deoxygenation from the vicinal diol does not occur due to the formation of a bridgehead double bond.[99]

Because titanium-based reagents can bring the two carbonyl groups close to each other, vicinal diols of not only five-[100] and six-membered rings but also large-sized rings[101] are produced by intramolecular cyclization. In addition, by choosing appropriate reaction conditions, the intramolecular coupling can be accomplished without affecting the co-existing functional groups such as benzyl ether, trimethylsilyl ether, acetal, and ester. Nicolaou *et al.* employed the McMurry diol formation in the synthesis of an eight-membered ring of taxol (Equation (19)).[102]



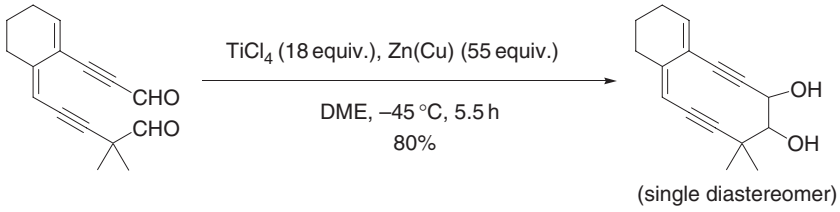
(19)

Mukaiyama, Shiina and co-workers used a reagent generated by $LiAlH_4$ reduction of a low-valent titanium derived from $TiCl_4$ and $Me_3SiSiMe_3$ for construction of a six-membered ring of taxol (Equation (20)).[103,104]



(20)

Vicinal diols of 10-membered ring enynes are also generated by a low-valent titanium derived from $TiCl_3$ and zinc–copper couple in DME (Equation (21)).[105]

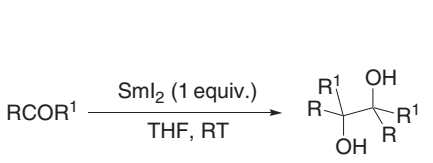


(21)

11.02.4.2 Samarium

11.02.4.2.1 Preparation of samarium(II) reagents for pinacol coupling

In 1983, Kagan reported the first pinacol coupling mediated by samarium(II) iodide that was generated by samarium and 1,2-diiodoethane in THF (Equation (22)).[106] Since then, many pinacol coupling reactions with samarium have been reported.[107] Most of the coupling reactions are mediated by a samarium(II) species generated by oxidation of samarium metal. The oxidants are: 1,2-diiodoethane (Equation (23)),[108,109] diiodomethane,[110] iodine,[111] and trimethylsilyliodide (Equation (24))[112,113] for samarium(II) iodide, and 1,1,2,2-tetrabromoethane[114] for samarium(II) bromide (Equation (25)), and sulfur(IV) compound for samarium(II) triflate (Equation (26); *vide infra*).[115] There are only a small number of solvents where samarium(II) iodide can be directly prepared from the samarium metal and 1,2-diiodoethane. This is possible in THF, tetrahydropyran (THP), acetonitrile, pivalonitrile, octanenitrile, and a mixed solvent of benzene and hexamethylphosphoramide (HMPA). The choice of the solvents and additives influences the reaction with samarium(II) markedly (*vide infra*). Although pinacol homocoupling reactions of aromatic carbonyl compounds with samarium(II) iodide proceed quickly at room temperature, those of aliphatic aldehydes require several hours to reach completion, and for ketones over 24 h is required.[106] Several modifications have been reported to overcome this difficulty. Pinacol coupling reactions of aliphatic carbonyl compounds proceed faster with samarium(II) chloride and bromide than with samarium(II) iodide.[116]



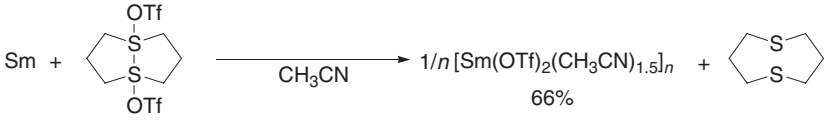
R	R^1	*Time*	*Yield* (%)
Ph	H	0.5 min	95
n-C_7H_{15}	H	3 h	85
Ph	Me	0.5 min	95
n-C_6H_{13}	Me	24 h	80

(22)

(23)

(24)

(25)



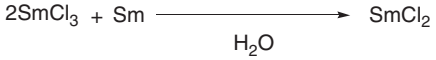
7

(26)

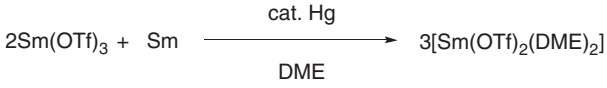
A samarium(II) species can also be obtained by reduction of samarium(III) bromide with lithium metal (Equation (27))[116] or samarium(III) triflate with *sec*-butyllithium (Equation (28)).[117] Proportionation between 1 equiv. of samarium(0) and 2 equiv. of a samarium(III) species can also be employed for generation of a samarium(II) species (Equations (29) and (30)).

(27)

(28)



(29)



(30)

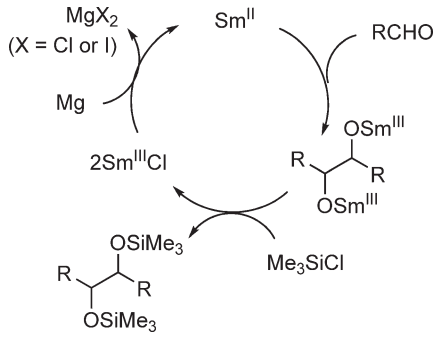
Samarium(II) triflate without halide ions, $Sm(OTf)_2(CH_3CN)_{1.5}$, can be generated by treatment of samarium with 1,5-dithioniabicyclo[3.3.0]octane bis(trifluoromethanesulfonate) **7** in acetonitrile at 50 °C. The salt promotes pinacol coupling of aromatic ketones even at −40 °C. In addition, the diastereoselectivity (*dl* : *meso*) of the coupling reaction of acetophenone in acetonitrile at −40 °C is 94 : 6.[115]

Samarium(II) triflate, a halogen-free samarium(II), can also be prepared by disproprotionation of samarium(III) triflate and samarium(0) in DMF in the presence of a catalytic amount of mercury.[118]

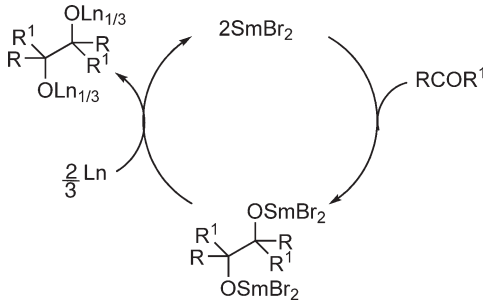
A combination of cerium and iodine is also effective for pinacol coupling of aromatic and alicyclic carbonyl compounds.[119]

11.02.4.2.2 Catalytic use of samarium complexes for pinacol coupling

In order to design a catalytic version of the coupling, it is important to find an appropriate reductant for samarium(III). The reduction potential of samarium is −2.41 V, and is almost the same as that of magnesium metal (−2.37 V). Magnesium was first employed to reduce the amount of samarium in an Sm/SmI_2-mediated deoxygenative coupling reaction of amides.[120] Although magnesium metal can reduce samarium(III) to samarium(II), there is still one requirement for its use in pinacol coupling reactions.[121] In order to avoid side-reactions such as benzoin condensation and Tishchenko reactions, the concentration of samarium(II) should be kept higher than that of the carbonyl



Scheme 4 Reprinted with permission from The American Chemical Society, *J. Am. Chem. Soc.* **1996**, *118*, 11666–11667.



Scheme 5

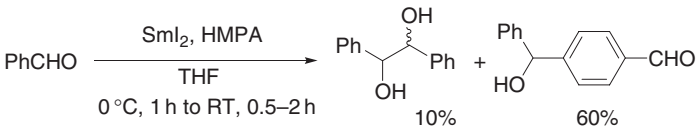
compounds. In other words, regeneration of samarium(II) from samarium(III) is first required. Because the reduction of samarium(III) pinacolate is rather slow, Me_3SiCl should be added to generate the trimethylsilyl ether of the pinacolate and samarium(III) halides that are easily reduced with magnesium. Also, carbonyl compounds should be added slowly to the reaction mixture recycling samarium(II). In the absence of the samarium salt, pinacol coupling reactions do not occur under the same reaction conditions.

Mischmetall is a cheap alloy of the light lanthanides and is used in large amounts for industrial applications.[114,122] The alloy can also be used as a reductant to recycle samarium(III) to samarium(II). Because pinacolate ligand exchange from samarium to light lanthanides proceeds smoothly, addition of Me_3SiCl is not necessary to complete the catalytic cycle (Schemes 4 and 5).

11.02.4.2.3 Additives and solvents to accelerate pinacol coupling

Electrochemical properties of samarium(II) iodide are very sensitive to the nature of solvents.[123] Reduction potential increases by replacing THF with a more polar solvent, such as DMF or CH_3CN. Addition of HMPA to a THF solution of samarium(II) iodide leads to a substantial increase in the electron-donating nature of samarium(II).[124] The principal samarium(II) species in a mixed solvent of THF and HMPA is an ionic cluster of $[Sm(HMPA)_4(THF)_2]^{2+}2I^-$ in HMPA–THF (4 : 1) or $[Sm(HMPA)_6]^{2+}2I^-$ in HMPA–THF (≥10 : 1). The reactivity order of the samarium(II) complexes is $[Sm(HMPA)_6]^{2+}2I^- > [Sm(HMPA)_4(THF)_2]^{2+}2I^- > SmI_2$ in the reaction with 1-iodobutane.

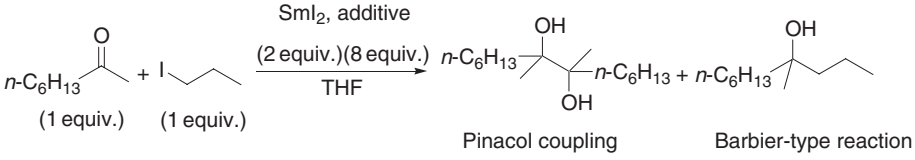
Addition of HMPA to SmI_2 in THF changes the reaction course of the benzaldehyde dimerization. Although samarium(II) iodide promotes pinacol coupling of benzaldehyde, use of 2.8 equiv. of HMPA leads to the formation of, in addition to the pinacol (10% yield), a dimer (60% yield) that results from the connection of a carbonyl carbon and a phenyl *para*-carbon (Equation (31)).[125]



(31)

Addition of LiBr or LiCl to a solution of SmI_2 in THF causes a color change from blue to purple. Oxidation potential of SmI_2 in THF changes from -1.33 V to -1.98 ± 0.01 V upon addition of I_2 or LiBr (more than 1 equiv.), or to -2.11 ± 0.01 V by addition of 12 or more equiv. of LiCl. In the presence of 4–12 equiv. of the bromide or chloride salt, the pinacol coupling reaction of cyclohexanone is accelerated. These salts should be dried before use; otherwise, simple reduction to cyclohexanol occurs. The co-existing lithium cation can also act as a Lewis acid to activate the carbonyl group by coordination.[126]

Treatment of a mixture of 1-iododododecane and 2-octanone with SmI_2 in THF in the presence of LiBr produces the pinacol coupling product of 2-octanone and leaves the 1-iododododecane unreduced. In contrast, only the Barbier-type product is produced when the reaction is conducted with a combination of SmI_2 and HMPA in the absence of LiBr. The Barbier-type carbonyl addition is shown to proceed through an outer-sphere electron-transfer process, while the pinacol coupling proceeds through inner-sphere reductive coupling, as evidenced by analysis of the samarium(II) reductants employing cyclic voltammetry and UV–VIS spectroscopy (Equation (32)).[127]

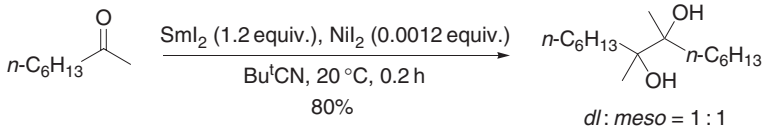


(32)

	Yield (%)		
Additive	*Pinacol*	*Barbier*	*Recovery (%) of 1-octanone*
None	23	59	18
HMPA	<1	91	8
LiCl	64	21	15
LiBr	98	<1	<1

Some additives accelerate the pinacol coupling reactions. Addition of Me_3SiCl to SmI_2 also accelerates the pinacol coupling reactions of aliphatic ketones and aldehydes.[128] Pinacol coupling reactions are also promoted with samarium metal and a Lewis acid such as Et_2AlCl or Me_3SiCl.[129,130] Coordination of such a Lewis acid to a carbonyl oxygen facilitates the one-electron reduction by samarium.

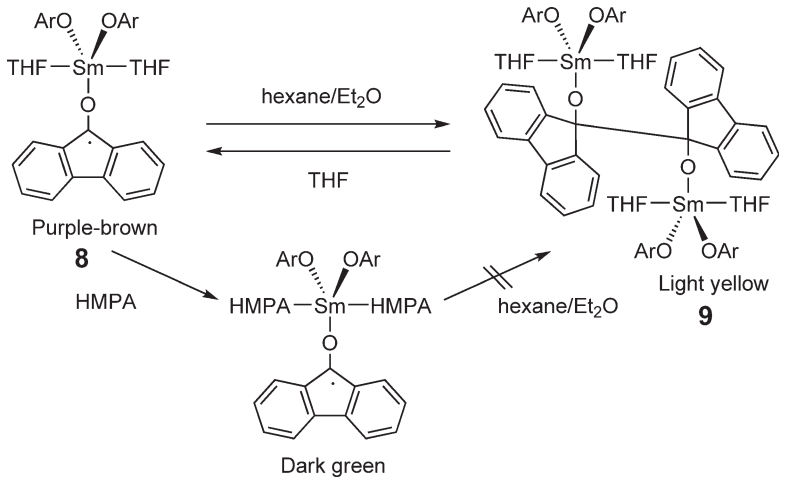
NiI_2 or $Fe(acac)_3$ in a catalytic amount also accelerates the pinacol coupling in pivalonitrile. The system can be applied to the coupling reactions of aromatic and aliphatic ketones (Equation (33)).[131]



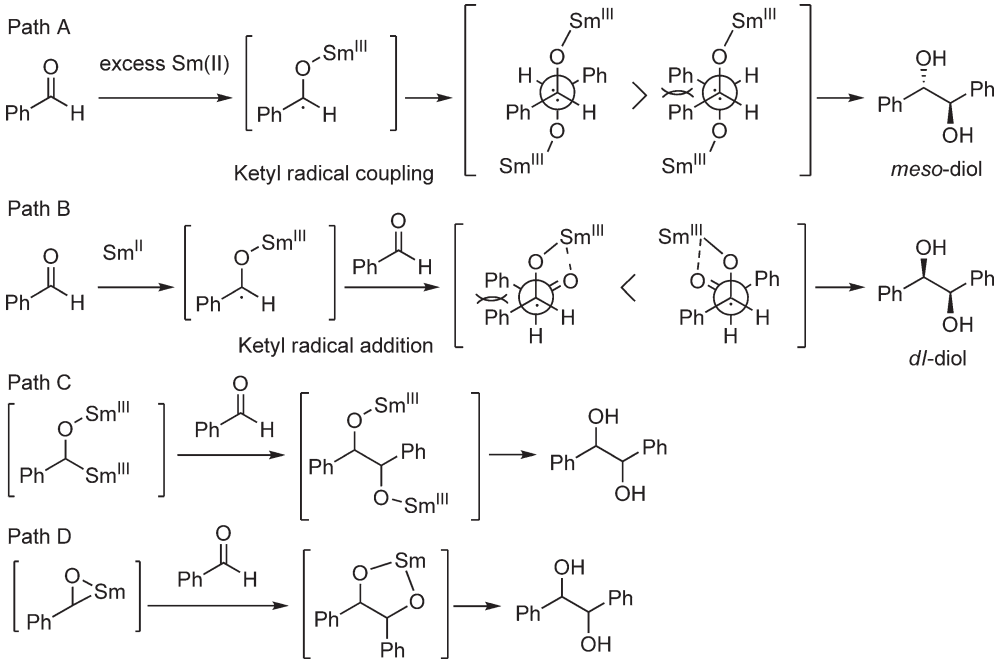
(33)

11.02.4.2.4 Samarium(III) ketyl radical and mechanism

Because of a strong one-electron reductant, the first step of the pinacol coupling with samarium(II) is a one-electron transfer to a carbonyl compound leading to a samarium(III) ketyl radical. Indeed, samarium(III) ketyl complex Sm(fluorenone ketyl)$(OAr)_2(THF)_2$ (8, Ar = 2,6-di-*t*-Bu-4-MeC_6H_2) is synthesized from samarium(II) aryloxide $Sm(OAr)_2(THF)_3$ and fluorenone. When the ketyl is dissolved in hexane/diethyl ether, pinacol coupling of the ketyl unit occurs to give a diethyl ether-coordinated pinacolate complex $[Sm(OAr)_2(OEt)_2]_2[\mu$-pinacolate] (9, pinacolate = 1,2-bis(biphenyl 2,2′-diyl)ethane-1,2-diolate). Dissolving this samarium(III) pinacolate complex in THF regenerates 8 by C–C bond cleavage of the pinacolate unit, showing that this pinacol coupling process is reversible. Addition of 2 equiv. of HMPA (per samarium) to the samarium ketyl complex 8 generates the corresponding HMPA-coordinated samarium complex, Sm(fluorenone ketyl)$(OAr)_2(HMPA)_2$, although this does not generate 9 by similar treatment with hexane/diethylether (Scheme 6).[132–134]

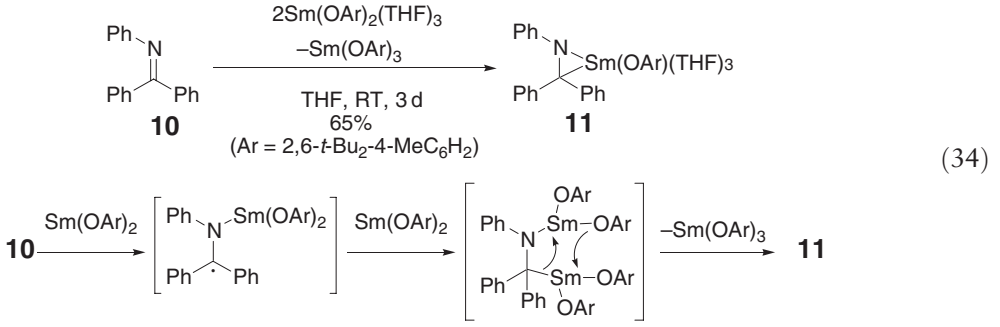


Scheme 6 Reprinted with permission of The American Chemical Society, *J. Am. Chem. Soc.* **1998**, *120*, 754–766.



Scheme 7

There are several possible pathways from the generated ketyl radical to pinacols, as shown in Scheme 7. Path A is a coupling reaction of the ketyl radicals. When two samarium(III) ions and two phenyl groups prefer *anti*-conformation due to their steric hindrances, the path A could produce a *meso*-diol selectively. Path B is an addition mechanism of the ketyl radical to benzaldehyde. Benzaldehyde approaches the ketyl radical by coordinating to its samarium(III); therefore, the mechanism could produce a *dl*-diol selectively due to the steric hindrances of the two phenyl groups. Path C contains a dianion which could be generated by further reduction of the ketyl radical. Addition of the dianion to benzaldehyde gives a diol. The reactive species in path D is an oxametallacyclopropane intermediate, which then undergoes benzaldehyde insertion followed by hydrolysis to give a diol. The reaction of *N*-phenyl benzophenone imine **10** with samarium(II) complex should give a samarium–imine azametallacyclopropane complex **11**, which is unambiguously confirmed by isolation (Equation (34)).[135] However, the corresponding oxametallacyclopropane complex (path D in Scheme 7) has not been isolated yet.



(34)

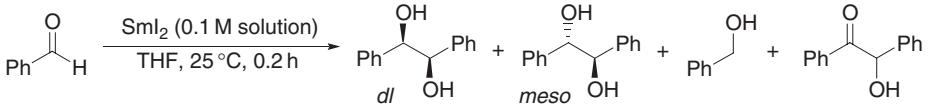
Several observations which provide mechanistic information have been reported recently (see Section 11.02.4.2.5); however, a detailed mechanism is still under investigation.

11.02.4.2.5 Diastereoselectivity

Diastereomeric ratios of pinacol dimers obtained by coupling of benzaldehyde and acetophenone with samarium reagents are summarized in Tables 3 and 4, respectively. In general, the stereochemical control of pinacol coupling reactions with a stoichiometric or catalytic samarium(II) reagent is poor, giving nearly a 1 : 1 *dl*/*meso* mixture.

There are several important stereochemical features in the coupling reaction of benzaldehyde with samarium(II).

(i) The *dl* : *meso* ratio is dependent on the aldehyde–samarium(II) ratio (Equation (35)).[139] When an excess amount of samarium(II) iodide is used, the reaction is moderately *meso*-selective. With ≤1 equiv. of samarium(II) iodide, moderate *dl*-selectivity is observed, although total yields of pinacol coupling products decrease. The observed equivalency-dependent diastereoselectivity can be explained by two different and competing reaction mechanisms discussed above (Scheme 7). When a large excess of samarium(II) is used for the reaction and the aldehyde is slowly added to the reaction mixture, the aldehyde is quantitatively transformed to the ketyl radical. In this case, coupling of the two ketyl radicals mainly gives sterically less requiring *meso*-diol (path A: ketyl radical coupling). When < 1 equiv. of samarium(II) is used, the formed samarium(III) ketyl adds to benzaldehyde that also is coordinating to the same samarium(III) ion. Again, a sterically less requiring transition state controls the stereochemical course to afford *dl*-diol (path B: ketyl radical addition).



PhCHO : SmI_2	Yield (%) 1,2-Diol	dl : meso	Yield (%) Benzyl alcohol	Benzoin
0.5	14	71 : 29	25	31
1.1	55	43 : 57	14	30
2.0	95	31 : 69		
3.0	93	32 : 68		

(35)

(ii) The effects of polyethylene glycols on the diastereoselectivity of samarium(II) iodide-promoted pinacol coupling of aldehydes have been studied.[137] In the case of benzaldehyde, the diastereoselectivity changes from *meso* : *dl* = 1 : 1.3 (95% yield) to 6 : 1 (85% yield) by addition of 1 equiv. of triglyme to samarium(II) iodide (Table 3, entry 11). In contrast, in the case of cyclohexane carboxaldehyde, the diastereoselectivity changes from *meso* : *dl* = 1 : 1.1 (95% yield) to 1 : 10 (25% yield) by addition of 1 equiv. of triglyme. In the latter case, the yield increases to 60% (*meso* : *dl* = 1 : 2.3) by addition of 10 equiv. of LiBr or LiCl to the reaction mixture. The same effect of tetraglyme is observed in the reactions of aromatic aldehydes using samarium(II) iodide in a catalytic amount and Me_2SiCl_2/magnesium in stoichi ometric amounts in THF (Table 3, entry 16; Table 4, entry 19).[140]

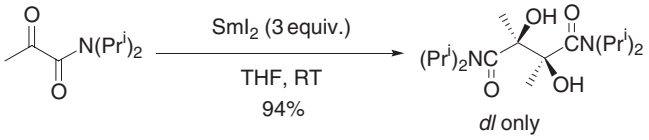
(iii) Although addition of a Lewis acid such as Me_3SiCl accelerates pinacol coupling reactions, prominent deviation of *meso* : *dl* selectivity is not observed.[128,141]

Table 3 Pinacol coupling of benzaldehyde with samarium reagents

Entry	*Samarium* (equiv.)	*Additive* (equiv.)	*Solvent*	*Conditions* (°C, min or h)	*Yield* (%)	*dl* : *meso*	*References*
1	SmI_2 (1)		THF	RT, 0.5 min	95	56 : 44	106
2	Sm (1)	Me_3SiCl (3), NaI (3)	CH_3CN	RT, 0.5 h	26	–	113
3	Sm (1)	Me_3SiCl (3), NaI (3), HMPA	CH_3CN	RT, 0.5 h	67	–	113
4	SmI_2 (2)		THF	0, 1 h	97[a]	–	125
5	SmI_2 (2)	HMPA (2.8)	THF	0, 1 h	10[b]	–	125
6	SmI_2 (2)	HMPA (5.6)	THF	0, 1 h	[c]	–	125
7	$SmBr_2$ (1.1)		THF	–, 2 min	70 (95)	Mixture	116
8	$Sm(OTf)_3$ (2)	*sec*-BuLi (2)	THF	RT, 1 h	97 (98)	–	117
9	Sm (0.75)	Me_3SiCl (5.4), H_2O (0.01)	THF	RT, 3 h	82	55 : 45	136
10	SmI_2 (1)	Dyglyme (1)	THF	–, 5 min	85	21 : 79	137
11	SmI_2 (1)	Triglyme (1)	THF	–, 5 min	85	14 : 86	137
12	Sm (3), $SmCl_3$ (1)		H_2O	RT, 36 h	81[d]	52 : 48	138
13	Sm (0.175)	$Br_2CHCHBr_2$ (0.35), mischmetall (1.25)[e]	THF	20, 16 h	62[f]	57 : 43	114
14	SmI_2 (2)		THF (0.1M)		95	31 : 69	139
15	Sm (1.5) + ICH_2CH_2 (2.3)		THF		52[g]	63 : 37	139
16	SmI_2 (0.2)	Mg (6.4), Me_2SiCl_2 (1.2), tetraglyme (0.4)	THF	RT, 4 h	83	20 : 80	140

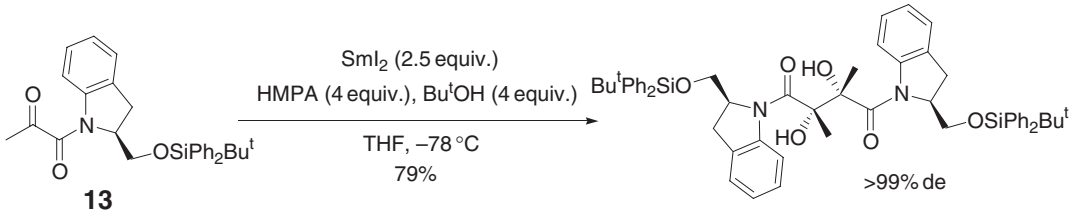
[a] *p*-[PhCH(OH)](C$_6$H$_4$)CHO **12** was produced in 1% yield.
[b] Compound **12** was produced in 60% yield.
[c] Compound **12** was produced in 72% yield.
[d] Benzyl alcohol was produced in 2% yield.
[e] Mischmetall is a cheap alloy of the light lanthanides: cerium, lanthanum, and neodymium are the main components.
[f] Benzaldehyde was added over a period of 14 h.
[g] Benzyl alcohol was produced in 18% yield.

Keto amides couple with samarium(II) iodide to give *dl*-isomers of pinacol dimers exclusively (Equation (36)).[142]



(36)

The pinacol coupling reactions of keto amides with samarium(II) can be extended to an asymmetric version by substrate control. Treatment of asymmetric keto amide **13** with samarium(II) iodide, HMPA, and *t*-butyl alcohol in THF gives one of the *dl*-diastereomers in 79% yield exclusively (Equation (37)).[143]



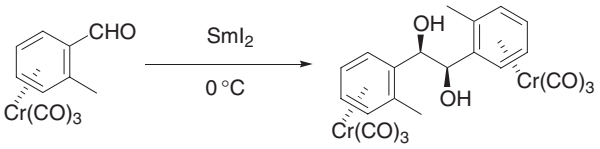
(37)

Table 4 Pinacol coupling of acetophenone with samarium reagents

Entry	*Samarium* (equiv.)	*Additive* (equiv.)	*Solvent*	*Conditions* (°C, min or h)	*Yield* (%)	*dl*:*meso*	*References*
1	SmI_2 (1)		THF	RT, 0.5 min	95		106
2	$SmBr_2$ (1.1) (Sm_2O_3 + Li)		THF	–, 2 min	75 (95)	Mixture	116
3	Sm (1)	Me_3SiCl (3), NaI (3)	CH_3CN	RT, 0.25 h	72		113
4	Sm (1)	Me_3SiCl (3), NaI (3)	THF	RT, 0.25 h	14		113
5	$Sm(OTf)_3$ (2)	Bu^sLi (2)	THF	RT, 75 min	94 (95)		117
6	SmI_2 (1.2)	$NiBr_2(PPh_3)_2$ (0.01)	Bu^tCN	RT, 6 min	94	79:21	131
7	SmI_2 (0.1)	Mg (8), Me_3SiCl (1.5)	THF	RT, –	68		121
8	Sm (1.7)	I_2 (1)	MeOH	RT, 5 min	71[a]	60:40	70
9	Sm (1)	Et_2AlI (3)	CH_3CN	0, 30 min	61	82:18	129
10	$Sm(OTf)_2(CH_3CN)_{1.5}$ (1) Sm + S(IV)$(OTf)_2$		CH_3CN	−40, 1 h	99	94:6	117
11	Sm (0.75)	Me_3SiCl (5.4), H_2O (0.01)	THF	RT, 3 h	80	50:50	136
12	$Sm(OTf)_2(dme)_2$ (2.2) ($2Sm(OTf)_3$ + Sm, cat. Hg/DME)		CH_3CN	–, 1 h	98	82:18	118
13	Sm (1.2)	Me_3SiCl (1.2)	THF	67, 20 h	69	75:25	130
14	Sm (1.2)	Me_3SiCl (1.2), ultrasonic irradiation	THF	67, 20 h	75	75:25	130
15	Sm (1.2)	Ultrasonic irradiation	THF	67, 20 h	19	54:46	130
16	Sm (2), $SmCl_3$ (1)		H_2O	RT, 36 h	75[b]	54:46	138
17	Sm (2.2)	$Br_2CHCHBr_2$ (1.1)	THF	20, 4 h	94	80:20	114
18	Sm (0.175)	$Br_2CHCHBr_2$ (0.35), mischmetall (1.25)[c]	THF	20, 16 h	72	80:20	114
19	SmI_2 (0.2)	Mg (6.4), Me_2SiCl_2 (1.2), tetraglyme (0.4)	THF	RT, 4 h	62	19:81	140

[a]1-Phenylethanol was produced in 24% yield.
[b]1-Phenylethanol was produced in 2% yield.
[c]See Table 3, footnote e.

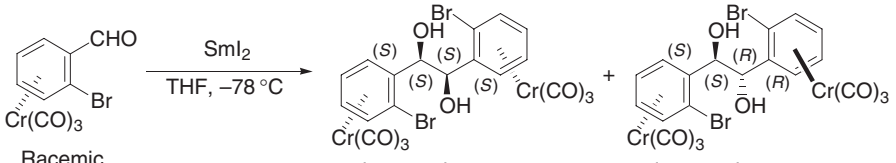
Aromatic carbonyl compounds whose benzene π-electrons coordinate to chromium(0) tricarbonyl also undergo pinacol coupling reactions with samarium(II) iodide. Benzaldehyde- and (*ortho*- or *para*-substituted benzaldehyde)$Cr(CO)_3$ afford predominantly the corresponding *dl*-diastereomers of pinacols except an *o*-bromobenzaldehyde complex, and addition of HMPA to the reaction mixture changes the predominance to *meso*-diastereomers (Equation (38)). A unique pair selection is observed in a reaction of racemic (*o*-bromobenzaldehyde)$Cr(CO)_3$ with samarium(II) iodide to *dl*- and *meso*-coupling products where *dl*-pinacol is produced by homocoupling of one of the enantiomers and a *meso*-pinacol is produced by hetereocoupling of the two enantiomers exclusively (Equation (39)). Therefore, treatment of enantiomerically pure (*o*-bromobenzaldehyde)$Cr(CO)_3$ with samarium(II) gives the corresponding *dl*-pinacol in 75% yield without forming the *meso*-pinacol (Equation (40)). In the reaction of (*o*-bromobenzaldehyde)$Cr(CO)_3$, heterocoupling leading to the *meso*-pinacol proceeds faster; however, only the *dl*-pinacol is produced via homocoupling because only one enantiomer is in the reaction mixture.[144]



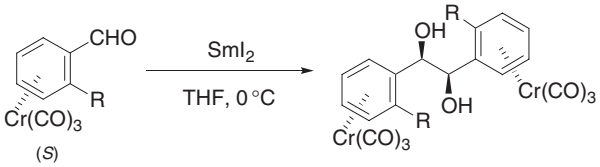
Solvent	*Yield* (%)	*dl* : *meso*
THF	83	95 : 5
THF, HMPA	80	20 : 80

(38)

(39)



(40)



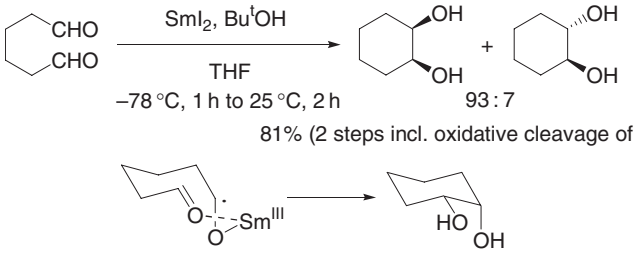
R	*Yield* (%)	*dr* (%)
Br	75%	100
Me	71%	100

Pinacol coupling of 2-substituted ferrocene carboxaldehydes with samarium(II) iodide in THF also affords *dl*-coupling products selectively.[145]

Although yields and diastereoselectivities are moderate, a cross-pinacol coupling reaction between a 1,2-diketone and an aldehyde is accomplished with SmI_2 in the presence of HMPA.[146]

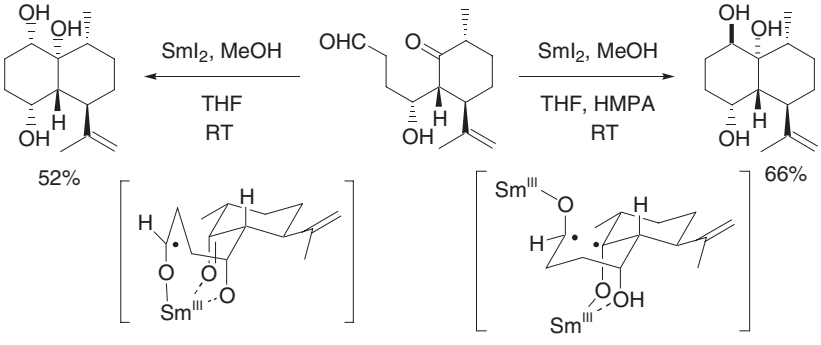
11.02.4.2.6 Intramolecular cyclization

Samarium(II) diiodide transforms aliphatic 1,5- and 1,6-dialdehydes (or keto aldehydes) into diols in the presence of an alcohol such as methanol or *t*-butyl alcohol (Equation (41)). The stereochemistry of the newly formed diols is usually *cis*-configuration.[147,148]



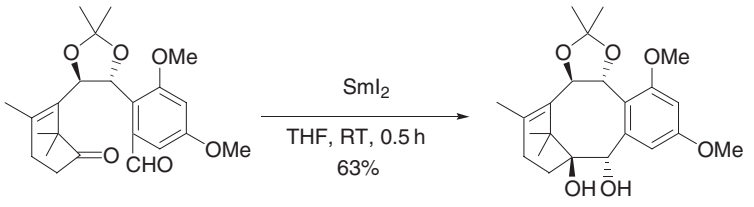
(41)

Diastereoselectivities in complex systems are determined by conformation of the transition states which are affected by chelation and steric effects of substituents and reaction conditions. For example, the stereochemistry of a hydroxyl group derived from a ketone is determined by coordination of hydroxyl and other functional groups, and depends on the presence or absence of HMPA (Equation (42)).[149]



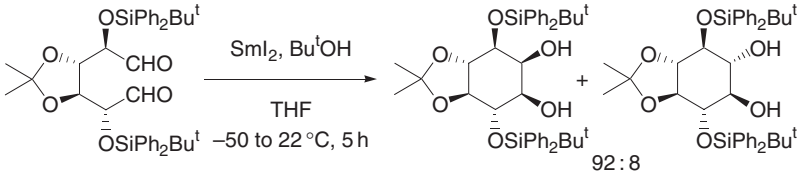
(42)

Not only 5- and 6-membered rings, but also 4-,[150] 8-,[151,152] and 14-membered rings[153] can be constructed from the corresponding acyclic dicarbonyl precursors through an intramolecular samarium(II) cyclization (Equation (43)).

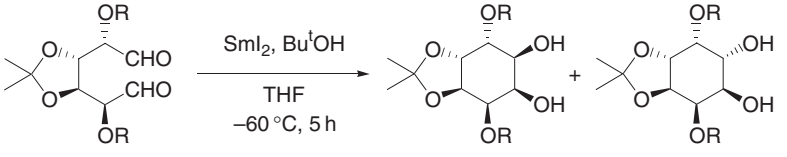


(43)

Sugars and inositols are synthesized by the samarium(II)-mediated cyclization methods. Stereoselectivity of newly introduced diol units is *cis*-configuration in most cases. However, coordinating substituents sometimes affect the synthesis to give *trans*-isomers (Equations (44) and (45)).[154,155]



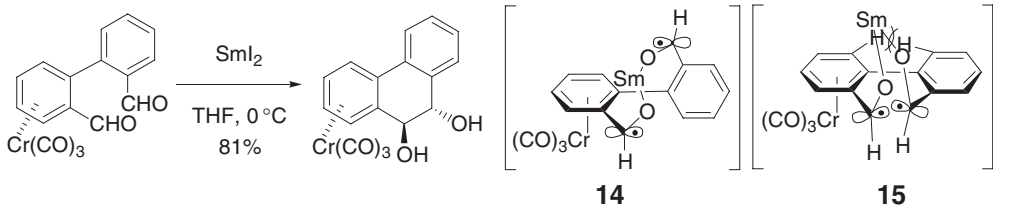
(44)



(45)

Intramolecular pinacol coupling of 2,2′-biaryldicarbaldehyde with samarium(II) iodide shows that axial chirality transfer to central chirality proceeds in a stereospecific manner.[156]

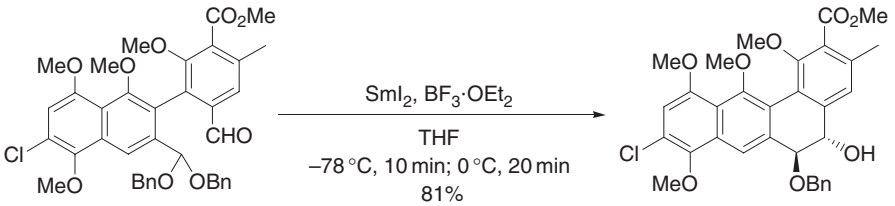
Intramolecular pinacol coupling of planar chiral mono-$Cr(CO)_3$ complexes of biaryls is accomplished with samarium(II) iodide in THF (Equation (46)). Enantiomerically pure *trans*-1,2-diol is produced stereoselectively, presumably, according to the mechanism suggested below. Samarium(II) iodide approaches from a less hindered *exo*-side of the arenechromium(tricarbonyl) moiety and two formyl groups coordinate to a samarium(III) ion. Electron transfer gives a bis-ketyl radical intermediate. Of the two possible intermediates, **14** is likely to be more favorable than the alternative intermediate **15**, because the two arene rings in **15** are required to be nearly coplanar to cause large ring strain.[157]



14 **15**

(46)

A monoprotected pinacol can be obtained in 81% yield by intramolecular coupling of 2,2′-biaryldicarbaldehyde mono-dibenzyloxy acetal, using samarium(II) iodide in THF in the presence of $BF_3{\cdot}OEt_2$ (Equation (47)). As in the case of homocoupling of 2,2′-biaryldicarbaldehyde, the *trans*-isomer is produced selectively. Addition of the Lewis acid is important to obtain high yields, otherwise the yield drops to 37%.[158]

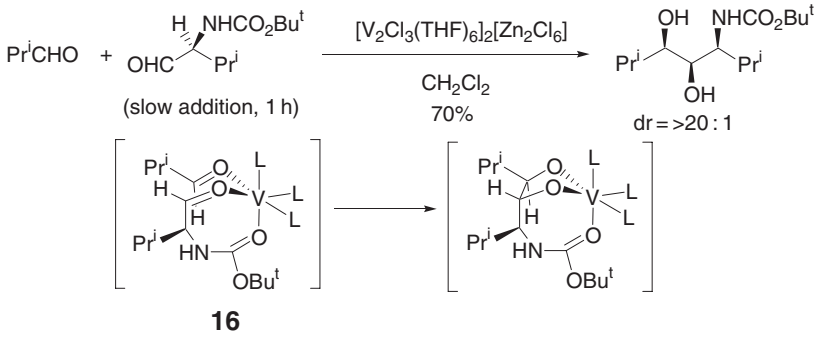


(47)

11.02.4.3 Pinacol Coupling with Other Low-valent Early Transition Metals

11.02.4.3.1 Vanadium-based reagent systems

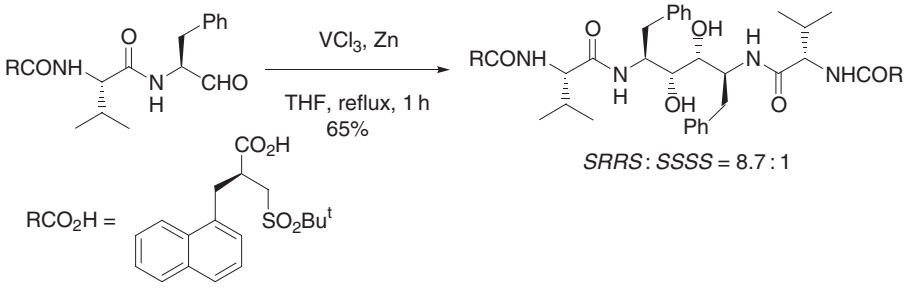
Vanadium(II) complex $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$ is effective for inter- and intramolecular pinacol coupling of carbonyl groups, as disclosed by Pedersen and co-workers.[159] Stereoselective cross-coupling between simple aliphatic aldehydes and 3-formyl-*N*,*N*-dialkylbutanamide is achieved with the vanadium(II) reagent. The *syn*-1,2-diols are produced selectively.[160] Aldehydes having a 2-[*N*-(benzyloxycarbonyl)amino] group can be used instead of the 3-formyl-*N*,*N*-dialkylbutanamide, and cross-coupling products with aldehydes are obtained in a diastereoselective manner (Equation (48)).[161] The selectivity is explained by model **16**, where aldehyde Pr^iCHO coordinates to V(II) from a less hindered side of the chelating α-Boc-amino-subsituted aldehyde, and reductive coupling proceeds with retention of the alignment.



16

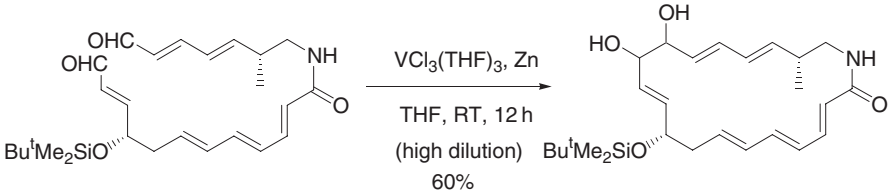
(48)

Homocoupling of (*S*)-2-[*N*-(benzyloxycarbonyl)amino]aldehydes with the vanadium reagent gives C_2-symmetric (1*S*,2*R*,3*R*,4*S*)-1,4-diamino-2,3-diols selectively.[162,163] The method has been applied to a kilogram-scale synthesis of C_2-symmetric HIV-protease inhibitors (Equation (49)).[164] The reductive dimerization is accomplished with $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$ generated *in situ* from VCl_3 and zinc. The reaction also proceeds with niobium complex $NbCl_3$(DME), but does not proceed with titanium(III) or samarium(II) reagents.



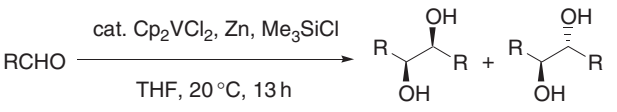
(49)

The 10- to 20-membered ring diols have also been obtained by intramolecular cyclization with $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$ under high dilution conditions (Equation (50)).[165,166]



(50)

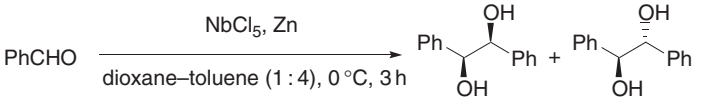
Homocoupling of aromatic and aliphatic aldehydes occurs with a catalytic amount of Cp_2VCl_2 or $CpV(CO)_4$ by using zinc and Me_3SiCl.[167,168] In particular, the Cp_2VCl_2 catalyst/Zn/Me_3SiCl system is also effective for homocoupling of aldimines leading to 1,2-diamines (Equation (51)). The stereoselectivity of the reactions is, however, moderate.



R	*Yield* (%)	*dl* : *meso*
c-C_6H_{11}	70	90 : 10
n-C_5H_{11}	97	50 : 50

(51)

Low-valent niobium and tantalum are also effective for homocoupling of aldehydes leading to 1,2-diols.[164,169–171] Not only commercially available $NbCl_3$(DME) but also a combination of $NbCl_5$ and zinc can be used for the pinacol coupling. Reactions in a mixed solvent of 1,4-dioxane and toluene (1 : 4) give better diastereoselectivity than those in DME or THF (Equation (52)).[172]

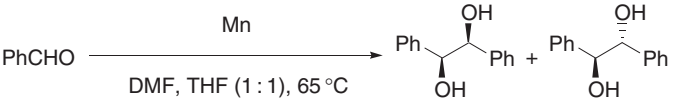


dl : *meso* = 98.8 : 1.2

(52)

11.02.4.3.2 Chromium-based reagent systems

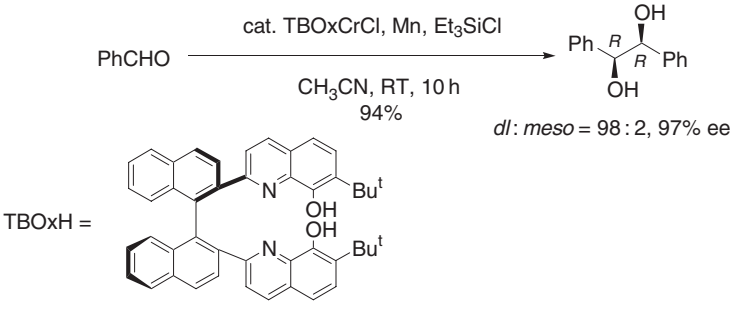
Chromium(II) salts such as $CrCl_2$ are mild reducing agents and usually inert to simple aliphatic aldehydes; however, they can reduce aromatic and even aliphatic aldehydes under appropriate conditions. An important factor for pinacol coupling in using a catalytic amount of $CrCl_2$ is the employment of a co-reductant of chromium(II), that is, manganese metal. Fürstner *et al*. have found that pinacol coupling of *p*-methoxycarbonyl-substituted benzaldehyde occurs when $CrCl_2$ is used in a catalytic amount, and manganese and Me_3SiCl in stoichiometric amounts in DMF–DME (20 : 3). Even an alkenyl triflate functional group tolerates to give the corresponding 1,2-diol in 73% yield.[173] The Fürstner's reagent system is applicable to the pinacol coupling of simple benzaldehyde using a catalyst of $CrCl_2$ in a mixture of DMF and THF,[174] or of a chromium–salen complex in THF.[175] Co-use of Me_3SiCl is indispensable to promote the coupling reaction, and a catalytic amount of $CrCl_2$ accelerates the reaction (Equation (53)).[174] The coupling proceeds with aliphatic aldehydes when the amount of $CrCl_2$ is increased and a catalytic amount of $PbCl_2$ is added; however, the yield is moderate.[176]



Additive	*Time* (h)	*Yield* (%)	*dl* : *meso*	*Recovery* (%) *of benzaldehyde*
$CrCl_3$ (5 mol%)	10	2		98
Me_3SiCl	19	73	48 : 52	27
$CrCl_3$ (5 mol%), Me_3SiCl	1	74	38 : 62	0

(53)

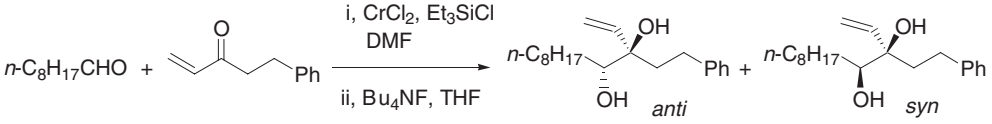
Asymmetric homocoupling of aromatic aldehydes is achieved in a high yield with high diastereo- (*dl*/*meso*) and enantioselectivity with a catalytic amount of a chromium complex having a chiral tethered bis(8-quinolinolate) ligand, manganese, and Et_3SiCl in acetonitrile (Equation (54)).[177] Although the yield is moderate, cyclohexane carboxaldehyde also gives a *dl*-diol in high diastereo- and enantioselectivity.



dl : *meso* = 98 : 2, 97% ee

(54)

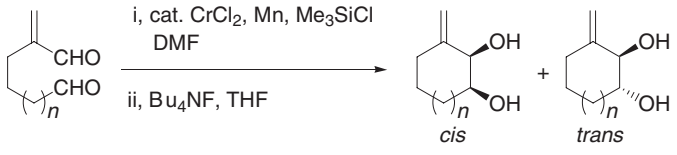
In DMF, which dissolves $CrCl_2$, one-electron reduction of α,β-unsaturated ketones proceeds with $CrCl_2$ alone. For example, treatment of a mixture of a vinyl ketone and an aldehyde with $CrCl_2$ in the presence of Me_3SiCl (or Et_3SiCl) produces cross-pinacol-type coupling products (Equation (55)).[178,179] Diastereoselectivity of the coupling reaction changes dramatically depending on the reaction temperatures.



Temp (°C)	*Time*	*Yield* (%)	*anti* : *syn*
0	5 h	99	93 : 7
75	15 min	85	10 : 90

(55)

The amount of $CrCl_2$ can be reduced by using manganese as a reductant.[180–182] The procedure can be applied to intramolecular cyclization (Equation (56)).[183] The diastereoselectivity depends on the ring size in the products.



n	*Yield* (%)	*cis* : *trans*
1	60	59 : 41
2	55	71 : 29
3	75	80 : 20

(56)

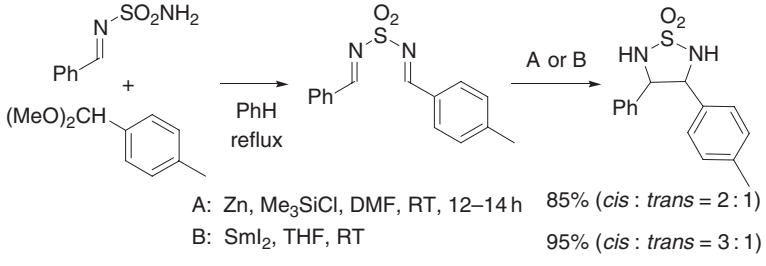
11.02.5 Reductive Coupling of Imines and their Derivatives

Because vicinal diamines and 2-aminoalcohols are important components of natural products and medicinal agents, and used as ligands for metal-catalyzed reactions, especially in asymmetric synthesis, efficient methods for the compounds have been extensively investigated over the past decade.[184]

11.02.5.1 Reductive Coupling of Imines

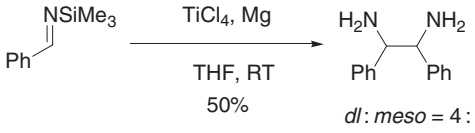
Metals such as zinc,[185,186] magnesium,[185] and aluminum[187] have been used in the presence of a proton source for homocoupling of imines leading to 1,2-diamines. Rieke manganese is also effective for the homocoupling of imines.[188] Ratios of *dl*- and *meso*-1,2-diamines produced with these metals are not usually high and fall to between 50/50 and 80/20. Among the 1,2-diamines, C_2-symmetrical chiral diamines are targets of synthesis due to the applicability for asymmetric synthesis. Isomerization of *meso*-1,2-diphenylethylene diamine into its C_2-symmetrical *dl*-isomers has been reported.[189] Optical resolution of *dl*-isomers gives *d*- and/or *l*-diamine(s).[190–192] Stereoselective synthesis of (1*R*,2*R*)-1,2-diarylethene-1,2-diamines is achieved by using intramolecular coupling of the corresponding chiral aromatic diimines.[193,194] Highly enantioselective homocoupling of imines is accomplished with a combination of a zinc–copper couple and a chiral camphor sulfonic acid in DMF.[195]

Unsymmetrical 1,2-diarylethane diamines, the formal cross-coupling products of two different imines, are produced by intramolecular reactions of dibenzylidene sulfamides with a combination of zinc and Me_3SiCl in DMF or SmI_2 in THF (Equation (57)).[196]



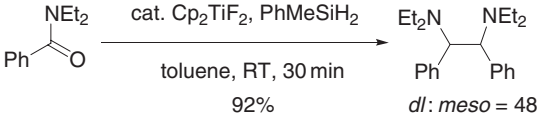
(57)

Although $TiCl_4$ shows a reducing potential under special conditions employed with Et_3N or *i*-Pr_2NEt in CH_2Cl_2,[77,197] it is usually employed with metal reductants such as magnesium and zinc for reductive coupling of imines. Treatment of *N*-(trimethylsilyl)arylimines with a black suspension derived from $TiCl_4$ and magnesium (turning or amargam) in THF gives 1,2-diarylethene-1,2-diamine upon work-up (Equation (58)).[198–200]



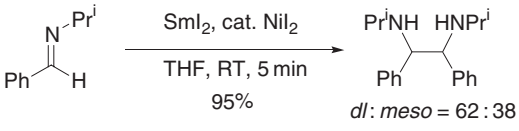
(58)

The following combinations have also been reported of titanium-mediated reductive coupling of imines: $TiCl_3$–Mg in DME (or THF),[201] $TiCl_3$–Li in DME (or THF),[201] $TiCl_4$–Et_3N in CH_2Cl_2.[77] Catalytic use of Cp_2TiCl_2 with Sm in THF[202] also produces low-valent titanium reagents. Aromatic oximes and azines couple to 1,2-diamines by treatment with a combination of Zn–methanesulfonic acid in acetonitrile or Zn–$TiCl_4$ in THF.[203] Reductive coupling of aromatic amides to the corresponding 1,2-diamines proceeds with a combination of a catalytic amount of Cp_2TiF_2 and $PhMeSiH_2$ in toluene at room temperature. Ratios of resulting *dl*- and *meso*-diamines are, however, low, falling to 1 : 1–2 : 3 (Equation (59)).[204]



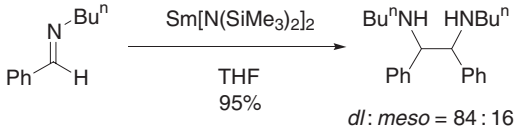
(59)

Reductive coupling of aromatic aldimines leading to vicinal diamines proceeds with SmI_2,[205] and is strongly accelerated by addition of a catalytic amount of NiI_2,[206] or a stoichiometric amount of $Yb(OTf)_3$.[207] In the former case, the coupling reaction proceeds at room temperature within 5 min. In contrast, it takes 6–12 h in refluxing THF in the absence of NiI_2. The ratios of *dl*- and *meso*-diamines are 2 : 1 to 1 : 1 (Equation (60)).



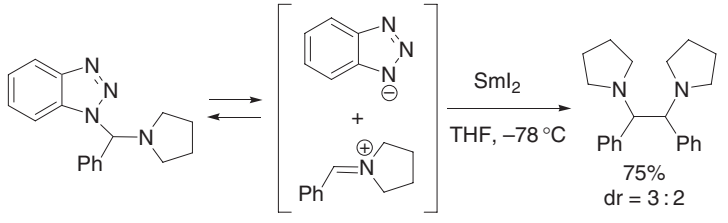
(60)

$Sm[N(SiMe_3)_2]_2$, a reductant stronger than SmI_2, is also effective for reductive coupling of imines. Diastereoselectivity of the coupling with the samarium(II) amide is higher than SmI_2 (Equation (61)).[208]



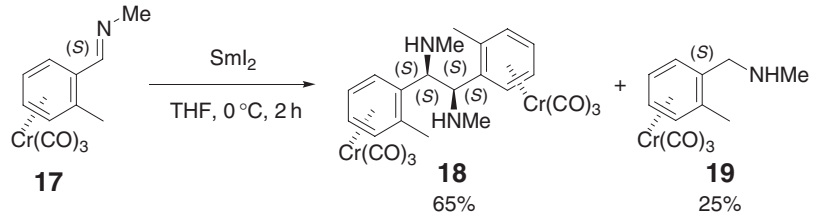
(61)

Treatment of an *N*-(*N*′,*N*′-dialkylaminoalkyl)benzotriazole, derived from an aldehyde and a secondary amine, with SmI_2 affords a vicinal diamine via generation of the corresponding imine, one-electron reduction of the imine, and homocoupling (Equation (62)).[209]



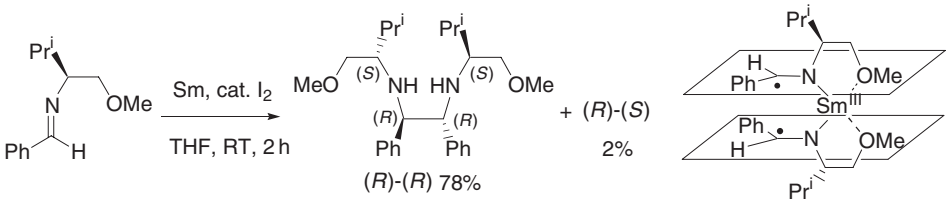
(62)

In a manner similar to the SmI_2-mediated homocoupling of enantiomerically pure (*o*-methylbenzaldehyde)-$Cr(CO)_3$, the coupling reaction of the [methyl(*o*-tolylmethylene)amine]$Cr(CO)_3$ complex **17** with SmI_2 gives only *syn*-diamine **18** along with the reduced amine **19** (Equation (63)).[210]

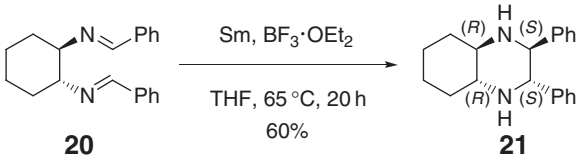


(63)

Optically active chiral vicinal diamines are produced by SmI_2-promoted reductive coupling of an imine derived from benzaldehyde and 1-isopropyl-2-methoxyethylamine. Intermolecular coupling proceeds in a diastereoselective manner (Equation (64)).[211,212] For example, coupling of diimine **20** with SmI_2 and $BF_3{\cdot}OEt_2$ proceeds at 65 °C to give enantiomerically pure 1,2-diamine **21** with C_2-symmetry in 60% yield (Equation (65)).[213]

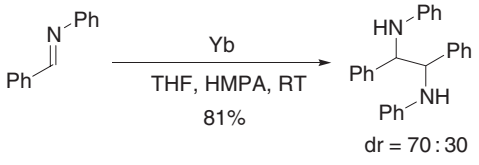


(64)



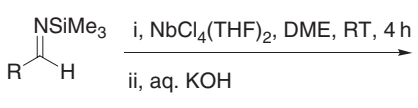
(65)

Reductive coupling of benzalimines with a ytterbium metal occurs in a mixture of THF and HMPA at room temperature (Equation (66)).[214] The reaction proceeds via an azaytterbiacyclopropane complex. This kind of metallacycle is isolated in the case of a benzophenone–imine.[215]



(66)

In 1987, Pedersen reported that reductive coupling of *N*-(trimethylsilyl)imines (or a combination of nitriles and Bu_3SnH) occurred with $NbCl_4(THF)_2$ in DME to give 1,2-diamines in 40–73% yields (Equation (67)).[216]



R	*Yield* (%)	*dl : meso*
Ph	69	95 : 5
$CH_2{=}CH(CH_2)_3$	61	67 : 33

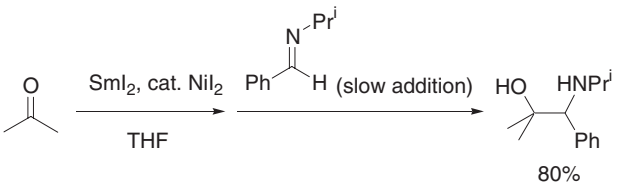
(67)

A combination of Cp_2VCl_2 in a catalytic amount and Me_3SiCl/zinc in stoichiomeric amounts mediates homocoupling of imines.[217] The selectivity of *dl*/*meso* is improved by changing the *N*-substituent from phenyl to allyl.

11.02.5.2 Cross-Coupling Reactions between Carbonyl Compounds and Imine Derivatives

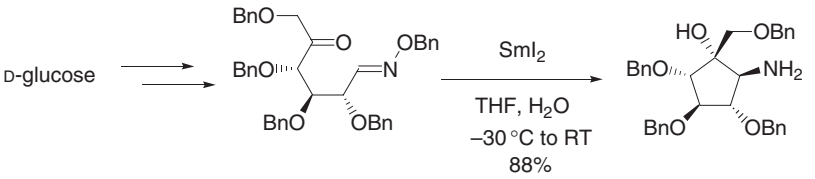
In 1991, Inanaga achieved SmI_2-mediated intermolecular cross-coupling between C═O (ketones or aldehydes) and C═N by using *O*-benzyl formaldoxime as a C═N component.[218] The reaction requires HMPA as a co-solvent and a suitable proton source such as *t*-butyl alcohol or ethylene glycol. A cross-coupling reaction between ketones and

aromatic aldimines is achieved by slow addition (over 10 min) of a solution of the imine in THF to a mixture of the ketone in excess, SmI_2, and a catalytic amount of NiI_2 in THF at 0 °C in order to prevent homocoupling of the imine (Equation (68)).[206]



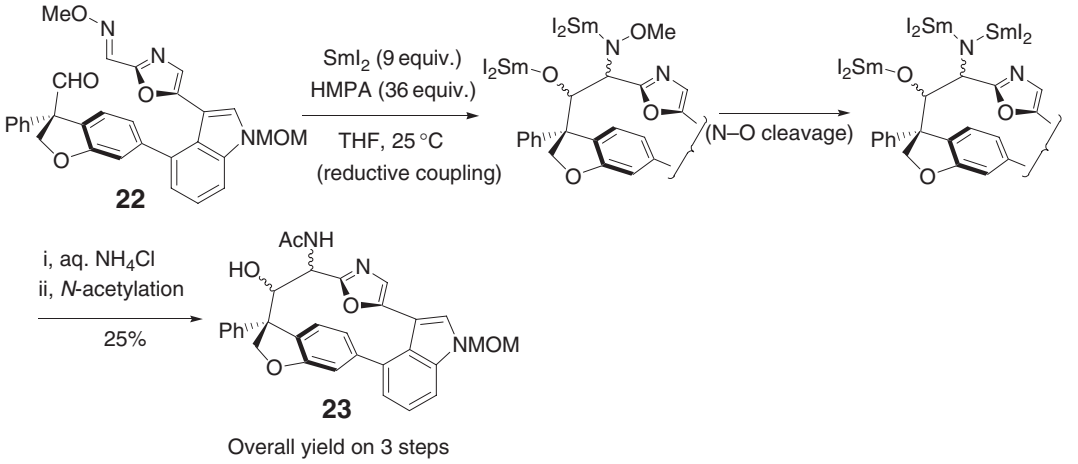
(68)

Intermolecular reactions between *O*-benzyl oximes and ketones (or aldehydes) are limited to those with formaldehyde *O*-benzyl oxime. However, intramolecular coupling proceeds with carbonyl-tethered oxime ethers (Equation (69)).[219,220]



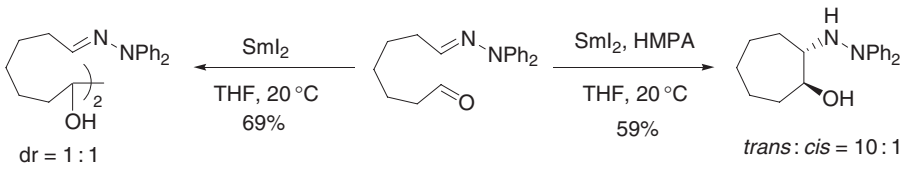
(69)

Aldehyde-oxime **22** undergoes intramolecular coupling upon treatment with 9 equiv. of SmI_2 and 36 equiv. of HMPA in THF at 25 °C for 1 h followed by quenching with aqueous NH_4Cl and *N*-acetylation to give **23** in 25% (Equation (70)).[221] This cyclization does not occur in the absence of HMPA. The ratio of HMPA/SmI_2 drastically affects the reaction course; when the ratio is increased from 4/1 to 2/1, formation of a significant amount of a cyclized initial product that still has an N–O linkage is observed along with the desired product **23**. This observation suggests that cleavage of the N–O linkage occurs after reductive cyclization, and is accelerated by a suitable donor ligand like HMPA.

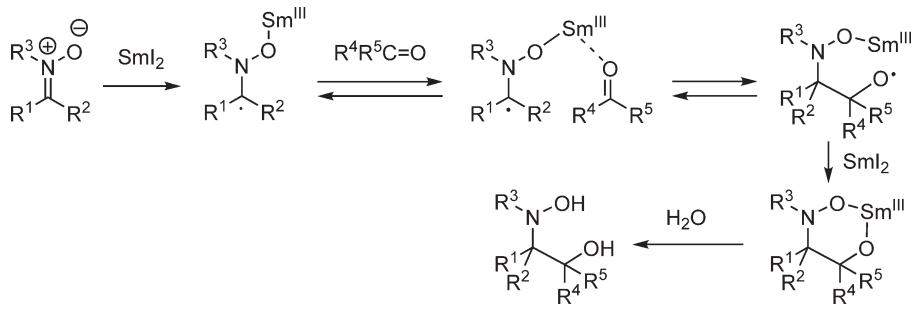


(70)

Intramolecular coupling of substrates having both carbonyl and diphenyldiazenyl groups proceeds with SmI_2 and HMPA in THF to give five- to seven-membered ring products (Equation (71)).[222,223] Selectivity of the cyclization is high: the resulting hydroxyl and diphenylhydrazine groups are *trans*. When HMPA is absent, the intermolecular pinacol coupling leading to 1,2-diols occurs selectively.[223]

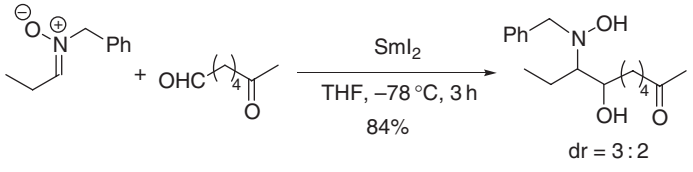


(71)

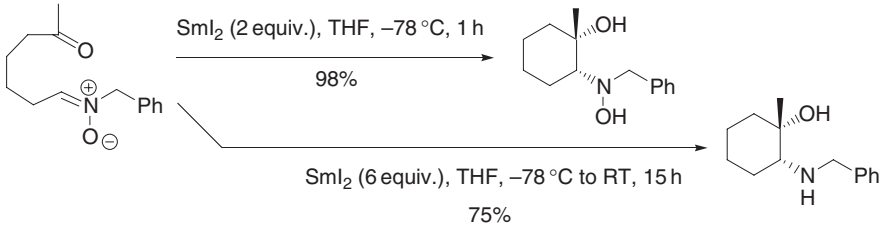


Scheme 8

Inter- and intramolecular cross-coupling reactions of wide applicability are achieved by using a nitrone (*N*-alkylidenebenzylamine *N*-oxide) as the imine derivative.[224] Treatment of a nitrone and a carbonyl compound with SmI_2 in THF at −78 °C gives the expected α-*N*-hydroxyamino alcohols as a mixture of diastereomers (Equations (72) and (73)). The coupling reaction does not require the presence of an alcohol or HMPA. Coupling reactions between a nitrone and a cyclopropyl ketone proceed without ring opening. In addition, when 6-ketoheptanal is treated with a nitrone, a coupling product derived from nitrone and aldehyde is isolated selectively, and no intramolecular pinacol coupling is observed. These results as well as the fact that homocoupling of a nitrone occurs without addition of an aldehyde suggest that the cross-coupling proceeds via reduction of nitrone with SmI_2 followed by addition to a carbonyl compound (Scheme 8).

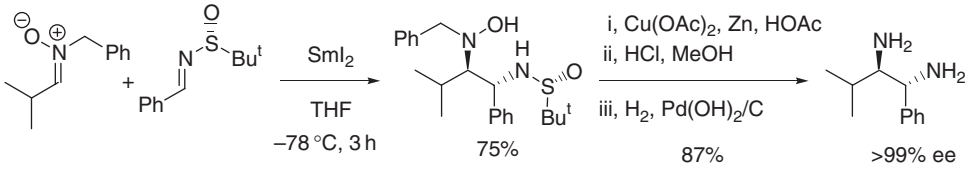


(72)



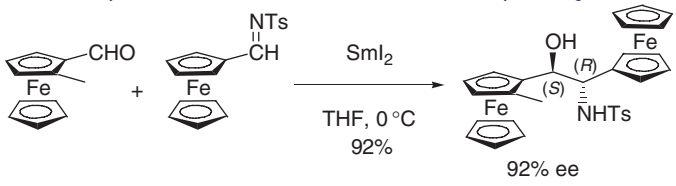
(73)

Unsymmetrical vicinal diamines are prepared by reductive cross-coupling between nitrones and *N*-*t*-butylsulfinyl imines with SmI_2. The coupling proceeds in a high diastereoselective manner. Thus, optically pure unsymmetrical vicinal diamines are produced by using enantiomerically pure sulfinyl imines (Equation (74)).[225]



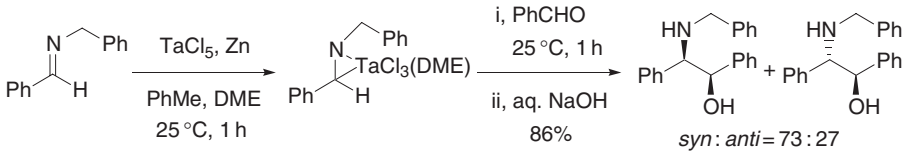
(74)

Enantioselective synthesis of β-amino alcohols by SmI_2-mediated cross-pinacol coupling of the planar chiral *N*-sulfonyl(ferrocenylidene)amine with ferrocene carboxaldehyde is achieved by facile reduction of the ferrocenylidene amine with SmI_2, followed by enantioselective addition to the aldehyde (Equation (75)).[226]



(75)

Low-valent niobium and tantalum react with imines to give the corresponding imine–niobium or –tantalum complexes. Some of these are isolated, and structures of the complexes are confirmed by X-ray analyses. These imine complexes react with aldehydes to give β-hydroxyamines in good to excellent yields (Equation (76)).[169,227,228]



(76)

11.02.6 Conclusion

Reductive coupling reactions such as the McMurry coupling reaction and pinacol coupling reaction are a powerful and straightforward method for combining two different (or identical) carbon skeletons. Because low-valent early transition metals have high reducing potential and the resulting metal ions have strong oxophilicity, namely, high Lewis-acidic nature, to bring two reactive carbonyl groups close to each other, they are employed as strong tools for intramolecular coupling. In contrast, an intermolecular pinacol coupling remains yet to be improved for the level of synthetic meaning. The present problems are as follows: (i) In contrast to the homocoupling reactions of aromatic carbonyl compounds, those of aliphatic compounds having wide applicability and high diastereoselectivity are not established. (ii) It is still difficult to obtain cross-coupling products selectively from two different carbonyl compounds in both aromatic and aliphatic cases. This is because most of the reactions are performed all at once, namely, the Barbier-type conditions rather than the Grignard-type conditions, possibly due to the instability of intermediates. (iii) It is difficult to obtain one enantiomer of *dl*-diols. Asymmetric coupling reactions with transition metal catalysts have only been introduced quite recently.

In view of the historical perspective and future requirements, it is important to reduce the amount of reductants for the coupling reactions. In the future, molecular hydrogen or electricity should be used in lieu of zinc in stoichiometric amounts for the reductive coupling reactions. In addition, catalytic transformations should be developed that may include oxidation of the resulting reductive coupling products so as to adjust the oxidation state.

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11.03
C–C Bond Formation (Part 2) by Substitution Reactions: Allylic Alkylation

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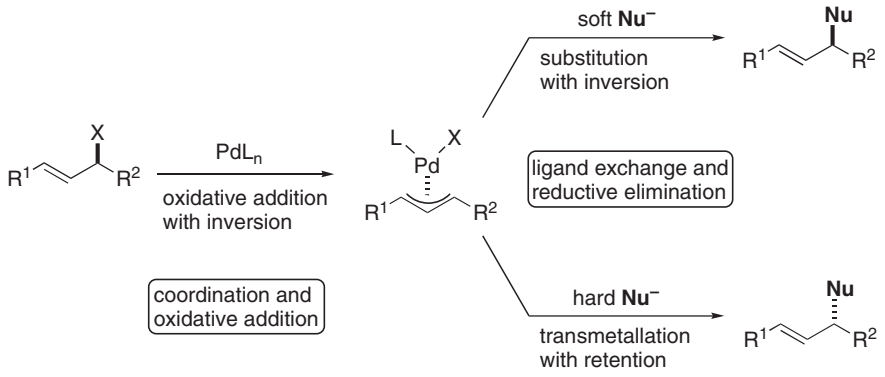
11.03.1 Introduction

Allylic substitution reactions of allylic alcohols and their derivatives catalyzed by transition metal complexes are currently one of the most important and widely studied catalytic reactions in organic synthesis. The reactions involve a (π-allyl) metal complex as a key intermediate, which can be exploited for various transformations with high chemo-, regio-, and stereoselectivities. Although the ambiphilic nature of a metal-bound allyl ligand allows the (π-allyl) metal species to behave as both an electrophile and a nucleophile, this review focuses on the reactions in which the allyl unit undergoes a nucleophilic displacement. This process is catalyzed by a variety of transition metal complexes derived from copper, nickel, palladium, platinum, rhodium, iridium, ruthenium, molybdenum, and tungsten. Especially in the last decade, enormous progress has been made to gain a high to excellent enantioselectivity in the asymmetric allylic alkylation. Various types of new chiral ligands have been synthesized and examined in the allylic alkylation with a wide range of substrates and nucleophiles. Several excellent reviews[1] have already appeared on this topic; thus, this chapter mainly presents an overview of various approaches to "asymmetric" allylic alkylation catalyzed by a variety of transition metal complexes.

Transition metal-catalyzed allylic alkylation is generally considered to involve mechanistically four fundamental steps as shown in Scheme 1: coordination, oxidative addition, ligand exchange, and reductive elimination.[1] A key step of the catalytic cycle is an initial formation of a (π-allyl)metal complex and its reactivity. The "soft" carbon-centered nucleophiles, defined as those derived from conjugate acids whose $pK_a < 25$, usually attack the allyl ligand from the opposite side



Scheme 1

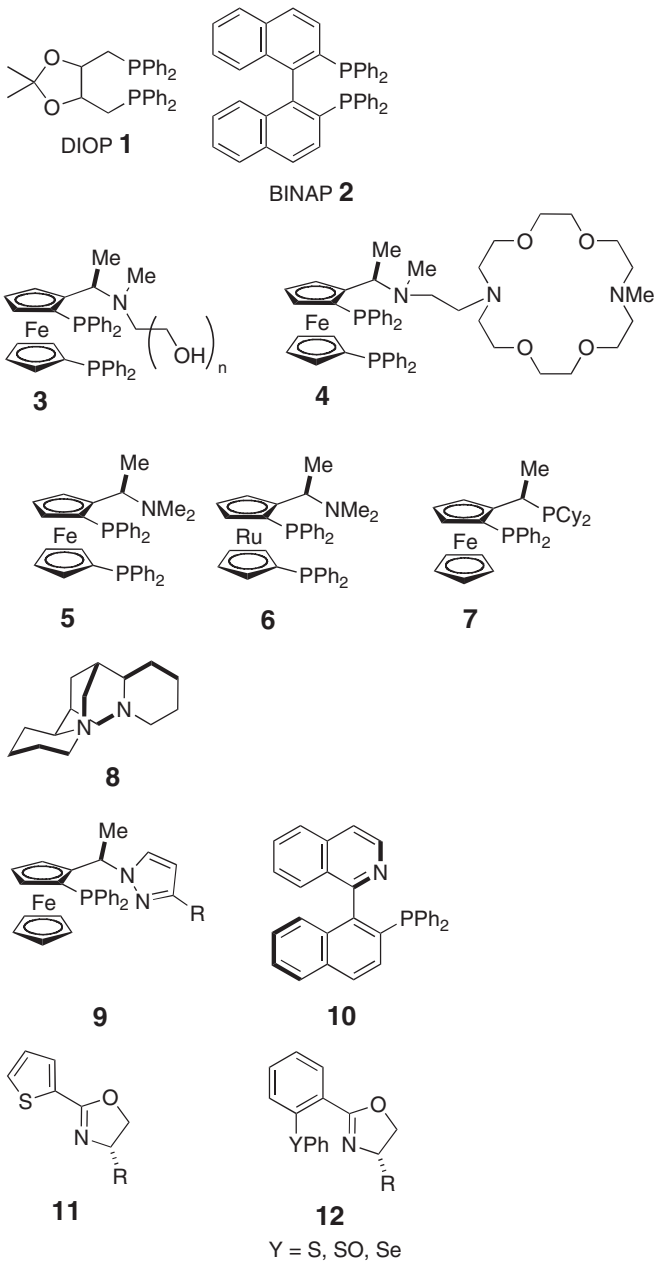
to the metal, giving the allylic alkylated compounds with an overall retention of stereochemistry. On the other hand, "hard" carbon-centered nucleophiles, defined as those derived from conjugate acids whose $pK_a > 25$, usually attack the metal center of the π-allyl intermediate, and the substitution normally occurs via transmetallation and reductive elimination, giving the compounds with an overall inversion of stereochemistry. In both cases, the efficient transfer of chirality from the attendant chiral ligand to the opposite site of π-allyl face is a key for successful asymmetric allylic alkylation.

11.03.2 Asymmetric Palladium-catalyzed Allylic Alkylation of Allylic Alcohols and their Derivatives

Among the transition metal-catalyzed allylic alkylations, asymmetric palladium-catalyzed allylic alkylation has been investigated most intensively with much successful results. A variety of optically active ligands **1–12** have been designed and prepared for the catalytic reactions, some of which are shown in Scheme 2 (e.g., see Refs: 2 and 2a). In addition to a series of C_2-symmetric diphosphines such as DIOP **1** and BINAP **2**, which generally give excellent enantioselectivity in asymmetric hydrogenation, use of new types of chiral ligands lacking C_2-symmetry has also provided excellent results in the allylic alkylation. In this section, recent examples of asymmetric palladium-catalyzed allylic alkylation using various types of optically active ligands are summarized. As a large number of reports have appeared on this subject during the last decade, the reference citation is generally limited to those presenting quite high to excellent enantioselectivity (~90–100% ee). Several useful reviews have appeared recently and should be consulted.[3–9]

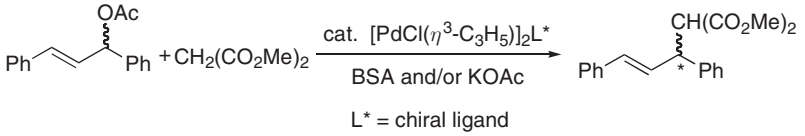
11.03.2.1 Alkylation of Acyclic and Symmetric Allylic Esters

The most well-studied system is the allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate as a carbon-centered nucleophile in the presence of a chiral ligand as well as a base such as *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and alkali metal acetate, where $[PdCl(\eta^3\text{-}C_3H_5)]_2$ is used as a palladium catalyst precursor (Scheme 3). It seems that almost all works have been devoted in the last decade to design and prepare effective chiral ligands. Use of various diphosphines bearing C_2-symmetry including DIOP **1** and BINAP **2** provides a significantly high enantioselectivity (>90% ee) in the reaction of 1,3-diphenyl-2-propenyl acetate or carbonate with dimethyl malonate. BINAP **2** also works as an effective ligand in the similar reaction with (acetamido)malonate as a carbon-centered nucleophile (up to 94% ee) (Equation (1)).[10] Fuji and his co-workers observed a high to excellent enantioselectivity in the allylic alkylation with some malonates and their analogs using BINAP **2** as a chiral ligand and in the presence of diethylzinc as a base (up to 99% ee) (Equation (2)).[11] Bolm and his co-workers found that MeO-BIPHEP **13** and its derivatives are suitable chiral ligands for the allylic alkylation with dimethyl malonate (up to 95% ee) (Equation (3)).[12] Ikeda and his co-workers reported a significantly high enantioselective allylic alkylation (up to 94% ee) by using C_2-symmetric diphsophines bearing only the planar chirality on ferrocenes **14** and **15**, which were easily prepared from the corresponding bisoxazolinylferrocenes (Equation (3)).[13–15] Achiwa reported the use of NORPHOS-7-NEt_2 **16** as a chiral ligand, where an amino group in the ligand showed a remarkable effect for obtaining an almost complete enantioselectivity by neighboring participation (up to 99% ee) (Equation (3)).[16] Osborn and his co-workers reported an excellent enantioselectivity and a kinetic resolution in allylic alkylation by using DUPHOS **17** and modified DUPHOS ligands **18a** and **18b** (up to 97% ee and $k_S/k_R = 5.8$)



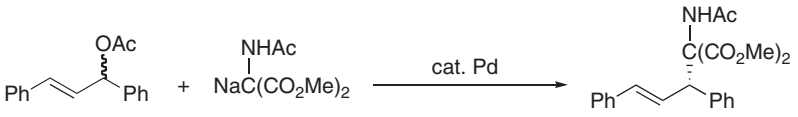
Scheme 2

(Equations (3) and (4)).[17,17a,17b,18] Widhalm and Yan prepared and applied the macrocyclic binaphthyl diphosphines **19** to the catalytic reaction (up to 98% ee) (Equation (3)),[19,19a,19b] where the introduction of larger substituents at 3 and 3′ positions in the ligand increased the enantioselectivity. Imamoto and his co-workers found that a P-chirogenic diphosphine, which was prepared from the prochiral phosphine–borane via enatioselective deprotonation, works as an effective



Scheme 3

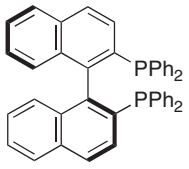
chiral ligand **20** (up to 95% ee) (Equation (3)).[20] Bis(diazaphospholidines) (FerriESPHOS **21** and DiPhenESPHOS **22**) and bis(phosphinous amide) **23** work as effective ligands (Equation (3)).[21,22] Use of an optically active spiro diphosphine **24** provides an almost complete enantioselectivity (up to 99% ee) (Equation (2)).[23] Some other diphosphines **25–28** bearing C_2-symmetry applied to the asymmetric allylic alkylation are shown in Scheme 4.[24,24a–24e]



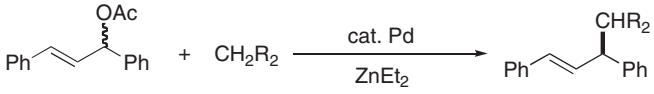
(1)

94% ee (*S*)

Pd: $[PdCl(\eta^3\text{-}PhCHCHCHPh)]_2$ + (*S*)-BINAP

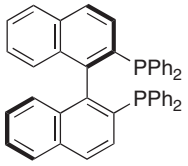


(*S*)-BINAP **2**



(2)

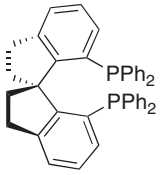
Pd: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ + (*R*)-BINAP



$CH_2(CO_2Me)_2$: 99% ee (*S*)
$CH_2(CO_2Bz)_2$: 95% ee
$CH_2(CN)_2$: 85% ee
$CH_2(SO_2Ph)_2$: 92% ee

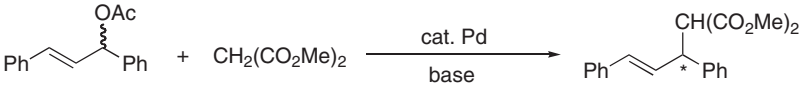
(*R*)-BINAP **2**

Pd: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ +



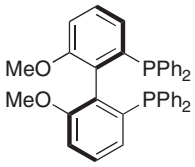
$CH_2(CO_2Me)_2$: 99% ee (*S*)

24



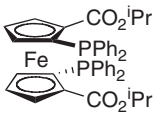
(3)

Pd: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ + L*

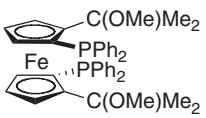


95% ee (*S*)

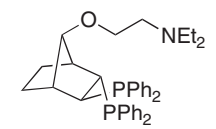
(*R*)-MeO-BIPHEP **13**



14
94% ee (*S*)

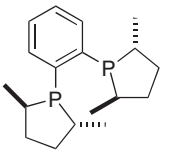


15
96% ee (*S*)



NORPHOS-7-NEt$_2$ **16**

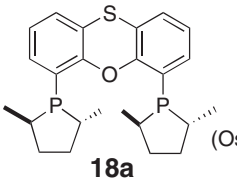
99% ee (*R*)



(Pregosin et al.)

DUPHOS **17**

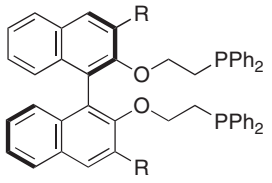
98% ee (*R*)



(Osborn et al.)

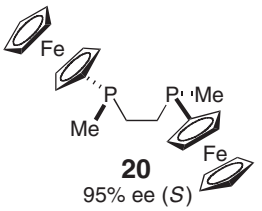
18a

97% ee (*R*)



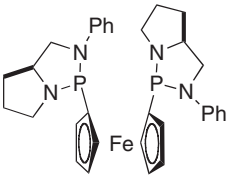
19

R	*ee* (%)
2-naphthyl	98
Ph	97
H	87



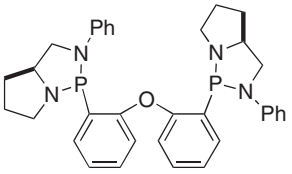
20

95% ee (*S*)



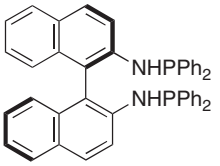
FerriESPHOS **21**

92% ee (*S*)



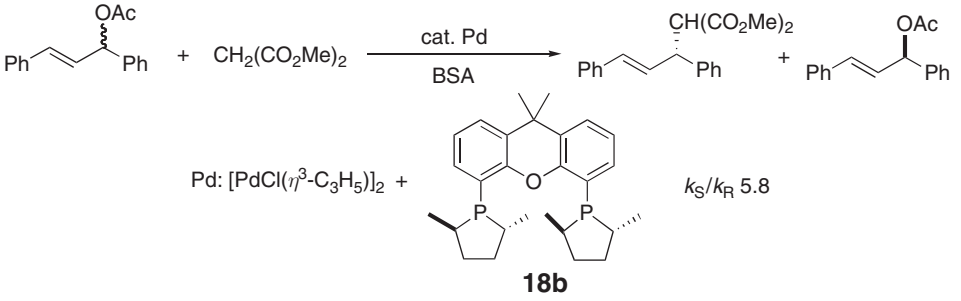
DiPhenESPHOS **22**

91% ee (*S*)



23

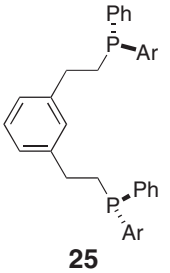
94% ee (*S*)



(4)

18b

Use of some diphosphines lacking C_2-symmetry sometimes provides a high to excellent enantioselectivity in the allylic alkylation. Metallocenylphosphines **7**, **29–31** bearing another phosphine in the side-chain of metallocene such as ferrocene, tricarbonyl(arene)chromium, and tricarbonyl(cyclopentadienyl)rhenium work as effective chiral ligands (Equation (5)).[25–28] In addition to the previous preparation of tricarbonyl(cyclopentadienyl)rhenium derivatives bearing an oxazolinyl moiety, Bolm and his co-workers prepared the diphosphine **30** bearing the same rhenium backbone as shown in Equation (5).[27] Hou and Dai reported the ligand electronic effect of diphosphine-oxazolinylferrocene **31** in



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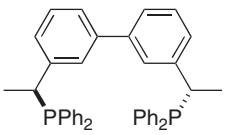
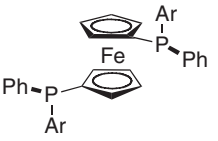
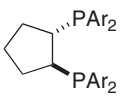


26



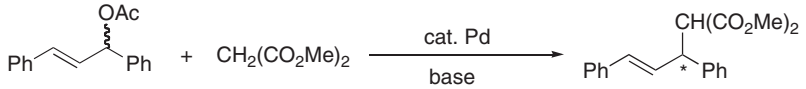
27



28

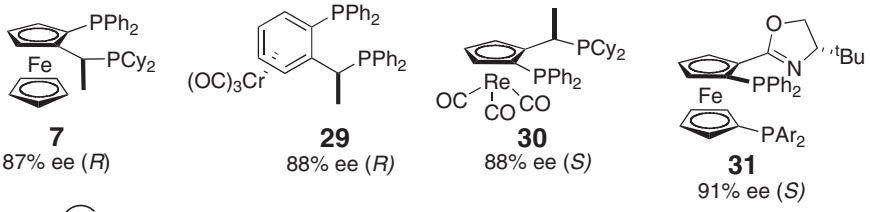
Scheme 4

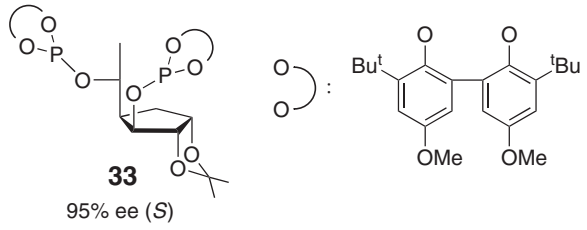
the allylic alkylation (up to 91% ee).[28] The introduction of a bulkier substituent at 2′-position increases the enantioselectivity. Hayashi and his co-workers have disclosed that the phosphino-phosphaferrocenes **32** work as quite effective chiral ligands (up to 99% ee) (Equation (6)).[29] The coordination by phosphine moiety to the palladium is necessary to achieve a high enantioselectivity. Some diphosphites **33**, derived from readily available D-(+)-glucose, work as effective chiral ligands (up to 95% ee) (Equation (5)).[30,30a] Ohta and his co-workers employed the phosphine ylides (Yliphos **34**) as chiral ligands and achieved 95% ee in the allylic alkylation when cyano-substituted Yliphos was used (Equation (5)).[31] Several other diphosphines **35–37** lacking C_2-symmetry applied to the asymmetric allylic alkylation are shown in Scheme 5.[32,32a–32d]

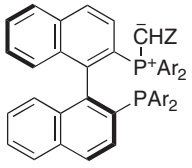


(5)

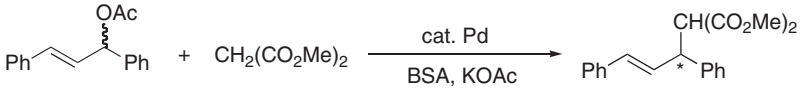
Pd: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ + L*



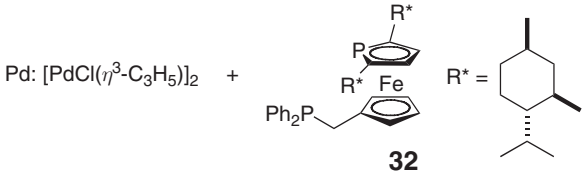


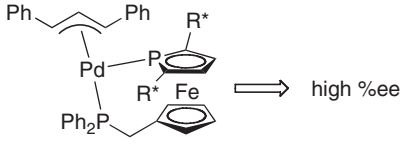


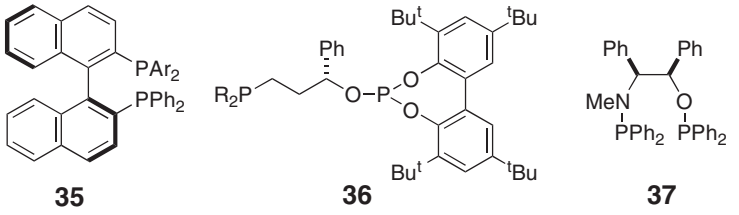
Z	ee (%)	(R)
CN	95	
CO_2Et	61	
$CO_2{}^tBu$	64	



(6)



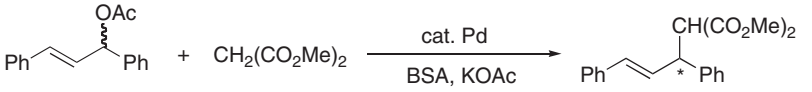




35 **36** **37**

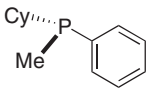
Scheme 5

Some monophosphines are also revealed to work as reasonably effective ligands. Imamoto and Tsuruta prepared and applied P-chirogenic monophosphines **38** to the allylic alkylation (up to 96% ee) (Equation (7)).[33] Nelson and Hilfiker found that monophosphines **39** bearing a tricarbonyl(arene)chromium moiety work as effective chiral ligands (up to 92% ee) (Equation (7)).[34] Some monophosphines **40–42**[35–37] bearing a binaphthyl moiety and some monodentate phosphoramidites **43–45**[38] work as quite effective chiral ligands (Equation (7)). Several other monophosphines **46–48** applied to the asymmetric allylic alkylation are summarized in Scheme 6.[39,39a–39h]

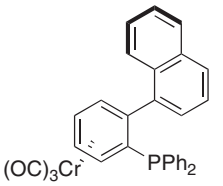


(7)

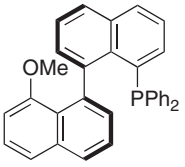
Pd: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ + L*



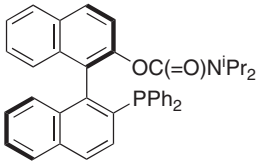
38
96% ee (*R*)



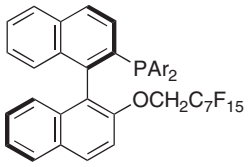
39
92% ee (*R*)



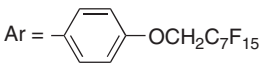
40
91% ee (*R*)



41
99% ee (*R*)

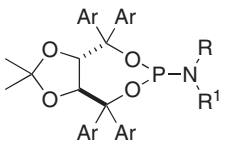


42

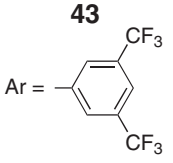


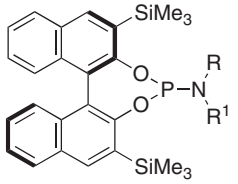
87% ee (*R*) in benzotrifluoride

99% ee (*R*) in toluene

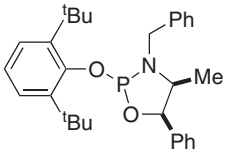


43

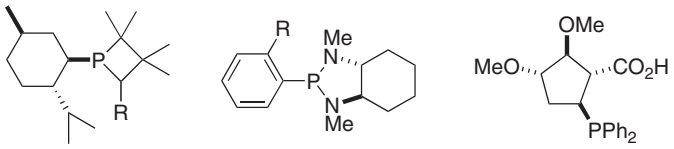




44
up to 93% ee



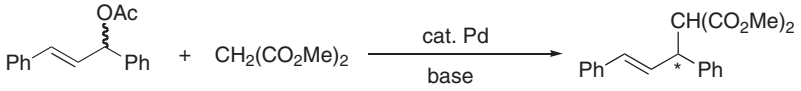
45



46 **47** **48**

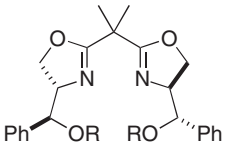
Scheme 6

Bidendate N–N chelating ligands also work effectively in the allylic alkylation. For example, some bis(oxazoline) ligands and their derivatives **49–52** are found to work as effective chiral ligands (up to 99% ee) (Equation (8)).[40–45] Tanner and co-workers achieved 99% ee in the allylic alkylation, using C_2-symmetric bis(aziridine) ligands **53** as chiral ligands (Equation (8)).[46,46a,46b] Bolm and his co-workers observed an excellent enantioselectivity by using bis(sulfoximine) ligands **54** (up to 98% ee) (Equation (8)).[47,47a] In addition to N–N chelating ligands bearing C_2-symmetry, several pyridinooxazolines and their derivatives also work quite effectively (up to 99% ee);[48–49b] especially, Moberg and his co-workers investigated the effect of substituents on the pyridinooxazolines **55** and **56** in detail (Equation (9)).[50,50a–50c] More examples of N–N chelating ligands applied to the asymmetric allylic alkylation have been reported by several groups.[51,51a–51c]



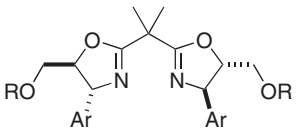
(8)

Pd: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ + L*



R = H, COPh, Me, etc.

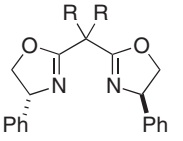
49



R = Me, Ch_2Ph, CPh_3, etc.

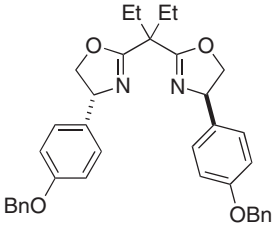
Ar = Ph, 1-naphthyl, etc.

50



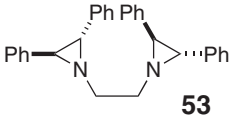
$R = (CH_2)_3C_8F_{17}$

51



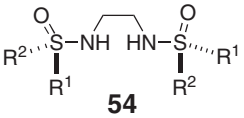
up to 99% ee

52



53

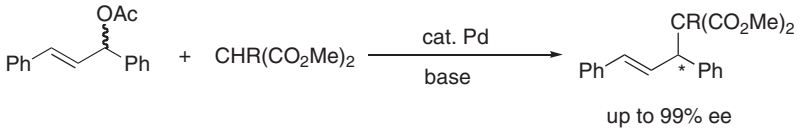
99% ee (*R*)



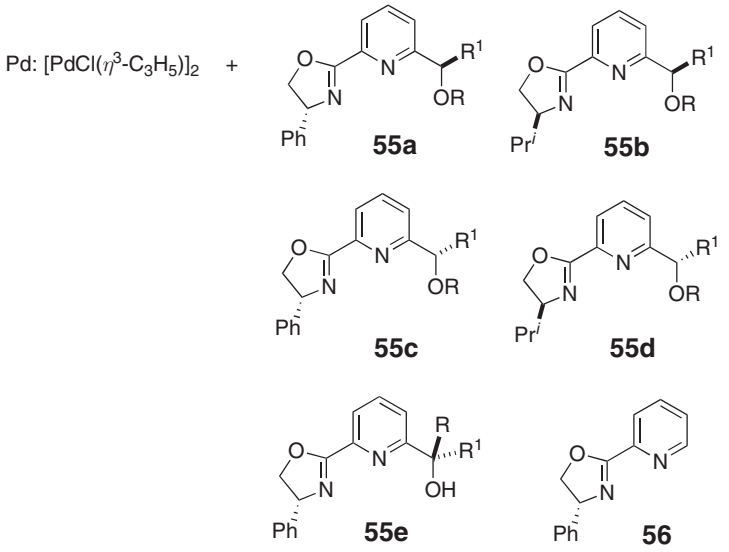
54

R^1 = c-Pen, R^2 = Ph

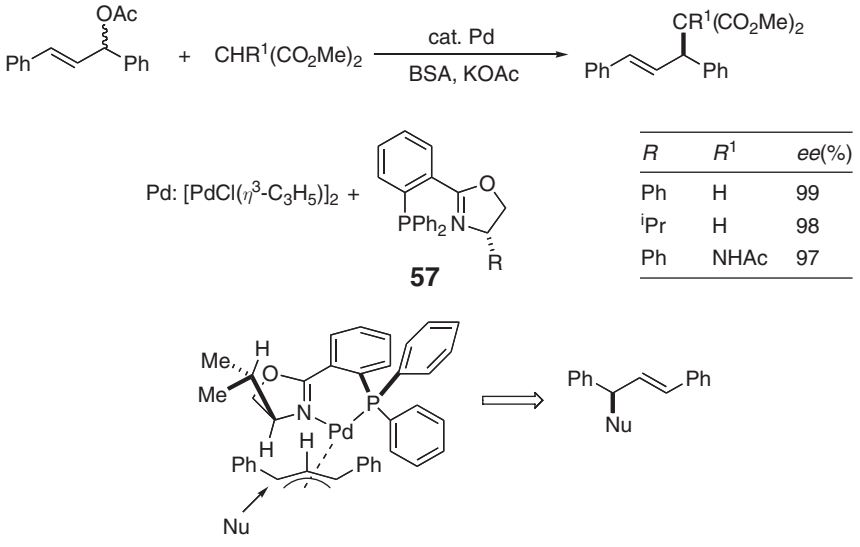
93% ee



(9)



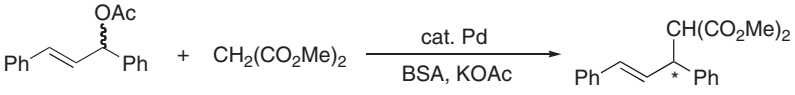
Since the effectiveness of optically active phosphinooxazolines **57** (P–N chelating ligands) for the aymmetric allylic alkylation was discovered by Pfaltz, Helmchen, Williams and their co-workers,[5,52] a variety of phosphinooxazolines bearing various backbones are prepared and investigated as chiral ligands for the palladium-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl esters with malonates, because phosphinooxazolines are easily available from the corresponding chiral amino alcohols. The NMR and X-ray studies support the difference of σ-donor and π-acceptor properties of nitrogen and phosphorus atoms on the intermediate 1,3-diphenylallylpalladium complexes (Scheme 7).[52,53] Use of



R	R^1	*ee*(%)
Ph	H	99
^{i}Pr	H	98
Ph	NHAc	97

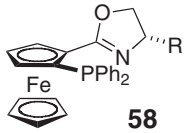
Scheme 7

various phosphinooxazolines bearing a ferrocenyl **58** and **59** or binaphthyl moiety **60** provides a significantly high to excellent enantioselectivity (Equation (10)). Ahn and his co-workers[54,55] prepared phosphinooxazolines **58** and **59** bearing a ferrocenyl moiety,[56] while Ikeda's and Hayashi's groups[57,58] independently reported phosphinooxazolines **60** bearing a binaphthyl moiety.[59] Hou and his co-workers investigated the role of planar chirality of phosphinooxazolines **61** bearing a ferrocenyl moiety in detail (Equation (11)).[60,61] Uemura and his co-workers prepared phosphinite-oxazolines **62** derived from D-glucosamine and applied them into the allylic alkylation (up to 96% ee) (Equation (10)).[62,62a] Bolm and his co-workers employed phosphinooxazolines **63** bearing a tricarbonyl(cyclopentadienyl)rhenium moiety (up to 72% ee) (Equation (10)).[63] Helmchen and Rieck achieved an almost complete enantioselectivity of allylic alkylation with nitromethane as carbon-centered nucleophiles in place of malonates (Equation (12)).[64] Hayashi and his co-workers investigated the allylic alkylation with cyclopentadienide and indenide as carbon-centered nucleophiles (Equation (13)).[65,66] Optically active metallocenes of iron, zirconium, and titanium were prepared with >99% ee by using this catalytic allylic alkylation. Some other phosphinooxazolines **64–67** available for the asymmetric allylic alkylation are shown in Scheme 8.[67,67a–67c]



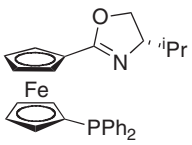
(10)

Pd: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ + L*



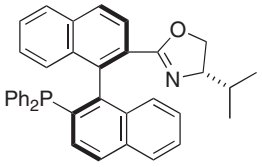
58

R	*ee* (%) (*S*)
^{i}Pr	95
^{t}Bu	99



59

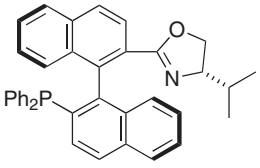
91% ee (*S*)



(*S*, *S*)

60a

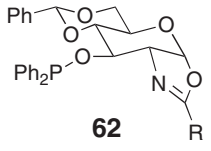
28% ee (*S*)



(*S*, *R*)

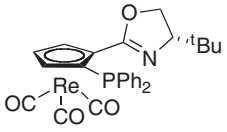
60b

91% ee (*R*)



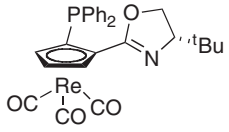
62

R	*ee* (%) (*S*)
Me	96
^{i}Pr	90
^{i}Bu	95
^{t}Bu	83



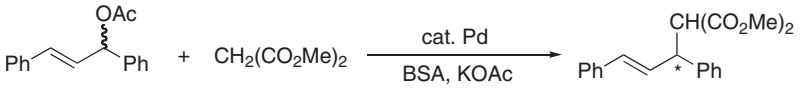
63a

73% ee (*S*)



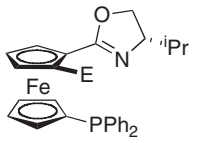
63b

21% ee (*S*)



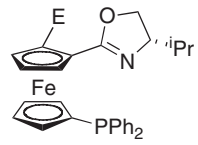
(11)

Pd: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ + L*



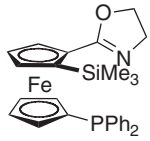
61a

E	*ee*(%)	(*R*)
Me	34	
$SiMe_3$	70	

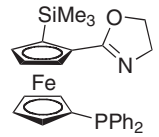


61b

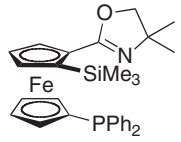
E	*ee*(%)	(*S*)
Me	99	
$SiMe_3$	99	



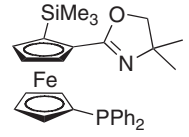
61c
79% ee (*R*)



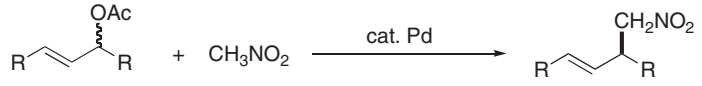
61d
80% ee (*S*)



61e
82% ee (*R*)



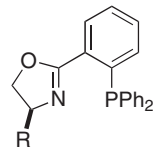
61f
84% ee (*S*)



R = Me, Et, Ph

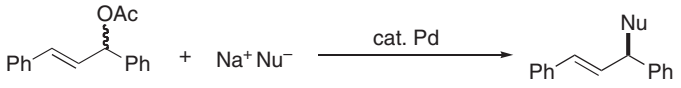
(12)

Pd: $[Pd_2(dba)_3]$ +



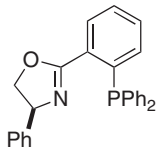
R = Ph: >99% ee (*S*)

57 (R = $CMe_2(CH_2S^iBu)$)



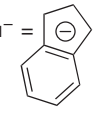
(13)

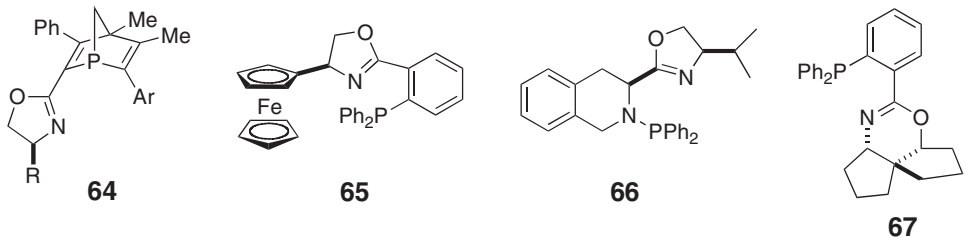
Pd: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ +



57 (R = Ph) 98% ee (*S*) Nu^- =

97% ee (*R*) Nu^- =

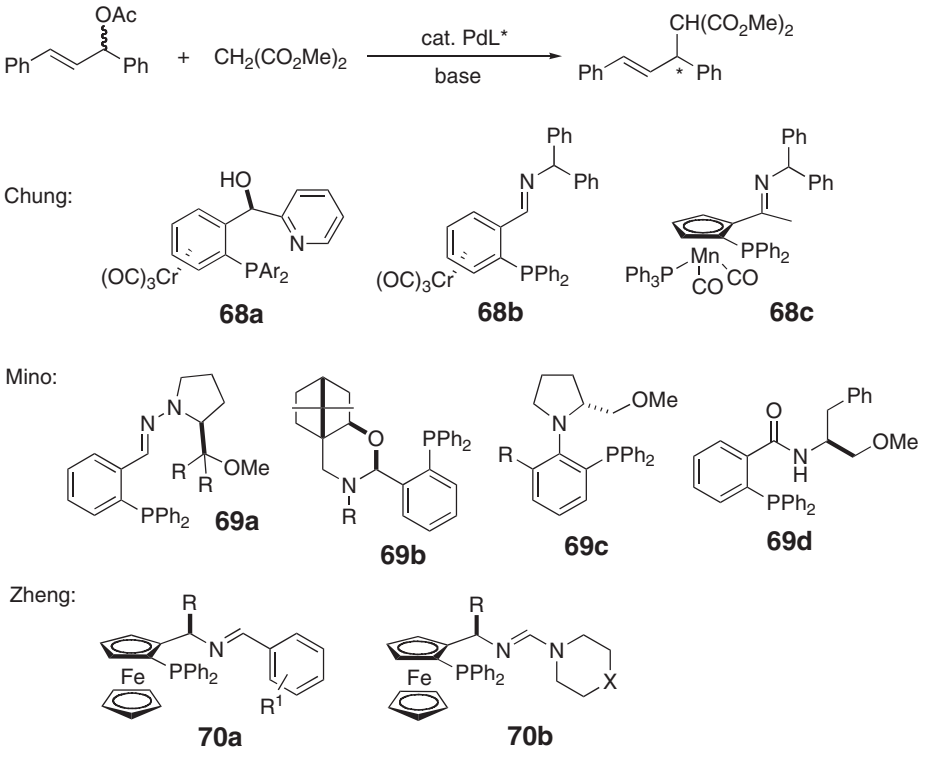




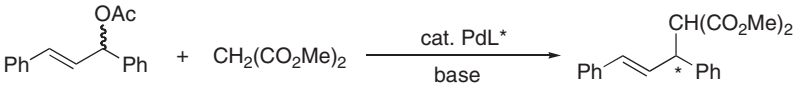
Scheme 8

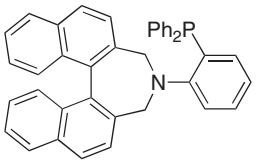
Use of other types of P–N chelating ligands also provided an excellent enantioselectivity. Especially, Chung's,[68,68a–68c] Mino's,[69,69a–69l] and Zheng's[70,70a–70d] groups independently investigated the palladium-catalyzed allylic alkylation in detail by preparing and applying various P–N chelating ligands **68–70** (Scheme 9). In addition to these ligands, the allylic alkylation using various P–N chelating ligands bearing a ferrocenyl or binaphthyl moiety is reported by many research groups.[71–72mm] Selected other examples of P–N chelating ligands **71–87** are summarized in Scheme 10 together with the enantioselectivity in the allylic alkylation.[71,71a–71aa]

The P–S chelating ligands developed by Williams and his co-workers have been found to be effective for the allylic alkylation.[5] Use of various P–S chelating ligands provides a significantly high to excellent enantioselectivity. Kang and his co-workers achieved 96% ee by employing P–S chelating ligands **88** bearing a binaphthyl moiety (Equation (14)).[73,74] Enders and his co-workers prepared P–S chelating ligands **89** bearing a ferrocenyl moiety (up to 97% ee) (Equation (14)).[75] Use of planar chirality on the ferrocenyl moiety (e.g., **90** and **91**) providing a high enantioselectivity is reported independently by Dai[76] and Carretero[77] (up to 97% ee) (Equation (14)). Nakano and his co-workers prepared phosphinooxathianes **92–94** as chiral ligands (up to 94% ee) (Equation (14)).[78,78a–78d] Dai and his co-workers reported a novel class of nonbiaryl atropisomeric P–O ligands **95** for the allylic alkylation (up to 95% ee) (Equation (15)).[79] Some other P–S chelating ligands **96–98** applied for the asymmetric allylic alkylation are shown in Scheme 11.[80,80a]

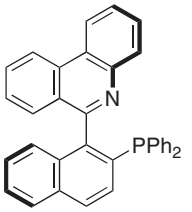


Scheme 9

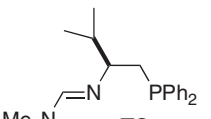




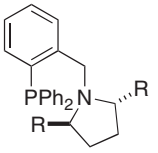
71
96% ee



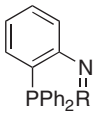
72
95% ee

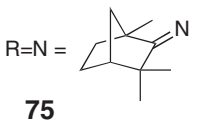


73
95% ee

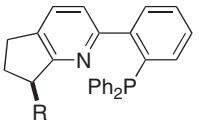


74
90% ee

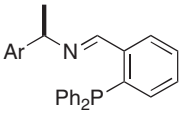




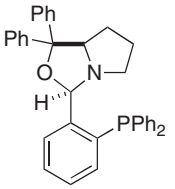
75
90% ee



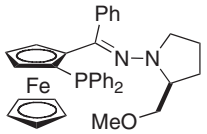
76
98% ee



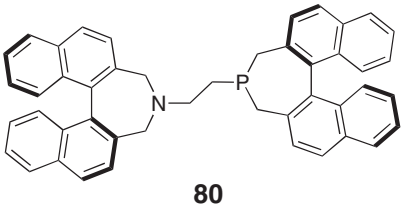
77
94% ee



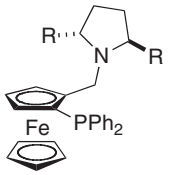
78
96% ee



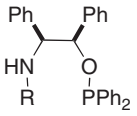
79
93% ee



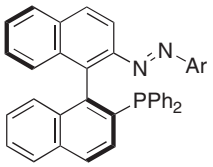
80
98% ee



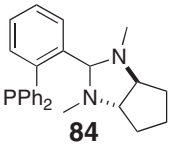
81
90% ee



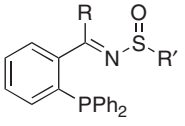
82
95% ee



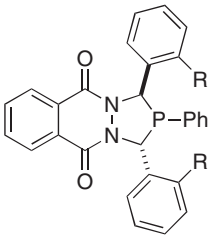
83
90% ee



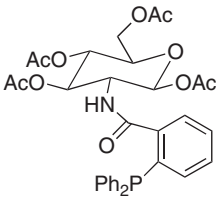
84
99% ee



85
94% ee

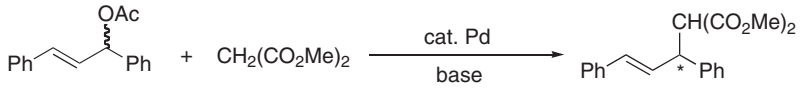


86
97% ee



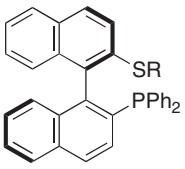
87
97% ee

Scheme 10



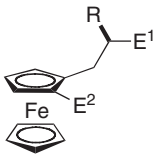
(14)

Pd: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ + L*



88

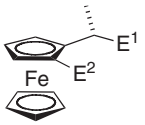
R	*ee* (%)
Me	96 (*S*)
^{i}Pr	72 (*R*)
CH_2Ph	77 (*S*)



E^1, E^2 = PPh_2 or SR

89

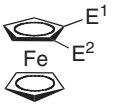
up to 97% ee



E^1, E^2 = PPh_2 or SR

90

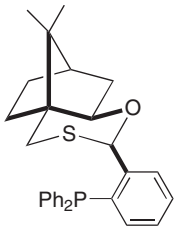
up to 94% ee



E^1, E^2 = PPh_2 or SR

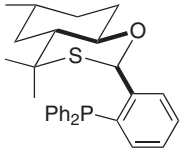
91

up to 97% ee



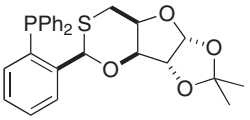
92

94% ee (*R*)



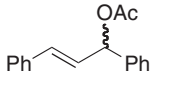
93

16% ee (*R*)

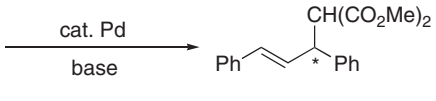


94

94% ee (*S*)



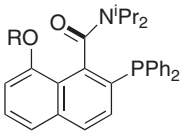
+ $CH_2(CO_2Me)_2$



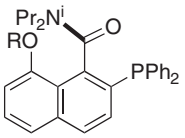
(15)

up to 95% ee

Pd: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ +

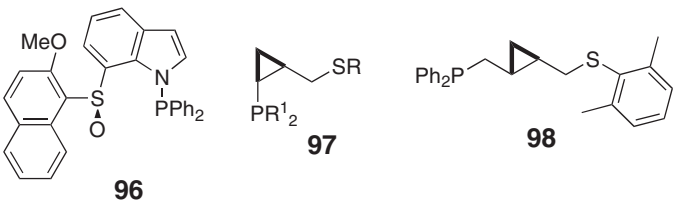


95a



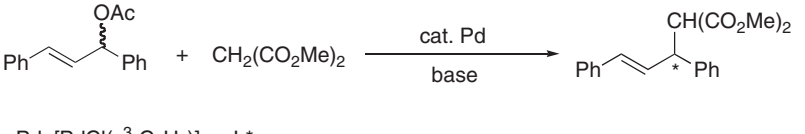
95b

As described above, the phosphorus atom generally plays an important role for the stereoselection in the allylic alkylation. However, other types of chelating compounds not having phosphorus are also revealed to work as effective chiral ligands. Some N–S chelating ligands **99–103** bearing an oxazoline moiety provide an excellent enantioselectivity



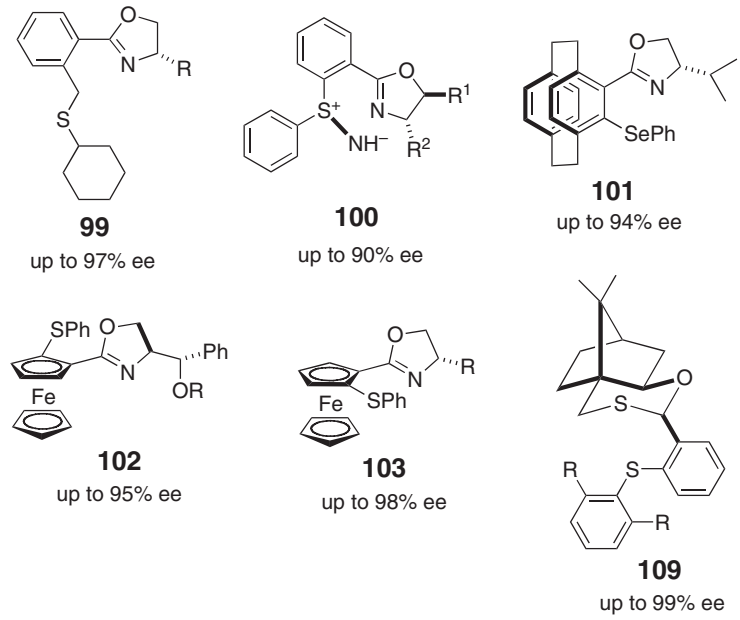
Scheme 11

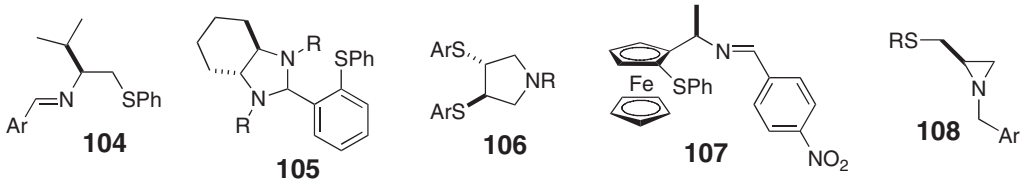
(Equation (16)).[81–85] In addition to other N–S chelating ligands **104–108** (Scheme 12),[86–91] optically active sulfideoxathiane ligands **109** (S–S ligand) also work as effective ligands (up to 99% ee) (Equation (16)).[92] A successful example of using optically active antimony ligands **110–113** is reported by Kurita and his co-workers (up to 96% ee) (Equation (17)).[93] Furthermore, C–N chelating ligands containing an *N*-heterocyclic carbene–imine moiety **114** were prepared by Douthwaite and his co-workers, who investigated the allylic alkylation using these ligands (up to 92% ee) (Equation (18)).[94] Many other examples of various chelating ligands applied to the asymmetric allylic alkylation are reported by many groups.[95–96l]



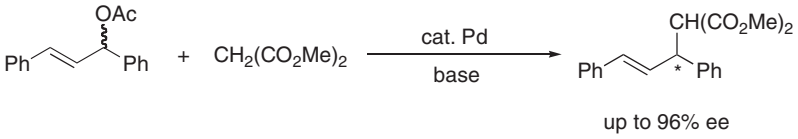
(16)

Pd: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ + L*



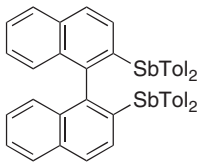


Scheme 12

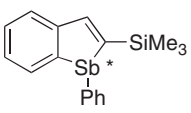


(17)

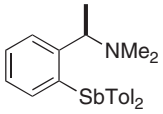
Pd: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ + L*



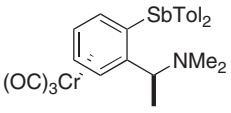
110



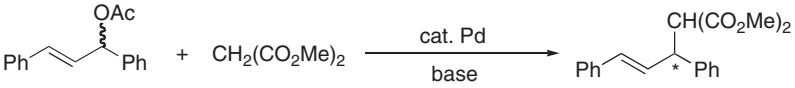
111



112

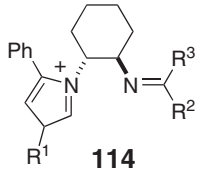


113



(18)

Pd: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ +

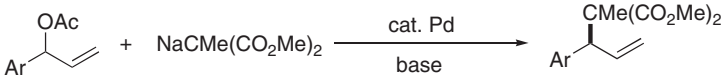


114

11.03.2.2 Alkylation of Acyclic Monosubstituted Allylic Esters

As described in the previous section, when acyclic and symmetric allylic esters such as 1,3-diphenyl-2-propenyl acetate and 1,3-dialkyl-2-propenyl esters are used as substrates, high to excellent enantioselective allylic alkylation is performed by using a variety of chiral ligands. In contrast, the number of successful examples of the asymmetric allylic alkylation of acyclic and unsymmetric allylic esters is relatively limited.

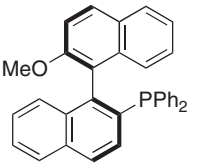
In 1997, as a pioneering work, Hayashi and his co-workers disclosed allylic alkylation of monosubstituted allylic esters by using a monophosphine (MOP **115**) as a chiral ligand (up to 87% ee) (Equation (19)).[97,97a,97b] Fuji and his co-workers slightly improved the enantioselectivity by modifying the MOP ligand **40** (up to 91% ee) (Equation (19)).[35] Pfaltz and Pretot reported an allylic alkylation of monosubstituted allylic esters by using phosphite-oxazoline ligands **116**. Alkylation takes place mainly at benzylic position with an excellent enantioselectivity (up to 96% ee) (Equation (20)).[98,98a] Steric factors of the bulky groups at the phosphorus atom affecting the equilibrium between allylic intermediates play an important role. Thus, a pathway via more stable allylic intermediate should be preferred and reaction at the substituted allylic end should be facilitated, assuming that nucleophilic attack at the allylic terminus *trans* to the Pd–P bond is electronically favored. Hou and his co-workers have found that using ferrocene-based P–N chelating ligands **117** provides a wide range of monosubstituted allylic compounds with an excellent regioselectivity as well as an excellent enantioselectivity (up to 97% ee) (Equation (20)).[99,99a,100]



(19)

Ar = Ph, *p*-$MeOC_6H_4$, etc.

Pd: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ +

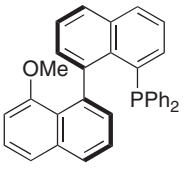


115

up to 87% ee

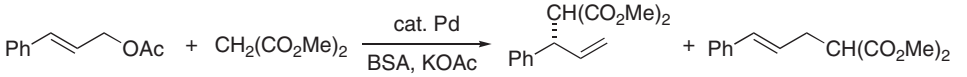
Ar = *p*-$MeOC_6H_4$

Pd: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ +



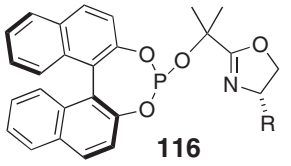
40

up to 91% ee



(20)

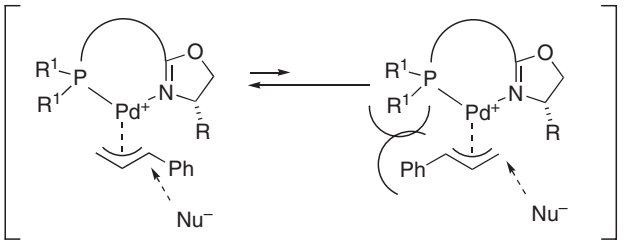
Pd complex: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ +



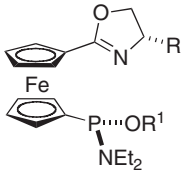
116

76 : 24

up to 96% ee



Pd complex: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ +



117

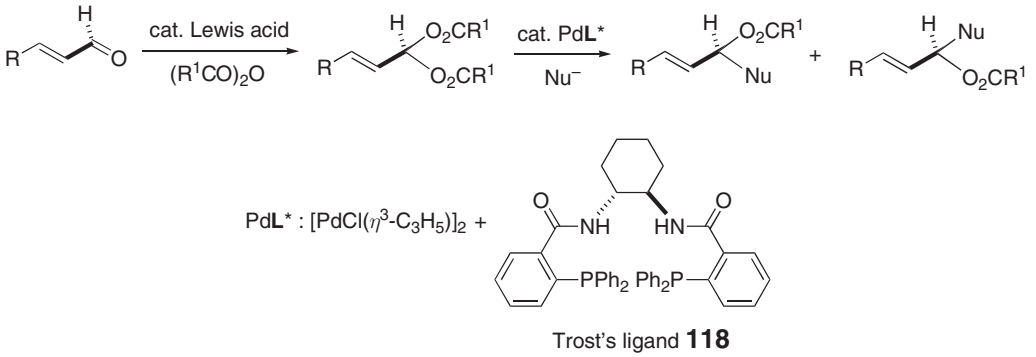
99 : 1

up to 97% ee

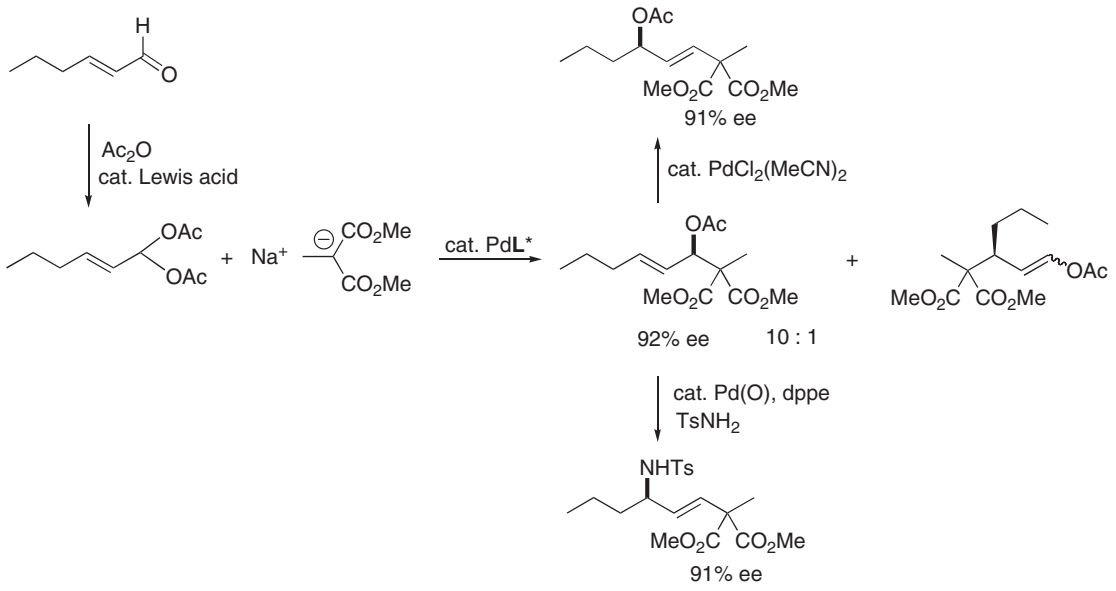
A formal asymmetric nucleophilic addition to carbonyl compounds is achieved by Trost and his co-workers in the allylic alkylation of acylals of alkenals. An excellent enantioselectivity is observed in this alkylation. The starting acylals are easily prepared by the Lewis-acid catalyzed addition of acid anhydrides to aldehydes, by use of Trost's ligand **118** (Scheme 13), where various carbon-centered nucleophiles are available (Scheme 14).[101,101a–101c] Asymmetric synthesis of some natural products is achieved according to this procedure.[102]

11.03.2.3 Alkylation of Cyclic Allylic Esters

As described in the previous sections, asymmetric allylic alkylation of acyclic allylic esters proceeds smoothly and effectively by using various types of chiral ligands. In contrast, allylic alkylation of cyclic allylic esters remains yet to be investigated. Thus, only a few examples are described in this section.



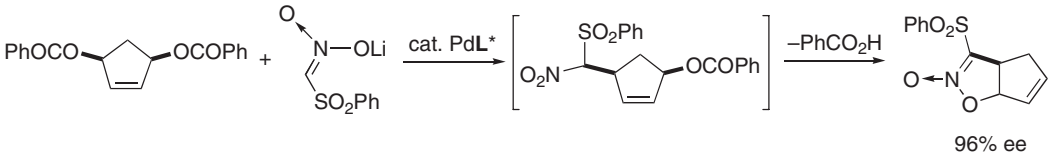
Scheme 13



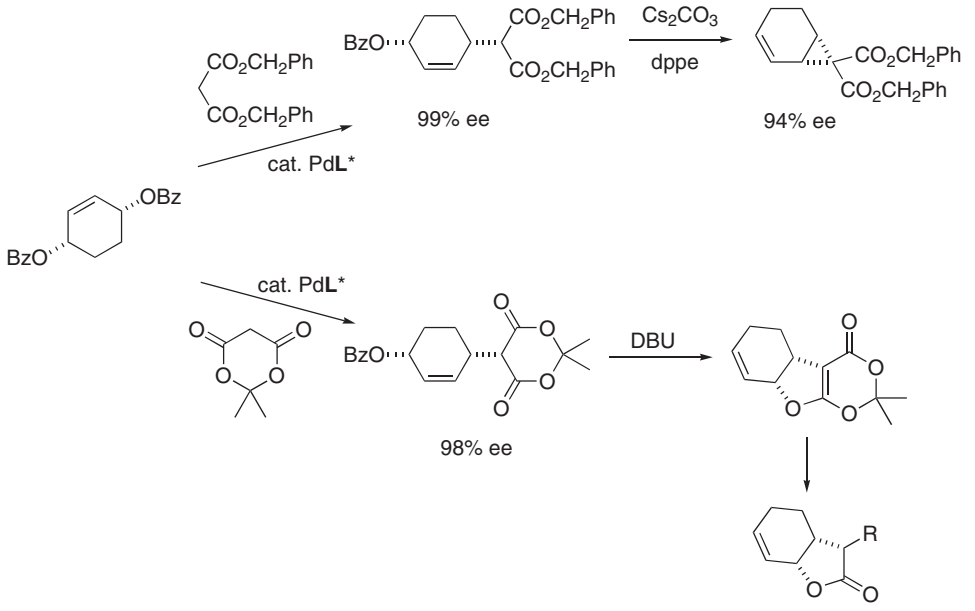
Scheme 14

In 1992, Trost and his co-workers investigated desymmetrization of cyclic *meso*-diesters with lithium sulfonylmethylenenitronate as a nucleophile in the presence of Trost's ligand **118**, where the corresponding cyclic compounds are obtained with an excellent enantioselectivity via intramolecular cyclization (Scheme 15).[103,103a] Asymmetric cyclopropanation and lactone annulation are achieved according to this protocol (Scheme 16).[104,104a] Nitroalkanes can also be employed as carbon-centered nucleophiles in lieu of malonates (Scheme 17).[105]

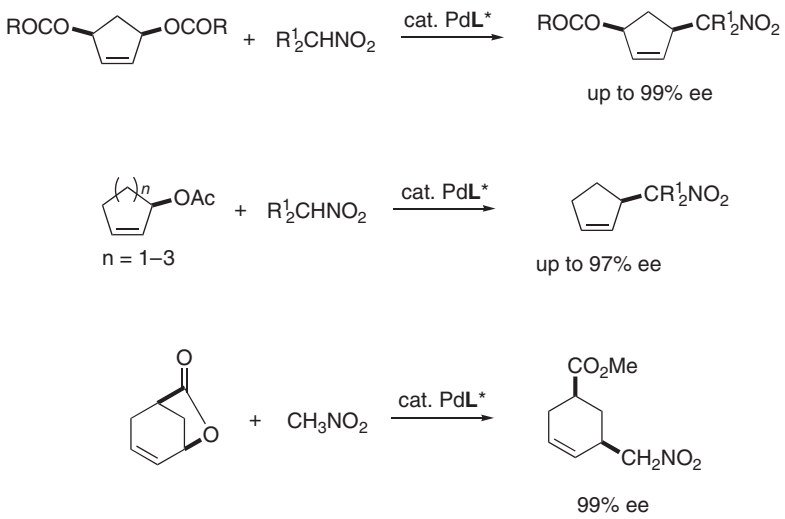
Use of some other diphosphines and monophosphines is also possible for this purpose. Osborn and his co-workers reported a highly enantioselective allylic alkylation of 2-cyclohexenyl acetate with malonates by using duthixantphospholane **18a** (up to 93% ee) (Equation (21)).[17,17a,17b] Ikeda and his co-workers succeeded in obtaining an optically active cyclic alkylated compounds by using a C_2-symmetric diphosphine **15** bearing only the planar chirality on ferrocene (up to 83% ee) (Equation (21)).[13a] Morimoto and his co-workers found that an optically active diphosphine **119** having a large bite angle worked as effective chiral ligands for the alkylation of cyclic allylic esters (Equation (22)).[106] Gilbertson and his co-workers prepared some peptides **120** bearing a diphosphine moiety and applied them to allylic alkylation of 2-cyclopentenyl acetate (up to 95% ee) (Equation (23)).[107]



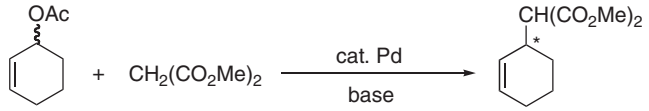
Scheme 15



Scheme 16

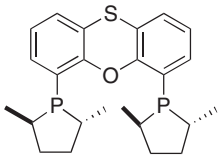


Scheme 17



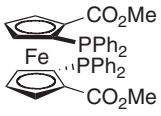
(21)

Pd: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ + L*



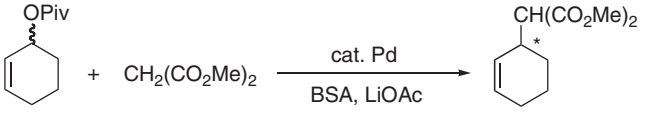
18a

93% ee (*S*)



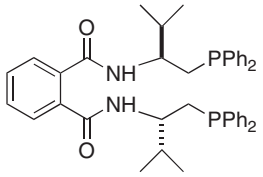
15

83% ee (*S*)



(22)

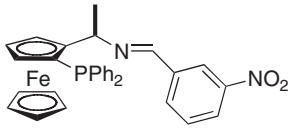
Pd: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ +



119

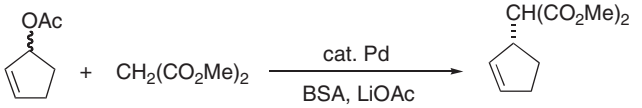
>99% ee (*S*)

Pd: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ +



125

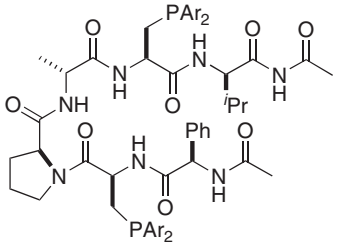
up to 91% ee



(23)

up to 95% ee

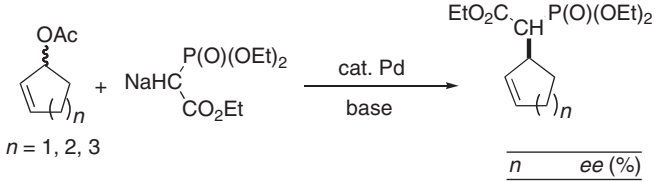
Pd: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ +



120

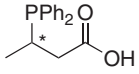
Some chelating ligands provide a high to excellent enantioselectivity in the alkylation of cyclic allylic esters. In 1995, Minami and Helmchen independently found some β-phosphinocarboxylic acids **121** and **122** as effective chiral ligands for the allylic alkylation (Equations (24)[108,108a] and (25)[109]). Helmchen and Kudis also discovered an excellent enantioselective allylic alkylation of cyclic allylic esters by using phosphinooxazolines bearing a

tricarbonyl(cyclopentadienyl)manganese moiety as chiral ligands **123** (up to >99% ee) (Equation (26)).[110,110a–110c] The product is successfully converted to enantiomerically pure Jasmonoids. Uozumi and Shibatomi prepared a recyclable amphiphilic resin-supported P–N chelating **124** palladium complex, which was applied to a highly enantioselective allylic alkylation of various cyclic allylic esters in water (Equation (26)).[111,111a] In the presence of this ligand, the reaction proceeds quite smoothly to give highly enantioselectively alkylated cyclic olefins (up to 98% ee). Zheng and his co-workers achieved a significantly high enantioselectivity by using P–N chiral ligands **125** (up to 91% ee) (Equation (22)).[89] Many other chiral P–N chelating ligands have been employed for asymmetric allylic alkylation of cyclic esters by several groups (for recent examples, see Refs: 112 and 112a.)

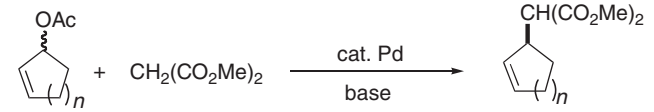


(24)

n	*ee* (%)
1	59
2	86
3	88

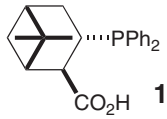
Pd: [Pd(OAc)$_2$] + 

121

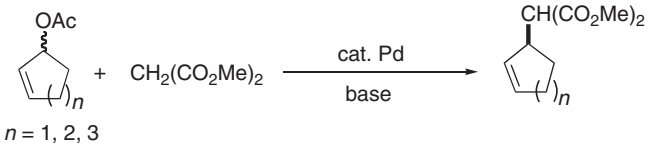


(25)

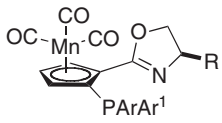
up to 99% ee

Pd: [PdCl(η^3-C$_3$H$_5$)]$_2$ + 

122



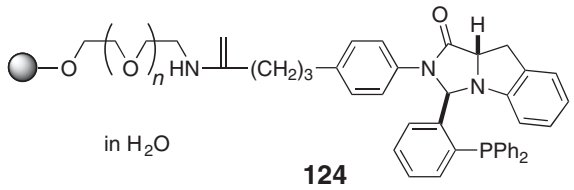
(26)

Pd: [PdCl(η^3-C$_3$H$_5$)]$_2$ + 

R = ^{t}Bu, Ar = Ph, Ar^1 = 2-Bp

up to 99% ee

123

Pd: [PdCl(η^3-C$_3$H$_5$)]$_2$ + 

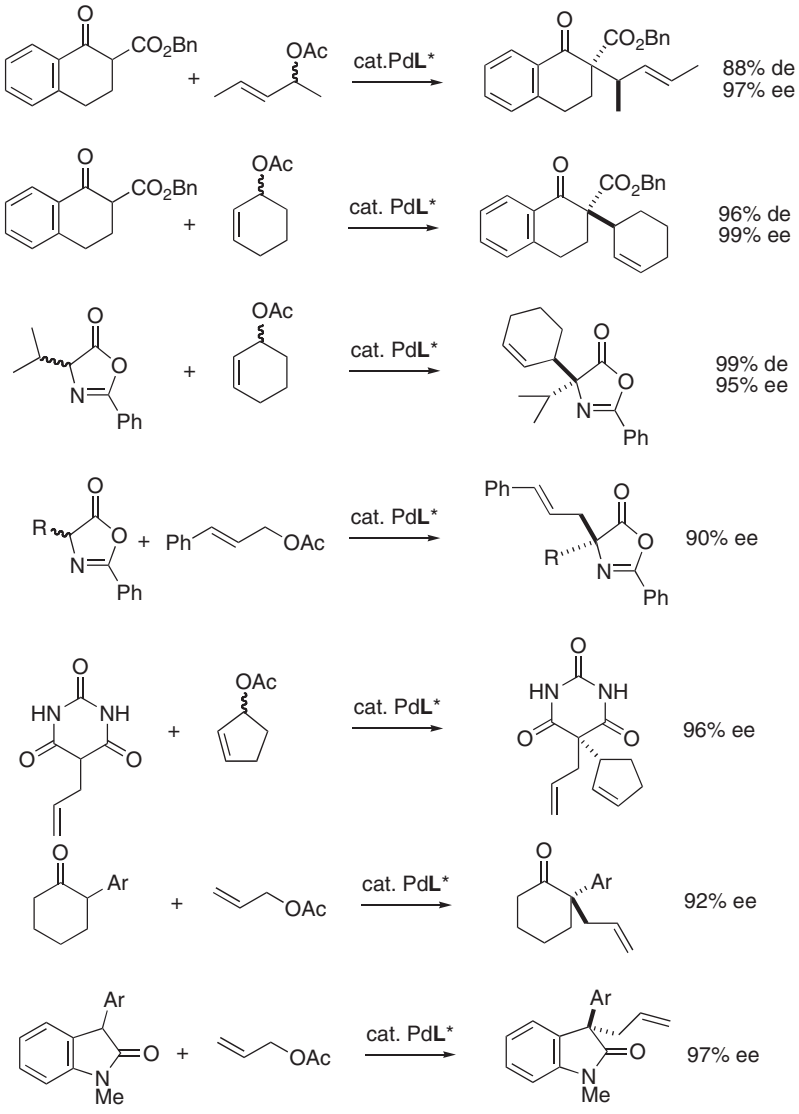
in H$_2$O

124

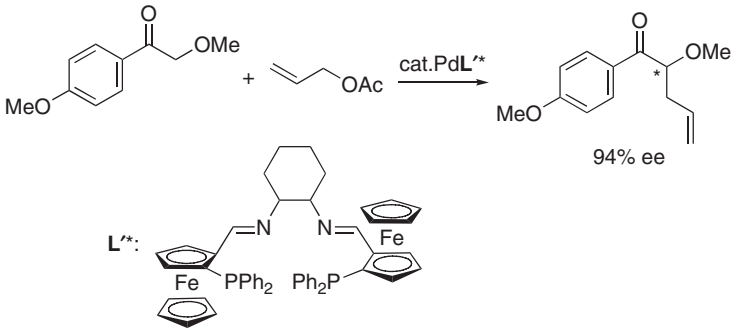
up to 98% ee

11.03.2.4 Allylation of Prochiral Nucleophiles

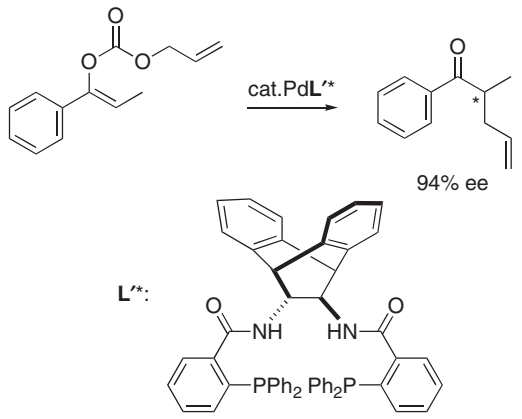
Trost and his co-workers succeeded in the allylic alkylation of prochiral carbon-centered nucleophiles in the presence of Trost's ligand **118** and obtained the corresponding allylated compounds with an excellent enantioselectivity.[113,113a–113i] A variety of prochiral carbon-centered nucleophiles such as β-keto esters, α-substituted ketones, and 3-aryl oxindoles are available for this asymmetric reaction (Scheme 18).[113,113a–113g] Quite recently, highly enantioselective allylation of acyclic ketones such as acetophenone derivatives has been reported by Hou and his co-workers,[113h] Trost and Xu,[113i] and Stoltz and Behenna[113j] (Scheme 18-1). On the other hand, Ito and Kuwano achieved highly enantioselective allylation of α-acetamido-β-keto esters, α-amino phosphonates, and 1,3-diketones by using BINAP **2** as a chiral ligand (Scheme 19).[114,114a] Braun employed BINAP **2** as a chiral ligand for a successful regioselective and enantioselective allylation of magnesium enolate (Equation (27)).[115] Interestingly, Sawamura and Ito reported the palladium- and rhodium-catalyzed allylic alkylation of activated nitriles to give the corresponding alkylated compounds **126** with an excellent enantioselectivity (Equation (28)).[116] Here, it is proposed that two component catalysts work cooperatively as shown in Scheme 20.



Scheme 18

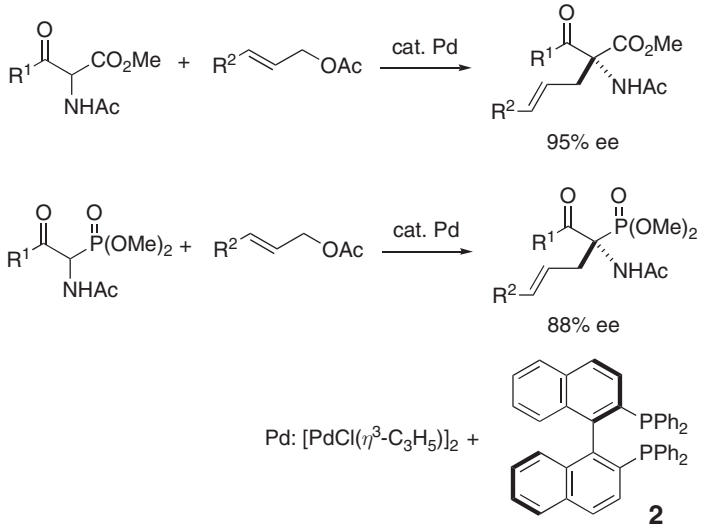


118-1

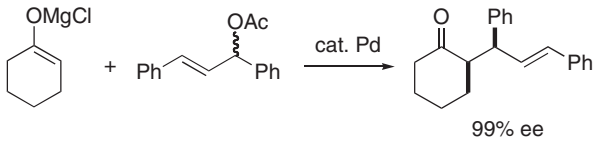


118-2

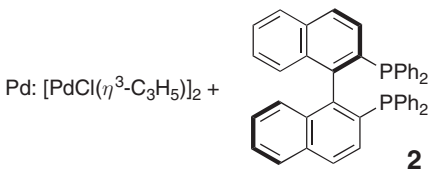
Scheme 18-1

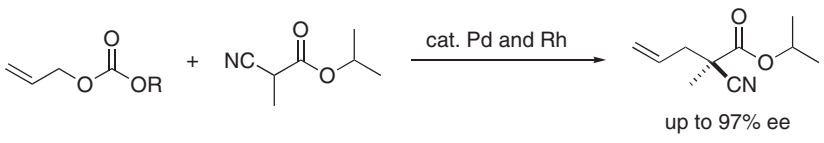


Scheme 19

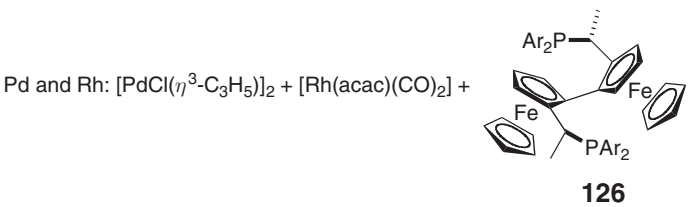


(27)



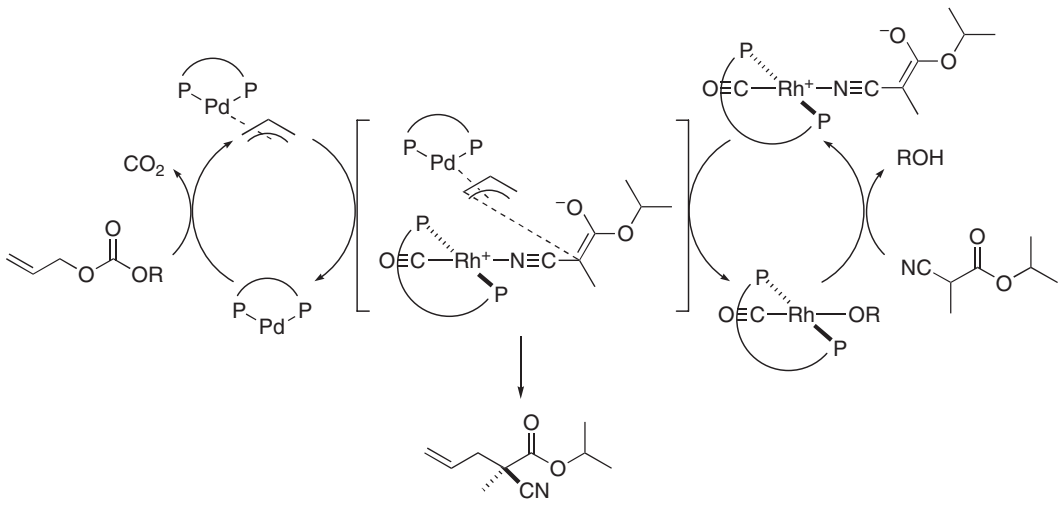


(28)



11.03.3 Asymmetric Allylic Alkylation of Allylic Alcohols and their Derivatives Catalyzed by Transition Metals other than Palladium

In sharp contrast to a fully developed asymmetric palladium-catalyzed allylic substitution as described in the previous sections of this chapter, similar reactions using transition metal complexes other than palladium have not yet been fully investigated and their application to organic synthesis is quite limited at the present. In this section, examples of Cu-, Ni-, Pt-, Rh-, Ir-, Ru-, Mo-, and W-catalyzed allylic alkylation are summarized including recent developments in this field.

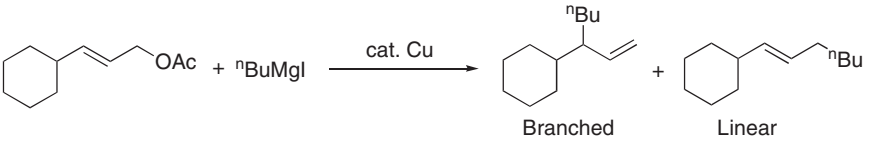


Scheme 20

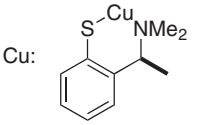
11.03.3.1 Copper-catalyzed Alkylation

It has so far been known that the allylic alkylation of unsymmetrical substrates catalyzed by copper complexes proceeds with a high S_N2' regioselectivity contrary to the palladium-catalyzed reactions. However, the corresponding enantioselective version of this reaction has been less developed, in sharp contrast to the copper-promoted asymmetric Michael addition to α,β-unsaturated systems.

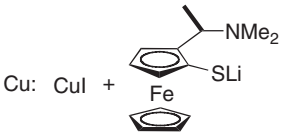
In 1995, Bäckvall and co-workers found the asymmetric copper-catalyzed allylic alkylation with Grignard reagents (Equation (29)).[117,117a] An optically active arenethiolatocopper complex promotes the allylic alkylation of allylic acetates with butylmagnesium bromide to give the corresponding branched alkylated compounds with a moderate enantioselectivity (42% ee). Enantioselectivity is improved up to 53% ee by study on the copper-catalyzed reaction system.[117a] Bäckvall and his co-workers further investigated the same reaction by using optically active ferrocenyl thiolates as chiral ligands (Equation (29)).[118] Alexakis and his co-workers have disclosed that using optically active phosphorus ligands **127** derived from TADDOL increases the enantioselectivity in the copper-catalyzed allylic alkylation (Equation (30)).[119] More effective chiral ligands, phosphoramidites **128–130**, are developed by the same research group to promote the copper-catalyzed allylic alkylation with Grignard reagents (Equation (31)).[120] Introduction of a methoxy group on the phenyl ring dramatically increases enantioselectivity up to 96% ee.[121]



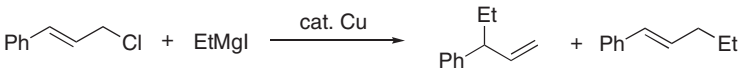
(29)



100 : 0
up to 42% ee

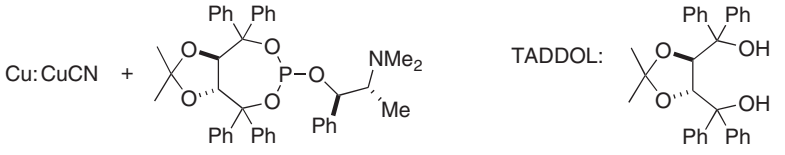


98 : 2
up to 64% ee

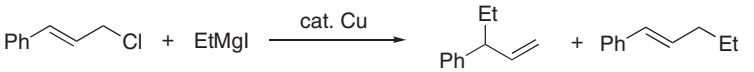


94 : 6
up to 73% ee

(30)

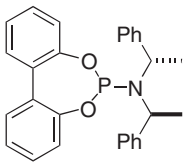


127

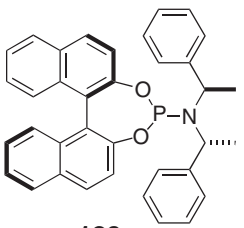


(31)

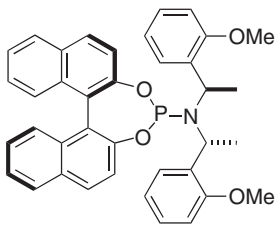
Cu: CuTC (copper thiophene 2-carboxylate) + L*



128
up to 86% ee

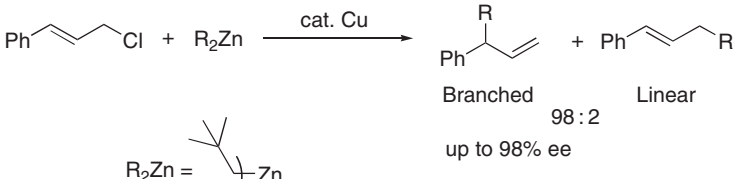


129a
up to 55% ee

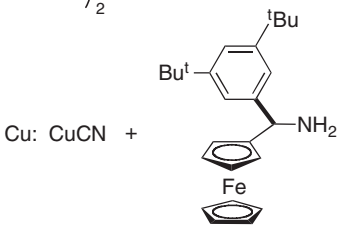


130a
up to 96% ee

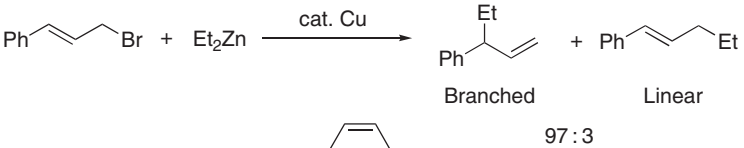
For the copper-catalyzed allylic alkylation, not only Grignard reagents but also dialkylzincs are available as carbon-centered nucleophiles. In 1999, Knochel and Dübner found that using optically active ferrocenylamines **131** as chiral ligands promoted the allylic alkylation of allylic chlorides with dialkylzincs with a high enantioselectivity (Equation (32)).[122] Introduction of a bulkier aryl moiety increases the enantioselectivity up to 98% ee.[123] Feringa and his co-workers reported the copper-catalyzed enantioselective allylic alkylation employing a variety of phosphoramidites **129a** as chiral ligands (Equation (33)).[124,124a] A similar reaction system is applied to a highly enantioselective desymmetrization of *meso*-cyclic allylic diphosphates (Equation (34)).[125,126] Zhou and his co-workers also reported a similar allylic alkylation by using chiral spiro phosphoramidites **132** and phosphates as chiral ligands (Equation (35)).[127]



(32)



131



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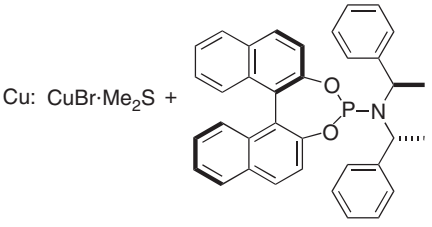
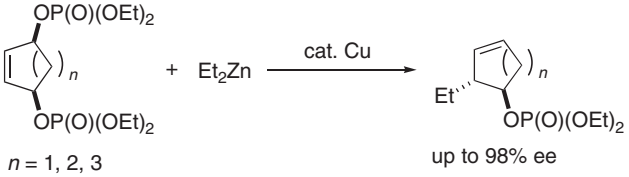
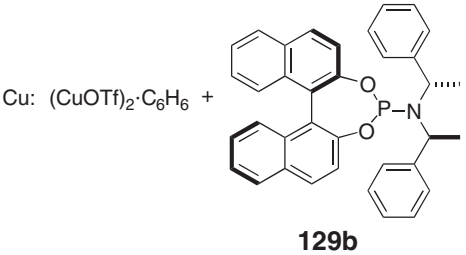


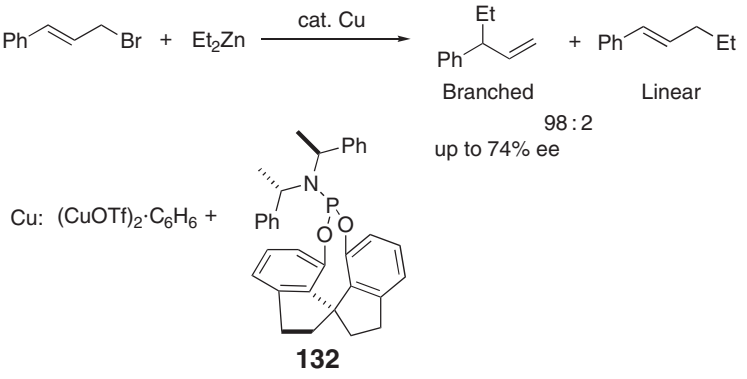
129a
up to 88% ee



(34)

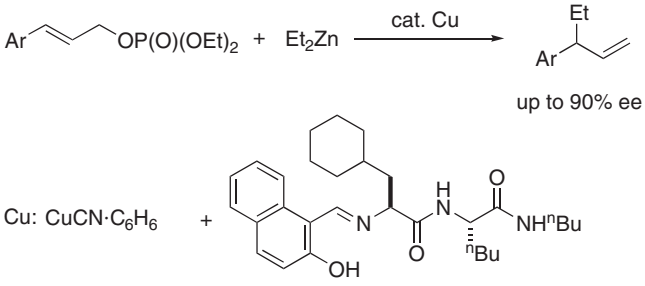


129b

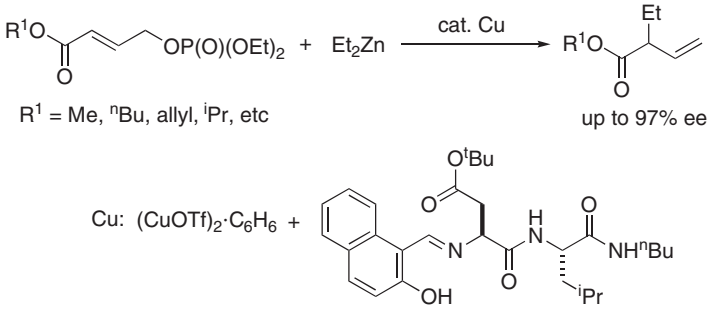


132 (35)

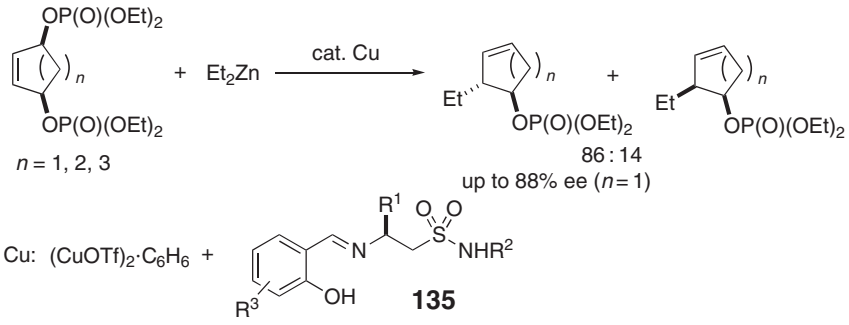
Hoveyda and his co-workers developed the copper-catalyzed allylic alkylation of allylic phosphates with diethylzinc by using optically active dipeptide **133** as a chiral ligand (Equation (36)).[128] Fine-tuning of dipeptides leads to **134** which gives an excellent enantioselectivity as shown in Equation (37).[129] This method can be used as a synthetic tool for the construction of a chiral tertiary carbon center by the allylic alkylation methodology.[129] The same research group achieved a further modification of the peptides to obtain an almost complete enantioselectivity in the allylic alkylation of allylic phosphates.[129a] Gennari and his co-workers found a highly enantioselective copper-catalyzed desymmetrization of some *meso*-cyclic allylic diphosphates ($n = 1$) using other type of ligands **135** than those reported by Feringa *et al.* (Equation (38)).[130] Optically active *N*-heterocyclic carbenes **136** are employed as chiral ligands in the copper-catalyzed allylic alkylation of allylic phosphates with an excellent enantioselectivity (Equation (39)).[131] Here, silver complexes of the *N*-heterocyclic carbenes broadened the scope of this reaction. A review article on the copper-catalyzed allylic alkylation is recently written by Yorimitsu and Oshima.[132]



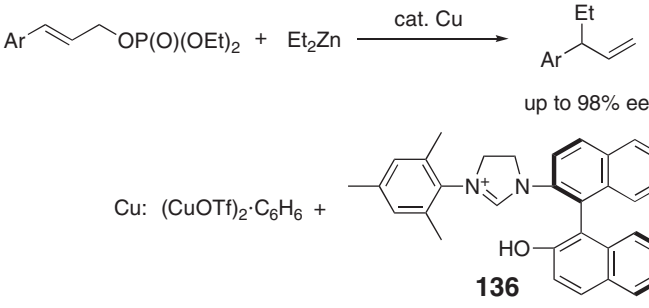
133 (36)



134 (37)



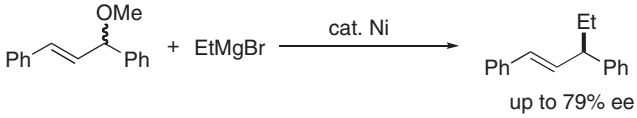
(38)



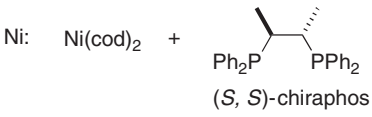
(39)

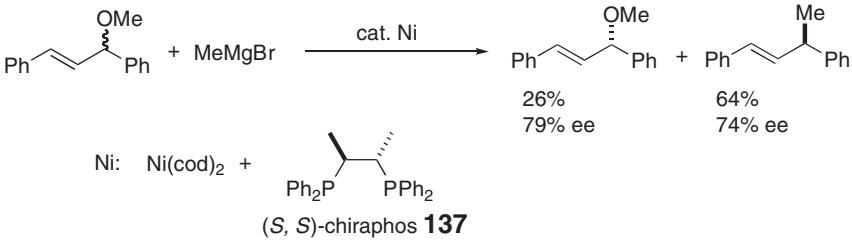
11.03.3.2 Nickel-catalyzed Alkylation

In 1997, RajanBabu and Nomura developed the asymmetric nickel-catalyzed allylic alkylation with "hard" carbon-centered nucleophiles such as Grignard reagents (Equation (40)).[133] A catalytic amount of [Ni(cod)$_2$] together with chiraphos **137** promotes the allylic alkylation of 1,3-diphenyl-2-propenyl methyl ether with methyl- and ethylmagnesium bromides to give the corresponding alkylated compounds with a good enantioselectivity (up to 79% ee). When DUPHOS **17** is used as a chiral ligand in place of chiraphos, lower enantioselectivity results (up to 66% ee). Interestingly, kinetic resolution is observed in this nickel-catalyzed allylic alkylation (Equation (41)): both recovered starting substrate and alkylated product exhibit, respectively, good enantioselectivities of 79% ee and 74% ee.



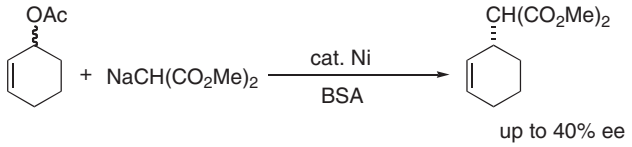
(40)



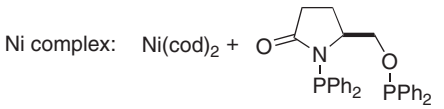


(41)

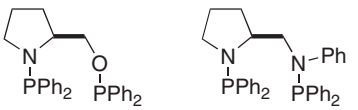
Asymmetric nickel-catalyzed allylic alkylation with "soft" carbon-centered nucleophiles was reported in 1996 by Mortreux and his co-workers.[134] Use of a catalytic amount of [Ni(cod)$_2$] together with chiral diphosphines **138** promotes the allylic alkylation of a cyclic ester such as 2-cyclohexenyl acetate with dimethyl malonate in the presence of BSA and gives the corresponding alkylated compounds only with a moderate enantioselectivity (40% ee) (Equation (42)).



(42)

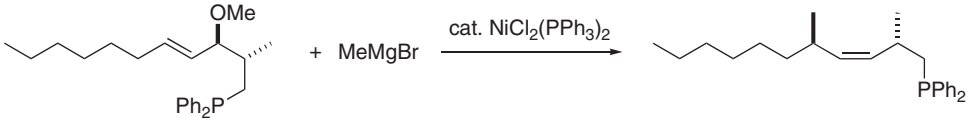


138a



138b **138c**

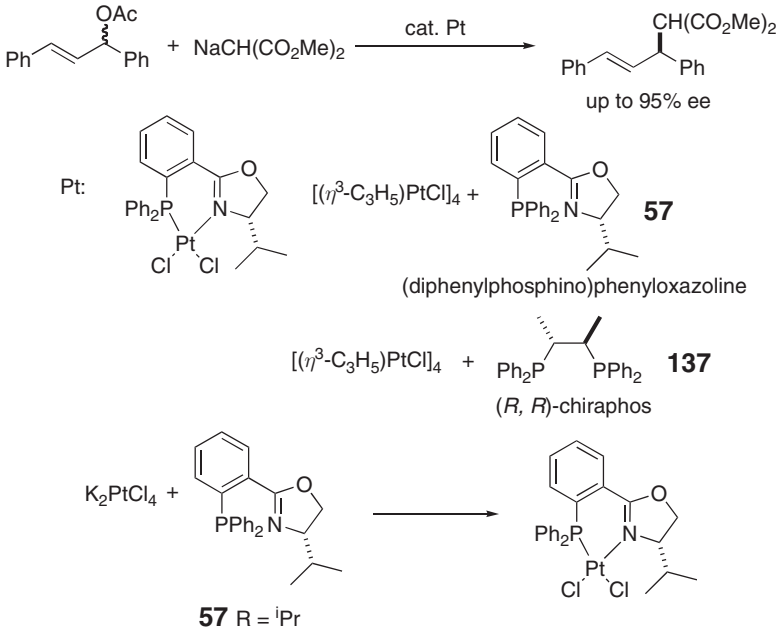
In 1995, Hoveyda and his co-workers reported the diastereoselective nickel-catalyzed allylic alkylation of allylic ethers bearing a directing group.[135] Allylic alkylation of allylic ethers having a (diphenylphosphino)alkyl moiety with methylmagnesium bromide proceeds in the presence of a catalytic amount of [$NiCl_2(PPh_3)_2$] and gives the corresponding methylated compounds with a complete diastereoselectivity (Equation (43)). Interestingly, without such a directing group as a diphenylphosphino moiety, no reaction occurs under the same reaction conditions. Thus, the directing group effectively controls both the regiochemistry and the stereochemical outcome of the alkylation.



(43)

11.03.3.3 Platinum-catalyzed Alkylation

The catalytic activity of platinum complexes toward allylic alkylation has been investigated without any success.[136,136a] In 1999, Williams and his co-workers developed for the first time the asymmetric platinum-catalyzed allylic alkylation of allylic esters with malonates (Equation (44)).[137,137a] A catalytic amount of the platinum complex bearing an optically active (diphenylphosphino)phenyloxazoline **57** as a chiral ligand (Equation (45)) promotes the allylic alkylation of 1,3-diphenyl-2-propenyl acetate with sodium dimethyl malonate to give the corresponding alkylated compound with a good enantioselectivity (up to 77% ee). The presence of **57** in excess slightly increases the enantioselectivity (up to 83% ee). When the same allylic alkylation is investigated in the presence of a palladium complex for comparison, a higher enantioselectivity results (up to 91% ee). By using a combination of [(η^3-C_3H_5)-PtCl]$_4$ and an excess amount of **57** as a catalyst, a higher enantioselectivity (up to 90% ee) is obtained albeit with lower catalytic activity. It is clear that both the enantioselectivity and the reactivity in the platinum-catalyzed reaction are much affected by the reaction conditions employed, compared to the palladium-catalyzed reaction. A combination of [(η^3-C_3H_5)PtCl]$_4$ and chiraphos **137** gives so far the highest enantioselectivity in the platinum-catalyzed allylic alkylation as shown in Equation (44) (95% ee). No reaction takes place when a cyclic allylic ester such as 2-cyclohexenyl acetate is employed as a substrate in place of 1,3-diphenyl-2-propenyl acetate.

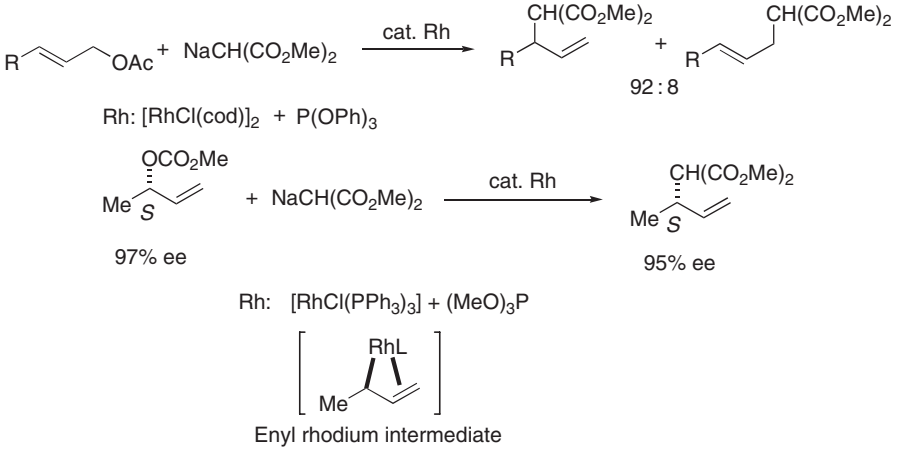


(44)

(45)

11.03.3.4 Rhodium-catalyzed Alkylation

A combination of rhodium complexes and phosphates promotes a highly regioselective allylic alkylation of unsymmetric allylic esters, where alkylation occurs at the more substituted allylic terminus of the esters (Equation (46)).[138] As Evans and his co-workers reported, both the regio- and stereochemistry of the starting allylic esters are maintained in the allylic alkylated products (Equation (47)). Thus, the rhodium-catalyzed allylic alkylation takes place at the carbon substituted by a leaving group with net retention of configuration.[139,139a–139g] A variety of carbon-centered nucleophiles are available for the rhodium-catalyzed allylic alkylation. Some pieces of mechanistic evidence indicate that a σ-allyl-type enyl rhodium intermediate is responsible for maintaining both regio- and stereochemistry of the products.[139,139a–139g] This rhodium-based procedure is considered to provide a practical alternative to traditional transition metal-catalyzed methods such as transformations that require retention of absolute configuration.

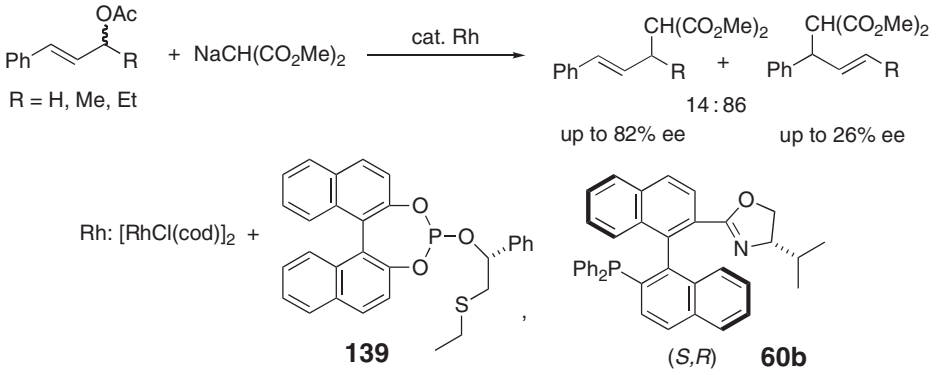


(46)

(47)

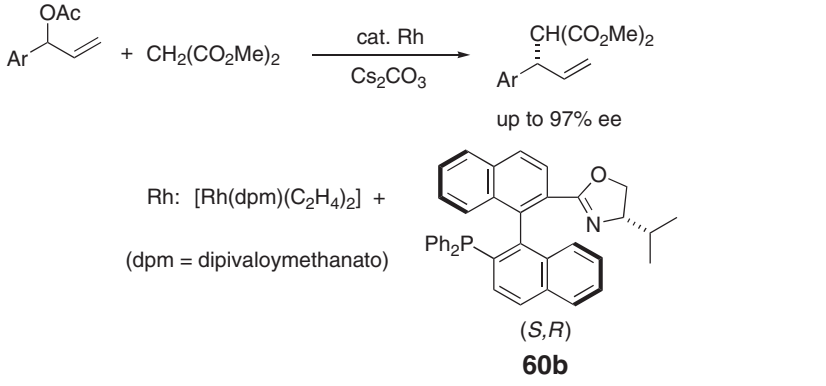
The high regio- and stereospecificity in the rhodium-catalyzed system does not seem to be compatible with the catalytic asymmetric synthesis using a chiral rhodium catalyst, and thus, there have so far been very few reports on the use of chiral rhodium catalysts for the asymmetric allylic alkylation. In 1999, Pregosin and his co-workers first reported asymmetric rhodium-catalyzed allylic alkylation of allylic esters (Equation (48)).[140] Use of optically active

phosphite-thioether ligands **139** promoted the allylic alkylation of unsymmetrical allylic esters to give the alkylated compounds as a mixture of two regioisomers with a good enantioselectivity. The same research group also used an optically active phosphine-oxazoline **60b** bearing a binaphthyl moiety in the rhodium-catalyzed allylic alkylation, but the enantioselectivity of the alkylated compounds was moderate.



(48)

In 2003, Hayashi and his co-workers found that highly enantioselective rhodium-catalyzed allylic alkylation took place with 1-aryl-2-propenyl acetates by using an achiral β-diketonate ligand for the rhodium complexes in the presence of (diphenylphosphino)binaphthyloxazoline **60b**. Fine-tuning of the β-diketonate part resulted in enhancement in enantioselectivity up to 97% ee (Equation (49)).[141]

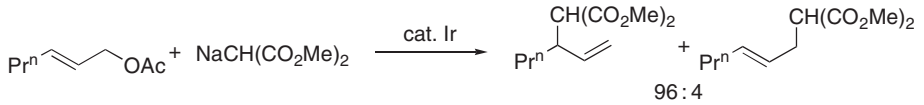


(49)

11.03.3.5 Iridium-catalyzed Alkylation

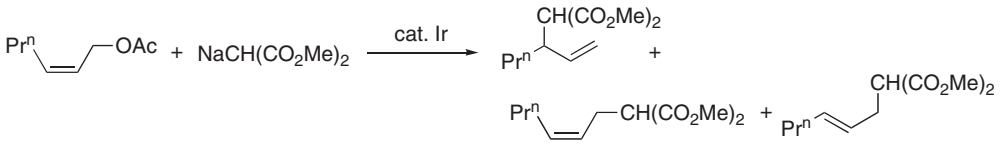
In 1997, Takeuchi and Kashio found efficient iridium-catalyzed allylic alkylation of allylic ester for the first time (Equation (50)).[142–143a] A combination of $[IrCl(cod)]_2$ and a phosphite ligand promotes the allylic alkylation of (*E*)-allylic esters with sodium dimethyl malonate to give the corresponding alkylated compounds with a high regioselectivity. Upon similar treatment, (*Z*)-allylic esters also give the corresponding (*Z*)-alkylated compounds but with lower selectivity (Equation (51)).[142–143a] On the other hand, Helmchen and his co-worker developed asymmetric iridium-catalyzed allylic alkylation of allylic esters (Equation (52)).[144,144a] A combination of $[IrCl(cod)]_2$ and a catalytic amount of optically active **57a** promotes the asymmetric allylic alkylation with a high enantioselectivity (up to 95% ee). Introduction of an electron-withdrawing group to the phenyl ring dramatically increases the enantioselectivity. The same research group reported the iridium-catalyzed asymmetric allylic alkylation of chiral and achiral allylic esters by using a phosphorusamidite **140** as a chiral ligand (Scheme 21).[145,145a] Fuji and his co-workers found the asymmetric iridium-catalyzed allylic alkylation using optically active phosphites **141** as chiral ligands (Equation (53)).[146,146a] In this case, a combination of both alkyllithium and zinc chloride is necessary as a counter cation source to obtain a high enantioselectivity. Recently, a highly regio- and enantioselective iridium-catalyzed allylic alkylation of allylic esters is found independently by Alexakis and Helmchen. Use of phosphorusamidites **130b** as chiral ligands in the presence of additives is effective.[147,148] In the Alexakis's system, the addition of LiCl is essential to achieve an excellent enantioselectivity (Equation (54)),[147] whereas in the Helmchen's system, use of THT (tetrahydrothiophene), TBD (1,5,7-triazabicyclo[4.4.0]undec-5-ene), and CuI increases both reactivity and selectivity (Equation (55)).[148]

Takemoto and his co-workers developed asymmetric allylic alkylation of allylic phosphates with (diphenylimino)glycinates as carbon-centered nucleophiles (Equation (56)).[149,149a] In this reaction system, use of optically active bidentate phosphites **142** bearing an (ethylthio)ethyl group as chiral ligands promotes the allylic alkylation, and chiral β-substituted α-amino acids are obtained with an excellent enantioselectivity.

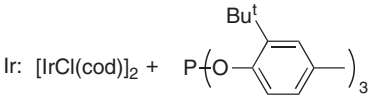


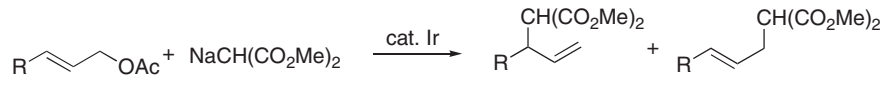
(50)

Ir: $[IrCl(cod)]_2$ + $P(OPh)_3$



(51)

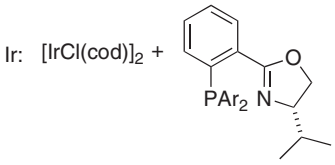




(52)

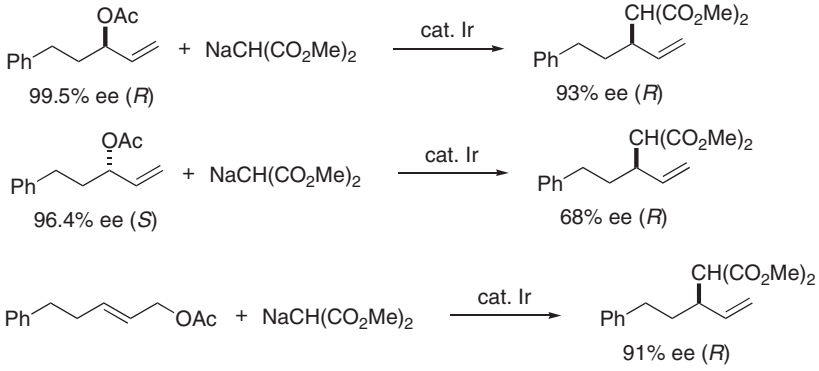
R = Ph, *p*-$MeOC_6H_4$

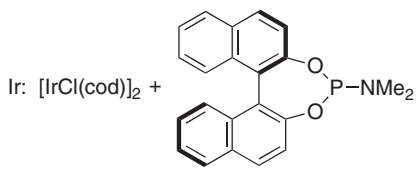
up to 95% ee



Ar = Ph, *p*-$CF_3C_6H_4$, 3,5-$(CF_3)_2C_6H_3$

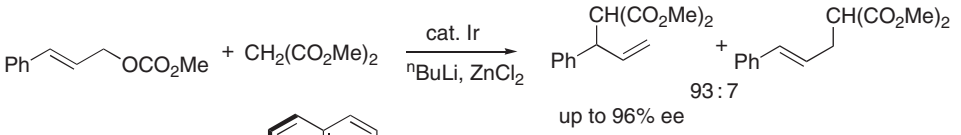
57a





140

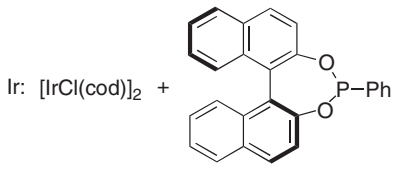
Scheme 21



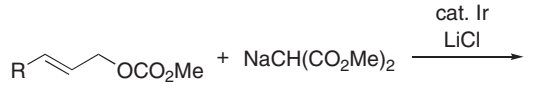
(53)

93 : 7

up to 96% ee



141

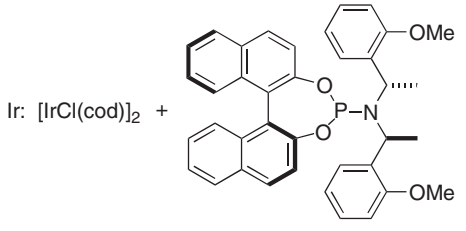


(54)

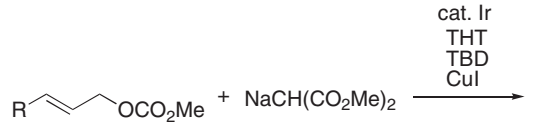
R = Ph, *p*-MeOC$_6$H$_4$, etc

99 : 1

up to 98% ee



130b

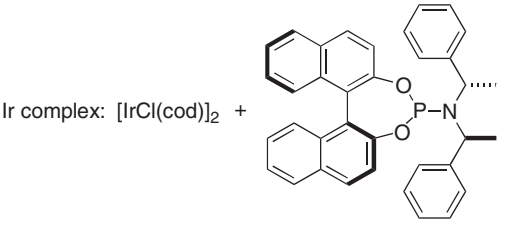


(55)

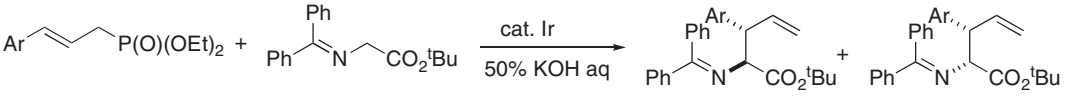
R = Ph, *p*-MeOC$_6$H$_4$, etc

98 : 2

up to 97% ee



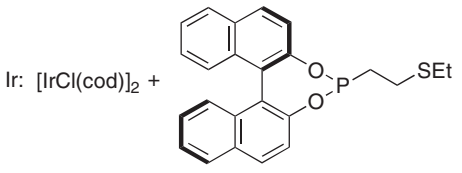
129b



(56)

82 : 18

up to 97% ee

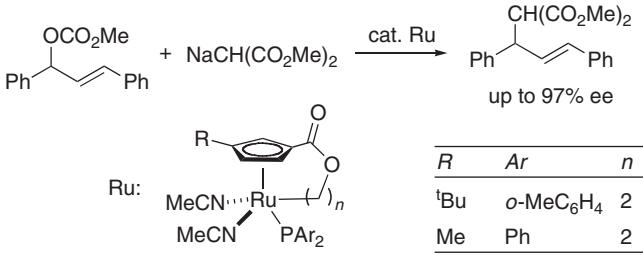


142

11.03.3.6 Ruthenium-catalyzed Alkylation

Several η^3-allylic ruthenium complexes can function as both a nucleophile and an electrophile, as Watanabe and his co-workers observed.[150] Namely, these ruthenium complexes smoothly react with a variety of carbon-centered nucleophiles such as aldehydes, alcohols, and β-diketones under mild reaction conditions and give the corresponding allylated compounds (Scheme 22).

In 2001, Takahashi and his co-workers developed the first asymmetric ruthenium-catalyzed allylic alkylation of allylic carbonates with sodium malonates which gave the corresponding alkylated compounds with an excellent enantioselectivity (Equation (57)).[151] Use of planar-chiral cyclopentadienylruthenium complexes **143** with an anchor phosphine moiety is essential to promote this asymmetric allylic alkylation efficiently. The substituents at the 4-position of the cyclopentadienyl ring play a crucial role in controlling the stereochemistry. A kinetic resolution of racemic allylic carbonates has been achieved in the same reaction system (up to 99% ee).[151a]

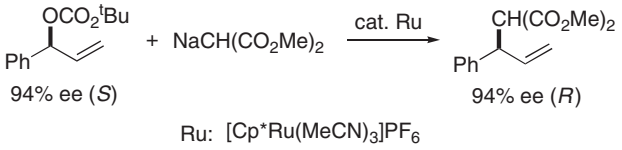


143

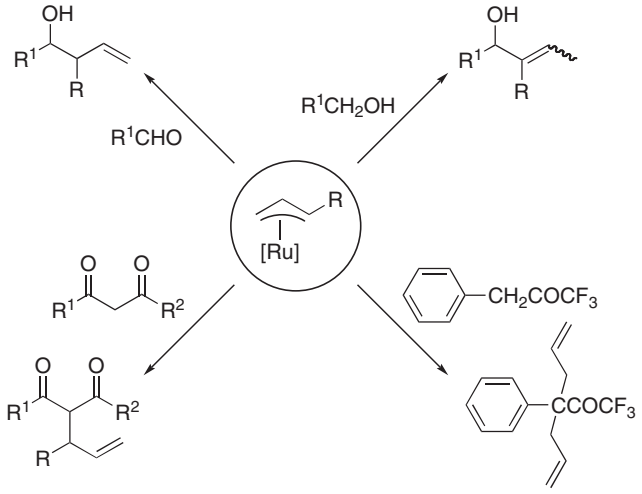
(57)

R	*Ar*	*n*	*ee* (%)
^{t}Bu	*o*-MeC$_6$H$_4$	2	97 (*S*)
Me	Ph	2	80 (*R*)

In 2002, Trost and his co-workers reported a stereospecific ruthenium-catalyzed allylic alkylation reaction (Equation (58)).[152] Treatment of an optically active allylic carbonate with carbon-centered nucleophiles in the presence of a ruthenium complex gives the corresponding allylic alkylated compounds with enantiomeric purity being completely maintained. Additionally, the regioselectivity is revealed not to be highly dependent on the nature of the starting carbonates.



(58)

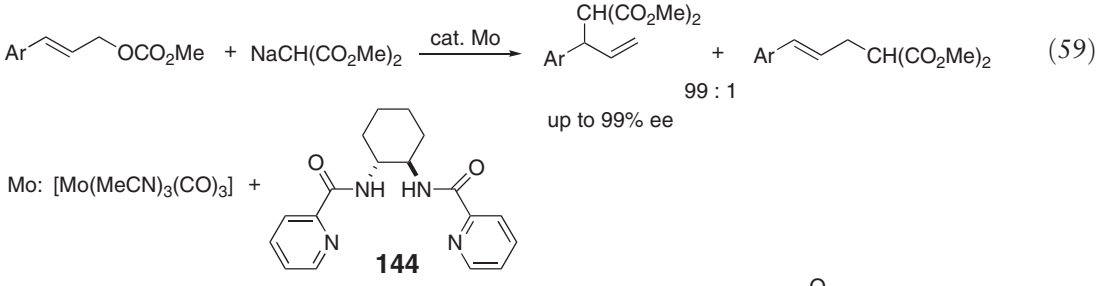


Scheme 22

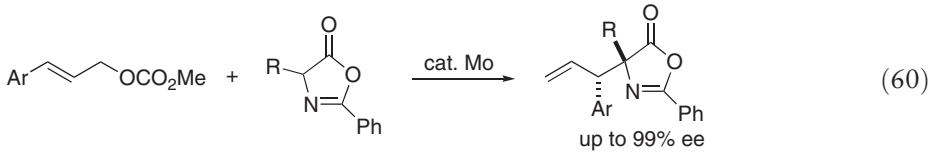
11.03.3.7 Molybdenum-catalyzed Alkylation

Molybdenum-catalyzed allylic alkylation has been used as a complementary synthetic procedure to the palladium-catalyzed process,[153] because allylic alkylation of unsymmetrical substrates takes place mostly at the more substituted carbon atom, in contrast to the palladium case.

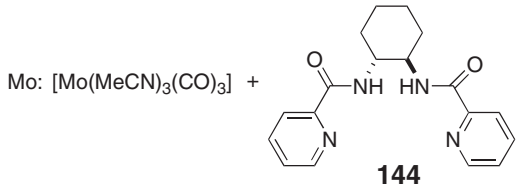
The first asymmetric molybdenum-catalyzed allylic alkylation was developed in 1998 by Trost and Hachiya (Equation (59)),[154] who used an $[Mo(MeCN)_3(CO)_3]$ catalyst and optically active bispyridylamide **144** to effect asymmetric allylic alkylation of allylic carbonates with dimethyl sodiomalonate with excellent regio- and enantioselectivities.[155,155a,155b] Other type of stabilized carbon-centered nucleophiles such as lithium salts of azalactones and 5*H*-oxazol-4-ones are also available for this molybdenum-catalyzed allylic alkylation (Equations (60) and (61)).[156,157] Several other pyridylcarboxamides **144–150** are used as chiral ligands in this allylic alkylation (Scheme 23).[158] Higher enantioselectivities are observed when one of the two picolinamide groups is replaced by a benzoylamide group. Thus, C_2-symmetry of ligand is not essential for high enantioselectivity in this alkylation. Kinetic resolution of branched racemic allylic carbonates was investigated by Hughes and his co-workers using the molybdenum system.[159] In 2000, Moberg and his co-workers reported that microwave heating accelerates the reaction rate without any significant loss of selectivity. Here, a more stable and cheaper molybdenum source, $[Mo(CO)_6]$, can be employed.[160,160a–160c] Treatment of a molybdenum complex with allylic carbonate produces a π-allylic complex, whose structure is determined by X-ray crystallography and NMR spectroscopy (Scheme 24).[161,161a] The π-allylic complex undergoes stoichiometric reaction with dimethyl sodiomalonate in the presence of $[Mo(CO)_6]$ in excess to give the alkylated compound with >95% ee, but no reaction occurs in the absence of $[Mo(CO)_6]$ (Scheme 25).

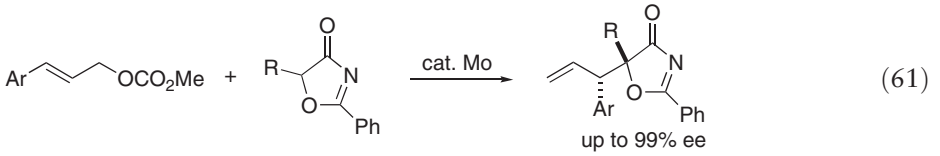


(59)

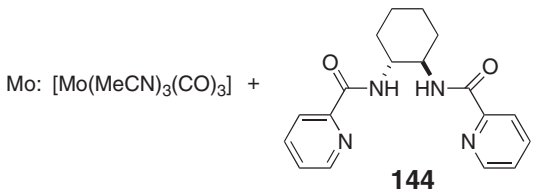


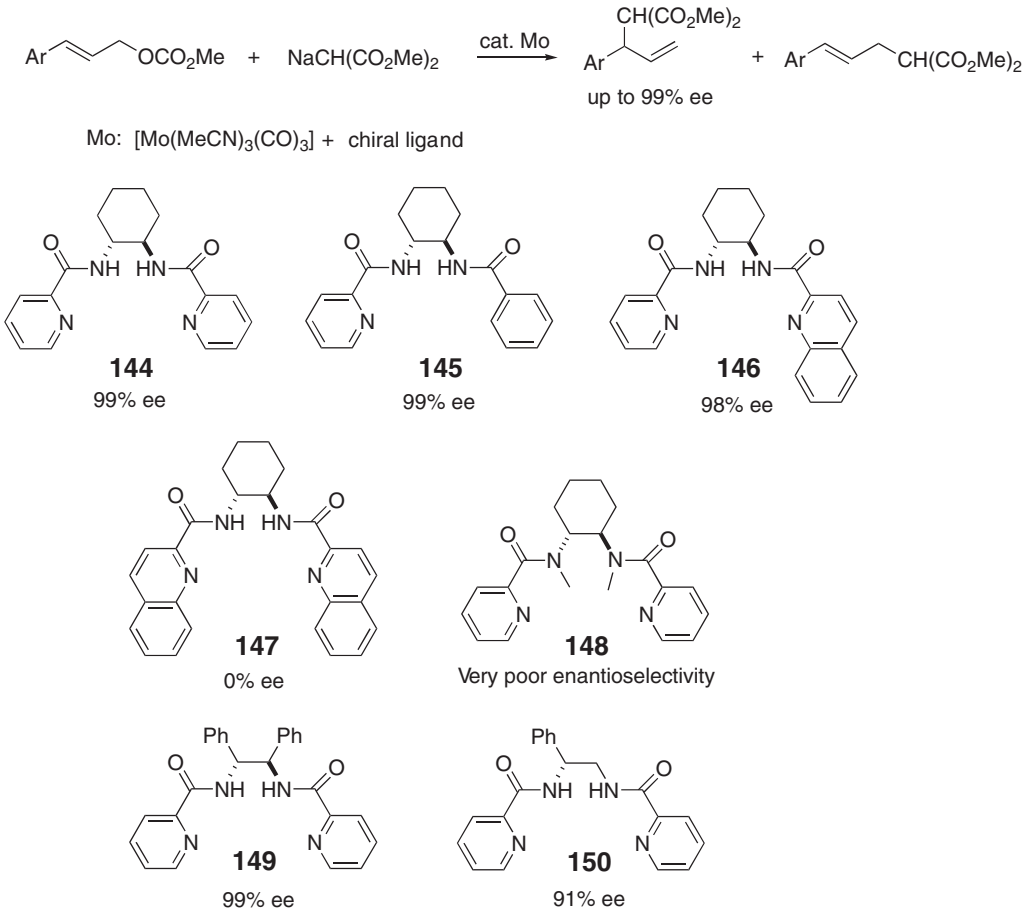
(60)





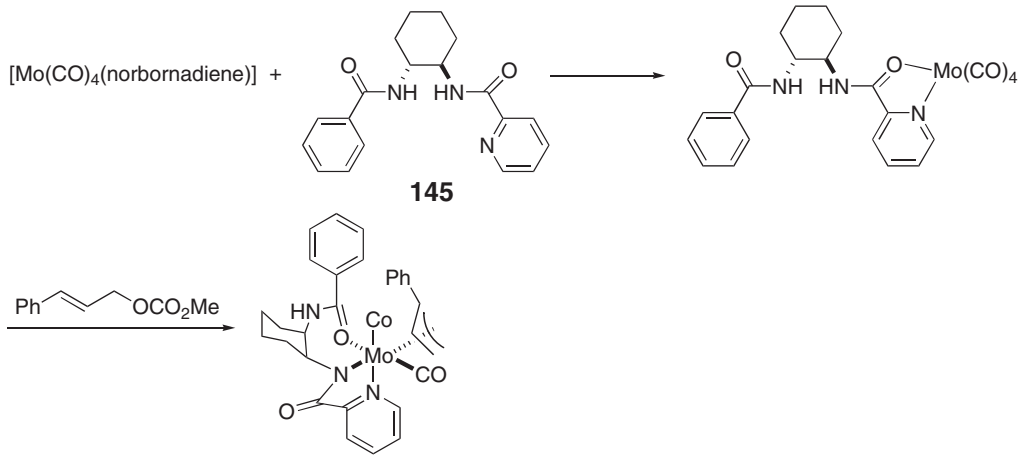
(61)



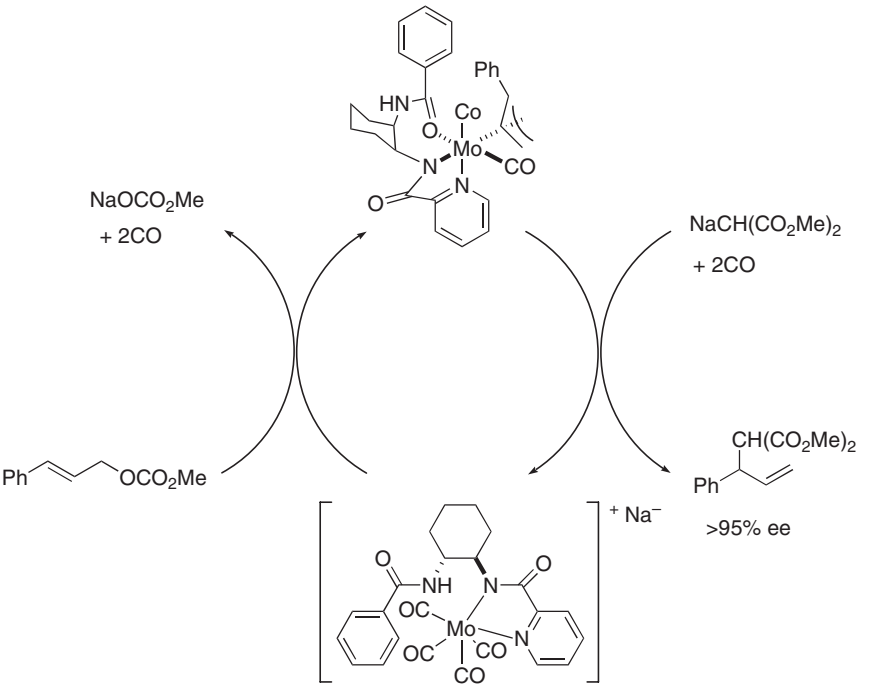


Scheme 23

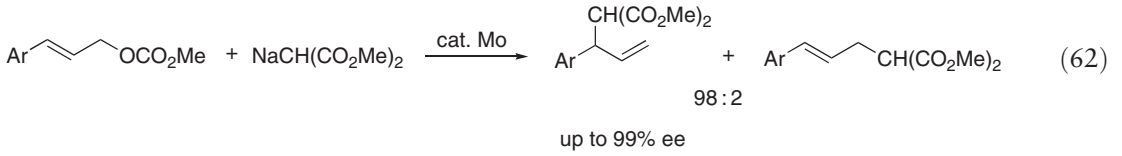
In 1999, Pfaltz and his co-workers found another successful example of the asymmetric molybdenum-catalyzed allylic alkylation using optically active bisoxazolines **151** and **152** as chiral ligands (Equation (62)).[162,162a] These ligands look analogous to the Trost's bispyridylamide ligands in the cyclohexylamide part, but additionally incorporate stereogenic centers in the heterocyclic rings. The nature of the substituent in the heterocyclic ring is shown to strongly influence the outcome of the reaction.



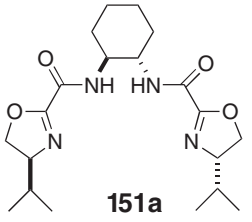
Scheme 24



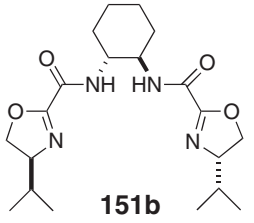
Scheme 25



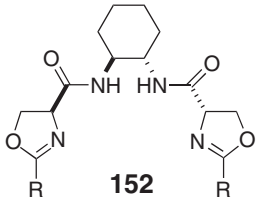
Mo: $[Mo(EtCN)_3(CO)_3]$ + chiral ligand



151a



151b

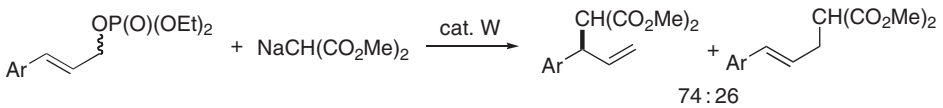


152

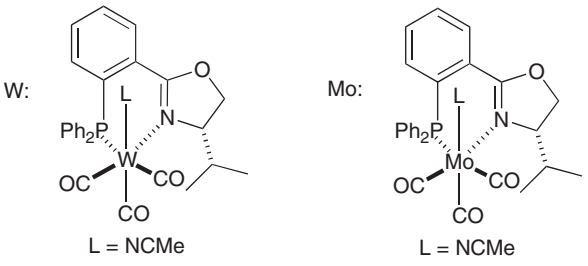
11.03.3.8 Tungsten-catalyzed Alkylation

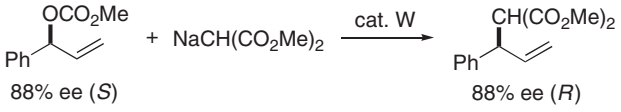
As described in many reviews, Trost and his co-workers have carried out a pioneering work on the molybdenum- and tungsten-catalyzed allylic alkylation of allylic esters; regioselectivity of the reaction is often complementary to the palladium-catalyzed allylic alkylation. The first asymmetric version was disclosed by Pfaltz and Lloyd-Jones in 1995 (Equation (63)).[163] They used a catalytic amount of a novel tungsten complex, prepared from $[W(CO)_3(MeCN)_3]$ or [W(cycloheptatriene) $(CO)_3$] and optically active (diphenylphosphino)phenyloxazolines **57**, for the allylic alkylation of 3-aryl-2-propenyl phosphate with dimethyl sodiomalonate to isolate the corresponding branched alkylated compounds as a major isomer with an excellent enantioselectivity (96% ee). Unexpectedly, 3-aryl-2-propenyl carbonates are shown to be unreactive. It is worth noting that an isostructural molybdenum complex does not promote the catalytic alkylation under the same reaction conditions. In contrast, Lloyd-Jones and Lehmann reported the stereocontrolled

tungsten-catalyzed allylic alkylation of chiral allylic carbonates, which proceeded with a complete retention of absolute configuration (Equation (64)).[164]



(63)



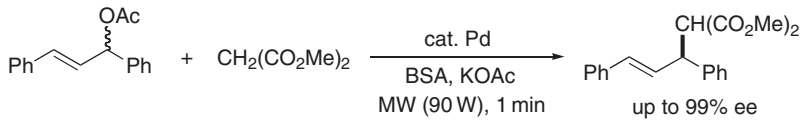


(64)

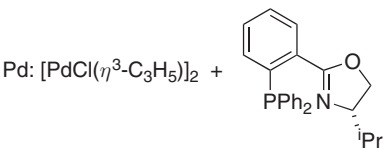
W: $[W(CO)_3(MeCN)_3]$ + 2,2′-bipyridine

11.03.4 Other Reaction Systems in Asymmetric Allylic Alkylation

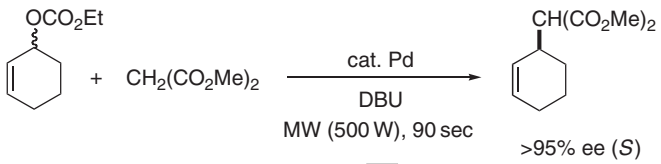
Hallberg and his co-workers reported in 1999 the first microwave-promoted asymmetric palladium-catalyzed allylic alkylation of acyclic and cyclic allylic esters with dimethyl malonate, using some chiral ligands **57** and **118** (Equations (65) and (66)).[165,165a,165b] In both cases, microwave irradiation reduces reaction time without any loss of enantioselectivity. The same group successfully applied this reaction system to the molybdenum-catalyzed allylic alkylation (Equation (67)).[160,160a–160c]



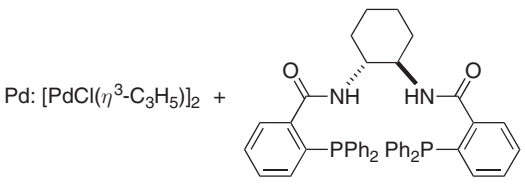
(65)



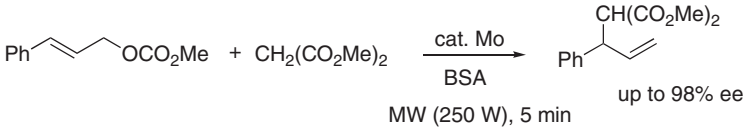
57 R = ^{i}Pr



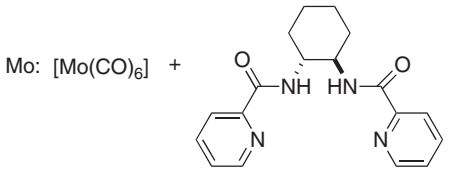
(66)



Trost's ligand **118**

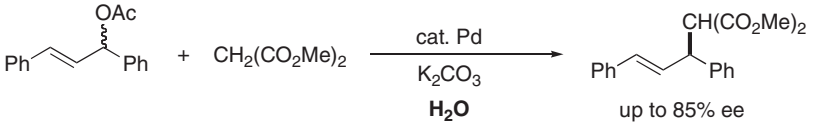


(67)

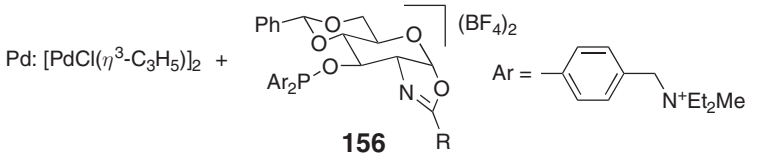


144

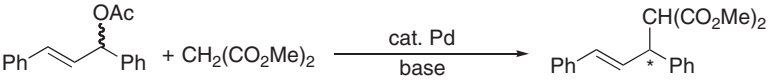
Highly enantioselective allylic alkylations by using solid-supported catalysts have been developed by several groups (Scheme 26).[166,166a–166c] The catalysts can be recycled for repeating reactions without any loss of enantioselectivity. In particular, some solid-supported palladium catalysts promote the allylic alkylation even in water with a high enantioselectivity as described in the Section 11.03.2.3.[111,111a,167] Chaudret and his co-workers reported the first example of asymmetric allylic alkylation by using palladium nanoparticles stabilized by chiral diphosphite **155** based on glucose (Scheme 27).[168] Uemura and co-workers prepared amphiphilic chiral P–N chelating ligands **156** derived from D-glucosamine and carried out the allylic alkylation in water by using a palladium complex bearing these ligands as a catalyst (Equation (68)).[169]

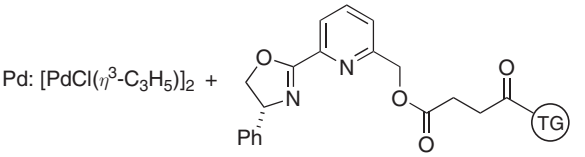


(68)

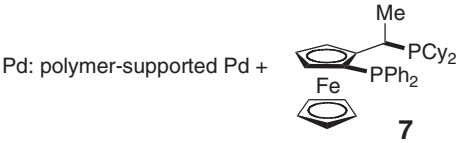


156

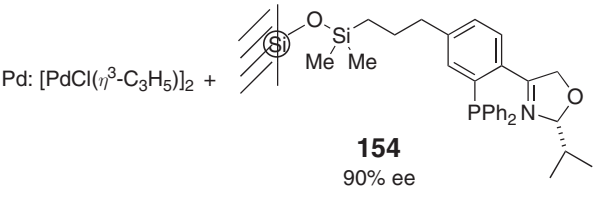




153 (TG = TentaGel resin)
80% ee

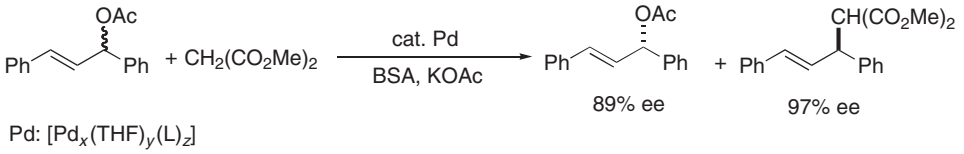


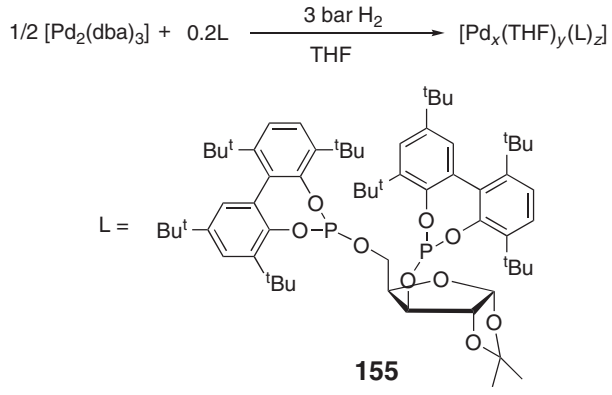
7
93% ee



154
90% ee

Scheme 26



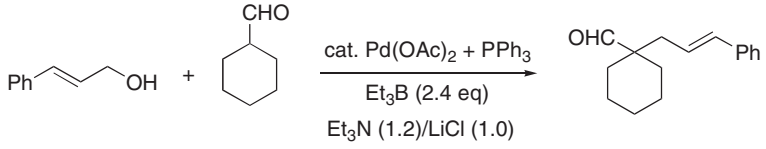


Scheme 27

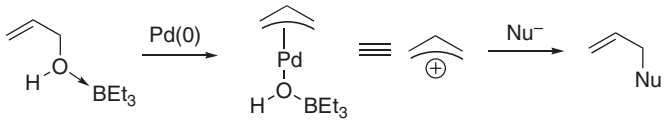
Togni and his co-workers prepared dendrimers containing chiral ferrocenyldiphosphines and investigated the palladium-catalyzed allylic alkylation using these phosphines as chiral ligands to obtain the corresponding allylic alkylated compounds with a high enantioselectivity (up to 91% ee).[170,170a] On the other hand, Malmström and his co-workers prepared dendrimers containing chiral oxazoline moieties and investigated similar palladium-catalyzed allylic alkylation (up to 91% ee).[171]

11.03.5 Catalytic Substitution Reactions Involving Allylic Alkylation

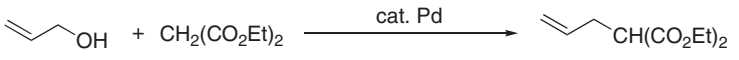
Direct alkylation of allylic alcohols is effected with palladium complexes but under harsh reaction conditions.[172,172a,172b] These reaction conditions have been modified mainly on the basis of *in situ* activation of allylic alcohols with inorganic acids such as AsO_3, B_2O_3, or CO_2 (gas), or with Lewis acids such as $Ti(O^iPr)_4$.[173,173a–173e] In 2001, Tamaru and his co-workers reported direct allylation of aldehydes with allylic alcohols by using a palladium catalyst amount together with triethylborane in excess (Equation (69)).[174,174a] In this reaction system, a π-allylpalladium species is produced by oxidative addition of allylic alcohols activated by triethylborane and attacked by aldehyde enolates to give α-allylated aldehydes selectively (Scheme 28). In 2002, Ozawa and his co-workers reported a facile method of direct substitution by using palladium complexes bearing sp^2-hybridized bidentate phosphane ligands. The reaction proceeds even at 50 °C, and the expected products are produced in high yields (Equation (70)).[175]



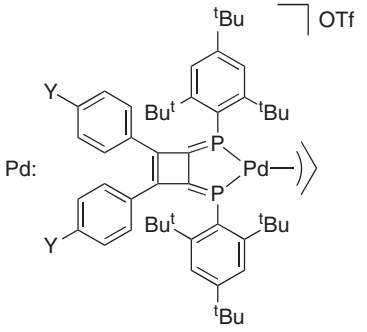
(69)



Scheme 28



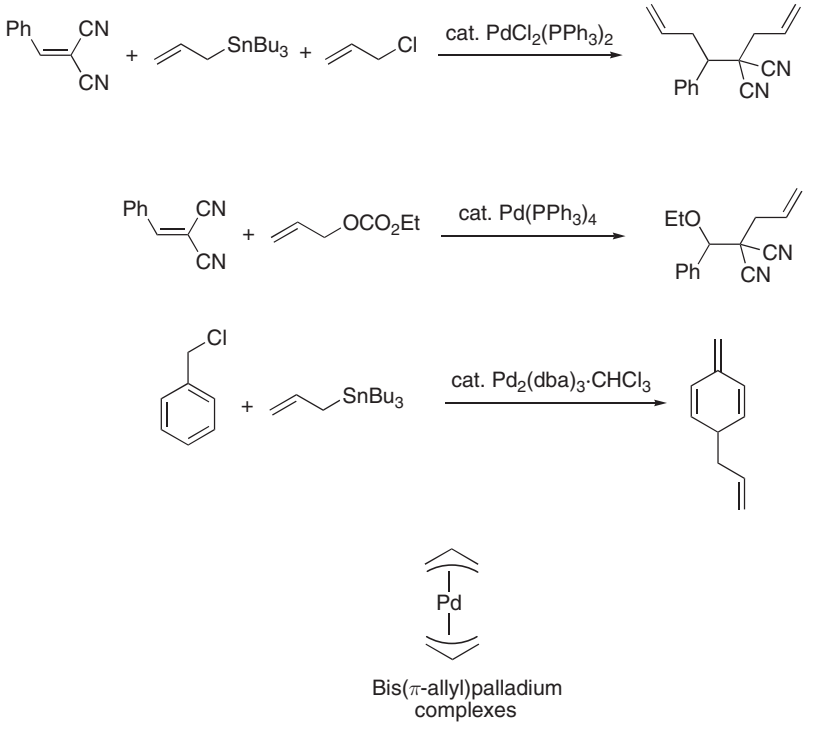
(70)



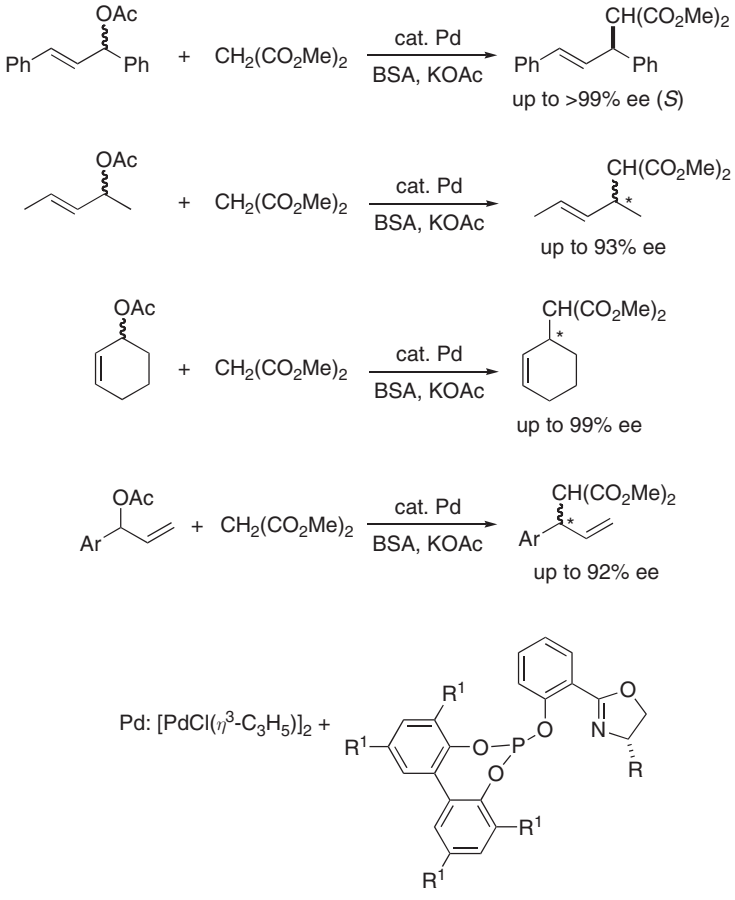
Y = OMe, H, CF_3

Novel palladium-catalyzed transformations of allylic alcohol and its derivatives are developed by Yamamoto and his co-workers. Bis(π-allyl)palladium complexes are considered to be the key intermediates for the allylation of benzylidenemalonitrile and benzyl chloride (Scheme 29) (for examples see Refs: 176,176a–176d). Asymmetric version of these reactions is being awaited.

After the preparation of the manuscript, a new family of phosphite-oxazoline ligands which shows excellent reactivity and enantioselectivity for a broad scope of different types of allylic alcohol derivatives has been reported, typical results being shown in Scheme 30.[177]



Scheme 29



Scheme 30

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11.04 C–C Bond Formation (Part 2) by Substitution Reactions: Substitution at Propargylic and Benzylic Positions

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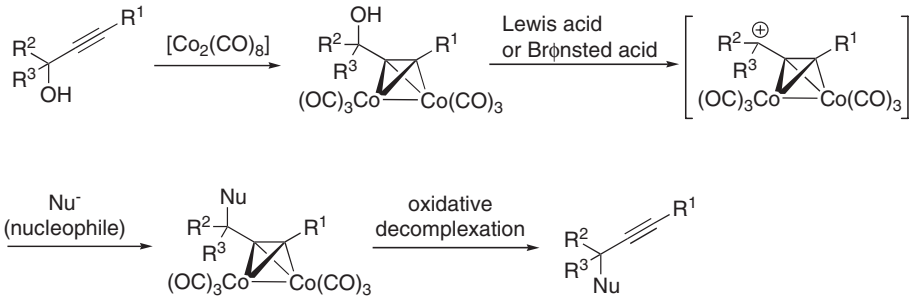
11.04.1 Introduction

Since the Nicholas' discovery of the activation of the propargylic position by the coordination of a dicobalthexacarbonyl cluster to a triple bond in 1971, the Nicholas reaction has been known to be one of the most useful synthetic tools for the propargylic substitution reaction (Scheme 1).[1] In this characteristic reaction, intermediate propargylic cations are first stabilized by the coordination with the dicobalthexacarbonyl [$Co_2(CO)_6$] moiety. Then, these complexes can serve as electrophilic propargylic equivalents because of their high reactivity toward a wide variety of heteroatom-centered nucleophiles as well as carbon-centered ones. Nucleophilic attack occurs exclusively at the propargylic carbon, thus avoiding the formation of allenic byproducts which are produced in most reactions using classical propargylic electrophiles. Finally, oxidative decomplexation gives the corresponding propargylic substituted products in high yields. The reaction has been applied to a variety of total syntheses. In addition to the Nicholas reaction, another propargylic substitution reaction has been recently developed by using a stoichiometric amount of ruthenium complexes, where ruthenium–allenylidene complexes work as key intermediates. In sharp contrast to the propargylic substitution reactions assisted by a stoichiometric amount of these transition metal complexes, the catalytic propargylic substitution reactions have been developed more recently using ruthenium, iridium, and rhenium complexes as catalysts. In this chapter, recent advances of non-catalytic and catalytic carbon–carbon bond-forming reactions at the propargylic position of propargylic alcohols and their derivatives are described. Recent examples of catalytic carbon–carbon bond-forming reactions at the benzylic position of benzylic alcohols and their derivatives are also included.



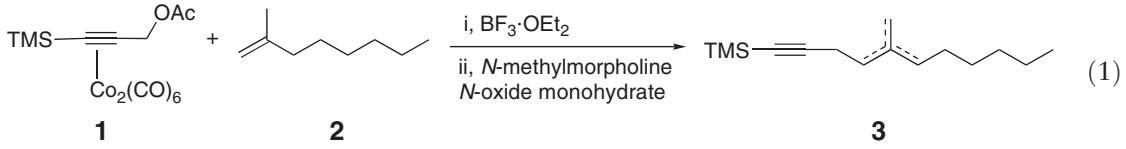
Scheme 1

11.04.2 Stoichiometric Propargylic Alkylation of Propargylic Alcohols Assisted by Cobalt Complexes

As described in the introduction, the Nicholas reaction has been known to be one of the most useful and reliable synthetic methods to form a carbon–carbon bond at the propargylic position of propargylic alcohols and their derivatives giving various propargylic substituted compounds, although a stoichiometric amount of cobalt complexes and several reaction steps are necessary to obtain the corresponding products. A variety of carbon-centered nucleophiles such as alkenes, enol derivatives, allylic metals, and aromatic compounds are available in the reactions of propargylic cations stabilized by $Co_2(CO)_6$-coordination. Whereas the original reaction patterns using these carbon-centered nucleophiles have already been described in COMC II (1995),[2] many synthetic applications including total synthesis by using these reactivities have since been reported. In this section, recent examples of the Nicholas reaction by using carbon-centered nucleophiles are summarized. Some excellent reviews on the Nicholas reaction from a viewpoint of organic synthesis have appeared recently and should be consulted.[3,4]

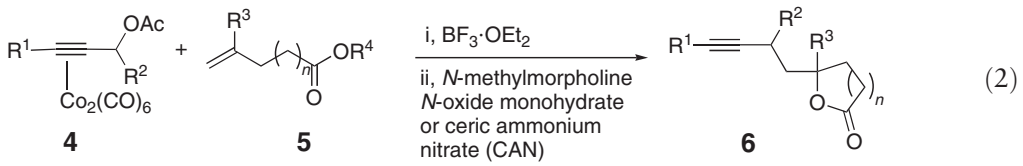
11.04.2.1 Alkenes as Nucleophiles

In 1996, Krafft and his co-workers found the intermolecular coupling reaction between the propargylic compound **1** stabilized by $Co_2(CO)_6$-coordination and simple alkenes such as 2-methyl-1-octene **2** and 1-heptene to give the corresponding enynes **3** as a mixture of regioisomers in good yields (Equation (1)).[5] When this reaction system is applied to an intermolecular coupling reaction of **4** with some alkenes **5** bearing a functional group such as ether, carboxylic acid, or carbonate, the corresponding cyclized products **6** such as lactones and ethers are produced in good overall yields (Equation (2)). In this reaction system, the carbocations formed *in situ* as intermediates **7** and **7′** are trapped intramolecularly by the functionalized group in the alkenes.



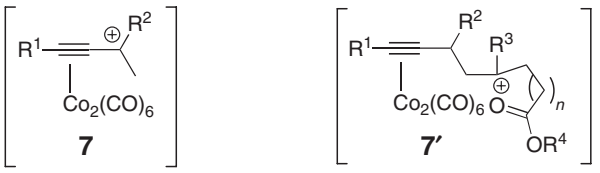
(1)

1 **2** **3**

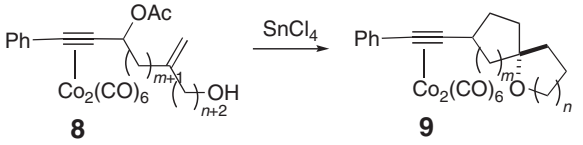


(2)

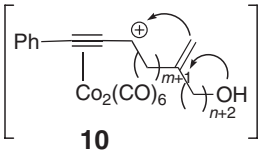
4 **5** **6**



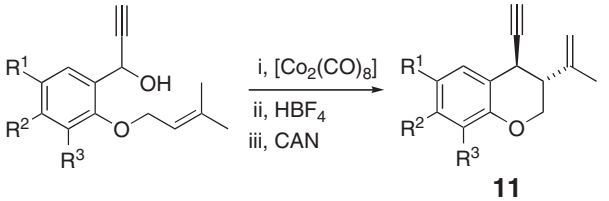
In 2002, Mukai and her co-workers developed an efficient synthetic method for the preparation of oxaspiro[*m.n*] skeletons **9** from the propargylic compound **8** bearing both methylidene and terminal hydroxy groups in the presence of a Lewis acid such as $SnCl_4$ (Equation (3)).[6] An initially generated propargylic cationic species **10** induces a cationic alkene cyclization with the methylene moiety anchimerically assisted by a terminal hydroxy group, resulting in formation of compounds having an oxaspiro skeleton such as 1-oxaspiro[4.4]nonane, 1-oxaspiro[4.5]decane, 6-oxaspiro[4.5]decane, and 1-oxaspiro[5.5]undecane derivatives.



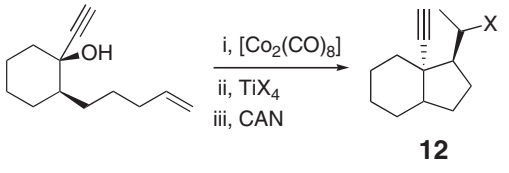
(3)



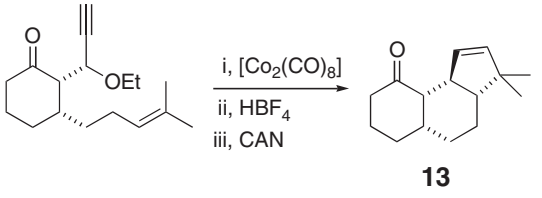
Similar intramolecular coupling reaction between the carbocation produced *in situ* and an alkenic part has already been investigated by Tyrrell and his co-workers where the corresponding functionalized benzopyranes and bicyclic compounds **11** were produced in high yields with a complete diastereoselectivity (Equation (4)).[7,7a,8] When Lewis acids such as $TiBr_4$ and $TiCl_4$ are used in place of HBF_4, halogenated bicyclic compounds **12** are obtained probably by alkyne isomerization followed by trapping an intermediate carbocation with a halide ion (Equation (5)). This reaction system is applied to a diastereoselective one-pot synthesis of tricyclic compounds **13** (Equation (6)).[9]



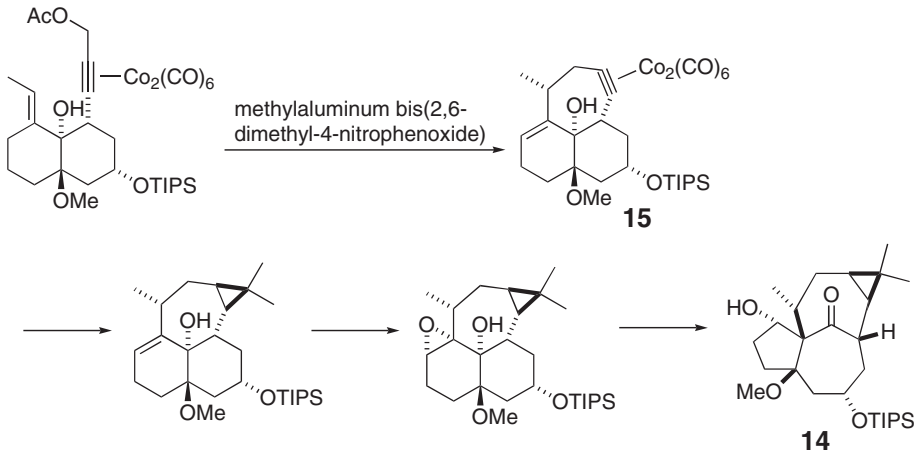
(4)



(5)



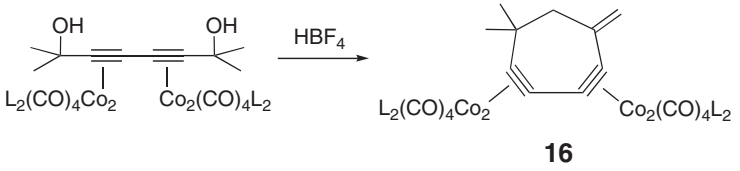
(6)



Scheme 2

A synthetic application is demonstrated by Tanino and his co-workers who reported a total synthesis of ingenol **14** using this methodology.[10,11] Use of methylaluminum bis(2,6-dimethyl-4-nitrophenoxide) promoted both cyclization and following rearrangement reactions smoothly to construct an ingenane skeleton **15** (Scheme 2).

Interestingly, seven-membered conjugated diyne complex **16** is produced by the acid-promoted Nicholas reaction of the dicobalt-coordinated bispropargylic complex (Equation (7)).[12] The cyclization proceeds via an intramolecular coupling reaction between a propargylic cation and an alkene produced after dehydration. The molecular structure of seven-membered diyne complex **16** is confirmed by X-ray analysis, although the decomplexation is not successfully carried out.

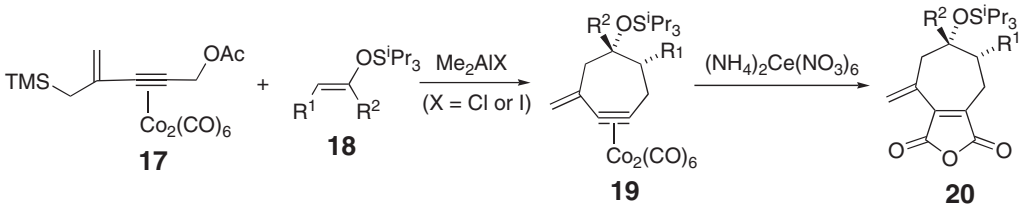


(7)

11.04.2.2 Enol Derivatives as Nucleophiles

Inter- and intramolecular reactions between a propargylic carbocation equivalent stabilized by $Co_2(CO)_6$-coordination and enol derivatives also provide a good method for the carbon–carbon bond formation at the propargylic carbon of propargylic alcohols and their derivatives. Many diastereoselective and enantioselective propargylic alkylation reactions at the propargylic position take place between chiral propargylic cation equivalents and enol derivatives.

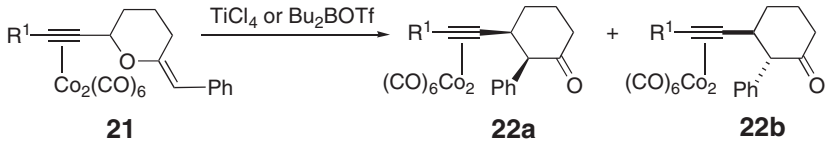
In 2000, Tanino and his co-workers developed the novel [5 + 2]-cycloaddition reaction of a propargylic cation equivalent bearing allylic silane **17** with enol silane **18** to give the corresponding cycloheptyne complexes **19** in good yields with an excellent diastereoselectivity (Scheme 3).[13] While ceric ammonium nitrate (CAN) is generally used to



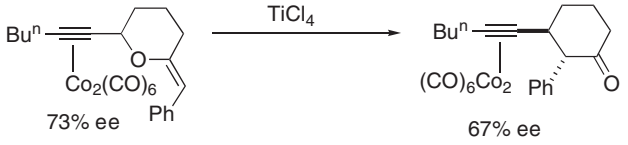
Scheme 3

regenerate an alkyne from the corresponding dicobalthexacarbonyl complex, it is not the case for these cycloaddition products. Thus, treatment of an alkyne complex with an excess amount of CAN in acetone–water yields a maleic anhydride derivative **20** in good yield (Scheme 3). This novel transformation involves the incorporation of two carbonyl groups on both of the acetylenic carbons.

In 2002, Harrity and his co-workers demonstrated the stereoselective rearrangement reaction of enol ethers **21** bearing a cobalt-coordinated alkyne moiety to afford α,β-disubstituted cyclohexanones **22** stereoselectively (Equation (8)).[14,14a] $TiCl_4$ and Bu_2BOTf promote the rearrangement, but ketonic products given by the reaction promoted by Bu_2BOTf are prone to epimerize to thermodynamically more stable *trans*-diastereoisomers **22b**. Interestingly, an enantioselective transformation proceeds smoothly when $TiCl_4$ is used as a Lewis acid (Equation (9)).[15] This rearrangement reaction involves the carbon–oxygen bond fission at the propargylic position followed by an electrophilic attack of propargylic cations to the alkenic carbon of the resulting titanium enolate.

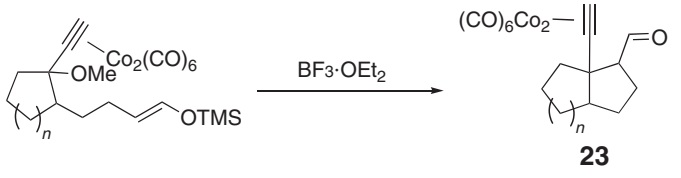


21 **22a** **22b** (8)

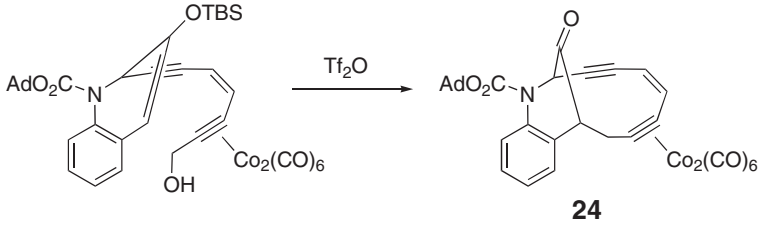


(9)

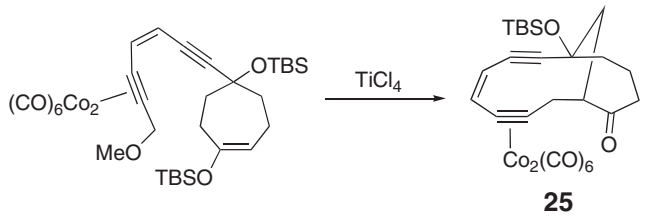
Intramolecular coupling reaction between a carbocation stabilized by $Co_2(CO)_6$-coordination and an enol silane moiety also proceeds smoothly to afford cycloalkane carbonyl compounds. Thus, Tyrrell and his co-workers extended this intramolecular reaction system to prepare fused bicyclic compounds **23** in good yields with high selectivity (Equation (10)).[16,16a] Magnus and his co-workers applied this methodology for the preparation of enediynes **24** by an intramolecular cyclization of a propargylic cation with an enol silane part (Equation (11)),[17,17a] achieving synthesis of the 13-keto-10-azabicyclo[7.3.1]enediyne core structure of dynemicin A. Maier and his co-worker prepared cyclic enediyne **25** by a similar intramolecular reaction of a propargylic cation with an enol silane (Equation (12)).[18] Montaña and his co-workers reported an intermolecular propargylic alkylation of a propargylic cation with chiral enol silane **26** to give alkylated products **27** with good enantioselectivity but with a low diastereoselectivity (Equation (13)). This methodology is also applied successfully to an enantioselective preparation of a *trans*-fused bicyclo[5.3.0]decane framework.[19,19a]



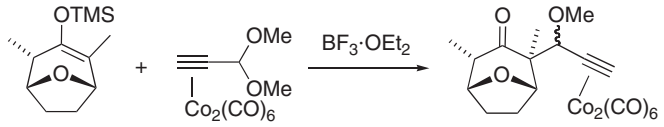
23 (10)



24 (11)



25 (12)

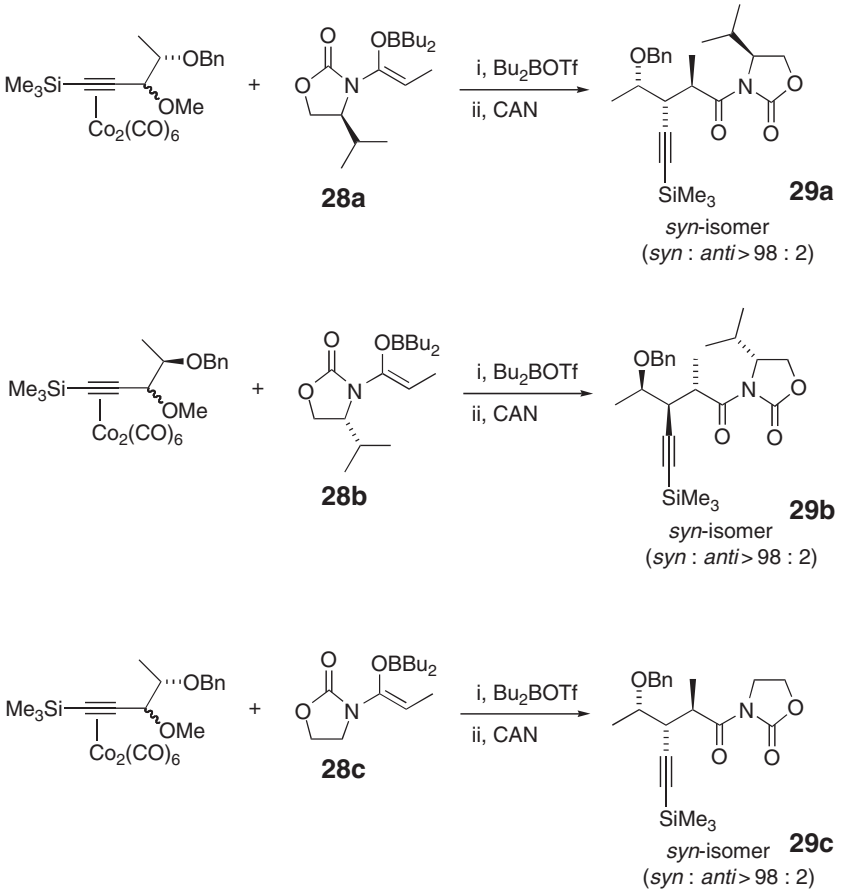


26 (13)

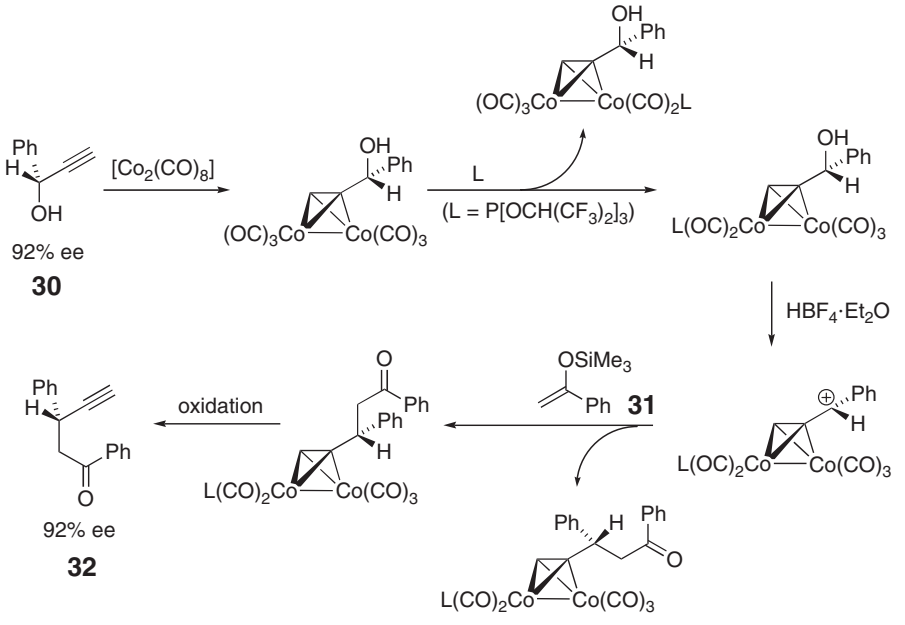
85% ee

27

In 1987, Schreiber and his co-workers showed that boron enolates derived from the Evan's chiral oxazolidinones reacted with a propargylic cation equivalent stabilized by $Co_2(CO)_6$-coordination to afford the chiral alkylated products in good yields with a high diastereoselectivity.[20] Schreiber elegantly rationalized this high diastereoselectivity by postulating a novel double stereodifferentiating process. As an extension of this study, Jacobi and his co-workers used other chiral and non-chiral oxazolidinone boron enolates **28** in the alkylation of the propargylic cation, where the corresponding alkylated products **29** were obtained in good yields with a high diastereoselectivity (Scheme 4).[21,21a–21d] Some natural products have been prepared by using this Nicholas–Schreiber reaction.

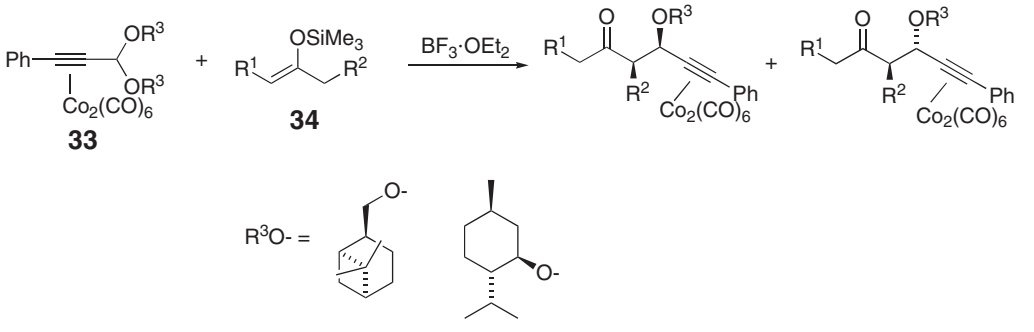


Scheme 4



Scheme 5

In 1993, Nicholas and his co-worker developed the stereospecific propargylic alkylation of chiral propargylic alcohols **30** with enol silanes **31** by using a stoichiometric amount of $[Co_2(CO)_5L]$ (L = phosphite), but separation procedures of the produced diastereoisomers are necessary twice on the way to obtain the compounds specifically alkylated at the propargylic position **32** (Scheme 5).[22] In 2001, Montaña and his co-worker reported the diastereoselective Nicholas alkylation of propargylic acetal complexes **33** bearing a chiral auxiliary with various enol silanes **34** (Equation (14)).[23,23a] A high diastereoselectivity is observed, but unfortunately, only low to moderate enantioselectivities are achieved in all cases.

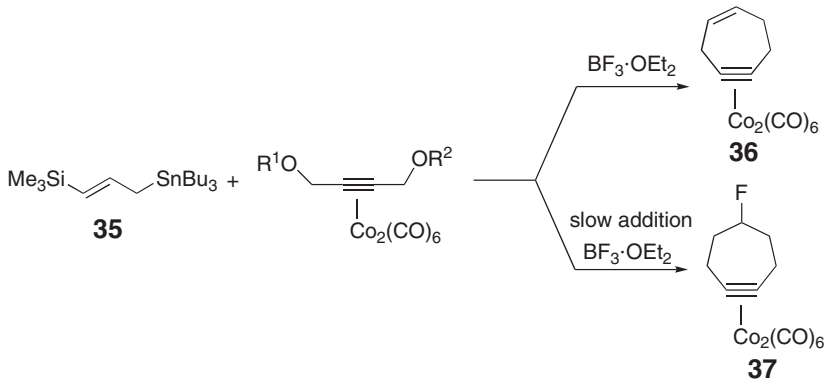


(14)

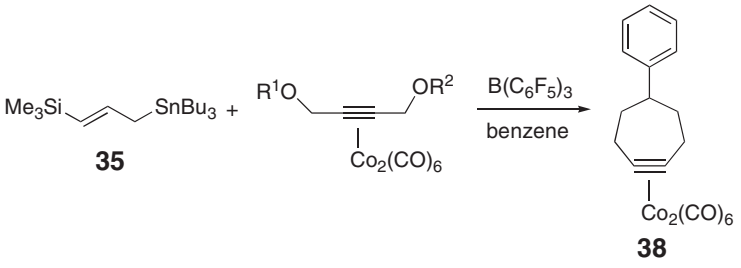
11.04.2.3 Allylic Metals as Nucleophiles

Allylic metals such as allylic silanes and allylic stannanes are also available for the allylation of propargylic position. For example, Green and his co-worker demonstrated a BF_3-catalyzed [4 + 3]-cycloaddition reaction of a 2-butyn-1,4-diyl ether complex with allylic dimetals **35** to give the corresponding cycloheptyne complexes **36** in high yields (Equation (15)).[24] Interestingly, slow addition of a Lewis acid catalyst $BF_3{\cdot}OEt_2$ to a more diluted solution of both the substrates affords fluoride derivatives **37** in good yields (Equation (15)). In the reactions of a propargylic dication equivalent with an allylic dimetal reagent **35**, a similar [4 + 3]-cycloaddition reaction proceeds in the presence of a

trapping reagent such as an aromatic compound.[25] Thus, when benzene is used as the solvent, it participates into the products **38** (Equation (16)).[25]



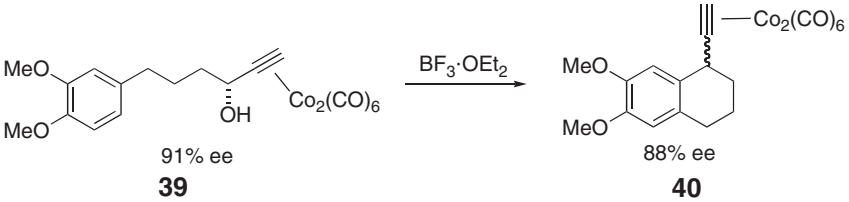
(15)



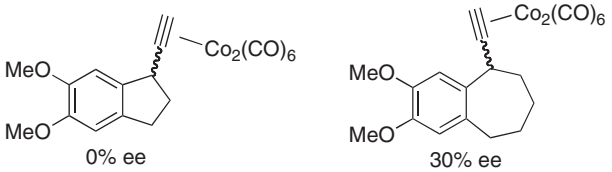
(16)

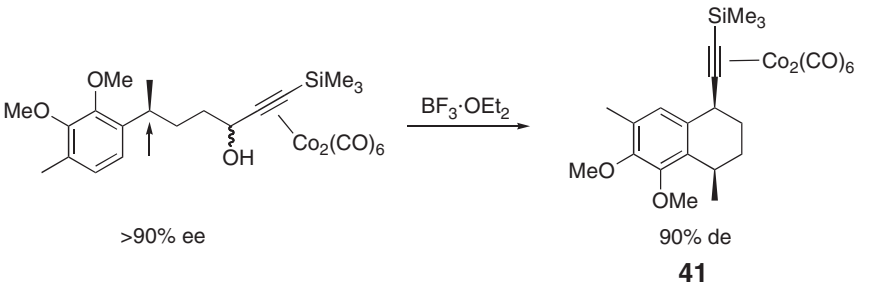
11.04.2.4 Aromatic Compounds as Nucleophiles

In 1994, Muehldorf and his co-workers carried out an intramolecular cyclization of chiral propargylic alcohols **39** coordinated with a dicobalthexacarbonyl moiety. Intramolecularly situated electron-rich benzenes successfully react with the propargylic alcohol to give cyclized products **40** in high yields (Equation (17)).[26] Interestingly, enantioselectivity of the products is dependent on the reaction temperature and the newly formed ring size of the products. In a similar way, Kocienski and his co-workers investigated diastereoselective intramolecular cyclization for the preparation of pseudopterosin G aglycone derivatives **41** in good yields with a high diastereoselectivity (Equation (18)).[27] Grove and his co-workers also reported a similar intramolecular cyclization, *cis*-fused octahydrophenanthrenes **42** being formed in good yields with a high diastereoselectivity (Equation (19)).[28]



(17)





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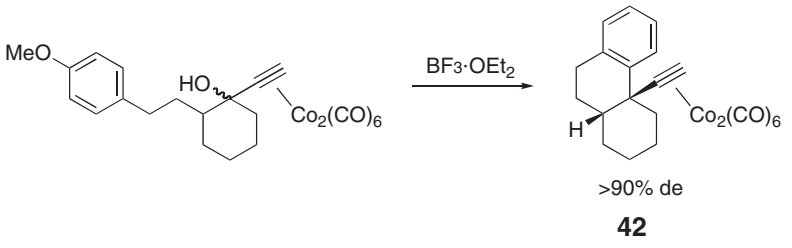
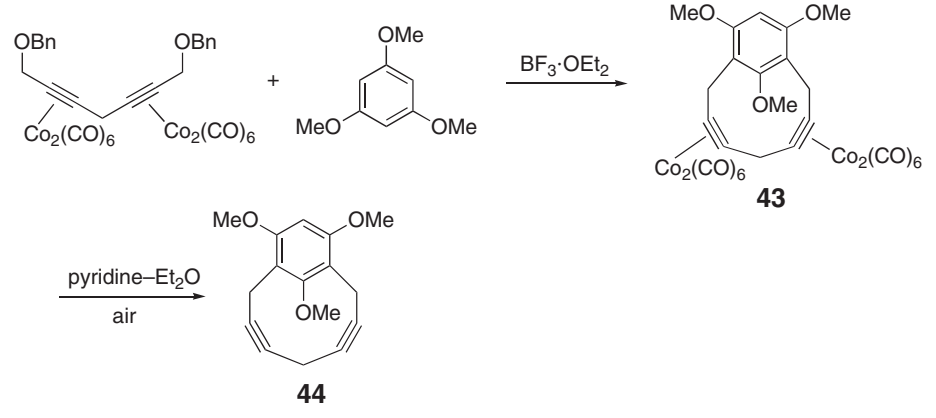
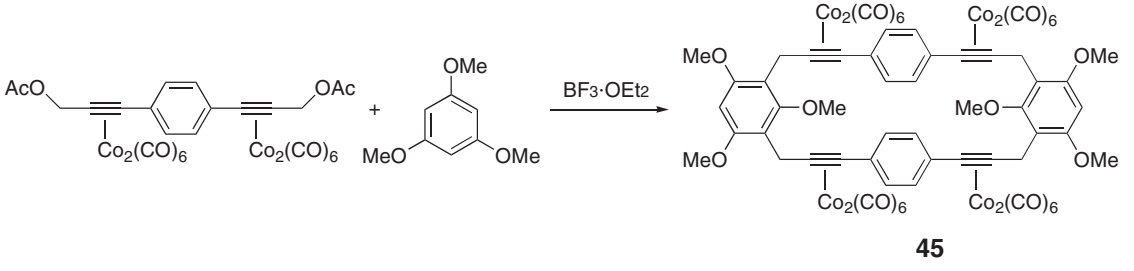


(19)

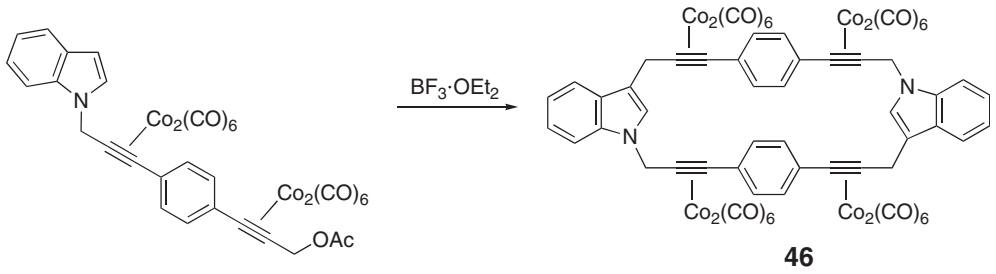
In 2000, Green and his co-worker extended the reaction of propargylic cations with aromatic compounds for the preparation of [7]metacyclophanediyne complexes **43** (Equation (20)).[29] After decomplexation, the corresponding [7]metacyclophanediyne parent molecule **44** is isolated in a good yield. Compound **44** is the smallest [*n*]metacyclophane including a triple bond reported so far. In addition, a one-pot synthesis of cyclophanetetrayne complexes **45** is successfully carried out from the corresponding bis(propargylic dicobalt) dication equivalents in good yields (Equation (21)).[30] Indolophanetetraynes **46** also are prepared by dimerization of propargylic cation equivalents in good yields (Equation (22)).[31]



(20)

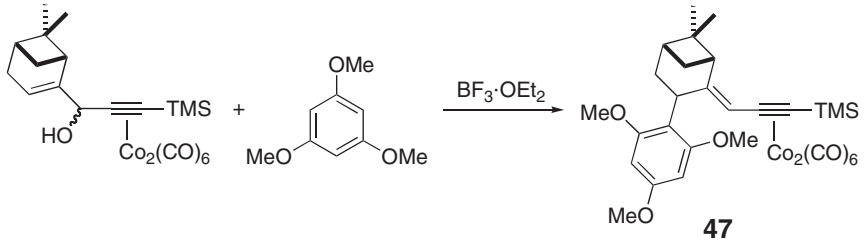


(21)



46 (22)

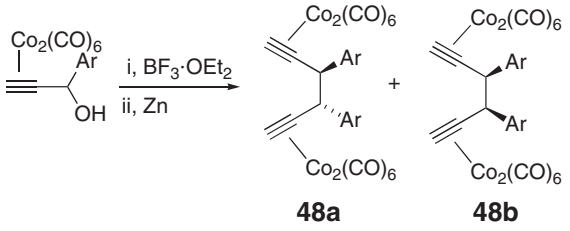
In 2003, Torre and his co-workers prepared new terpene-aromatic hybrids **47** in high yields in the reactions of cobalt-coordinated propargylic compounds, derived from commercial (*1R*)-myrtenal, with a variety of aromatic compounds (Equation (23)).[32] Interestingly, any terpene-aromatic hybrids are not produced from propargylic compounds without cobalt coordination.



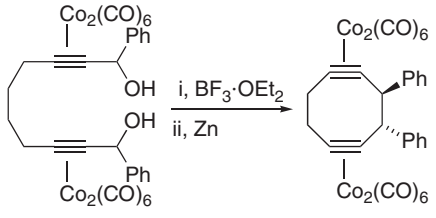
47 (23)

11.04.2.5 Radical Reaction

Since Nicholas and his co-workers studied the dimerization of propargylic radical stabilized by $Co_2(CO)_6$-coordination to give the corresponding 1,5-diynes **48** in good yields (Equation (24)),[33] propargylic radicals have been much used as a synthetic tool for the coupling reaction.[34,34a–34c] Intramolecular version of this reaction was reported which uses dipropargylic alcohols to give the corresponding cyclized products **49** in high yields (Equation (25)),[35] providing a direct method for 1,5-cyclooctadiynes.



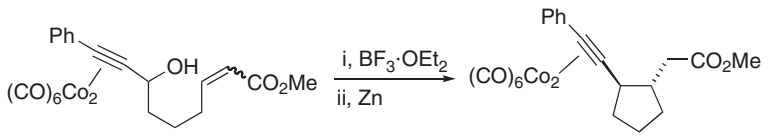
48a 48b (24)



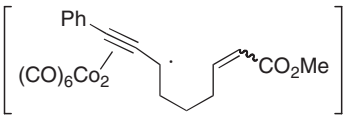
49 (25)

In 1997, Nicholas and his co-workers developed a novel radical cyclization, where propargylic radical **50** is trapped intramolecularly by activated alkenes (Equation (26)).[36,36a] This reaction proceeds with exclusive

trans-stereoselection in a 5-*exo* mode and with unusual regioselectivity, favoring either 5-*exo*- or 6-*endo*-cyclization depending on the radical stabilizing ability of the alkenyl substituents.



(26)

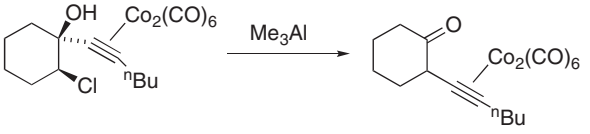


Propargylic radical

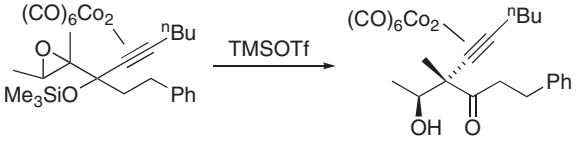
50

11.04.2.6 Migration Reaction

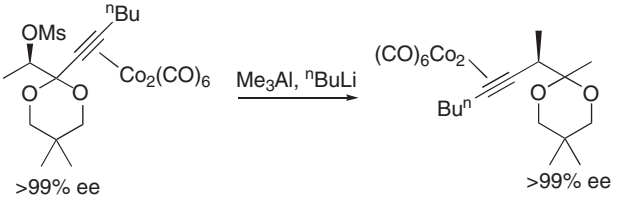
In 1996, Suzuki and his co-workers found a novel migration of an alkynyl group in coordinated dicobalthexacarbonyl–propargylic alcohols (Equations (27) and (28)).[37,37a] In this system, the migration occurs with the complete inversion of stereochemistry at the migration terminus that is chiral originally (Equation (29)). They employed the epoxide fragmentation/migration protocol for the preparation of the dihydrofuran having a side-chain chirality in the synthesis of several furaquinocins.[38]



(27)



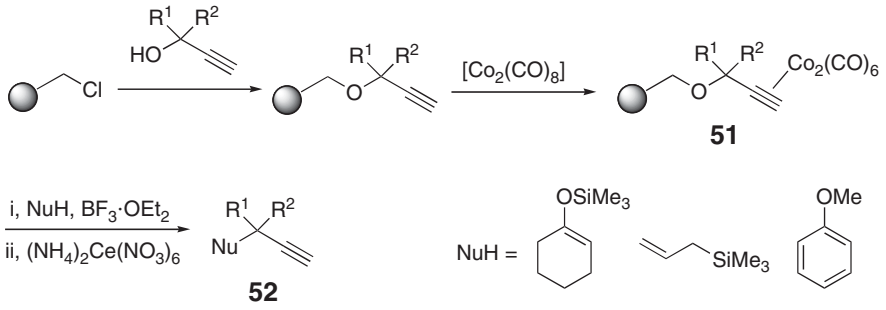
(28)



(29)

11.04.2.7 New Method for the Nicholas Reaction

Combinatorial chemistry and solid-phase synthesis have evolved in the last decade to become one of the most important techniques to save time for drug discovery. To reach its full potential, the solid-phase synthesis has to incorporate many versatile organometallic reactions developed over recent several decades. The first example of the Nicholas reaction on solid phase was reported by Kann and his co-workers in 2002, which involves the reaction of polymer-bound cobalt complexes **51** with various carbon-centered nucleophiles in the presence of a Lewis acid to



Scheme 6

give the propargylic substituted products **52** in good yields (Scheme 6).[39] Here, the Merrifield resin is attached to propargylic alcohols. The resulting -yne compounds bound to the resin are treated with $Co_2(CO)_8$; the produced complex reacts with carbon-centered nucleophiles such as enol silane, allylic silane, and electron-rich aromatic compounds to afford various substituted products after oxidative decomplexation. A distinct advantage is that unreacted substrate complexes remain attached to the resin and do not contaminate the final product. The method certainly has a potential to be more developed and applied to many organic syntheses.

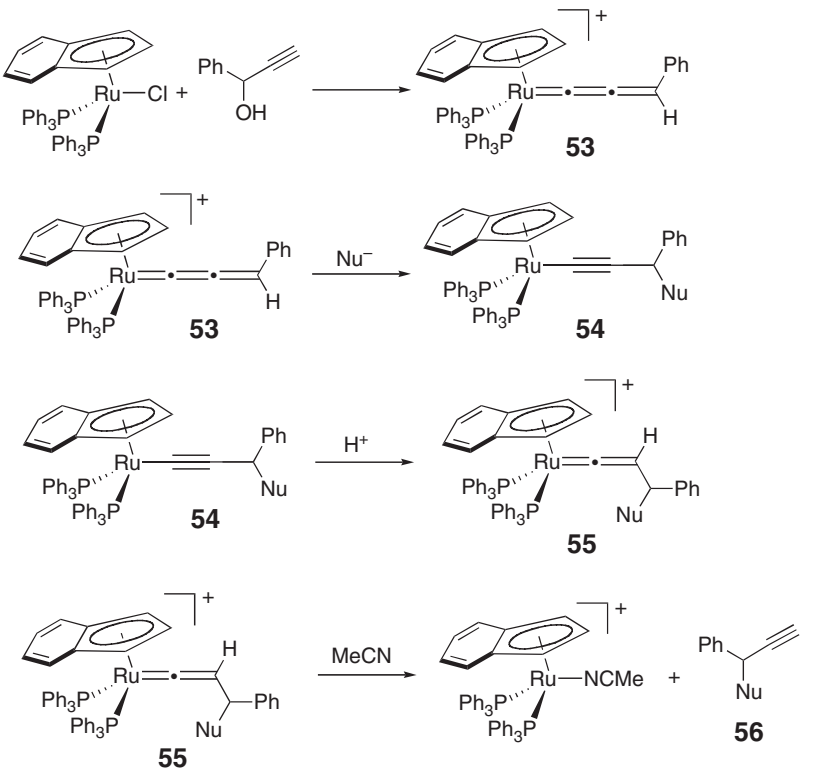
11.04.3 Stoichiometric Propargylic Alkylation of Propargylic Alcohols Assisted by Ruthenium Complexes

Since the first discovery of transition metal allenylidene complexes (M═C═C═C<) in 1976,[40,40a] these complexes have attracted a great deal of attention as a new type of organometallic intermediates.[41,41a–41d] Among a variety of such complexes, cationic ruthenium allenylidene complexes $Ru^+{=}C{=}C{=}CR^1R^2$, readily available by dehydration of propargylic alcohols coordinated to an unsaturated metal center, can be regarded as stabilized propargylic cation equivalents because of the extensive contribution of the ruthenium–alkynyl resonance form $Ru{-}C{\equiv}C{-}C^+R^1R^2$.[42,42a] Theoretical studies also indicate that C_α and C_γ of the allenylidene ligands can work as electrophilic centers, while C_β behaves as a nucleophilic site.[43,43a] In fact, "stoichiometric" reactions of ruthenium allenylidene complexes with a variety of nucleophiles have been reported, where nucleophiles attack either the allenylidene C_α or C_γ to afford Fischer-type carbenes or alkynyl complexes, respectively.[43,43a]

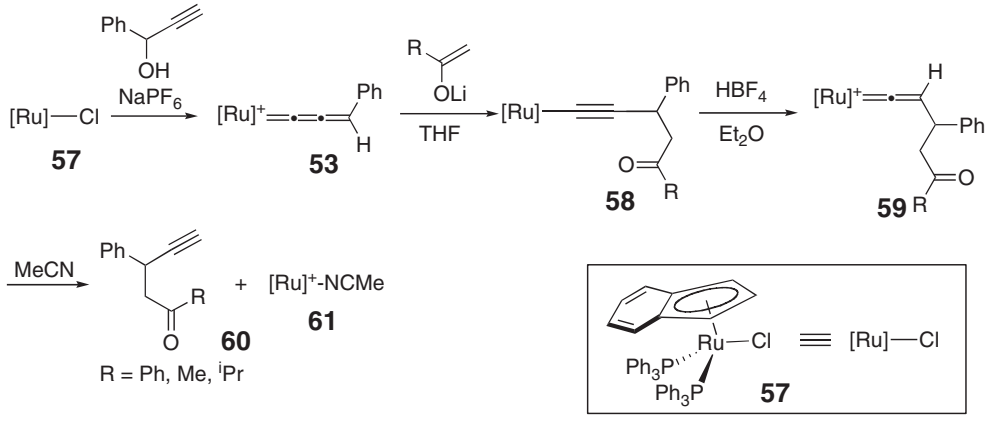
It is now well known that nucleophilic addition at C_γ occurs regioselectively when electron-rich and/or bulky metallic fragments are used, leading to a large variety of σ-alkynyl complexes $Ru{-}C{\equiv}C{-}C(Nu)R^1R^2$.[44] Recently, Gimeno and his co-workers have developed an interesting synthetic procedure for the propargylic substitution reaction of 2-propyn-1-ols mediated by the monoruthenium complex $[(\eta^5\text{-}C_9H_7)Ru(PPh_3)_2]^+$ (Scheme 7).[45] Here, allenylidene complexes **53** are formed in the first step and then subsequently transformed into the corresponding σ-alkynyl derivatives **54** which are selectively protonated to give vinylidene complexes **55**. Finally, demetallation from vinylidene complexes **55** by acetonitrile leads to functionalized terminal alkynes **56** in high yields. This synthetic methodology is considered to be an alternative to the Nicholas reaction described in the previous section,[1–4] although a stoichiometric amount of ruthenium complex is required and also several reaction steps are necessary to obtain propargylic-substituted products from propargylic alcohols. Quantitative recovery of the metal fragment represents an advantage compared with the Nicholas reaction where the metal auxiliary cannot be recovered after oxidative decomplexation.

Allenylidene complexes **53**, prepared by a stoichiometric reaction of ruthenium complex $[(\eta^5\text{-}C_9H_7)RuCl(PPh_3)_2]$ **57** with propargylic alcohols, react with lithium enolates in tetrahydrofuran (THF) to afford the neutral σ-alkynyl complexes **58** by the regioselective addition of the nucleophile at the C_γ atom. Treatment of σ-alkynyl complexes **58** with HBF_4 in diethyl ether generates vinylidene complexes **59** in high yields. Finally, demetallation proceeds rapidly in refluxing acetonitrile to afford γ-ketoacetylenes **60** and cationic nitrile complex **61** (Scheme 8).[46]

Other kinds of propargylic-substituted products were prepared by this procedure. When Grignard reagents such as allylic and homoallylic magnesium bromides are used in place of lithium enolates as carbon-centered nucleophiles,



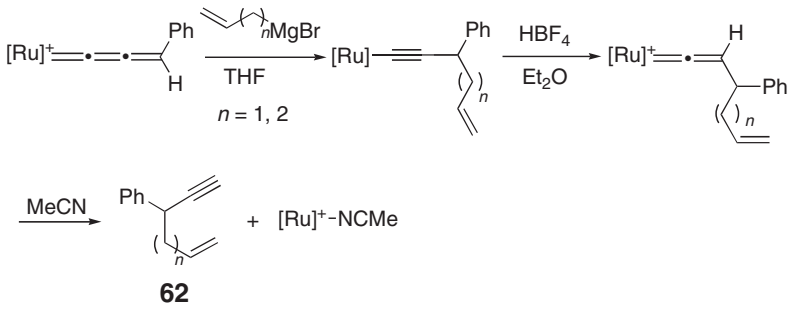
Scheme 7



Scheme 8

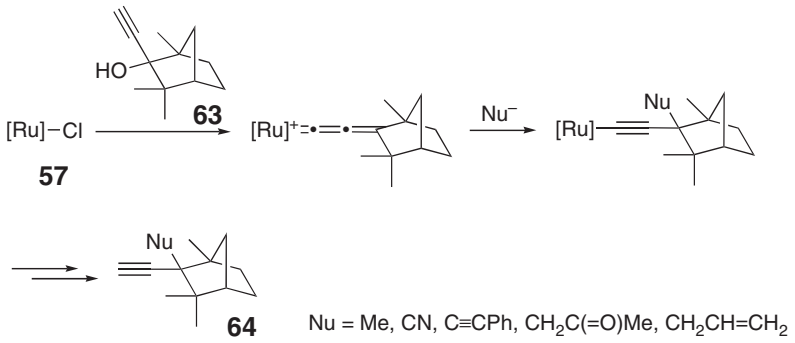
the corresponding 1,5- and 1,6-enynes **62** are obtained in good yields (Scheme 9).[47] This synthetic approach can be regarded as a formal coupling reaction of propargylic moiety with propene and 1-butene.

Diastereoselective propargylic substitution reactions of optically active propargylic alcohols such as 2-*exo*-ethynyl-1,3,3-trimethyl-2-*endo*-norbornanol **63** with carbon-centered nucleophiles were investigated using ruthenium complex **57** in a stoichiometric amount (Scheme 10).[48] In addition to lithium enolates and Grignard reagents, sodium cyanide, methyllithium, and lithium acetylide are available as the carbon-centered nucleophiles. In all cases, the corresponding substituted products **64** are obtained in high yields with high diastereoselectivity. The same method



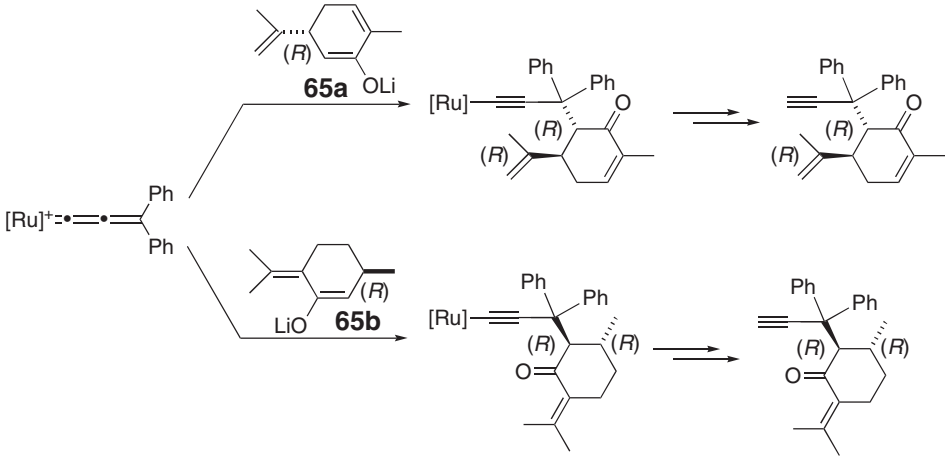
62

Scheme 9



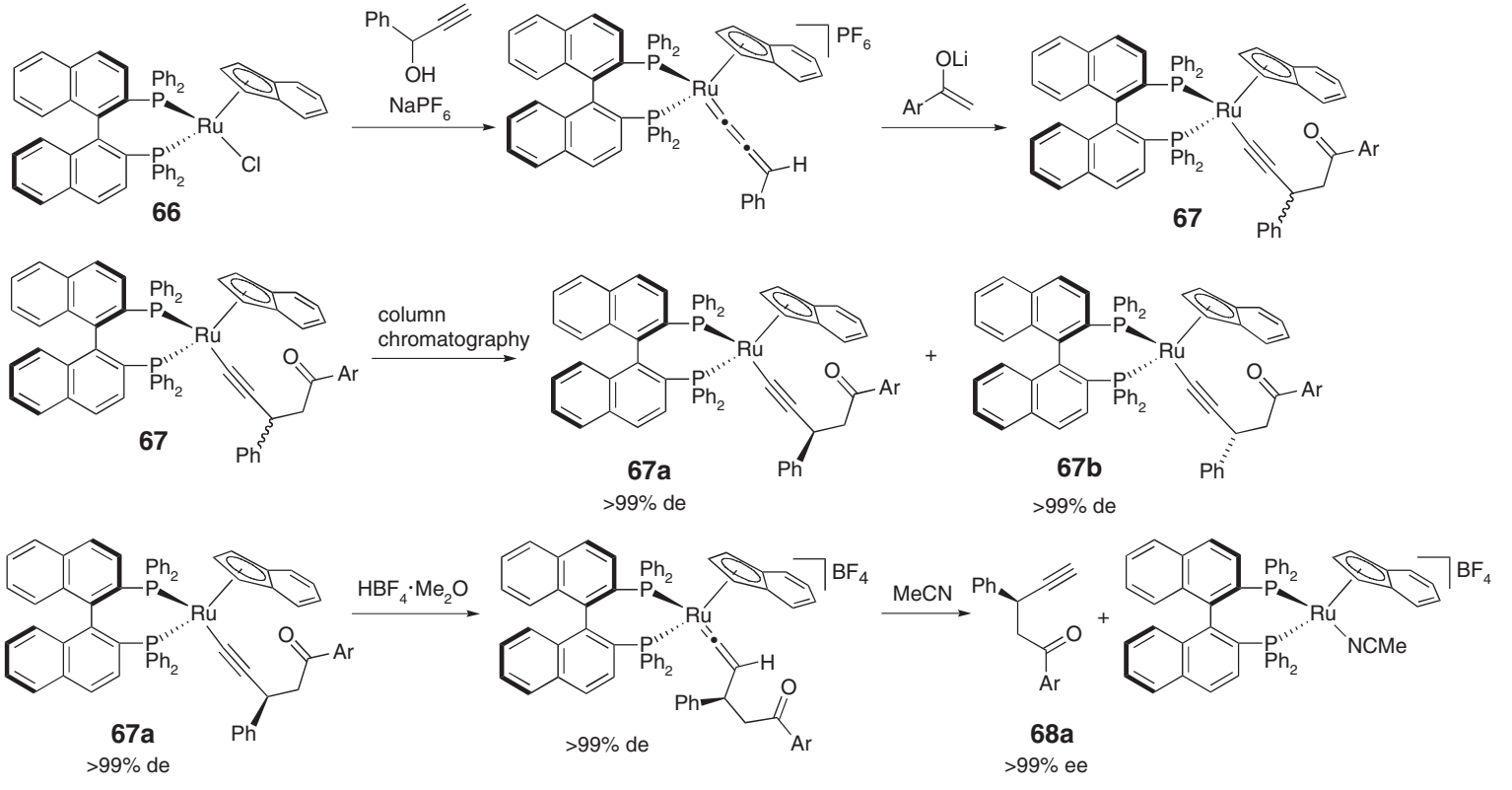
Scheme 10

allows diastereoselective propargylic substitution reactions of achiral propargylic alcohols with optically active lithium enolates **65** derived from carvone and pulegone (Equation (30)).[48a]

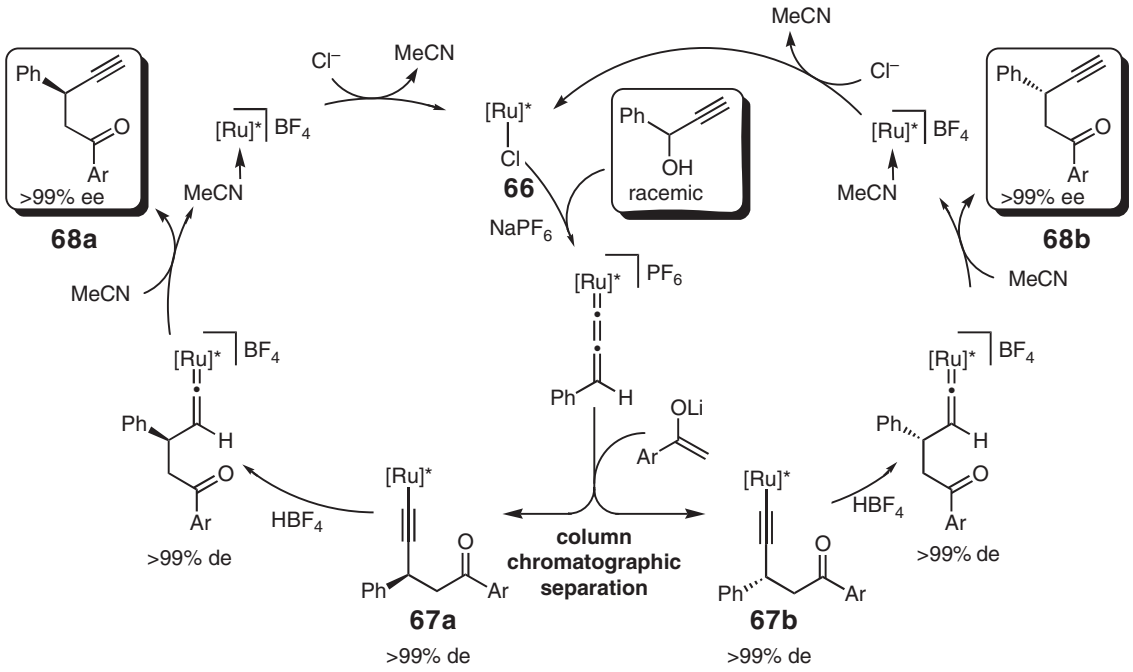


(30)

Enantioselective propargylic substitution reactions of racemic propargylic alcohols with lithium enolates have been achieved by Nishibayashi and Uemura using ruthenium complex **66** bearing BINAP as a chiral ligand.[49] The column chromatographic separation of two diastereoisomers of σ-alkynyl complexes **67** gives the enantiomerically pure propargylic substituted products **68** bearing completely opposite configurations with almost 100% ee (Scheme 11).


66
NaPF6
PF6
OLi
Ar
67
column
chromatography
67a
>99% de
67b
>99% de
HBF4·Me2O
BF4
MeCN
NCMe
68a
>99% ee

Scheme 11



Scheme 12

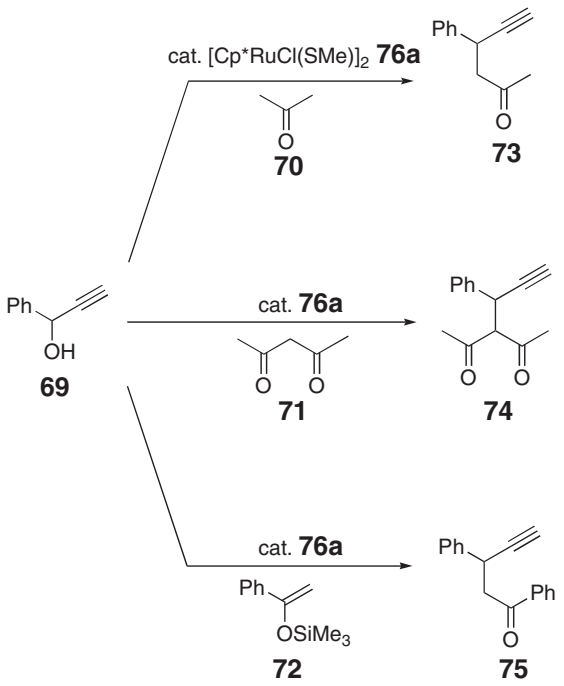
Thus, a synthetic cycle for the formation of enantiomerically pure propargylic alkylated compounds from an achiral propargylic alcohol has been accomplished by starting from the ruthenium–BINAP complex **66** (Scheme 12). This stepwise reaction provides the first synthetic approach to highly enantioselective propargylic substitution reactions.

11.04.4 Catalytic Propargylic Alkylation of Propargylic Alcohols and their Derivatives

As described in previous sections, the Nicholas reaction has been used as an effective tool for the propargylic substitution reaction of propargylic alcohols and their derivatives with heteroatom-centered nucleophiles as well as carbon-centered ones to give the corresponding propargylic substituted products in high yields.[1–4] This reaction, however, has some drawbacks: a stoichiometric amount of $Co_2(CO)_8$ is required, and several steps are necessary to obtain propargylic substituted products from propargylic alcohols via cationic propargyl complexes $[(propargyl)Co_2(CO)_6]^+$.[1–4] On the other hand, several catalytic propargylic substitution reactions with carbon-centered nucleophiles have been recently reported, where some transition metal complexes work as effective catalysts to give the corresponding propargylic compounds from propargylic alcohols or its derivatives. The type of available nucleophiles, however, depends much on the nature of the transition metal complexes. In this section, recent examples of propargylic substitution reactions catalyzed by transition metals such as ruthenium, iridium, and rhenium complexes are summarized.

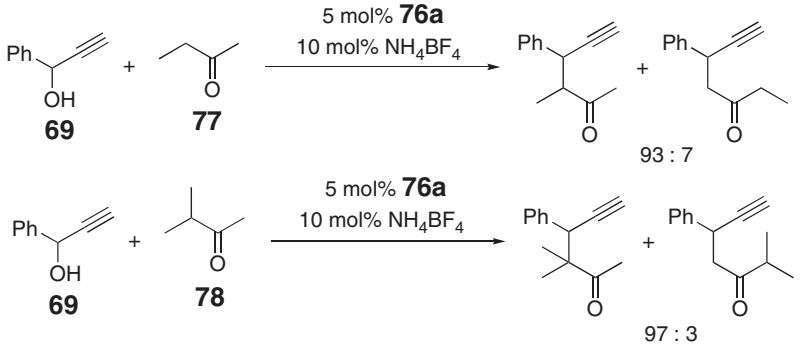
11.04.4.1 Ruthenium-catalyzed Reaction

In 2001, Nishibayashi *et al.* found a ruthenium-catalyzed efficient propargylic alkylation of propargylic alcohols **69** with carbon-centered nucleophiles such as ketones **70**, β-diketones **71**, and silyl enol ethers **72** to give the corresponding propargylic alkylated products **73–75** in high yields with a significantly high regioselectivity as shown in Scheme 13.[50] It is noteworthy that the reactions are catalyzed only by thiolate-bridged diruthenium complexes **76** and not by monoruthenium complexes, providing a facile preparative method for alkynes



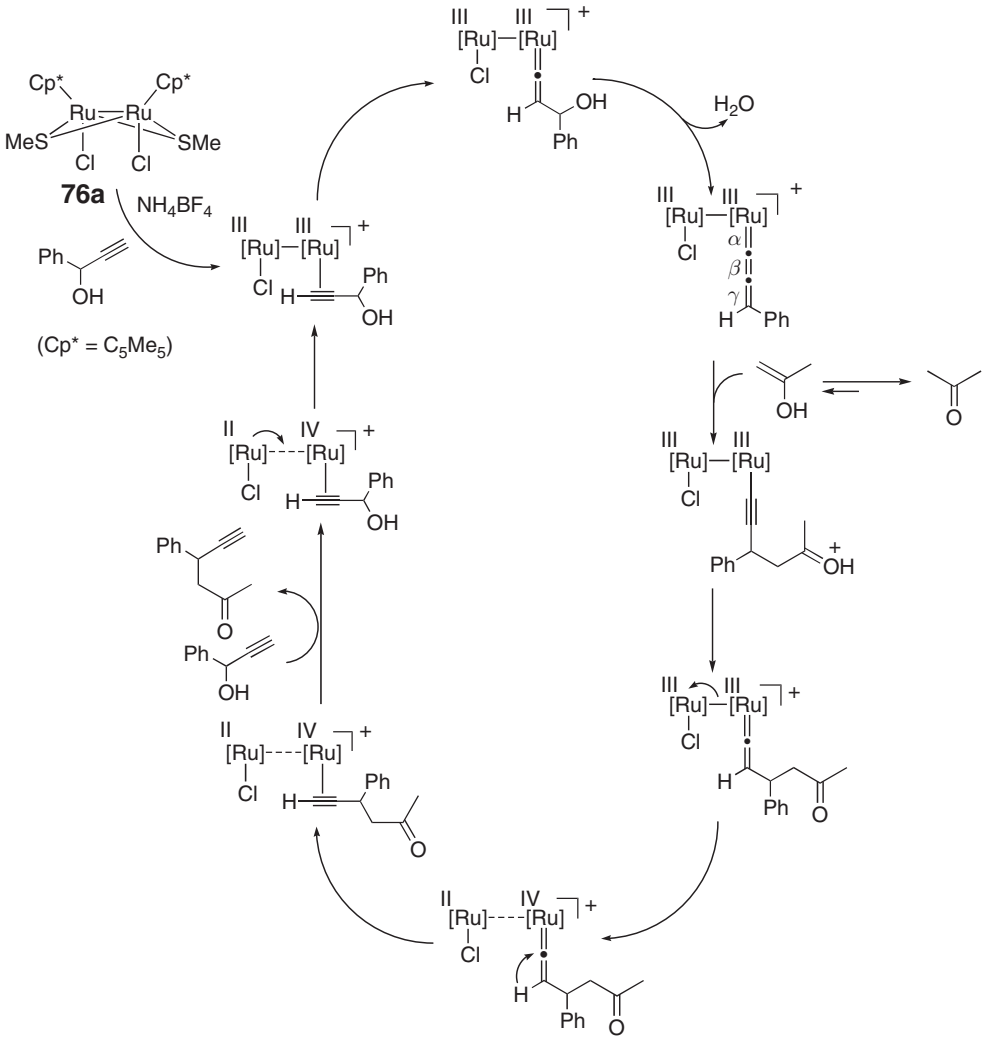
Scheme 13

functionalized at the propargylic position directly from propargylic alcohols. Results of some stoichiometric and catalytic reactions indicate that this novel propargylic substitution proceeds via allenylidene complexes as key intermediates. A proposed pathway is shown in Scheme 14. This propargylic alkylation proceeds smoothly under neutral and extremely mild reaction conditions, in sharp contrast to the allylic alkylation catalyzed by a variety of transition metal complexes where a stoichiometric amount of a base is required to activate carbon-centered nucleophiles.[51,51a] Interestingly, a striking regioselectivity is observed when unsymmetrical simple ketones **77** and **78** are used as carbon-centered nucleophiles (Equation (31)). Thus, the propargylic alkylation occurs at the more encumbered α-site of the ketones.

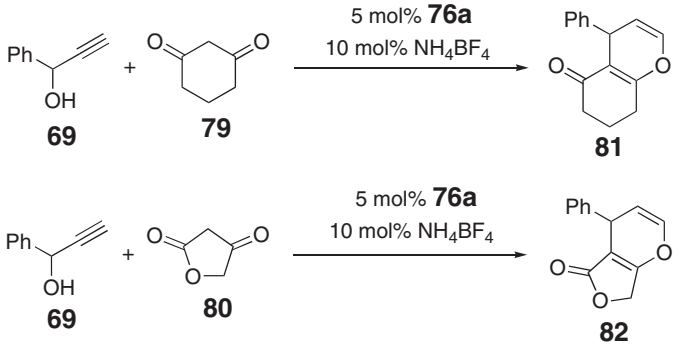


(31)

Interestingly, the reactions of propargylic alcohols with cyclic 1,3-dicarbonyl compounds **79** and **80** in the presence of a catalytic amount of the thiolate-bridged diruthenium complexes give either the corresponding 4,6,7,8-tetrahydrochromen-5-ones **81** or 4*H*-cyclopenta[*b*]pyran-5-ones **82** in high yields with complete regioselectivity (Equation (32)).[52] This catalytic cycloaddition provides a simple and one-pot synthetic protocol for a variety of substituted chromenones and cyclopenta[*b*]pyranones.

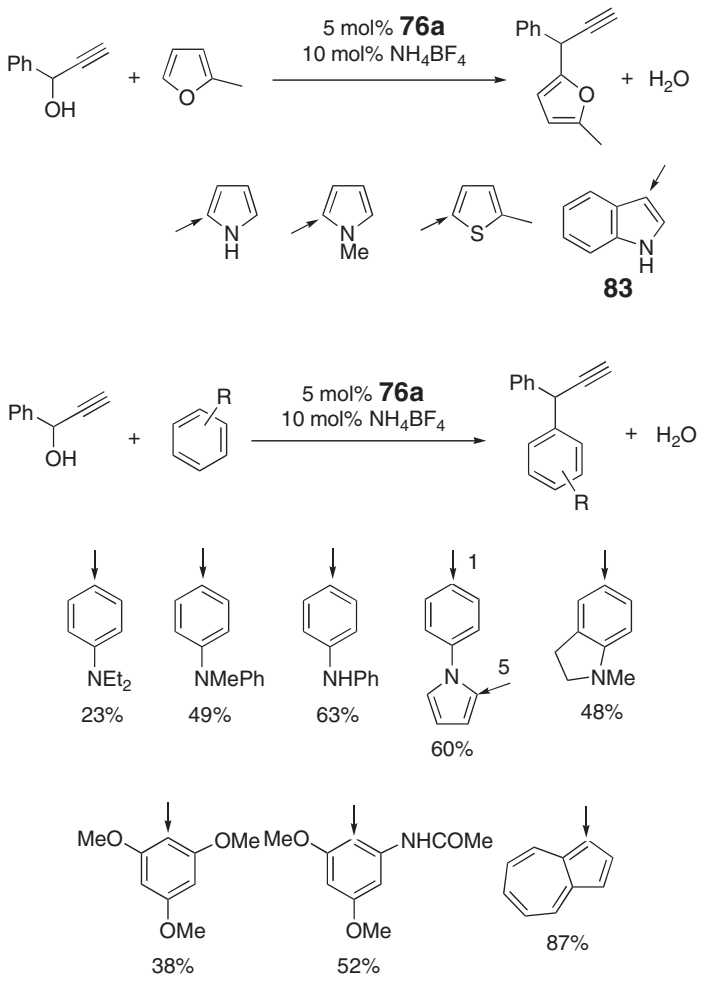


Scheme 14



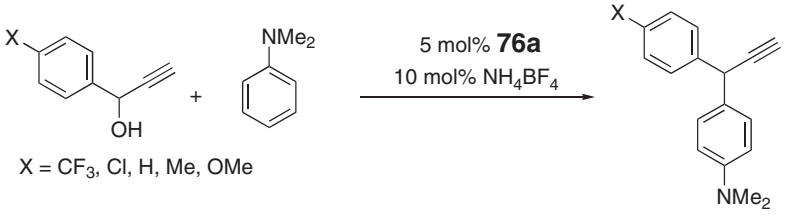
(32)

The thiolate-bridged diruthenium complexes promoted the propargylation of heteroaromatic compounds such as furans, thiophenes, and pyrroles with propargylic alcohols to give the corresponding propargylated aromatic compounds in good yields (Scheme 15).[53] In all cases, the propargylation occurs selectively at the α-position of the



Scheme 15

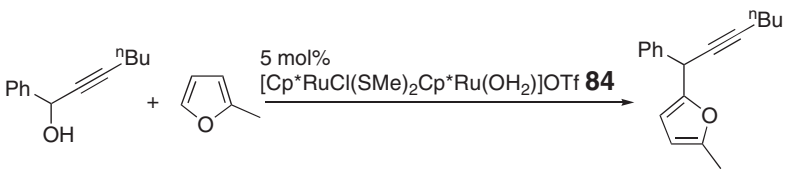
heterocyclic rings, while a β-propargylated indole is produced by the reaction with indole **83**. The regioselectivity observed here is exactly in accord with that of the electrophilic substitution reactions of heteroaromatic compounds. Not only heteroaromatic compounds but also benzene derivatives are available for this propargylation (Equation (33)). In addition to various *N*-substituted anilines, electron-rich arenes such as 3,5-dimethoxyacetanilide, 1,3,5-trimethoxybenzene, and azulene are available for this propargylation.



(33)

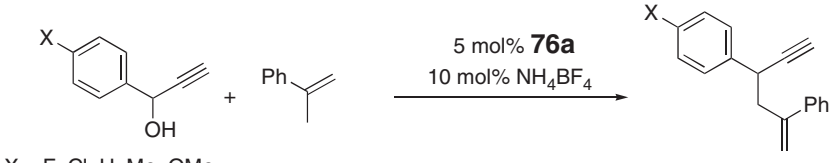
Use of cationic thiolate-bridged diruthenium complexes **84** promotes the catalytic propargylation of aromatic compounds with propargylic alcohols bearing not only a terminal alkyne but also an internal alkyne unit (Equation (34)).[54] A variety of propargylated aromatic compounds are isolated in high to excellent yields. Although

direct evidence of the reactive intermediates remains yet to be studied, the catalytic propargylation is considered to proceed via (η^3-propargyl)ruthenium species.

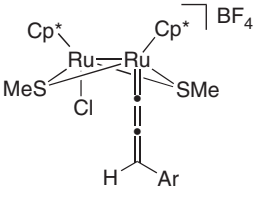


(34)

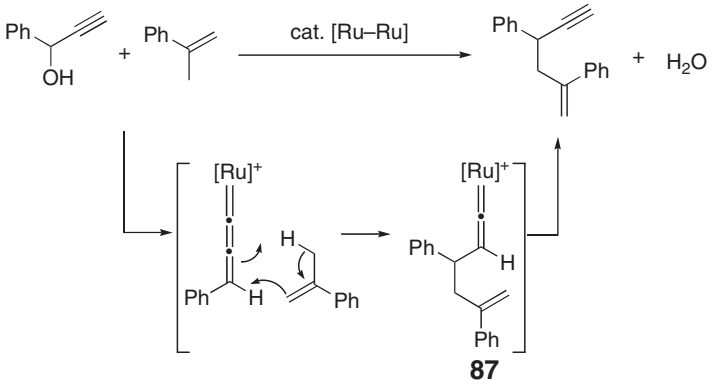
The reactions of propargylic alcohols with alkenes in the presence of a catalytic amount of the thiolate-bridged diruthenium complexes afford the corresponding 1-en-5-ynes **85** in moderate yields (Equation (35)).[55] This carbon–carbon bond-forming reaction between propargylic alcohols and alkenes is considered to proceed via allenylidene intermediates such as **86**. Thus, the C_β–C_γ double bond of the allenylidene complex reacts with α-methylstyrene, where the allenylidene complex works as an enophile, to afford the corresponding vinylidene complex **87** via allenylidene–ene reaction as shown in Scheme 16. Intramolecular reactions of propargylic alcohols **88** bearing an alkene unit at a suitable position proceed smoothly to give the corresponding substituted chromanes **89** in high yields as a mixture of two diastereomers, the *syn*-isomer being major (Equation (36)). Interestingly, use of diruthenium complexes bearing sterically more demanding groups such as **76b** (R = ^{n}Pr) and **76c** (R = ^{i}Pr) improves the diastereoselectivity of the substituted chromanes dramatically, although a prolonged reaction time is required.



(35)

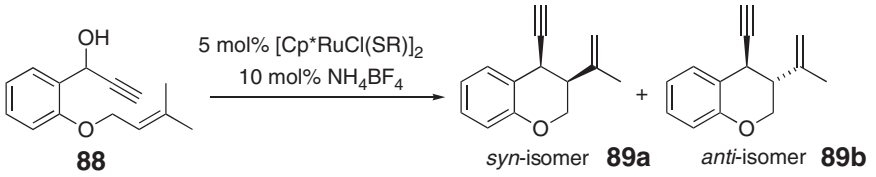


Allenylidene complexes
86

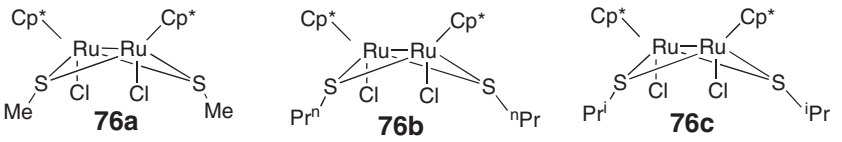


87

Scheme 16



(36)

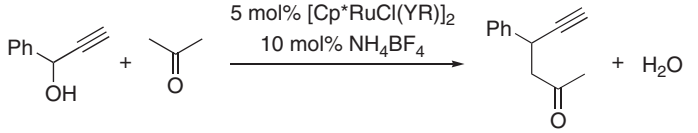


74% yield (2 h)
syn : *anti* = 3.7 : 1 (78% de)

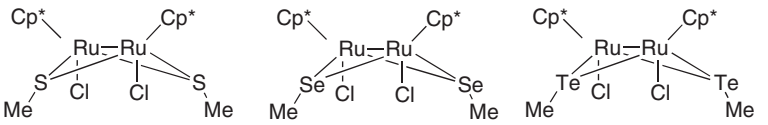
84% yield (5 h)
syn : *anti* = 7.1 : 1 (87% de)

74% yield (20 h)
syn : *anti* = 19 : 1 (95% de)

These novel propargylic substitution reactions are considered to proceed via allenylidene complexes as key intermediates, where a synergistic effect of two ruthenium atoms in the thiolate-bridged diruthenium complexes is one of the essential factors to promote the catalytic reactions.[56,56a–56d] To get an insight into the reaction mechanism, a series of chalcogenolate-bridged diruthenium complexes **76d** and **76e** are prepared. Their catalytic activities toward the propargylic substitution reactions are compared with those using the corresponding thiolate-bridged diruthenium complexes **76a**.[57,57a] As a result, it is revealed that S- and Se-bridged complexes **76a** and **76d** are quite effective as catalysts for many propargylic substitution reactions, while Te-bridged ones **76e** do not show any catalytic activity (Equation (37)). By comparing these results with the structure of these complexes determined by X-ray as well as their redox potentials, it is proposed that the charge transfer from one Ru atom to the other may be one of the important factors for the above catalytic reactions, one Ru moiety working as an electron pool or a mobile ligand to another Ru moiety (synergistic effect) (Scheme 17).



(37)

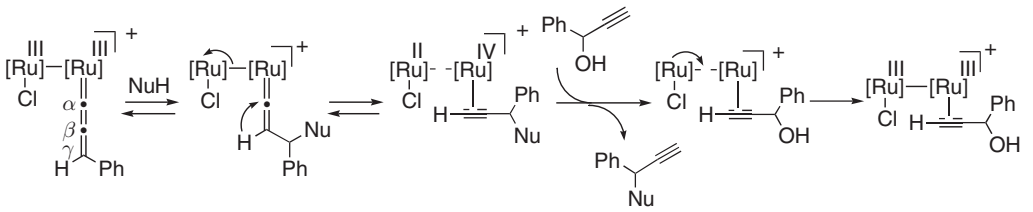


88% yield
76a

95% yield
76d

0% yield
76e

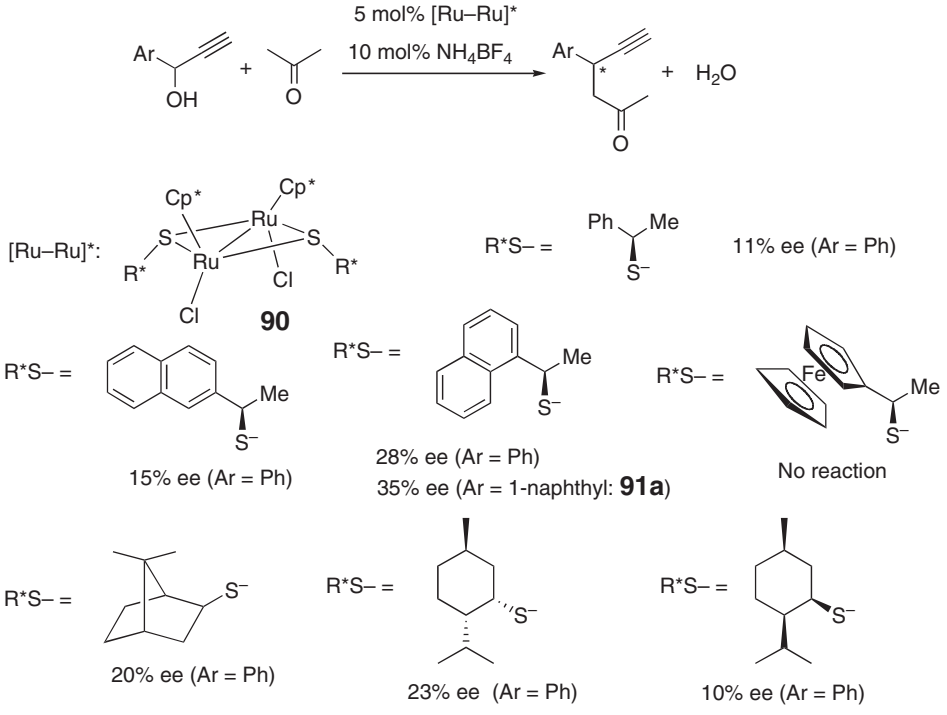
The enantioselective propargylic alkylation of propargylic alcohols with acetone is investigated in the presence of chiral thiolate-bridged diruthenium complexes **90**.[58] The best enantioselectivity (35% ee) is observed in the reaction



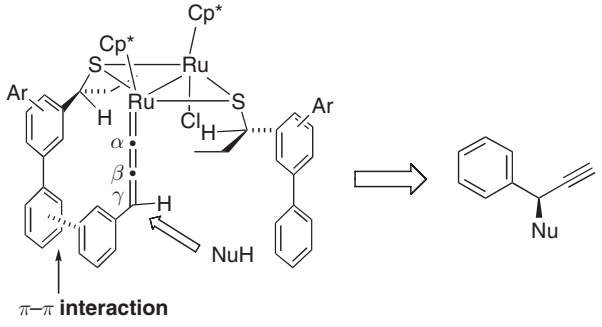
Scheme 17

of 1-(1-naphthyl)-2-propyn-1-ol (**91a**: Ar = 1-naphthyl) with acetone in the presence of a complex bearing a 1-naphthylethylthiolato moiety as a chiral ligand (Scheme 18). This is the first example of enantioselective propargylic substitution reaction catalyzed by transition metal complexes, although the enantioselectivity is not yet satisfactory. It is noteworthy that the chiral thiolate-bridged ligands work to control the chiral environment around the diruthenium site.

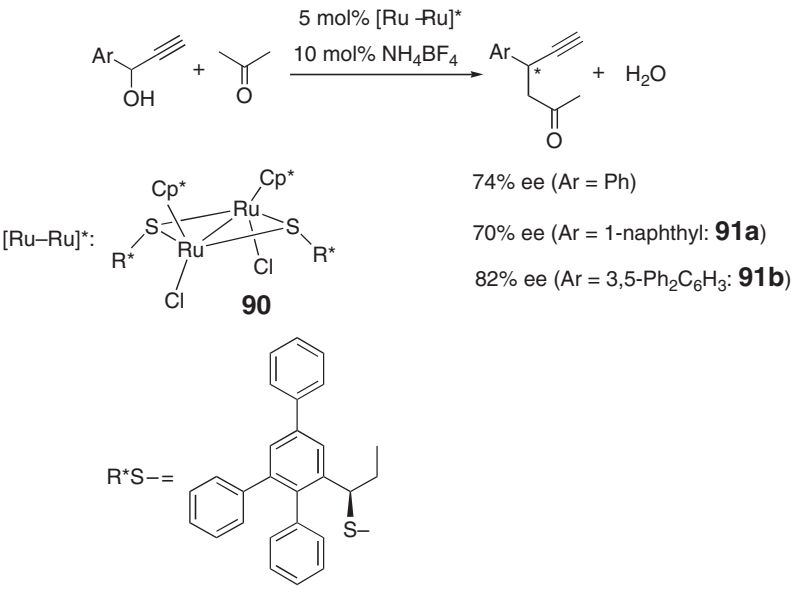
More recently, a different concept other than steric repulsion between substrates and chiral ligands is introduced to improve the enantioselectivity; thus, a new type of chiral alkanethiolato ligands having a phenyl ring (second generation chiral ligands) has been prepared which might interact with a phenyl ring of ruthenium–allenylidene complexes by a π–π interaction.[58a] In this system, nucleophilic attack of nucleophiles on the Cγ of the allenylidene ligand should occur from the side which is not blocked by a chiral ligand as shown in Scheme 19. In fact, a significantly high enantioselectivity (up to 82% ee) is observed in the catalytic propargylic alkylation (Scheme 20). The development of a more suitable catalytic system is still awaited.



Scheme 18



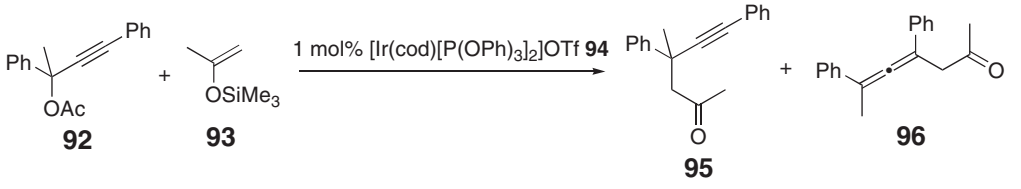
Scheme 19



Scheme 20

11.04.4.2 Iridium-catalyzed Reaction

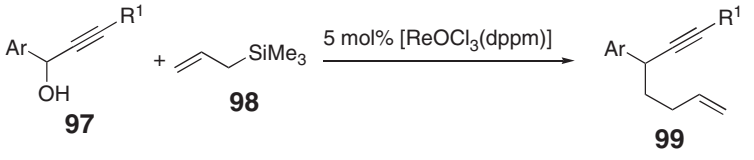
In 2002, Matsuda and his co-workers reported the propargylic alkylation of propargylic esters **92** with silyl enol ethers **93** catalyzed by [Ir(cod)[P(OPh)$_3$]$_2$]OTf **94** to give the corresponding alkylated products **95** in high yields (Equation (38)).[59] In this reaction system, pretreatment of the iridium complex with 1 atm of H_2 is necessary to carry out the catalytic reaction. The corresponding allenyl-type products **96** are concomitantly formed in some cases. Ketene acetal and ketene monothioacetal can be used as carbon-centered nucleophiles to form only the corresponding alkylated products in excellent yields. When the reaction of optically active propargylic acetate with silyl enol ether is carried out under the same reaction conditions, only a racemic alkylated product is obtained as the sole product. This result indicates that the catalytic alkylation proceeds via some cationic species derived from propargylic esters.



(38)

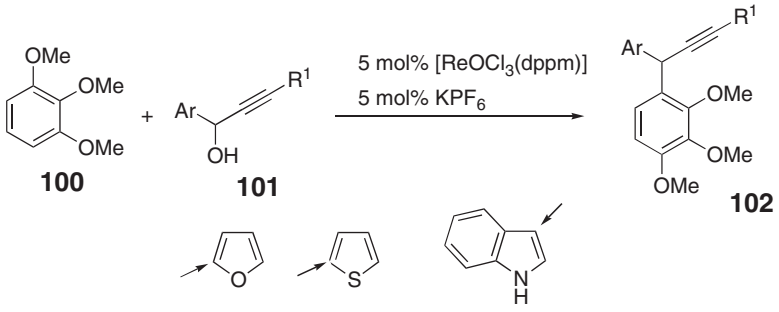
11.04.4.3 Rhenium-catalyzed Reaction

In 2003, Toste and his co-worker reported rhenium-catalyzed propargylic allylation of propargylic alcohols **97** with allylsilanes **98** to give the corresponding 1-en-5-ynes **99** in high to excellent yields (Equation (39)).[60] Various allylic silanes are available as carbon-centered nucleophiles, but propargylic alcohols bearing only an internal alkyne moiety can be used as substrates. The stability of the high oxidation state of rhenium complex allows the recovery of the catalyst in some cases. The recovered rhenium complex can be reused in this catalytic reaction without a noticeable deterioration in activity.



(39)

A rhenium complex also promotes the propargylation of aromatic compounds **100** with propargylic alcohols **101** to give the corresponding propargylated aromatic compounds **102** in good yields (Equation (40)).[61] Not only benzene derivatives such as 1,2,3-trimethoxybenzene, anisole, and phenols but also heteroaromatic compounds such as furan, thiophene, and N-tosylindole are available for this propargylation. Regioselectivity of this propargylation is consistent with that of usual electrophilic aromatic substitution reactions. In this reaction system, only propargylic alcohols bearing an internal alkyne moiety can be used as the substrates. Toste and his co-workers also succeeded in a short total synthesis of (±)-podophyllotoxin from propargylic alcohols and safrole using this rhenium-catalyzed reaction system.[61]

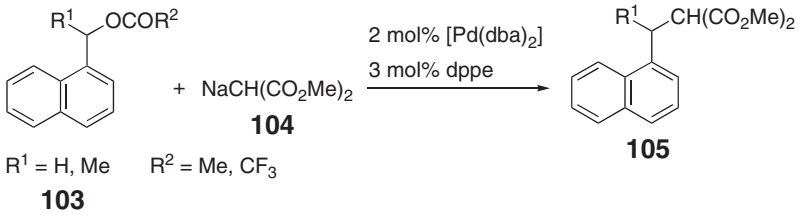


(40)

11.04.5 Catalytic Benzylic Alkylation of Benzylic Alcohols and their Derivatives

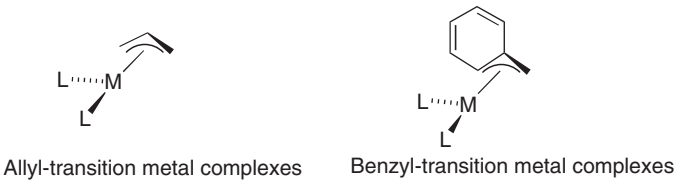
In sharp contrast to the transition metal-catalyzed allylic alkylation of allylic alcohols and their derivatives (see Chapter 11.03) where η^3-allyl-transition metal complexes are key intermediates, the benzylic alkylation of benzylic alcohols and their derivatives catalyzed by transition metal complexes has been quite unexplored, although η^3-benzyl-transition metal complexes have often been considered to explain the regioselectivity of transition metal-catalyzed addition to vinylarenes (Scheme 21).[62,63,63a]

In 1992, Legros and Fiaud found palladium-catalyzed benzylic alkylation of naphthylmethyl and 1-naphthylethyl esters **103** with sodium dimethyl malonate **104** in dimethylformamide (DMF) to give the corresponding benzylic alkylated products **105** in high yields (Equation (41)).[64] When trifluoroacetyl group is used as a leaving group of the ester partner, catalytic alkylation proceeds quite smoothly even at room temperature. In this reaction system, no reaction occurs with benzylic acetates.



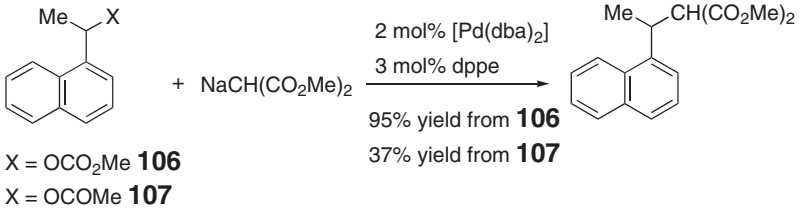
(41)

In this catalytic alkylation, naphthylethyl carbonates **106** are shown to be more reactive than the corresponding naphthyl acetates **107** under the same reaction conditions (Equation (42)).[65] Other naphthylethyl carbonates can be

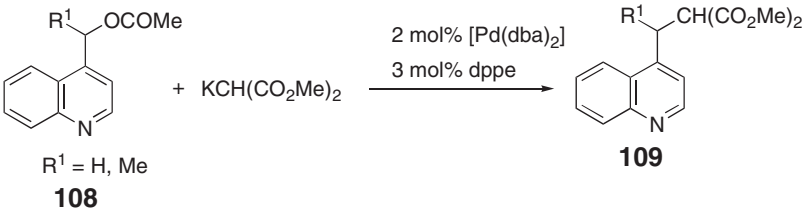


Scheme 21

used as substrates for the palladium-catalyzed benzylic alkylation. Unfortunately, no reaction takes place between some naphthylethyl carbonates such as 1-(9-anthracyl)ethyl and 1-(pyrenyl)ethyl carbonates and dimethyl sodiomalonate. Quinolylmethyl, 1-(isoquinolyl)ethyl, and 1-(quinolyl)ethyl acetates **108** react with the dimethyl malonate anion to give the corresponding alkylated products **109** in good yields together with the formation of side-products (Equation (43)).[66] When THF is used as the solvent in place of DMF, formation of the side-products is suppressed and the yields of the alkylated products increase.

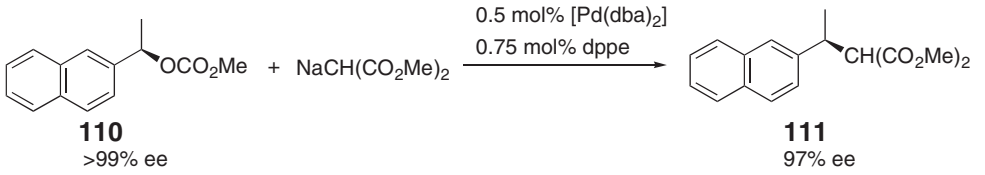


(42)



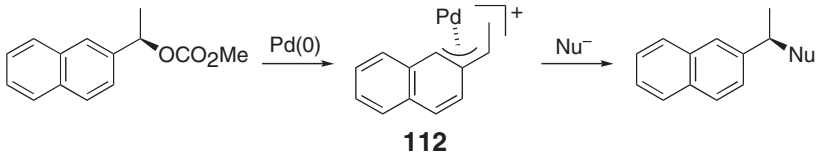
(43)

When the enantiomerically pure 1-naphthylethyl and 2-naphthylethyl carbonates are used as substrates, chiral benzylic alkylated products are obtained in high yields with high enantioselectivity (Equation (44)).[65] Introduction of a methoxy group at 6-position of naphthalene ring decreases both reactivity and enantioselectivity under the same reaction conditions. The stereochemistry is also investigated to obtain some information on the reaction mechanism. When an optically active (*R*)-2-naphthylethyl carbonate **110** is allowed to react with dimethyl sodiomalonate in the presence of a catalytic amount of a palladium complex in DMF, the alkylated product **111** bearing *S*-configuration is isolated with 97% ee (Equation (44)). Thus, net retention of configuration is observed (Scheme 22). This catalytic alkylation is considered to proceed with a double inversion mechanism by assuming that the nucleophilic attack of dimethyl sodiomalonate to naphthyl cationic complex **112** proceeds via inversion of configuration in analogy with the Tsuji–Trost allylic substitution reactions of allylic alcohol derivatives with nucleophiles.[65]



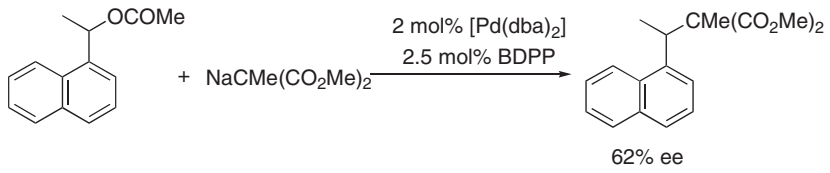
(44)

Legros and Fiaud also developed enantioselective benzylic alkylation of 1-naphthylethyl esters with dimethyl sodiomalonate and dimethyl sodiomethylmalonate in the presence of a catalytic amount of a palladium complex and a chiral diphosphine such as BINAP **113**, Chiraphos **114**, or DIOP **115** (Equation (45)).[67] Use of BDPP **116** as a chiral

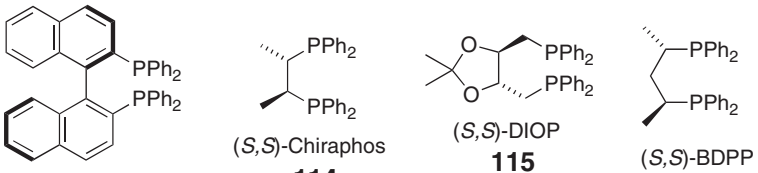


Scheme 22

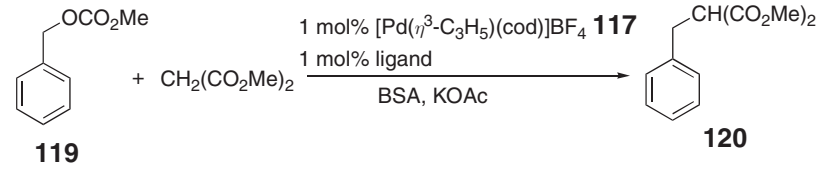
ligand in the reaction of 1-naphthylethyl acetate with dimethyl sodiomethylmalonate gives the corresponding alkylated product with 62% ee. Further investigation and development focusing on organic synthesis are awaited.



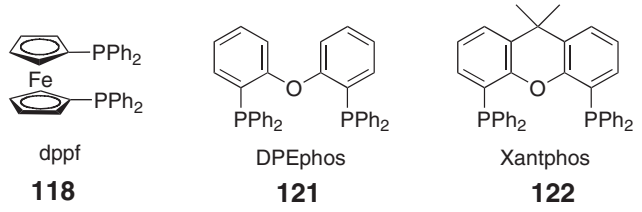
(45)



As described above, the reaction system by using a palladium complex and dppe displayed a catalytic activity toward benzylic alkylation of naphthylmethyl acetates and carbonates and quinolylmethyl carbonates. However, this reaction system failed to promote the benzylic alkylation of benzylic carbonates and acetates. After detailed study, Kuwano and his co-workers have found that the combination of [Pd(η^3-C_3H_5)(cod)]BF_4 **117**, the ligand dppf **118**, and *N,O*-bis(trimethylsilyl)acetimidate (BSA) promotes the benzylic alkylation of not only naphthylmethyl carbonates but also benzylic carbonates **119** with dimethyl malonate to give the corresponding benzylic alkylated products **120** in good yields (Equation (46)).[68] In this case, the choice of the ligand on the palladium complex is one of the most important factors, where the diphosphines bearing a larger P–Pd–P angle such as DPEphos **121** and Xantphos **122** were also found to work as suitable ligands. Reactions of various combinations of benzylic carbonates with 3-substituted malonates under the same reaction conditions proceeded quite smoothly, the alkylated products being obtained in high yields in all cases. In addition, acetamidomalonate and methoxymalonates can be used as the carbon-centered nucleophiles.

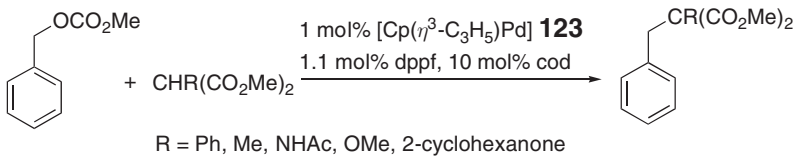


(46)



Kuwano and his co-workers also found a more effective reaction system by using [Cp(η^3-C_3H_5)Pd] **123** in place of [Pd(η^3-C_3H_5)(cod)]BF_4 **117** as a palladium catalyst precursor.[69] In this reaction system, benzylic alkylation of benzyl carbonates with a variety of active methine compounds gives alkylated products in excellent yields even in the absence of a base (Equation (47)). Addition of a catalytic amount of 1,5-cyclooctadiene (cod) to this reaction system promotes benzylic alkylation of benzylic carbonates with a variety of active methine compounds to give the

corresponding alkylated products in high to excellent yields. Cod is considered to prevent unfavorable aggregation of the palladium complex to form inactive palladium species and to prolong the lifetime of the catalyst.



(47)

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11.05 Synthetic Reactions of M═C and M═N Bonds: Ylide Formation, Rearrangement, and 1,3-Dipolar Cycloaddition

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11.05.1 Introduction

One of typical reactions of the Fisher-type metal carbene is interaction of the electron-deficient carbenic carbon with a pair of non-bonding electrons contributed by a Lewis base (B:) to generate a metal complex-associated ylide or a free ylide. The ylide intermediate thus generated is usually highly reactive and undergoes further reactions to give stable products (Figure 1).

Ethers, sulfides, amines, carbonyl compounds, and imines are among the frequently encountered Lewis bases in the ylide formation from such metal carbene complex. The metal carbene in the ylide formation can be divided into stable Fisher carbene complex and unstable reactive metal carbene intermediates. The reaction of the former is thus stoichiometric and the latter is usually a transition metal complex-catalyzed reaction of α-diazocarbonyl compounds. The decomposition of α-diazocarbonyl compounds with catalytic transition metal complex has been the most widely used approach to generate reactive metal carbenes. For compressive reviews, see Refs 1,1a.

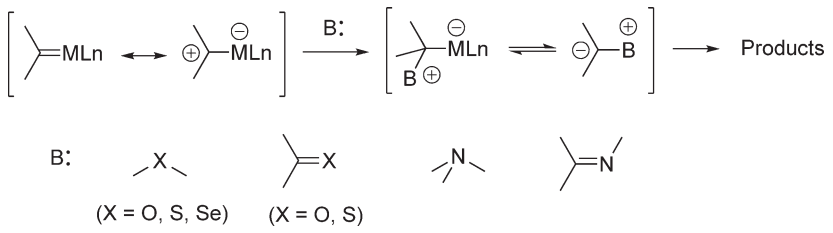


Figure 1 Reaction of electron-deficient metal carbene with Lewis base.

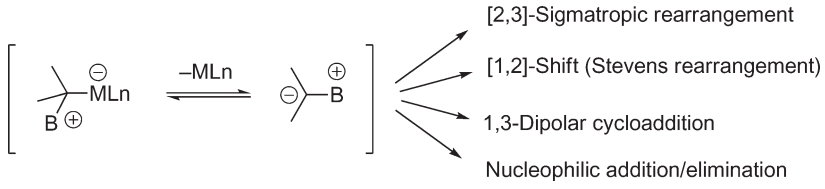


Figure 2 Major reaction pathway of ylide.

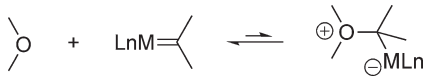
Common reactions of the ylide include: (i) [2,3]-sigmatropic rearrangement of allylic, propargylic, and allenic ylides; (ii) [1,2]-shift (Stevens rearrangement); (iii) 1,3-dipolar cycloaddition of the ylide generated from carbonyl compounds or imines with dipolarophiles, usually C=C or C≡C bonds; and (iv) nucleophilic addition/elimination, leading to the formation of epoxides or cyclopropanes (Figure 2).

The diverse reactivities of ylide make these transformations valuable in organic synthesis. The ylide formation from metal carbene and the subsequent reaction can occur in either inter- or intramolecular manner. With these cascade transformations, it is possible to rapidly assemble organic compounds with considerable complexity from relatively simple starting materials. In addition, some of these reactions show excellent chemo-, regio-, and stereoselectivity. Recent advances in asymmetric catalysis in this field add further merits in these transformations. This chapter will highlight the recent development in the area. Since the majority of the research activities are focused on the metal carbenes that are generated by transition metal catalysis, this review only deals with the catalytic ylide formations from α-diazocarbonyl compounds. Moreover, the synthetic application aspects of the metal carbene-generated ylide and the subsequent transformations are the primary concern, although mechanistic issues are also briefly discussed. Basically, the literatures published after 1993 are reviewed in this chapter. For the achievements before 1993, several excellent reviews are recommended.[2,2a] As additional sources of information, there are several comprehensive reviews published during the period between 1993 and present, which cover the similar topics.[3,3a–3f] This chapter will focus on the most recent advances in the field.

Although not as common as the ylide derived from metal carbenes, the ylide-like species generated from metal nitrene or free nitrene has been attracting increasing attention in recent years. The overall transformation is parallel to that of metal carbene reactions. Progress in this direction is also covered in this chapter.

11.05.2 Formation of Oxygen Ylide from Metal Carbene Complexes and Subsequent Reactions

The oxygen as heteroatom in ethers or carbonyl compounds is weak to moderate Lewis base. Nevertheless, a highly reactive metal carbene complex can interact with the oxygen to generate oxygen ylide. The interaction between ether and metal carbene functional groups is believed to be rather weak as demonstrated by the facts that other metal carbene reactions, such as C–H insertion and cyclopropanation, can proceed in ethereal solvents.[4] These experiments demonstrate that the formation of the metal ylide is much less favored in the equilibrium shown in Equation (1).[5]



(1)

However, the investigations in the past years have demonstrated that oxygen formation is an effective process in some cases and thus have significant synthetic utilities. In particular, the carbonyl ylide formations followed by 1,3-dipolar cycloaddition have been extensively explored as an efficient approach to heterocyclic compounds.

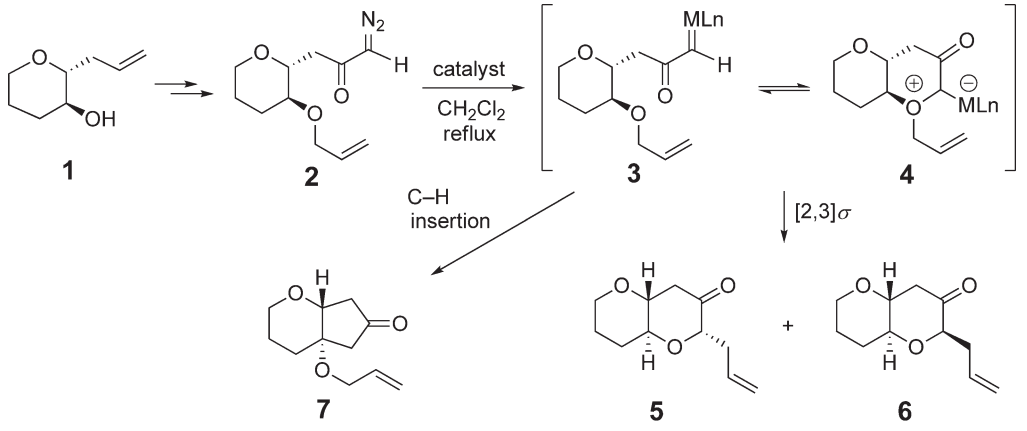
11.05.2.1 Oxonium Ylides and the Subsequent Reactions

As mentioned above, the oxonium ylide is highly unstable and usually its formation is not competitive with other reactions of metal carbenes. The oxonium ylide formation may become significant when cyclic oxonium ylide is formed by intramolecular reaction, and/or when the subsequent reaction of the ylide is highly efficient. Under these circumstances, the equilibrium in Equation (1) may shift to the right side. On the other hand, both metals and ligands of the catalysts can affect chemoselectivity of metal carbene reactions.[6]

11.05.2.1.1 [2,3]-Sigmatropic rearrangement

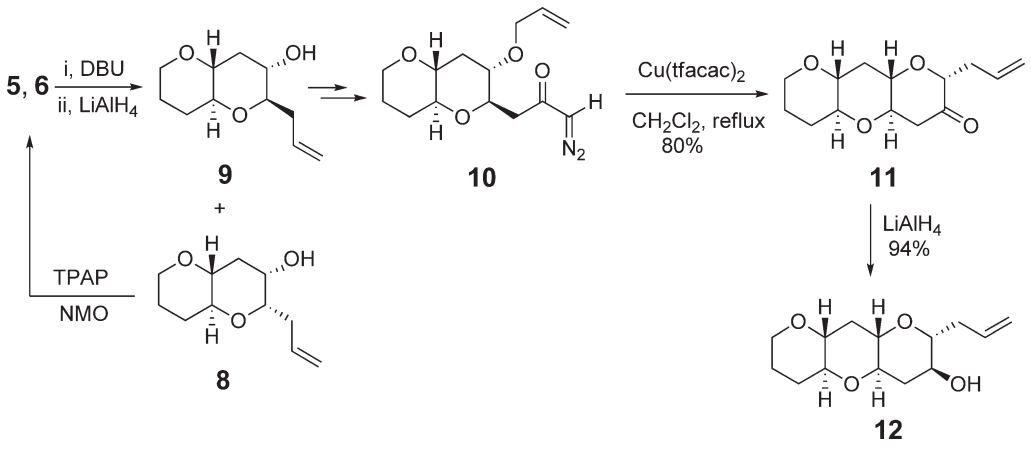
When an allyl ether is used for the ylide formation, the oxonium ylide thus generated may undergo [2,3]-sigmatropic rearrangement, which is one of the most remarkable bond reorganizations in organic reactions.[7] For intermolecular reactions, the ylide formation from allyl ether and metal carbene is complicated due to competitive cyclopropanation, a reaction of the metal carbene with an olefin moiety. Although there are many reports demonstrating predominant ylide formation and the subsequent [2,3]-sigmatropic rearrangement, the intermolecular reaction has found limited utilities in organic synthesis. Cyclic oxonium ylides, however, can be readily generated through intramolecular reaction of the metal carbene and a suitably positioned ethereal oxygen. This cyclic ylide formation/[2,3]-sigmatropic rearrangement reaction sequence has been employed by several groups in the synthesis of oxygen-containing cyclic compounds.[8–10c]

West and co-workers have developed an iterative approach to polycyclic ethers based on the [2,3]-sigmatropic rearrangement of cyclic oxonium ylides.[8,8a–8c] The polycyclic ethereal structure occurs in marine ladder toxins, such as brevetoxin B. These marine toxins have highly potent biological activities, and the unique structure represents formidable challenge for synthetic organic chemists. In the West's approach,[8c] the diazo compound **2**, which can be prepared from **1**, is treated with copper(II) trifluoroacetylacetonate [Cu(tfacac)$_2$] to give rise to the ylide formation/[2,3]-sigmatropic rearrangement product as a diastereomeric mixture of **5** and **6** in a ratio of 93 : 2 and 66% yield, accompanied by a minor formation of C–H insertion product **7** (Scheme 1). It is noted that the catalyst ligand affects the ratio of the products. When copper(II) hexafluoroacetylacetonate [Cu(hfacac)$_2$] is employed as the catalyst, the **5** to **6** ratio decreases to 72 : 14. An $Rh_2(OAc)_4$ catalyst, on the other hand, gives considerable amount of C–H insertion product **7**. In fact, in the transition metal-catalyzed reaction of α-diazo compounds, it is demonstrated that copper catalysts generally favor ylide formation, while rhodium catalysts prefer C–H bond insertion.[5,9,10]



Catalyst	*Yield* (%)	**5 : 6 : 7**
Cu(tfacac)$_2$ (10 mol%)	66	93 : 2 : 5
Cu(hfacac)$_2$ (10 mol%)	41	72 : 14 : 14
$Rh_2(OAc)_4$ (3 mol%)	59	40 : 10 : 50

Scheme 1

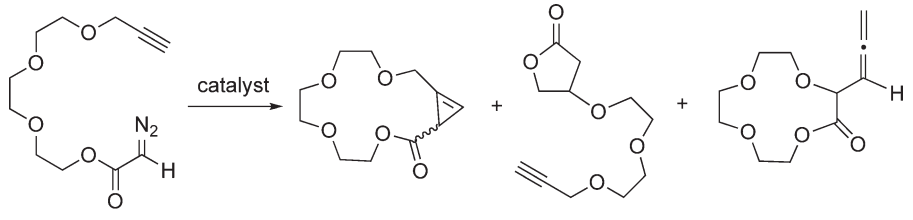


Scheme 2

The mixture of **5** and **6** can be converted to **9** by reduction, separation and then epimerization/reduction of one isomer. Alcohol **9** is then further subjected to similar procedure as for **1** to give tricyclic ether **12**, through the same $Cu(tfacac)_2$-catalyzed ylide formation/[2,3]-sigmatropic rearrangement of diazo compound **10** (Scheme 2).

The ylide formation/[2,3]-sigmatropic rearrangement approach has been used by Clark and co-workers in the construction of highly oxidized sesquiterpene structures such as the functionalized core of neoliacinic acid **21** (Scheme 3).[9,9a–9e] Starting with (*R*)-isopropylideneglyceraldehyde **13**, ketone **15** is prepared through intramolecular C–H insertion of α-diazo ketone **14** catalyzed by rhodium(II) trifluoroacetamidate $[Rh_2(NHCOCF_3)_4]$.[9c] The ketone **15** is further converted to α-diazo ketone **16**. Treatment of **16** with $Cu(tfacac)_2$ in CH_2Cl_2 at reflux gives the ylide formation/[2,3]-sigmatropic rearrangement product **19** as a mixture of (*E*)- and (*Z*)-isomers (3 : 2) in 61% yield, along with the formation of **18**, which is derived from the [1,2]-shift of the intermediate oxonium ylide. The bridged bicyclic ether **19** is further converted to epoxide **20**, which is an advanced intermediate toward the synthesis of neoliacinic acid **21**.

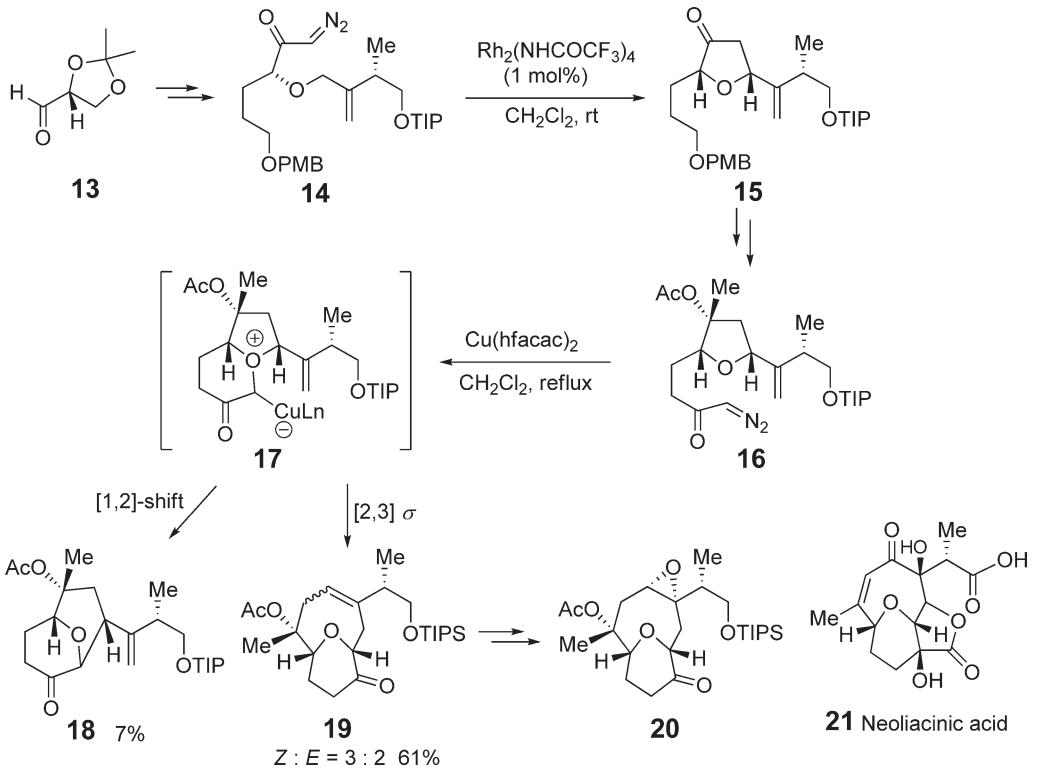
Besides the formation of five- and six-membered oxonium ylides, Doyle and co-workers have demonstrated that macrocyclic oxonium ylide formation and the subsequent [2,3]-sigmatropic rearrangement is also possible.[10a,c] When propargyl-linked diazoacetate **22** is treated with $Cu(MeCN)_4PF_6$, [2,3]-sigmatropic rearrangement product **25** is formed as a major product, along with intramolecular cyclopropanation product **23** (Equation (2)).[10c] When **22** is treated with $Rh_2(OAc)_4$, intramolecular cyclopropanation becomes predominant with intramolecular C–H insertion as a minor pathway. No trace of cyclic ylide formation/[2,3]-sigmatropic rearrangement product **25** can be detected in $Rh_2(OAc)_4$-catalyzed reaction. The results demonstrate again the remarkable effect of catalyst on the competition between intramolecular ylide formation and other metal carbene reaction pathways.



(2)

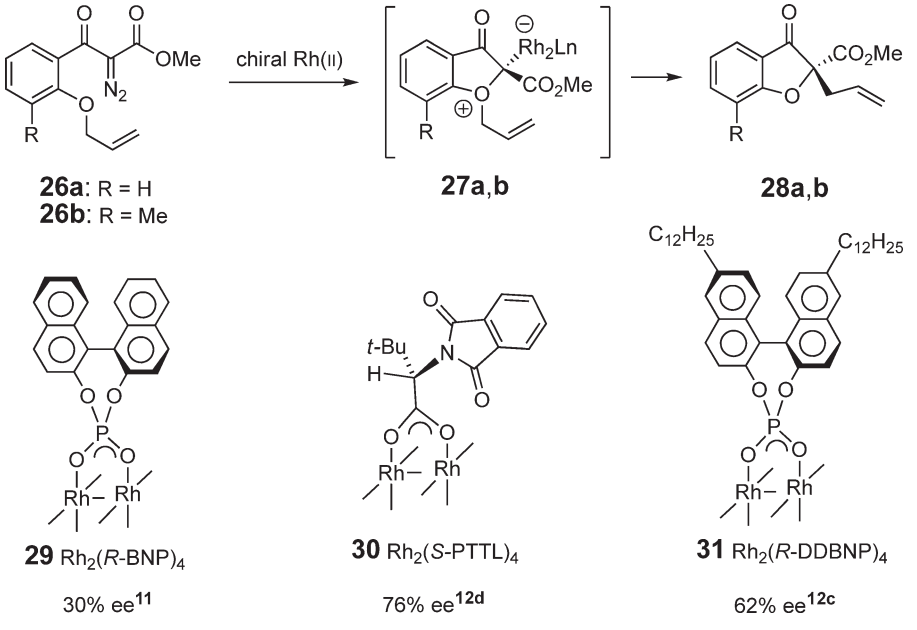
Catalyst	*Yield* (%)	**23 : 24 : 25**
$Rh_2(OAc)_4$	62	96 : 4 : 0
$Cu(MeCN)_4PF_6$	61	25 : 0 : 75

Stereoselective oxonium ylide reaction, in particular the asymmetric catalysis, has been a problem of considerable challenge in this field.[3d] Since the first report by McKervey and co-workers in the asymmetric induction in metal carbene-mediated ylide formation/[2,3]-sigmatropic rearrangement in 1992,[11] there have been efforts being directed



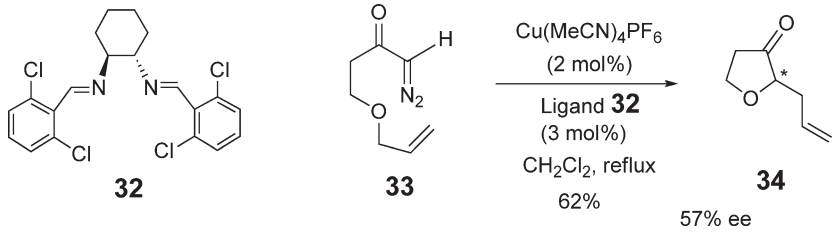
Scheme 3

to this area. However, only limited success has been gained so far. Following the initial study with dirhodium(II) tetrakis[(*R*)-binaphtholphosphate] [Rh_2(*R*-BNP)$_4$], in which up to 30% ee is obtained for the reaction of **26a**, a series of other chiral Rh(II) catalysts[12,12a–12d] have been tested and up to 76% ee is achieved with Hashimoto's dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate] [Rh_2(*S*-PTTL)$_4$] **30**[12d] (Scheme 4).



Scheme 4

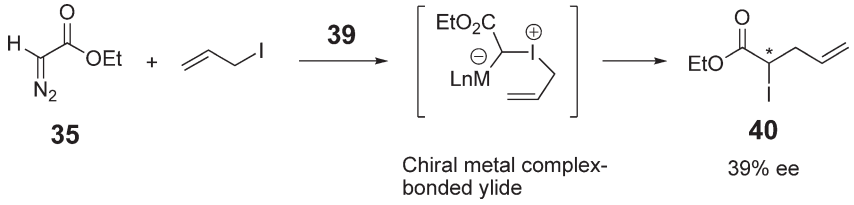
On the other hand, a Cu(I)/chiral diimine complex in the cyclic ylide formation/[2,3]-sigmatropic rearrangement has been examined by Clark and co-workers (Equation (3)).[13] Up to 57% ee has been obtained when C_2-symmetric ligand **32** is used.



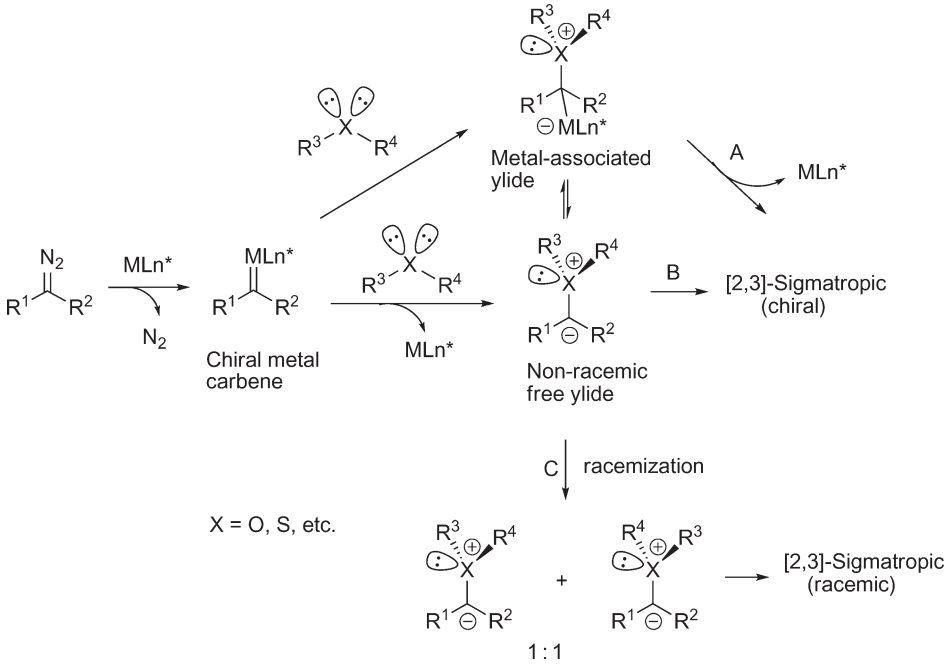
(3)

An important issue concerning asymmetric induction in the oxonium ylide reaction is whether the metal complex is associated with ylide in the final product-forming step. Since the oxonium ylide is highly unstable and is suggested to be in equilibrium with the corresponding carbene,[5] the observation of significant asymmetric induction in rhodium- or copper-catalyzed oxonium rearrangement indicates that the reaction most likely proceeds through catalyst-associated ylide (path A, Scheme 5). However, the possibility that asymmetric induction may arise from a free ylide after dissociation of a chiral metal catalyst but before configurational inversion (path B) at an onium center cannot be strictly ruled out.

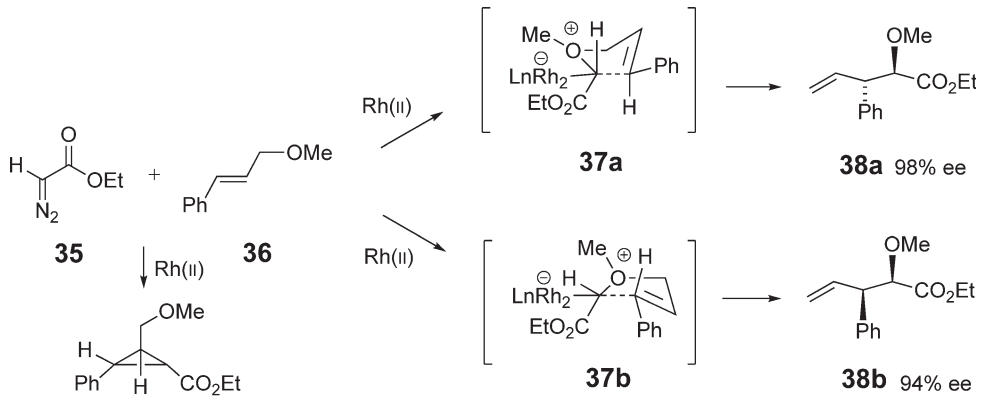
Doyle *et al.* have demonstrated the catalyst-dependent diastereoselectivity in Rh(II) complex-catalyzed reaction of cinnamyl methyl ether **36** and ethyl diazoacetate **35** (Scheme 6).[14] The change of the diastereoselectivity of the products **38a** and **38b** with different Rh(II) catalyst provides strong evidence that Rh(II) catalyst is associated with the ylide in the rearrangement process. The moderately high level of asymmetric induction (4–69% ee) is also observed with allyl iodide (Equation (4)). In this case, the chiral metal complex must be in the product-forming step, because free iodo ylide is achiral.

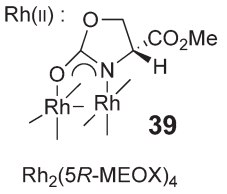


(4)



Scheme 5





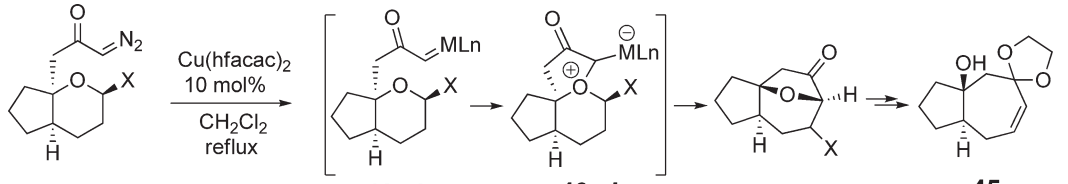
Catalyst	Yield (%) 38a : 38b
$Rh_2(OAc)_4$	83 : 17
Rh_2(*R*-MEOX)$_4$	15 (94% ee) : 85 (98% ee)
Rh_2(*S*-MEOX)$_4$	15 (94% ee) : 85 (98% ee)

Scheme 6

11.05.2.1.2 [1,2]-Shift (Stevens rearrangement) and related reactions

The other major reaction pathway for oxonium ylide is [1,2]-shift (Stevens rearrangement). Compared with [2,3]-sigmatropic rearrangement, which is an orbital symmetry-allowed concerted process, the [1,2]-shift has higher activation barrier. [1,2]-Shift is generally considered as stepwise process with radical pair as possible intermediates.[15,15a]

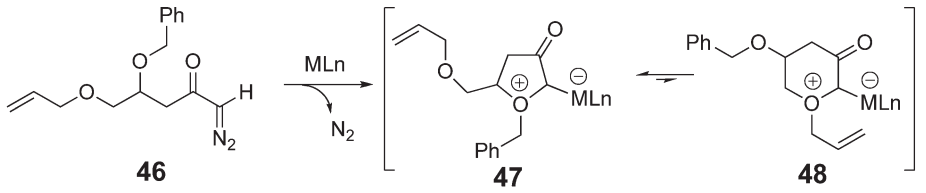
Formation of cyclic oxonium ylide followed by [1,2]-shift can be a useful approach to medium-sized or bridged cyclic compounds.[8,8b,16,16a–16d] West and co-workers have recently reported the synthesis of cyclooctanoid ring system based on such an approach.[16b] α-Diazo ketones **41a** and **41b**, when treated with 10 mol% $Cu(hfacac)_2$ in CH_2Cl_2 at reflux, generate a five-membered oxonium ylide which then undergoes [1,2]-shift to give **44a** and **44b** in good yields, respectively. Structure **44b** can be converted to **45**, which may be used in the synthesis of natural products with fused five to six bicyclic skeletons (Equation (5)). For the metal carbene intermediate **42a** or **42b**, obviously there are other possible reaction pathways. When $Rh_2(OAc)_4$ or rhodium(II) triphenylacetate [$Rh_2(O_2CCPh_3)_4$] is used as the catalyst, the reaction gives primarily intramolecular C–H insertion products. Treatment of **41a** or **41b** with the $Cu(tfacac)_2$ in CH_2Cl_2 at reflux, conditions for ylide formation/[2,3]-sigmatropic rearrangement,[8a] resulted in only low yields of several unidentified products.



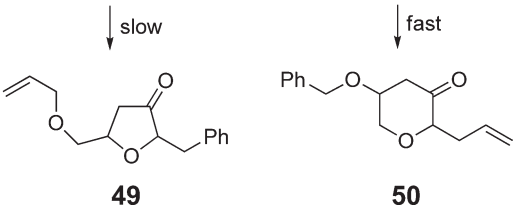
(5)

An interesting feature in this reaction is that the [1,2]-shift of ylides **43a** and **43b** proceeds mostly with high degree of retention of configuration. Such high stereospecificity is unusual, because the [1,2]-shift is believed to be a stepwise process with radical pair intermediates. The results may be rationalized by assuming a very rapid radical recombination as compared with bond rotation.

As discussed above, accumulated data demonstrate that the catalyst, the substrate structure, and other competing metallocarbene pathways significantly affect the ylide formation and the subsequent rearrangement process. West and co-workers have recently studied selectivity in rearrangement via five- or six-membered oxonium ylides by



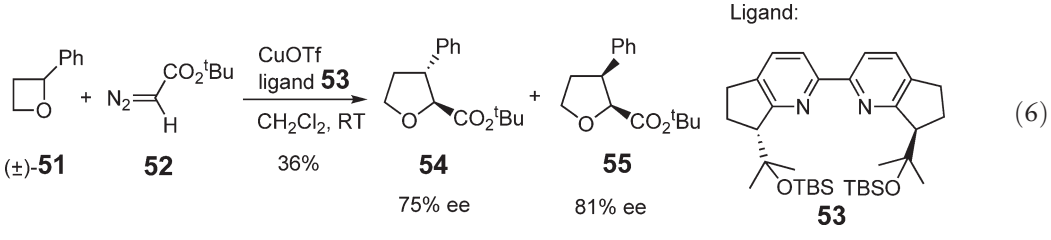
Catalyst	*Yield* (%)	**49 : 50**
$Cu(tfacac)_2$ (10 mol%)	83	19 : 81
$Cu(hfacac)_2$ (10 mol%)	67	57 : 43
$Rh_2(OAc)_4$ (3 mol%)	77	65 : 35



Scheme 7

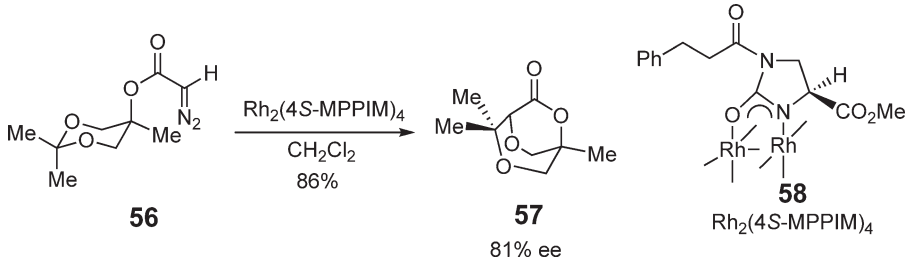
intramolecular competitive formation and rearrangement of two different oxonium ylides via the same metallocarbene (Scheme 7).[17] The study reveals that five-membered ylide formation is generally favored. However, the properties of the migrating group in the subsequent rearrangement may override the five-membered ring preference. In the reaction with α-diazo ketone **46** with $Cu(tfacac)_2$, pyranone **50** is formed predominantly since allylic [2,3]-sigmatropic rearrangement is more feasible than [1,2]-shift. The results strongly suggest that five-membered ylide **47** is in equilibrium with its six-membered counterpart **48**. It is also observed that the catalyst can dramatically affect the reaction selectivity. When $Rh_2(OAc)_4$ or $Rh_2(O_2CCPh_3)_4$ is employed as the catalyst, the reaction gives five-membered ylide formation/[1,2]-benzyl shift product predominantly. Moreover, even a relatively minor change in the ligand of the copper catalyst (from $Cu(tfacac)_2$ to $Cu(hfacac)_2$) significantly alters the selectivity. The catalyst-dependent selectivity strongly suggests the metal-associated ylide in the product-forming step. Catalyst may thus alter the properties of ylide. It may also affect the equilibrium between different ylide species such as **47** and **48**.

Asymmetric induction in the ylide formation/[1,2]-shift has also been studied with chiral metal complexes. Katsuki and co-workers examined the reaction of (±)-2-phenyloxetane with 0.5 equiv. of *tert*-butyl diazoacetate in the presence of Cu(I) catalyst. With chiral bipyridine ligand **53**, *trans*- and *cis*-tetrahydrofurans **54** and **55** are obtained with 75% and 81% ee, respectively (Equation (6)).[18,18a] This asymmetric ring expansion was applied by the same group to their enantioselective synthesis of *trans*-Whisky lactone.[19,19a]



(6)

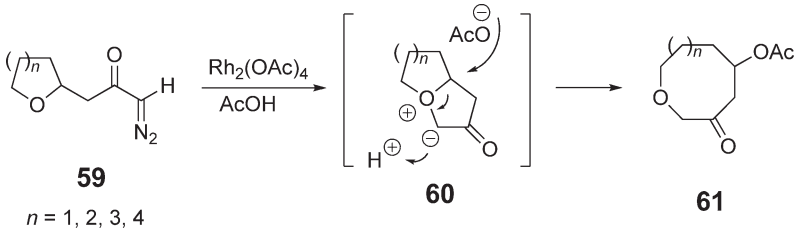
Desymmetrization strategy in enantioselective oxonium ylide formation/[1,2]-shift reaction has been reported by Doyle and co-workers.[20] With dirhodium(II) tetrakis[methyl 1-(3-phenylpropanoyl)-2-oxoimidazolidine-4(*S*)-carboxylate] [Rh_2(4*S*-MPPIM)$_4$] as the catalyst, up to 88% ee is obtained (Equation (7)).



(7)

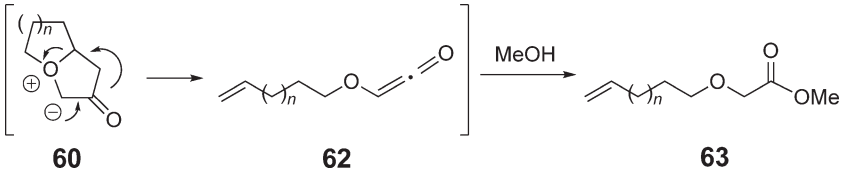
11.05.2.1.3 Miscellaneous reaction of oxonium ylides

Besides [2,3]-sigmatropic rearrangement and [1,2]-shift reactions, the oxonium ylide may undergo other reactions. The oxonium ylide intermediate can be trapped by a protic nucleophile. Oku and co-workers have developed a method for ring expansion of cyclic ethers through oxonium ylide formation.[21,21a–21f] Bicyclic oxonium ylide intermediate **60**, which is formed upon interaction of an Rh(II) carbene with a pendant cyclic ethereal moiety, is trapped by AcOH to give medium-sized cyclic compounds **61** (Equation (8)).



(8)

When a relatively week nucleophile such as MeOH is used instead of AcOH, ylide **60** undergoes a sigmatropic cleavage of the bicyclic ring, a process termed as [3 + 2]-cycloreversion, to give a ketene intermediate **62** which is trapped by MeOH to yield alkenyloxyacetate **63** as the final product (Equation (9)).[22]



(9)

11.05.2.2 Carbonyl Ylide Formation and the Subsequent Reactions

The oxygen lone pair electrons in a carbonyl group can react with an electron-deficient carbenic carbon of a metal carbene complex to generate a carbonyl ylide. Unlike oxonium ylide, a positive charge in such carbonyl ylide is partially localized at the carbonyl carbon. Consequently, carbonyl ylides behave as 1,3-dipolar species. They are generally more stable than the corresponding oxonium ylides. Stable carbonyl ylides have been focused and reported (Figure 3).[23]

11.05.2.2.1 1,3-Dipolar cycloaddition

Carbonyl ylides possess versatile reactivities, among which the 1,3-dipolar cycloaddition is the most common and important reaction. The reaction sequence of ylide formation and then 1,3-dipolar cycloaddition can occur in either inter- or intramolecular manner. When the reaction occurs intermolecularly, the overall reaction is a one-pot three-component process leading to oxygen-containing five-membered cyclic compounds, as demonstrated by the example shown in Scheme 8. A mixture of diazo ester **64**, benzaldehyde, and dimethyl maleate, upon heating to reflux in CH_2Cl_2 in the presence of 1 mol% rhodium(II) perfluorobutyrate [$Rh_2(pfb)_4$], yields tetrahedrofuran derivative **65** in 49% yield as single diastereomer.[24]

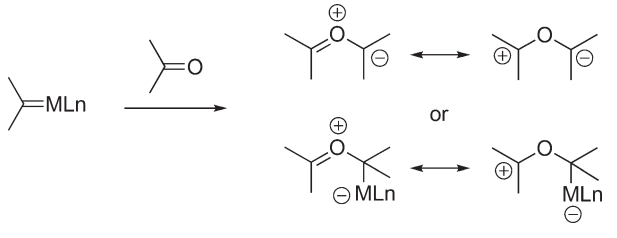
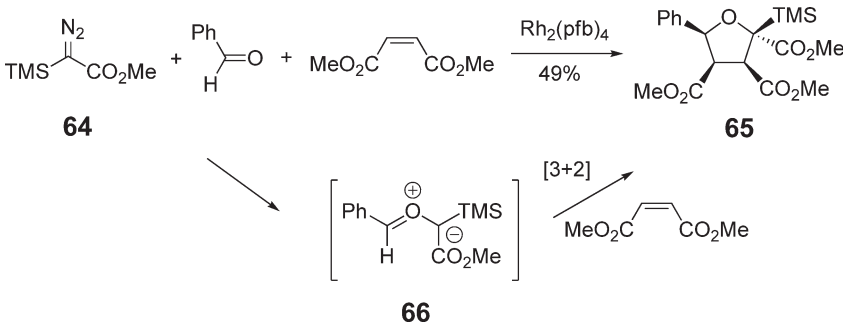
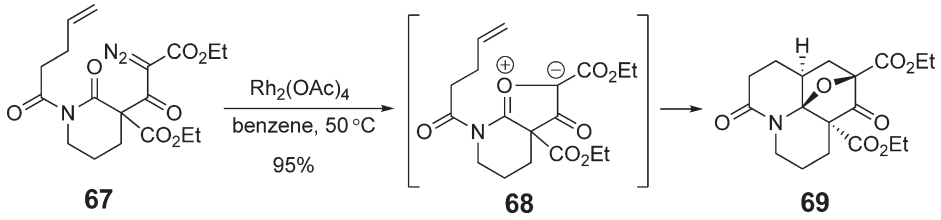


Figure 3 Generation of carbonyl ylide from metal carbene.



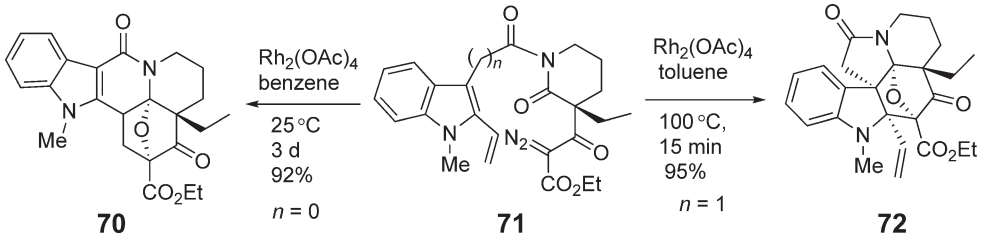
Scheme 8

Cyclic carbonyl ylides can be generated through an intramolecular reaction of metal carbene complex with a pendent carbonyl group. The ylides are then trapped by dipolarophiles to give oxygen-bridged bicyclic products. This tandem cyclic ylide formation/[3 + 2]-cycloaddition sequence has been widely utilized in organic synthesis.[3a,3d,3f,26–28i] For literatures prior to 1996, see Ref. 3. For publications later than 1996, see Refs 26–26u. Following their initial investigation,[25] Padwa and co-workers have extensively developed the tandem cyclization–cycloaddition approach over the past years. An important expansion of the method is generation of isomunchnone dipole, a push–pull carbonyl ylide, from Rh(II)-catalyzed reaction of α-diazo imides. The isomunchnone dipole can be trapped efficiently by various dipolarophiles to give nitrogen-containing polycyclic compounds. When the dipole is trapped intramolecularly by a pendent dipolarophile, heterocylic compound with multi-functional group, such as **69**, can be obtained in one step in a high yield and with complete diastereoselectivity (Equation (10)).[26l]



(10)

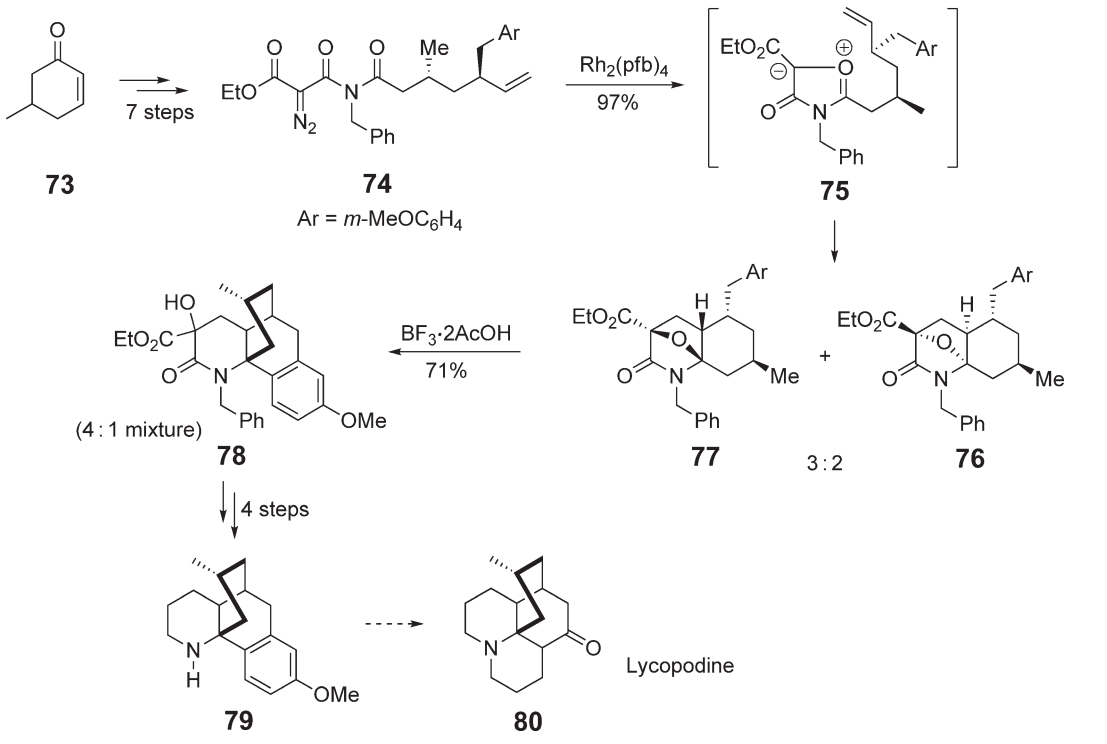
A recent example of this intramolecular tandem transformation is the Rh(II)-catalyzed reaction of diazo keto ester **71**. Depending on the structure of the diazo compound, a push-pull dipole intermediate derived from **71** can be trapped either by a tethered vinyl group (when $n = 0$) or by an indole π-bond (when $n = 1$) (Equation (11)).[26t] This result clearly demonstrates a critical role of the conformation of the cycloaddition transition state.



(11)

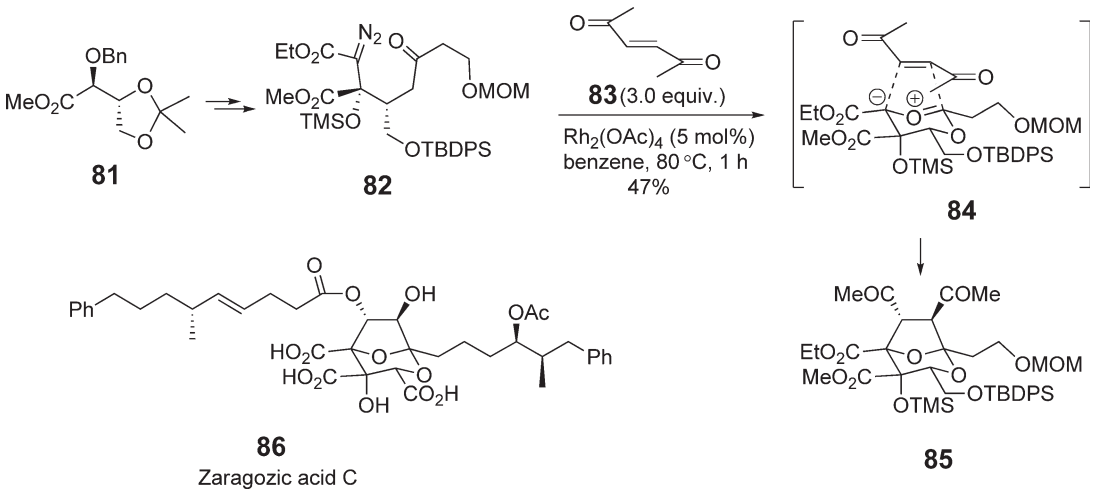
The isomunchnone dipole approach has been successfully applied to the synthesis of alkaloids (±)-lycopodine.[26k] As outlined in Scheme 9, 5-methylcyclohexenone **73** was converted to α-diazo imide **74** in seven steps. The diazo decomposition of **74** with $Rh_2(pfb)_4$ in CH_2Cl_2 at 25 °C gives expected tandem ylide cycloaddition products **76** and **77** in 97% yield as a 3 : 2 diastereomeric mixture. Treatment of this mixture with $BF_3 \cdot 2AcOH$ gives tetracyclic amide **78** as a 4 : 1 mixture of diastereomers in 71% yield. Structure **78** was then converted into **79** in four steps, thus constituting a formal total synthesis of (±)-lycopodine **80**.

Toward the synthesis of zaragozic acids, a novel family of fungal metabolites that has been shown to be picomolar competitive inhibitors of squalene synthease, Hodgson's group and Hashimoto's group have used cyclic carbonyl ylide formation/[3 + 2]-cycloaddition approach.[27,27a–27d] In Hashimoto's synthesis, the 2,8-dioxabicyclo[3,2,1]octane core

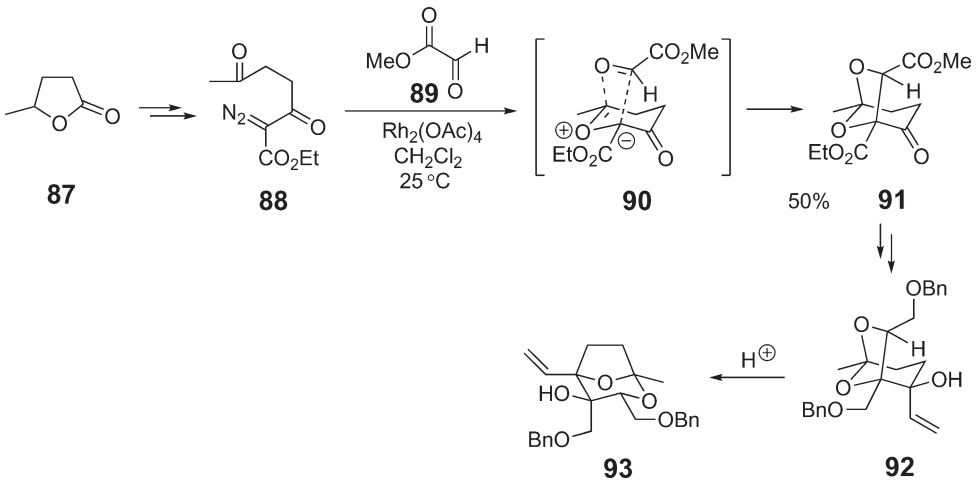


Scheme 9

structure is constructed directly by the Rh(II)-mediated intramolecular carbonyl ylide formation from α-diazo ester **82** and the subsequent stereocontrolled 1,3-dipolar cycloaddition with (*E*)-3-hexene-2,5-dione 83 (Scheme 10).[27b] The tandem cyclization–cycloaddition reaction was performed by slowly adding a solution of α-diazo ester **82** in benzene to a refluxing benzene solution of $Rh_2(OAc)_4$ and the dipolarophile **83**. The reaction afforded the desired cycloadduct **85** as a single diastereomer. It is noted that appropriate choice of a dipolarophile is crucial in the cycloaddition. Use of (*E*)-vinylene diacetate or vinyl acetate as the dipolarophile did not give the expected cycloadduct.



Scheme 10

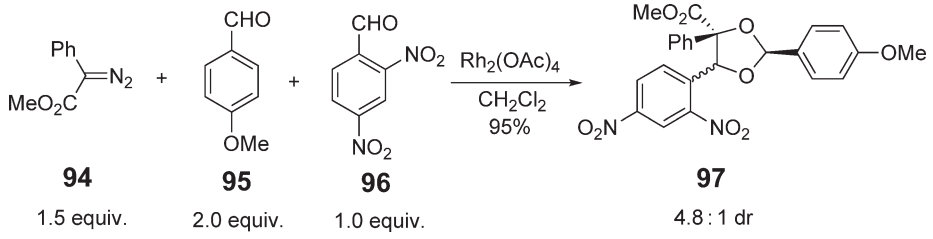


Scheme 11

In the Hodgson's approach, a cyclic carbonyl ylide is trapped by a carbonyl group to afford 6,8-dioxabicyclo[3,2,1] octane **91**. This cycloadduct was further converted to alcohol **92**, which was subjected to acid-catalyzed rearrangement to give the desired 2,8-dioxabicyclo[3,2,1]octane skeleton **93** (Scheme 11).[27a,d]

Mechanistic and theoretical investigation has been carried out on the carbonyl ylide formation and the subsequent 1,3-dipole addition. Chemo- and stereoselectivity have been found to be affected by the ligands of the Rh(II) catalysts.[26a,26d,26f,26l,26r,26u] These results imply that in the cycloaddition process, the Rh(II) catalyst may be associated with the 1,3-dipole. Theoretical calculation indicates that the Rh(II) catalyst-associated ylide has the lowest energy in the catalytic cycle.[26r] The suggestion that metal complex-associated ylide may be involved in the cycloaddition has great implication for the asymmetric catalysis in this type of reaction.

The carbonyl ylide generated from metal carbene can also add to C═O or C═N bonds. The [2 + 3]-cycloaddition of carbonyl ylide with C═O bond has been used by Hodgson and co-workers in their study toward the synthesis of zaragozic acid as shown in Scheme 11.[27a,27d] Recently, a three-component reaction approach to *syn*-α-hydroxy-β-amino ester based on the trapping of the carbonyl ylide by imine has been reported.[29] The reaction of carbonyl ylide with aldehyde or ketone generally gives 1,3-dioxolanes.[30,30a–30j] Hu and co-workers have reported a remarkable chemoselective $Rh_2(OAc)_4$-catalyzed reaction of phenyl diazoacetate with a mixture of electron-rich and electron-deficient aryl aldehydes. The Rh(II) carbene intermediate reacts selectively with electron-rich aldehyde **95** to give a carbonyl ylide, which was chemospecifically trapped by the electron-deficient aldehyde **96** to afford 1,3-dioxolane in a one-pot reaction (Equation (12)).



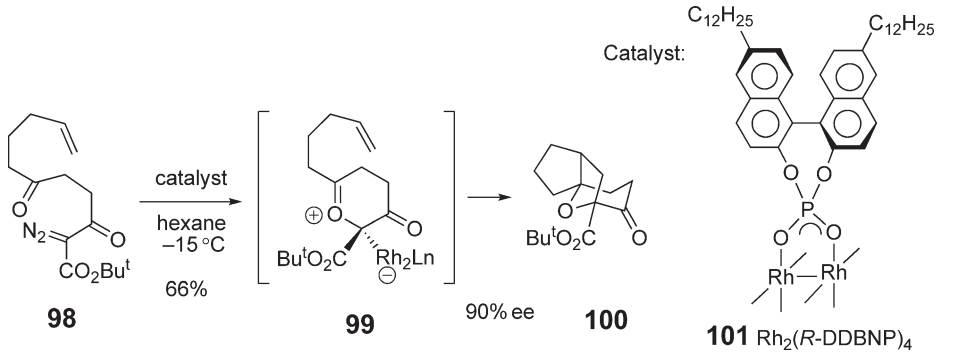
(12)

11.05.2.2.2 Asymmetric catalysis of 1,3-dipole addition of carbonyl ylides

As demonstrated by Padwa and co-workers, the 1,3-dipole cycloaddition has become a powerful and diverse tool in organic synthesis. It should be highly desirable if high stereoselectivity, in particular enantioselectivity, could be achieved. The catalytic asymmetric 1,3-dipole cycloaddition of carbonyl ylide generated from metal carbene complex has been a challenging problem. The study toward this goal was largely retarded by the hypothesis that the cycloaddition proceeds through free ylide rather than metal-associated ylide. The reports by Padwa and co-workers that chemo- and stereoselectivity are affected by the catalyst ligands suggest that this may not be the case. Inspired

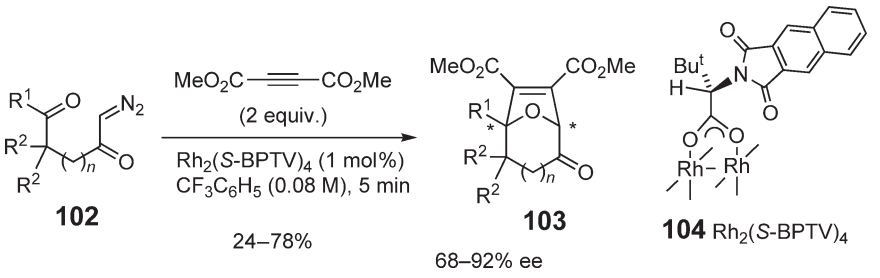
by those discoveries, the catalytic asymmetric 1,3-dipole cycloaddition has been pursued by several groups over the past years, and progress has been made steadily.[3e,31–33a]

Hodgson and co-workers have studied the intramolecular cascade carbonyl ylide formation–cycloaddition with chiral Rh(II) catalysts.[31,31a–31h] After screening a series of chiral Rh(II) catalysts, high enantioselectivity was achieved in the reaction of **98** by using the Rh(II) catalyst with binaphthyl phosphate-derived chiral ligands dirhodium(II) tetrakis[(*R*)-6,6′-didodecylbinaphtholphosphate] [Rh_2(*R*-DDBNP)$_4$] (Equation (13)).



(13)

Hashimoto and co-workers, on the other hand, studied the intramolecular reaction between cyclic carbonyl yield and dimethyl acetylenedicarboxylate (DMAD) (Equation (14)).[32,32a] With dirhodium(II) tetrakis[*N*-benzene-fused phthaloyl-(*S*)-valinate] [Rh_2(*S*-BPTV)$_4$] **104**, high enantioselectivity (68–92% ee) was achieved over a range of diazo substrates.[32] The high level of enantiocontrol provided conclusive evidence that chiral Rh(II) catalyst is associated with the ylide in the cycloaddition step.

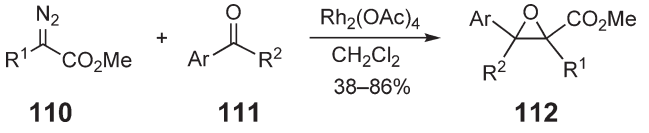


(14)

An alternative approach in the asymmetric catalysis in 1,3-dipole cycloaddition has been developed by Suga and co-workers. The achiral 1,3-dipole **106** was generated by intramolecular reaction of an Rh(II) carbene complex with an ester carbonyl oxygen in the $Rh_2(OAc)_4$-catalyzed diazo decomposition of *o*-methoxycarbonyl-α-diazoacetophenone **105** (Scheme 12). The asymmetric induction in the subsequent cycloaddition to C=C and C=N bond was achieved by chiral Lewis acid Sc(III)-Pybox-*i*-Pr or Yb(III)-Pybox-Ph, which can activate the dipolarophile through complexation. With this approach, up to 95% ee for C=O bond addition and 96% ee for C=C bond addition have been obtained, respectively.[33,33a]

11.05.2.2.3 Miscellaneous reaction of carbonyl ylides

Besides the cycloaddition, the carbonyl ylide intermediate may undergo ring closure to give epoxides if the reaction with a dipolarophile is slow. However, there have been very few examples of epoxide formation in the reaction with metal carbene-generated carbonyl ylide. For example, when ethyl diazoacetate is decomposed with an Rh(II) catalyst in the presence of benzaldehyde, 1,3-dioxolane is formed though the reaction of the carbonyl ylide with aldehyde.[30] Doyle *et al.* have observed that when methyl aryldiazoacetate **110** (R^1 = aryl group) is catalyzed with $Rh_2(OAc)_4$ in the presence of aryl aldehyde **111** (R^2 = H), (*Z*)-epoxide **112** was obtained as a single isomer in high yields (Equation (15)).[34]



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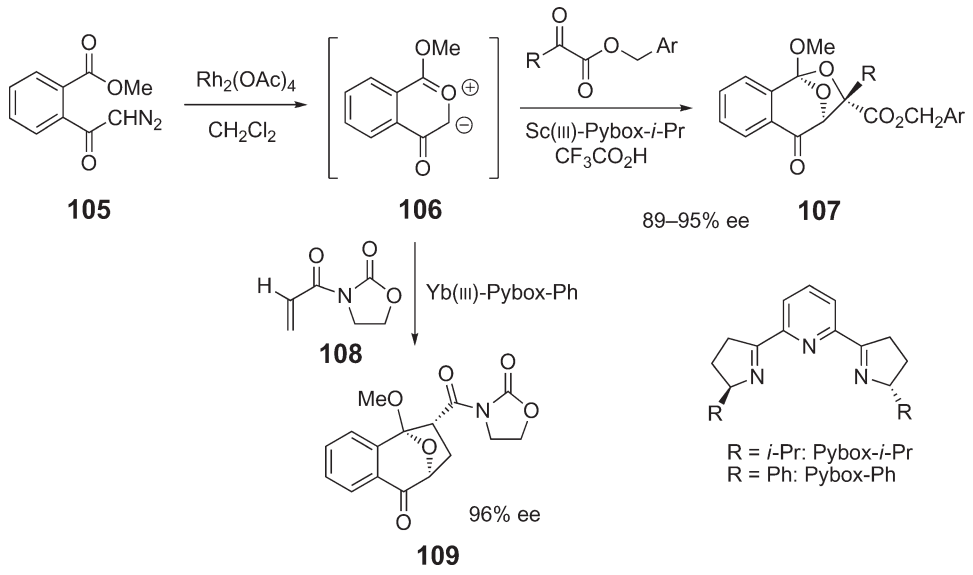


Scheme 12

11.05.3 Formation of Sulfur Ylide from Metal Carbene Complexes and Subsequent Reactions

Similar to ethers and carbonyl compounds, sulfides or thiocarbonyl groups interact with metal carbene to generate the corresponding ylides. These ylides undergo similar subsequent reactions as their oxygen counterparts (Figure 4).

Compared to oxygen, sulfur is more nucleophilic. Consequently, sulfur ylide formation is easier than the corresponding oxygen ylide. In competition experiments with substrates containing both olefinic and thioether groups, both copper and rhodium carbene complexes react preferentially with sulfur atom to generate sulfonium ylide, while similar competition between olefin and ether gives both cyclopropanation and ylide products.[35] On the other hand, sulfide or thiocarbonyl compound can associate with catalysts, thus inhibiting the diazo decomposition process. In some cases, higher temperature is required to achieve efficient diazo decomposition.

11.05.3.1 Sulfur Ylide Formation and Subsequent Reactions

Sulfonium ylides generated through base-promoted deprotonation of sulfonium salt have been extensively studied. The reaction of sulfides with a diazo carbonyl compound in the presence of a transition metal catalyst is an alternative approach to obtain sulfonium ylides. Sulfonium ylides are more stable than the corresponding oxonium ylides. Stable sulfonium ylides generated by the reaction of an Rh(II) carbene complex with thiophene have been reported (Figure 5).[36]

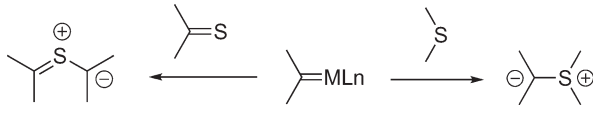


Figure 4 Formation of sulfur ylide.

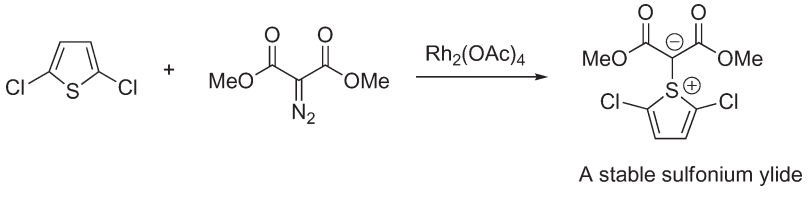


Figure 5 A stable sulfonium ylide.

The major reaction pathways for sulfonium ylide formation generated from a metal carbene complex and sulfide are [2,3]-sigmatropic rearrangement and [1,2]-shift, similar to those of the oxonium ylide formation.

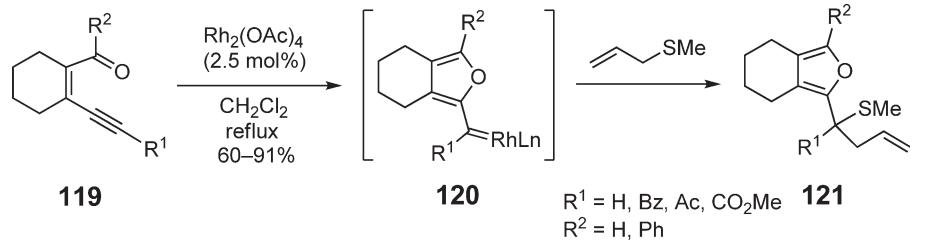
11.05.3.1.1 [2,3]-Sigmatropic rearrangements

Sulfonium ylides generated from the reaction of a metal carbene complex and allylic, propargylic, or allenic sulfides readily undergo [2,3]-sigmatropic rearrangement. Like the corresponding oxonium ylide, this type of rearrangement represents one of the most versatile bond reorganization processes in organic chemistry. The reaction is an orbital symmetry-controlled process with complete allylic inversion. This rearrangement has found many applications in organic synthesis.[37,37a,37b]

Intramolecular sulfur ylide formation and subsequent [2,3]-sigmatropic rearrangement has been utilized in construction of ring systems, as demonstrated by the total synthesis of (+)-β-elemenone **118** and (+)-eleman-8β,12-olide **117** (Scheme 13).[37a,37b] With α-diazo β-keto esters **113** as the starting material, the core structure is formed in one step by $Rh_2(OAc)_4$-catalyzed reaction of intramolecular sulfonium ylide formation followed by [2,3]-sigmatropic rearrangement. It is noted that the rearrangement proceeds with high diastereoselectivity.

Recent study on sulfonium ylide [2,3]-sigmatropic rearrangement has been focused on the development of new catalytic systems, including new catalysts and alternative carbene precursor other than commonly used α-diazocarbonyl compounds. Besides the most commonly used Cu(I) and Rh(II) catalysts, Ru[38,38a] and Fe[39] complexes have been found to catalyze the decomposition of diazo compounds to generate a metal carbene complex, which is trapped by allyl sulfide to induce [2,3]-sigmatropic rearrangement. For the carbene precursor, commercially available trimethylsilyldiazomethane (TMSD) can be used which shows some advantages over the conventional α-diazocarbonyl compounds.[39,40,40a]

Uemura and co-workers developed an interesting and unique catalytic system, in which the Rh(II) intermediate is generated by $Rh_2(OAc)_4$-catalyzed reaction of conjugated ene–yne–carbonyl compounds (Equation (16)). The Rh(II)-carbene is trapped by allyl sulfide to give [2,3]-sigmatropic rearrangement product **121** in good yields.[41]



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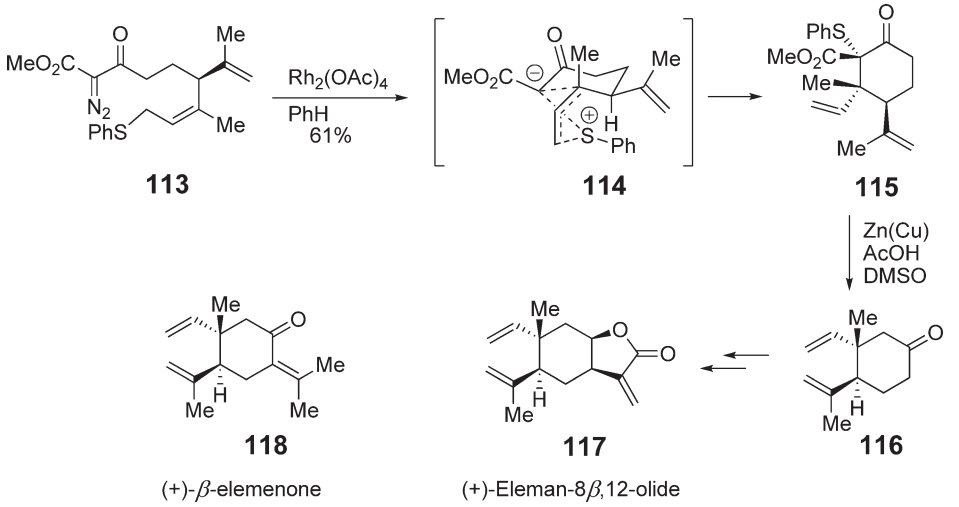
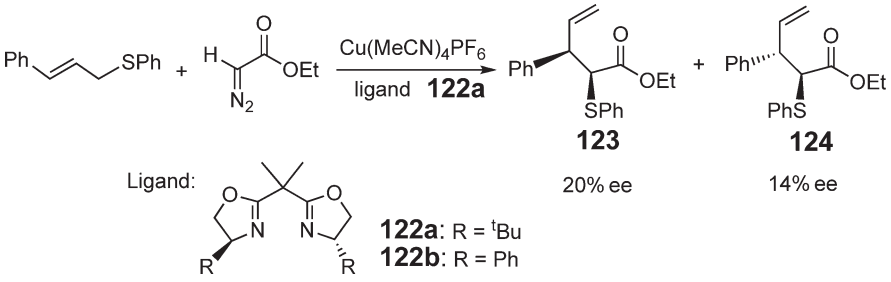


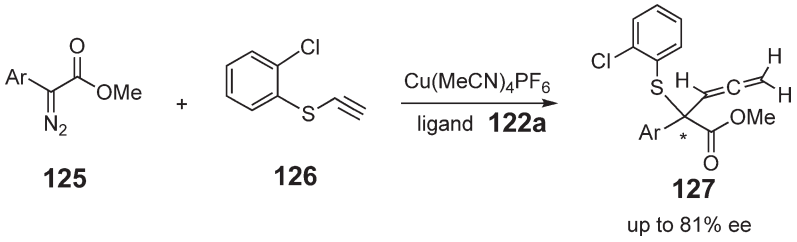
Scheme 13

Asymmetric catalysis in the sulfonium ylide reactions has been attracting attention only recently. Delayed development in this field is also due to a hypothesis that [2,3]-sigmatropic rearrangement proceeds through a free sulfonium ylide, rather than a metal catalyst-associated ylide reaction. Compared with the oxonium ylide, sulfonium ylides have considerable configurational stability. The [2,3]-sigmatropic process is an orbital symmetry-controlled concerted process. Consequently, even if the rearrangement proceeds through a free ylide, asymmetric catalysis is still possible because the chiral catalyst may induce chirality on sulfur atom in the ylide-forming step. The sulfur chirality can be transferred to carbon if the subsequent [2,3]-sigmatropic rearrangement proceeds faster than racemization of the ylide (Scheme 5). In 1995, Uemura and co-workers reported the first catalytic asymmetric sulfonium ylide [2,3]-sigmatropic rearrangement (Equation (17)).[42] Although only low enantioselectivity was obtained, this seminal work demonstrated the possibility of catalytic asymmetric induction in this type of reaction.



(17)

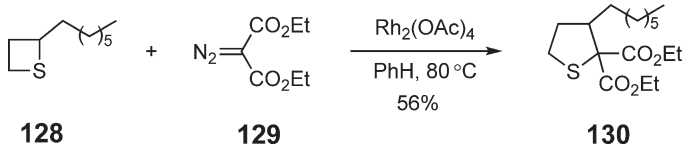
Further study by Katsuki, McMillen, Hashimoto, and Wang improved the enantioselectivity up to a moderately high level.[43,43a–43e] Wang and co-workers further extended the asymmetric catalysis to the [2,3]-sigmatropic rearrangement of propargyl sulfonium ylide to give allenic products with up to 81% ee (Equation (18)).[43d]



(18)

11.05.3.1.2 [1,2]-Shift (Stevens rearrangements) and related reactions

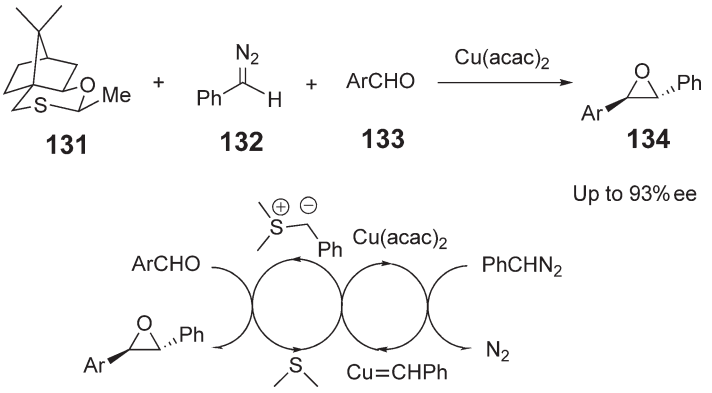
[1,2]-Shift of sulfonium ylide has been applied in organic synthesis as a useful methodology for carbene insertion into a C–S bond. This reaction has been particularly applied in the synthesis of cyclic thioethers, as shown in Equation (19).[44]



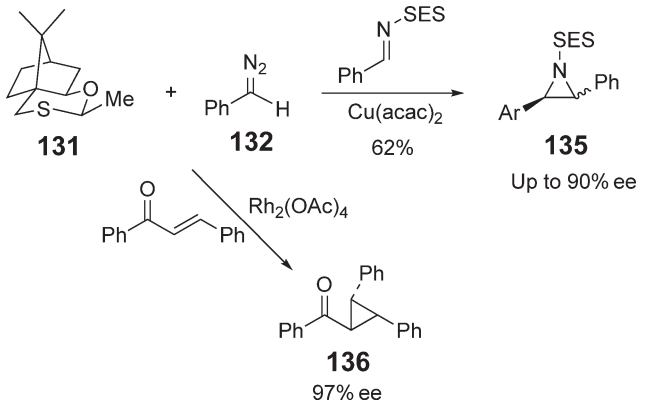
(19)

11.05.3.1.3 Addition to C=O and C=N bonds

Nucleophilic addition of sulfonium ylides to a C=O bond gives epoxides as the product, with release of sulfides. This epoxidation process, originally developed by Corey and Chaykovsky,[45] has found wide applications in organic synthesis. Sulfonium ylides in this reaction are usually generated by base treatment of sulfonium salt precursors. Although sulfides are released upon the formation of epoxides, the reaction requires stoichiometric amount of sulfides. The reaction of a metal carbene complex with sulfides provides an alternative way to generate sulfonium ylides. Thus, a catalytic reaction is possible. Aggarwal and co-workers have developed a catalytic cycle to achieve catalytic asymmetric epoxidation with a sulfonium ylide as a reactive intermediate (Scheme 14).[3f,46,46a–46e] In this catalytic cycle, the chirality of chiral sulfide **131** is transferred to the epoxide product **134** through a sulfonium ylide,



Scheme 14



Scheme 15

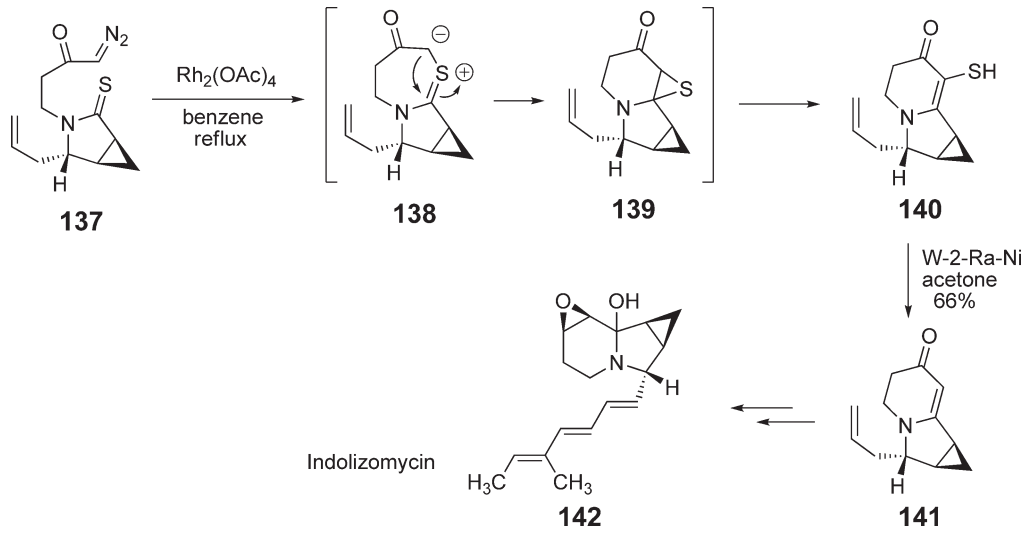
which adds to aldehyde. Subsequent ring closure and release of sulfide **131** give epoxide product **134**. Chiral sulfide **131** returns to the catalytic cycle. Structure **131** (20 mol%) is enough for efficient epoxidation and gives **134** with high enantioselectivity.

Similar catalytic asymmetric approach has been successfully used in the reaction of a sulfonium ylide with electron-deficient imines[47,47a] and alkenes,[48,48a] giving aziridines **135** and cyclopropane **136** with high enantioselectivity, respectively (Scheme 15).

11.05.3.2 Thiocarbonyl Ylide from Catalytic Reaction of α-Diazocarbonyl Compounds

In a manner similar to a carbonyl group, a thiocarbonyl group can readily interact with a metal carbene complex to give a thiocarbonyl ylide that is another reactive 1,3-dipole. Although thiocarbonyl compounds presumably coordinate to a transition metal catalyst, thus inhibiting its ability to decompose diazo substrate, Rh(II) carboxylate catalysts have been proved to be effective in generation of Rh(II) carbene complexes in the presence of thiocarbonyl compounds. The reaction generally requires high reaction temperatures (in refluxing benzene or toluene). Thiocarbonyl ylide generated from a metal carbene complex undergoes further reactions, mostly intramolecular ring closure and 1,3-dipole cycloaddition.

Ring closure to an episulfide is a feasible reaction for thiocarbonyl ylides. In most cases, the sulfur is further extruded under the reaction conditions to afford an olefin as the final product. This cascade transformation has been utilized by Danishefsky and co-workers in their total synthesis of (±)-indolizomycin (Scheme 16).[49] In the Danishefsky's approach, diazo ketone **137** is treated with a catalytic amount of $Rh_2(OAc)_4$ to generate thiocarbonyl ylide **138**, which cyclizes to give episulfide **139**. This episulfide isomerizes to mercaptan **140**, which is then desulfurized by partially deactivated W-2 Raney nickel.



Scheme 16

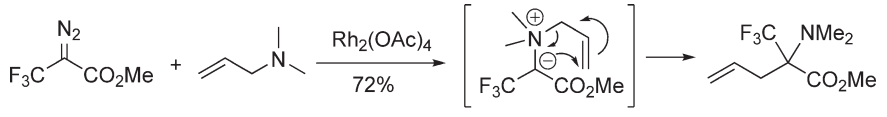
11.05.4 Formation of Nitrogen Ylide from Metal Carbene Complex and Subsequent Reactions

Similar to those of oxygen and sulfur ylide, ammonium ylide or azomethine ylide can be generated by the interaction of metal carbene and amine or imine, respectively. As is the case of sulfur, nitrogen also has a strong coordinating ability to a metal complex. Consequently, metal complex-catalyzed diazo decomposition in the presence of an amine or imine usually requires high reaction temperatures (Figure 6).

11.05.4.1 Nitrogen Ylide and Subsequent Reactions

11.05.4.1.1 [2,3]-Sigmatropic rearrangements

Allyl or propargyl ammonium ylides undergo rapid [2,3]-sigmatropic rearrangement. This reaction is an effective approach to synthesize α-amino acid derivatives. Burger and co-workers reported use of 3,3,3-trifluoro-2-diazopropanoate **143** as a carbene precusor in ammonium ylide formation. Subsequent [2,3]-sigmatropic rearrangement gives α-trifluoromethyl-substituted amino esters **146** (Equation (20)).[50]



(20)

Intramolecular generation of cyclic ammonium ylide and subsequent [2,3]-sigmatropic rearrangement has been demonstrated to be a powerful method for synthesis of cyclic amines.[51,51a,51b] For example, Clark and Hodgson generated spiro cyclic ammonium ylide **148** by $Cu(acac)_4$-catalyzed reaction of diazo compound **147**. Subsequent [2,3]-sigmatropic rearrangement gave **149**, which is a key structural unit of alkaloid manzamine A (Equation (21)).[51,51a] McMills and

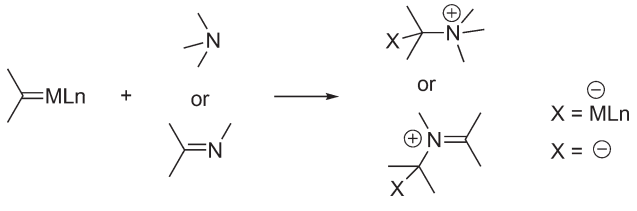
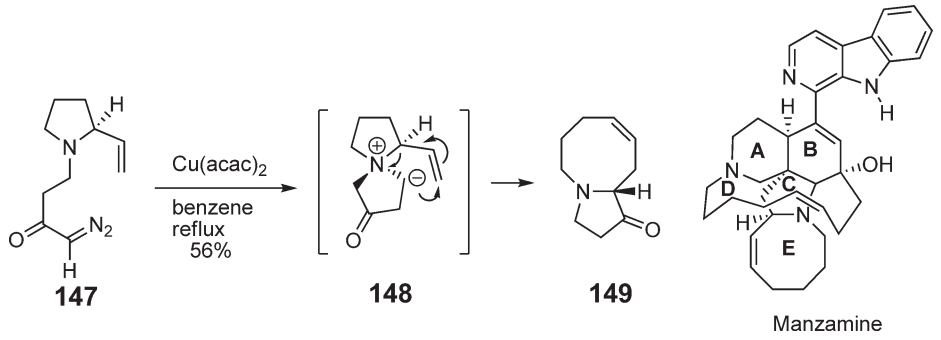


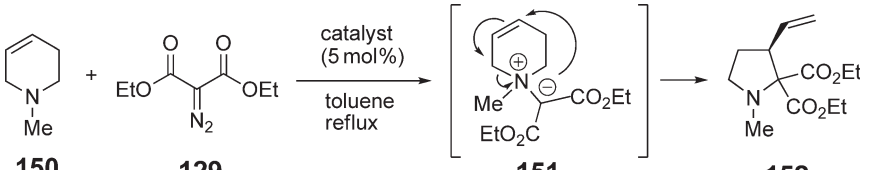
Figure 6 Generation of nitrogen ylide.

co-workers have developed a new approach to azacyclooctene- and azacyclononene-containing substrates based on similar reaction.[52]



(21)

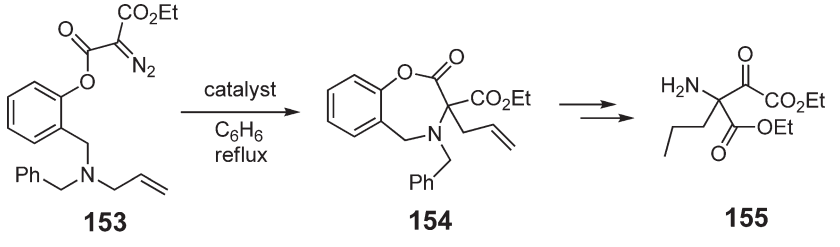
It has been noted that for the ammonium ylide generation copper catalysts such as copper(II) acetylacetonate [$Cu(acac)_2$] and $Cu(hfacac)_2$ are superior over Rh(II) catalysts. Sweeney and co-workers have recently reported copper-catalyzed [2,3]-sigmatropic rearrangement of ammonium ylide generated from tetrahydropyridines **150** and diazo ester **129** (Equation (22)).[53,53a] A detailed study on the reaction conditions has revealed that $Cu(acac)_2$ is the best catalyst for this reaction.



catalyst
$Cu(acac)_2$ 80%
$Rh_2(OAc)_4$ 25%

(22)

A new synthesis of α-substituted and α,α-disubstituted α-amino acid derivatives based on the ammonium ylide formation/[2,3]-sigmatropic rearrangement has been recently reported by Clark's group.[54,54a] Decomposition of α-diazo β-keto ester **153** was studied in detail with $Rh_2(OAc)_4$, $Cu(acac)_2$, and $Cu(hfacac)_2$ as the catalyst. $Cu(acac)_2$ and $Cu(hfacac)_2$ gave similar results, but $Rh_2(OAc)_4$ turned out less effective (Equation (23)).



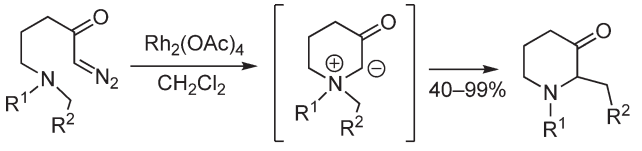
(23)

Catalyst	*Yield* (%)
$Cu(acac)_2$	59
$Cu(hfacac)_2$	81
$Rh_2(OAc)_4$	42

11.05.4.2 [1,2]-Shift (Stevens rearrangement) and Related Reactions

Ammonium ylides undergo [1,2]-shift in a manner similar to oxonium and sulfonium ylides. A preferentially migrating group is usually a benzyl group. A sequence of intramolecular formation of ammonium ylide and subsequent rearrangement was extensively explored by West and co-workers in the synthesis of cyclic amines.[55,55a–55g]

$Rh_2(OAc)_4$-catalyzed reaction of diazo ketone **156** gave ammonium ylide **157**, which undergoes [1,2]-shift to give piperidine derivatives **158** (Equation (24)).[55a] In this case, the migrating group is $CH_2C_6H_5$, CO_2Et, and *p*-XC_6H_4. When X is MeO or Ac, homocoupling product **159** is also isolated in 19% or 25% yield, respectively. Formation of the homocoupling products is a strong evidence that the [1,2]-shift proceeds through a radical pair intermediate.[15,15a]



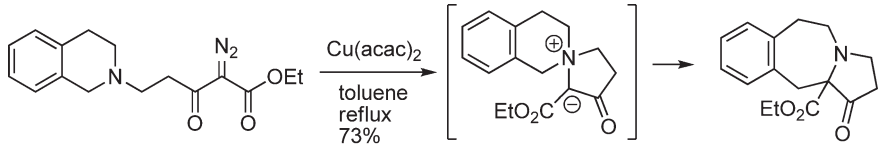
(24)

R^1 = Me, Et
R^2 = C_6H_5, CO_2Et, *p*-$MeOC_6H_4$, *p*-$NO_2C_6H_4$, *p*-AcC_6H_4

The cyclic ammonium ylide/[1,2]-shift approach has been successfully applied by West and Naidu to a key step in the total synthesis of (−)-epilupinine, one of the biologically active lupin alkaloids. $Cu(acac)_2$-catalyzed diazo decomposition of enantiomeric pure diazoketone **160** in refluxing toluene generates a spiro ammonium ylide **161** and **162**, which then undergoes [1,2]-shift to give rise to a quinolizidine skeleton as a mixture of diastereomers (95 : 5) (Scheme 17).[55b,55e] Major diastereomer **164** has enantiomeric purity of 75% ee. The partial retention of stereochemistry indicates predominant formation of ylide **162**, which subsequently undergoes stereospecific [1,2]-shift.

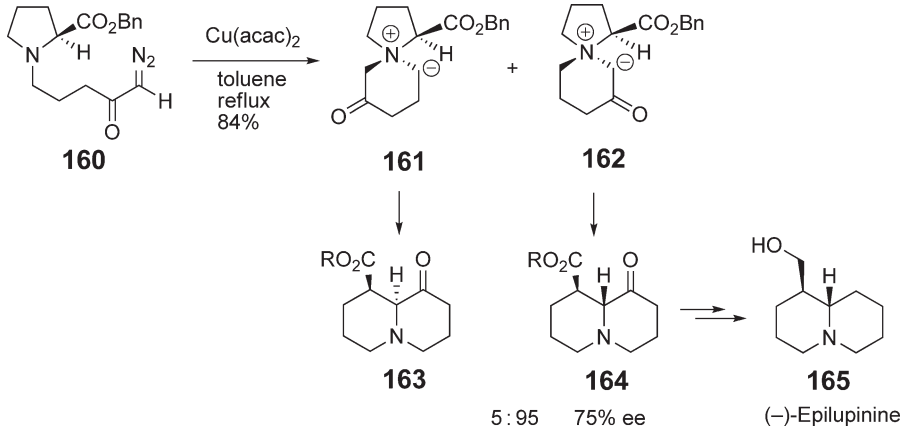
More recently, Naidu and West have utilized a ring expansion reaction of spiro azetidinium ylide **167** in the synthesis of pyrrolizidine alkaloids. Spiro azetidinium ylide **167** is generated through a $Cu(acac)_2$-catalyzed intramolecular reaction of a copper carbene complex with a pendant amino moiety. Subsequent [1,2]-shift gives fused bicyclic products **168** and **169** as a diastereomeric mixture. Each diastereomer was further converted to naturally occurring pyrrolizidines (±)-turneforcidine and (±)-platynecine, respectively (Scheme 18).[55e]

Padwa *et al*. utilized the ammonium ylide [1,2]-shift in the synthesis of tetrahydroisoquinoline and benzazepine fused with a five-membered ring, a structure found in a cephalotaxine family.[56,56a] When diazo ester **172** is treated with a catalytic amount of $Cu(acac)_2$ in refluxing toluene, 5,7-fused compound **174** is isolated in 73% (Equation (25)). Again, use of $Rh_2(OAc)_4$ results in slow reaction and eventually gives a complex mixture of the products after a prolonged reaction time.

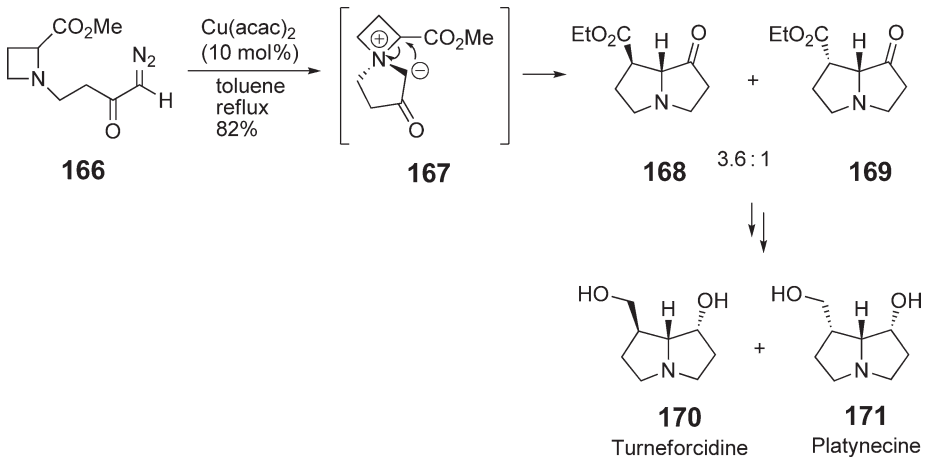


(25)

The asymmetric catalysis has not been well explored in the reaction of a metal carbene complex-generated ammonium ylide. The ammonium ylide reaction is assumed to proceed through a free ylide rather than a metal

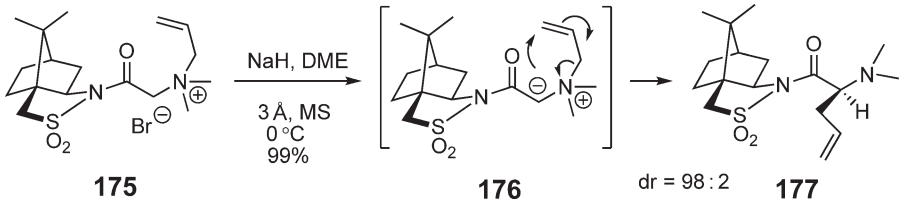


Scheme 17



Scheme 18

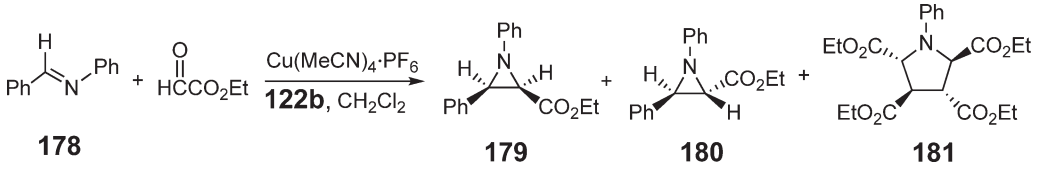
complex-associated ylide, because the catalytic diazo decomposition in the presence of an amine generally requires high temperature possibly due to complexation of the amine with the metal catalyst. Very recently, Sweeney and co-workers have reported asymmetric [2,3]-sigmatropic rearrangement of glycine-derived allyl ammonium ylide **176** (Equation (26)).[57] The results demonstrate that the [2,3]-sigmatropic rearrangement of allyl ammonium ylide **176** is highly feasible and proceeds efficiently at 0 °C. Although the ammonium ylide in this case is generated by deprotonation of ammonium salt precursor **175**, the high stereoselectivity is induced by Oppolzer's camphorsultam to suggest a possible catalytic asymmetric reaction through a metal carbene complex. The key to this goal may be the search for an efficient catalytic system that allows the reaction to be carried out at lower temperatures.



(26)

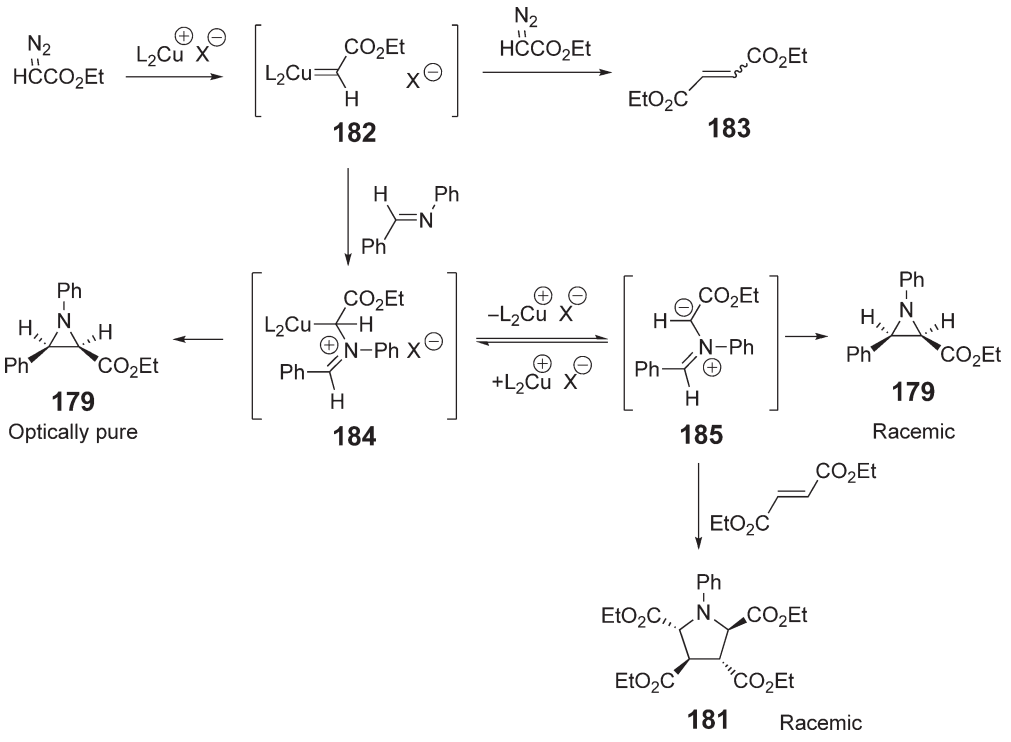
11.05.4.2.1 Azomethine ylide and related reactions

Like the reaction of carbonyl compounds with a metal carbene complex to generate carbonyl ylides, a metal carbene reacts with imine readily and generates azomethine ylides. The major reaction pathways of azomethine ylides are ring closure and 1,3-dipolar addition, which afford aziridine and pyrrolidine derivatives, respectively. The aziridines are useful precursors for synthesis of nitrogen-containing compounds of biological importance. Jacobsen and co-workers utilized a chiral Cu(I) complex in the asymmetric catalytic carbenoid transfer to imines (Equation (27)).[58] The reaction of imine **178** and ethyl diazoacetate in the presence of $Cu(MeCN)_4 \cdot PF_6$/bisoxazoline **122b** gives aziridine **179** and **180** as a mixture of diastereomers (37%), together with pyrrolidine **181** (10%). Enantioselectivity for the *cis*- and *trans*-aziridines is 44% ee and 35% ee, respectively, while the pyrrolidine product **181** is racemic.



(27)

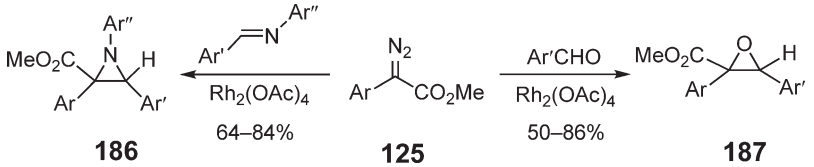
A plausible reaction mechanism for this reaction was proposed by the authors. The Cu(I) carbene **182** generated from ethyl diazoacetate and the chiral Cu(I) complex can either react with another molecule of ethyl diazoacetate to form a mixture of diethyl maleate and fumarate **183**, or with the imine lone pair to form a Cu(I)-complexed azomethine ylide



Scheme 19

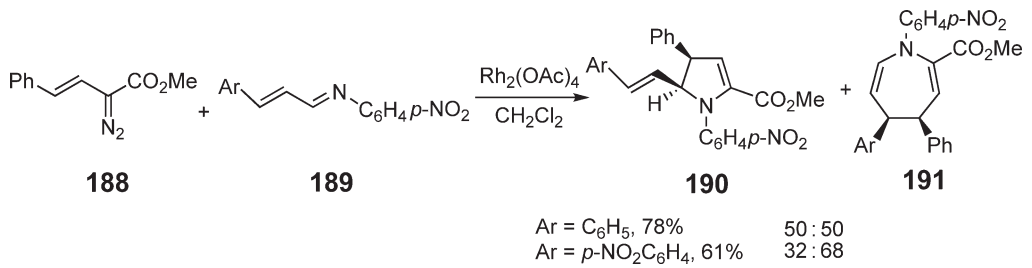
184, which is reasonably considered to be in an equilibrium with the corresponding free azomethine ylide 185. If the intramolecular ring closure occurs from the complexed ylide 184, the aziridines 179 can be formed enantioselectively. The free azomethine ylide can either undergo 1,3-dipole cycloaddition to ylide diethyl fumarate or intramolecularly cyclize to afford aziridine, giving the products in racemic form in both cases (Scheme 19). This seminal study is the first demonstration that catalytic asymmetric induction is possible in this type of reaction.

Doyle and co-workers have recently reported Rh(II) or copper complex-catalyzed reaction of aryldiazoacetate or vinyldiazoacetate with imines.[34,59,59a,59b] Diastereoselective aziridine formation is observed in the $Rh_2(OAc)_4$-catalyzed diazo decomposition of diazo phenylacetate in the presence of arylimine (Equation (28)).[34] When the reaction was carried out with aldehyde, epoxide 187 was obtained.

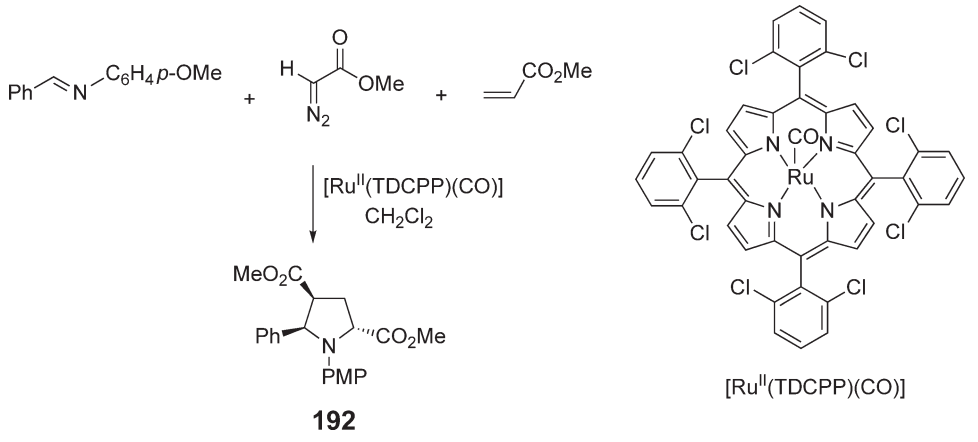


(28)

Further study with $Rh_2(OAc)_4$-catalyzed reaction styryldiazoacetate 188 and cinnamaldehyde derived imine 189 found the formation of dihydropyrrole 190 and dihydroazepine 191 in high yields and with high stereocontrol. No aziridine products were observed in these cases (Equation (29)).[59]



(29)

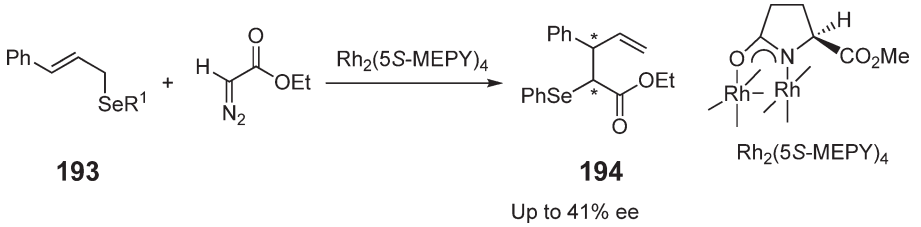


Scheme 20

In addition to copper and rhodium catalysts commonly used in the generation of metal carbene complexes, other transition metals have also been explored in the diazo decomposition and subsequent ylide generation.[1a] Che and co-workers have recently studied ruthenium porphyrin-catalyzed diazo decomposition and demonstrated a three-component coupling reaction of α-diazo ester with a series of *N*-benzylidene imines and alkenes to form functionalized pyrrolidines in excellent diastereoselectivities (Scheme 20).[60]

11.05.5 Ylide Generation from Other Heteroatoms and Subsequent Reactions

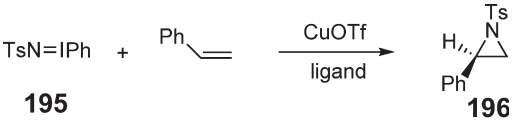
Transfer of a metal carbene moiety from a metal carbene complex to a heteroatom other than oxygen, sulfur, and nitrogen is possible. One such example is the report by Uemura and co-workers, who disclosed catalytic asymmetric reaction of ethyl diazoacetate with (*E*)-cinnamyl phenyl selenide **193** (Equation (30)).[42] The reaction afforded **194** as a diastereomeric mixture (58 : 42). Using Rh_2(5*S*-MEPY)$_4$, they achieved up to 41% ee.



(30)

11.05.6 Reaction of Lewis Base with Nitrene or Metal Complexed Nitrene

In 1993, Jacobsen and Evans simultaneously reported that [*N*-(*p*-tolylsulfonyl)imino]phenyliodinane (TsN=IPh, **195**) is an efficient asymmetric nitrene transfer reagent to alkenes in the presence of a catalytic amount of a copper(I) salt and a chiral diimine ligand or a chiral bis(oxazoline) ligand (Equation (31)).[61,61a] Mechanistic study by Jacobsen and co-workers suggests that a discrete copper(III) nitrene complex is an intermediate responsible to the reaction.[62]



(31)

ligand = **122a**, 89%, 63% ee
ligand = **34**, 79%, 66% ee

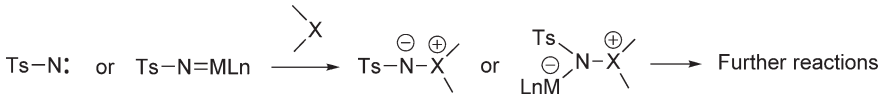
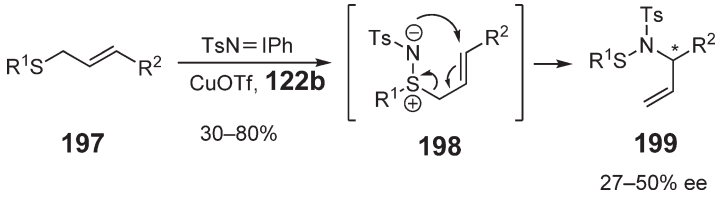


Figure 7 Generation of ylide from nitrene.

In view of the chemistry of a metal carbene complex, it is reasonable to expect that nitrene or metal-complexed nitrene will similarly interact with Lewis base to generate ylide-like species, which then proceeds to undergo further transformations (Figure 7).

Uemura and co-workers studied the reaction of TsN=IPh and allyl sulfide in the presence of chiral Cu(I) complex. The initially generated nitrene intermediate reacts with allyl sulfide **197** to give sulfimide **198**, which undergoes [2,3]-sigmatropic rearrangement to yield sulfonamide **199** (Equation (32)).[63,63a] With chiral bis(oxazoline) ligand **122b**, they have achieved moderately high enantioselectivity. The significantly high level of asymmetric induction supports a metal-associated ylide in the product-forming step.



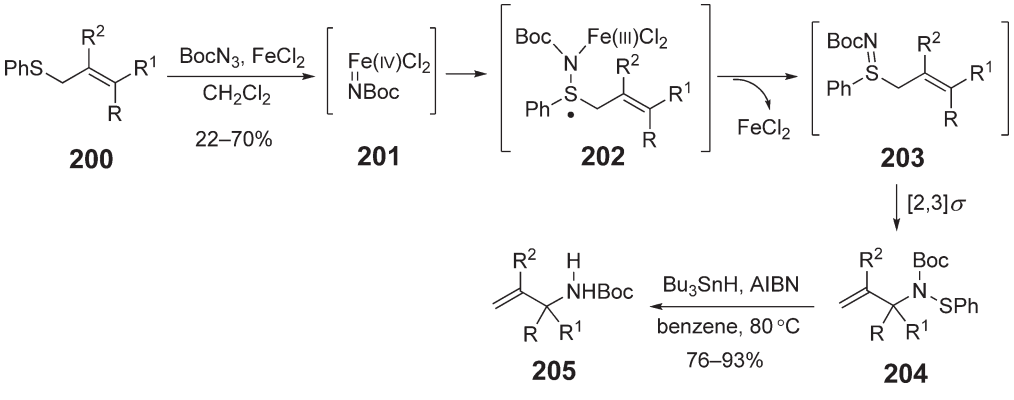
(32)

Besides commonly used TsN=IPh, TsN_3 can also be employed as a nitrene source. Bach and Körber have recently reported an Fe(III)-catalyzed imidation of allyl sulfides **200** with *N-tert*-butyloxycarbonyl azide ($BocN_3$), followed by [2,3]-sigmatropic rearrangement (Scheme 21).[64] The azide reacts with $FeCl_2$ to generate Fe(IV) nitrene complex **201**, which then reacts with allyl sulfide **200**, to give an intermediate sulfimide **203**, presumably through Fe(III) intermediate **202**.

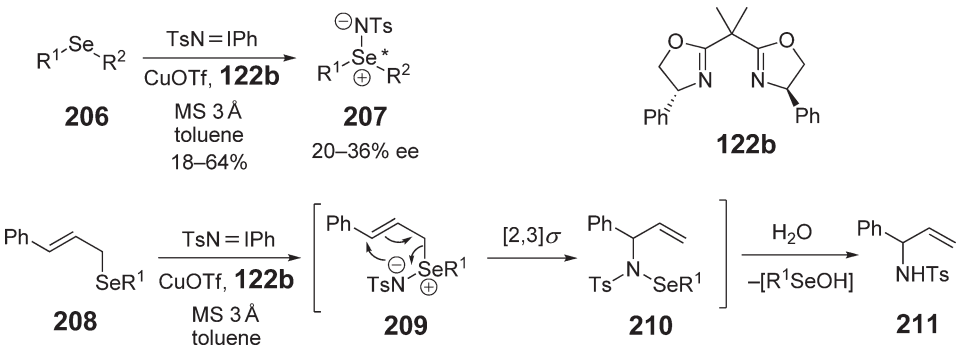
Nitrene transfer to selenide is also possible. Catalytic asymmetric induction in this process has been studied with Cu(OTf)/bis(oxazoline) catalyst (Scheme 22).[65] When prochiral selenide **206** and TsN=IPh are allowed to react in the presence of Cu(OTf)/chiral bis(oxazoline) **122b**, selenimide **207** is obtained with enantioselectivity of 20–36% ee. When arylcinnamyl selenide **208** is applied to this reaction, corresponding selenimide **209** is produced which undergoes [2,3]-sigmatropic rearrangement to afford chiral allylic amides **211** in up to 30% ee.

11.05.7 Concluding Remarks

In the past 10 years, studies on the reaction of ylides generated from metal carbene complexes have witnessed tremendous progress. In particular, synthetic applications of the three most common reactions of ylides, namely [2,3]-sigmatropic rearrangement, [1,2]-shift, and 1,3-dipole cycloaddition, have gained considerable success to demonstrate



Scheme 21



Scheme 22

their high potential. The cascade process based on the ylide formation allows one to construct complex structures from relatively simple starting diazo compounds in one-pot reactions. On the other hand, mechanistic insights into these reactions have been gained steadily over the past years. The effect of the catalyst or even the catalyst ligand on the reaction is remarkable. These findings serve as guidelines for designing highly chemoselective metal carbene reactions.

With the development of synthetic methodologies based on the reaction of metal carbene-derived ylides, the stereoselectivity of the reaction has become an important issue. Especially, asymmetric catalysis is a challenging problem. Although some progress has been made, the study along this line much lags behind other types of reactions with metal carbene complexes, such as C–H insertion and cyclopropanation. With the understanding of the reaction mechanism, highly enantioselective metal carbene-derived ylide reaction may be expected in the following years.

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11.06
Olefin Cross-Metathesis

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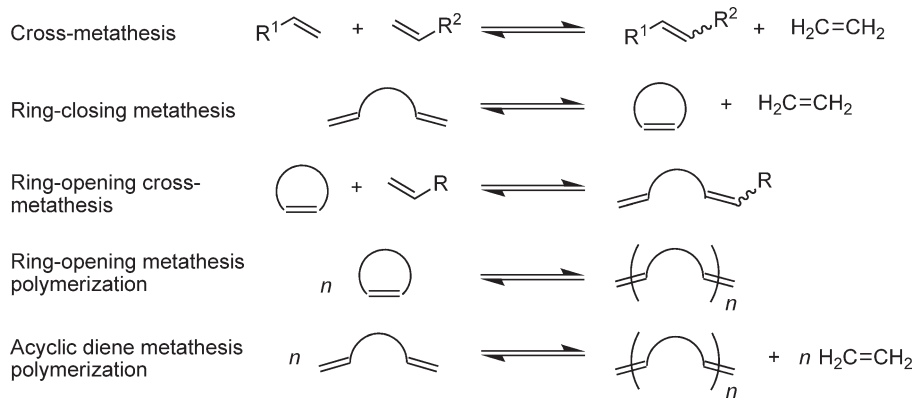
11.06.1 Introduction

The reliable and efficient generation of carbon–carbon bonds underpins the foundation of chemical synthesis.[1] In this, the preparation of olefins is of particular interest, as alkenes represent a ubiquitous element in many complex molecules. In addition, olefins frequently serve as versatile intermediates in the preparation of other functional groups, such as epoxides, aziridines, and diols.[2] Consequently, reaction methodologies that are capable of effecting the stereoselective preparation of olefins are of great value. To date, several organometallic and non-metal-mediated processes for olefin preparation have been developed.[3] Of the organometallic methods, a majority are palladium-catalyzed and typically require the synthetic investment of an activating group to proceed (e.g., Suzuki–Miyaura,[4] Stille,[5] and Heck[6] coupling reactions). In the case of non-metal-mediated processes – for example, the Wittig reaction[7] – reactive functional groups such as aldehydes or ketones are generally employed, often mandating the use of protecting group strategies prior to olefin formation. In addition, the stoichiometric formation of non-volatile byproducts is commonly observed.

An alternative approach to alkene formation is the olefin cross-metathesis (CM) reaction (Scheme 1). In contrast to the methods described above, olefins serve exclusively as the starting materials in CM, and no change in oxidation state is required. Furthermore, the reaction byproduct is typically a volatile olefin (e.g., ethylene) that can readily be removed from the reaction system. The abundant commercial availability of terminal olefins as starting materials additionally highlights the synthetic utility of a CM protocol. Despite these attractive features, challenges in controlling both the product selectivity and stereochemistry of CM reactions have previously limited the widespread application of this methodology. Fortunately, recent advances in metathesis catalyst development and an improved understanding of the factors affecting product selectivity have led to the increased usage of this reaction, as evidenced



Scheme 1 General examples of olefin metathesis reactions.

by the exponential growth of CM applications reported in the literature. For example, between the years 1990 and 1999, 85 articles and 10 patents were published regarding CM; since 2000, over 450 new journal reports and 22 patents have been reported. (These data were obtained from keyword searches conducted on cross-metathesis; SciFinder Scholar; American Chemical Society (June 1st, 2005).)

Due to the copious amount of recent literature pertaining to olefin CM, a comprehensive review would prove repetitive, as this reaction is now a widespread synthetic tool. Fortunately, numerous reviews are now readily available on this subject.[8,8a–8e,9] This chapter therefore focuses on reports pertaining to important aspects in either the concept or the application of alkene CM. Allene,[10] alkyne,[11,11a] and enyne[12,12a] CM reactions are not included within the scope of this review. Drawing from the examples discussed, a series of general guidelines toward constructing a desired olefin CM transformation will be presented.

11.06.2 Olefin Metathesis

Olefin metathesis is a thermodynamically controlled reaction that has become a highly versatile synthetic method for alkene preparation. Although originally discovered in the 1950s,[13,13a–13c] it was not until the mid-1980s that well-defined, homogeneous catalyst systems were developed and investigated for a wide range of organic transformations, including: ring-closing metathesis (RCM),[14] ring-opening metathesis polymerization (ROMP),[15] acyclic diene metathesis polymerization (ADMET),[16] ring-opening/cross metathesis (ROCM),[17] and CM (Scheme 1). Asymmetric variants of RCM[18,18a–18c] and ROCM[19,19a,19b] have also been developed.

Representative examples of commonly used homogeneous olefin metathesis catalysts are listed in Figure 1. The commercially available alkoxy-amido molybdenum complex **1**[20,20a,20b] and ruthenium-based complex **2**[21,21a,21b] were the first of such catalysts to be widely used. In general, the utility of both catalysts is complementary.[22] Molybdenum catalyst **1** is typically more active than **2**; however, it is extremely sensitive to air and moisture due to the oxophilicity of the metal center, necessitating its synthesis and handling under an inert atmosphere. The oxophilicity of **1** also decreases functional group tolerance toward Lewis-basic substrates, such as aldehydes or alcohols, thereby limiting its application in organic synthesis.[23] In contrast, late-transition metal systems preferentially react with olefins in the presence of heteroatomic functionalities. For this reason, ruthenium catalyst **2** is preferentially employed in organic applications, as it readily tolerates metathesis substrates containing unprotected alcohols, amides, aldehydes, and carboxylic acids.[21a]

Efforts to optimize catalyst **2** led to the development of the more active *N*-heterocyclic carbene- (NHC-) derived catalysts **3**–**5**.[24–26] In particular, several references have discussed unsaturated NHC catalyst **4**.[25,25a–25d] Reports investigating the mechanism of ruthenium alkylidene-catalysed olefin metathesis have been discussed.[26,26a,26b] Compared to catalyst **2**, ruthenium NHC systems possess greater electron density at the metal center due to the increased σ-donation of the imidazoylidene ligand relative to phosphine. This factor, coupled with the reduced ability of NHC ligands to accept π-backbonding from the metal, affords enhanced selectivity for olefin binding and contributes to the remarkable performance of these systems in metathesis reactions. Subsequent modification of catalyst **5**'s neutral, or L-type, ligands led to the development of pyridine and isopropoxystyrene-derived catalysts **6**[27,27a] and **7**,[28,28a–28g] respectively, which displayed a further increase in metathesis activity.

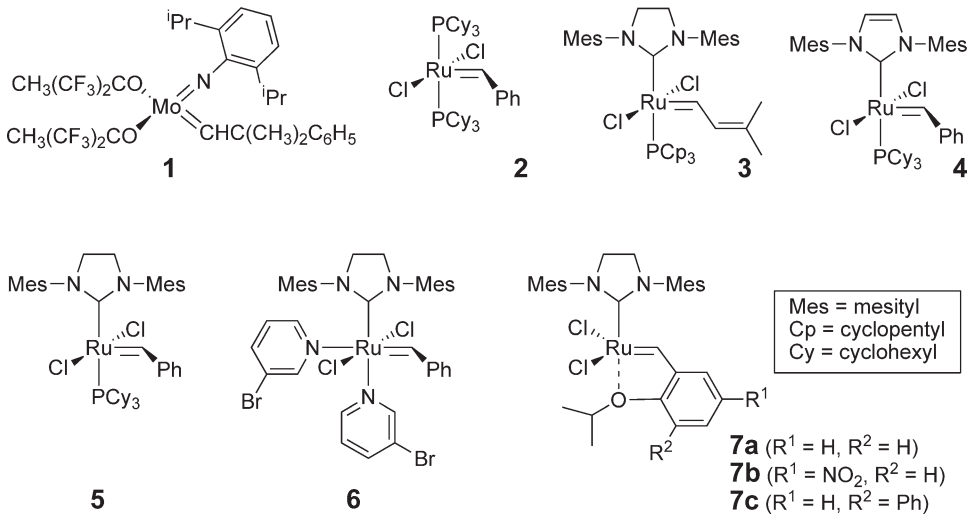


Figure 1 Examples of well-defined olefin metathesis catalysts.

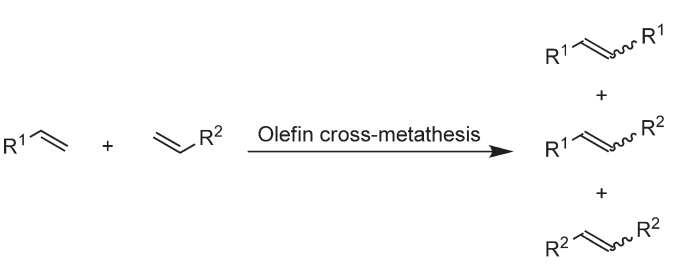
11.06.3 Selectivity in CM

While catalyst optimization is pertinent to all olefin metathesis procedures, the challenge to CM is not merely functional group tolerance and olefin reactivity, but also the participation of these functionalities in determining CM product selectivity. Product selectivity in olefin CM, driven by improving the yield of the desired cross-product relative to homodimer formation, is both catalyst and substrate dependent. An understanding of the factors directing product selectivity is therefore crucial to the utility of olefin CM, and will be introduced in this section. Two main selectivity issues will be addressed: (i) CM heterocoupling versus homocoupling, and (ii) stereoselective product formation.

11.06.3.1 Heterocoupling versus Homocoupling in Olefin CM

As olefin CM is a thermodynamically controlled intermolecular reaction, there are several inherent challenges toward achieving product selectivity. First and foremost, if a catalyst cannot distinguish between the two olefin cross-partners, a statistical mixture of products will result (Scheme 2). In this situation, one of the olefin cross-partners would need to be added to the reaction in excess to achieve a synthetically useful yield (e.g., 10 equiv. required to attain a 91% yield).

The statistical distribution scenario in Scheme 2 assumes that complete conversion of the starting terminal olefins is achieved and that any internal olefins formed over the course of the reaction react equally with the catalyst. However, in cases where low catalytic activities do not ensure complete conversion, CM reactions become increasingly difficult to execute, as the desired product must now be separated from a reaction mixture containing five distinct olefins. The use of excess olefin cross-partner compounds this problem by lowering the effective catalyst



$R^1:R^2$	*CM yield*
1 : 1	50%
2 : 1	66%
4 : 1	80%
10 : 1	91%
20 : 1	95%

Scheme 2 Statistical distribution of CM products.

loading, which translates to lower reaction rates and an increased rate of catalyst decomposition[29,29a] relative to productive cross-product formation. Fortunately, the development of the highly reactive NHC catalysts **3–7** has served to counteract this problem and expand the utility of CM reactions, as these catalysts possess the capacity for complete starting material consumption, thereby simplifying product purification.

Product selectivity in olefin CM, as previously mentioned, is dependent upon both catalyst reactivity and olefin substitution. If both of these factors could be tailored to overcome the statistical distribution of products, the starting olefins could potentially be used in equal stoichiometries. To do this, two olefins that do not react at equal rates with the catalyst must be employed. At first, this goal appears unrealistic, as there is no apparent orthogonality in cross-coupling partners when dealing with two terminal olefins. As a result, external means of control are often employed to limit alkene homodimerization in the CM of equireactive olefins. One of the first examples, reported by Blechert and co-workers in 1996, was to immobilize one olefin on a polymeric support to improve CM efficiency via site separation.[30] While non-statistical yields of the heterocoupled product were observed, tethering failed to completely suppress unwanted homodimerizations, and the use of a large excess of one olefin was still required. This use of substrate immobilization was further investigated by Tang and Wareing,[31] who found that site separation does not necessarily assure physical separation when using 1% cross-linked polystyrene resin, a phenomenon that had previously been observed by Collman and co-workers in the immobilization of transition metal complexes.[32] However, by forgoing the use of a solid support, a recent example using two different, but complementary, oligoamide strands in a template-based approach has achieved the first highly selective CM reactions of equireactive olefins.[33] In this example, product selectivity was attributed to the selective formation of non-covalent heterodimers prior to CM.

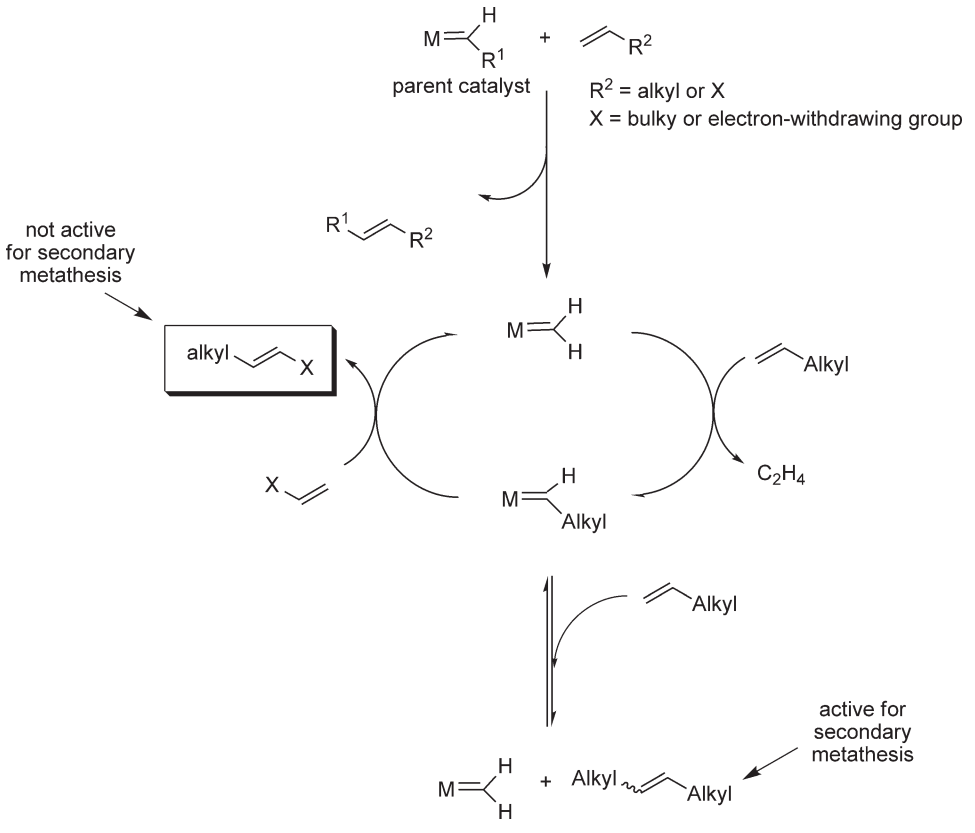
In the absence of template-based control, extensive experimental investigation has determined that there are several important conditions that must be met for selective CM to occur. First, decreasing the electron density or increasing the steric bulk associated with one cross-partner relative to the other generally suppresses homodimerization. In product-selective CM reactions, the underlying implication is that one cross-partner reacts to form the resting-state metal carbene (Scheme 3). As a result, the less active cross-partner, such as an electron-deficient olefin, only reacts in a productive manner to afford the desired CM product. However, a terminal olefin also has the potential to rapidly homodimerize prior to reacting with a bulky or electron-deficient cross-partner. If this occurs, the capacity of the homodimer to undergo secondary metathesis also becomes relevant.

Understanding the relative rates of both productive heterocoupling and homodimerization reactions allows for the judicious selection of cross-partners that can participate in a highly selective CM reaction, even when equal stoichiometries of reactants are employed. There are five relevant equilibria and 10 rate constants in CM (Scheme 4; the rate constants for olefin *E*/*Z* isomerization have been excluded for simplicity). In the simple scenario where all the rates are similar, and the reaction can achieve equilibrium, the expected statistical cross-product yield is 50%. If, however, one olefin (e.g., $R^2CH{=}CH_2$), as a consequence of either steric or electronic factors, reacts at a slower rate (k_3) than the other reactions, such that k_1, k_{-1}, k_2, $k_4 \gg k_3$, and it is assumed that the productive cross-product is metathesis inactive (k_{-2}, k_{-4}, and k_{-5} are negligible), then the selective removal of ethylene from the reaction system should funnel all olefins toward selective cross-product formation.[34] In this reaction scenario, cross-product yields much greater than the statistically predicted 50% could be attained.

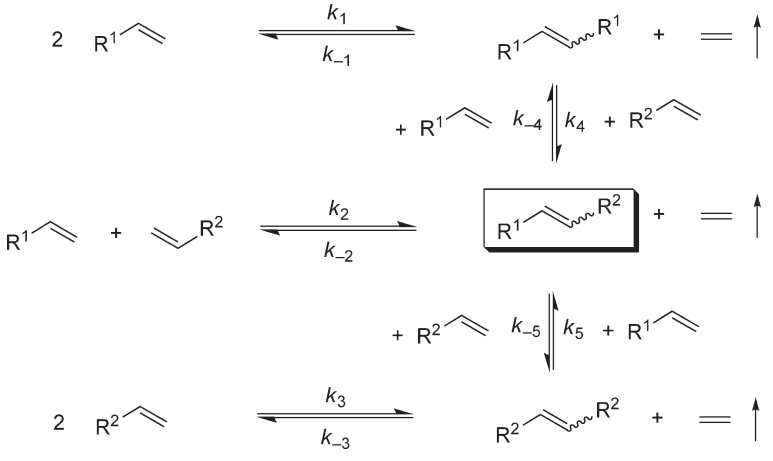
As illustrated above, various possible alkylidene intermediates and numerous primary and secondary pathways are involved in olefin CM. To simplify selective reaction design, an empirical product selectivity model was recently developed by Grubbs and co-workers, in which some degree of orthogonality amongst olefin cross-partners was established by categorizing the relative capacity of olefins to homodimerize in the presence of a given metathesis catalyst.[35]

Olefins can be divided into four categories on the basis of their propensity to homodimerize (Figure 2). Type I olefins are able to undergo rapid homodimerization and whose homodimers can equally participate in CM. A CM reaction between two olefins of this type will generally result in a statistical product mixture. Type II olefins homodimerize slowly, and, unlike type I olefins, their homodimers can only be consumed with difficulty in subsequent metathesis reactions. Type III olefins are unable to undergo homodimerization, but have the capacity to undergo CM with either type I or II olefins. As with type I olefins, the reaction between either two type II or type III olefins should result in non-selective CM. Type IV olefins are inert to olefin CM, but do not inhibit the reaction; therefore, they can be regarded as spectators to CM.

Section 11.06.4 of this chapter highlights the substrate scope of olefin CM reactions. Based on this survey of the literature, olefins will then be placed into their appropriate category based upon catalyst activity and substrate tolerance, citing specific examples (Section 11.06.4.6). It is important to note that olefin-type characterization can change in response to catalyst reactivity. For example, an olefin may be characterized as a type III olefin in CM



Scheme 3 Proposed reaction pathway for selective cross-metathesis.



Scheme 4 Equilibria involved in olefin cross-metathesis.

reactions using the highly active catalyst **5**, but may be downgraded to a type IV olefin when using a less-active catalyst such as **2**. In addition, as olefin categorization is based upon experimental observation, the boundaries between each olefin class are not absolute. For example, non-bulky 1,1-disubstituted olefins are classified as type III olefins when using catalyst **5** (Table 4); however, the point at which this olefin class transitions to type IV upon increasing steric bulk is not well defined. Nevertheless, the ability to, if only partially, discriminate between olefin types enables chemoselectivity to be employed in the design of selective CM reactions.

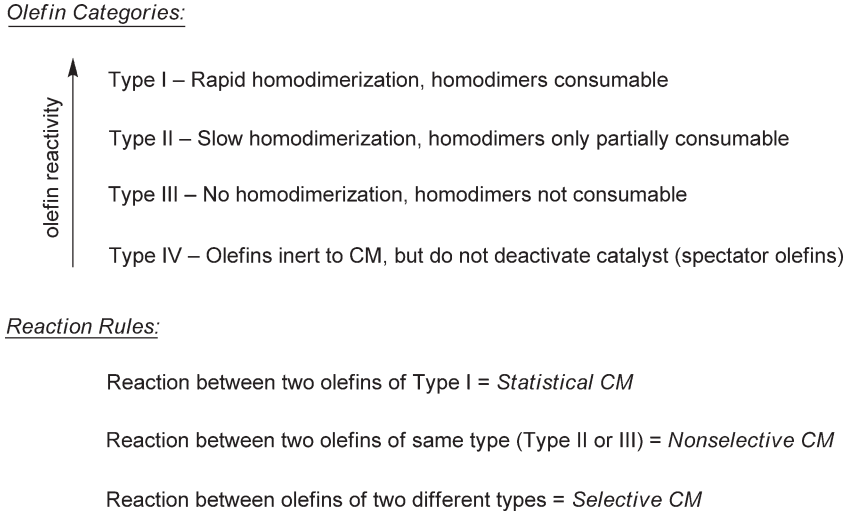


Figure 2 Olefin categorization and rules for selective CM.

11.06.3.2 Stereoselective Olefin CM Reactions

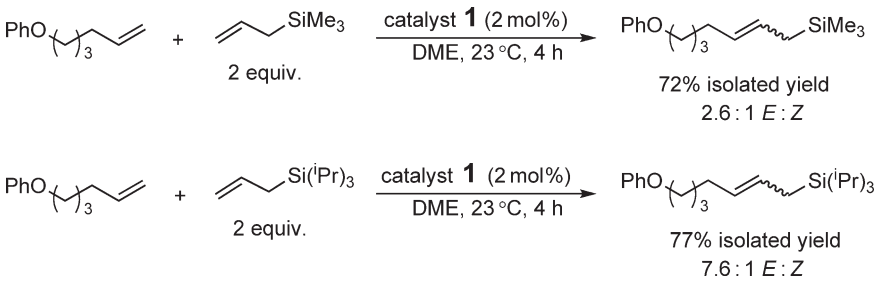
Despite the remarkable success of olefin metathesis catalysts in organic applications, one major challenge that remains is the diastereomeric control of olefin geometry. Olefin stereoselectivity is an issue in all metathesis reactions. However, prior to the widespread use of CM processes, it was only pertinent to the RCM of large rings (>8 carbons)[36] and in the backbone structure of ROMP-derived polymers.[37,37a,37b]

The stereoselectivity of olefin formation is crucial to the utility of CM. To date, a general metathesis catalyst capable of effecting diastereomeric control over a broad range of substrates has yet to be realized. Of particular interest is the development of a *Z*-selective catalyst, as *Z* olefins are a prevalent structural motif within both natural products and pharmaceutical agents.[38,38a–38c] Current examples of *Z*-selective olefin CM have proved to be substrate dependent. These include: the CM of enynes with alkenes,[39,39a,39b] acrylonitrile CM,[27a,40,40a,40b] the CM reaction of an allylstannane with an acetyl-protected allyl glucoside,[41] and isolated examples involving the homodimerization of homoallylamides[42] or 2,3-disubstituted benzo[*b*]furans.[43] In the absence of substrate selectivity, the creative use of removable tethers via an RCM protocol has been demonstrated to be an effective strategy for the preparation of *Z*-olefins.[44,44a,44b]

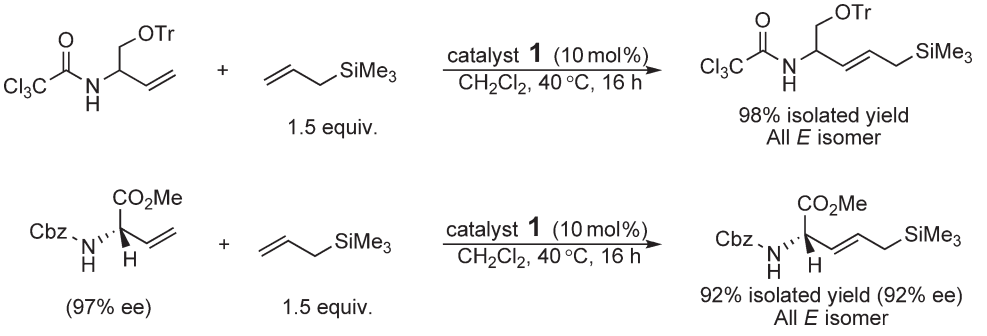
The design and development of a *Z*-selective CM reaction faces two major challenges: first, the thermodynamic preference for the formation of *E*-olefins renders their *Z*-counterparts difficult to prepare; second, any inherent kinetic *Z*-preference demonstrated by a catalyst can erode via secondary metathesis if the *E*-pathway is not blocked. Consequently, most efforts to effect stereoselective olefin formation have focused on the preparation of *E*-olefins.

A general strategy toward achieving *E*-selectivity in olefin CM relies upon the addition of steric bulk to the allylic position of the olefin. Crowe and co-workers reported one of the first examples of remote stereocontrol, where, in allylsilane CM reactions using catalyst **1**, enhanced *E*-selectivity was observed upon increasing the steric bulk of the silicon substituents.[45] For example, in the reaction of phenyl-4-pentenyl ether with allyltrimethylsilane, the resulting CM product was obtained with an *E*/*Z* ratio of 2.6 : 1; however, use of the bulkier allyltriisopropylsilane as a cross-partner afforded an improved *E*/*Z* ratio of 7.6 : 1 (Scheme 5). Analogously, using catalyst **2**, Grubbs and co-workers have reported that increasing the steric bulk of an allylic alcohol cross-partner can also improve *E*/*Z* selectivity. In this case, increasing the size of an alcoholic protecting group from acetoxy to *tert*-butyldimethylsiloxy was found to improve the *E*/*Z* ratio of the resulting CM product from 4.7 : 1 to 10 : 1.[8] In substrates containing an allylic 1,2-diol, bulky cyclic acetals have proved to be effective protecting groups, affording the desired cross-products with greater than 10 : 1 *E*/*Z* selectivity.[8,46]

Using catalyst **1**, Blechert and co-workers were able to demonstrate the first sterically controlled CM reaction for the exclusive preparation of *E*-olefins (Scheme 6).[47] The best results were obtained using various substituted allylic amines, where the completely stereocontrolled installation of allylsilanes was observed. The mild conditions employed in these examples are noteworthy, as minimal racemization occurred when highly epimerizable chiral allyl amino esters were employed.



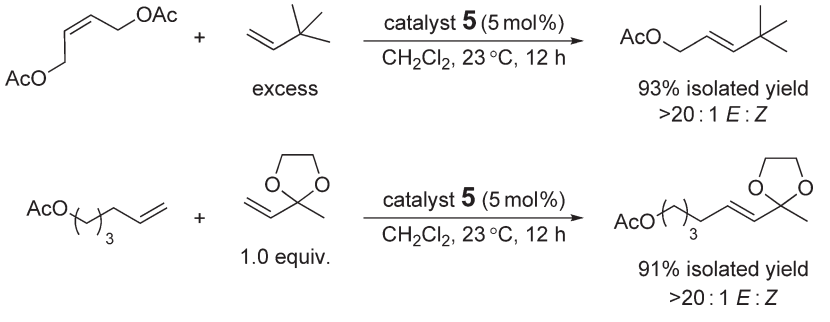
Scheme 5 Olefin stereoselectivity based on allylsilane substituents.



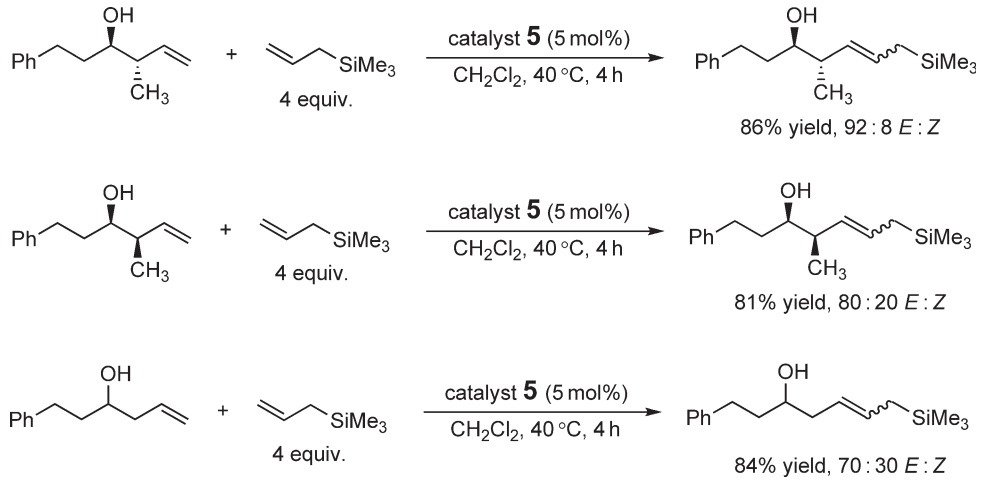
Scheme 6 Allylic substitution effects on CM olefin stereoselectivity.

Grubbs and co-workers have further investigated the influence of allylic substitution on *E*/*Z* diastereocontrol in olefin CM reactions using catalyst **5**. In some cases, it was found that secondary and tertiary allylic alcohols could afford complete *E*-selectivity, particularly when a cross-partner bearing allylic heteroatom substitution was used.[35] Also, in contrast to the less reactive catalyst **2**,[8] catalyst **5** was found to promote the CM reaction of olefins bearing quaternary allylic substitution (Scheme 7). The cross-partners in these examples represent type III olefins with respect to **5**; therefore, they can be applied either stoichiometrically or in excess without a reduction in yield. *E*/*Z* ratios of >20 : 1 were typically observed.

Stereoselectivity in olefin CM reactions can be further influenced by the relative stereochemistry of the substituents proximal to the olefin. In an example reported by Taylor and co-workers, the substitution pattern of a homoallylic alcohol was found to greatly affect the diastereoselectivity of allylsilane CM reactions (Scheme 8).[48] Homoallylic alcohols possessing *anti*-substitution were generally found to afford a higher proportion of *E*-cross-product than either *syn*-homoallylic alcohols or those bearing no allylic substituents at all. This result is intriguing, as it implies the possibility of using existing stereocenters to direct CM stereoselectivity. Indeed, this strategy has already been applied in a recent synthetic route toward the preparation of D-*erythro*-ceramide.[49]



Scheme 7 Quaternary allylic carbons in CM reactions with ruthenium catalyst **5**.



Scheme 8 Relative stereochemistry effects on olefin diastereoselection.

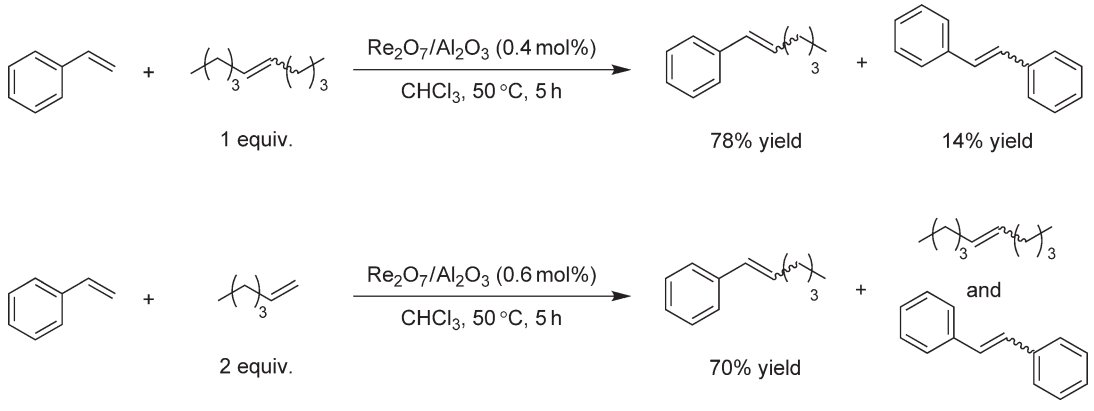
In addition to the examples outlined above, various functionalized olefins are also known to undergo CM with high *E*-selectivity.[50] Functional groups that contribute to high *E*-olefin formation will be discussed in Section 11.06.4. In these cases, CM provides an orthogonal route to products that are typically generated via either the selective C–H activation of alkenes or allylic oxidation.

11.06.4 Substrate Scope of the Olefin CM Reaction

11.06.4.1 Styrene CM

In 1985, Warwel and Winkelmüller reported a series of catalyst systems for the CM of either styrene or 4-vinylcyclohexane with unfunctionalized olefins (Scheme 9).[51] Using heterogeneous catalyst systems of Re_2O_7/Al_2O_3, among others, the authors demonstrated that both a substrate's electronic and steric properties govern CM product selectivity. Unfortunately, as the stereoselectivities of these reactions were not reported, the effect of a secondary allylic carbon on olefin stereoselectivity was not determined. Nevertheless, the non-statistical product distribution obtained in these reactions constitutes the first example of a product selective CM reaction.

The results obtained by Warwel and Winkelmüller provided the groundwork for the development of product-selective CM. In these reactions, the observed product selectivity was attributed to the diminished CM reactivity of stilbene relative to styrene. Indeed, subjecting an isolated homodimer to CM conditions constitutes a general strategy

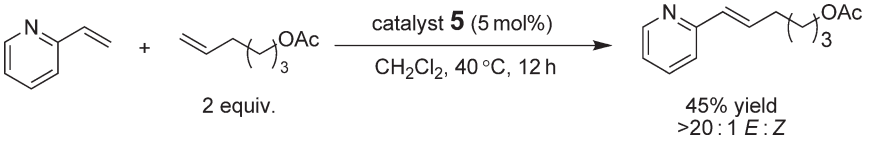


Scheme 9 Styrene CM using ill-defined, heterogeneous catalysts.

for determining whether or not a product-selective reaction is in operation. For example, when stilbene was submitted to the same reaction conditions as those employed with styrene, higher catalyst loadings and elevated reaction temperatures were required. Hence, Warwel and Winkelmüller were able to identify styrene as the first example of a type II olefin. It was further observed that higher yields of the desired CM product could be obtained when symmetrical internal aliphatic olefins were utilized rather than their terminal olefin counterparts, allowing for lower catalyst loadings and fewer equivalents of the respective cross-partner. The use of internal olefins to boost CM efficiency has proved to be invaluable in executing reactions with other metathesis systems, particularly those employing homogeneous ruthenium-based catalysts, where the methylidene intermediate derived from the metathesis of terminal olefins is prone to decomposition.[8a,52]

Styrene CM reactions were reinvestigated in the 1990s using well-defined, homogeneous catalyst systems. Schrock and co-workers demonstrated that molybdenum catalyst **1** could be applied in styrene homodimerization reactions, albeit with poor yields (~35%) relative to those obtained with aliphatic olefins (80–99%).[53] Concurrent work by Crowe and Zhang corroborated Schrock's results by demonstrating that, while catalyst **1** homodimerizes styrene very slowly, efficient CM reactions could be achieved upon combining styrene with a terminal olefin.[54] For example, the CM of styrene with 1-octene afforded the corresponding cross-product in 89% yield with >20 : 1 *E*-selectivity. Unlike the results obtained with the Re_2O_7/Al_2O_3 catalyst system, stilbene proved to be an inactive CM partner using **1**. In addition, the reaction between styrene and an internal olefin dimer was found to proceed only with difficulty. These results suggest that the CM reaction of styrene with terminal olefins using **1** is under kinetic control, where neither homodimer is readily formed, and only the cross-product is obtained (Scheme 4; k_2 is greater than all other rates). These results were later extended to include the highly *E*-selective CM reactions of vinylferrocene with various vinylarenes.[55]

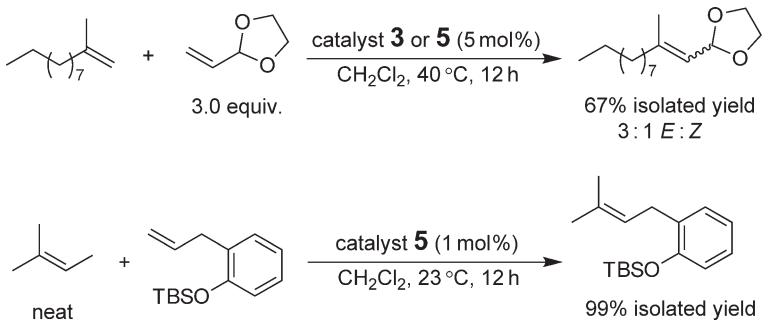
In addition to catalyst **1**, ruthenium-based systems can be used to effect styrene CM reactions. Catalyst **2** was the first to be employed in such systems; unfortunately, only moderate yields were typically obtained, and the methodology was restricted to the use of terminal olefin cross-partners.[56,56a–56e] Utilizing the more reactive NHC catalyst **5**, however, highly selective CM reactions between styrene and various mono- and disubstituted olefins were achieved in up to 99% yield with >20 : 1 *E*/*Z* selectivity.[57] Capitalizing on the remarkable functional group tolerance of this catalyst, heteroaromatic compounds were also found to be CM-active. For example, in the CM reaction of 2-vinylpyridine with 5-hexenyl acetate, the desired cross-product was produced in moderate yield (45%), despite the ability of pyridine to serve as an excellent ligand (Equation (1)).[27]



(1)

11.06.4.2 Preparation of Trisubstituted Olefins

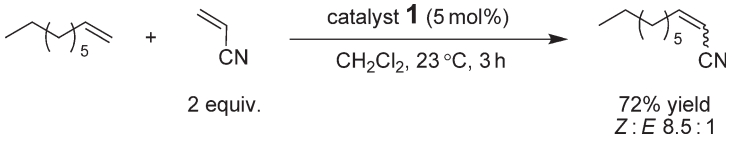
Geminally disubstituted olefins represent a particularly challenging class of substrates for CM. In fact, 1,1-disubstituted olefins can be regarded as spectator, or type IV, olefins in CM reactions using either catalyst **1**[54] or **2**.[58] The development of the highly active ruthenium-based NHC catalysts **3** and **5**, however, enabled the first application of 1,1-disubstituted olefins to selective CM reactions.[58] Using these catalysts, Grubbs and co-workers were able to demonstrate that geminally disubstituted alkenes serve as viable substrates in CM reactions with both terminal and internal olefins, providing the direct access to valuable products such as protected trisubstituted α,β-unsaturated aldehydes (Scheme 10). While moderate to high yields were achieved (53–87%), these reactions exhibited low stereoselectivities (~3 : 1) and required moderately high catalyst loadings (5 mol%). Grubbs and co-workers later found that the use of a symmetrically 1,1-disubstituted olefin, such as isobutylene or 2-methyl-2-butene, as a cross-partner circumvented the stereochemistry issue and enabled CM reactions using catalyst **5** to proceed in improved yield (up to 99%) with catalyst loadings as low as 1 mol%.[59] During the course of these investigations, it was determined that the 1,1-disubstituted olefins do not undergo homodimerization when either catalyst **3** or **5** is employed, thereby classifying them as type III olefins. These reactions provide a convenient alternative to the Wittig reaction in the preparation of prenyl functionalities, a ubiquitous structural element within both natural products (for examples of allyl to prenyl conversion in organic synthesis, see Refs: 60 and 60a) and ene reaction[61] chemistry.



Scheme 10 CM of 1,1-disubstituted olefins.

11.06.4.3 Electron-poor Olefins in CM

The CM of olefins bearing electron-withdrawing functionalities, such as α,β-unsaturated aldehydes, ketones, amides, and esters, allows for the direct installment of olefin functionality, which can either be retained or utilized as a synthetic handle for further elaboration. The poor nucleophilicity of electron-deficient olefins makes them challenging substrates for olefin CM. As a result, these substrates must generally be paired with more electron-rich cross-partners to proceed. In one of the initial reports in this area, Crowe and Goldberg found that acrylonitrile could participate in CM reactions with various terminal olefins using catalyst **1** (Equation (2)).[40] Acrylonitrile was found not to be active in secondary metathesis isomerization, and no homodimer formation was observed, making it a type III olefin. In addition, as mentioned in Section 11.06.3.2, this reaction represents one of the few examples of *Z*-selectivity in CM. Subsequent to this report, ruthenium complexes **6** and **7a** were also observed to function as competent catalysts for acrylonitrile CM.[27a,40a,40b]



(2)

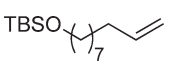
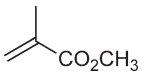
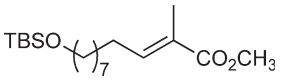
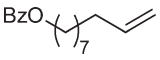
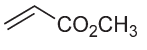
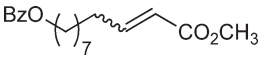
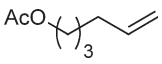
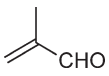
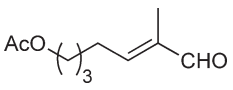
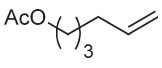
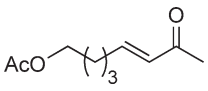
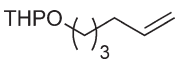
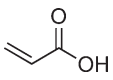
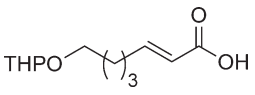
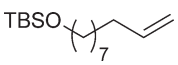
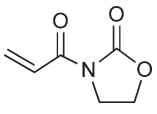
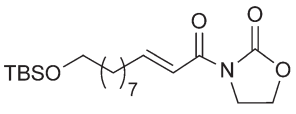
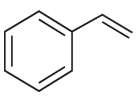
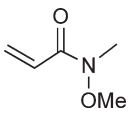
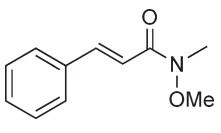
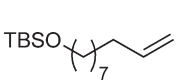
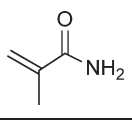
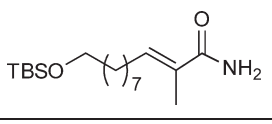
In reactions with other α,β-unsaturated compounds, molybdenum catalyst **1** proved too oxophilic,[40] and ruthenium catalyst **2** too unreactive,[62] to effectively promote CM reactions with substrates containing vinyl carbonyl moieties. However, ruthenium alkylidenes **3**,[63] **5**,[64,64a,64b] and, more recently, **7a**[65] have demonstrated unique activity toward these previously metathesis-inactive substrates. When employed in the CM reactions of α,β-unsaturated carbonyl compounds, these catalysts afforded excellent product selectivities with high diastereocontrol (Table 1). Of particular note is the CM of acrylic amides with styrene (entry 7), thereby allowing for the facile preparation of *E*-cinnamides. Moderate yield (66%) was obtained in this example despite the electronic similarity between the two substrates. This result indicates that electronic structure is not the sole governing feature in CM reaction selectivity, an observation that has also been made by Kawai and co-workers in the molybdenum-catalyzed CM of styrene with vinylferrocene.[55]

11.06.4.4 Reagent Synthesis by CM

The ability to provide highly functionalized reagents, such as unsaturated silanes and vinyl boronates, starting from terminal olefins is one of the most attractive attributes of CM, particularly when traditional methods for the preparation of such compounds are not synthetically straightforward. Therefore, significant research has been undertaken to determine the broad-spectrum chemoselectivity of olefin metathesis catalysts. In many cases, the use of a CM protocol in reagent synthesis is completely orthogonal to alternative methods of preparation.

Allyl- and vinylsilane chemistry was one of the first areas of reagent synthesis impacted by CM methodology. Allylsilanes are commonly employed in nucleophilic additions to carbonyl compounds, epoxides, and Michael acceptors (the Sakurai reaction);[66] vinylsilanes are useful reagents for palladium-coupling reactions.[67] As the ubiquitous application of CM to this substrate class has recently been described in several excellent reviews,[8b,68,68a] this topic will not be discussed in detail, with the exception of the use of silane moieties to direct CM stereoselectivity (previously discussed in Section 11.06.3.2).

Table 1 Examples of CM reactions with α,β-unsaturated carbonyl compounds[a]

Entry	*CM partner*	*Unsaturated carbonyl*	*Equiv.*	*Product*	*Percentage isolated yield (E : Z)*
1			0.5		62 (>20 : 1)
2			2.0		91 (4.5 : 1)
3			0.5		92 (>20 : 1)
4			2.0		95 (>20 : 1)
5			0.5		100 (>20 : 1)
6			0.8		87 (>20 : 1)
7			0.8		66 (>20 : 1)
8			0.8		71 (>20 : 1)

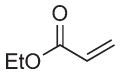
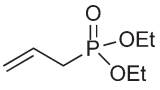
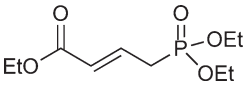
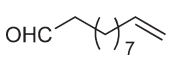
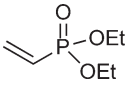
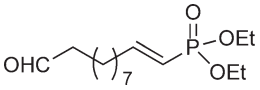
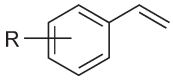
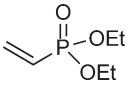
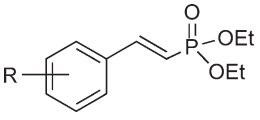
[a]Reactions conducted using either catalyst **3** or **5** (5 mol%) in CH_2Cl_2, 40 °C.

In addition to allylsilanes, CM can also be applied to allylstannanes, which serve as valuable reagents for nucleophilic additions[69,69a] and radical reactions.[70] To date, only catalyst **1** has been shown to demonstrate CM reactivity in the preparation of 1,2-disubstituted allylstannanes, as ruthenium catalysts were found to be inactive in the presence of this substrate class.[41] Poor stereoselectivities were generally observed, with the exception of one instance of >20 : 1 *Z*-selectivity in the reaction of allyltributylstannane with an acetyl-protected allyl glucoside.

The preparation of unsaturated phosphonates and phosphine oxides represents another class of reagents that are extensively used in organic synthesis. For example, allylic phosphonates are commonly employed in the preparation of dienes and polyenes via Horner–Emmons olefination.[71] Vinyl phosphonates have numerous uses as both synthetic intermediates[72] and bioactive compounds.[73,73a,73b]

In 2001, Grubbs and co-workers reported the first intermolecular CM reactions for the preparation of unsaturated phosphonates.[74] Using the highly active NHC catalyst **5**, the CM reactions of both allyl and vinyl phosphonates were

Table 2 CM reactions of allyl and vinyl phosphonates[a]

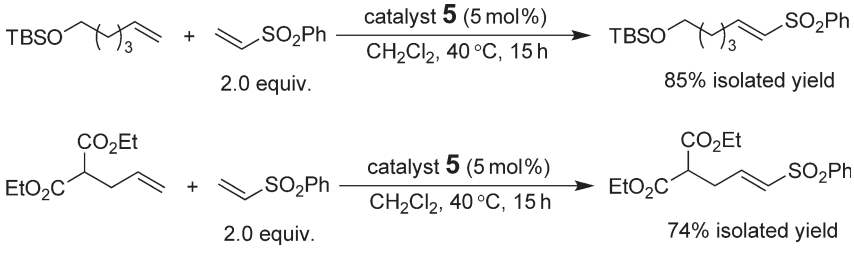
Entry	*CM partner*	*Unsaturated phosphonate*	*Equiv.*	*Product*	*Isolated yield (%)*
1			0.5		87
2			0.6		72
3			0.6		97 (R = H) 97 (R = 4-OMe) 93 (R = 4-Br) 77 (R = 2,4-$(CH_3)_2$)

[a]Reactions conducted using catalyst **5** (5 mol%) in CH_2Cl_2, 40 °C.

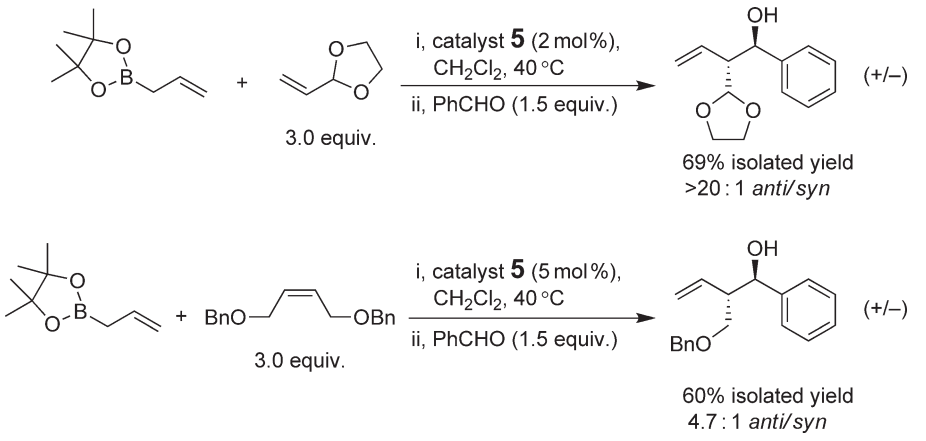
achieved in high yields with excellent *E*-stereoselectivity (Table 2). In these reactions, vinyl phosphonates can generally be regarded as type III olefins and allyl phosphonates as type I. The tolerance of **5** toward unprotected aldehyde cross-partners is of particular interest, as it highlights the orthogonality of CM and Horner–Emmons chemistry. In addition, variability in product regioselectivity can easily be obtained via the judicious selection of cross-partners. This stands in marked contrast to other methods used for the preparation of unsaturated phosphonates, such as palladium-catalyzed hydrophosphorylation, where 1,1-disubstituted products are predominantly formed. Analogous to the CM reactions using acrylic amides (Table 1), styrene CM reactions with vinyl phosphonates represent another rare example of metathesis between two electron-deficient olefins. Spilling and co-workers later reported that the substrate scope could be extended to include chiral allylic hydroxy phosphonates and their derivatives, which were observed to undergo CM in good yields without racemization.[75] Using catalysts **5**, **7a**, and **7b**, Grubbs,[76] Grela,[77] and Gouverneur[78] have also reported the CM reactions of allyl and vinyl phosphine oxides. In these reactions, the *E*-stereoisomer was predominantly formed, and, in the metathesis of chiral vinyl phosphine oxides, no racemization of the chiral phosphorus center was observed.

The CM of vinyl sulfones is of great synthetic value, as α,β-unsaturated sulfones are becoming increasingly utilized in stereocontrolled organic synthesis.[79,79a] The compatibility of remote sulfone and sulfoxide moieties in RCM[80,80a] and CM[8,58] is well established. However, initial attempts to employ catalyst **3** in the CM of methyl vinyl sulfones proved unsuccessful.[63] Fortunately, Grela and co-workers found that selective CM reactions between phenyl vinyl sulfones and monosubstituted olefins could be achieved using catalyst **5** (Scheme 11).[81] In all examples, the *E*-stereoisomer was exclusively observed. This methodology was later used in conjunction with a Sharpless asymmetric dihydroxylation reaction to effect the rapid, stereoselective synthesis of α-hydroxy aldehydes.[82] It is important to note that the corresponding CM reactions using vinyl sulfoxides did not proceed.[83] This result is not surprising given that sulfoxides are known to readily sequester and promote the decomposition of metal carbene complexes.[84,84a,85]

The preparation of allyl boronates via CM is of significant interest due to their widespread use in allylation reactions.[86,86a] In 2002, Grubbs and co-workers reported a one-pot CM/allylboration reaction for the preparation of



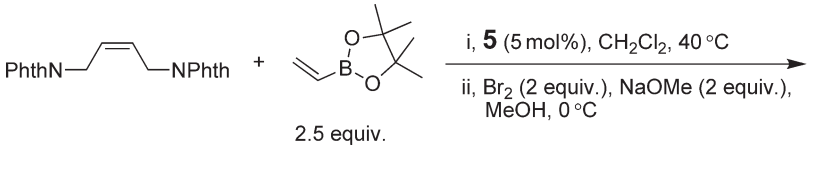
Scheme 11 CM of vinyl sulfones.



Scheme 12 Tandem CM/allylboration reaction.

homoallylic alcohols (Scheme 12).[87] Using catalyst **5**, pinacol allylborane was found to be a type I olefin. However, by utilizing an excess of cross-partner (3–5 equiv.), moderate yields could be achieved. Substrate scope was extended to include bulky terminal olefins, 1,1- and 1,2-disubstituted olefins, and styrenes. In general, poor *E*/*Z* ratios in cross-product formation translated to poor *anti*/*syn* ratios in the resulting allylation reactions. Fortunately, the use of either bulky or symmetrical 1,1-disubstituted olefins could circumvent this. Miyaura and co-workers later reported an asymmetric version of this methodology.[88]

In addition to allylboranes, vinyl boronates have been found to participate in CM reactions with terminal olefins. Grubbs and co-workers reported the first examples of CM reactions between functionalized vinyl pinacol boronates and various olefins, including 1,1-disubstituted alkenes (Table 3).[8,89,89a] The formation of 1,2-disubstituted vinyl boronates proceeded in good yield (55–92%) with generally high *E*/*Z* stereoselectivity (up to >20 : 1). In reactions employing α-substituted vinyl boronates, product stereochemistry proved to be strongly substrate dependent. Reaction scope was recently extended to include the preparation of fluorous 1,2-disubstituted vinyl boronates.[90] Products of vinyl boronate CM reactions are useful for the preparation of various di- and trisubstituted olefins via Suzuki cross-coupling.[91,91a,91b] Vinyl boronate cross-products can also be converted into the corresponding *Z*-vinyl bromides and *E*-vinyl iodides using a halogenation procedure developed by Brown and co-workers.[89,92,92a] In the case of vinyl bromides, a two-step, one-pot CM/halogenation protocol affords the formal equivalent of a *Z*-selective vinyl bromide CM reaction (Equation (3)).

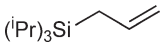
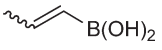
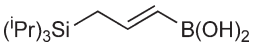
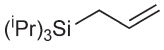
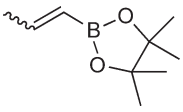
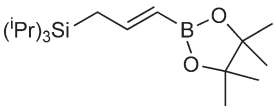
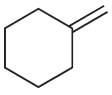
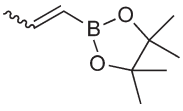
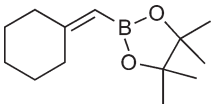
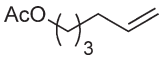
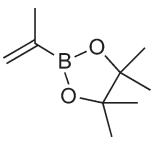
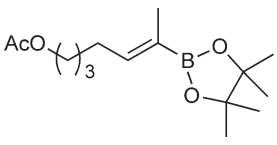
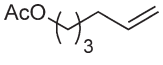
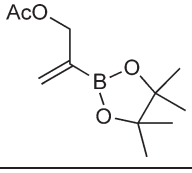
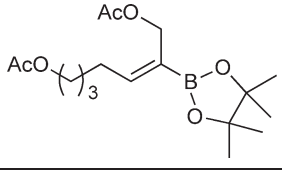


(3)

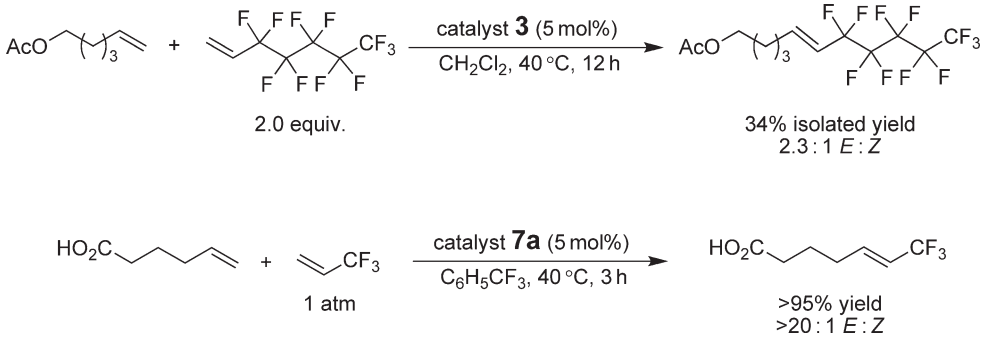
The preparation of halogenated alkenes represents another area of avid synthetic interest. Grubbs and co-workers have reported that catalyst **3** is capable of effecting the CM reactions of fluoroalkyl-containing olefins, albeit with low yields (Scheme 13).[63] Fortunately, the more active catalysts **5** and **7** were found to readily promote the CM reactions of various mono- and 1,2-disubstituted allyl halides (X = F, Cl, Br, I).[57,87,93,93a–93c] In general, allyl fluorides and chlorides afford higher yields and superior *E*-selectivity over allyl bromides. Allyl iodides represent particularly challenging substrates for CM – yields for reactions utilizing these compounds are typically low.[93a] In addition to the CM of allyl halides, the homologation of terminal olefins with trifluoropropene is particularly useful and high yielding.[93] The direct use of vinyl halides in CM remains an unsolved problem,[57,94] which is unfortunate due to the prevalent use of these compounds in Heck-type reactions. However, as previously discussed, vinyl halide preparation can be achieved indirectly via the halogenation of vinyl boronate cross-products (Equation (3)).

Vinyl epoxides represent another class of compounds known to participate in CM reactions mediated by ruthenium NHC catalysts.[57] The reactivity of these catalysts is unique, as catalyst **2** is typically limited to allyl glycidyl ether[8]

Table 3 Examples of CM reactions with vinyl boronates[a]

Entry	*CM partner*	*Vinyl boronate*[b]	*Product*	*Percentage isolated yield (E : Z)*
1				55 (>20 : 1)
2				99 (>10 : 1)
3				91 (–)
4				58 (1 : >20)
5[c]				40 (1 : 1)

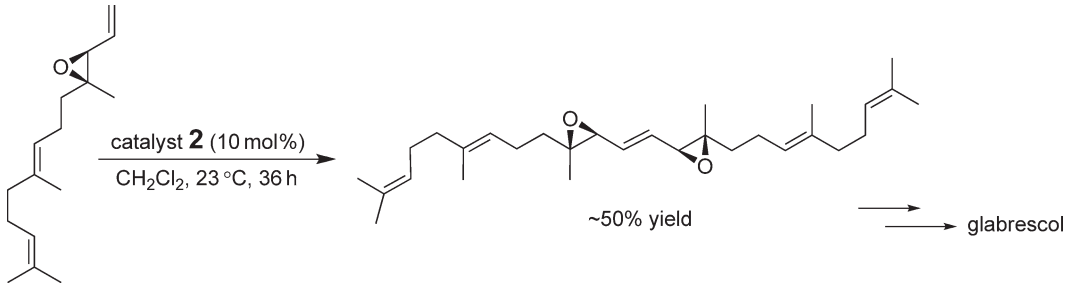
[a]Reactions conducted using **5** (5 mol%) in CH_2Cl_2, 40 °C.
[b]Unless otherwise indicated, 1.0 equiv. vinyl boronate used.
[c]2.0 equiv. vinyl boronate used.



Scheme 13 CM of fluorinated alkane olefins.

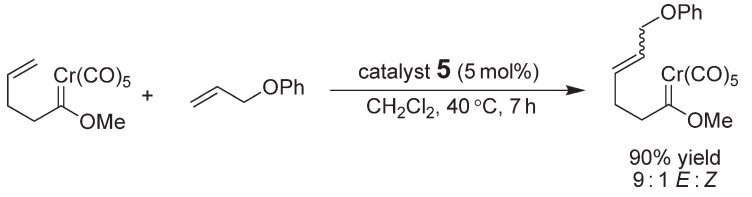
and homoallylic epoxide[95] CM reactions. A noteworthy exception to this is Corey's vinyl epoxide homodimerization strategy for the preparation of the squalenoid glabrescol and its *meso*-diastereomers (Scheme 14).[96] Of particular interest in this reaction is the remarkable chemoselectivity of **2** for the desired metathesis transformation in the presence of other substituted olefins.

One of the most unique applications of CM to reagent synthesis is described in a report by Zhang and Herndon, where catalysts **2** and **5** were used to effect the homologation of homoallylic Fischer carbene complexes (Equation (4)).[97] The *E*/*Z* ratios observed in these reactions using catalyst **5** were typically 9 : 1. Highly reactive, electron-neutral olefins were



Scheme 14 Dimerization of vinyl epoxides in the preparation of glabrescol.

required to achieve high yields. In reactions employing electron-deficient olefins, such as ethyl acrylate, CM was not competitive with chromium-mediated olefin cyclopropanation. This reaction highlights the importance of tuning olefin reactivity in CM reactions, a crucial design concept in the implementation of tandem reactions (Section 11.06.5).

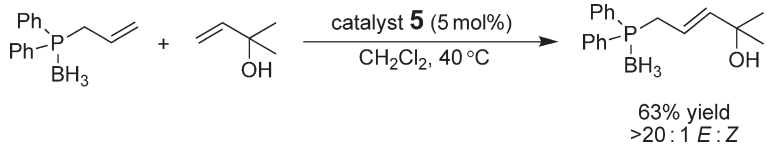


(4)

11.06.4.5 CM of Lewis-basic Substrates

In 2001, mechanistic work began to provide greater insight into the increased reactivity of NHC catalysts **3**–**7** relative to bisphosphine catalyst **2**.[26a] Utilizing ^{31}P magnetization transfer experiments, it was found that the preference for olefin binding relative to phosphine in catalyst **5** was over 10,000 times greater than that of catalyst **2**. In addition, it was determined for catalyst **5** that the upper limit of the rate of olefin binding is nearly equivalent to that of binding phosphine. The preference of NHC catalysts to turn over olefin instead of irreversibly binding phosphine suggested the intriguing possibility that substrates with Lewis-basic functional groups containing phosphorus, nitrogen, and sulfur could be effectively employed in metathesis reactions.

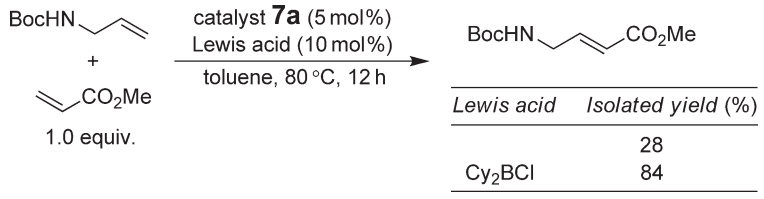
In 2002, Grubbs and co-workers reported the first CM reactions of allyl phosphines.[76] In an initial reaction, subjecting allyl diphenylphosphine to catalyst **5** (5 mol%) failed to produce any of the desired cross-product. However, by protecting the phosphine as its borane complex, CM reactions could be achieved in good yield with high *E*-selectivity (Equation (5)). Notably, catalyst **5** failed to dimerize borane-protected vinyl diphenylphosphine. This result was attributed to substrate trapping of the catalyst as an unreactive Fischer carbene, a situation analogous to that observed in the CM reactions of alkyl vinyl ethers.[26a]



(5)

The CM of nitrogen-containing substrates is of significant importance, as many of the resulting compounds are of biological interest. With regard to this substrate class, vinylpyridyl, acrylonitrile, and acrylic amide CM reactions have already been discussed (Sections 11.06.4.1 and 11.06.4.3). Other compounds within this substrate class include: amino acids, β-lactams, amino alcohols, allylamines, homoallylamines, and oxazolines. The CM of nitrogen-containing substrates was comprehensively reviewed in 2003.[98]

In general, amino-containing compounds are poor partners in CM due to their tendency to coordinate to the metal catalyst, even when late-transition metal systems are employed. To preserve catalyst activity, amino groups are therefore typically masked as cyanides, carbamates, amides, or phthalimides. In substrates where *N*-coordination to the catalyst is less favored, such as with hindered *N*-aryl-*N*-allylamines, no protecting group is required.[74]



Lewis acid	*Isolated yield* (%)
	28
Cy_2BCl	84

Scheme 15 Addition of Lewis acids to the CM of allylamines.

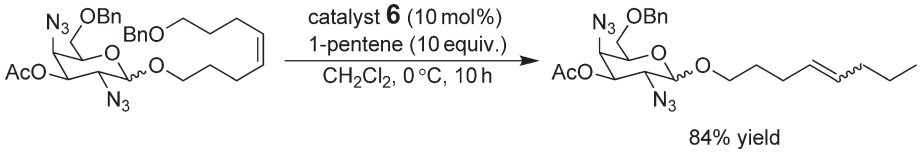
Despite the use of protecting group strategies, compounds containing amino moieties are often plagued with poor reactivities in CM. For instance, the CM reactions of unsubstituted allylic carbamates typically proceed in low yields (Scheme 15).[56a,99] The predominant side-products obtained in these reactions are alkene homodimerization and olefin migration in the allylamine to form the corresponding enamine. In particular, a few studies have discussed olefinic isomerization in the metathesis of nitrogen-containing compounds.[100,100a] One method to circumvent this problem is to employ an indirect route to substituted allylamines via the CM of allyl cyanide.[101] However, in a recent report by Elkaïm and Grimaud, it was found that the addition of a Lewis acid (Cy_2BCl, 10 mol%) could completely suppress olefin migration and dramatically increase reaction yields, thereby allowing for direct access to the desired cross-product.[102]

The protection of amines as azides is a common and convenient strategy for the assembly of oligosaccharides, aminoglycoside antibiotics,[103,103a–103c] glycosaminoglycans,[104] and various other synthetic intermediates. The failure of CM reactions in the presence of azide-containing molecules is well precedented, and is generally due to either metal-mediated nitrene processes or the incompatibility of azide moieties with the phosphorus ligands on the catalyst.[105,105a] The development of phosphine-free ruthenium catalysts **6** and **7** has enabled the first applications of CM to azide-containing substrates. However, yields in these reactions are typically quite low (~20–36%).[105a,106] An exception to this was a report in 2003 by Seeberger and co-workers, where catalyst **6** was found to cleave the octenediol linker of an azide-containing sugar in high yield (Scheme 16).[107] Use of 1-pentene as a cross-partner in place of ethylene proved crucial to attaining high reaction yields. This methodology was later successfully adapted to solid-phase synthesis.

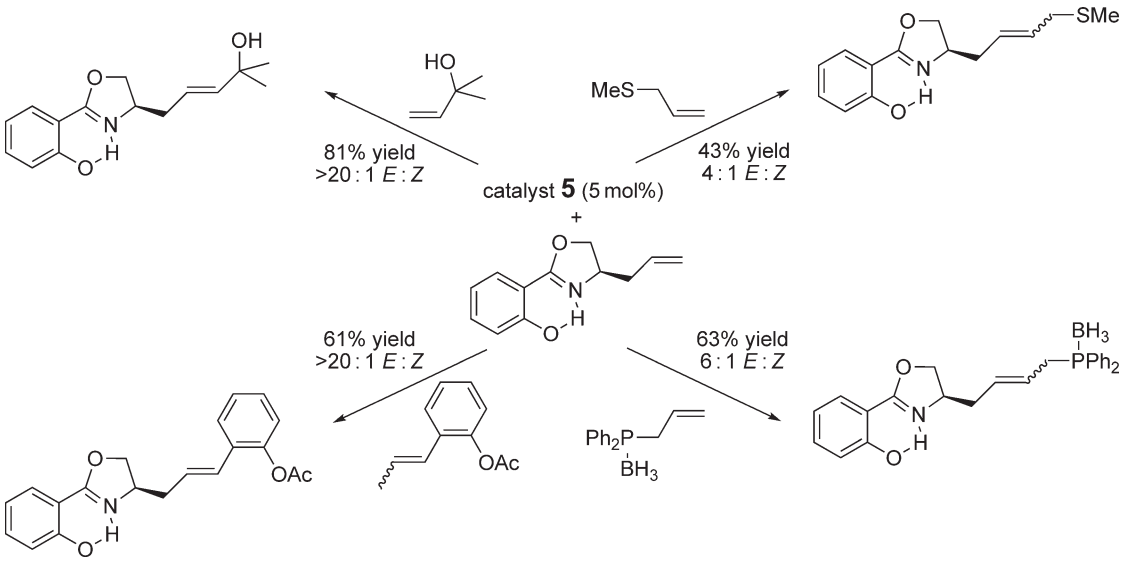
CM has also been applied toward the preparation of nucleoside dimers. During the course of medicinal investigations into nucleotide analogs for anti-retrovirus activity, Krauz and co-workers found that catalyst **2** (10–20 mol%) could promote the CM of 3′-allylic analogs of thymidine, 2′-deoxyuridine, and 2′-deoxycytosine to afford the corresponding nucleoside dimers in modest yields (15–45%).[108] Poor catalyst turnovers were attributed to the inhibiting coordination of nitrogen to ruthenium. Unfortunately, increasing both the catalyst loadings and reaction times had no positive effect on yield. In addition, catalyst **2** was found to be completely inactive in the dimerization reactions of vinyl phosphonate-linked nucleic acids.[109] Fortunately, by switching to the more electron-rich catalyst **5**, dimerization could be achieved in up to 58% isolated yield with >20 : 1 *E*/*Z* stereoselectivity.

In addition to nitrogen, sulfur in reduced oxidation states is a notoriously good ligand for late-transition metals due to soft–soft ligand–metal compatibility. Prior to the development of catalysts **3**–**7**, sulfides were only tolerated in metathesis reactions using early-metal catalyst systems, such as **1**[110] or the Basset tungsten system.[111] However, the remarkable tolerance of **5** toward Lewis-basic substrates prompted Grubbs and co-workers to investigate CM reactions with allyl methyl sulfide.[76] Remarkably, CM was observed to proceed in good yield (up to 69%) with moderate stereoselectivities. Mioskowski and co-workers subsequently reported the substrate scope of sulfur-containing compounds, including free thiols, in CM reactions using catalyst **4**.[112]

To further explore the functional group tolerance of catalyst **5**, CM reactions using a 2-oxazolylphenol-substituted olefin scaffold were investigated (Scheme 17).[76] Cross-partners containing sulfides, protected phosphines, and



Scheme 16 CM of azide-containing sugars.



Scheme 17 Diversity-oriented ligand synthesis by CM.

unprotected alcohols were all tolerated, providing the resulting products in moderate to good yields (43–81%). The products of these reactions constitute a family of chiral, tridentate ligands, illustrating the applicability of CM toward the preparation of diversity-oriented catalyst libraries. Moreover, the results in Scheme 17 provide a quintessential example of the unprecedented chemoselectivity afforded by ruthenium NHC catalysts.

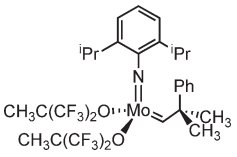
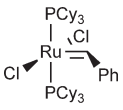
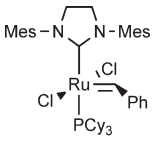
11.06.4.6 Summary of Substrate Scope – Olefin Chemoselectivity in CM

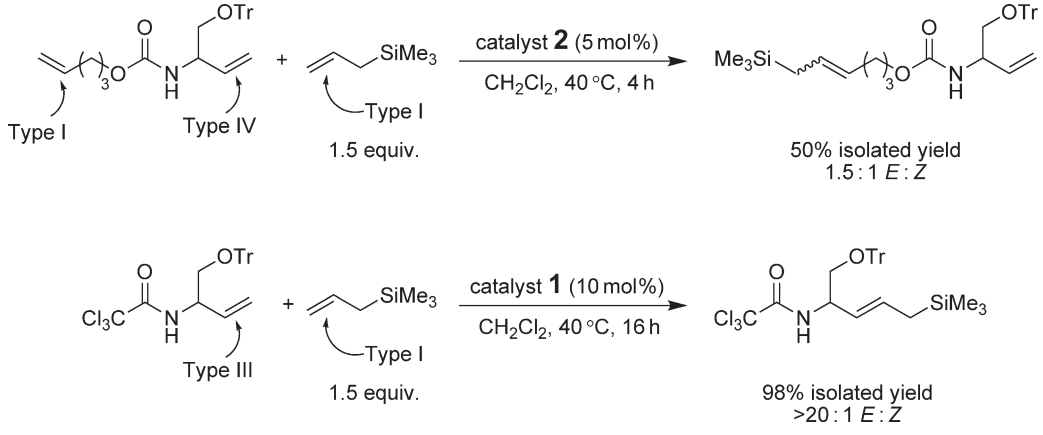
In Section 11.06.3.1, olefin categories for product-selective CM were introduced and characterized based upon the propensity of a particular olefin to undergo homodimerization (types I–IV; Figure 2). This empirical model can be further elaborated by categorizing the olefin functionalities presented in the preceding sections of this chapter (Table 4). Olefin "type" classifications listed in Table 4 emphasize catalyst chemoselectivity for a particular olefin, and are meant to provide a series of guidelines for CM reaction design. It is important to note that olefin classifications for catalysts **6** and **7** generally correlate with those of **5**, as these catalysts all possess the same propagating species.[26,26a,26b] When using this model, it is as important to identify substrates that are metathesis-inactive (type IV) for a given catalyst as it is to find those that are active (types I, II, and III), as olefin-type classifications are catalyst-specific. For example, a type IV olefin for catalyst **2** may be upgraded to type III when a more active catalyst, such as **1** or **5**, is used. This is best illustrated by further examining a report by Blechert and co-workers (previously discussed in Section 11.06.3.2), where both steric constraints and heteroatom substitution were used to sufficiently deactivate a secondary allylamine (type IV for catalyst **2**) in the presence of two type I olefins to promote selective CM (Scheme 18).[47] Later, in the same report, catalyst **1** was used to effect a highly selective CM reaction of a related allylamine in high yield (now type III).

In a related example, Cossy and BouzBouz reported the chemoselective CM of dienols for the preparation of the C1–C14 fragment of amphidinol 3 (Scheme 19).[113] When unprotected dienol was treated with catalyst **7a** in the presence of acrolein (3 equiv.), unselective CM was observed. However, by protecting the alcohol as the corresponding acetate, the allylic double bond was deactivated such that selective CM occurred. The deactivating capability of the acetate-protecting group can potentially be attributed to either electronic deactivation of the allylic double bond or the unfavorable complexation of the carbonyl oxygen to the catalyst, both of which are precedented.[114,114a–114d] Steric[115] and electronic[116] constraints have also been used to direct the chemoselective CM of bishomoallylic diols.

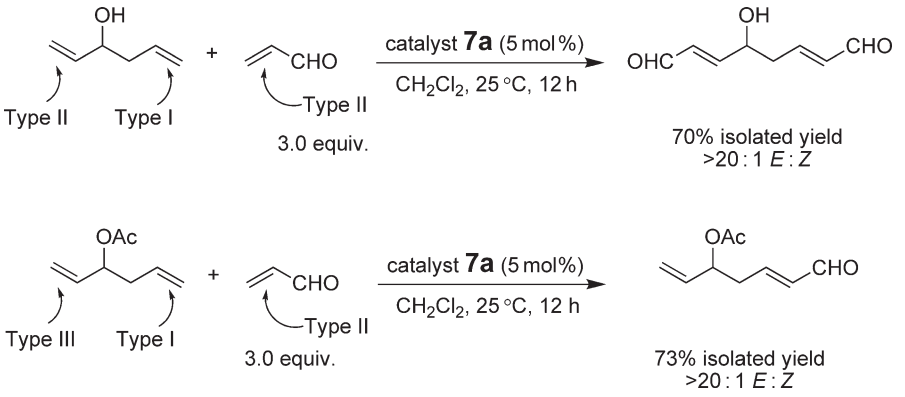
An understanding of olefin chemoselectivity in CM is also crucial when homologating 1,3-dienes, which represent a particularly challenging substrate class. In 2005, Grubbs and co-workers demonstrated that, by employing either an electronic or steric barrier to reaction, one of the olefins in a conjugated diene could be deactivated relative to the other for CM.[117] For example, in the reaction of ethyl sorbate with 5-hexenyl acetate in the presence of **5** (10 mol%),

Table 4 Olefin categories for selective CM

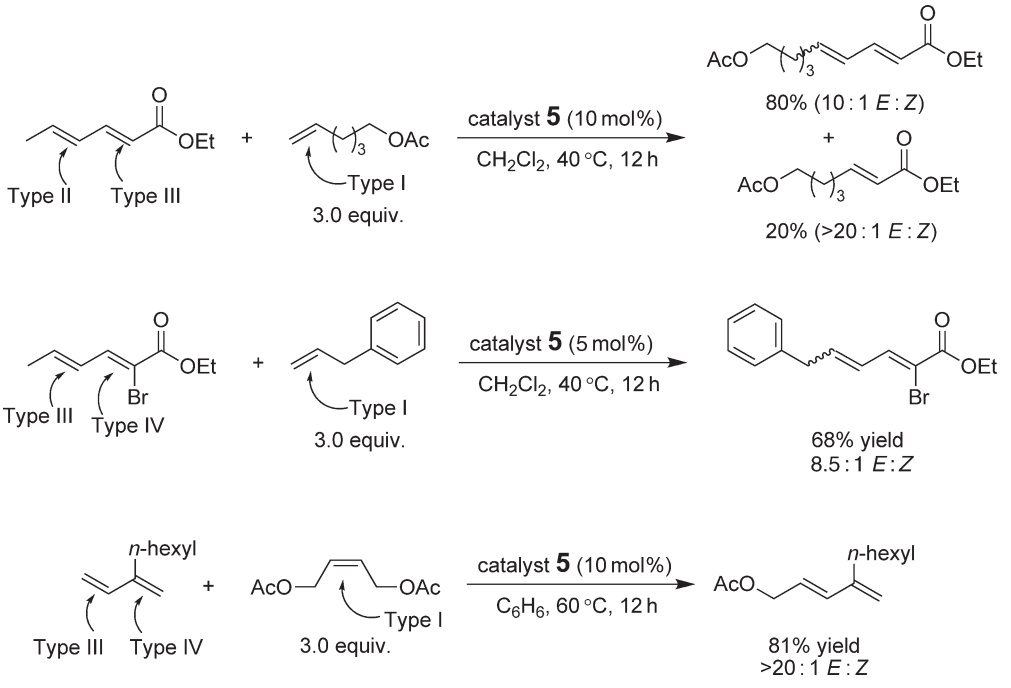
Olefin type	 **1**	 **2**	 **5**
Type I (fast homodimerization)	Terminal olefins,[40,45,47,54] allylsilanes[45]	Terminal olefins,[8] allylsilanes,[45,95] 1° allylic alcohols, ethers, and esters,[8,46,95] allyl boronate esters,[56e] allyl halides,[35] alkyl-substituted allenes[10]	Terminal olefins,[58] allyl boronate esters,[87] 1° allylic alcohols, ethers, and esters,[76,97] styrenes (no large ortho substit.),[57,64a,74,87] allyl halides[56,56a–56e,86,86a,92a] allylsilanes,[8b,68,68a] allyl sulfides,[76] allyl phosphonates,[74] allyl phosphine oxides,[76,78] protected allylamines[76]
Type II (slow homodimerization)	Styrene,[45,54,55] allylstannanes[41]	Styrene,[35] 2° allylic alcohols,[8,35] vinyl dioxolanes,[8] vinyl boronates[8]	Styrenes (large ortho substit.)[59,64a,74,87] 2° allylic alcohols,[35] vinyl epoxides,[63] unprotected 3° allylic alcohols,[76,87] acrylates,[57,63] acrylamides,[35,57] acrylic acid,[35,57] acrolein,[63,113] vinyl ketones,[35,63] vinyl boronates[89,89a] perfluorinated alkane olefins[63,93]
Type III (no homodimerization)	Acrylonitrile,[40] protected 3° allylamines[47]	Vinyl trialkoxysilanes,[35,68,68a] vinyl siloxanes[35,68,68a]	1,1-Disubstituted olefins,[58,59,64] non-bulky trisubstituted olefins,[58,59] vinyl phosphonates,[74] vinyl phosphine oxides,[78] phenyl vinyl sulfone,[81] acrylonitrile,[27a] 4° allylic carbons (all alkyl substituents),[35,87] protected 3° allylic alcohols,[35] γ,δ-olefin of 2-subst. 1,3-butadienes,[117] γ,δ-olefin of electronically deactivated 1,3-butadienes[117]
Type IV (spectators to CM)	1,1-Disubstituted olefins[54]	1,1-Disubstituted olefins,[35] disub. α,β-unsaturated carbonyls,[62] 4° allylic carbon-containing olefins,[8] perfluorinated alkane olefins,[8] 3° allylamines (protected)[47]	Vinyl nitro olefins, protected trisubstituted allyl alcohols,[35] α,β-olefin of 2-subst. 1,3-butadienes,[117] α,β-olefin of electronically deactivated 1,3-butadienes[117]



Scheme 18 Chemoselective CM using catalysts **1** and **2**.



Scheme 19 Chemoselective CM of dienols.

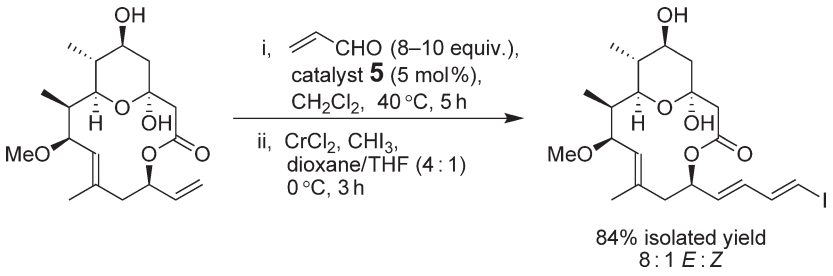


Scheme 20 Chemoselective CM of conjugated 1,3-butadienes.

both olefins were observed to react to afford a mixture of two products (Scheme 20). However, by introducing a vinylic bromide at the α-carbon, the α,β-double bond was sufficiently deactivated so as to completely suppress its participation in CM (type III → type IV). As a result, only the γ,δ-olefin of the diene was observed to react, affording the desired cross-product in 68% isolated yield (8.5 : 1 *E*/*Z*). Selective CM reactions could also be achieved using 2-substituted butadienes (up to 81% yield). The substrate scope of 1,3-diene CM has been further investigated by Blechert and co-workers.[118]

11.06.5 Use of CM in One-Pot Sequential and Tandem Reactions

The remarkable chemoselectivity of ruthenium NHC catalysts to bind olefins in the presence of heteroatomic moieties makes them ideally suited for use in one-pot sequential reactions, as they are stable toward a variety of reaction conditions and reagents and, often, their presence does not impede subsequent transformations. The

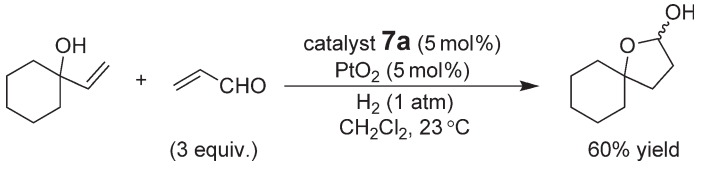


Scheme 21 One-pot CM-Takai olefination protocol.

addition of benzaldehyde following allyl boronate CM represents one of the first examples of this (Scheme 12).[87] In some cases, such as in the halogenation of vinyl boronate cross-products (Equation (3)), employing a one-pot procedure serves to improve the overall reaction yield.[89] More challenging, however, is the use of CM in sequential organometallic protocols, as these systems are often highly sensitive to reaction impurities. Fortunately, a growing number of organometallic reactions are proving to be amenable to the presence of ruthenium alkylidene complexes. For example, in 2005, Grubbs and co-workers reported a one-pot CM–Suzuki coupling protocol for the homologation of 1,3-butadienes.[117] Yields using this sequence were found to be comparable to the analogous two-step procedure.

Within the context of total synthesis, the application of CM to a one-pot sequential protocol has the potential to dramatically simplify the preparation of complex natural products. Trost and co-workers recently demonstrated an elegant example of this, wherein a one-pot CM–Takai olefination reaction was used for the preparation of the anti-tumor agent callipeltoside A and various analogs (Scheme 21).[119] By using a three-step, two-pot sequence employing this protocol, the synthetic route toward these compounds was shortened by five steps and olefin stereoselectivity was increased (4 : 1 to >8 : 1 *E*/*Z*) relative to previous syntheses employing a classical Emmons–Wadsworth–Horner approach.

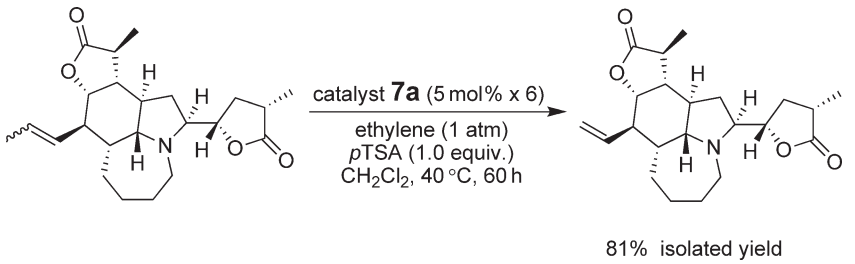
The application of CM to tandem reactions is dependent not only upon catalyst chemoselectivity, but also the rates of competitive reaction processes. For example, in 2001, Grubbs and co-workers demonstrated that catalyst **5** could be employed in a sequential CM hydrogenation procedure for the preparation of allylic alcohols.[120] However, the hydrogenation reaction using catalyst **5** required relatively high pressures (70 bar) and elevated temperatures (~100 °C) to proceed. Subsequently, Cossy and co-workers determined that, by conducting this protocol as a tandem, rather than sequential, process using catalyst **7a** in the presence of the active hydrogenation catalyst PtO_2, moderate yields could be achieved (up to 46%) at ambient temperature using only 1 atm of hydrogen.[121] These results demonstrate that CM can favorably compete with hydrogenation when applied in tandem. This methodology was later extended to include the formation of lactones and lactols in up to 60% yield (Equation (6)).[122]



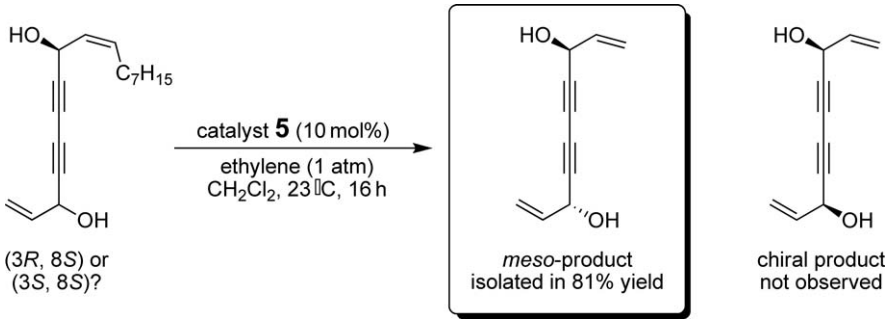
(6)

11.06.6 Ethenolysis

Most of the preceding sections in this chapter have emphasized the use of CM for the homologation of terminal olefins. The microscopic reverse of this reaction, however, is also of great synthetic interest, as it provides a mild method for the cleavage of olefins. When ethylene gas is used as the cross-partner, the resulting CM reaction is known as "ethenolysis." Prior to 2000, ethenolysis was almost exclusively used within the oleochemical industry to process unsaturated fatty oils or triglycerides into compounds of lower molecular weight.[123,123a,124] With the advent of catalysts **1**–**7**, however, this reaction is becoming increasingly employed as a general synthetic method. For



Scheme 22 Ethenolysis in natural product synthesis.



Scheme 23 Ethenolysis to determine natural product stereochemistry.

example, in 2001, Seeberger and co-workers utilized ethenolysis as a reliable resin cleavage method for the automated solid-phase synthesis of oligosaccharides.[125]

Within the field of natural product synthesis, ethenolysis serves two major functions: (i) as a means to dehomologate an olefin prior to further synthetic elaboration, and (ii) as a tool in natural product degradation to determine absolute stereochemistry. An example of the former is illustrated by Wipf's synthetic route to (−)-tuberostemonine, reported in 2002 (Scheme 22).[126] Utilizing catalyst **7a**, ethenolysis was performed on a late-stage intermediate to generate the corresponding terminal olefin, which was subsequently hydrogenated to afford the target molecule. A stoichiometric amount of *p*-toluenesulfonic acid (*p*TSA) was used as an additive in this reaction to prevent substrate coordination to the catalyst via the tertiary amine.[127] The best results were afforded by adding catalyst **7a** in six portions (5 mol% each) over a 60 h period. Phosphine-free conditions (the use of catalyst **7a** relative to **5**) were required to minimize decomposition of the resulting cross-product during chromatographic purification.

Hemscheidt's determination of the absolute stereochemistry of the anti-tumor agent (+)-falcarindiol highlights the utility of natural product degradation via ethenolysis (Scheme 23).[128] Previous work had demonstrated that the stereochemistry at C8 was (*S*); however, the relative stereochemistry of the two stereocenters remained unclear.[129,129a] It was reasoned that, by cleaving the aliphatic side-chain via ethenolysis, the relative stereochemistry of (+)-falcarindiol could be unambiguously determined by distinguishing between either a chiral or *meso*-compound. Subjecting the natural product to an atmosphere of ethylene in the presence of **5** (10 mol%) resulted in selective removal of the aliphatic side-chain in 81% yield. The resulting product was demonstrated to possess a *meso*-configuration, confirming that the natural product possesses a (3*R*,8*S*) configuration. More recently, Nakanishi and co-workers have reported the use of catalyst **5** in a general ethenolysis protocol to determine the absolute stereochemistry of ene moieties, such as allylic alcohols and amines, via a circular dichroic (CD) exciton chirality method.[130]

11.06.7 Additives to Prevent Olefin Migration in CM

Alkene isomerization/migration is a potential side-reaction in olefin metathesis processes that can significantly decrease the yield of a desired product, particularly in reactions that employ electron-rich allylic or homoallylic

alcohols, ethers, and amines as substrates.[131,131a] Olefin migration also poses a significant challenge to product selectivity in the ethenolysis of oleochemicals, thereby limiting its commercial practicality.[123,123a,124] While this side-reaction is particularly prevalent when using ill-defined catalysts, it can also sometimes effect product yields in reactions that employ more functional group tolerant catalysts, such as **5** or **7**. Various mechanisms responsible for olefin migration have been proposed (metal-based hydride, π-allyl pathways, etc.).[132,132a,132b] Recent results suggest that, at least with ruthenium-based systems, olefin migration is promoted by metal hydrides, which are known products of catalyst decomposition.[133] Fortunately, it has been demonstrated that the use of an additive, such as Elkaïm and Grimaud's use of Cy_2BCl in CM reactions with unsubstituted allylic carbamates (discussed in Section 11.06.4.5),[102] has the capacity to completely suppress olefin migration.

Grubbs and co-workers have recently completed a comprehensive screen of additives to prevent olefin isomerization in various metathesis reactions using catalyst **5**.[134] It had previously been demonstrated that acids of moderate pK_a, such as acetic, benzoic, and acrylic acids, could serve to accelerate metathesis reactions by acting as phosphine scavengers without reducing yields or accelerating catalyst decomposition.[135] When these additives were applied to metathesis reactions known to exhibit olefin migration, it was found that selectivity for the desired product was dramatically improved. Of these, acetic acid (10 mol%) generally provided the best results. In addition to acids, 1,4-benzoquinone (10 mol%) proved to be an effective additive for suppressing olefin migration reactions, often providing complete suppression in situations where the addition of acetic acid failed. The mechanistic role of 1,4-benzoquinone in preventing olefin migration (via redox reactions,[136,136a] charge transfer complexes (e.g., it has previously been reported that catalyst **2** forms radical anions on treatment with 1,4-benzoquinone),[137,137a] etc.,) has not yet been determined.

11.06.8 Applications of CM

Olefin metathesis chemistry has had a profound impact in several areas of chemical research, including organometallics,[8a,138] polymer chemistry,[139,139a,139b] and small molecule synthesis,[8e,140] many of which have industrial applications. For example, CM is currently utilized in the commercial preparation of several agrochemicals, polymer and fuel additives, and pharmacophores.[141,141a] Unlike RCM reactions, which are typically conducted under dilute conditions with high catalyst loadings, CM procedures can be performed neat using minute amounts of catalyst (<1 ppm Ru).[142] Despite this proven utility, the initial lack of product selectivity relegated CM primarily to combinatorial,[143,143a] bioorganic,[144,145,145a–145g] and materials[8b,146,147,147a–147e] applications before it was employed in complex total syntheses. Interestingly, poor product selectivity in CM is viewed as a particularly attractive feature in the design of combinatorial libraries, as it generates structural diversity. CM has also been extensively used in carbohydrate chemistry, and is the topic of several comprehensive reviews on this subject.[8b,148,148a,148b] In addition to the examples discussed in the text, several other references discuss examples of CM in carbohydrate chemistry.[149,149a–149c]

As our understanding of the factors governing product selectivity has advanced, CM has seen increased usage in complex total syntheses, where product selectivity in the homologation of advanced intermediates is crucial.[8b,8e,150,150a–150i] In several cases, CM has been successfully applied to late-stage intermediates, illustrating the remarkable chemoselectivity of this reaction process.[60,60a,126] In addition, the ready availability of terminal olefins makes CM a particularly attractive tool for the preparation of natural product analogs, a pursuit of significant interest within pharmaceutical chemistry.[119,144,145,150c]

11.06.9 Summary

Olefin CM has become an indispensable tool for efficient carbon–carbon bond formation. Fundamental studies on functional group tolerance and an understanding of the steric and electronic factors crucial to product selectivity have led to the development of an empirical model for reaction design. As a result, CM is now widely employed in many bioorganic and materials applications that would not have been feasible 10 years ago. Despite this, many challenges remain. Ongoing CM research focuses on improving reaction stereoselectivities and further expanding substrate scope. To date, a general catalyst for effecting *Z*-selective CM reactions has yet to be developed. In addition, tetrasubstituted olefins and various functionalized products, such as vinyl halides, sulfoxides, ethers, amines, and stannanes, cannot yet be prepared via CM using catalysts **1**–**7**. Fortunately, recent successes with these substrates in

RCM protocols suggest that these challenges are surmountable. As work toward catalysts with properties tailored to meet these limitations continues, we can look forward to exciting future developments.

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11.07
Ring-closing Olefin Metathesis for Organic Synthesis

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11.07.1 Introduction

Since its first description,[1] the olefin ring-closing metathesis (RCM) (Figure 1) has been developed into a key reaction, comparable in its impact on organic synthesis to such classical transformations as the Wittig/Diels–Alder reaction. For reviews on metathesis reactions, see Refs: 2 and 2a–2j. This is mainly due to the introduction of the relatively stable and highly active ruthenium catalysts such as **B–F** by Grubbs, Hoveyda, Blechert, and Fürstner (Figure 2), which have been a clear improvement on Schrock's earlier molybdenum catalyst **A**. For reviews on catalyst development, see Refs: 3 and 3a–3i. Thermodynamically, the RCM is a reversible process and receives driving force only via strain release or via removal of the volatile olefinic partner (normally ethylene). This is easily achieved by using open systems. On the other hand, reversal of the RCM can be accomplished by working under ethylene pressure.

In 1993, RCM was hardly known to the synthetic organic chemist. Meanwhile, the application of RCM to the total synthesis of complex natural products has led to spectacular achievements which have been highlighted in excellent and comprehensive reviews.[4,4a–4c] Our aim is to show, in recent examples, the applicability of RCM to almost any kind of natural products, such as alkaloids, terpenes, polyketides, and carbohydrates, thus emphasizing the compatibility of the RCM with a vast variety of functional group arrangements. Furthermore, it will be shown that ring size, to date a serious problem in other macrocyclization reactions, is no issue in RCM, as even the most critical ring sizes (9–11) can be generated with ease. Even ring strain is not a serious obstacle, as demonstrated by the examples of

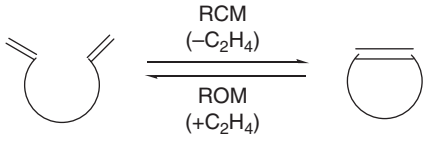


Figure 1 Ring closing metathesis (RCM) vs ring opening methathesis (ROM).

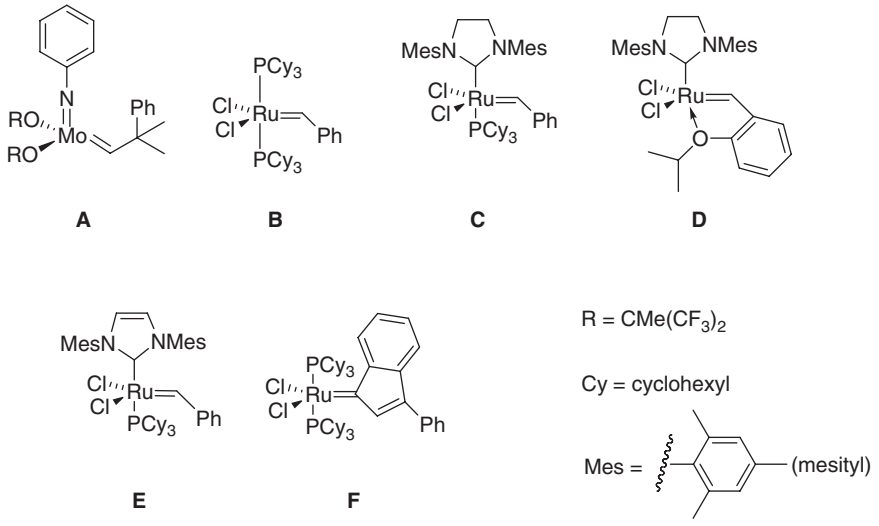


Figure 2 Important metathesis catalysts.

Section 11.07.2.2.3. Naturally, such an overview can never claim completeness; so we apologize for any omissions we may have made.

11.07.2 Ring-Closing Diene Metathesis

11.07.2.1 Formation of Five-, Six-, and Seven-membered Rings

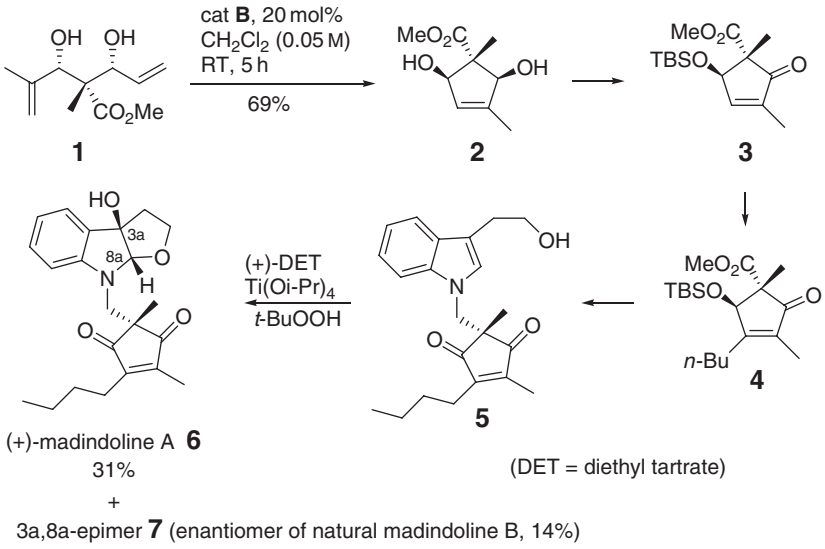
In recent years, a wealth of information has been accumulated on RCM reactions leading to five-, six-, and seven-membered carbocycles and heterocycles, so that it is impossible to refer to all the new, natural-product directed work. Therefore, we will concentrate here on a few selected examples that can illustrate (i) the progress made by the advent of the second generation ruthenium catalysts **C–E**, (ii) the use of RCM in concert with other innovative methodology, and (iii) the use of RCM in total syntheses of newly discovered natural products, which due to an outstanding biological profile have attracted specific interest from the synthetic community.

11.07.2.1.1 Carbacycles

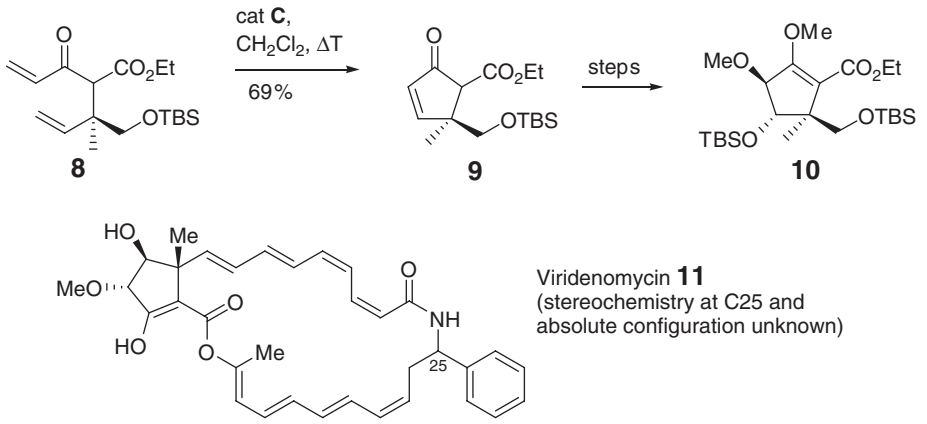
Madindoline A **6** and B (*ent*-**7**) are potent inhibitors of interleukin 6. In a total synthesis[5] that also intended to determine relative and absolute configuration of these antibiotics, the densely functionalized cyclopentene-1,3-dione ring of **6** and **7** was elaborated via RCM of diene–diol **1** (Scheme 1).

The densely functionalized cyclopentyl core **10** of the potent anti-tumor antibiotic viridenomycin **11** was prepared by treatment of enone **8** with catalyst **C** (Scheme 2).[6] This reaction proved to be very slow, requiring 3.5 days to give still only incomplete conversion leading to cyclization product **9** in 69% (86%, based on recovered **8**).

Kedarcidin[7] is a chromoprotein anti-tumor antibiotic, produced by an actinomycete strain. It is an acidic complex with an apparent molecular weight of 12,400 Da, and it consists of an apoprotein and a cytotoxic highly unstable non-protein chromophore **12** that possesses a conformationally defined ansamacrocyclic bridge. Retrosynthetically,



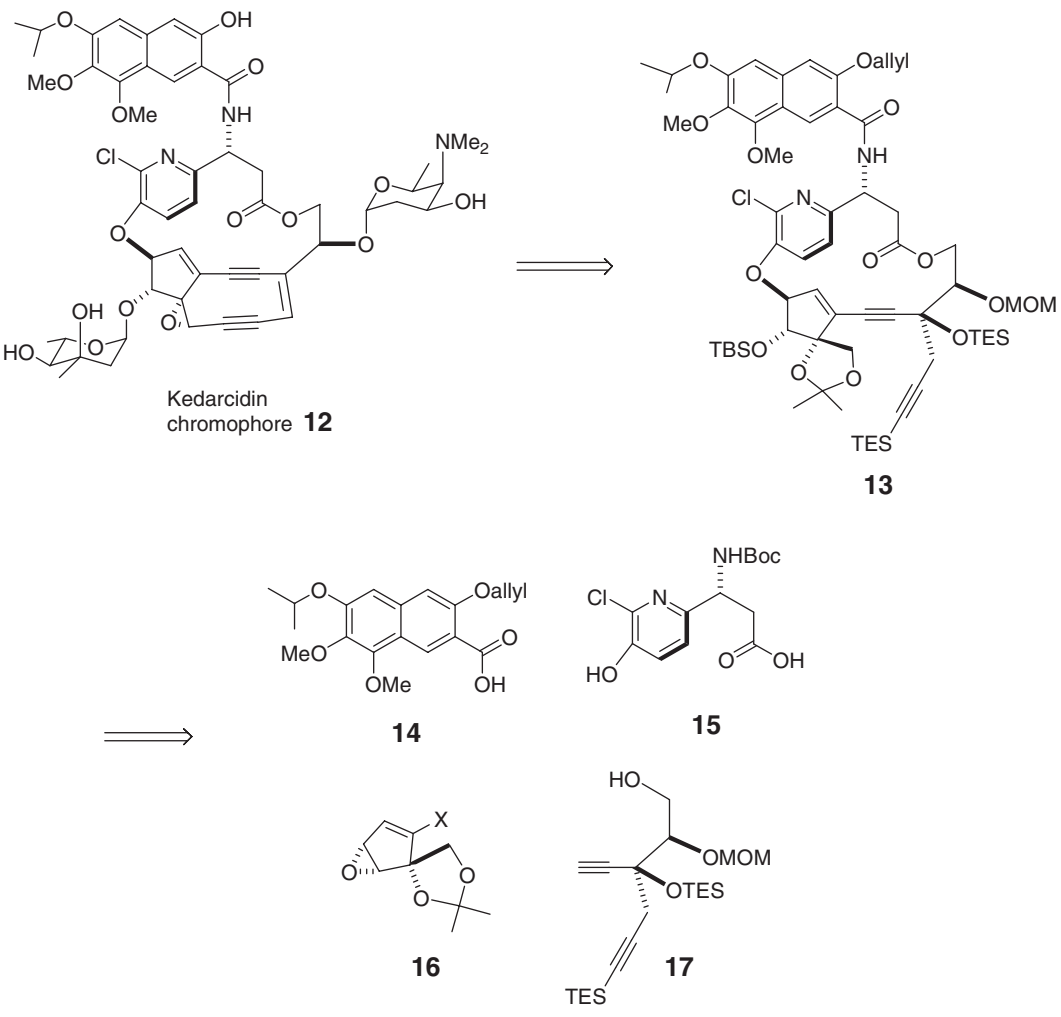
Scheme 1



Scheme 2

compound **13**, which was targeted,[8] can be disconnected into fragments **3–6** (Scheme 3). Cyclopentene **16** was prepared via an RCM protocol, as shown in Scheme 4. The synthesis started with the methyl glycoside **18** which was converted into the tetrahydrofuran derivative **20** via a reductive ring contraction. A Wittig methylation was used to generate the bis-alkene **21** which was subjected to RCM with catalyst **B** for 3 days at room temperature (RT) to furnish 92% of the cyclopentene derivative **22**. The authors claim that this reaction can be performed reliably on a large scale, which in view of an allylic MOM-ether-moiety is surprising (where MOM = methoxymethylene).[9,9a–9d] **22** was then modified along an 11-step sequence to generate epoxide **23** which served for attaching phenol fragment **15** to give **24**. Esterification with partially protected triol **17** delivered fragment **25**, which was adequately functionalized for a Sonagashira-type ring closure to give the 17-membered macrolide **26**. Removal of the Boc-protecting group and amide formation with carboxylic acid **14** furnished **13** eventually.

A striking example of the power of *N*-heterocyclic carbene (NHC)-bearing catalysts with sterically demanding substrates was disclosed by Chavez and Jacobsen,[10] who presented a route to several iridoid natural products, exemplified by the enantio- and diastereoselective synthesis of boschnialactone **31** outlined in Scheme 5. Chiral aldehyde **27**, available from citronellal by Eschenmoser-methylenation in a single step, reacted despite the presence of an isoprenyl moiety and a *gem*-disubstituted double bond, in the presence of catalyst **C** smoothly to form



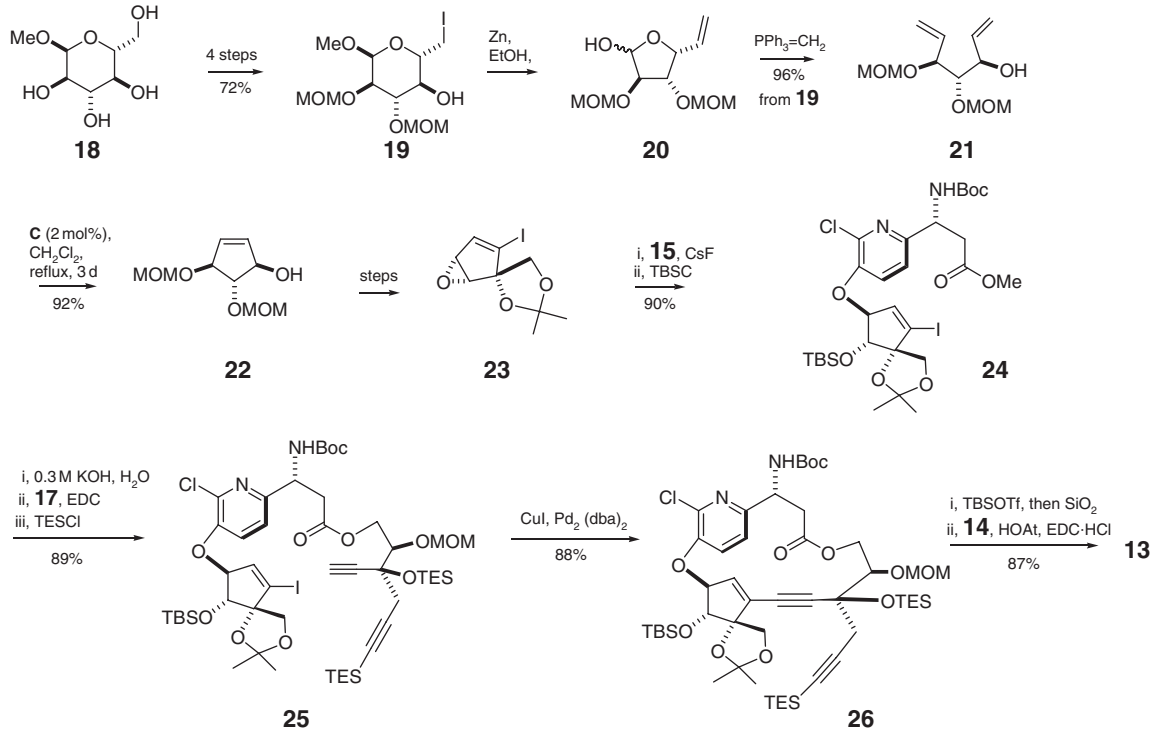
Scheme 3

cyclopentene carboxaldehyde **28**. Aldehyde **28**, in turn, underwent, in the presence of tridentate (Schiff base) Cr(III) complex **30**, an efficient and highly selective inverse-electron-demand hetero-Diels–Alder reaction with ethylvinyl-ether to produce cyclo-adduct **29** in 85% yield. Compound **29** was then converted to boschnialactone **31** by hydrogenation and subsequent introduction of the carbonyl group.

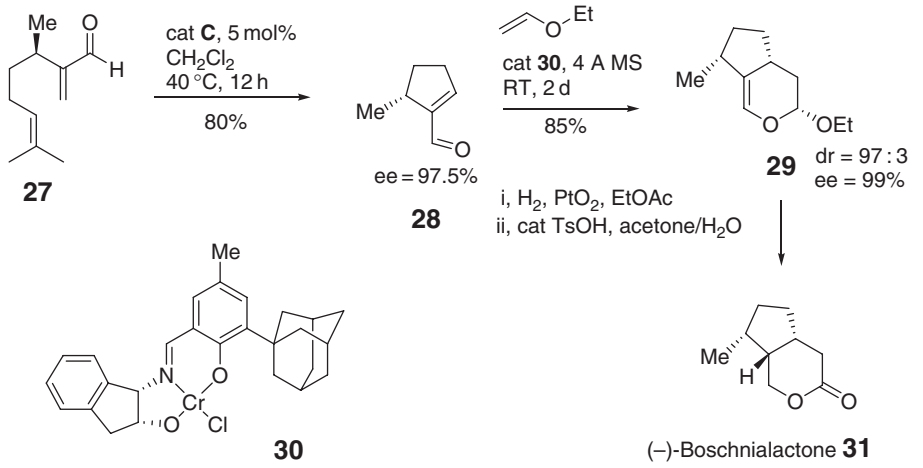
In a total synthesis of the neurotrophic agent merrilactone A (**36**, Scheme 6) by Inoue and Hirama,[11] key intermediate **35** was elaborated from cyclobutane **32** by a sequence of RCM and cleavage of the resulting bicyclic vicinal diol **33** to *meso*-diketone **34**. Cyclooctenedione **34** then underwent regioselective transannular aldol reaction at low temperature (LHMDS, THF, −100 °C) to produce a 3 : 1 mixture of isomers in 85% combined yield. The major isomer **35** with the required stereochemistry was then converted to compound *rac*-36 in 19 steps.

The widespread occurrence and biological significance of polyoxygenated carbocycles provided the impetus to apply RCM to sugar-derived dienes. Carbohydrate carbocyclization based on a sequence of Vasella reductive opening of iodo-substituted methyl glycosides,[12] and RCM of the dienes available from the resulting unsaturated aldehydes, were used to prepare a series of natural compounds (Schemes 7–9).

Two groups reported independently the synthesis of the potent glucosidase inhibitor calystegine B_2 **42**, a polyhydroxylated alkaloid with nortropane ring system (Scheme 7). The RCM precursor **38** was prepared from the iodo-substituted methyl pyranoside **37** by using a zinc-mediated triple domino reaction (ultrasound-accelerated reductive fragmentation of **37** to generate the 5,6-unsaturated aldehyde, trapping of the aldehyde as the benzylimine, and zinc-mediated allylation of the latter).[13] After Cbz-protection, diene **38** was exposed to catalyst **B**[14] or **C**[15], to



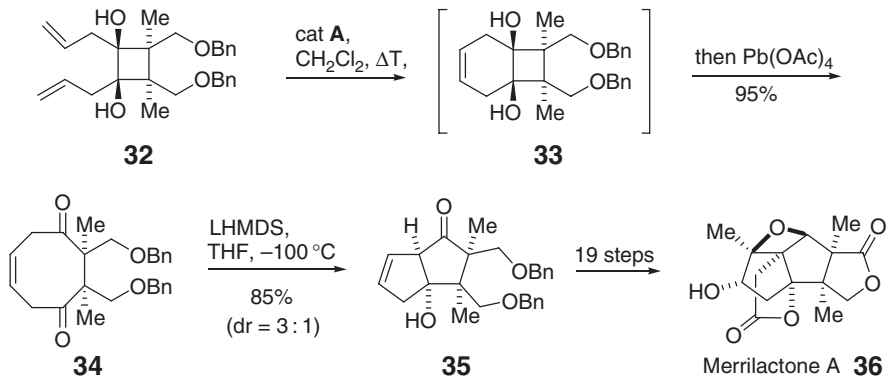
Scheme 4



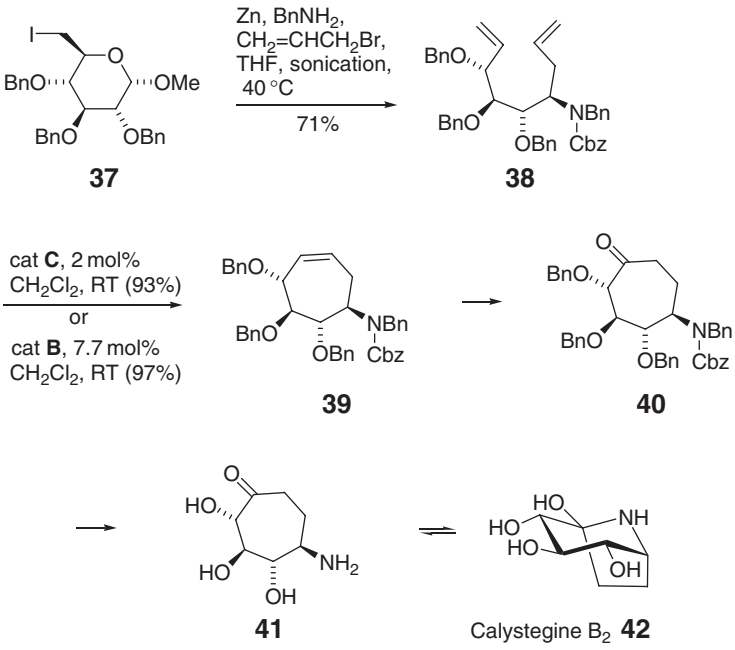
Scheme 5

provide in both cases the desired cycloheptene **39** in good yield. The synthesis (Scheme 7) was then terminated by regioselective introduction of the carbonyl group. The 5-amino-cycloheptanone **41** formed in the deprotection step finally cyclized to the bicyclic aminoketal structure of **42**.

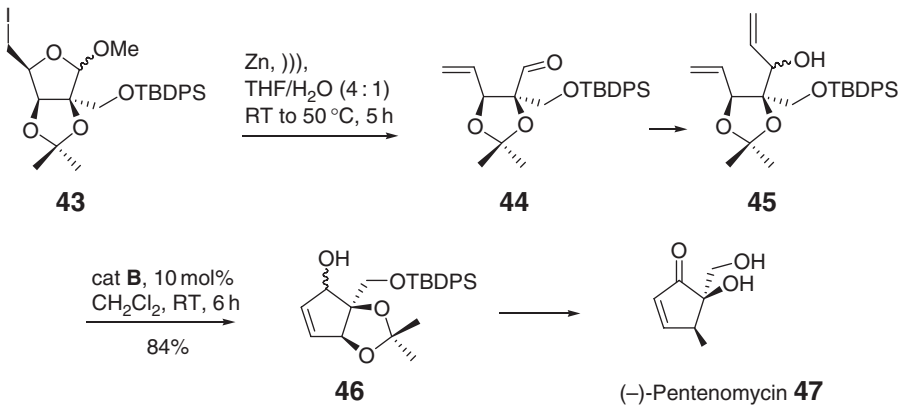
(−)-Pentenomycin **47**, a highly oxygenated cyclopentenoid with a quaternary chiral center (Scheme 8), was prepared by a similar reaction sequence.[16] The RCM precursor **45** was prepared in eight steps from D-mannose via iodo compound **43** and aldehyde **44** (1 : 1 diastereomeric mixture). RCM of **45** led to the epimeric cyclopentenols **46**. A formal total synthesis of the anti-tumor agent and glycogen synthase kinase-3β inhibiting alkaloid (−)-agelastatin



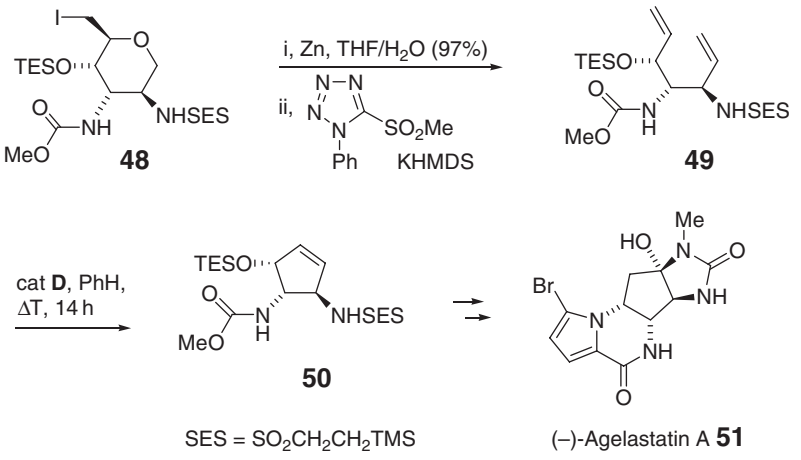
Scheme 6



Scheme 7



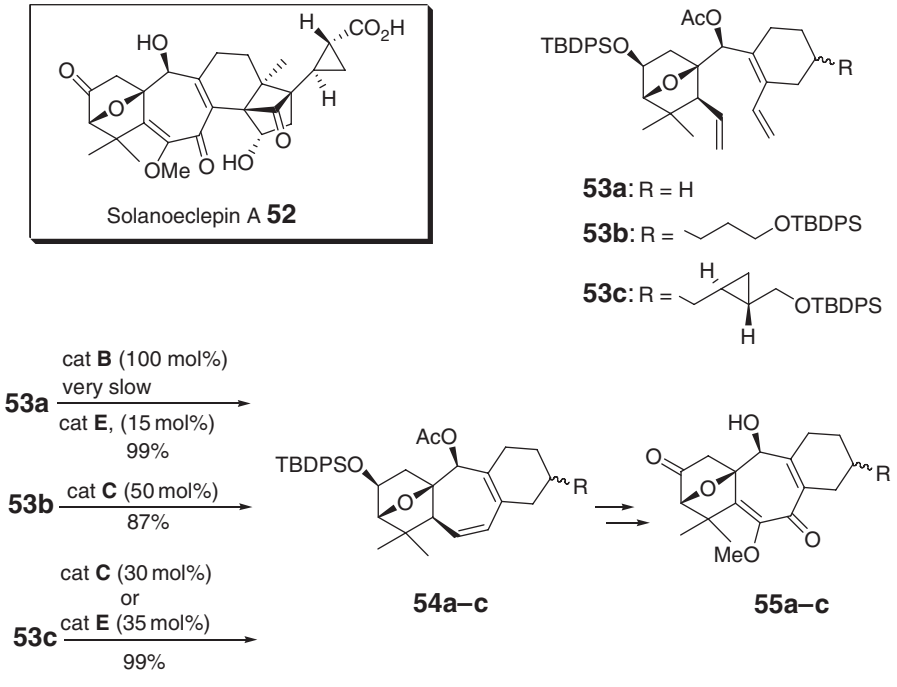
Scheme 8



Scheme 9

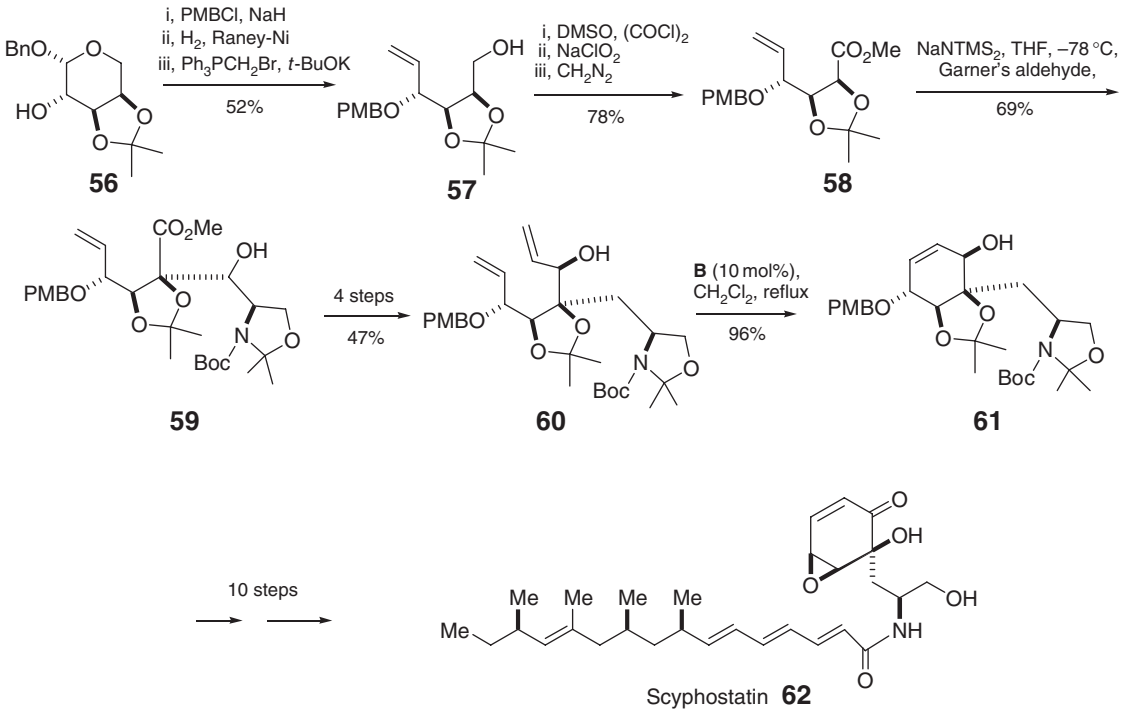
A **51** was disclosed by a British team (Scheme 9).[17] The highly functionalized diene **49** was prepared from iodo compound **48** via Vasella-type reductive ring opening[12] followed by Julia–Kocienski methylenation of the resulting aldehyde. The ring closure to cyclopentene **50** in the presence of catalyst **D** proceeded smoothly, despite the complex functionalization.

Solanoeclepin A **52**, a natural hatching agent of potato cyst nematodes, possesses a seven-membered ring in a complex pentacyclic framework. Hiemstra and co-workers achieved the synthesis of several analogs **55** containing the enantiopure tetracyclic left-hand substructure of **52** (Scheme 10)[18,18a] When the cyclization experiments on triene **53a** were performed with catalyst **B**, the cycloheptadiene forming process to **54a** was very slow requiring a stoichiometric amount of the catalyst for completion. The use of the more reactive catalyst **E**, however, provided quantitative closure to form the tetracyclic diene **54a** with only 15 mol% of **E** after 16 h in refluxing toluene. The more elaborate precursors **53b** and **53c** reacted sluggishly, but the use of 0.35–0.50 equiv. of catalysts **C** or **E** led to

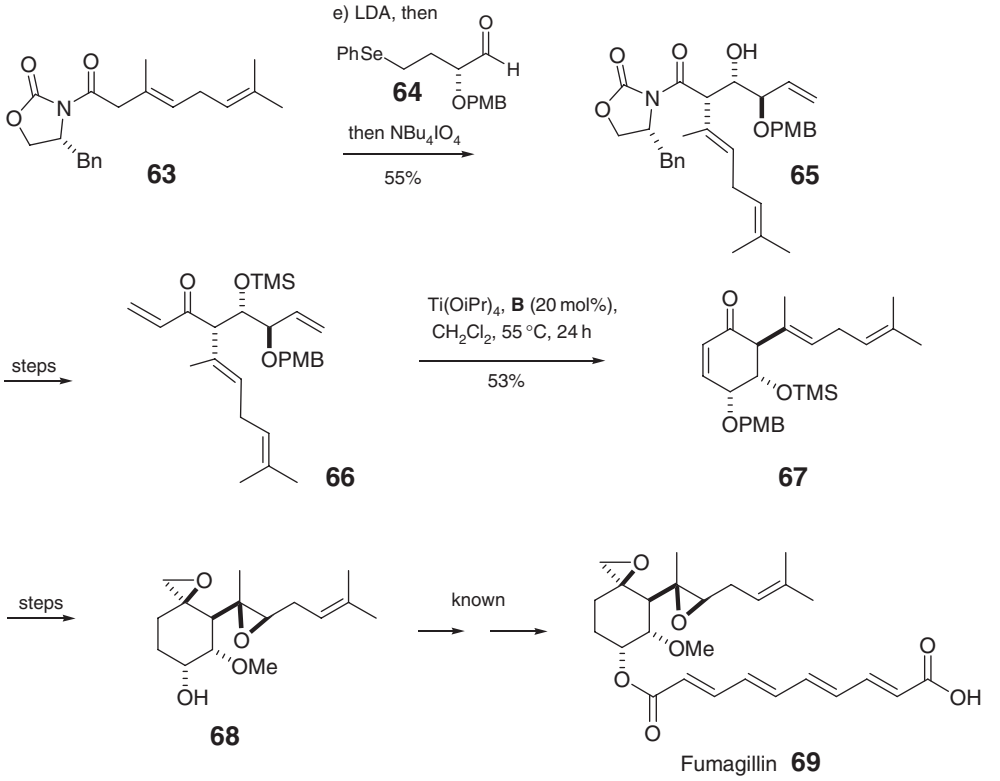


Scheme 10

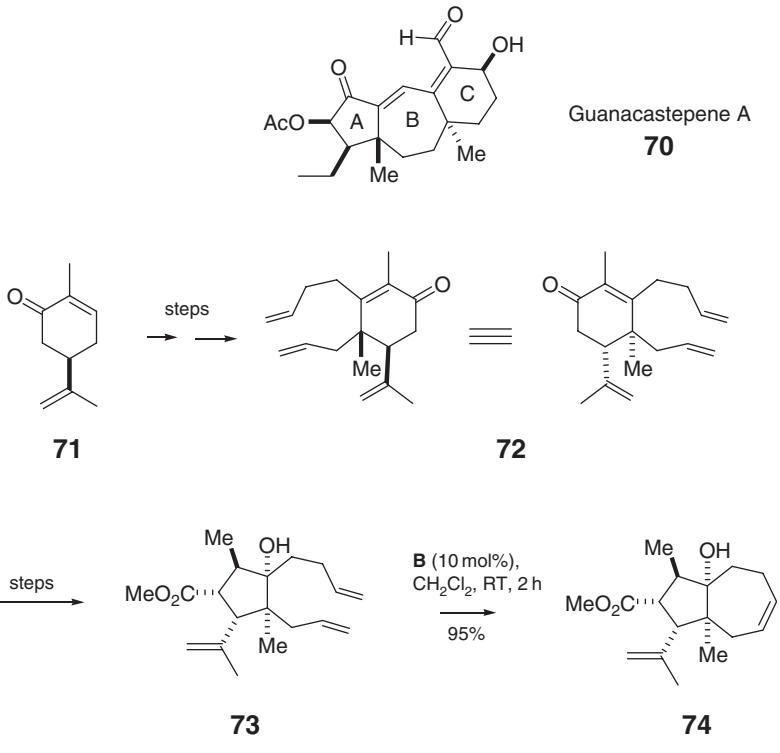
cyclization products **54b** and **54c** in high yield. Scyphostatin **62** is a metabolite of the microorganism *Dasyscyphus molissimus* and is expected to be a promising drug for the treatment of AIDS, inflammation, and immunological and neurological disorders. Structurally, it features a highly oxygenated cyclohexene ring and an aminopropanol side chain linked to a C20 unsaturated fatty acid moiety. The first total synthesis (Scheme 11) of **62**, which is described here,[19] began with a Wittig methylenation of the arabinose derivative **56** to give olefin **57**. The introduction of the amino alcohol side chain was achieved via an aldol-type addition of Garner's aldehyde to ester **58**. Further manipulation of adduct **59** led to di-olefin **60** which on treatment with catalyst **B** formed cyclohexenol **61** in quantitative yield. A number of additional steps led eventually to scyphostatin **62**. Inhibition of angiogenesis has emerged as a promising approach for the treatment of cancer. Among antiangiogenic agents, fumagillin **69** and its analogs have received close attention. For these compounds, methionine aminopeptidase 2 (Met-AP2), a ubiquitous enzyme involved in protein post-translational processing, has been identified as the likely target. The most extensively studied fumagillin analogs are esters of fumagillol **68**, which, so far, is difficult to obtain in appreciable quantity. The current total synthesis by Eustache and co-workers[20] promises to remedy this situation by employing an RCM reaction as the key step. The sequence (Scheme 12) started with the Evans's oxazolidinone **63**. Aldol addition of **63** to aldehyde **64** furnished, after oxidative elimination of the PhSe-moiety, adduct **65**. Conversion of the imide into the Weinreb amide followed by silylation of the secondary OH-function delivered **79**, which was transformed into the enone **66** with vinylmagnesium bromide. RCM with catalyst **B** and $Ti(OiPr)_4$ as an additive furnished cyclohexenone **67** in moderate yield, which was converted into **68** and **69**, respectively. Guanacastepene A **70** is the first member of a small group of diterpenes possessing a challenging [5.7.6]-tricyclic ring system. Guanacastepenes engender enormous interest among synthetic chemists due to their potent activity against the methicillin-resistant strain of *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecalis* (VREF). In the present model study (Scheme 13),[21] RCM reactions were tested for closing the seven-membered B-ring of the molecule. To construct the [B/C]-part, (*R*)-carvone **71** was converted into **72** by two successive alkylations. From there cyclopentane **73** was obtained via ring contraction and converted into **74** via RCM with catalyst **B** in quantitative yield. No further attempts were made to convert the model system into guanacastepene A **70**. The thapsigargins are a family of guaianolides isolated from the Mediterranenan plant genus *Thapsia*. Among 15 related compounds trilobolide **80** has been found, which is a potent inhibitor of the ubiquitous sarco-endoplasmatic reticulum Ca^{2+} ATP-dependent pump. Ley *et al.*[22] reported the first total synthesis of **80**, which features the formation of the seven-membered ring via an RCM between an olefin and an enol ether.



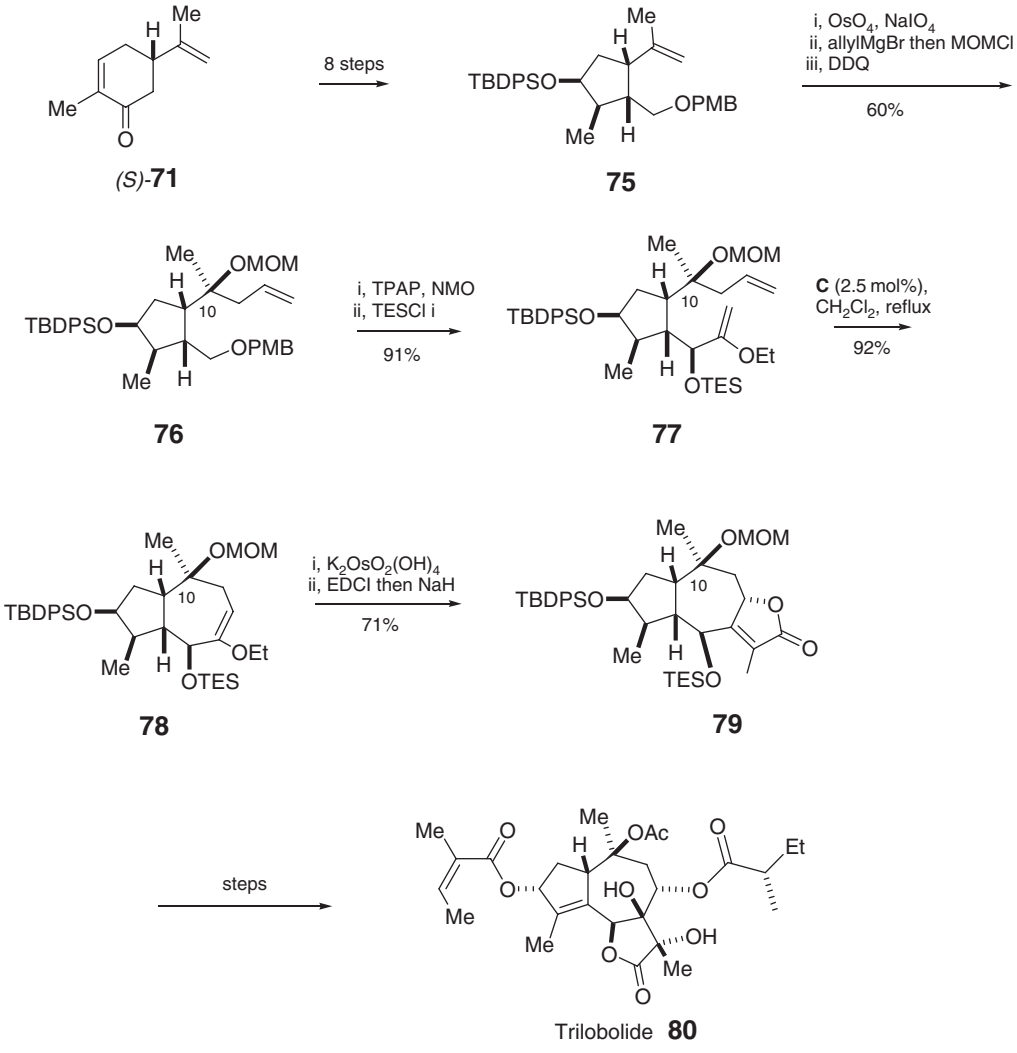
Scheme 11



Scheme 12



Scheme 13



Scheme 14

The synthesis (Scheme 14) began with an eight-step conversion of (*S*)-**71** into the highly substituted cyclopentane derivative **75**, which was available on a multigram scale. Then, an allylic side chain was introduced to form **76**, and from that intermediate the RCM substrate **77** was obtained via addition of 1-ethoxy-vinyllithium. Catalyst **C** was used for the RCM to produce intermediate **78**; slow addition of the catalyst was required to obtain high yield (92%) at low catalyst loading (2.5 mol%). Annulation of the butenolide ring was performed in two steps and the resulting intermediate **79** was then transformed into **80** via a couple of steps.

11.07.2.1.2 Cyclic ethers and lactones

5,6-Dihydro-2*H*-pyran-2-ones (α-pyrones **II**) and dihydropyrans **VIII** are present in a large number of biologically active natural products. Both types of compounds are now routinely prepared by RCM, either via path A or via path B in Figure 3. Additionally, chiral lactones **II** can be used to induce stereospecificity to the neighboring carbons via substrate-controlled reactions, as illustrated by the transformation **II** → **IV** or **II** → **V** in Figure 3. While the formation of pentenolides by RCM of acrylates (path A) mediated by Grubbs's first-generation catalyst **B** often proceeded sluggishly, needing $Ti(OiPr)_4$ as an additive in many cases, the ring closure occurs generally without problems in the presence of second generation catalysts **C**, **D**, and **E**. Disubstituted dihydropyrans of the type **VIII** are prepared

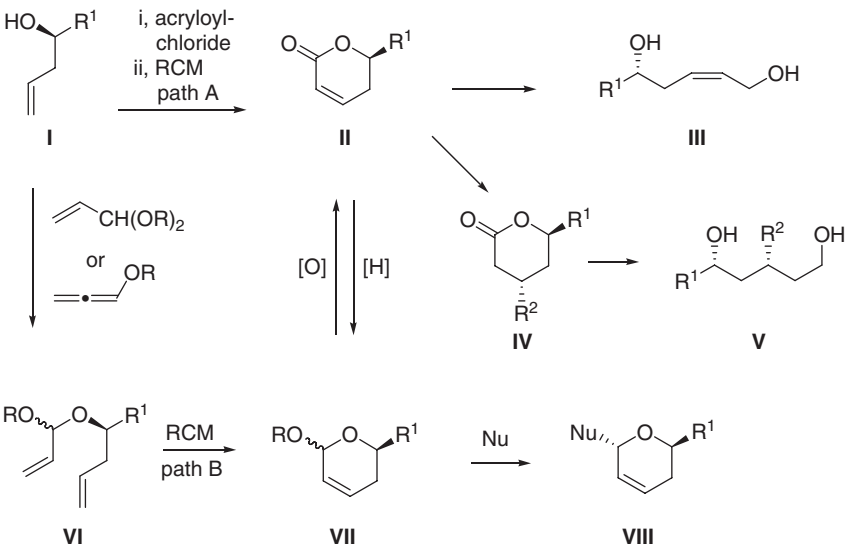
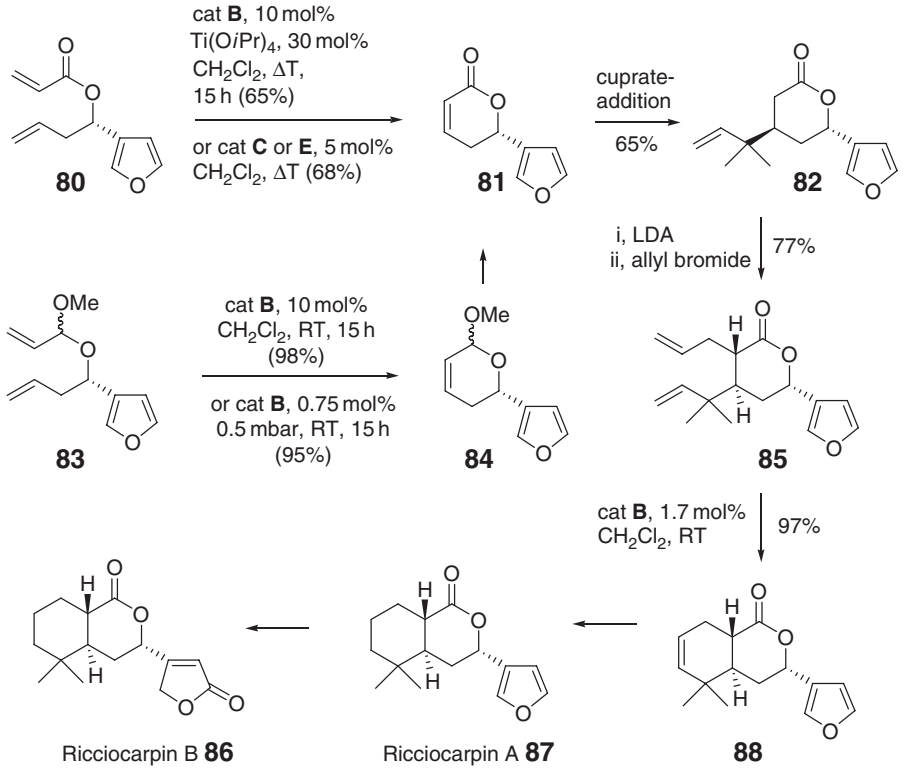


Figure 3 Preparation of α-pyrons and dihydropyrons by RCM.

preferably via path B, by RCM of mixed acrolein acetals **VI**, rather than via the corresponding lactones **II**, as the former cyclizes uneventfully with catalyst **B**.

The difference in reactivity is perfectly revealed in Metz's total synthesis of the molluscicidal furanosesquiterpene lactones ricciocarpin A **86** and B **87** (Scheme 15).[23] Attempts to convert acrylate **80** into lactone **81** using catalyst **B** or Schrock's molybdenum catalyst **A** resulted in very low yields of the desired product. With $Ti(OiPr)_4$ as an additive,



Scheme 15

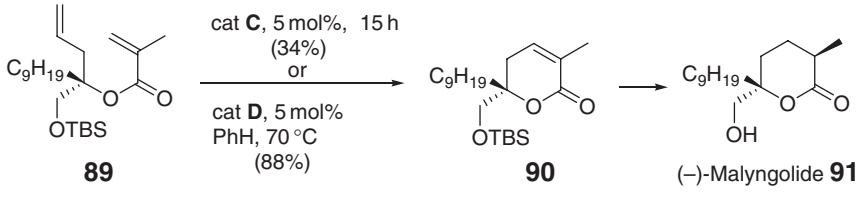
which is suggested to reduce deactivation of catalytic intermediates by the Lewis-basic carbonyl oxygen,[24] the yield was improved to 65%. With second-generation catalysts **C** and **E**, the catalyst loading could be reduced, and the reaction led – without additive – to **81** in comparable yields. RCM of mixed acetal **83**[25] proceeded smoothly with catalyst **B** at RT leading to dihydropyran **84** in almost quantitative yield. The best results, however, were obtained when the reaction was performed without any solvent using only 0.75 mol% of catalyst **B** at reduced pressure, which guaranteed the efficient removal of ethylene produced during metathesis. The conversion of lactone **81** to the natural compounds was continued by sequential *trans*-selective conjugate addition of a cuprate and α-allylation of intermediate **82**. The resulting diene **85** was subjected to another high yielding RCM reaction to **88**, which finally was transformed to **86** and **87**.

The unique power of Hoveyda's recyclable ruthenium catalyst **D** in RCM with electron-deficient and sterically demanding substrates is illustrated in Honda's total synthesis of the simple marine lactone, (−)-malyngolide **91**, which contains a chiral quaternary carbon center (Scheme 16).[26] Attempted RCM of diene **89** with 5 mol% of catalyst **C** for 15 h produced the desired product **90** only in 34% yield. When 5 mol% of catalyst **D** were used, the yield was improved to 88%. RCM was also one of the key steps in many other total or partial syntheses of natural products with a δ-lactone moiety. The α-pyrone moiety of the potent anti-tumor agent (+)-fostriecin has been closed in Hatakeyama's total synthesis[27] and in Cossy's synthesis of an advanced intermediate.[28] In addition, the cytotoxic styryllactone (+)-goniodiol[29,29a] and the plant metabolite (+)-boronolide[30] were prepared via ruthenium-catalyzed RCM. RCM-based synthesis of some lactones with the proposed structures of passifloricin A,[31] and a total synthesis[32] have led to a correction of the structure of the natural compound. Syntheses of an advanced fragment of the microbial metabolite and dimeric polyketide SCH 351448,[33] of the saturated lactone moiety of the potent HMG-Co A reductase inhibitors compactin and mevinolin,[34] and Ghosh's synthesis of the highly functionalized C1–C9 segment of the microtubule stabilizing agent peloruside A,[35] are examples for the additional introduction of stereocenters to the lactone after the RCM step.

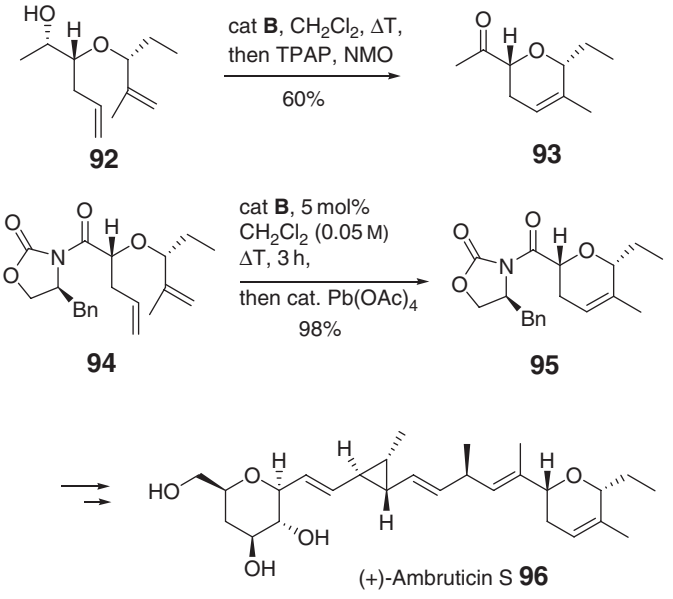
The utility of RCM methodology for the synthesis of open chain building blocks from α,β-unsaturated δ-lactones is exemplified by the partial syntheses of Cossy aimed toward (+)-methynolide (the aglycon of the methymicin family of macrolide antibiotics),[36] and the anticancer agent discodermolide,[37] as well as during a total synthesis of the highly cytotoxic marine natural depsipeptide apratoxin A by Forsyth and Chen.[38]

The orally active antifungal agent ambruticin S **96**, which exhibits activity against a variety of pathogenic fungi has attracted intense synthetic interest. In two of the total syntheses the 2,6-*cis*-disubstituted tetrahydropyran unit in **96** was prepared by RCM (Scheme 17). In Martin's synthesis,[39] secondary alcohol **92** was used as the metathesis substrate, and the reaction led to ketone **93** in 60% yield after tetrapropylammonium perruthenate (TPAP) oxidation (substrate concentration, catalyst loading, and reaction time were not given). In Lee's work,[40] the ring closure of diene **96** was effected under high dilution with catalyst **B**, leading to cyclization product **95** in 98% yield, when $Pb(OAc)_4$ was added to the reaction mixture before workup to remove traces of ruthenium and phosphine byproducts derived from the catalyst.[41,41a–41c]

The marine natural product laulimalide **102**, a metabolite of various sponges, has received attention as a potential anti-tumor agent due to its "taxol-like" ability to stabilize microtubules. There has been considerable synthetic effort toward **102**, culminating within not more than 2 years in as many as 10 total syntheses by seven groups and numerous fragment syntheses.[42] Both, the exocyclic and the inner 2,6-*trans*-disubstituted dihydropyran unit in **102**, have been prepared by RCM,[43] and it was shown that the ring closure can also be performed chemoselectively in the presence of additional double bonds leading to the advanced intermediates **97–101** depicted in Figure 4. Intermediate **101** was prepared by bidirectional RCM under high dilution from the corresponding D-mannose derived tetraene, and served as an efficient precursor for the volatile dihydropyran carboxaldehyde.[44,44a] The RCM reactions leading to dihydropyrans **97**, **98**,[45] **100**,[46] and **101**[47] were all performed with catalyst **B**, while the tributylstannyl-substituted dihydropyran **99**[48] was prepared with molybdenum catalyst **A**.



Scheme 16



Scheme 17

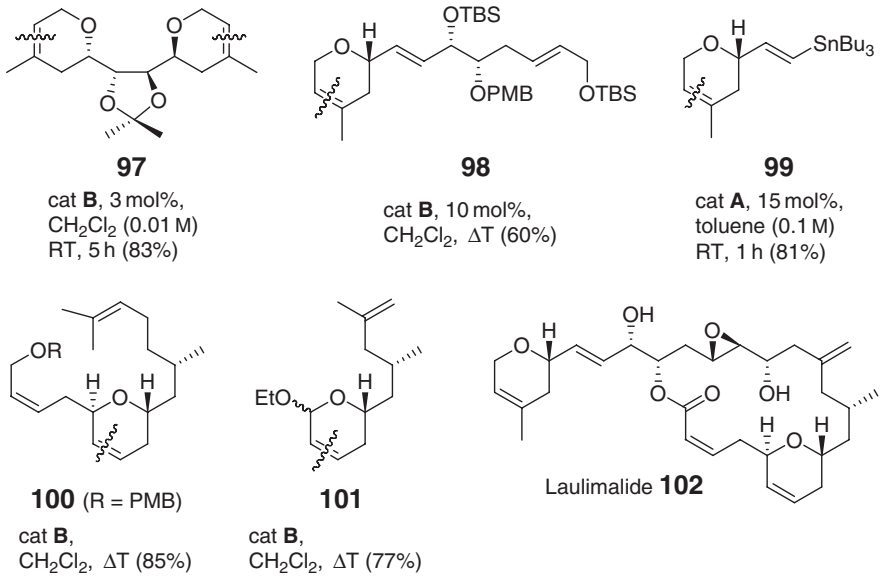
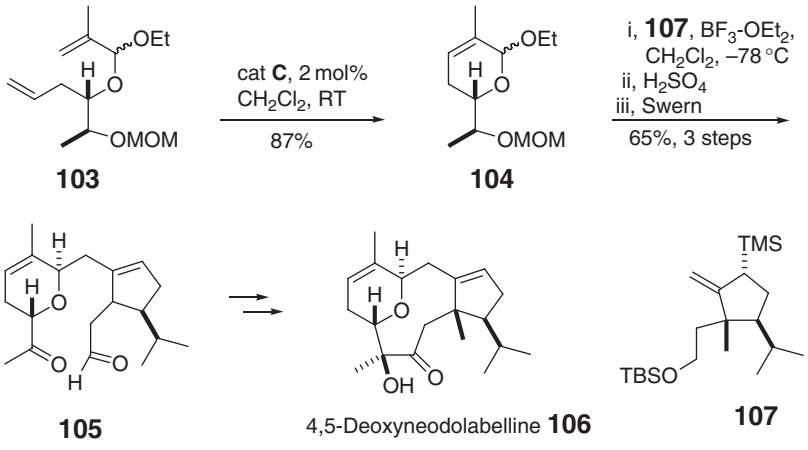


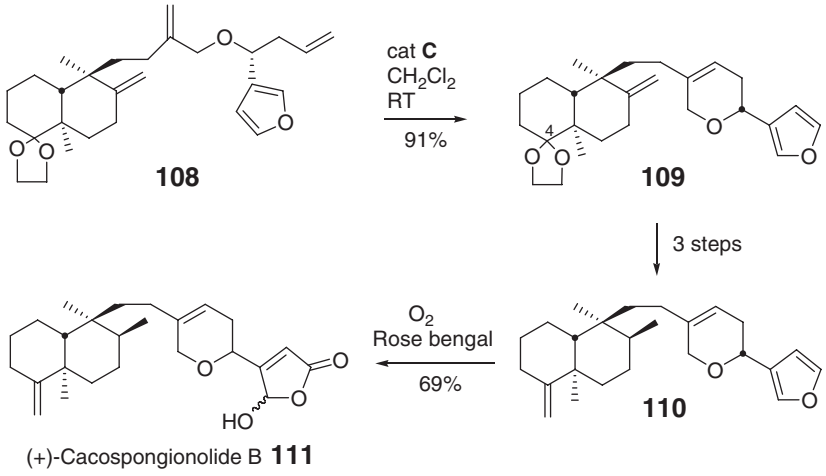
Figure 4 RCM approaches to laulimalide.

The first total synthesis of the marine dolabellane diterpene (+)-4,5-deoxyneodolabelline **106** has been accomplished by Williams *et al.*[49] The *trans*-disubstituted dihydropyran moiety in key intermediate **69** was efficiently prepared from mixed acetal **103** by RCM with catalyst **C** and subsequent Lewis acid-catalyzed allylation of ethyl glycosides **104** with allylsilane **107** (Scheme 18).

The formation of a highly complex 2,5-disubstituted dihydropyran by RCM was one of the key steps in Snapper's total synthesis of the cytotoxic marine natural product (+)-cacospongionolide B **111** (Scheme 19).[50] With catalyst **C**, RCM of triene **108** proceeded regioselectively to produce only the dihydropyran



Scheme 18

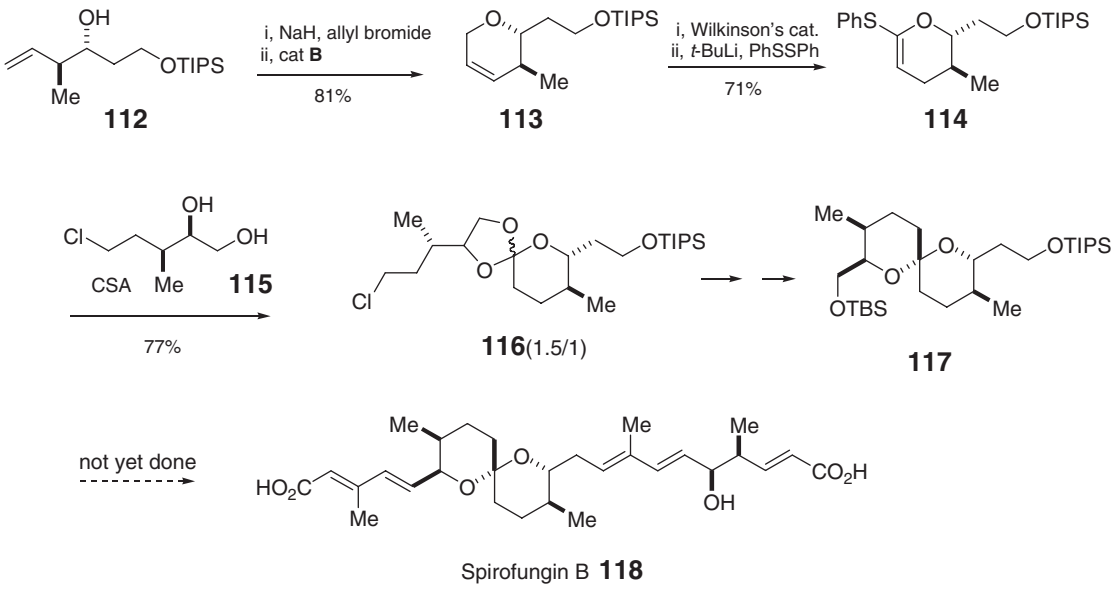


Scheme 19

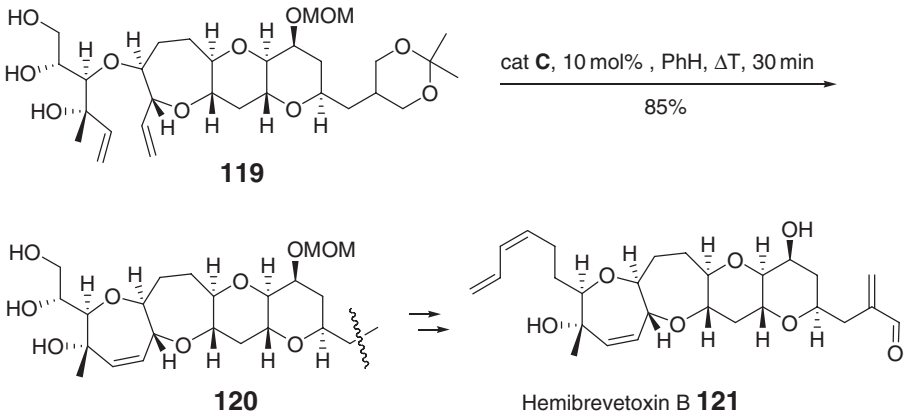
ring, leading to compound **109** in 91% yield. The synthesis of **111** was then completed in four steps, by selective reduction of the *exo*-methylene group, followed by introduction of the methylene group at C4 and photooxygenation of the furan ring in intermediate **110**. Spirofungin B **118** is a metabolite from *Streptomyces* strain Tü 4113 with an interesting spiroketal core. Biologically, the spirofungins show high inhibition activity against yeast and moderate activity against some fungi with an MIC of 15 mg ml^{-1} against *Candida albicans*. The absolute configuration of the anomeric center is uncertain yet, and, hence, the synthesis (Scheme 20) of the core fragment **117** was performed by Rychnovsky and La Cruz[51] to confirm the stereochemistry postulated by Rizzacasa *et al*.[52] The spiroketal **117** was formed from fragments **114** and **115**. The synthesis of **114** started with the known alcohol **112** which was *O*-allylated and then subjected to RCM with catalyst **B**. Dihydropyran **113** was formed in 81% yield. The double bond was shifted to form the enol ether which is then metallated and treated with diphenyldisulfide to give hemithioketene acetal **114**, which was combined with diol **115** to give **116** as an anomeric mixture. This was elaborated into **117**.

In the synthesis of the marine neurotoxin hemibrevetoxin B **121**,[53] dienetriol **119** was used as an RCM substrate for elaboration of the seven-membered A ring in **121** (Scheme 21). While catalyst **B** was ineffective in this case, the ring closure occurred smoothly with catalyst **C** providing the tetracyclic intermediate **120** in high yield.

RCM was also used in Yamamoto's synthesis of the marine neurotoxin gambierol **125**,[54,54a,54b] to close the central seven-membered E ring, thereby completing the octacyclic polyether core **124** (Scheme 22). Following previously developed methodology,[55] metathesis precursor **123** was produced as the major epimer, by boron



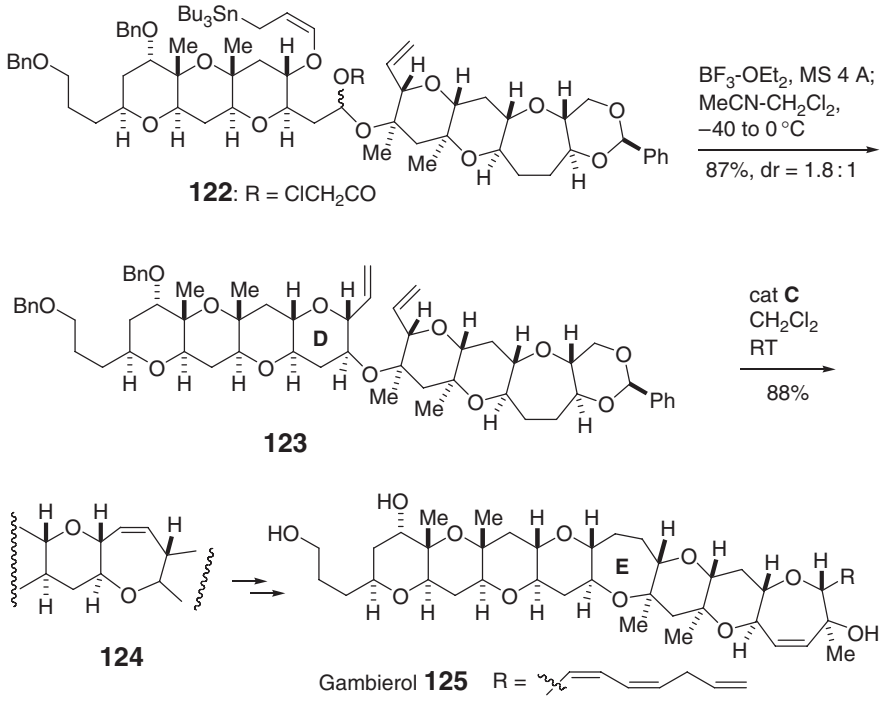
Scheme 20



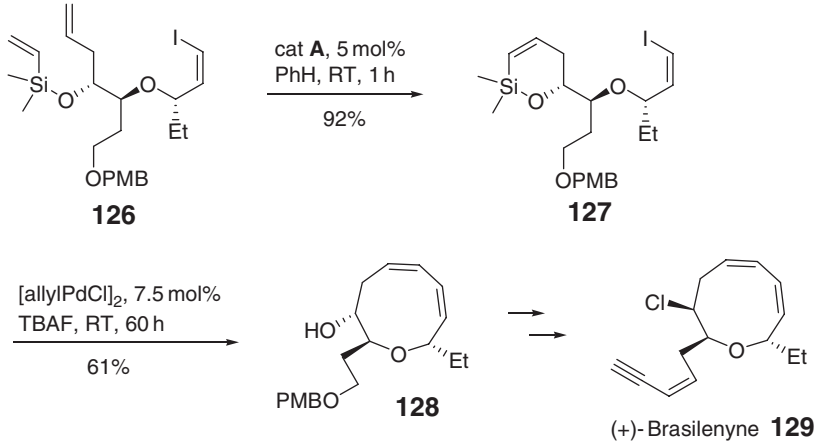
Scheme 21

trifluoride etherate-mediated intramolecular allylation of α-chloroacetoxy ether **122**. Subsequent treatment of **123** with catalyst **C** produced the octacyclic ether **124** in 88% yield.

In application of his previously developed synthesis of medium-sized rings containing a 1,3-*cis*,*cis*-diene unit,[56] Denmark disclosed a synthesis of the nine-membered cyclic ether (+)-brasilenyne **129**, through a sequence of RCM with formation of a six-membered cyclic silylether followed by silicon-assisted intramolecular cross-coupling (Scheme 23).[57] When RCM precursor **126** was subjected to Schrock's catalyst **A**, compound **127** with the silicon-based temporary linker was formed in 92% yield. The intramolecular cross-coupling leading to the nine-membered ring was then carried out with $[allylPdCl]_2$ as the catalyst and TBAF as the activator and led to intermediate **128** in 61% yield. In contrast to the ruthenium-mediated RCM discussed so far, Rainier *et al.*[58] used a titanium carbene species to effect the formation of seven-membered ring E in the polyether ladder toxin gambierol **135**. Specifically, the two fragments **130** and **131** shown in Scheme 24 were connected via a Yamaguchi esterification to form **132**. The ester group was then subjected to the Takai–Utimoto reagent, prepared from ethylidene dibromide. Presumably, a titanium carbene **133** was formed as an intermediate which underwent RCM with the olefin appendage to furnish the cyclic enol ether **134**. This compound was converted into gambierol **135** in 10 steps.



Scheme 22



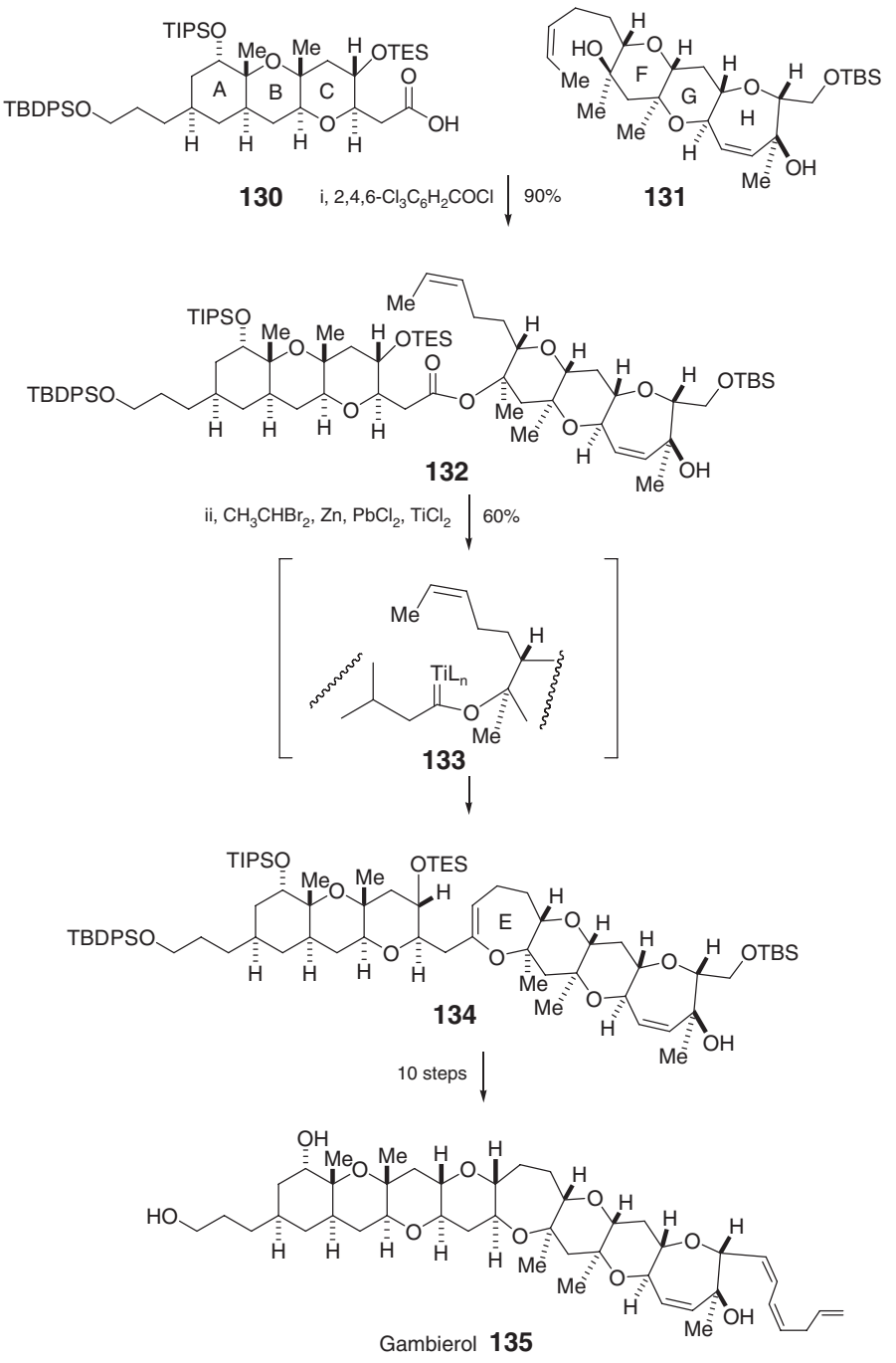
Scheme 23

11.07.2.1.3 Alkaloids

The marine natural product dynosin A **144** is a member of the aeruginosin family and an inhibitor of thrombin and Factor VIIa. In Hanessian's total synthesis of **144**,[59] both the dihydroxy-octahydroindole **137** and the Δ^3 pyrroline moiety **138** have been prepared by RCM-based routes (Scheme 25).

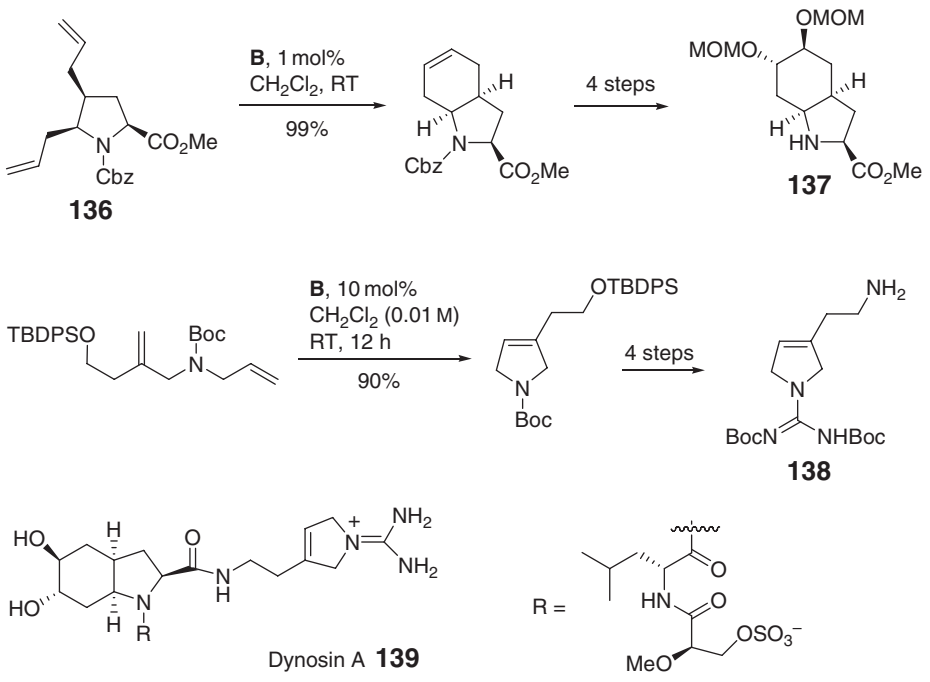
The phenanthroindolizidine alkaloid (−)-antofine **142** exhibits high cytotoxicity to drug-sensitive and multidrug-resistant cancer cells by arresting the G2/M phase of the cell cycle. In the asymmetric total synthesis of (−)-**142**, the late-stage construction of pyrrolidine **141** was performed by RCM and subsequent hydrogenation (Scheme 26).[60]

A concise total synthesis of the indole alkaloid dihydrocorynantheol **148** (Scheme 27) that features two RCM steps and a zirconocene-catalyzed carbomagnesation[61] is a further example of Martin's interest in applying RCM as a key

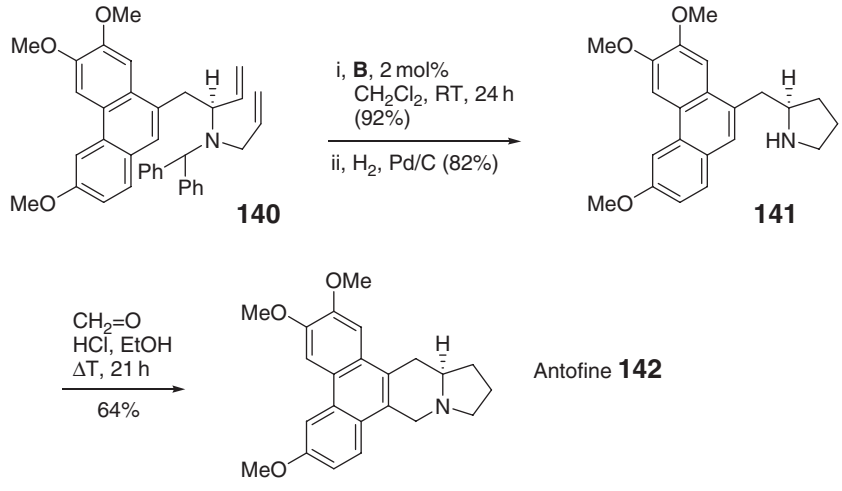


Scheme 24

reaction for the construction of alkaloid frameworks. The first RCM step was applied to bis-allylamide **143**. The resulting intermediate **144** was directly subjected to carbomagnesation and subsequent elimination to deliver **145**. Amide **145** was then transformed to acrylamide **140** in two steps. RCM of **146** furnished lactam **147** in 91% yield which was converted into racemic **148** in four additional steps. Securinine **154** is a tetracyclic alkaloid isolated from "Euphorbiaceae" plants, which is a specific gamma-aminobutyric acid (GABA) receptor antagonist and has been found to have significant *in vivo* central nervous system (CNS) activity. Additionally, securinine has been shown to be an antimalarial and an antibacterial agent which causes apoptosis in leukemia cells.[62] The total synthesis (Scheme 28)



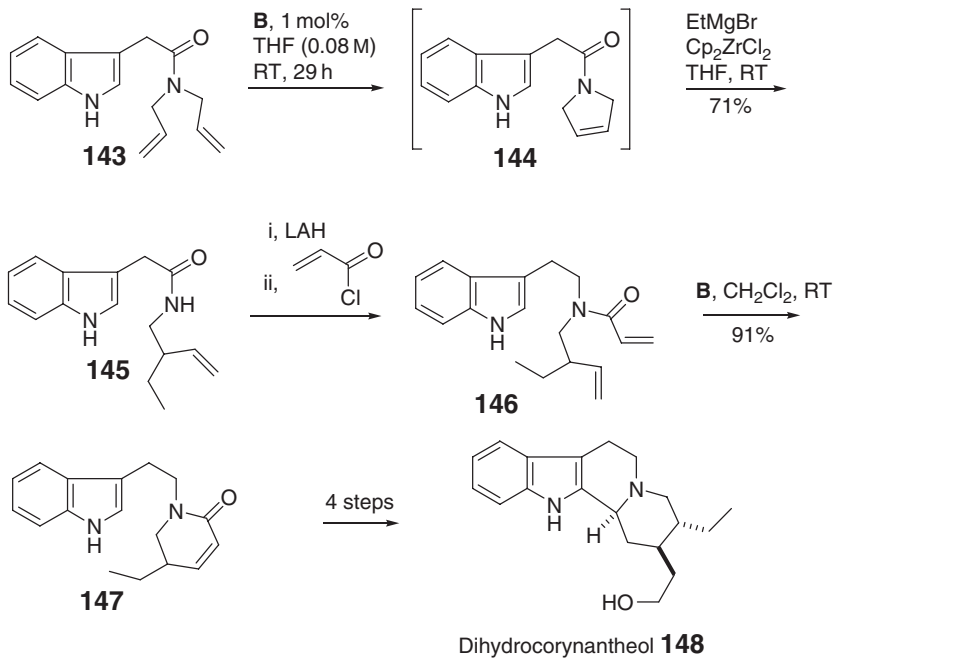
Scheme 25



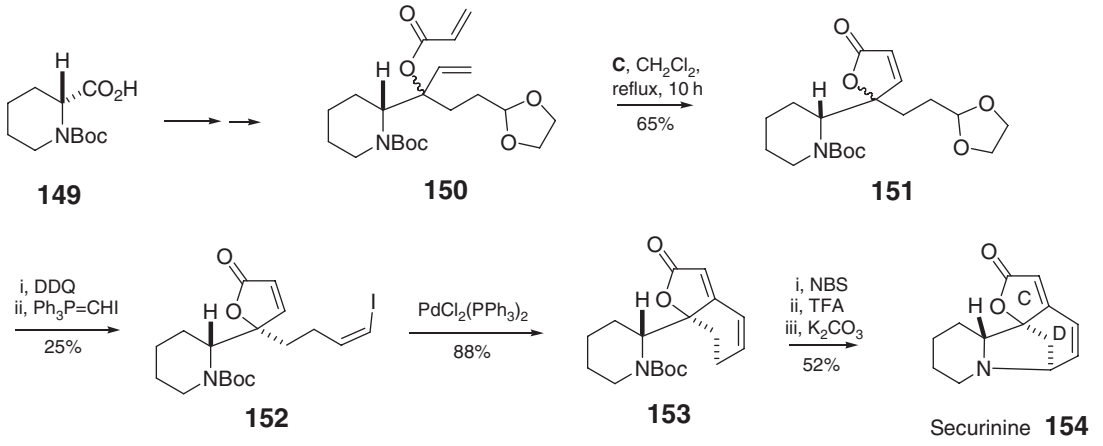
Scheme 26

by Alibes and de March[63] features an RCM step, which closes the butenolide ring C, and a Heck cyclization, by which cyclohexene D is annulated. The synthesis starts with *N*-Boc pipecolinic acid **149**, which is converted into a 6/1 diastereomeric mixture of di-olefin **150** through a six-step sequence. The RCM reaction to **151** was performed by refluxing dichloromethane with catalyst **C** which was added consecutively in 2% molar amounts every 2 h until reaching 10%. In two further steps (*Z*)-vinyl iodide **152** was prepared and subjected to a Heck cyclization which furnished **153** in 88% yield. The remaining ring B was closed by allylic bromination, and *N*-Boc deprotection and *N*-alkylation were the last two steps.

Allosedamine **157** is a relatively simple piperidine alkaloid which was isolated more than 60 years ago by Wieland and co-workers from *Lobelia inflate*.[64] It has good activity against respiratory disorders such as asthma, bronchitis, and pneumonia. The key step of the current synthesis (Scheme 29)[65] is an RCM of enone ester **155** which closes the

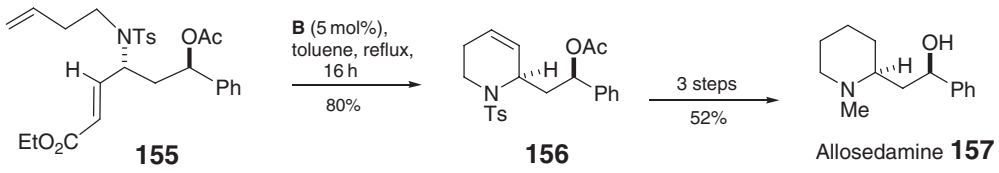


Scheme 27

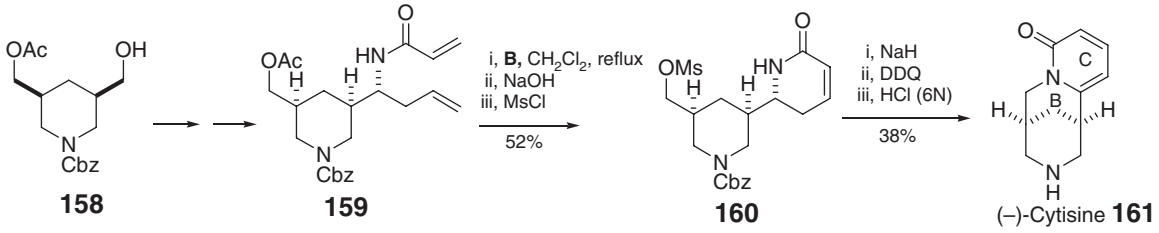


Scheme 28

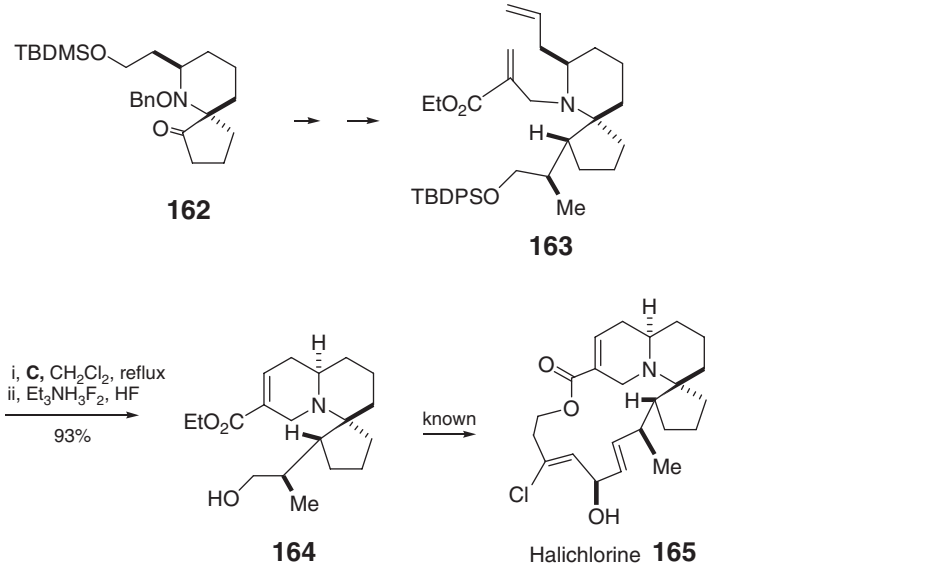
tetrahydropyridine ring across an *N*-tosyl tether to form **156**. (−)-Cytisine **161** is an important ligand of the nicotinic receptor and may thus be of importance for the treatment of various CNS disorders. The current synthesis (Scheme 30)[66] started from piperidine **158**, which was obtained by an enzymatic desymmetrization of the corresponding diacetate. Via a routine six-step sequence, amide **159** was prepared and subjected to an RCM reaction with catalyst **B** in 79% yield. Intermediate **160** was then converted into **161** via S_N2-type cyclization of ring B. Halichlorine **165** has been isolated from the Japanese sponge *Halichondria okadai* and features an interesting 6-azaspiro[4.5]decane ring system. Biologically, **165** is a selective inhibitor of the induced expression of VACAM-1, a member of the immunoglobulin superfamily which regulates the migration of certain leukocytes in inflamed tissue.[67] The formal synthesis of racemic **165** described here (Scheme 31)[68] aims for Danishefsky's intermediate **164**, which has been converted into **165** previously.[69] The synthesis started with compound **162** which was converted into **163**. When this di-olefin was heated with catalyst **C**, a quantitative yield six-membered ring formation resulted to give **164** after desilylation.



Scheme 29

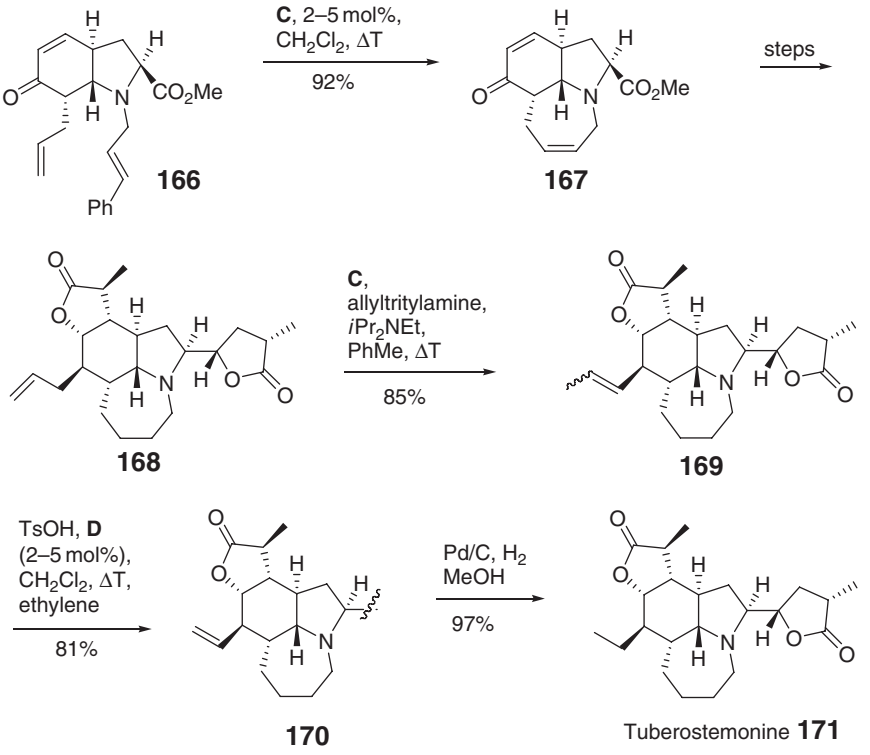


Scheme 30



Scheme 31

A further example of the rapid progress in Ru-catalyzed metathesis reactions is Wipf's total synthesis of (−)-tuberostemonine **171**.[70] This complex polycycle belongs to the family of *Stemona* alkaloids which cover a broad range of biological activities including applications in Eastern folk medicine against pulmonary tuberculosis and bronchitis. The first total synthesis of **171** (Scheme 32) highlights the threefold use of Ru catalysts, first by an azepine ring-closing step and, in the endgame of the synthesis, by an Ru-catalyzed allyl to 1-propenyl isomerization/Ru-catalyzed cross-metathesis (CM) sequence leading to a propenyl–vinyl interchange. When key intermediate **166** was exposed to 2–5% of NHC catalyst **C**, tricyclic azepine **167** was smoothly formed in a high yield. After stereoselective elaboration of the complete pentacyclic skeleton, the allyl substituent in the advanced intermediate **168** was isomerized using a modification of a method developed by Roy *et al.* for allyl ethers.[71] Thus, heating a solution of **168** in toluene in the presence of catalyst **C**, allyl tritylamine, and diisopropylethylamine led to the 1-propenyl-substituted isomer **169** in high yield. Subsequent CM of **169** with ethylene in the presence of catalyst **D** and TsOH gave access to the desired vinyl group in **170**, which was hydrogenated to provide (−)-**171**.



Scheme 32

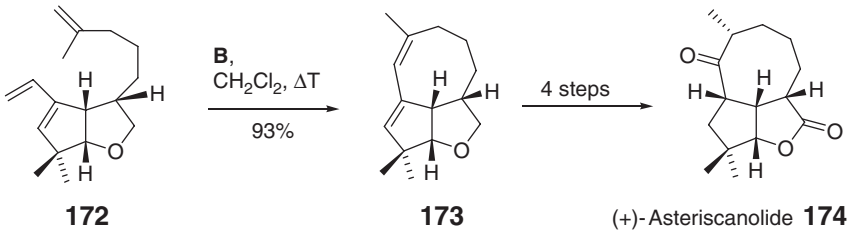
11.07.2.2 Formation of Medium-sized Rings (Ring Sizes of 8–11)

Because of enthalpic (increasing strain in the transition state) and entropic influence (probability of the chain ends meeting), medium-sized rings are the most difficult to prepare. Additionally, the formation of medium-sized rings by RCM may pose considerable challenges, as due to the inherent ring strain, 8–11-membered cycloalkenes are prone to the reverse process that is to ROM or ring-opening metathesis polymerization (ROMP) sequences. One approach to circumvent this problem is to incorporate control elements (cyclic conformational constraints by pre-existing rings or acyclic constraints by the substitution pattern of the cyclization precursor) which forces the cyclization substrate to adopt a conformation suitable for ring closure. These constraints will facilitate RCM and stabilize the product against the competing ROMP pathway. While up to early 2000, only a limited number of successful RCM reactions for the synthesis of natural products with medium-sized rings were reported,[2i] the number rapidly increased during the last three years.[72] Most importantly, we will see that in some cases also the stereochemical outcome of the reactions could be mediated by the choice of the catalyst, which is deemed to reflect kinetic versus thermodynamic control of the cyclization reaction.

11.07.2.2.1 Carbacycles

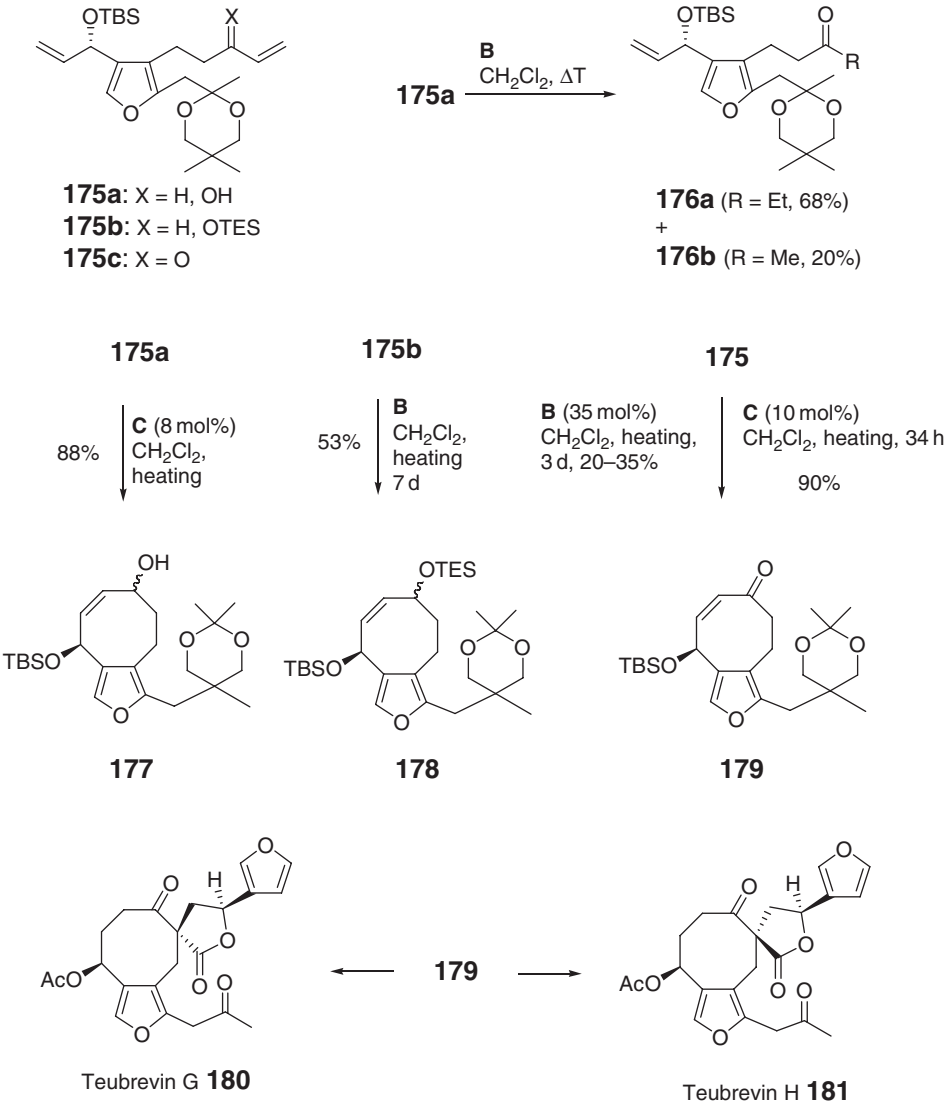
The importance of conformational restriction for the ring-closing reaction is nicely demonstrated during Paquette's concise total synthesis of natural (+)-asteriscanolide **174**,[73] whose framework consists of a rather uncommon bicyclo[6.3.0]octane ring system bridged by a butyrolactone fragment (Scheme 33). Despite the presence of a conjugated diene unit and a *gem*-disubstituted double bond in precursor triene **172**, the cyclooctene ring in **173** was formed in high yield (93%, based on recovered starting material), when a total of 30 mol% of Ru catalyst **B** was sequentially added within 48 h to a boiling solution of **172** in dichloromethane.

An illustrative example for the potency of catalyst **C** is Paquette's highly efficient total synthesis of the natural products teubrevin G **180** and teubrevin H **181**, which feature a cyclooctane core fused and spiroannulated to smaller oxygen containing rings.[74] In the retrosynthetic analysis, the viability of an RCM step for annulation of a cyclooctenone ring to the furan played a central role. Despite the presence of a conformational constraint by the furan ring in

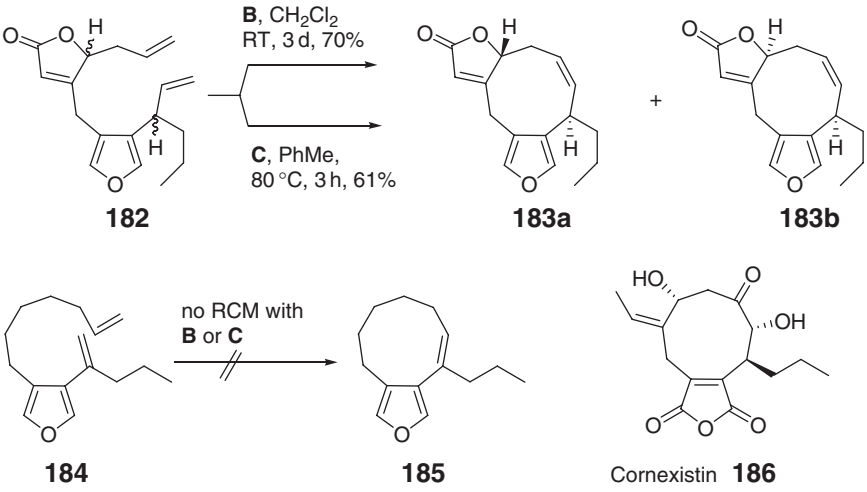


Scheme 33

the cyclization substrate, only poor results were obtained, when catalyst **B** was examined to effect the ring closure of TES ether **175b** and ketone **175c** (Scheme 34). Using very high catalyst loading and reaction times up to 1 week in boiling dichloromethane produced the desired RCM products **178** and **179** only in low yield (53% and 35%, respectively). In the case of allylic alcohol **175a**, the use of catalyst **B** provided no cyclization product **177** at all,



Scheme 34



Scheme 35

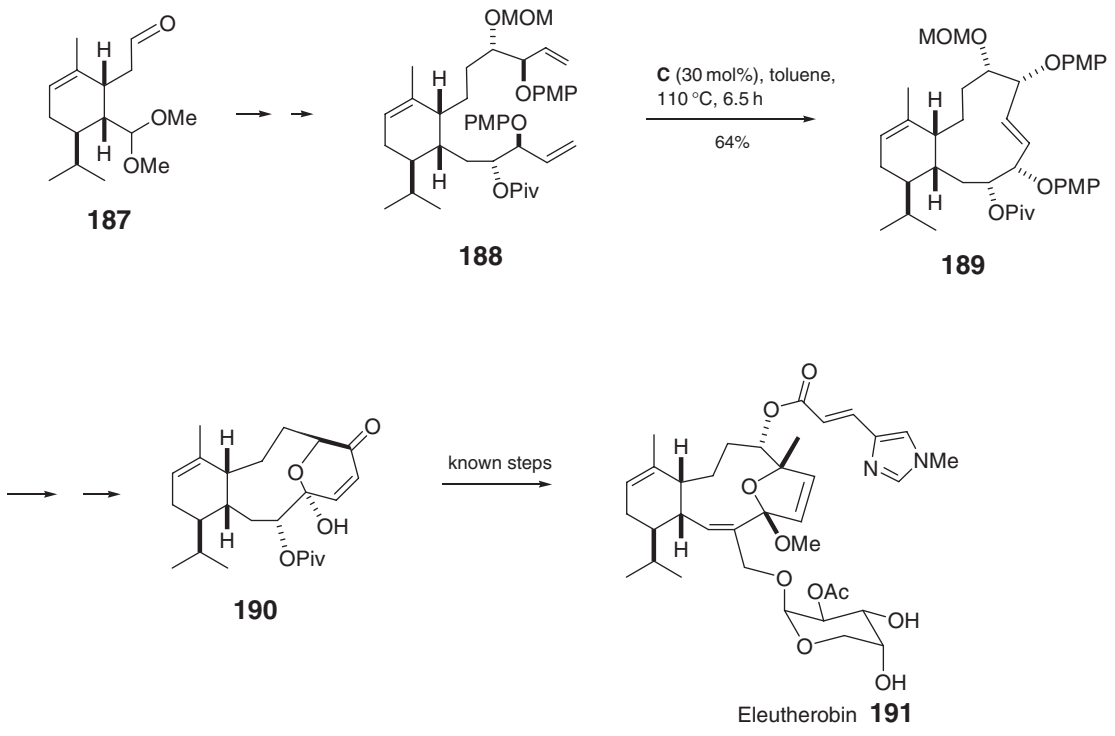
leading instead to ethyl ketone **176a** (68%) and methyl ketone **176b** (20%) as the sole reaction products. When the cyclization was performed in the presence of 10 mol% of Ru catalyst **C**, the RCM reaction of allylic alcohol **175a** and vinyl ketone **175c** proceeded smoothly within several hours to furnish alcohol **177** and ketone **179** in high yield. Cyclooctenone **179** was then successfully converted to **180** and **181**.

En route to a planned total synthesis of the phytotoxic natural compound cornexistin **186**, Clark reported the first example of direct construction of a nine-membered carbocycle, using a sequence of Pd-catalyzed fragment coupling followed by RCM (Scheme 35).[75] With catalyst **C** in toluene at 80 °C, RCM of precursor **182** (1 : 1 mixture of diastereomers) was complete within 3 h leading to isomers **183** in 61% yield. When the cyclization was performed with catalyst **B**, the reaction was only complete after 3 days. However, when the RCM reaction was attempted with model compound **184** containing a *gem*-disubstituted double bond in conjugation to the furan ring, both catalysts failed to provide the ring closure to **185**.

Eleutherobin **191** is a diterpene glycoside, isolated from a marine soft coral, which has been shown to have a microtubule stabilizing activity similar to paclitaxel and epothilone B (epo B). The scarcity of the natural product makes total synthesis vital for biological investigations. The current approach (Scheme 36) by Gennari *et al.*[76] constitutes a formal synthesis of **191** by preparing key intermediate **190**, which has previously been converted into **191** by the Danishefsky group.[77] The Gennari synthesis started from aldehyde **187**, which was available from (*R*)-carvone in six steps and 30% overall yield. Two successive Duthaler–Hafner oxyallylations provided the di-olefin **188** with high stereocontrol. The RCM was performed with catalyst **C** (30 mol%) to give the 11-membered (*E*)-cycloolefin **189** exclusively in 64% yield. The presence of a PMB ether was crucial for the success of this reaction, and the catalyst had to be added slowly to a refluxing toluene solution of the diene (where PMB = *p*-methoxybenzyl). The formation of the *E*-olefin is rather unusual, as similar dienes preferentially give the *Z*-geometry. Nevertheless, quantitative *E*/*Z*-isomerization was observed during the oxidation to enedione **190**.

11.07.2.2.2 Alkaloids

In 1999, a total synthesis of ircinal A **192** and hence a formal synthesis of the potent anti-tumor agent manzamine A **193** was disclosed by the team of Martin (Scheme 37).[78] Two RCM reactions were exploited to elaborate sequentially the requisite 13- and 8-membered rings. When triene **194** (0.005 M in dichloromethane) was exposed to Ru catalyst **B** (13 mol%), a facile and regioselective RCM reaction occurred to furnish a mixture (*Z*/*E* = ~8 : 1) of geometric isomers from which the major isomer **197** was isolated in 67% yield. In contrast to a previous observation,[79] protonation of the tertiary amine prior to the metathesis reaction was not necessary in this case. Hydrolytic removal of the cyclic carbamate in **197** followed by acylation led to the precursor **196** for the second RCM reaction. However, the formation of the eight-membered lactam was problematic, leading to the desired reaction product **195** in only 26% yield with 1.1 equiv. of catalyst **B**. In the subsequent full account in 2002, additional details concerning the RCM steps were revealed. In initial experiments, it had been shown that model compound **198** underwent smooth ring



Scheme 36

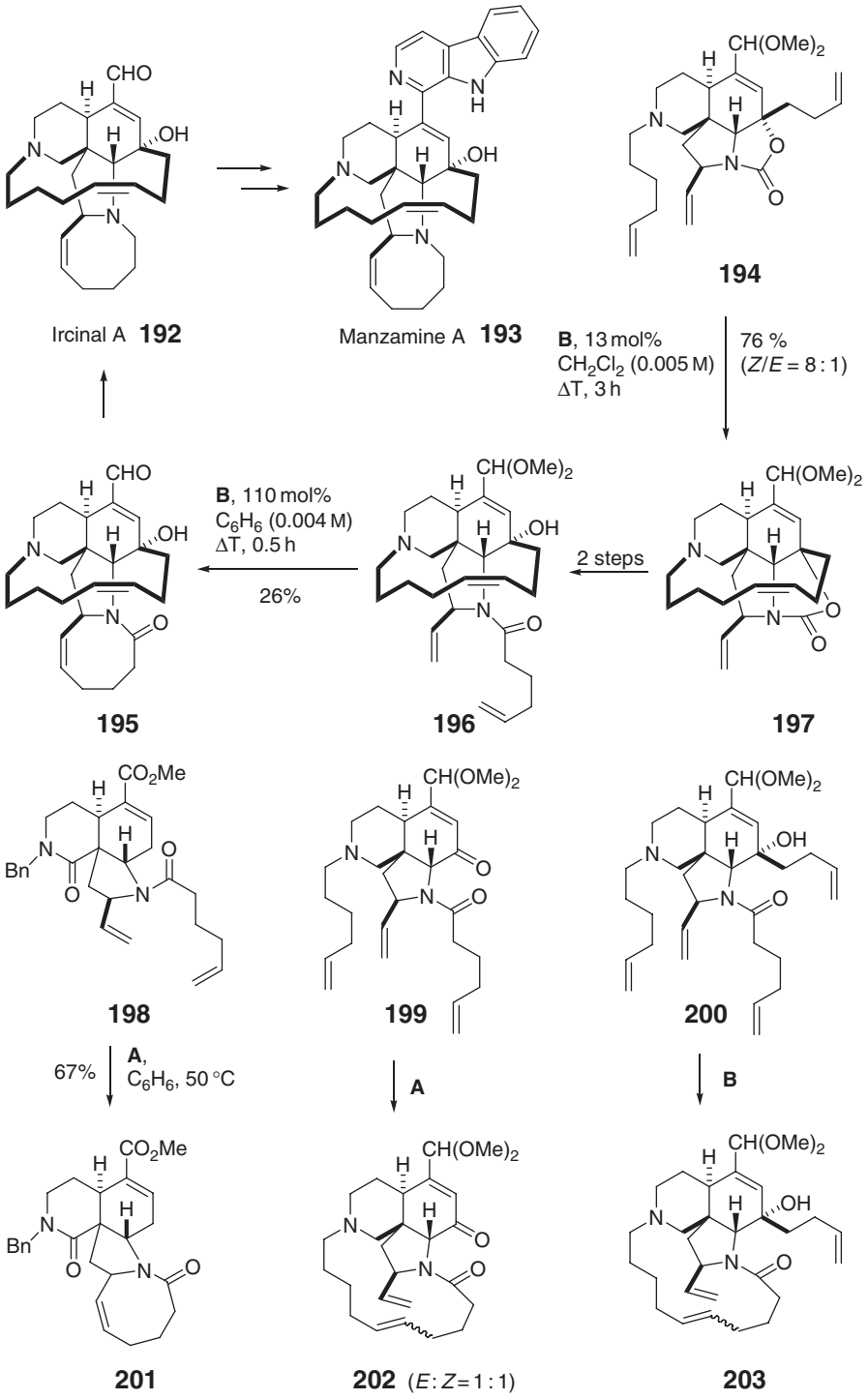
closure with Schrock's molybdenum catalyst **A** to provide the tetracyclic product **201**. It was also attempted to effect double RCM to construct the pentacyclic skeleton in a single operation. However, compound **200** only gave tetracycle **203** with a 15-membered ring. In addition, compound **199** underwent rapid ring closure in the presence of catalyst **A**, leading to **202** as a mixture (~1 : 1) of *E*/*Z*-isomers. The inability to effect double RCM made it necessary to elaborate the 8- and the 13-membered ring successively.

Nakadomarin A ((−)-**208**) is a marine natural product with a unique hexacyclic structure (Scheme 38). The first total synthesis of its enantiomer (+)-**208** features two sequential RCM reactions to form the 8- and the 15-membered azacycles.[80] However, compared with the above synthesis of ircinal A, the order of ring-closing steps was reversed. When diene **204** (0.002 M in dichloromethane) was exposed to catalyst **C**, a facile RCM reaction ensued leading within 1.5 h to azocine lactam **205** in 70% yield. It is noteworthy that, when **204** was exposed to catalyst **A**, **205** was obtained in only 15% yield after 48 h with recovery of 204 (36%), underlining again the high potency of the second-generation Ru catalysts. Pentacyclic compound **205** was then elaborated to diene **206** in five steps. The second RCM reaction to close the 15-membered lactam was performed with catalyst **B** and delivered a mixture (*Z*/*E* ≈ 2 : 3) of isomers, from which the desired minor isomer (*Z*)-**207** was separated in only 26% yield. Reductive removal of both carbonyl groups in bis-lactam (*Z*)-**207** finally led to (+)-**208**.

11.07.2.2.3 Lactones

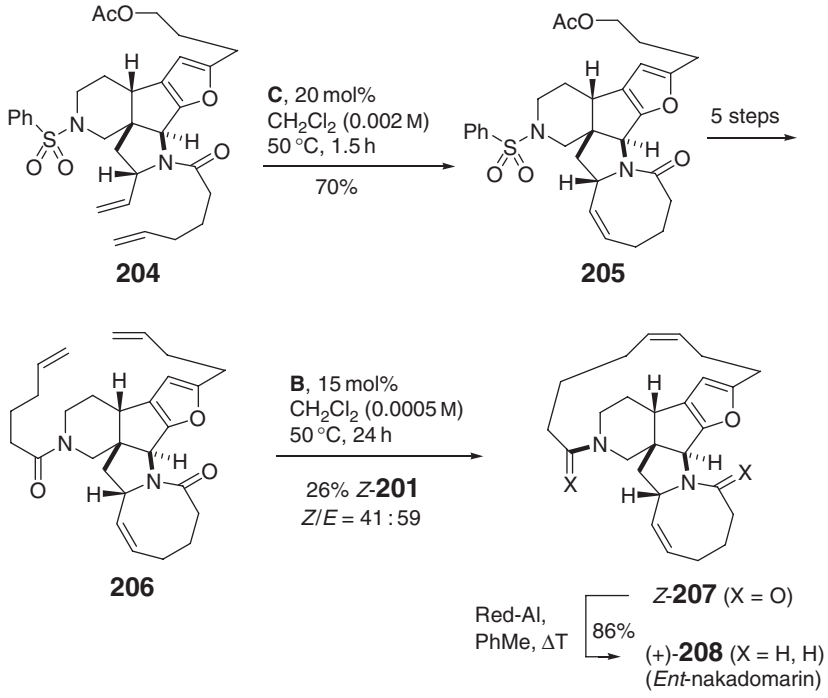
An example of a surprisingly facile and stereoselective formation of an eight-membered lactone from an acyclic precursor diene ester was observed during a total synthesis of the anti-tumor agent octalactin A **211** (Scheme 39).[81] The dense substitution pattern in cyclization substrate **209** presumably imposes conformational constraints in a way that leads to a conformation favorably disposed for the ring closure. Thus, exposure of **209** to 10–20 mol% of catalyst **B** afforded cyclization product **210** within 24 h in 86% yield. In contrast, the diene ester with epimeric PMB ether group (3-*epi*-**209**) underwent ring closure under analogous conditions only with difficulty, leading to lactone 3-*epi*-**210** in 20% yield after 7 days in boiling dichloromethane.

Halicholactone **214**, a marine metabolite with lipoxygenase inhibitory activity, belongs to the family of oxylipins which all contain a lactone moiety substituted by a *trans*-disubstituted cyclopropane subunit. Stereoselective RCM for the formation of the nine-membered lactone core in **214** was the penultimate step (**212** → **213**) in a asymmetric

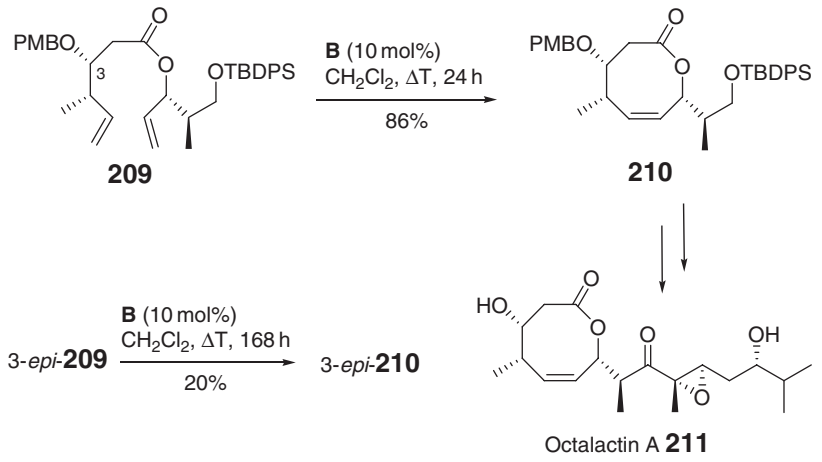


Scheme 37

total synthesis of **214** by a Japanese group (Scheme 40).[82] After extensive experimentation, it was found that reaction of **212** with catalyst **B** under high dilution (0.1 mM in boiling dichloromethane) in the presence of a catalytic amount of $Ti(OiPr)_4$ gave rise to the desired (*Z*)-isomer **213** in 72% yield along with the corresponding dimer (11%). When the reaction was performed in more than 1.0 mM concentration, monomer **213** and its dimer was formed in almost



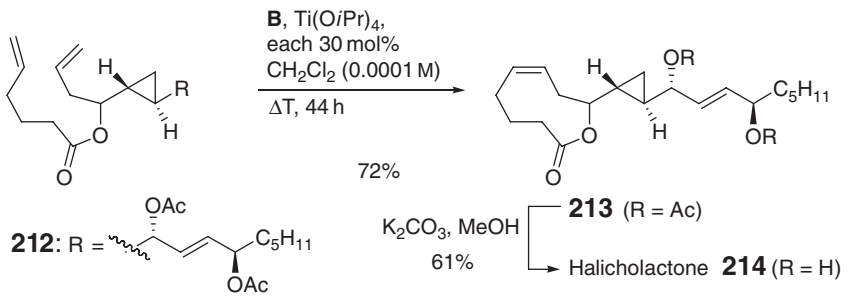
Scheme 38



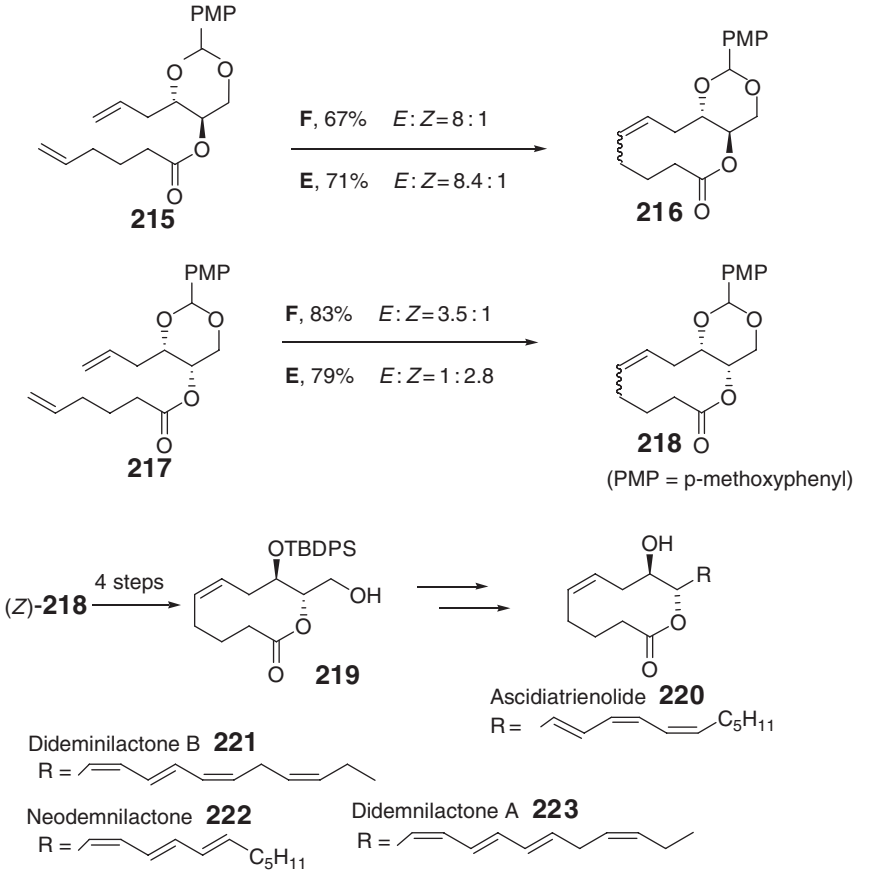
Scheme 39

equal amounts (each 20–30%). It is noteworthy that, the (*E*)-isomer of **213** was not detected under any reaction conditions. The total synthesis of **214** was then completed by methanolysis of the two acetyl groups.

The marine natural product ascidiatrienolide A **220** is a strong inhibitor of phospholipase A2. Compound **220** and the closely related didemnilactones **221–223** feature a common hydroxy-substituted (*anti* to the ring oxygen) (*Z*)-nonenolide core. Lactone **219**, which constituted the key intermediate in a previous total synthesis of **220** and can also be elaborated to lactones **221–223**, has been the subject of an interesting study by Fürstner's group,[83] that revealed once more the very subtle and cooperative influence of different parameters on the stereochemical course of metathesis reactions. Thus, it was shown that the *E*/*Z* ratio obtained in an RCM step is not only dependent on the relative configuration of the cyclization substrate, but also on the chosen catalyst (Scheme 41). When applied to the



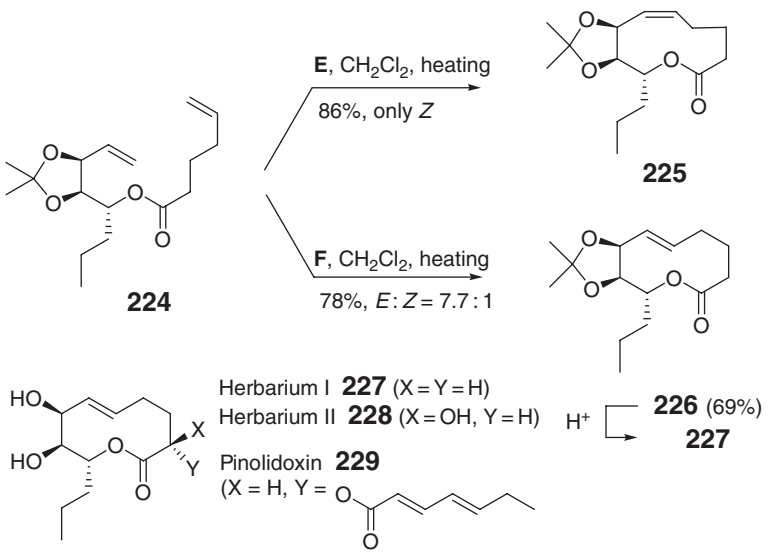
Scheme 40



Scheme 41

anti-configured diene ester **215**, both ruthenium indenylidene complex **F** and second generation catalyst **E** induced the preferential ($E/Z \approx 8:1$) formation of the undesired lactone (*E*)-**216** in comparable yield, but opposite results were obtained with the *syn*-analog **217**. Specifically, indenylidene catalyst **F** still favored (3.5 : 1) the (*E*)-isomer of **218**, while NHC catalyst **E** favored the formation of the required nonenolide (*Z*)-**218** ($Z:E = 2.8:1$), which was converted to target **219** in four steps.

In related contributions, Fürstner disclosed a concise RCM-based approach to a family of potent herbicidal 10-membered lactones with an (*E*)-double bond, which led to the first total syntheses of herbarium I **227**[84] and II **228**,[85] and allowed also to establish the stereostructure of pinolidoxin **229** (Scheme 42).[85] Again, the stereochemical



Scheme 42

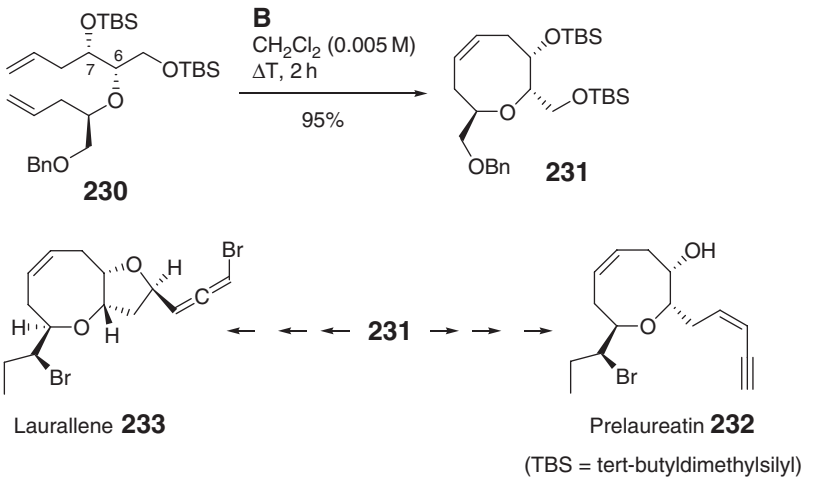
outcome of the ring-closing step could be controlled by the choice of the catalyst, which is deemed to reflect kinetic versus thermodynamic control. *En route* to herbarium I **225**, cyclization precursor **224** containing an isopropylidene protecting group, which should align the olefinic side chain in a "cyclization-friendly" conformation, was prepared in six steps from protected D-ribonolactone. Semi-empirical calculations carried out for both possible cyclization products derived from **224** indicated that (*Z*)-isomer **225** is about 3.5 kcal mol^{-1} more stable than (*E*)-isomer **226**. That means that only under kinetic control would it be possible to obtain the desired (*E*)-isomer, and that highly active catalysts known to favor the retro-reaction and hence leading to equilibration, would be counterproductive. The results obtained with indenylidene catalyst **F** and with the second-generation NHC catalyst **E** were fully consistent with the above predictions: catalyst **F** exhibiting activity similar to Grubbs' benzylidene catalyst **B**, produced mainly (7.7 : 1) the less stable and desired (*E*)-isomer **226** (the *E*/*Z* ratio did not evolve with time), while catalyst **E** led exclusively to the thermodynamically more stable (*Z*)-isomer. It seems that complex **E** and congeners, due to their higher overall activity, are able to isomerize the cycloalkenes formed during the course of the reaction and hence enrich the mixture in the thermodynamically favored product. Further support for this interpretation was provided by a control experiment showing that pure (*E*)-iomer **226** was slowly isomerized to (*Z*)-isomer **225** in the presence of catalyst **E** when the reaction was performed under an atmosphere of ethylene.

11.07.2.2.4 Cyclic ethers

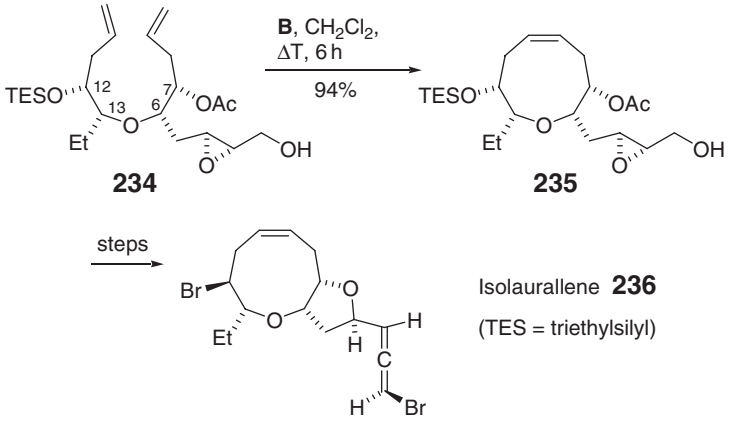
A range of topographically unique structures with seven- to nine-membered ether rings is produced by marine organisms. Several total syntheses of natural monocyclic eight-membered ring ethers (oxocenes) and the less common homologous oxonenes, produced by *Laurencia* red algae, have been reported by Crimmins's team, by merging asymmetric aldol addition (or alkylation) of glycolates with an RCM reaction. Thereby, it is demonstrated that medium-sized cyclic ethers are readily available without cyclic conformational constraint by exploiting the acyclic bias of the gauche effect of substituents on the carbons flanking the ether linkage.

One year after the total synthesis of (+)-laurencin,[86] Crimmins disclosed total syntheses of (+)-prelaureatin **232** and (+)-laurallene **233**, applying a similar strategy (Scheme 43).[87] The critical RCM reaction was undertaken with precursor **230**, anticipating that the gauche effect of the C6 and C7 oxygens would accelerate the ring closure. Exposure of **230** (0.005 M in dichloromethane) to catalyst **B** proceeded smoothly to provide the key Δ^4-oxocene **231** in 95% yield with no detectable dimerization.

In subsequent reports,[88,88a] the principle of asymmetric glycolate alkylation/RCM sequence was applied to the first total synthesis of isolaurallene **236** which contains a densely functionalized Δ^5-oxonene core (Scheme 44). Anticipating that the gearing effect created by two synergistic gauche effects at C6–C7 and C12–C13 would facilitate



Scheme 43

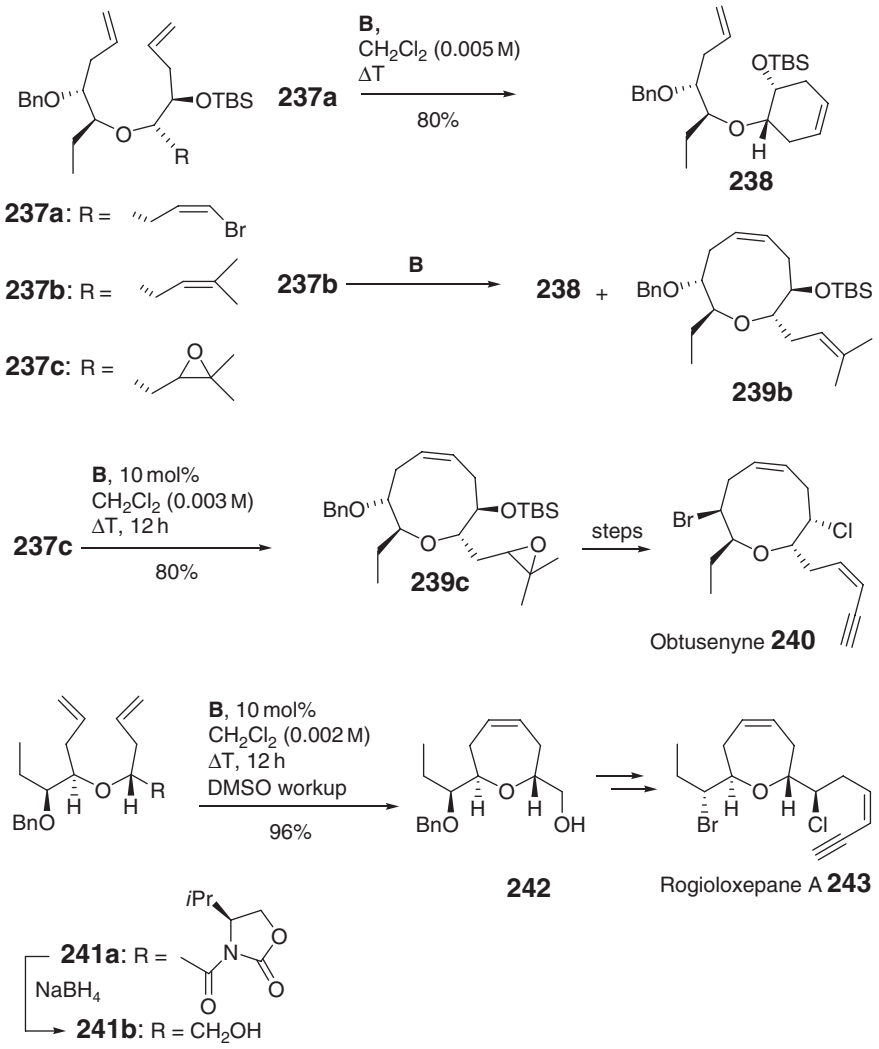


Scheme 44

the ring closure, acyclic diene **234** was chosen as the metathesis substrate. Indeed, exposure of **234** to catalyst **B** provided cyclization product **235** in 94% yield within 6 h, without the aid of a cyclic conformational constraint.

Crimmins's syntheses of the nine-membered cyclic ether obtusenyne **240**,[89] and the oxepene rogioloxepane A **243**,[90] both feature a *trans*-orientation of the substituents flanking the ether linkage (Scheme 45). Three different RCM precursors **231a–c** were investigated during the synthesis of **240**. Attempts to form the nine-membered ring from the bromo-substituted triene **231a** resulted in loss of the vinyl halide by regioselective formation of cyclohexene derivative **238** in 80% yield. Triene **237b** with a trisubstituted double bond provided a 3 : 1 mixture of oxonene **240b** and cyclohexene **238**. Finally, conversion of **237b** to epoxy-diene **239c** followed by treatment with catalyst **B** effected rapid closure to **239c**, which was converted to **240** in 13 steps.

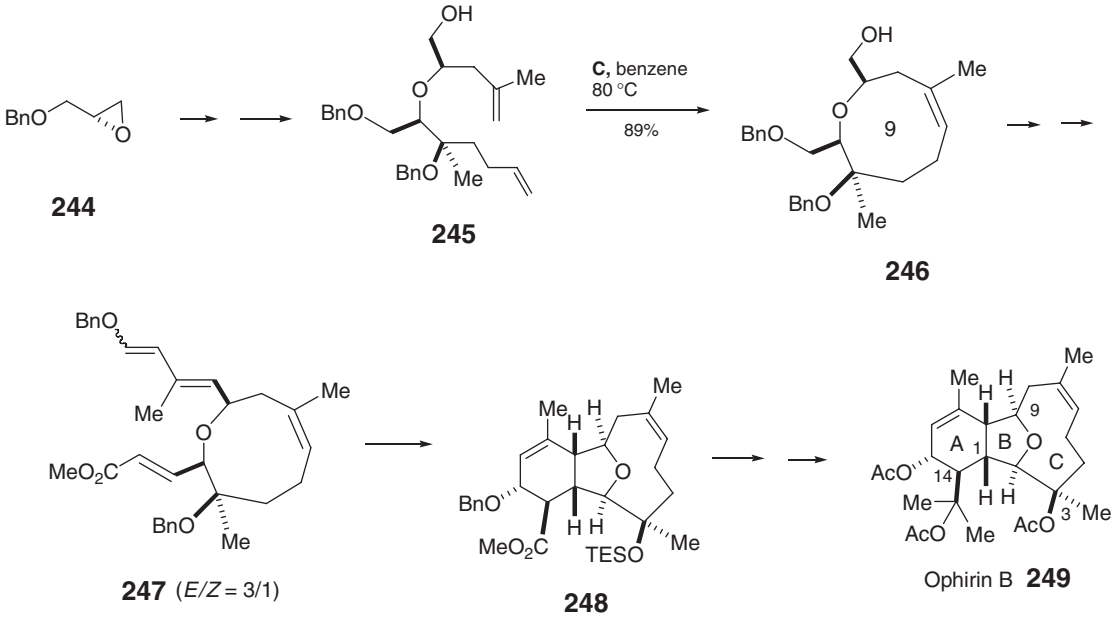
In the total synthesis of rogioloxepane A **243**, oxazolidinone **241a** was primarily examined as the metathesis substrate. However, the subsequent removal of the auxiliary with sodium borohydride proceeded with low yield due to concomitant hydrogenation of the oxepene by remaining traces of the ruthenium catalyst. Therefore, the order of steps was reversed and the RCM step performed with primary alcohol **241b**, which additionally could bias the diene conformation by a hydrogen bond with the ether oxygen. Treatment of **241b** with catalyst **B**, followed by dimethylsulfoxide (DMSO) workup to remove traces of catalyst derived materials led then to key intermediate **242** in excellent yield.



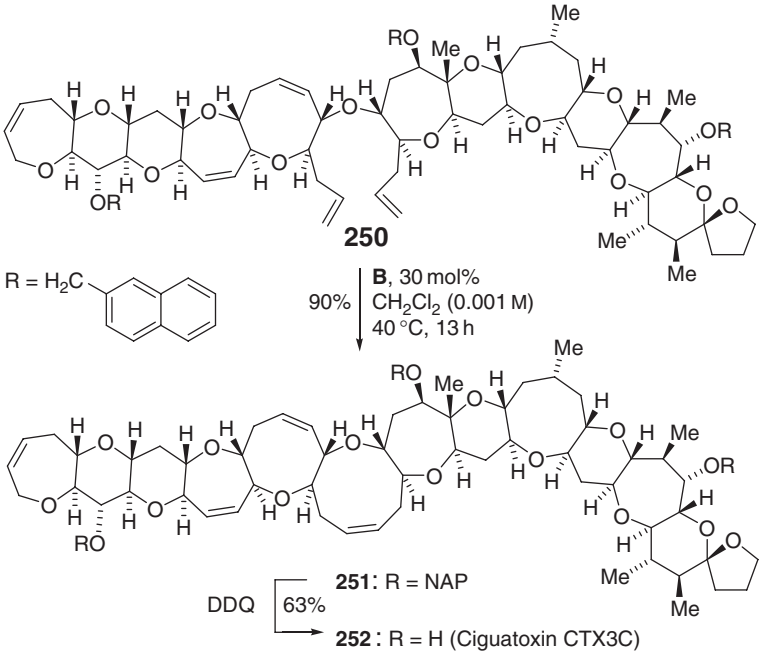
Scheme 45

Yet another example is Crimmins's total synthesis of ophirin B **249**, a structurally complex biologically interesting cembranoid diterpene produced by a gorgonian octocoral (Scheme 46). Some members of this class of compounds display activity as insect growth factor inhibitors.[91] Typical is the oxatricyclic ring system with stereogenic centers at C1–C3, C9, C10, and C14. The synthesis[92] features RCM for closing the nine-membered ether ring C and an intramolecular Diels–Alder addition (IMDA), which generates rings A and B. The synthesis started from glycidyl ether **244**, which was transformed into alcohol **245**, which in turn gave the (*Z*)-cyclo-olefin **246** with catalyst **C** under forcing conditions in 89% yield. After elaboration of the C2 and C9 side chains, the Diels–Alder substrate **247** was prepared as a 3/1 *E*/*Z*-mixture of the enol ether side chain. The (*E*)-isomer underwent the IMDA reaction to **248** spontaneously, whereas the (*Z*)-isomer remained unchanged and was recycled via a free radical-induced double bond isomerization. The conversion of **248** to **249** was achieved in 53% overall yield.

A highlight in the application of the RCM methodology in natural product synthesis is Hirama's total synthesis of ciguatoxin CTX3C **252**,[93] including the more improved protective group strategy, as depicted in Scheme 47. The structure of **252** spans more than 3 nm and is characterized by 12 six- to nine-membered *trans*-fused cyclic ethers and a spiroannulated terminal tetrahydrofuran ring. Causative toxins such as **252** are produced by the marine dinoflagellate *Gambierdiscus toxicus* and accumulate in fishes of many species through the food chain. In the penultimate step of the improved total synthesis, pentaene **250**, that only misses the central nine-membered ring, was exposed to catalyst **B** in boiling dichloromethane to provide 2-naphthylmethyl (NAP)-protected CTX3C **251** chemoselectively



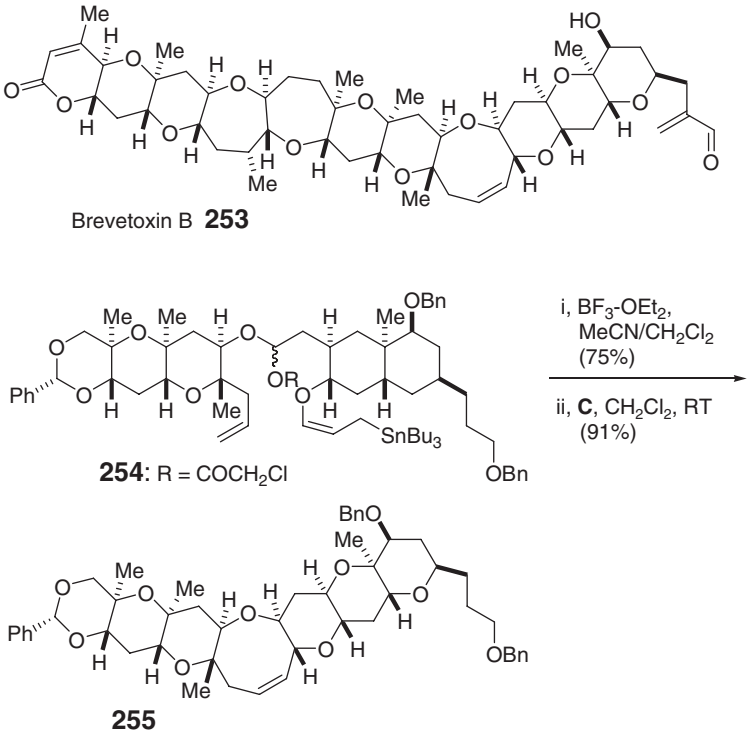
Scheme 46



Scheme 47

in 90% yield and to set all rings in place. The three NAP groups in **251** (the deprotection of the corresponding tris-benzyl ether in the original synthesis proceeded with low yield) were then removed with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to furnish the natural compound **252** in 63% yield.

Intramolecular allylation of α-chloroacetoxy ether **254** followed by RCM (Scheme 48) was used by Yamamoto and co-workers to construct the eight-membered cyclic ether in the F–K ring segment **255** of the marine neurotoxin brevetoxin B **253**.[94]



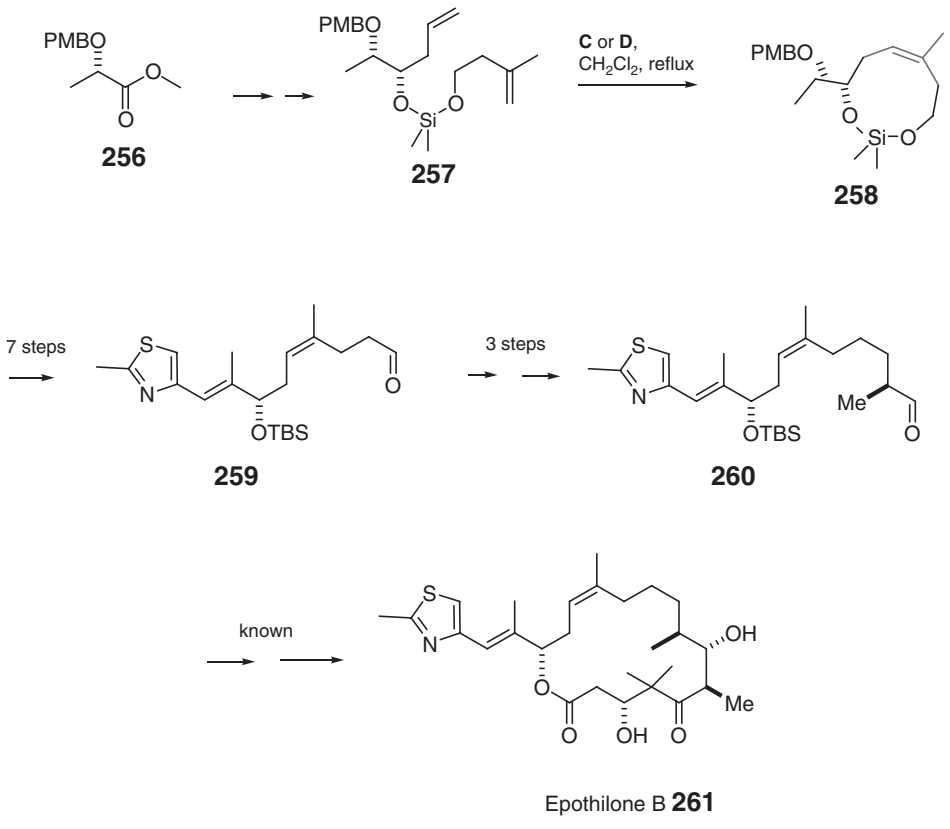
Scheme 48

11.07.2.2.5 Nine-membered siladioxane

Epo B **261** is a highly promising anticancer agent, which, similar to paclitaxel, exerts microtubule stabilization and thus inhibits the mitosis of tumor cells. There are numerous total syntheses of **261** so far. For reviews, see Refs: 95 and 95a–95g. However, the introduction of the trisubstituted 12,13-(*Z*)-double bond into the northern fragment **260** still remains a problematic operation. Recently,[96] this problem was accessed (Scheme 49) by preparing the di-olefinic siloxane **257** from (*S*)-lactic ester **256** and subjecting it to RCM with catalyst **C** or **D** in refluxing dichloromethane. Yields of the RCM step turned out to be strongly dependent on the rate of catalyst addition. Quantitative yields were only obtained when up to 15 mol% of the catalyst was added continuously over 16 h. The *Z*/*E* ratio thus obtained was 85 : 15, and after chromatographic separation the (*Z*)-olefin was converted into aldehyde **259** and chain-elongated to aldehyde **260** which had been elaborated into **261** previously.

11.07.2.3 Formation of Macrocycles

RCM-based formation of – (unstrained) macrocycles is, due to the concomitant loss of a volatile alkene, mainly entropically driven and therefore high-yielding. However, there exists still a lack of prediction for the configuration of the newly formed double bond of cycloalkenes with more than 10 ring atoms. The products formed are frequently obtained as *E*/*Z* mixtures with the (*E*)-isomer dominating in most of the recorded cases. This obvious drawback in target-oriented synthesis already became evident from the early and most prominent RCM-based epothilone syntheses (for reviews, see Refs: 95 and 95a–95g), which suffered from very low stereoselectivity in the formation of the required (*Z*)-12,13 double bond. The following examples of RCM-based syntheses of macrocyclic natural products will reveal that the success and/or the stereochemical outcome of macrocyclic RCM is highly sensitive to steric or electronic substituent effects in the precursor diene, and can also depend on the choice of the catalyst, as well as on the solvent and the reaction temperature applied in the metathesis process. Additionally, we will see that for the formation of strained products, large enthalpic barriers can be overcome by altering the shape of the metathesis substrate through the introduction of additional conformational constraints.



Scheme 49

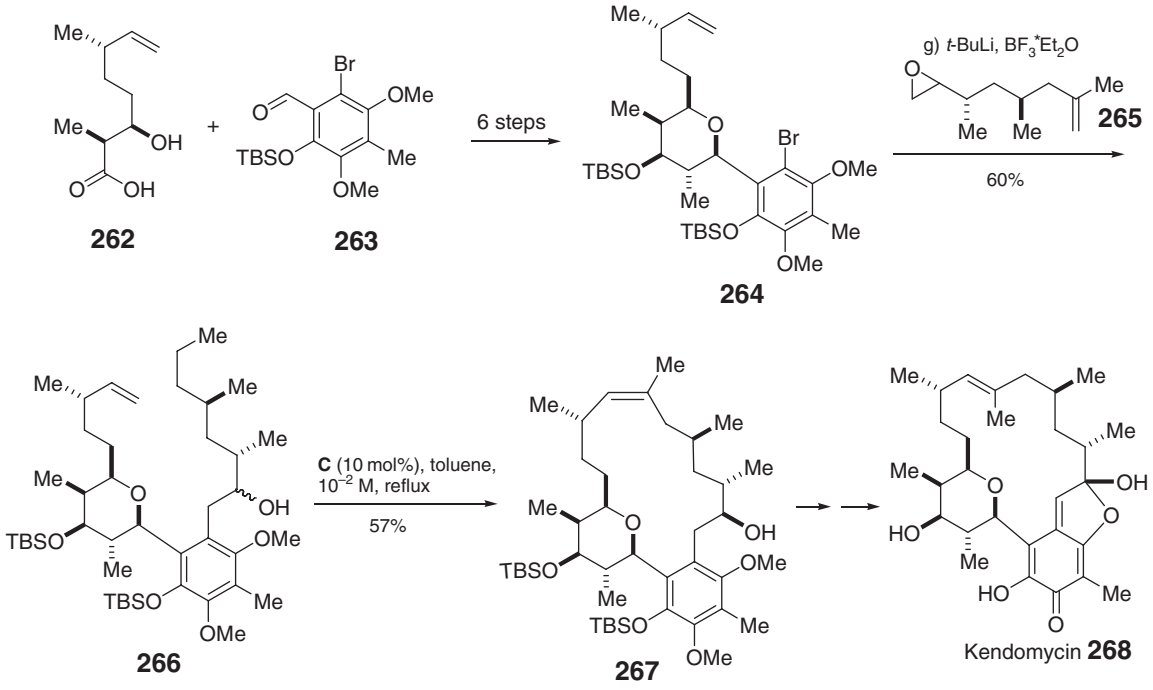
11.07.2.3.1 Carbacycles

Kendomycin **268**, isolated from *Streptomyces violaceoruber*, is a macrocyclic polyketide with manifold interesting biological activities. Thus, **268** is an endothelin receptor antagonist and it is also active against osteoporosis. Furthermore, it has antibacterial and anticancer activity.[97] The structure of **268** comprises a unique quinone–methide–lactol chromophore attached to a densely substituted tetrahydropyran ring in conjunction with an aliphatic *ansa*-ring. The current synthesis (Scheme 50)[98] started with the formation of a ketal from hydroxy acid **262** and aldehyde **263** to form **264** stereoselectively after six steps. Lithiation and addition of epoxide **265** furnished **266** as an epimeric mixture, which was subjected to RCM with catalyst **C**. Remarkably, only the 19(*S*)-epimer underwent ring closure to form the undesired (*Z*)-cycloolefin **267** in 57% yield. A number of steps were therefore needed to invert the olefin configuration, and finally the aromatic ring was oxidized to give **268** in low yield. Remarkably, similar attempts to close the *ansa*-bridge across a benzofuran core via RCM failed.[99]

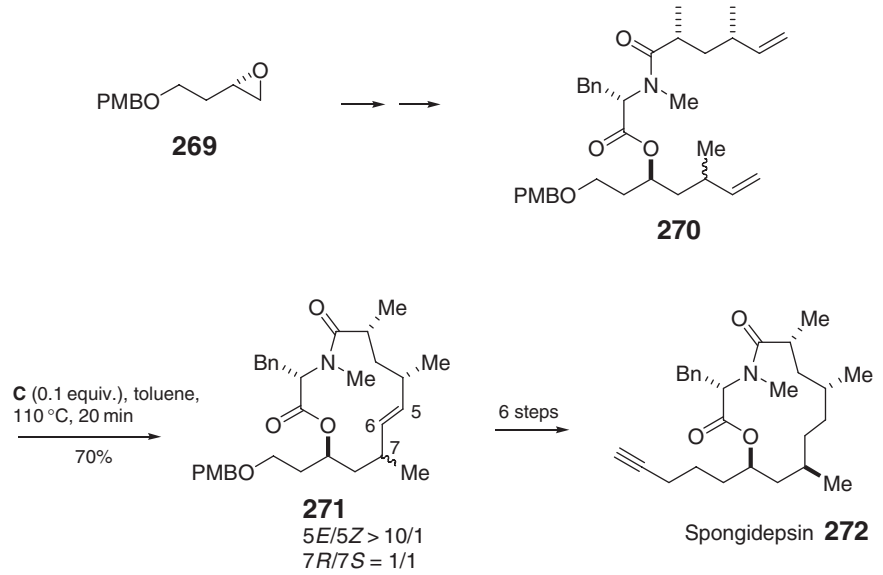
11.07.2.3.2 Macrolides

Spongidepsin **272** has been isolated from an Australian sponge and shows interesting cytotoxic and antiproliferative activities against various cancer cell lines. The structure of **272** combines amino acid and ketide motifs within a 13-membered macrolide ring. The synthesis by Forsyth and Chen (Scheme 51)[100] primarily served to elucidate the configuration at C7. Hence, di-olefin **270** was prepared from epoxide **269** as a diastereomeric mixture and was subjected to RCM with catalyst **C** to provide olefins **271** with >10/1 *E*/*Z*-selectivity. The C7-epimers were separated chromatographically and the 7*S*-diastereomer gave spongidepsin **272**, identical with the natural product.

Three RCM-based syntheses of the 18-membered α,β-unsaturated macrolide aspicilin **273**, all performed with catalyst **B** and differently protected precursor trienes **275a–d** (Scheme 52),[101,101a,101b] illustrate the importance of substituent effects on regio- and stereochemistry of the metathesis reaction, albeit in this case the stereochemical outcome of the ring-closing step is inconsequential. Hatakeyama's isopropylidene-protected precursor **275a** led exclusively to macrolactone **274a** with (*Z*)-configuration at the newly formed double bond. In contrast, Banwell's



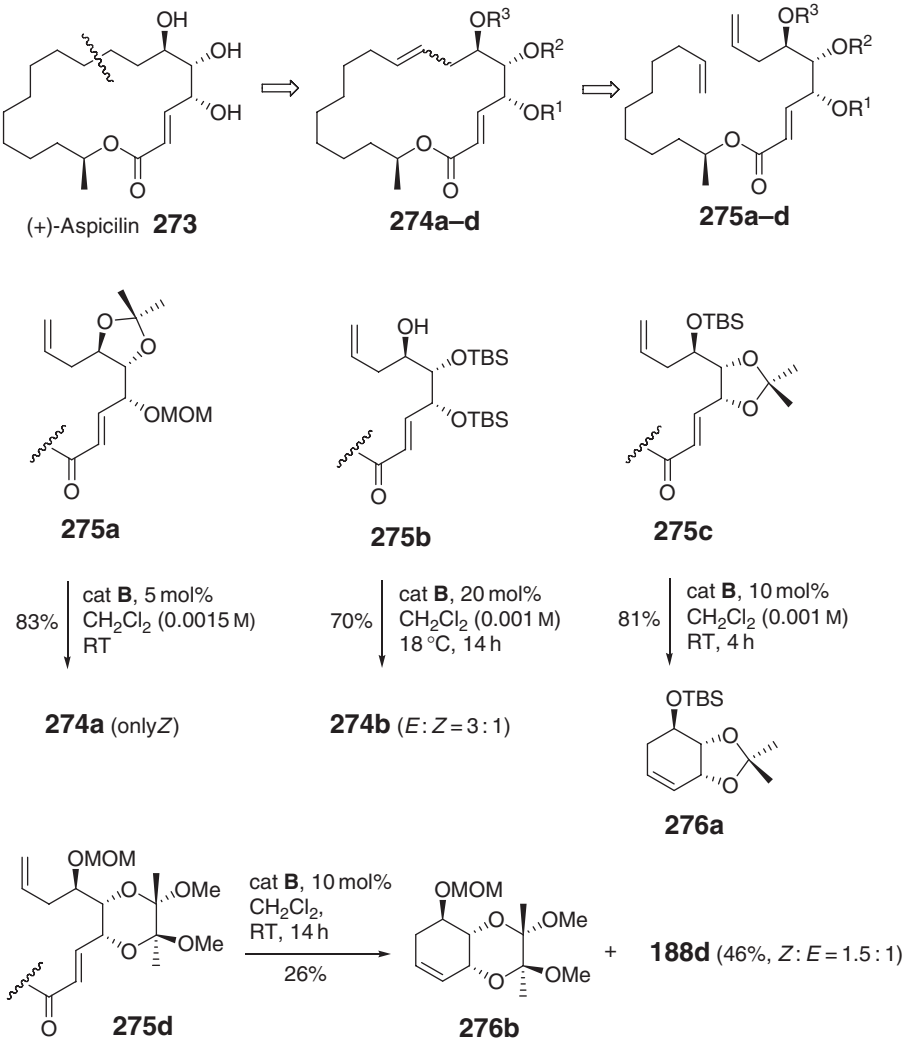
Scheme 50



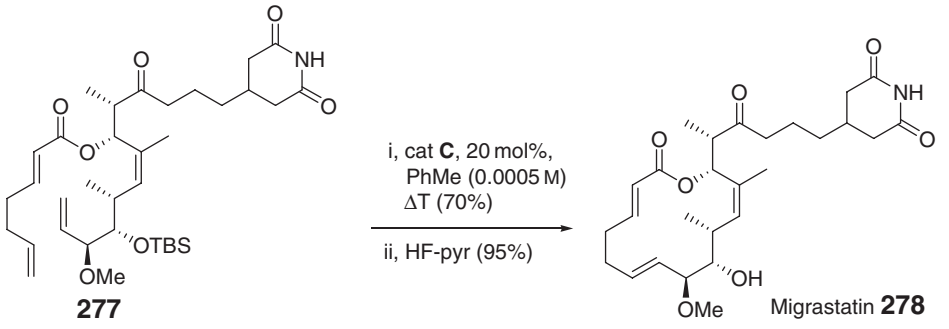
Scheme 51

first precursor **275c** reacted regioselectively with formation of the undesired cyclohexene **276a**, while the open-chain precursor **275b** furnished a 3 : 1 mixture of macrolides in favor of the (*E*)-isomer. Partial cyclohexene formation was also observed by Ley, who isolated from the cyclic metathesis substrate **275d** a mixture of macrolide **274d** (1.5 : 1 *Z*/*E*-mixture) and cyclohexene **276b**.

Migrastatin **278** (Scheme 53) is a macrolide natural product that displays inhibitory effect on the migration of human tumor cells. After an RCM based synthesis of the 14-membered macrolide core of **278**,[102] Danishefsky also achieved the first total synthesis of the natural compound,[103] using the fully functionalized tetraene **277** as the



Scheme 52

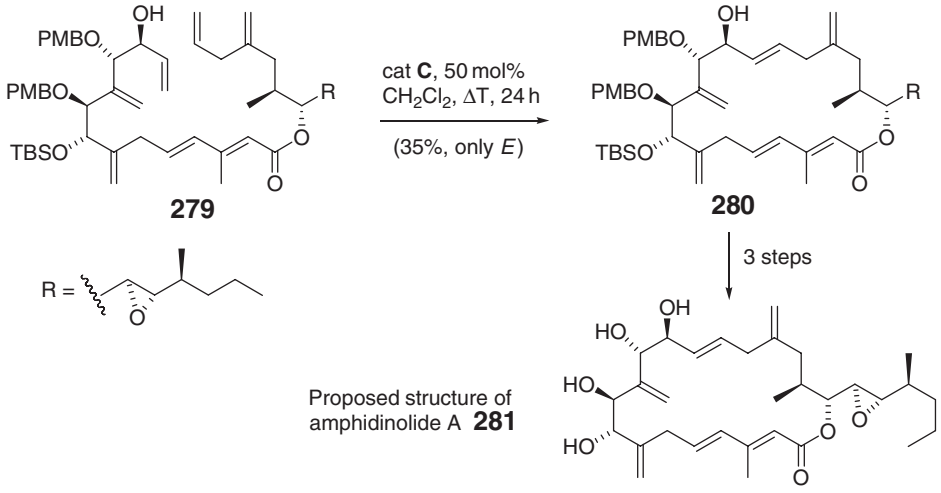


Scheme 53

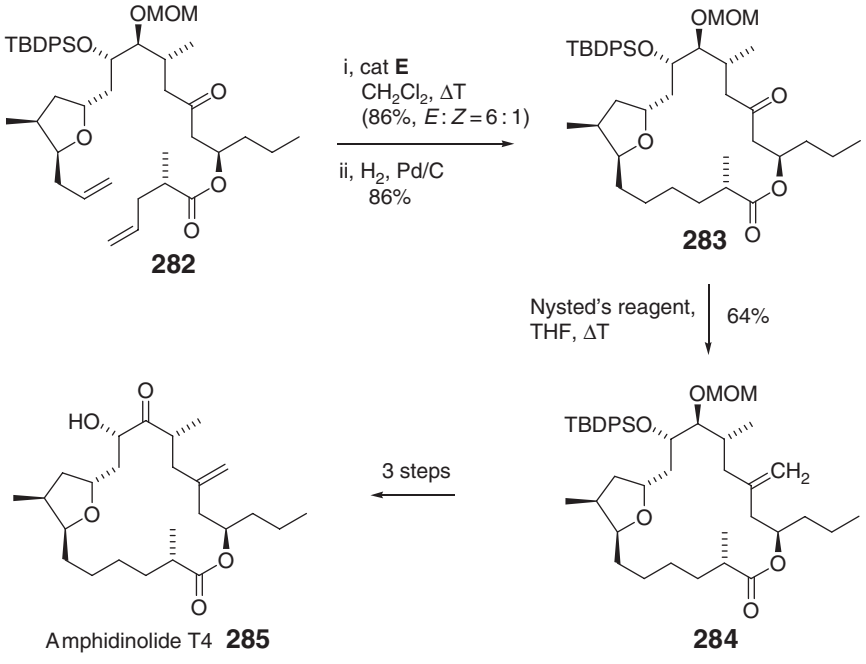
metathesis precursor. Under the conditions shown in Scheme 53, the ring-closing step proceeded (*E*)-selectively between the two terminal double bonds in **277**, delivering only the (*E*,*E*,*Z*)-trienyl-arrangement present in **278**.

Three total syntheses aiming for the cytotoxic marine natural product amphidinolide A (Scheme 54) were disclosed in 2002.[104,104a,104b] These all confirmed that the reported structure **281** was incorrect. In Maleczka's synthesis, the highly unsaturated 20-membered ring of **281** was formed by a late-stage RCM reaction. Given the array of olefinic functionality in metathesis substrate **279**, the authors used the less active first-generation catalyst **B** which should guarantee regioselectivity, in their first attempt, but this catalyst only truncated the allylic alcohol in **279** leading to the corresponding methyl ketone.[105] With second-generation catalyst **C**, the ring closure occurred, but 0.5 equiv. of the catalyst was necessary to provide regio- and (*E*)-stereoselectively macrolide **280** in low yield.

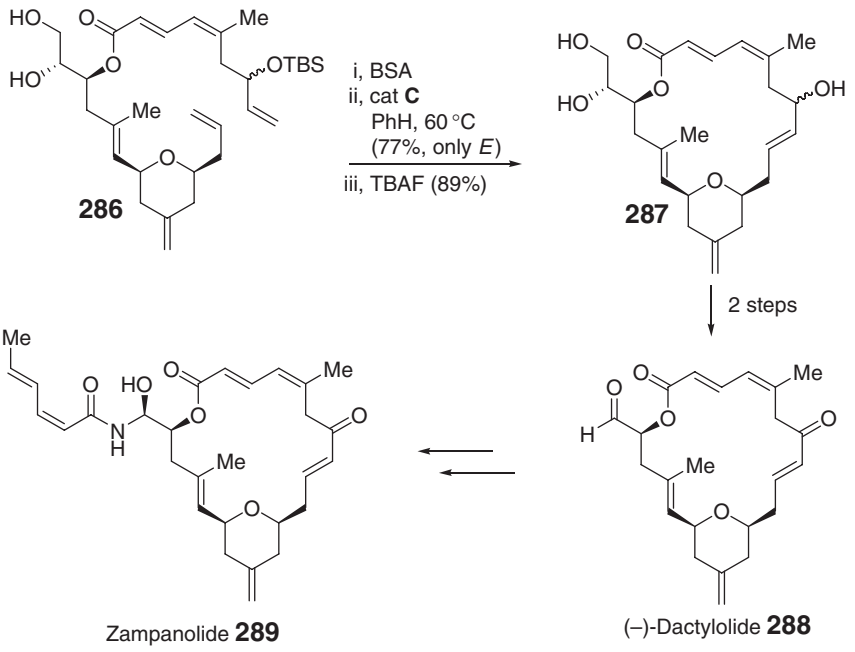
Amphidinolide T4 **285**, another member of the amphidinolide family containing a saturated 19-membered lactone core, was synthesized by Fürstner and co-workers (Scheme 55).[106,106a] The macrocyclization was achieved by



Scheme 54



Scheme 55



Scheme 56

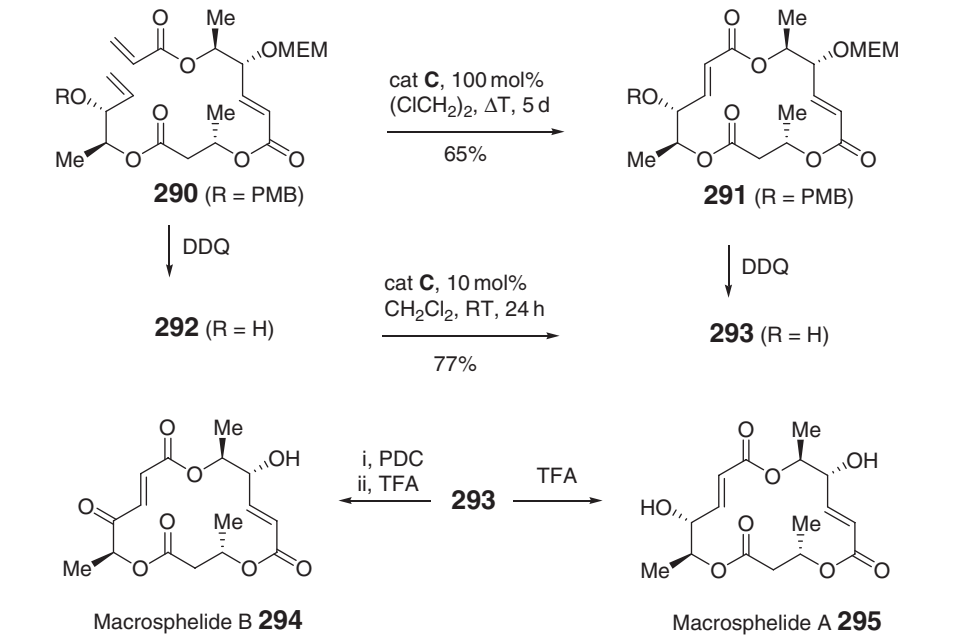
treatment of diene **282** with second-generation catalyst **E**. The resulting cycloalkenes, obtained in 86% yield as an inconsequential isomeric mixture ($E:Z = 6:1$) were hydrogenated to **283**. After methylenation to **284** with Nysted's reagent, the synthesis of **285** was completed in three additional steps.

Hoye described an RCM-based total synthesis of the 20-membered marine macrolide dactylolide **288** and its subsequent conversion to the natural carbinolamide zampanolide **289** (Scheme 56), both feature a common highly unsaturated macrolide core, bridging a *cis*-2,6-disubstituted 4-methylene tetrahydropyran unit.[107] When the polyunsaturated acyclic lactone **286** (1 : 1 epimeric mixture around the *tert*-butyldimethylsilyl (TBS)-protected carbinol center) was *in situ* protected with bis-trimethylsilylacetamide (BSA) and then treated with catalyst **C** in benzene at 60 °C, each diastereomer smoothly cyclized to the corresponding cycloalkene **287** with exclusive (*E*)-geometry at the newly formed double bond.

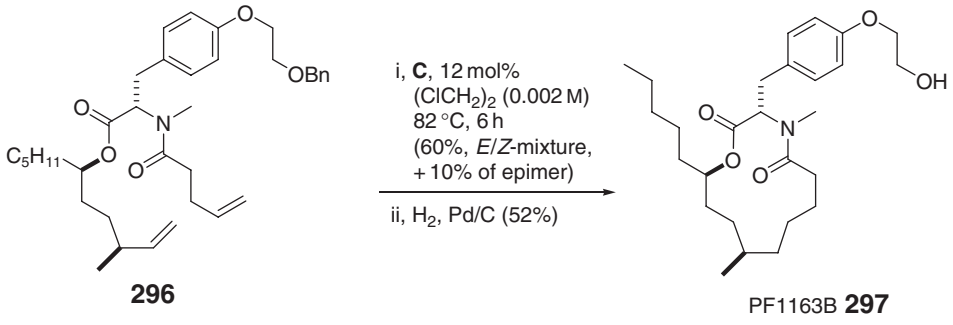
An example for the efficient formation of an electron-deficient double bond by RCM was disclosed by a Japanese group in a total synthesis of the macrosphelides A **295** and B **294** (Scheme 57).[108] When PMB-protected compound **290** was examined as the metathesis substrate, the ring closure did not proceed at all in dichloromethane using catalysts **B** or **C**. When the reaction was carried out using equimolar amounts of catalyst **C** in refluxing 1,2-dichloroethane, the cyclized product **291** was obtained in 65% after 5 days. On the other hand, free allylic alcohol **292** reacted smoothly at RT leading to the desired macrocycle **293** in improved yield.

The antifungal antibiotic (−)-PF1163B **297** isolated from *Streptomyces* sp., which features a 13-membered macrocycle incorporating both lactone and lactam units, was synthesized by an RCM route too (Scheme 58).[109] While only poor results were obtained by treatment of diene **296** (containing 8% of an unidentified epimer) with catalyst **B**, the use of NHC catalyst **C** led, under the conditions outlined in the scheme, to the corresponding cyclization product in 60% yield along with 10% of a diastereomer resulting from epimerization in a previous step.

The salicylihalamides A **298a**[110,110a] and B **298b** are the first members of a growing class of secondary marine metabolites with a 12-membered benzolactone core incorporating salicylic acid in conjunction with a dienylenamide side chain (Scheme 59). Salicylihalamide A **298a** was reported to be a unique and highly differential cytotoxin and a potent inhibitor of the mammalian vacuolar (H^+)-ATPase. To date, there exist several total syntheses of **298a**, which rely on an (*E*)-selective RCM of dienes **300** or **301** to construct the benzolactone core **299**.[111,111a–111g] The results obtained with the various metathesis substrates depicted in Scheme 44 demonstrate the lack of a stereopredictive model for the RCM-based formation of macrocycles, not only by the strong influence that may be exhibited by *remote* substituents, but also by the fact that the use of more reactive second-generation catalysts may be unfavorable for the stereochemical outcome of the reaction. Dienes **300a–f** illustrate the influence of the substitution pattern: all

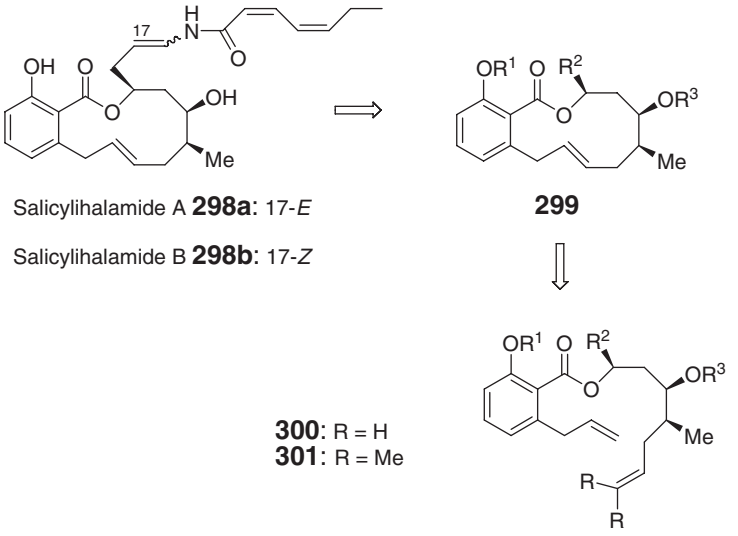


Scheme 57



Scheme 58

reactions have been performed with Grubbs' first-generation catalyst **B** in dichloromethane, but the isomeric ratio varied from favorable $E/Z = 10:1$ obtained by Smith with **300a**, to "mainly (*Z*)," observed by Snider with **300e** featuring a remote free phenolic hydroxy group, while no ring closure occurred with Snider's bicyclic model **300f**. The RCM precursors **301a–d** used by Fürstner's group differ from compounds of the type **300** mainly by the *gem*-disubstitution at one of the olefinic moieties, so that the ring-closing step had, in this case, to be conducted with a more reactive ruthenium catalyst of the second generation. The macrocyclizations with compounds **301a–d** were all performed with catalyst **E** in toluene at 80 °C, and again it turned out that the stereochemical outcome was strongly dependent on the phenolic protective group, ranging from "only *Z*" for the unprotected phenol **301a**, 1.5 : 1 in favor of the (*Z*)-isomer for the corresponding silylether **301b**, to a 2 : 1 ratio in favor of the required (*E*)-isomer for both, methyl and MOM ether derivatives **301c** and (**310d**). Finally, a detailed study of the metathesis step conducted with dienes **300g** and **300h** in De Brabander's full account brought some more light in this confusing situation, identifying the high (*E*)-stereoselection obtained with catalyst **B** at RT as a result of a kinetically favored process. On the other hand, with second-generation catalyst **C** (or **E**), an equilibrium is quickly reached, so that the identical isomeric ratios ($E:Z \approx 2:1$) obtained with Fürstner's precursors **301c**,**301d** and De Brabander's substrates **300g**, **300h** reflect a thermodynamic distribution, where secondary metathesis isomerization can compete at the timescale of the



Scheme 59

experiment. It should be pointed out, however, that the pronounced influence of a remote phenolic OH group which favors the undesired (*Z*)-stereochemistry with catalysts **A** and **E**, still remains unclear (Scheme 60).

An example of RCM-based macrocyclization with a highly complex metathesis substrate is the formation of macrolide **302** from the corresponding diene precursor in Fürstner's total synthesis of the resin glycoside woodrosin I **304** (Scheme 61).[112] The site of ring closure was chosen far away from potential donor sites in the oligosaccharide scaffold, so that the formation of unreactive metal chelate complexes was avoided. Accordingly, a virtually quantitative formation of **302** ($E:Z = 9:1$) was observed on treatment with catalysts **B** or **F**. Subsequent exposure of **302** to glycosyl donor **303** led not only to the introduction of the missing rhamnose unit, but also to concomitant rearrangement of the *ortho*-ester into the desired β-glycoside. The synthesis of **304** was then completed in two steps.

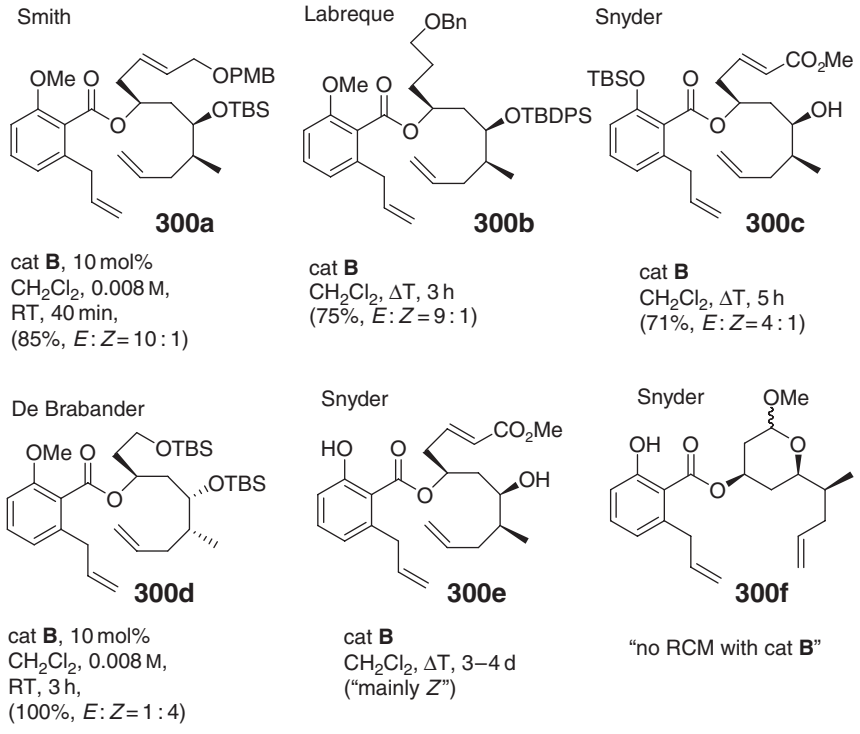
11.07.3 Diene–Ene RCM

An increasing number of natural product syntheses feature RCM of diene–ene systems to produce macrocyclic dienes. However in some cases, divergences in regioselectivity of catalyst attack have been observed depending on structural features of the metathesis substrate and also on the catalyst used to promote the metathesis event.[113] The first example of regioselective diene–ene metathesis was contributed by a Novartis group in 1999, during synthesis of simplified macrolide analogs of the immunosuppressant sanglifehrin (Scheme 62).[114,114a,114b] Treatment of trienes **305a**, **305b** with first-generation catalyst **B** led to the desired cyclic (*E*,*E*)-dienes **306** in satisfactory yield, along with the corresponding (*E*,*Z*)-analogs as minor components (<5%). In subsequent work[114a] it turned out that unexpectedly for the authors, second-generation catalyst **E** involved predominantly the more substituted internal double bond in precursors **305**, leading to the ring-contracted cyclic monoenes **307** in moderate yields, while the desired cyclodienes **306** were detected only as minor components.

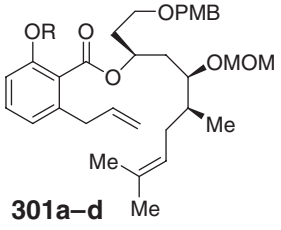
Another example of macrocyclic RCM with a diene–ene was disclosed in 2000 by Meyers and co-workers in the first total synthesis of griseoviridin **309**.[115] Griseoviridin is a highly complex member of the family of streptogramin antibiotics, featuring a 23-membered unsaturated bis-lactam core incorporating an oxazole and a nine-membered lactone with an ene-thio linkage. The macrocyclic ring of **309** was (*E*)-selectively elaborated in the penultimate step, by exposing allylamine **308** to catalyst **B** (Scheme 63).

Hsp90 is a molecular chaperon required for the refolding of proteins in cells exposed to environmental stress. It contains an ATP-binding pocket in its amino terminus. Several natural products, for example, radicicol **317** (Scheme 64), bind to this pocket and inhibit its chaperon function, which is mirrored in enhanced proteosomal degradation of Hsp90 client proteins, so that compounds like **317** are of interest as anticancer agents.

Danishefsky's total synthesis of **317** and its chlorine free precursor monocillin I **316**[116] features an RCM reaction with a substrate **310** that in addition to a dithiane protective group contains a vinyl epoxide and a diene moiety at



Fürstner (all reactions performed with cat **E**)



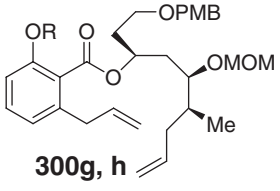
301a (R = H) cat **E**, 10 mol%
PhMe, 80 °C, 20 h
(69%, only *Z*)

301b (R = TBS) cat **E**, 5 mol%
PhMe, 80 °C, 1 h
(91%, *E*:*Z* = 1 : 1.5)

301c (R = Me) cat **E**, 5 mol%
PhMe, 80 °C, 1.5 h
(93%, *E*:*Z* = 1.9 : 1)

301d (R = MOM) cat **E**, 10 mol%
PhMe, 80 °C, 3 h
(91%, *E*:*Z* = 2.1 : 1)

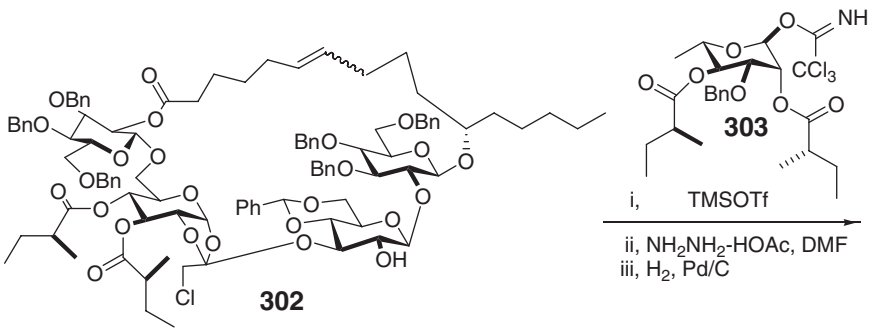
De Brabander (reactions performed with cat **B** or cat **C**,
10 mol%, CH_2Cl_2, RT, all combined yields >93%)



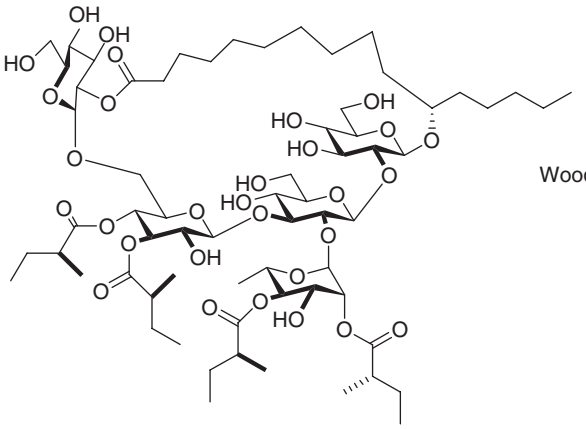
	cat **B**	cat **C**
300g (R = Me)	1.3 h (*E*:Z = 9 : 1) 18.3 h (*E*:*Z* = 4 : 1)	1.3 h (*E*:Z = 1.9 : 1) 18.3 h (*E*:*Z* = 2 : 1)
300h (R = MOM)	1.3 h (*E*:Z = 9 : 1) 18.3 h (*E*:*Z* = 5 : 1)	1.3 h (*E*:Z = 1.8 : 1) 18.3 h (*E*:*Z* = 2.1 : 1)

Scheme 60

both termini involved in the metathesis process (Scheme 64). Reaction of **310** with catalyst **B** furnished only traces of the desired product. Application of catalyst **C** gave the desired 14-membered benzolactone **312** with (*Z*)-configuration at the newly formed double bond, which was deprotected to **316** and finally chlorinated to **317**. Later on, with the aim of improving unfavorable pharmacokinetics of **317**, a similar RCM-based route was examined to obtain the cyclopropa-analog **315**.[117] Thereby, it turned out that under the reaction conditions applied to **310**, cyclopropa-derivative **311** furnished the desired cyclization product **314** in only 20% yield together with substantial amounts of dimers. Carrying out RCM in refluxing toluene at higher dilution afforded improved yield of the monomeric

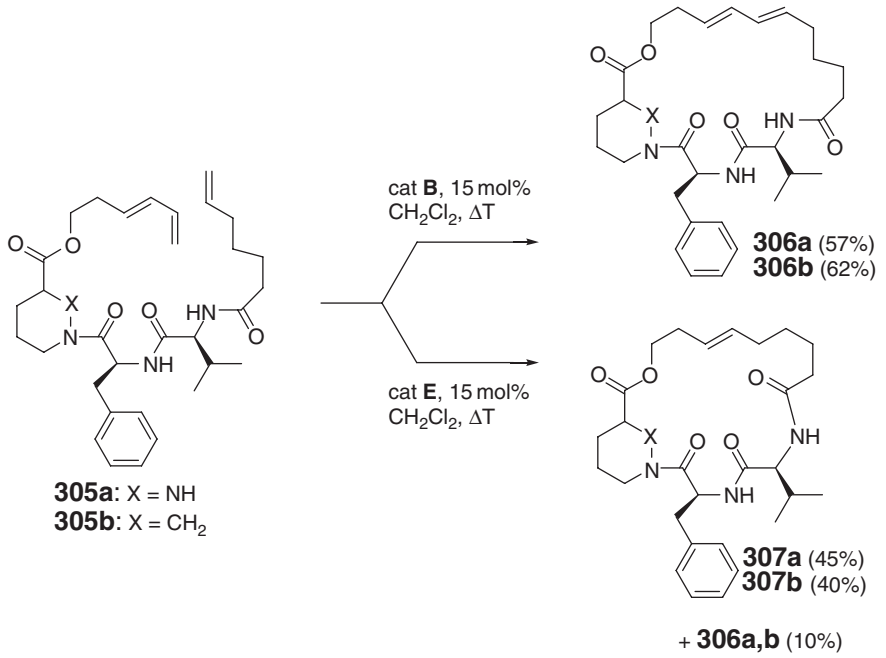


cat **B** or cat **F**
CH_2Cl_2
ΔT, 24 h (94%, $E:Z = 9:1$)



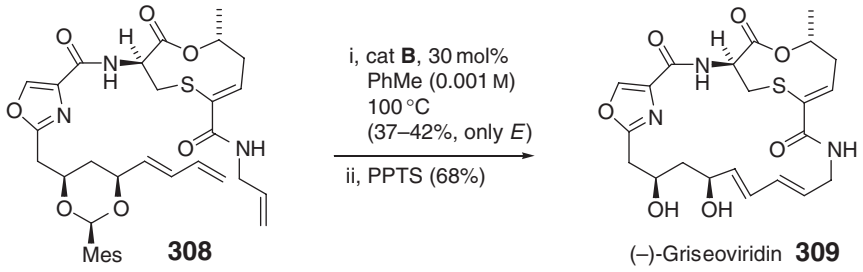
Woodrosin I **304**

Scheme 61



305a: X = NH
305b: X = CH_2

Scheme 62



Scheme 63

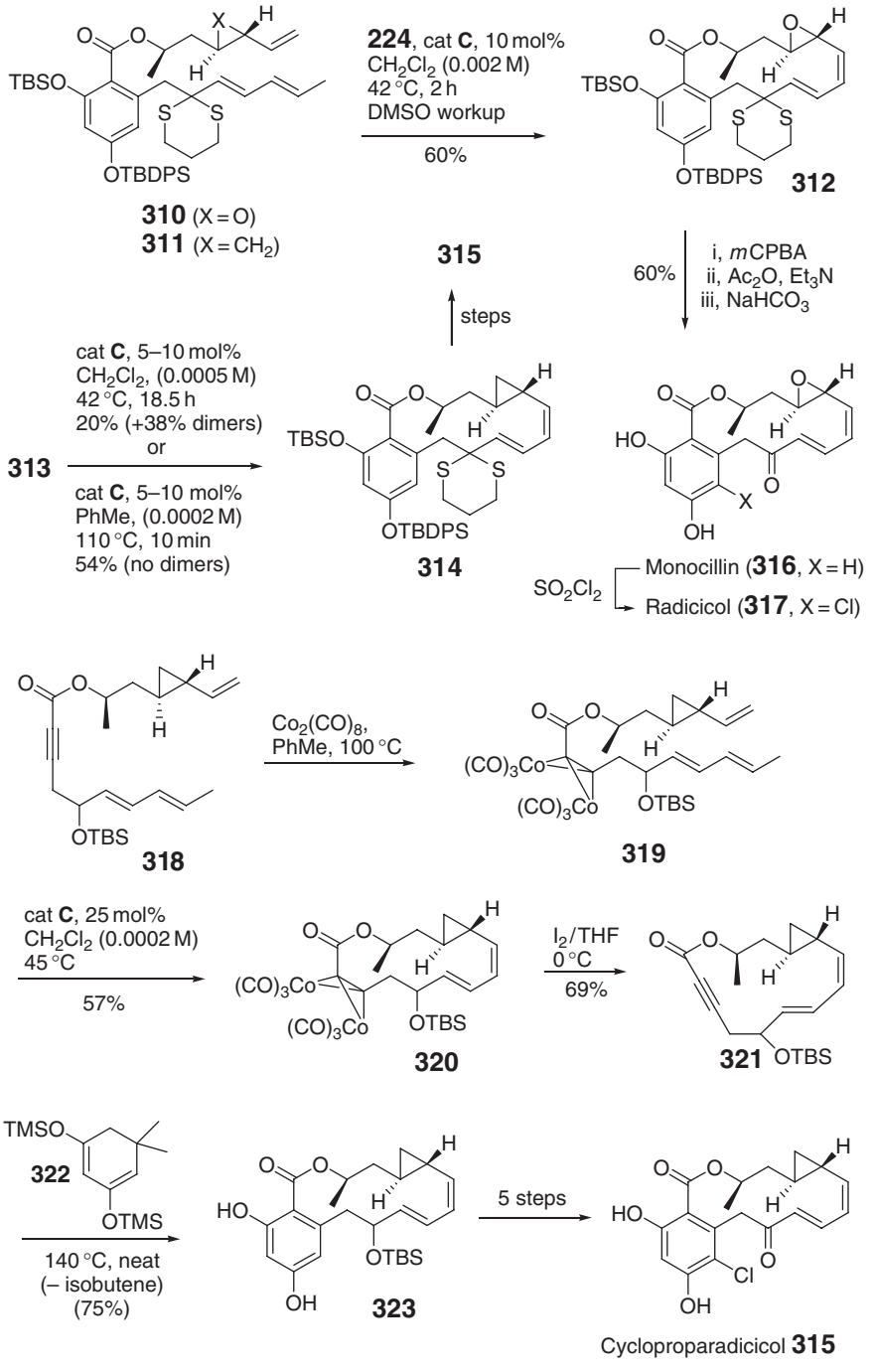
macrocycle **314**, when the reaction was quenched after a few minutes. Runs with prolonged reaction times resulted in the formation of more dimer, indicating that the monomer might eventually revert to the thermodynamically more favored dimers.

In an approach to cyclopropa-radicicol **315**,[118] also outlined in Scheme 64, the synthesis was achieved via ynolide **318** which was transformed to the stable cobalt complex **319**. RCM of **319** mediated by catalyst **C** led to cyclization product **320** as a 2 : 1 mixture of isomers in 57% yield. Oxidative removal of cobalt from this mixture followed by cycloaddition of the resulting cycloalkyne **321** with the cyclic diene **322** led to the benzofused macrolactone **323**, which was converted to cyclopropa-radicicol **315**.

As has been mentioned earlier, RCM approaches to epothilone syntheses have been plagued by a lack of stereocontrol in the generation of the desired (*Z*)-12,13-olefin geometry. For reviews, see Refs: 95, 95a–95g, and 96. An alternative RCM-based "bond connection between C10 and C11" in the epothilone series was used in Danishefsky's total synthesis of epo490 **325d**, a naturally occurring co-metabolite which differs from epoD **326** by the presence of an additional (*E*)-10,11-double bond.[119] This alternative macrocyclization proved also to be a viable and route to **326** (Scheme 65). Initially, the metathesis step was performed with differently protected precursor diene-enes **324a–c** using catalyst **C** in refluxing dichloromethane. It turned out that triene **324a** led to a mixture of two compounds in a 2.3 : 1 ratio with a total yield of 50% (no reaction at all was observed with ruthenium catalyst **B**, while molybdenum catalyst **A** led to decomposition of **324a**). The major component of the mixture was the desired RCM product **325a**, while the 14-membered byproduct **326a** arose from extrusion of a propene unit from attack at the internal olefin. When the cyclization of **324a** was performed in refluxing toluene for a few minutes, the yield of **324a** was distinctly improved, while the amount of the byproduct decreased (a similar beneficial effect by performing ene–diene RCM in toluene was also observed for analogous compounds with only slight structural variations). Performing the ring closure as the last synthetic step with unprotected diol **324d**, led directly to epo490 **325d** in 64% yield. As both the C3 and the C7 alcohols in **324d** are β to carbonyl groups, it is assumed that intramolecular H-bonding attributes for a higher degree of favorable rigidity to the cyclization precursor. Finally, selective diimide reduction of **325d** led to epoD **326**, a current clinical candidate in the epothilone series. For the synthesis of ring enlarged epothilone analogs by the same principle, see Refs: 120 and 120a.

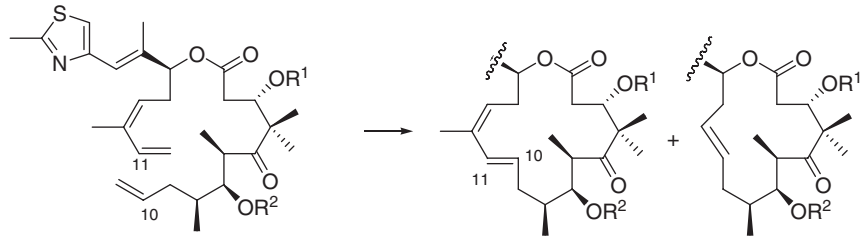
The synthesis of an epothilone model system via an alternative "C9–C10 disconnection" was first examined by Danishefsky in 1997. However, extension of this C9–C10 strategy to a fully functionalized epothilone intermediate was not successful, demonstrating the limitations of RCM with the early catalysts **B** and **C**.[121] In 2002, Sinha and Sun disclosed a stereoselective total syntheses of epoA **329a** and epoB **329b** by RCM of epoxy compounds **327** in the presence of catalyst **C** (Scheme 66).[122] The reaction furnished an inconsequential mixture of isomers **328** ($E : Z \approx 1 : 1$) in high yield. Subsequent selective hydrogenation of the newly formed double bond followed by deprotection led to epoA and epoB. Alternatively, diene–ene **330** was also efficiently cyclized in the presence of catalyst **C** to produce macrolides **331** (*E*/*Z*-mixture at the newly formed double bond) in 75% yield. Global deprotection of **331**, followed by a sequence of selective hydrogenation at C9–C10, sharpless asymmetric epoxidation, and deoxygenation of the primary hydroxy group, provided an alternative route to epoB **329b**. By contrast, analog **332** with an unsubstituted 1,4-diene moiety gave the 13-membered macrocycle **333** instead, while tetraene **334** with a bulky $TBSOCH_2$-group at C12 underwent RCM at the thiazole-substituted double bond. In the supporting information provided by Sinha *et al.*, the formation of cycloheptadienes from **334** was reported.

A similar approach, outlined in Scheme 67, was disclosed by Danishefsky, using diene–ene methyl and trifluoromethylketones **336a** and **336b** as the RCM substrates.[123,124] Treatment of **336** in refluxing toluene with catalyst **C** for a few minutes afforded exclusively (*E*)-isomers **337** in high yield. The thiazole moiety was then installed

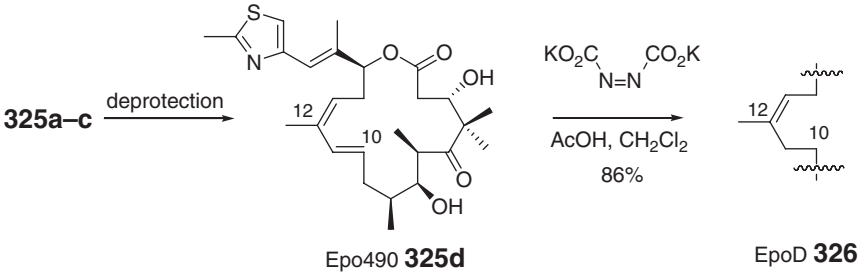


Scheme 64

(*E*)-selectively by olefination with tributylphosphonium salt **338**. Subsequent deprotection of the olefination product obtained from **337a** led to (*E*)-9,10-dehydro-epoB **339a**, which was "not identical" with a previously reported compound presumed to be the same entity.[125,125a] Moreover, the compound **339a** proved to exhibit highly promising *in vitro* and *in vivo* potencies, as well as encouraging pharmacokinetic properties. Site-selective diimide reduction of **339a** led to epoD **326**. It is noteworthy that 12-CF_3-analog **339b** was meanwhile recognized to feature even more favorable therapeutic activities, and alternative routes to the key fragments leading to metathesis substrate **336b** have been developed.[124]

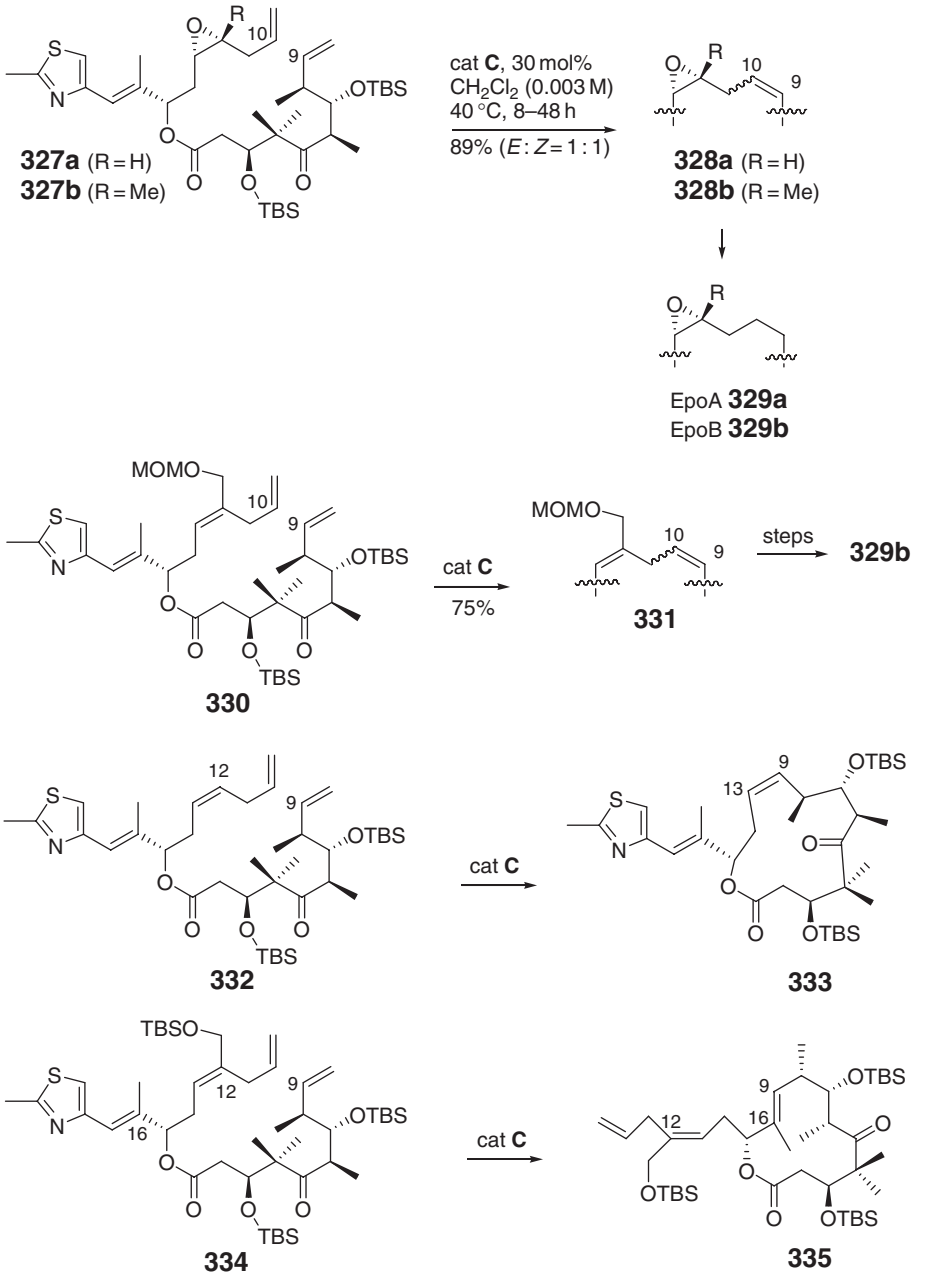


324		325	326
324a (R^1 = TES, R^2 = Troc)	cat **C**, 10 mol%, CH_2Cl_2 (0.002 M) 35 °C, 5.5 h	**325a** (35%)	**326a** (15%)
	cat **C**, 20 mol%, PhMe (0.0005 M) 110 °C, 25 min	**325a** (58%)	**326a** (5%)
324b (R^1 = H, R^2 = Troc)	cat **C**, 10 mol%, CH_2Cl_2 (0.002 M) 35 °C, 5.5 h	**325b** (41%)	**326b** (0%)
324c (R^1 = TES, R^2 = H)	cat **C**, 10 mol%, CH_2Cl_2 (0.002 M) 35 °C, 5.5 h	**325c** (57%)	**326c** (0%)
324d (R^1 = R^2 = H)	cat **C**, 10 mol%, CH_2Cl_2 (0.002 M) 35 °C, 5.5 h	**325d** (64%)	**326d** (0%)



Scheme 65

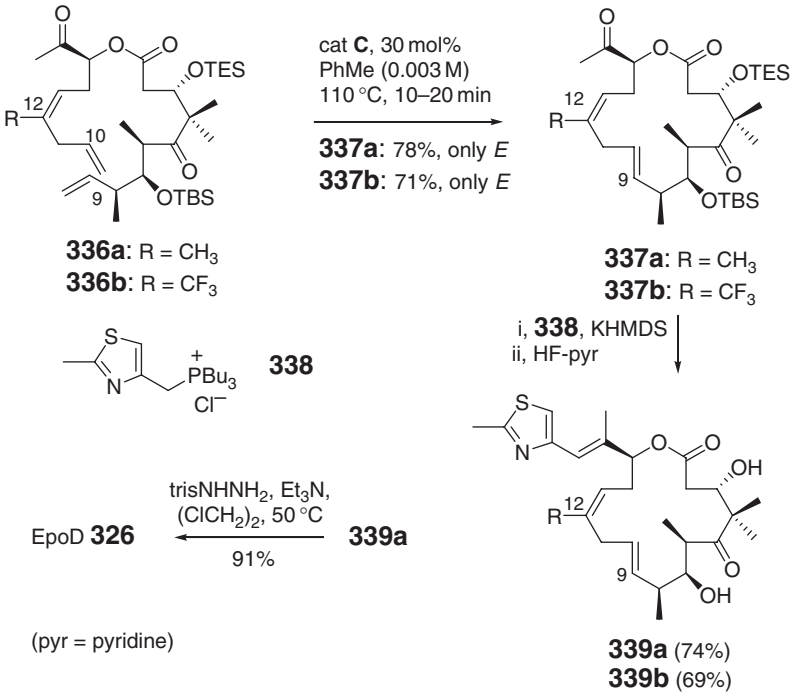
The first example of successful "diene–diene RCM" to construct a macrocyclic conjugated triene, was disclosed by Wang and Porco in the first total synthesis of oximidine II **340** (Schemes 68, Scheme 69).[126,127] In this synthesis, the principle of relay-RCM[128] was applied successfully. Oximidines are a growing subclass of the salicylate enamides and contain both macrocyclic triene and diene epoxide moieties. Oximidine III **340** from *Pseudomonas* sp. QN05727 exists in two conformers at RT and, as a vacuolar-type (H^+)-adenosine triphosphatase inhibitor, is highly active against transformed 3Y1 cells. On planning RCM of diolefin **341**, the authors detected that the desired ruthenium–carbene intermediate **342** is not formed. Instead, the reaction stops at the highly stabilized dienyl carbene **343**. However, **341** may be formed indirectly by starting RCM with tetraene **344**. Now the first ruthenium carbene to be formed is **345**, which, via eliminating cyclopentene in a first RCM reaction, generates the desired intermediate **342**. From this species **340** is obtained at last, albeit in low yield (32%). The synthesis started with epoxide **345**, which was converted into epoxy-alcohol **346** via a set of routine operations. Condensation with ester **347** generated **344** which via the aforementioned relay RCM furnished **348** (*Z*)-selectively. A detailed study of this RCM revealed that only the (*Z*)-isomer of **344** cyclized to **348**, whereas the (*E*)-olefin gave oligomers. Further steps led to a 1/1-*E*/*Z* mixture of vinyl iodides **350** via another "Kocienski" olefination with sulfone **349**.[129] This mixture was used in the final "Suzuki" type reaction with amide **351** which gave the (*Z*)-enamide **340** selectively in moderate yield.



Scheme 66

11.07.3.1 Strained Compounds

Ingenol **356** is a diterpenoid isolated from *Euphorbia ingens*, possessing a bicyclo[4.4.1]undecane skeleton with a highly strained inside–outside intrabridgehead stereochemistry. Apart from that, ingenol and its derivatives are of interest due to their protein kinase C (PKC)-activating and anti-HIV activities. The present synthesis (Scheme 70)[130,130a] is a formal one and aims for intermediate **355** which has been converted into **356** via a 21-step sequence by the Winkler group.[131] Specifically, keto ester **352**, available from optically active 3-carene in five known steps, was converted into *spiro*-di-olefin **353** whose RCM with catalyst **C** furnished **354** in a remarkable yield of 87%, despite the high ring strain. The success of the RCM reaction was attributed to the stability of the trisubstituted double bond in **354** and a high-frequency factor in encountering the two olefins. Allylic oxidation with SeO_2 delivered **355**.



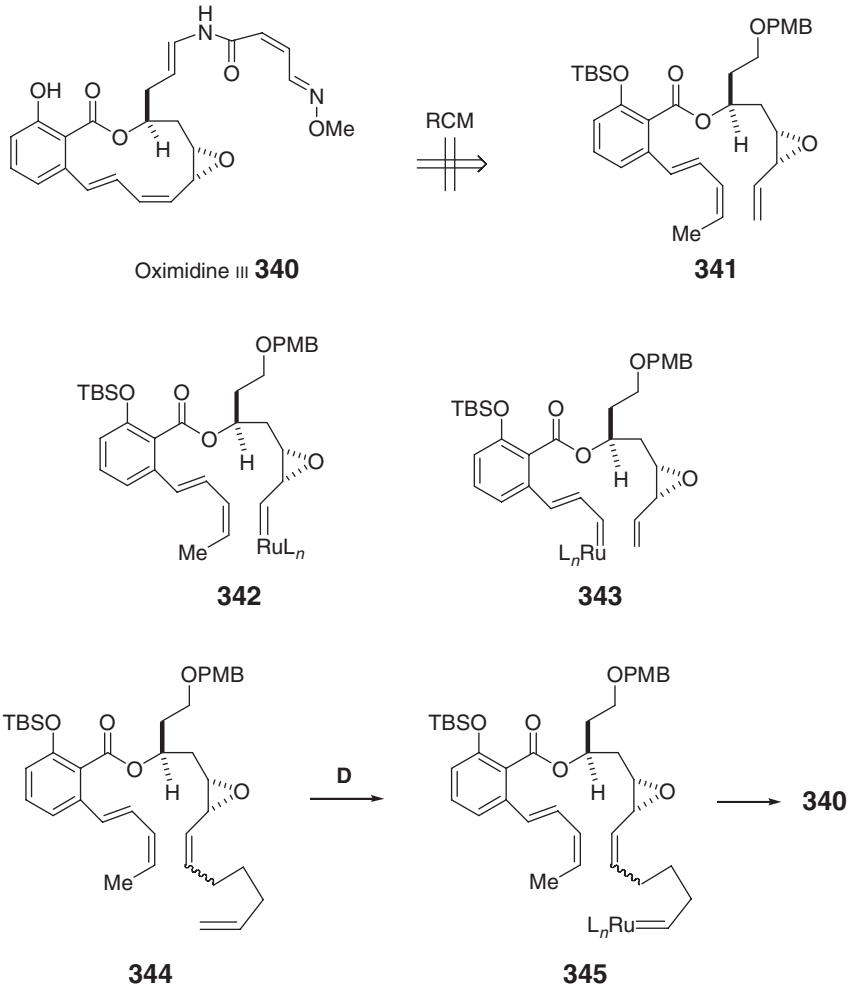
Scheme 67

An RCM-based approach to the strained 6-aza[3.2.1]bicyclooct-3-ene **358** and hence a formal total synthesis of the antitumor antibiotic (−)-peduncularine **359** (Scheme 71) was disclosed by Martin's group.[132] Initial experiments to effect RCM of alcohol **357** with catalyst **B** were not successful (possibly by formation of unreactive intermediate **362**), while TMS ether **360** led to cyclization product **361** in 64% yield. When alcohol **357** was treated with catalyst **C**, the ring closure proceeded smoothly leading to **358** in nearly quantitative yield.

The marine natural product (+)-chatancin **370**, a platelet factor antagonist with several interesting biological activities, features a *cis-anti-cis*-dodecahydrophenantrene framework possessing seven stereogenic centers (Scheme 72). In an attempt by Deslongchamps to prepare **370** by a transannular Diels–Alder (TADA) reaction,[133,133a] furanophane **367** was projected as a key intermediate to generate tetracycle **368** stereoselectively. Subsequent hydride shift-mediated oxygen transposition should then generate **370**. The furanophane **367** in turn, featuring a trisubstituted double bond with (*E*)-configuration (necessary for the success of the TADA reaction), was to be generated by RCM.

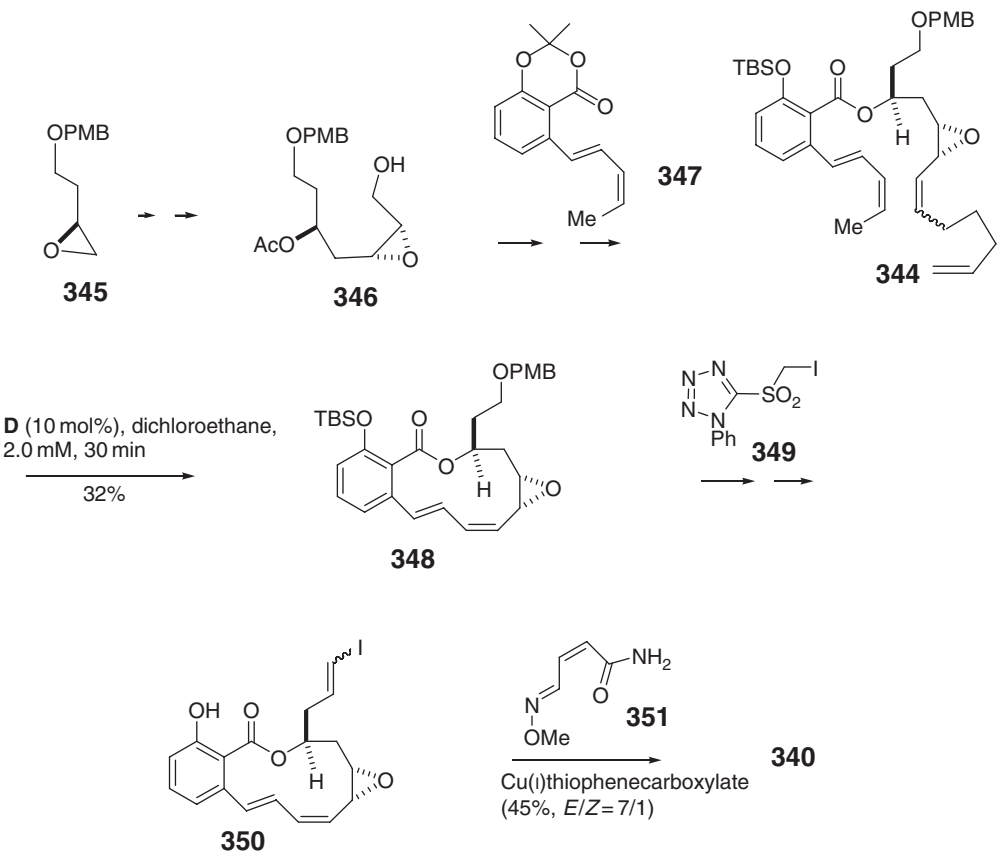
Diene **363** substituted by a bulky silyl ether to prevent cycloaddition before the metathesis process produced in the presence of catalyst **C** the undesired furanophane **364** with (*Z*)-double bond as the sole reaction product in high yield. The same compound was obtained with Schrock's molybdenum catalyst **A**, while catalyst **B** led, even under very high dilution, only to an isomeric mixture of dimerized products. The (*Z*)-configurated furanophane **364**, after desilylation did, in accordance with earlier observations, not produce any TADA product. On the other hand, dienone **365** furnished the desired macrocycle (*E*)-**366**, although as a minor component in a 2 : 1 isomeric mixture with (*Z*)-**366**. Alcohol **367** derived from *E*-**366** then underwent the projected TADA reaction selectively to produce in a reversible process after 3 days cycloadduct **368** (70% conversion). The final Lewis acid-mediated conversion to **370** however failed and led to anhydrochatancin **369** instead.

Roseophilin **371**, a deep-red pentacyclic compound isolated from the culture broth of *Streptomyces griseoviridis*, is an anti-tumor antibiotic. **371** possesses a topologically unique pentacyclic skeleton, consisting of a 13-membered macrocycle incorporated in an *ansa*-bridged azafulvene, which in turn is linked to a conjugated heterocyclic ring system. The absolute stereochemistry of roseophilin as depicted in Figure 5, was unknown until the first total synthesis, published by Tius and Harrington in 2001.[134,134a] All synthetic approaches toward **371** known to date rely on tricyclic ketone **372** as one of two main fragments.[135] Various approaches to **372** (*ent*-**372** or *rac*-**372**) were performed via an RCM step to form the 13-membered macrocycle. The respective metathesis substrates used by

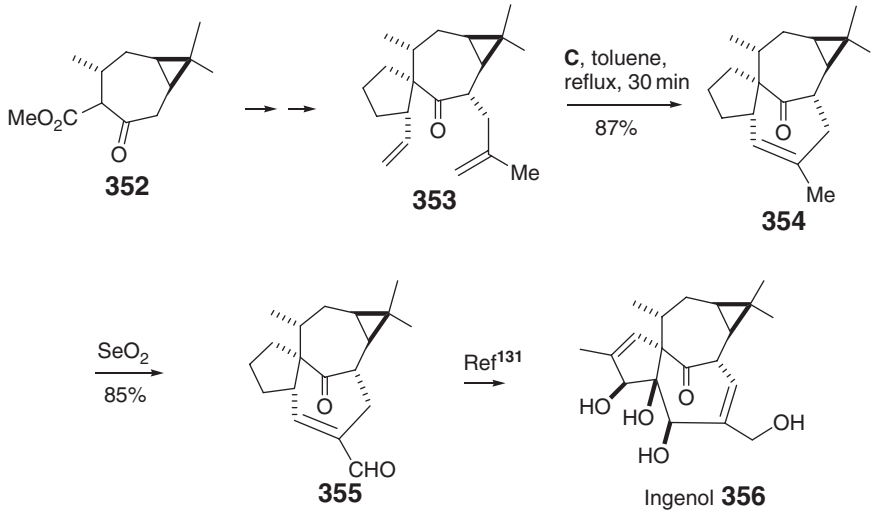


Scheme 68

the different groups, as well as the reaction conditions used in the RCM steps are presented in Figure 5. In the approach pursued by Fuchs,[136] the racemic dienes **373a–e** were investigated. The unsubstituted compound **373a**, as well as the diastereomeric alcohols **373b** and **373c**, did not cyclize in the presence of catalyst **B**. From the bulky silyl ethers derived from alcohols **373b** and **373c**, only one **373e** underwent cyclization. Evidently, in this special case, the bulky TIPS ether helped to orient the olefinic side chains into a favorable conformation. In the approach of Hiemstra and co-workers leading to *ent*-**372**,[137] the phenylsulfonyl-substituted diene **374** proved to be a very efficient metathesis substrate, providing the desired macrocycle (mixture of *E*/*Z*-isomers) in 91% yield. The efficiency of this reaction was ascribed to both, the conformational restriction induced by the phenylsulfonyl group and the concave shape of the *cis*-fused bicyclic system present in **374**, which cooperatively bring the reacting double bonds in close proximity. In the case of Fürstner's acyclic metathesis substrate *rac*-**375**,[138] no additional conformational assistance was necessary, and treatment with catalyst **B** led to the corresponding macrocycles in high yield. In Boger's total synthesis of *ent*-**371**,[139] the macrocycle was closed efficiently by treatment the monocyclic triene **376** with catalyst **B**. The formation of the *ansa*-macrocycle prior to formation of the cyclopentanone avoids in a large part the strain to be overcome in compounds **373**. The cyclopentanone ring was subsequently introduced by a 5-*exo*-*trig* radical-alkene cyclization of the acyl selenide derived from the ester group. Also in Tius's first total synthesis of enantiomerically pure **373**,[134,134a] a monocyclic diene **377** was used to produce the macrocycle efficiently. After selective hydrogenation of the newly formed double bond, the missing pyrrole ring was formed by involving the 1,4-dicarbonyl moiety to undergo a Paal–Knorr reaction.

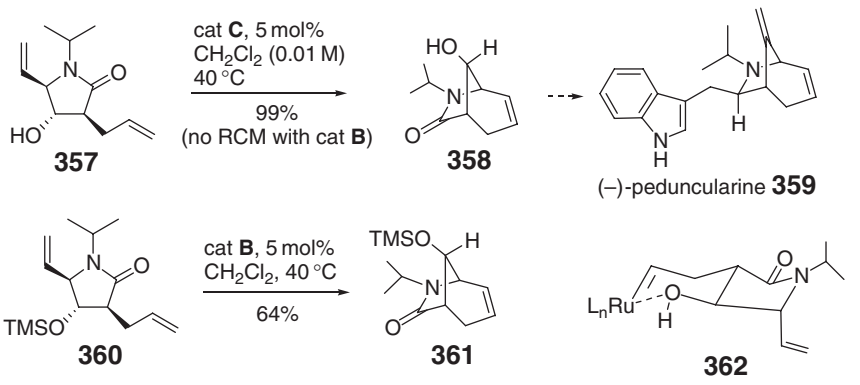


Scheme 69

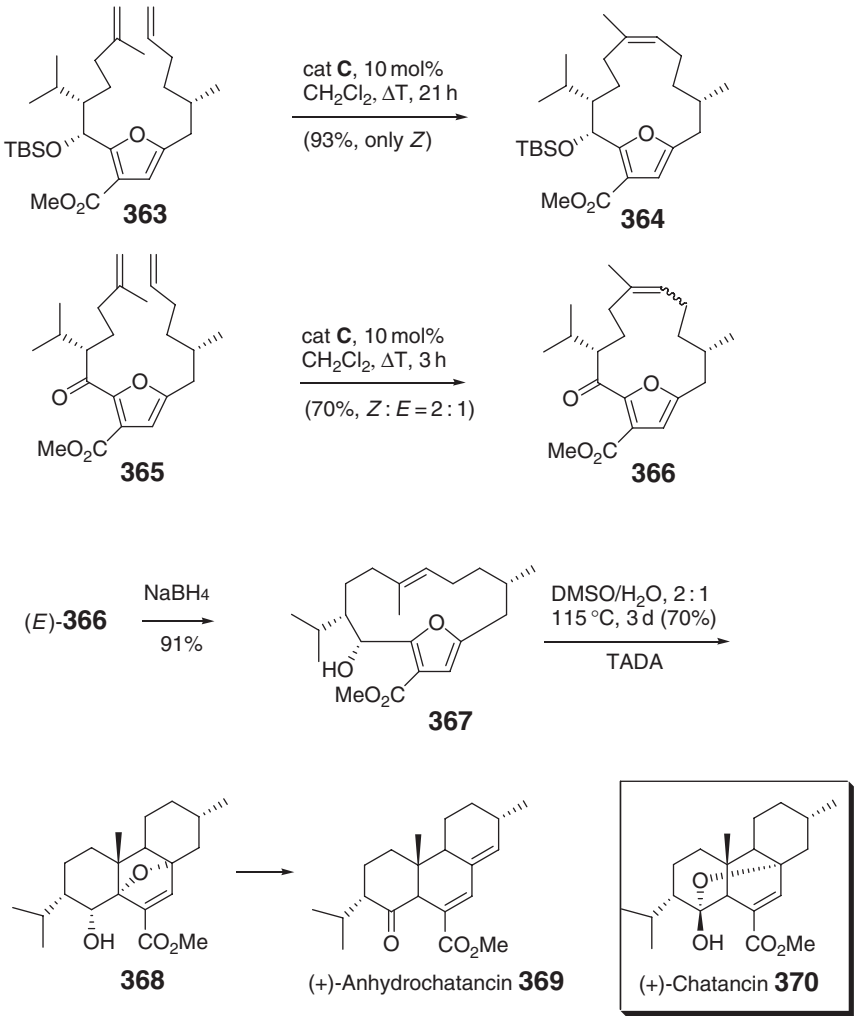


Scheme 70

The marine alkaloid sarain A **383** features an exceptionally challenging pentacyclic architecture (Figure 6). To date, **383** has not succumbed to a total synthesis. Two groups however have completed the tricyclic core of **383** and have annulated the western 13-membered ring using quite similar RCM approaches.[140,140a] The results obtained with different metathesis substrates and catalysts are outlined in Figure 6. RCM of Weinreb's dienes **378**, **379**, and **380**[140]



Scheme 71



Scheme 72

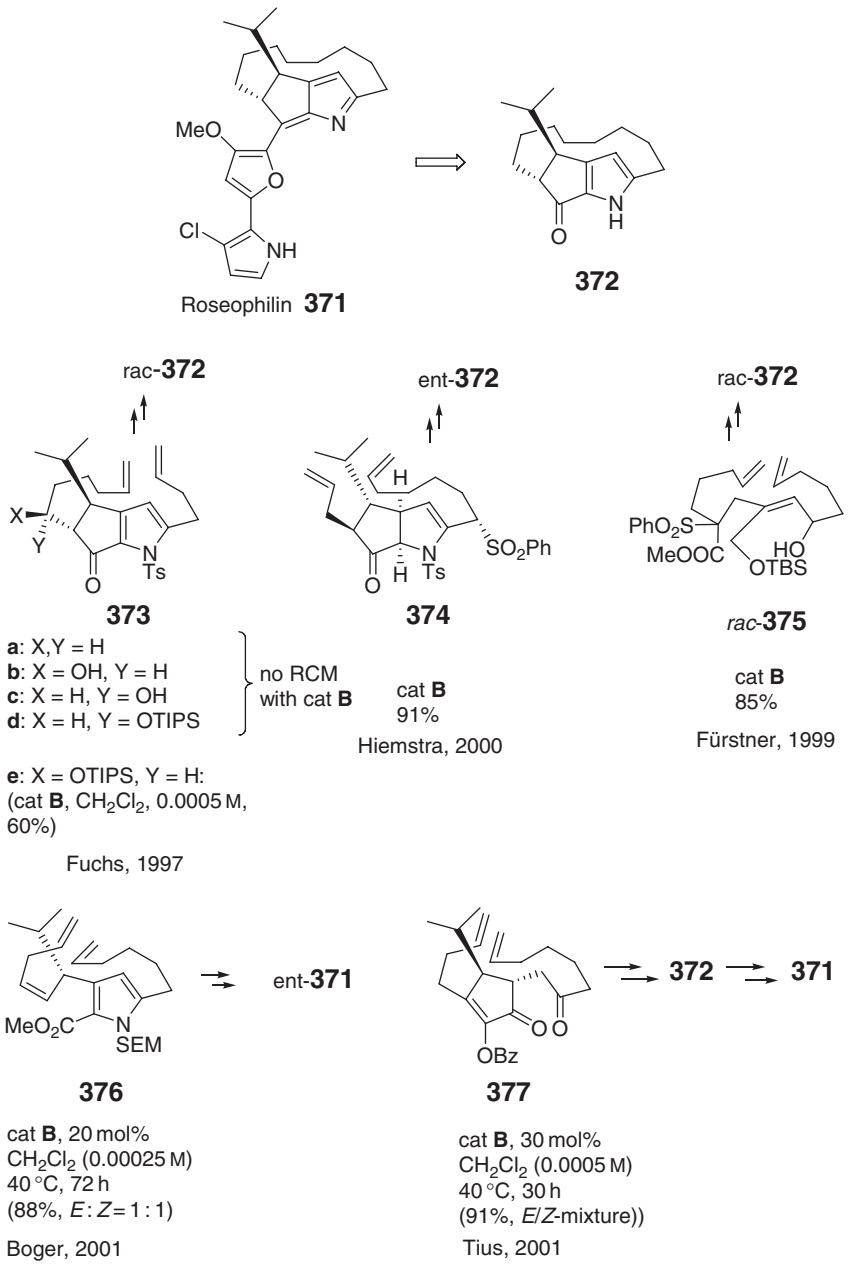
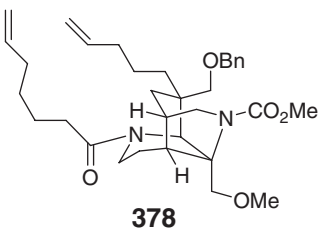


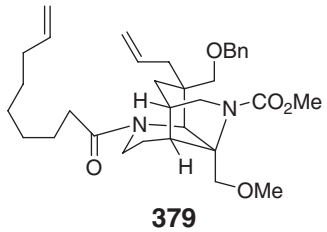
Figure 5 RCM approaches to roseophilin in **371**.

which differ by the site of ring closure were mediated by catalyst **B**. Dienes **378** and **380** furnished comparable results leading to the corresponding cyclization products in moderate yields along with substantial amounts of "cyclic dimmers." RCM of diene **379** very sluggishly furnished an inseparable mixture of the desired macrocycle along with a "linear dimer" in a poor overall yield, suggesting that the allylic side chain was too close to the tricyclic core for participating efficiently in the metathesis. Four years later, when the strategy was adapted by Cha and co-workers,[140a] RCM of dienes **381** and **382** was performed with catalyst **C**. In contrast to the uncomplicated ring closure of the N-PMB-protected derivative **381** (71% yield within 5 h), it was surprising that diene **382** with its more elaborate alkyl chain produced the macrocycle in distinctly lower yield (42%) along with a dimer. Silylation of **382** prior to RCM gave a reliably higher overall yield.



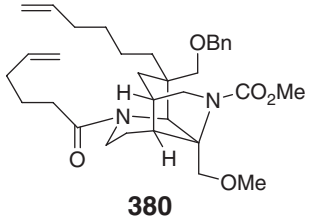
378

cat **B**, 20 mol%
CH_2Cl_2 (0.0005 M)
ΔT, 2 d
(49%, *E*/*Z*-mixture)
+
macrocyclic dimer (39%)



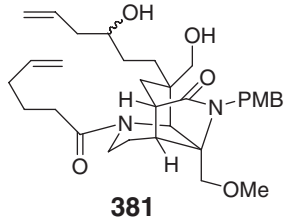
379

cat **B**, 20 mol%
CH_2Cl_2 (0.0005 M)
ΔT, "very slow"
(*E*/*Z*-mixture) +
linear dimer
(overall poor yield)



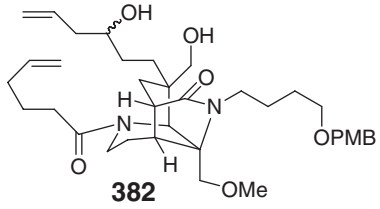
380

cat **B**, 20 mol%
CH_2Cl_2 (0.0005 M)
ΔT, 2 d
(39%, *E*/*Z*-mixture)
+
macrocyclic dimer (18%)



381

cat **C**, 10 mol%
CH_2Cl_2 (0.0004 M)
ΔT, 5 h
(71%, *E*/*Z*-mixture)

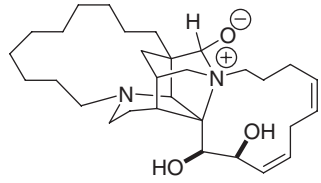


382

cat **C**, 10 mol%
CH_2Cl_2 (0.0004 M)
ΔT, 2 d
(42%, *E*/*Z*-mixture)

or

i, TBSOTf
ii, cat **C**, 8.5 mol%
CH_2Cl_2 (0.0004 M)
ΔT, 2 h
iii, TBAF
(54%, *E*/*Z*-mixture)

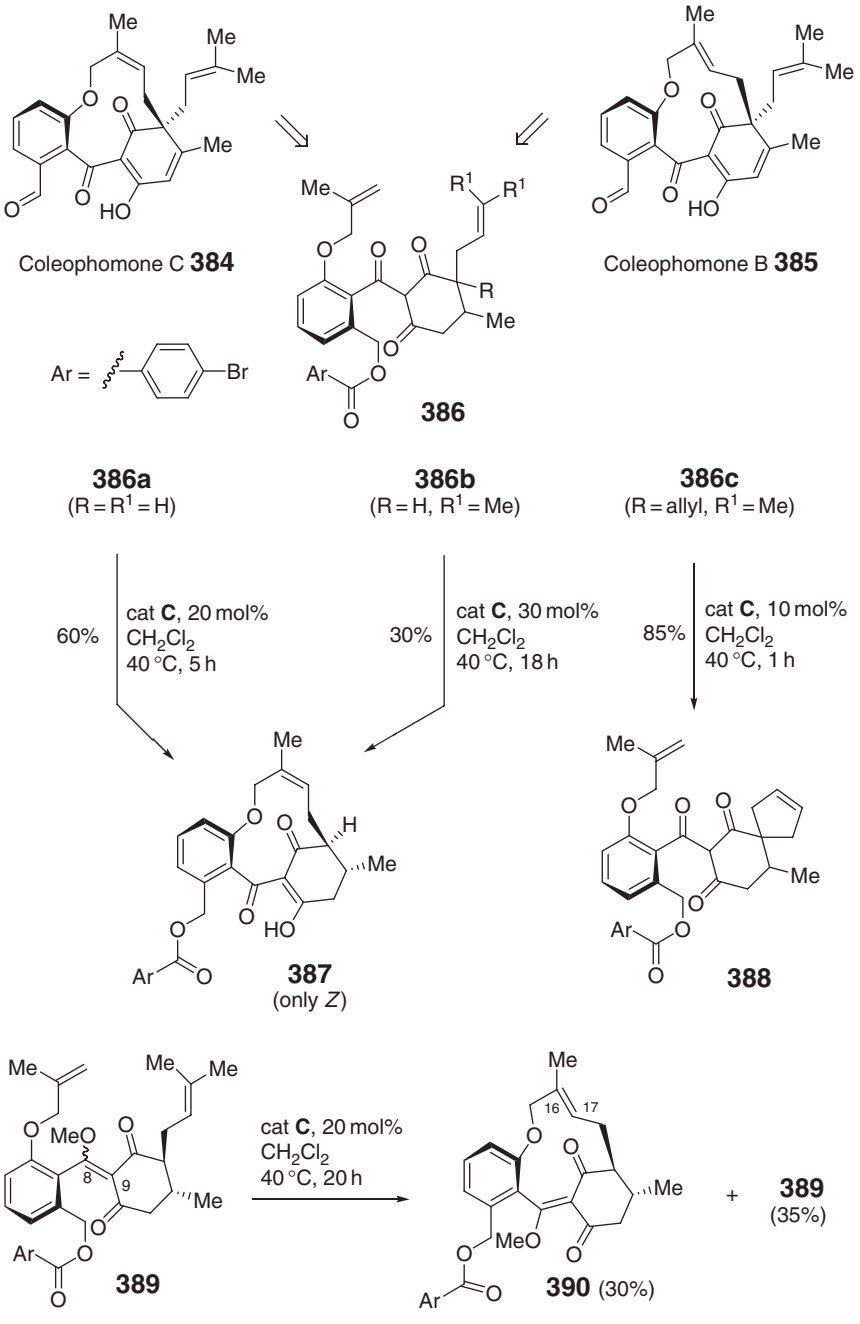


Sarain A **383**

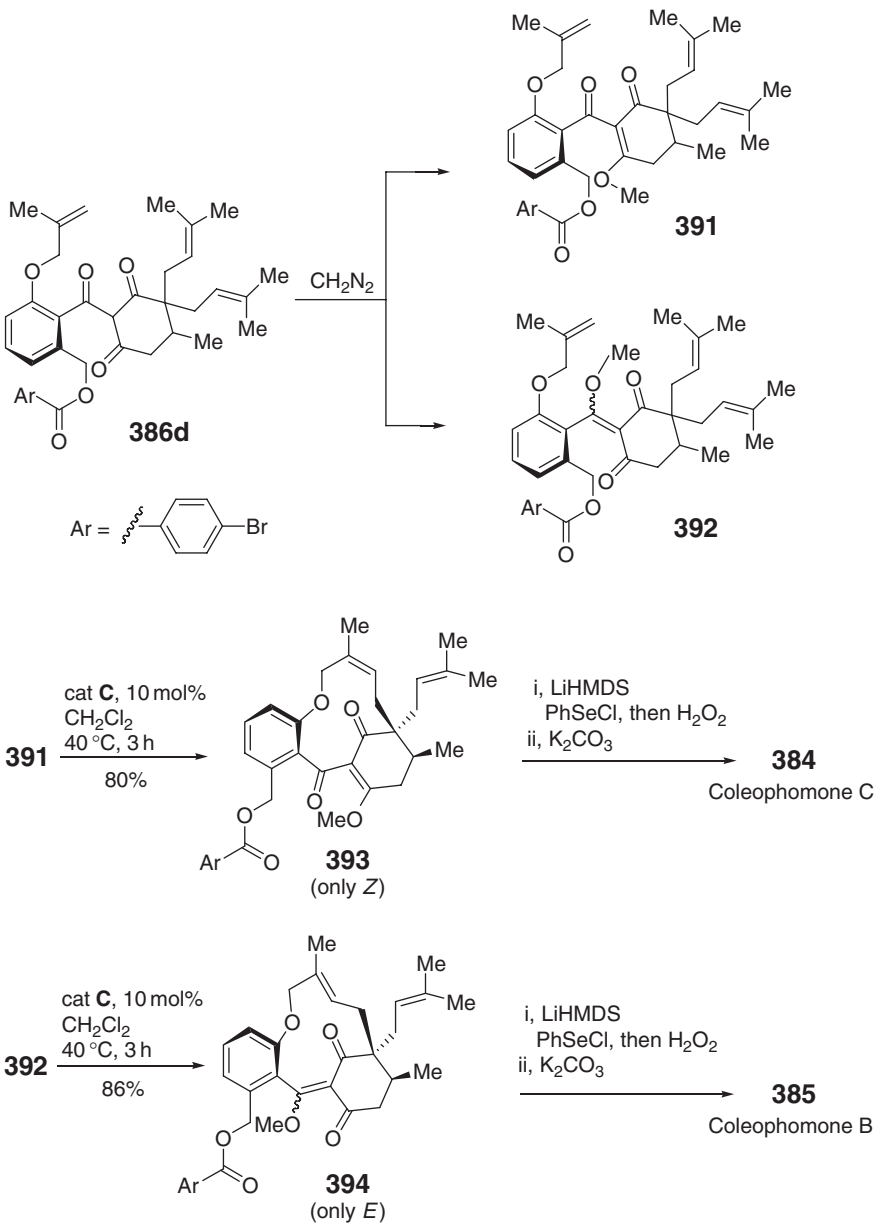
Figure 6 RCM approaches to Sarain A **383**.

In the application of RCM to strained products, it is sometimes of the essence to preorganize the substrate into a conformation that favors cyclization. In the above roseophilin case, the stereochemical outcome of the ring-closing step was inconsequential for the successful formation of a saturated macrocyclic ring. A highlight among RCM-based natural product syntheses that pushes the limits of olefin metathesis as a means to construct highly strained and complex targets with total stereocontrol, is found in Nicolaou's synthesis of coleophomone B **385** and C **384**.[141] These compounds differ only in the geometry of the double bond in the macrocyclic *ansa*-bridge (Scheme 74). In addition to an interesting biological profile, the coleophomones feature a strained and rigid framework with a sensitive tricarbonyl system tethered into an 11-membered macrocycle, whose strain is derived from a fused aryl ring and an internal cyclohexadienone. During the exploration of the crucial metathesis step, various dienes **386** and enol ether **389** synthesized from **386a** were investigated. Already in the case of the simplest substrate **386a** bearing a monoalkylated cyclohexadione moiety, first-generation catalyst **B** failed to induce ring closure. With second-generation catalyst **C**, the tricycle **387** with (*Z*)-double

bond was formed in 60% yield. Also with diene **386b**, bearing a di- and a trisubstituted double bond, the exclusive formation of **387** was observed, albeit in reduced yield (30%). The simplest dialkylated cyclohexadione triene **386c** (bearing an allyl and a prenyl substituent), however, did produce rapidly within 1 h only spirocyclopentene **388** in 85% yield. Additional and unexpected information was gained by the RCM reaction of enol ether(s) **389** (1 : 1-mixture of $\Delta^{8,9}$-isomers, each of which consisting as a 1 : 1 pair of atropisomers). When this mixture was subjected to the usual metathesis conditions, a single macrocycle **390** with (*E*)-configuration at both the $\Delta^{8,9}$ and the newly formed $\Delta^{16,17}$ double bonds was isolated in 30% yield, together with a considerable amount of the starting material which was found to be enriched in the (*Z*)-isomer around the enol ether ($\Delta^{8,9}$) double bond (Scheme 73).



Scheme 73



Scheme 74

The final solution of the coleophomone problem is outlined in Scheme 74. The fully substituted diprenylated compound **386d**, itself a very poor RCM substrate, was treated with diazomethane, which led to a separable mixture of regioisomeric enol ethers **391** and **392**, the latter being a ca. 1.3 : 1 mixture of geometrical isomers ($\Delta^{8,9}$). Treatment of **391** with catalyst **C** led within 3 h exclusively to the (*Z*)-configured macrocycle **393** in 80% yield. Regioisomer **392** in turn furnished under the same conditions the (*E*)-configured macrocycles **394** (ca. 1 : 1 mixture of isomers at $\Delta^{8,9}$). Remarkably, in both cases only the prenyl group in *cis*-position to the vicinal C12 methyl group participated in the ring-closing step. Thus, two different coleophomone frameworks had been obtained stereospecifically from a single precursor **386d**. Conversion of compounds **393** and **394** into coleophomone C **384** and B **385** respectively was accomplished in both series by introducing the missing $\Delta^{11,12}$ double bond and global deprotection.

11.07.4 Domino Metathesis Reactions

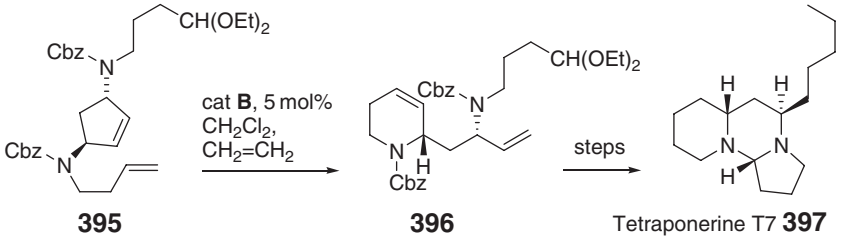
11.07.4.1 Ring-Rearrangement Reactions

An alternative access to complex heterocyclic structures is the Ru- or Mo-catalyzed ring-rearrangement metathesis (RRM), in which a strained carbocyclic alkene is transformed into a heterocyclic product by an intramolecular ring-opening/ring-closing or double ring-closing domino metathesis. Due to the reversibility of the processes involved, the amount of rearrangement product depends on thermodynamic effects, for example, ring strain and substitution pattern of the starting cycloalkene. A particularly attractive aspect of these transformations is the catalytic transfer of stereochemical information from readily available carbocyclic olefins to one or two newly formed heterocyclic rings. This methodology, initially investigated by Grubbs,[142] was extensively applied in natural product synthesis by Blechert *et al.*

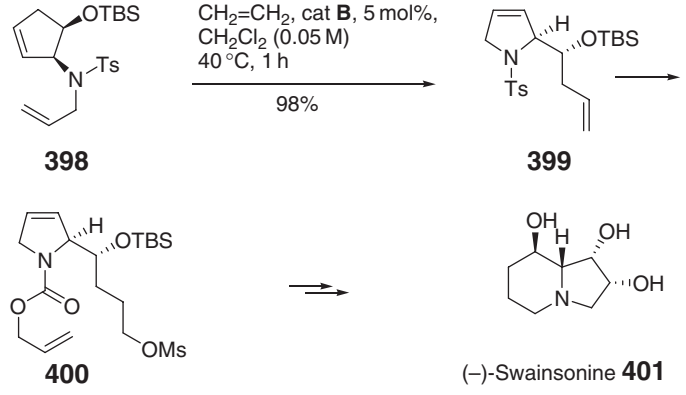
Four members of the tetraponerine family (the major constituents of the contact poison of the New Guinean ant *Tetraponera* sp.) have been prepared by RRM methods.[143] The key step leading to tetraponerine T7 **397** from the readily available cyclopentene precursor **395** is shown in Scheme 75. When compound **395** was exposed to Grubbs' first-generation catalyst **B** in the presence of ethylene, the desired ROM–RCM sequence proceeded smoothly to furnish heterocycle **396** with complete conversion, whereas the corresponding di-nosyl (2-nitrophenylsulfonyl)-protected analog of **395** led only to an 1 : 2 equilibrium mixture of starting material and RRM product.

The same principle of sequential cyclopentene opening RCM resulting in the formation of a dihydropyrrole ring was the key step in Blechert's approach to the polyhydroxylated indolizine alkaloid (−)-swainsonine **401** via RRM of **398** (Scheme 76) via **399** and **400**.[144]

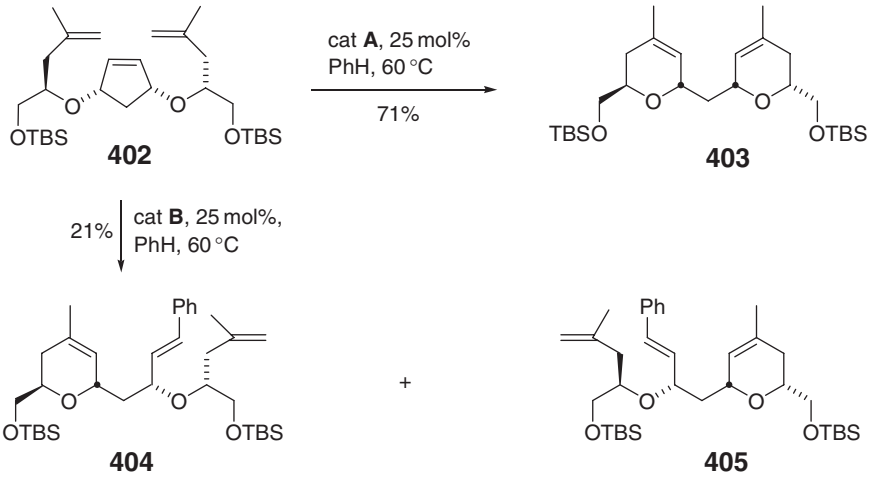
An early example of cyclopentene-opening/double RCM leading to bis-dihydropyran **403** (the C22–C34 segment of the potent anti-tumor agent halichondrin A) was disclosed by Burke *et al.* (Scheme 77).[145] In this case, the ROM–RCM sequence was performed with Schrock's Mo catalyst **A**, leading from cyclopentene **402** to **403** in 71% yield. When metathesis precursor **402** was exposed to Grubbs' first-generation catalyst **B**, only one dihydropyran ring was formed and the reaction led to a mixture of the isomeric compounds **404** and **405** in low yield.



Scheme 75



Scheme 76



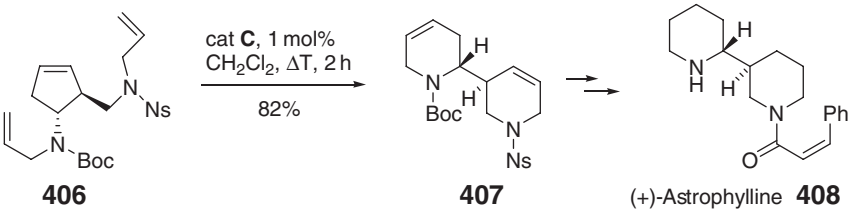
Scheme 77

RRM of enantiopure cyclopentene **406**, induced by commercially available second-generation catalyst **C** was the key step in Blechert's total synthesis of the bis-piperidine alkaloid (+)-astrophylline **408**.[146] Exposure of metathesis precursor **406** to only 1 mol% C provided within 2 h bicycle **407** in 82% yield (Scheme 78).

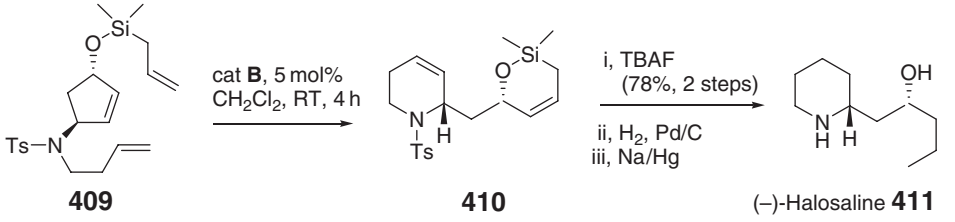
Blechert's synthesis of the piperidine alkaloid (−)-halosaline **411** by RRM is outlined in Scheme 79.[147] In the presence of 5 mol% of catalyst **B**, the ring rearrangement of metathesis precursor **409** proceeded cleanly with formation of both heterocyclic rings in **410**. *In situ* deprotection of the cyclic silyl ether in **410** followed by selective reduction and removal of the tosyl group led to **411**.

The utility of strained disubstituted cycloheptenes in alkaloid syntheses is highlighted by Blechert's total syntheses of the bis-pyrrolidine alkaloid (+)-dihydrocuscohydrine **414**,[148] the bis-piperidine alkaloid (−)-anaferin (in form of its dihydrochloride **417**),[149] and indolizine 167B **421**[150](Scheme 80). In these examples, the C_2-symmetry of the enantioenriched precursors **412**, **415**, and **418** is nicely exploited.

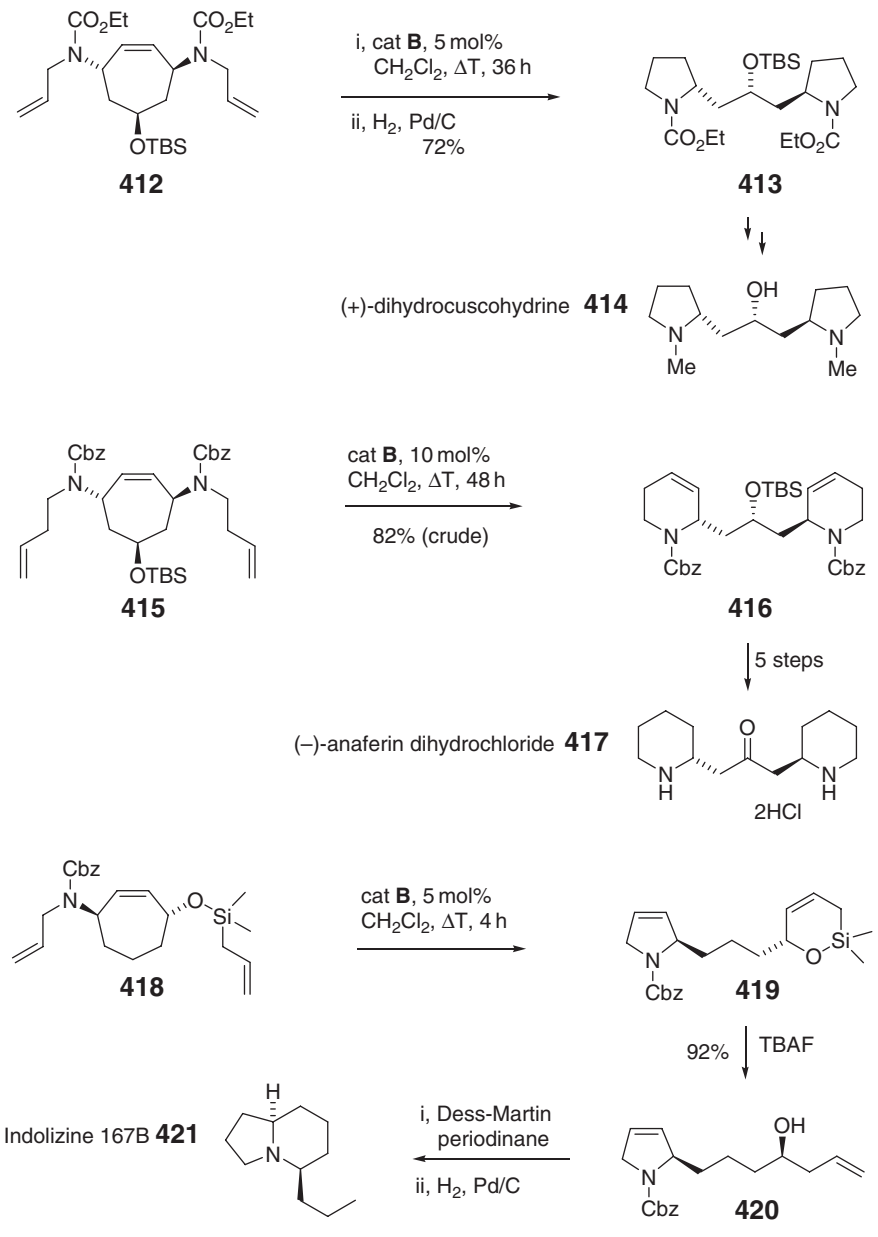
A type of ROM–RCM based tandem reaction was discovered by Lazarova *et al.*[151] When various natural 16-membered macrolide antibiotics with a 1,3-diene unit in the marocyclic core (e.g., josamycin **422**) were exposed to catalyst **E** (20 mol%) in the presence of 1-hexene (2 equiv.), an ROM–RCM sequence occurred with excision of



Scheme 78



Scheme 79

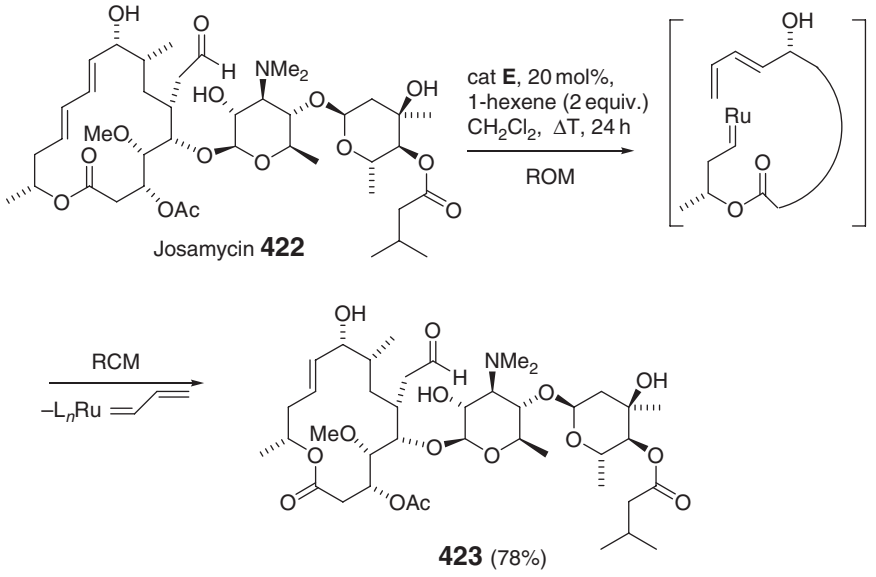


Scheme 80

ethylene and ring contraction to 14-membered ring lactones **423** (Scheme 81). The reaction did not occur with catalyst **B**, and demanded, without additives, a stoichiometric amount of catalyst **E**.

11.07.5 Metathesis on Solid Supports

Chemistry on solid supports has gained tremendous importance during last years, mainly driven by the needs of pharmaceutical sciences. Due to the robust and tolerable nature of the available catalysts, metathesis was soon recognized as a useful technique in this context. Three conceptually different, RCM-based strategies are outlined in Figure 7. In the approach delineated in Figure 7a, polymer-bound diene **424** is subjected to RCM. The desired product **425** is formed with concomitant traceless release from the resin. This strategy is very favorable, since only



Scheme 81

compounds with the correct functionality will be liberated, while unwanted byproducts remain attached to the polymer. However, as the catalyst is captured in this process by the matrix **426**, a higher catalyst loading will be required, or "ancillary" alkenes have to be added to liberate the catalyst. With polymer-bound diene **427**, two different strategies are possible. Following path A, RCM results in the formation of a (volatile) alkene **428a** and a cyclic product **429a**, which remains attached to the polymer support. This product can undergo further manipulation, with cleavage from the resin at a later stage (**429a** → **430**, Figure 7b). Alternatively, RCM of a diene **427** can also be used for the traceless release of a polymer-bound cycloalkene **429b**, with concomitant formation of a terminal alkene **428b** as the desired reaction product (Figure 7c).

The feasibility of multi-step natural product total synthesis via solid-phase methodology, and its application to combinatorial chemistry, was first achieved by Nicolaou and co-workers in epothilone synthesis and in the synthesis of an epothilone library.[152,152a] The traceless release of TBS-protected epoC **432** by RCM of resin-bound precursor **431** (Scheme 82), is an early and most prominent example for the strategy outlined in Figure 7a.

An illustrative example for the alternative strategy, (cf Figure 7c) by the use of a traceless linker, is found in the multi-step synthesis of 6-*epi*-dysidiolide **434** and several dysidiolide-derived phosphatase inhibitors by Waldmann and co-workers[153,153a] outlined in Scheme 83. During the synthesis, the growing skeleton of **434** remained attached

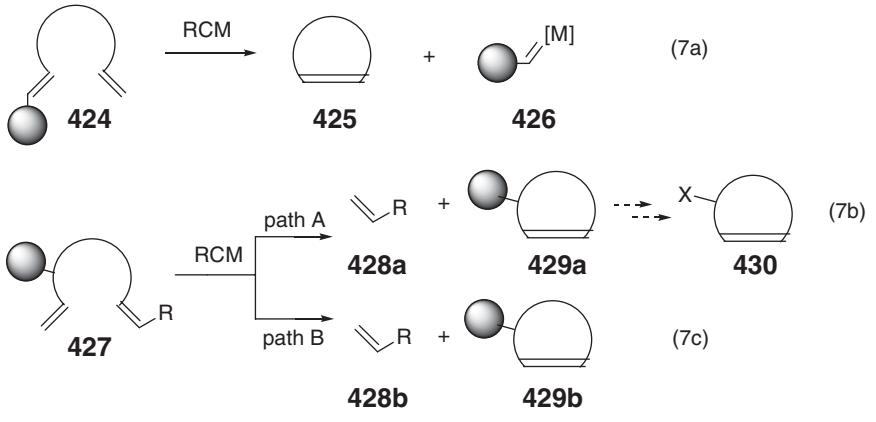
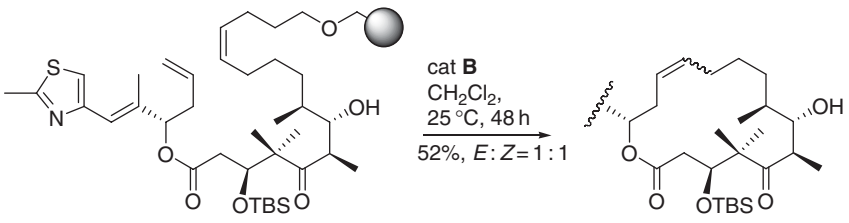
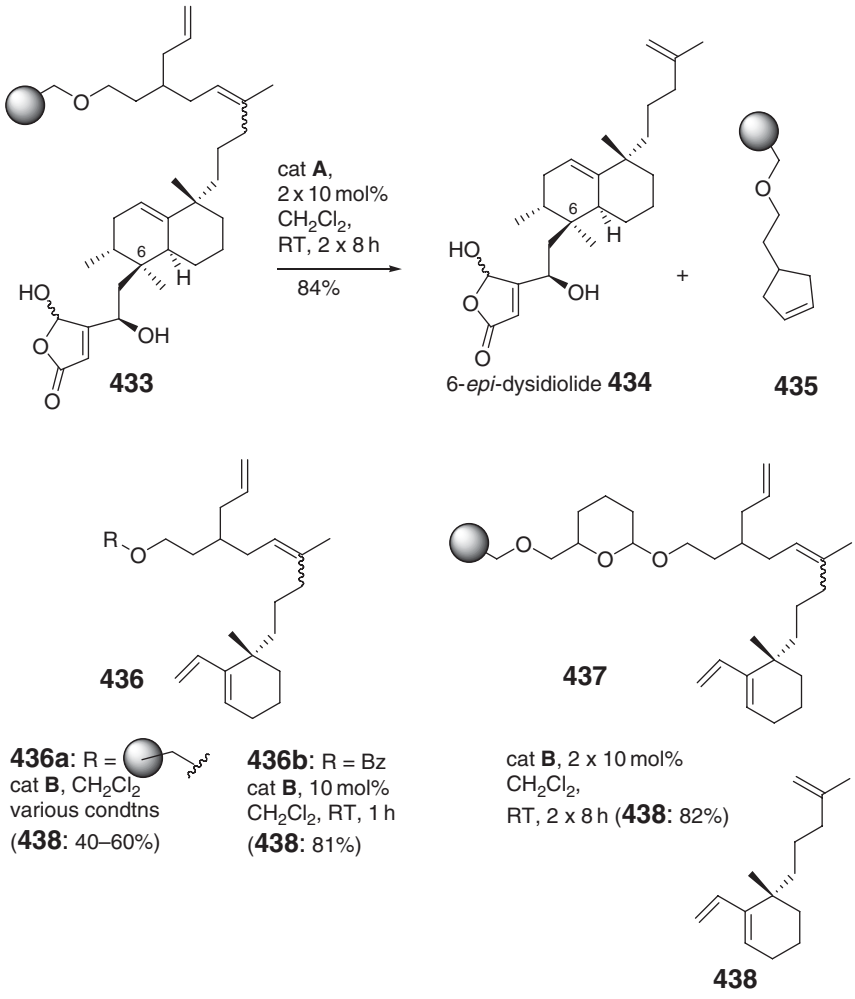


Figure 7 RCM on solid support.



431 **432**

Scheme 82



433 **435** **436** **437** **438**

Scheme 83

to a robust dienic linker. After completion of intermediate **433**, the terminal olefin in **434** was liberated from the solid support by the final metathesis process with concomitant formation of a polymer-bound cyclopentene **435**. Notably, during the synthesis it turned out that polymer bound intermediate **436a**, in contrast to soluble benzoate **436b**, produced diene **438** only in low yield. After introduction of an additional linker (cf. intermediate **437**), diene **438** was released in distinctly improved yield by RCM.

11.07.6 Conclusions and Outlook

The last ten years have witnessed an exponential growth in the application of ruthenium-catalyzed metathesis reactions in target-oriented synthesis. The development of highly active metathesis catalysts that are commercially available and combine high functional group tolerance with "user-friendly" low sensitivity to moisture and air, has rendered metathesis as a mature tool for the rapid construction of small-, medium- and large-ring carbo- and heterocycles. Consequently, the logic of modern retrosynthetic planning is strongly affected by metathesis, since this transformation can now be applied in a strategic manner to increasingly complex targets, as exemplified by metathesis-based total syntheses of polyether marine toxins, as well as by regio- and stereoselective marocyclizations of diene–enes in the epothilone series.

Intermolecular olefin metathesis starts to compete with traditional C═C-bond forming reactions such as the Wittig reaction and its modifications, as illustrated by the increasing use of electron-deficient conjugated alkenes for the (*E*)-selective construction of enals and enoates.

The use of metathesis cascades applied in various ring-rearrangement reactions allowed for an uniquely short access to various heterocyclic natural compounds, while diene–yne metathesis led to the formation of complex polycyclic structures. Also, tandem sequences combining a metathesis event with other reactions in the current synthetic repertoire such as [3,3]-sigmatropic rearrangement, Pd-catalyzed alkene coupling, or Diels–Alder reaction have been used as key steps in total syntheses of highly complex natural products. Particularly attractive tandem processes occur, when two or more sequential reactions are mediated by the same catalytic precursor. The ability of ruthenium alkylidenes to function directly or by simple modifications also as pre-catalysts for non-metathetic processes (radical additions, olefin and carbonyl hydrogenations, hydrogen transfer reactions, olefin isomerizations)[154,154a] broadens its synthetic utility toward efficient catalytic tandem sequences that combine metathesis events with one ore more non-metathesis reactions. To date, this strategy has led to highly efficient syntheses of relatively simple natural products[155] and will certainly be utilized for more complex targets in future work.

Thus far, chemists have been able to influence stereoselectivity of macrocyclic RCM through steric and electronic substrate features or by the choice of a catalyst with appropriate activity, but there exists still a lack of prediction over the stereochemistry of macrocyclic RCM. One of the most important extensions of the original metathesis reaction for the synthesis of stereochemically defined (cyclo)alkenes is alkyne metathesis followed by selective partial hydrogenation.

An area, in which catalytic olefin metathesis could have a significant impact on future natural product directed work, would be the desymmetrization of achiral molecules through asymmetric RCM (ARCM) with chiral molybdenum-(for a chiral molybdenum-based catalyst available *in situ* from commercial components, see Refs: 156 and 156a–156c) or ruthenium-based[157,157a] catalysts.

Ongoing research efforts will lead toward the arrival of even more efficient and selective metathesis catalysts with specifically tailored properties. For a ruthenium catalyst with two pyridine-ligands, see Refs: 158 and 158a–158f. Due to the synergistic relationship between catalyst design and subsequent application in advanced synthesis,[159] these progresses will further expand the scope of metathesis and its popularity among the synthetic community.

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11.08
Ene–Yne and Alkyne Metathesis

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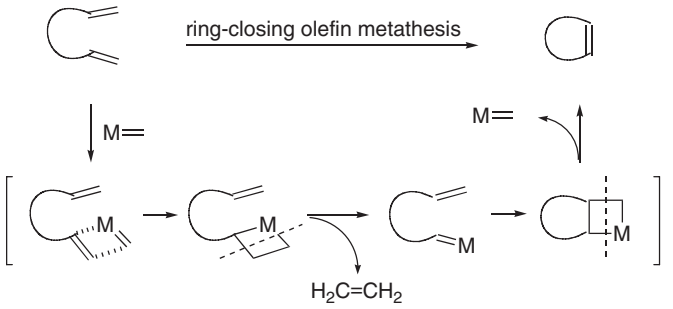
11.08.1 Ene–Yne Metathesis

11.08.1.1 Introduction

Metathesis is the most useful reaction in recent synthetic organic chemistry.[1,1a–1d] In this reaction, bond fission of two double bonds occurs and two new double bonds are simultaneously formed after exchange (Equation (1)). Ring-closing olefin metathesis is now used for the synthesis of five-membered to macrocyclic ring compounds.



(1)

Since the discovery of molybdenum and ruthenium carbene complexes by Schrock and Grubbs in 1990[2] and 1992,[3] synthetic organic chemistry has made rapid progress using metathesis reactions. Grubbs *et al*. found that molybdenum carbene complex **1a** is effective for olefin metathesis.[4] Then they synthesized ruthenium carbene complex **1b** for olefin metathesis[3] and reported results of many studies on olefin metathesis.[4,4a–4c] In 1995, Grubbs found that ruthenium carbene complex **1c** has the same reactivity as that of **1b**;[3a] it is also commercially available. Complexes **1b** and **1c** are stable and easy to handle. Thus, many researchers can use these catalysts, and various cyclic compounds have in fact been synthesized from dienes using ring-closing metathesis (RCM). In 1999, Herrmann,[5,5a,5b] Nolan,[6,6a] and Grubbs[7,7a] developed simultaneously novel ruthenium carbene complexes **1d–1g** having a heterocyclic carbene

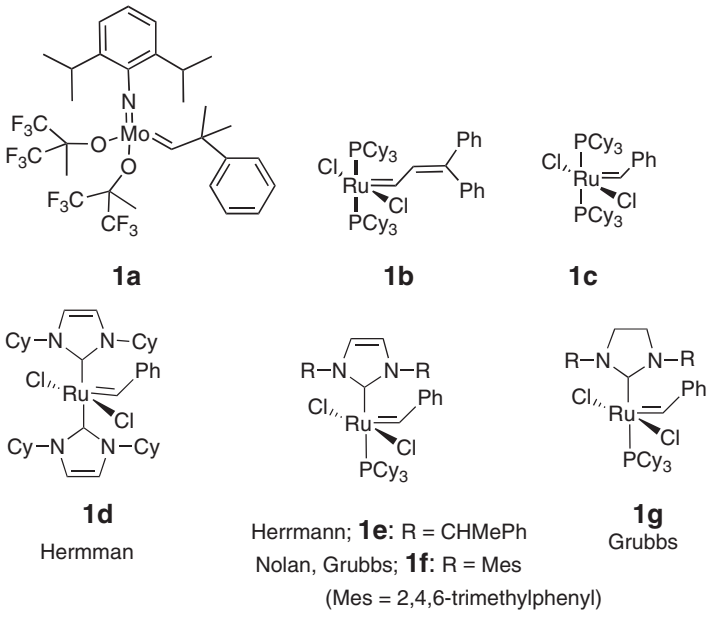
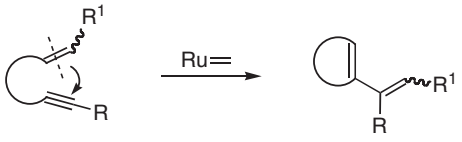


Figure 1 Mo- and Ru-carbene catalysts.

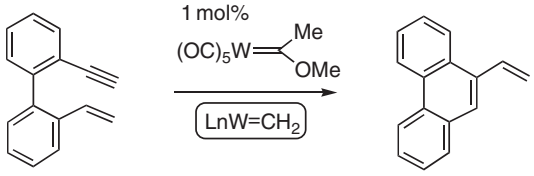
as a ligand. These catalysts are very effective for olefin metathesis compared with the first-generation ruthenium catalysts **1b** and **1c**.[8] Using these catalysts, olefin metathesis has been further developed and cross-metathesis (CM) of alkene has also been developed (Figure 1).[9,9a,9b]

Metathesis of enynes, which have alkene and alkyne moieties in the molecule, is also a very interesting reaction. In this reaction, the double bond is cleaved and carbon–carbon bond formation occurs between the double and triple bonds, and the cleaved alkylidene part migrates onto the alkyne carbon to produce a cyclic compound having a diene moiety (Equation (2)).[10,10a–10c]



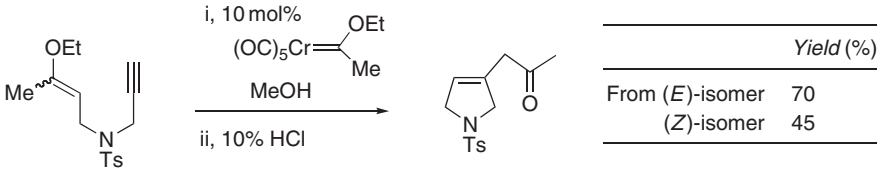
(2)

The first enyne metathesis was reported by Katz,[11,11a,11b] who used a Fischer tungsten-carbene complex. However, the reaction was shown to be catalyzed by a methylidene tungsten-carbene complex rather than the Fischer tungsten carbene complex. They proposed that the reaction would proceed by [2 + 2] cycloaddition of the tungsten carbene complex with the alkyne in Equation (3), ring opening, and another [2 + 2] cycloaddition with the alkene moiety to finally give the cyclized product.



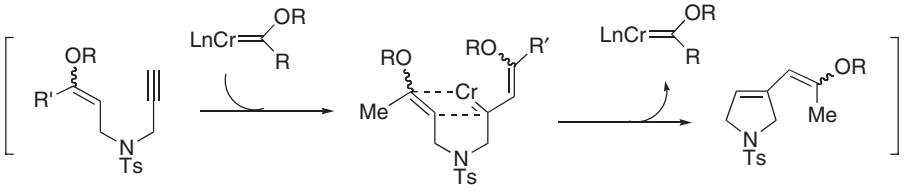
(3)

Mori has reported that a chromium carbene complex is applicable to enyne metathesis.[12,12a,12b] Since the substituent on the alkene part in the enyne substrate is the same as that on the chromium carbene complex, the reaction proceeds with a catalytic amount of the Fischer chromium carbene complex (Equation (4)).

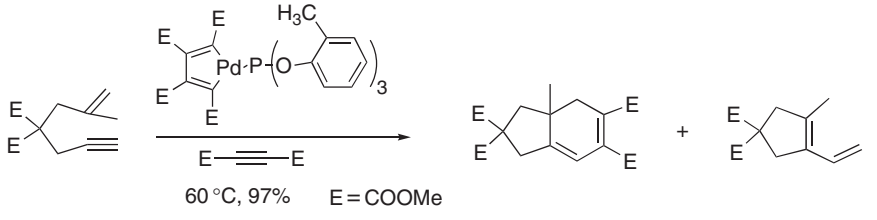


	Yield (%)
From (*E*)-isomer	70
(*Z*)-isomer	45

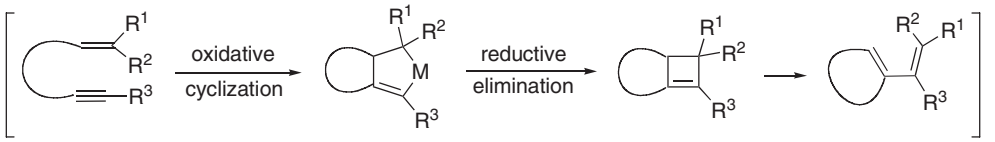
(4)

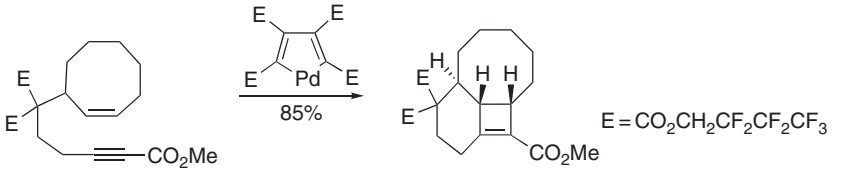


Trost and Tanoury found an interesting skeletal reorganization of enynes using a palladium catalyst.[13] In this reaction, the second product is derived from a metathesis reaction (Equation (5)). It was speculated that the reaction would proceed by oxidative cyclization of enynes with the palladium complex followed by reductive elimination and then ring opening. To confirm this reaction mechanism, they obtained a compound having a cyclobutene ring, which was considered to be formed by the reductive elimination (Equation (6)).



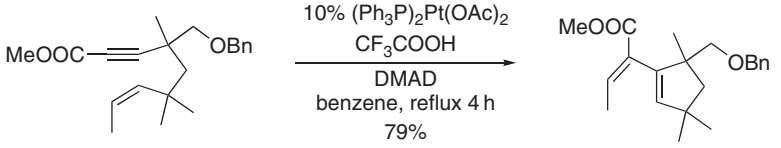
(5)





(6)

The skeletal reorganization is found by Trost to proceed by a platinum complex, but the reaction course is suggested to differ from the one previously mentioned (Equation (7)).[14]



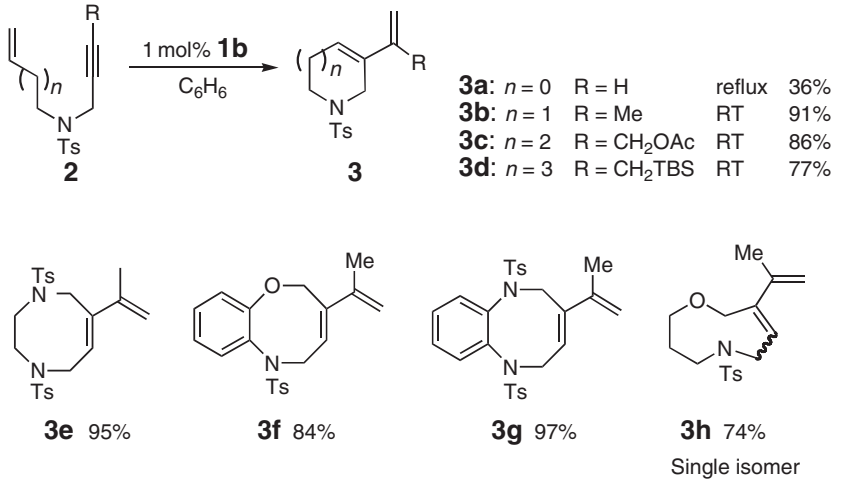
(7)

On the other hand, it has been shown that ruthenium carbene complexes **1b** and **1c** are also effective for enyne metathesis. Intramolecular reaction of enyne metathesis is now a useful method for synthesizing cyclic compounds having a diene moiety, and intermolecular enyne metathesis has provided a method for synthesis of 1,3-dienes.

11.08.1.2 Ring-Closing Metathesis

It has been shown that ruthenium carbene complex **1b** developed for olefin metathesis can catalyze RCM of enynes. Using this catalyst **1b**, five- to nine-membered ring compounds **3** are synthesized from enyne **2** (Scheme 1).[15,15a–15c] The reaction procedure for RCM of an enyne is very simple. A benzene solution of enyne **2b** is stirred in the presence of 1 mol% of ruthenium carbene complex **1b** at room temperature (RT) under argon gas to give cyclic compound **3b** having a diene moiety.

A possible reaction course is shown in Figure 2. The real catalytic species **1h** is generated from an alkyne part in **2** and carbene complex **1b** or **1c** according to the scheme shown in Figure 2. The [2 + 2] cycloaddition of **1h** and **2** gives ruthenacyclobutene **I**; ring opening of **I** gives ruthenium carbene complex **II**, which reacts with an alkene part intramolecularly to give ruthenacyclobutane **III**. Ring opening of this affords **3**, and ruthenium carbene complex **1h** is regenerated.



Scheme 1 Synthesis of heterocycles using a ruthenium carbene complex.

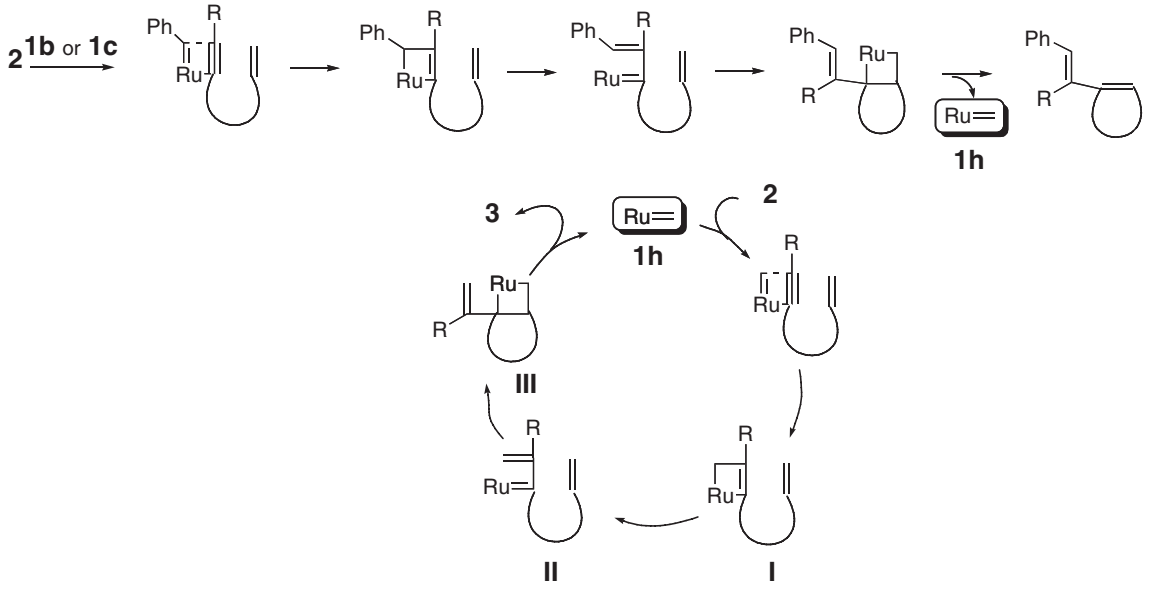
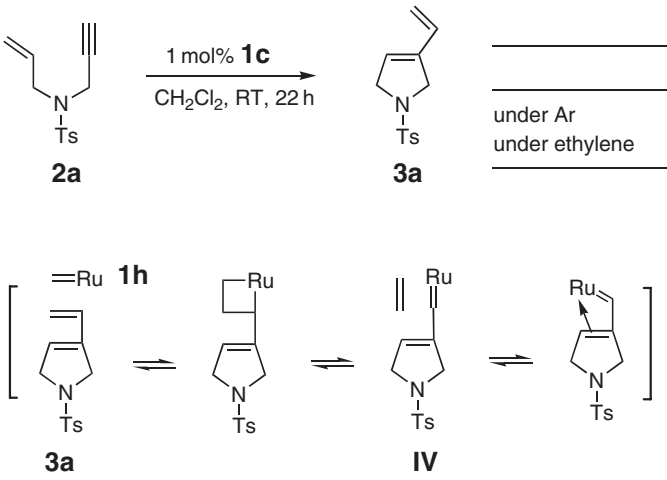


Figure 2 Possible reaction course.



Scheme 2 Reaction of enyne having teminal alkyne with **1c**.

In this reaction, enynes having a terminal alkyne do not give a satisfactory result (Scheme 2). Presumably, the alkene part in product **3a** further reacts with **1h** to afford ruthenium carbene **IV**, which would be coordinated by the alkene part of the product. Thus, the catalytic activity would decrease (Scheme 2). It is thought that if this reaction is carried out under ethylene gas, **1h** would be regenerated since the equilibrium reaction would shift to the left side because of a large amount of ethylene. When the reaction of **2a** is carried out under ethylene gas, the catalytic activity is recovered, and **3a** is obtained in 90% yield even with the use of 1 mol% of the ruthenium catalyst.[16]

In 1999, Herrmann, Nolan, and Grubbs independently synthesized novel ruthenium carbene complexes **1d–1g** (Figure 1).[5,5a,5b,6,6a,7,7a] These complexes have an *N*-heterocyclic carbene ligand in common and are called second-generation ruthenium carbene complexes. It has been shown that they are very effective for olefin metathesis particularly of dienes having substituents.[8] Thus, the reactivity of these complexes for enyne metathesis has been reexamined.[17,17a] When enyne **4a** is treated with 5 mol% of **1f**, two products are formed: one is expected metathesis product **5a** and the other is six-membered ring compound **6a**. Use of another second-generation ruthenium carbene complex **1g** (see Figure 3) gives similar results and enyne **4b** also is converted into two products **5b** and **6b**. Thus, the results are due to the use of the second-generation ruthenium carbene complex. Presumably, when methylidene carbene complex **1h** reacts with an alkyne part in **4**, two regiochemically different pathways are possible (Scheme 3). Each gives two different products. However, it is not clear why the two products result when the second-generation ruthenium carbene complex is used.

Enyne **7a** having a silyloxy group on the alkyne gives cyclic compound **8a** having a vinyl silyloxy moiety, which is converted into methyl ketone **9a** by desilylation. In a similar manner, enyne **7b** affords bicyclic methyl ketone **9b** in 68% yield after deprotection of the silyl group. However, ynoate **7c** and yne-phosphonate **7d** do not give cyclized compounds.[18] Ene-ynoate **12**, which is obtained by treatment of enol ether **11** with BuLi affords cyclic enol ether **13** in good to moderate yields[19] (Scheme 4).

Ene-ynamide **14a** gives cyclic enamide **15a**, which gives indole derivative **16a** by Diels–Alder reaction. In a similar manner, metathesis of ene-ynamide **14b**, a one carbon-elongated homolog, followed by Diels–Alder reaction, affords quinoline derivative **16b** in a high yield by a one-pot reaction (Scheme 5).[20]

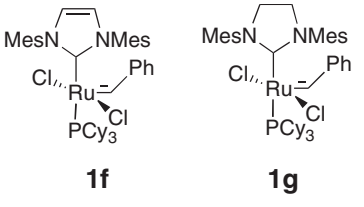
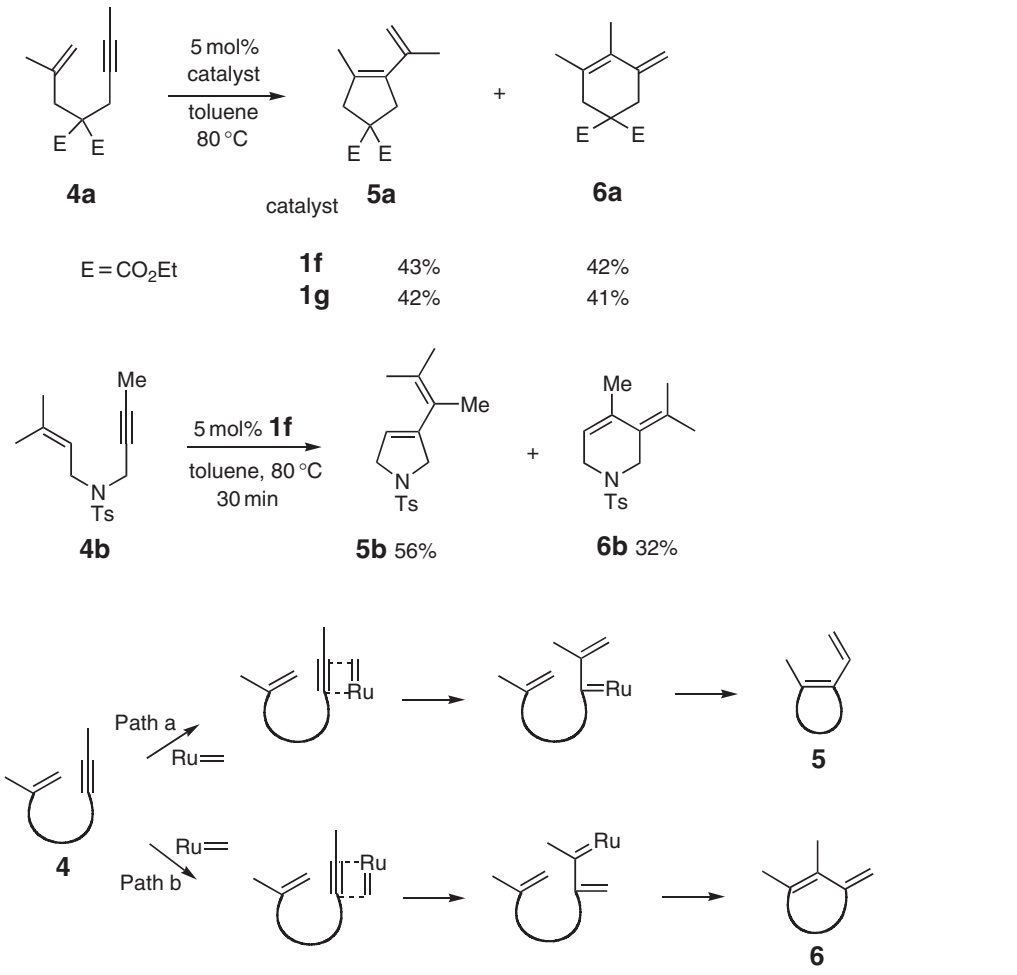
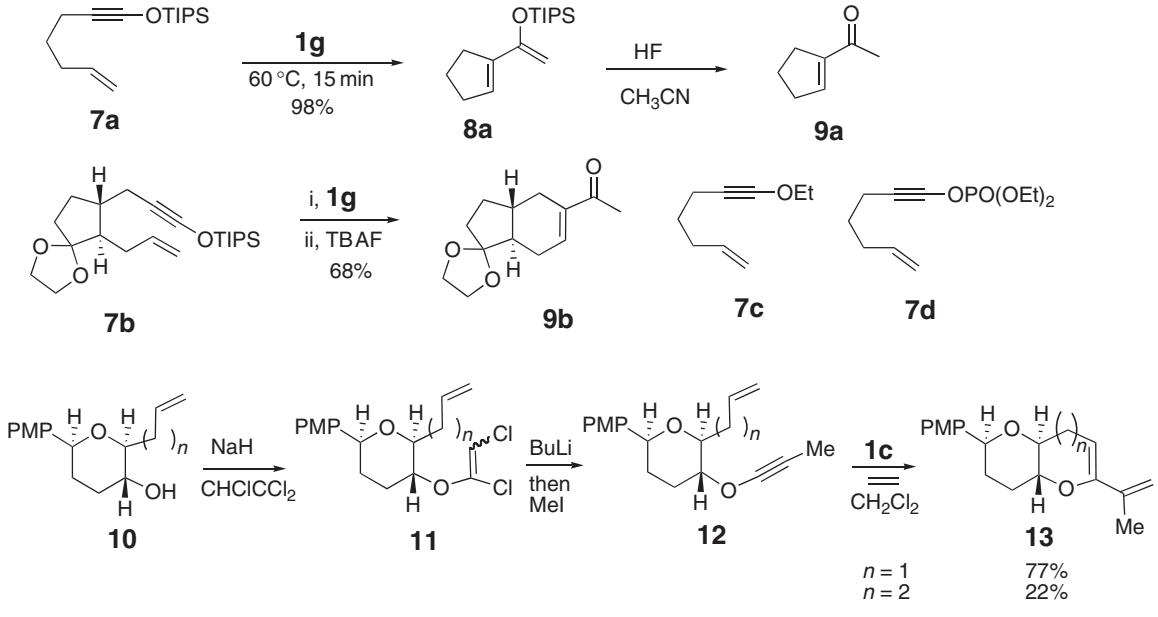


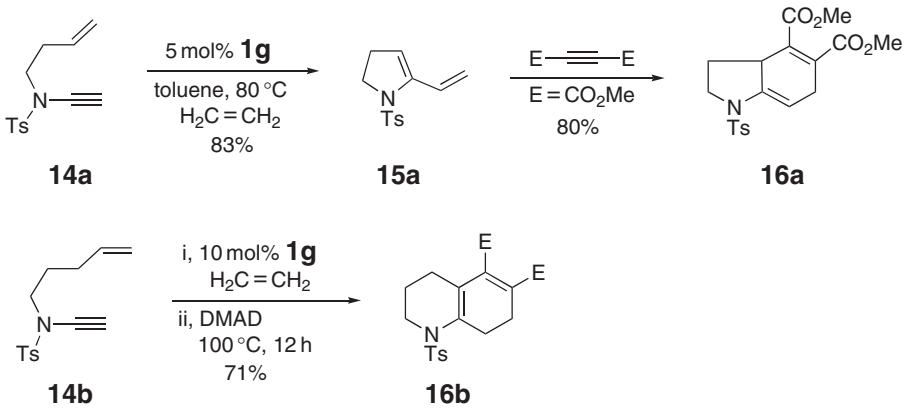
Figure 3 Typical second-generation ruthenium–carbene complexes.



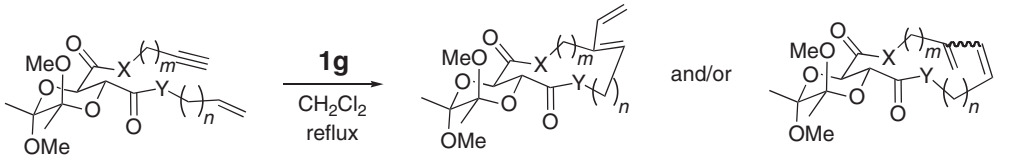
Scheme 3 Enyne metathesis using second-generation ruthenium carbene complexes.



Scheme 4 Metathesis of ene-ynoate.



Scheme 5 Ring-closing metathesis of ene-ynamide.

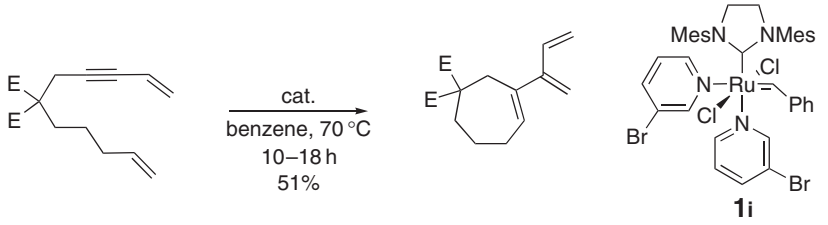


		exo (%)	*endo* (%)
$m = n = 1$	X = Y = O	52	
$m = 1, n = 2$	X = Y = O	45	45
$m = 1, n = 2$	X = NH, Y = O		35
$m = 2, n = 2$	X = Y = O		61
$m = 3, n = 2$	X = Y = O		54

Scheme 6 RCM of enyne to form macrocycles.

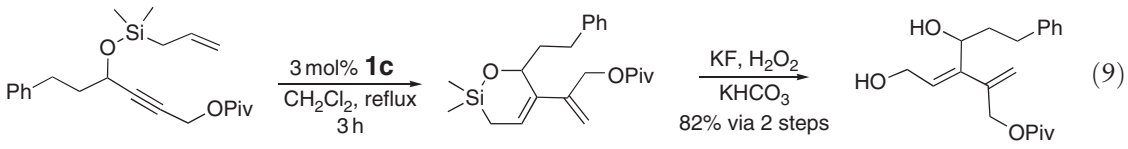
Macrocyclic compounds are readily synthesized by enyne metathesis.[21] RCM of enynes **17** to form 10-membered rings and smaller rings invariably gives *exo*-products **18**, whereas that forming 12-membered or larger rings provides *endo*-products **19** (Scheme 6).

Metathesis of conjugated enyne–enes has been carried out using bispyridine-substituted ruthenium benzylidene catalyst **1i**.[22] An intramolecular version with conjugated enynes affords novel butadienyl cycloalkenes (Equation (8)).[23] The reaction does not proceed with **1c** or **1g**.



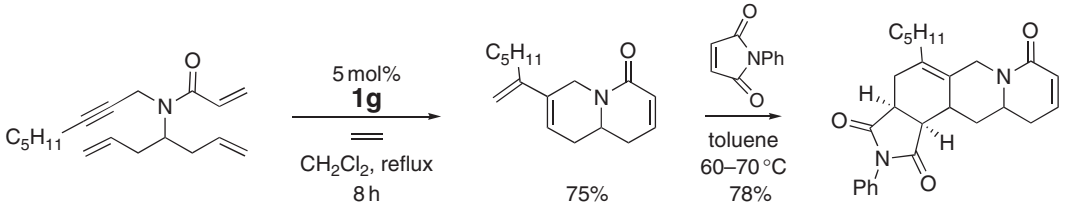
(8)

A highly functionalized conjugated diene has been synthesized through sequential silicon-tethered ring-closing enyne metathesis by ruthenium-carbene catalyst **1c** followed by Tamao oxidation (Equation (9)).[24]



(9)

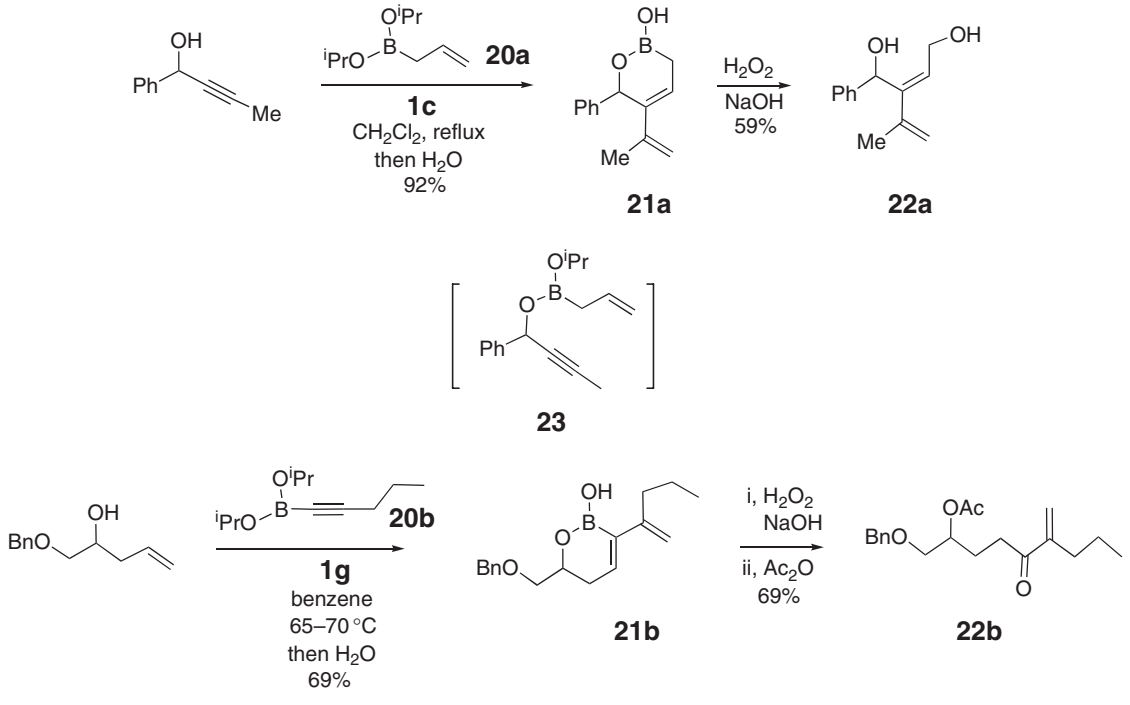
Double ring-closing metathesis using second-generation Grubbs catalyst **1g** affords a quinolizidine derivative bearing a 1,3-diene moiety in a highly regioselective manner (Equation (10)). A Diels–Alder reaction of the product with a dienophile affords an N-containing polycyclic compound.[25]



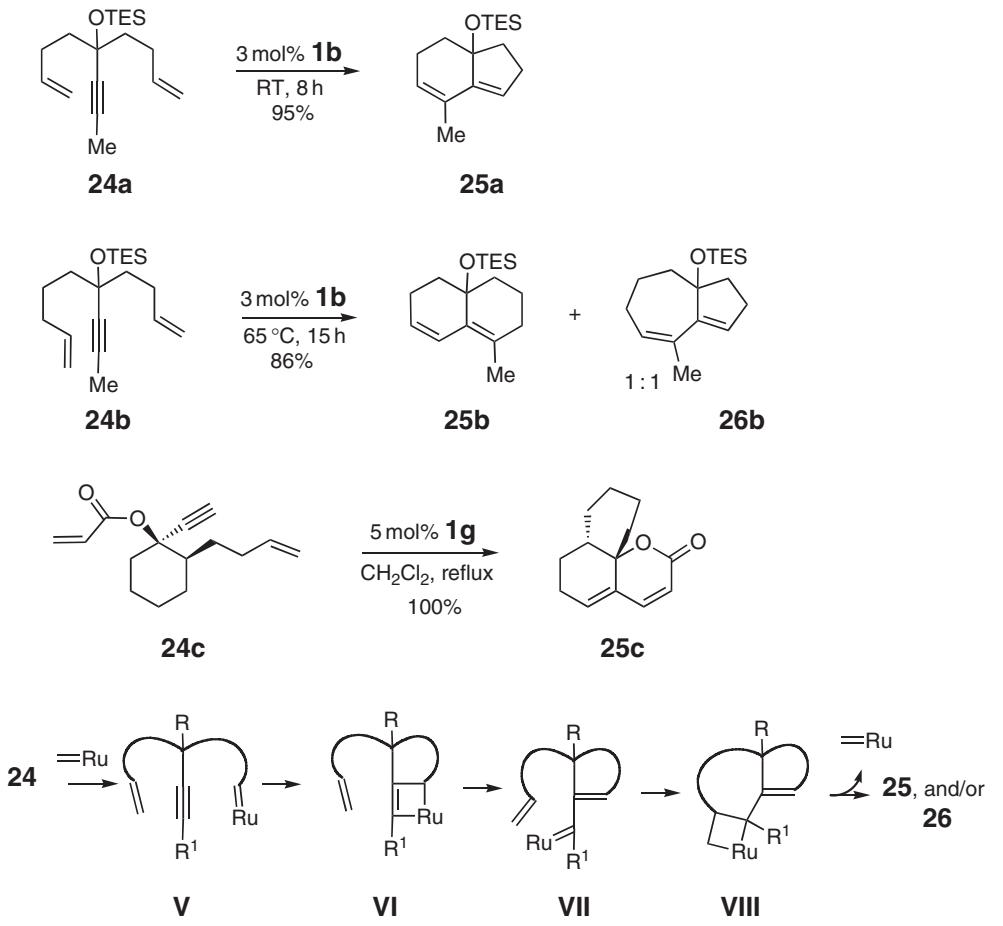
(10)

A new annulation reaction of unsaturated boronic esters with propargylic alcohol has been reported (Scheme 7).[26,26a] The reaction of propargyl alcohol and **20a** in the presence of **1c** gives cyclic boronic ester **21a**. Transesterification of **20a** and propargyl alcohol is considered to afford a mixed organoboronic ester **23**, which could be trapped through ring-closing ene–yne metathesis. Treatment of cyclic boronic ester **21a** with H_2O_2 in aq. NaOH gives diol **22a**. Electron-deficient alkynylboronic ester **20b** reacts with homoallylic alcohol to finally provide functionalized dialkenylboronic acid **21b**, which is converted into ketone **22b**.

Grubbs reported an ingenious method for synthesizing bicyclic compounds from dienynes taking advantage of the metathesis reaction (Scheme 8).[27,27a] When a benzene solution of dienyne **24a** is stirred in the presence of 3 mol% of **1b**, bicyclic compound **25a** is obtained in 95% yield in one step. In the case of **24b**, two bicyclic compounds **25b** and **26b** are formed. Furthermore, dienyne **24c** gives tricyclic compound **25c** in a quantitative yield. Probably,



Scheme 7 Boronic ester and alkynyl boric ester annulations.

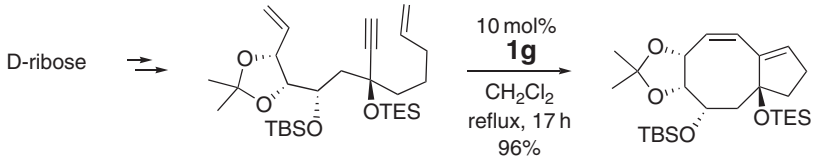


Scheme 8 Dienyne metathesis.

methylidene carbene complex **1h** reacts with an alkene part in dienyne **24** to give ruthenium carbene complex **V**, which reacts with an alkyne part to give ruthenacyclobutene **VI**. Ring opening of this complex gives ruthenium carbene complex **VII**, which reacts with an alkene part intramolecularly to give ruthenacyclobutane **VIII**. Ring opening of this complex gives bicyclic compounds, **25** and/or **26**.

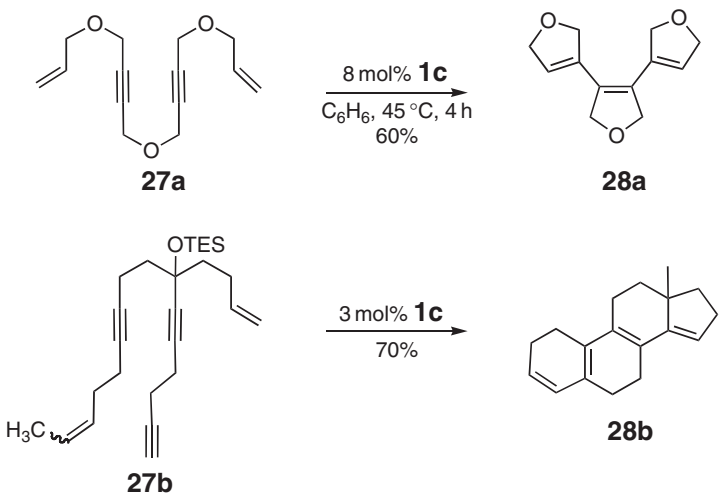
Dienyne metathesis has been further extended to the synthesis of polycyclic compounds **28** from poly ene–ynes **27** by one step (Scheme 9).[28]

Synthesis of a polyoxygenated bicyclic compound containing a medium-sized ring is achieved via tandem metathesis of the dienyne derived from D-ribose (Equation (11)).[29]

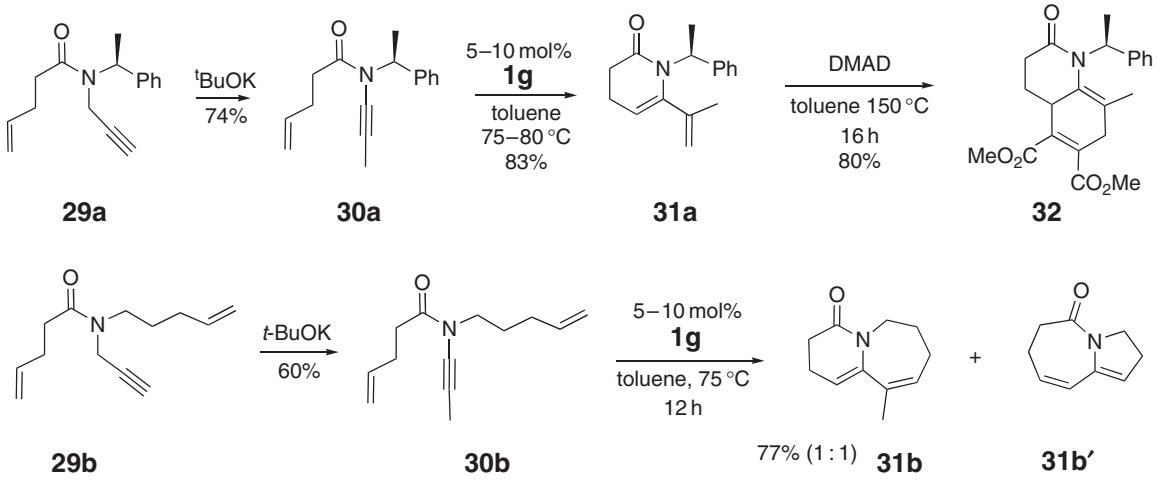


(11)

Base-induced isomerization of propargyl amide **29a** gives chiral ynamide **30a**, which is subjected to ring-closure metathesis to afford cyclic enamide **31a**. Diels–Alder reaction of **31a** with dimethyl acetylene dicarboxylate (DMAD) gives quinoline derivative **32**.[30] In a similar manner, propargyl amide **29b** is converted into ynamide **30b**, RCM of which gives bicyclic compounds **31b** and **31b′** in a ratio of 1 to 1 (Scheme 10).



Scheme 9 Synthesis of polycyclic compound by one-step reaction.

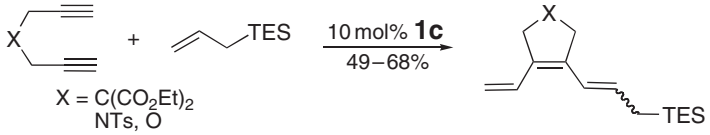


Scheme 10 Base-promoted isomerization of propargyl amide followed by RCM.

In the presence of **1g** in CH_2Cl_2, enyne **33a** having an alkynyl boronate gives alkenyl boronate **34a** in high yield. Cyclic alkenylboronate **34b**, obtained by dienyne **33b**, can be easily converted into bicyclic ketone **35** or bicyclic compound **36** having an aromatic ring using palladium-catalyzed C–C bond formation (Scheme 11).[31]

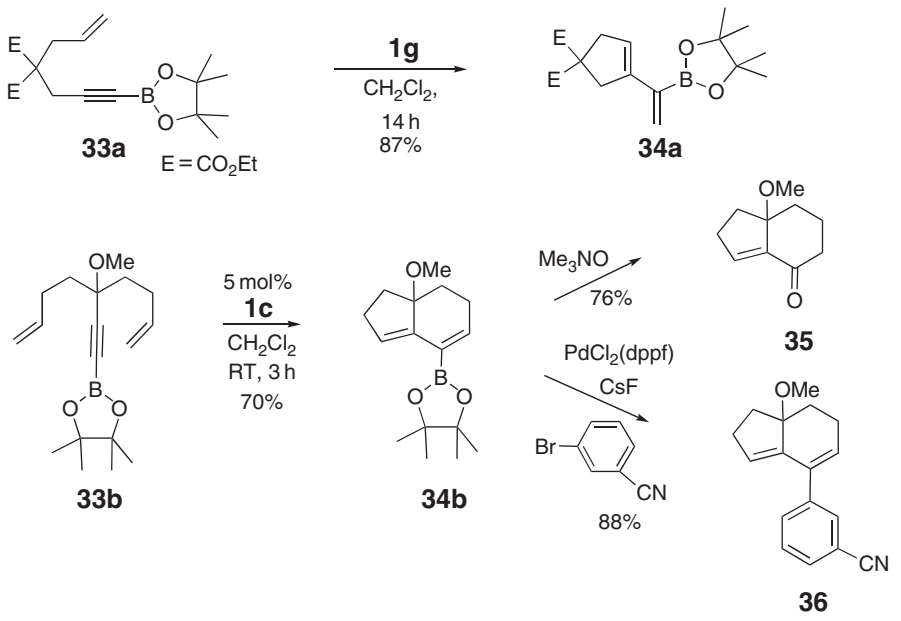
A versatile route for the synthesis of a phosphorus oxide template is presented (Scheme 12).[32] Ring-closing enyne metathesis using **1g** on these types of substrates **37a** and **37b** led to the formation of mono- and bicyclic phosphorus heterocycles **38a** and **38b**.

Diynes are treated with **1c** in the presence of an allylsilane to give cyclic trienes (Equation (12)).[33]

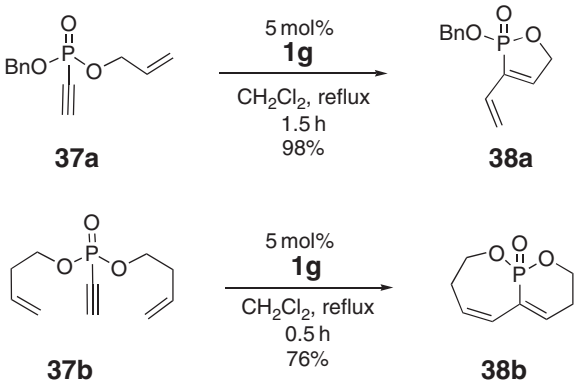


(12)

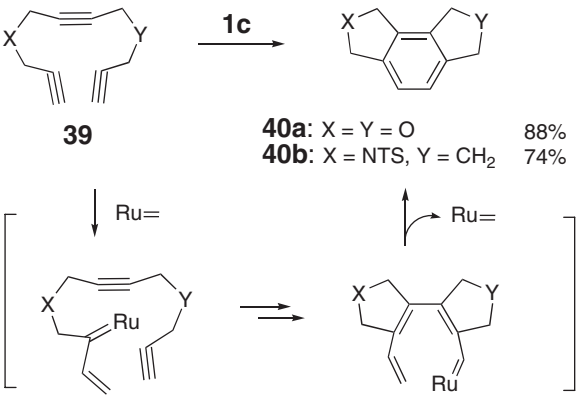
Trienes **39** can be converted into tricyclic compounds having an aromatic ring using **1c** (Scheme 13).[33a] Triple reaction of three alkynes with ruthenium-carbene complexes finally forms the tricyclic aromatic ring.



Scheme 11 Reaction of enyne having alkynyl boronate.



Scheme 12 Synthesis of phosphorus mono- and bicycles by RCM.



Scheme 13 Aromatization of triene using **1c**.

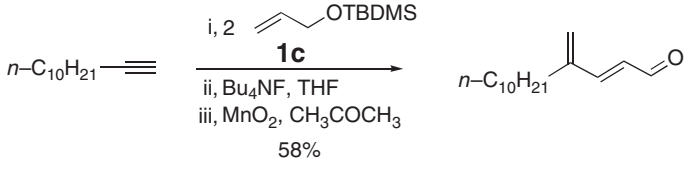
11.08.1.3 Cross-Metathesis

It is difficult to realize CM of enynes, because this reaction proceeds competitively with CM of alkene and CM of alkyne simultaneously. Thus, various CM products should be produced. Mori succeeded in the synthesis of 1,3-dienes from alkynes and ethylene through cross enyne metathesis.[34,34a] The idea is shown in Scheme 14. Ruthenium methylidene carbene complex **1h** reacts with alkyne **41** to produce ruthenacyclobutene **IX**. Ring opening of this gives ruthenium vinylcarbene complex **X**, which reacts with ethylene, not alkyne, because a large amount of ethylene is present in the reaction vessel to give ruthenacyclobutane **XI**. Ring opening of **XI** gives 1,3-diene **42** and **1h** is regenerated. The most important point of this idea is that ethylene is very reactive to ruthenium carbene complex **1c** and the reaction is carried out under an ethylene gas atmsophere.

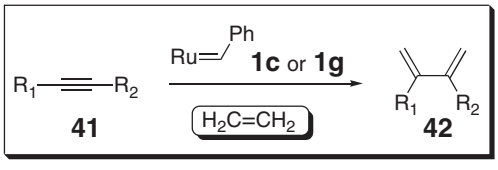
When a CH_2Cl_2 solution of alkyne **41a** is stirred under ethylene gas (1atm) at RT for 45 h, 1,3-diene **42a** is obtained in 62% yield. However, this method has a problem, and propargyl esters or amides give good results: propargyl amide **41b** is treated in a similar manner to give 1,3-diene **42b** in 81% yield, while homopropargyl amide **41c** affords 1,3-diene **42c** in only 11% yield (Scheme 15). Presumably, a heteroatom at the propargylic position is important, and the ruthenium catalyst is coordinated by the heteroatom at first and then the reaction starts to proceed.

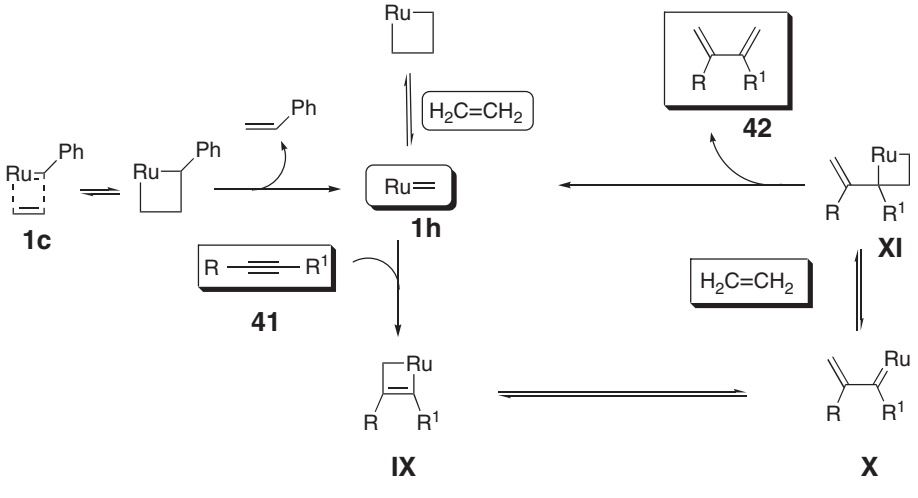
Since the second-generation ruthenium carbene complex has been developed, this unique 1,3-diene synthesis has been reexamined. The results are good in general and desired 1,3-dienes **42** are obtained in high yields in only 30 min (Table 1).[35,35a] Even silyl acetylene and alkyne having an ester group afford the corresponding 1,3-dienes (entries 4 and 5), although the first-generation ruthenium carbene complex **1c** fails to give the 1,3-dienes from these alkynes.

Blechert *et al*. succeeded in intermolecular CM of terminal alkyne and terminal alkene.[36] A reaction carried out in CH_2Cl_2 at RT in the presence of 5–7 mol% **1c** gives a mixture of (*E*)- and (*Z*)-isomers (Table 2). Because of the nonselective stereochemical course, a silyl-protected ally alcohol is employed and the resulting metathesis product is deprotected and oxidized to afford the desired diene having an *E*-configuration (Equation (13)).

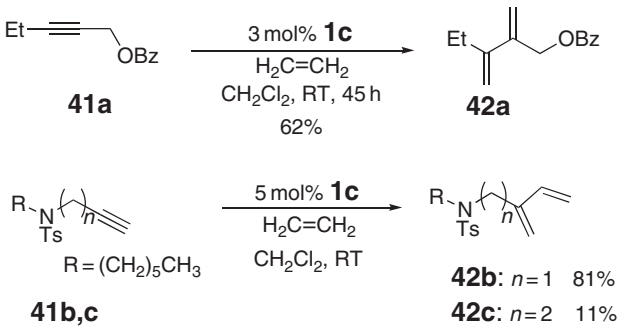


(13)



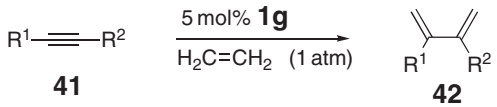


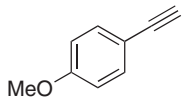
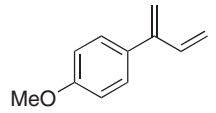
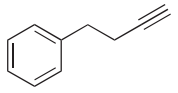
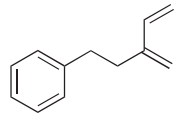
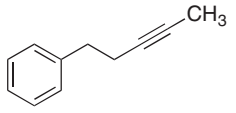
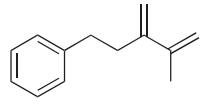
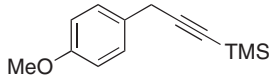
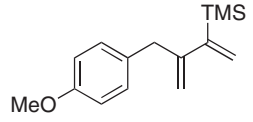
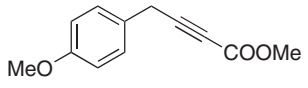
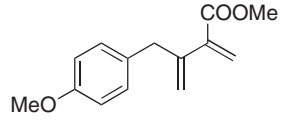
Scheme 14 Plan for synthesis of 1,3-diene using cross-metathesis.



Scheme 15 Synthesis of 1,3-diene using cross-metathesis.

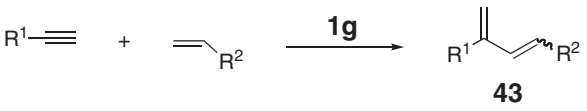
Table 1 Synthesis of various 1,3-dienes[a]



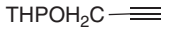
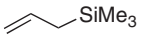
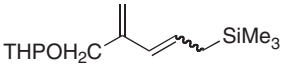
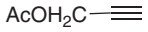
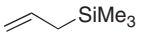
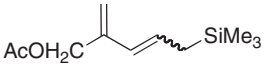
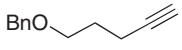
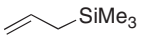
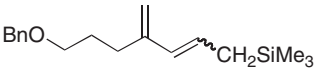
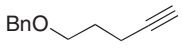
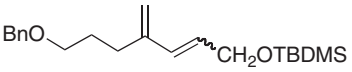
Entry	*Alkyne* **41**	*Diene* **42**	*Time* (h)	*Yield* (%)
1			0.5	88
2			0.5	71
3			0.5	85
4			16	87[b]
5			16	43[b]

[a]All reactions were carried out using 5 mol% of **1g** under 1 atm pressure of ethylene gas in toluene at 80 °C.
[b]The starting material was recovered in 10% (entry 4) and 34% (entry 5) yields, respectively.

Table 2 Synthesis of 1,3-diene from alkyne and olefin

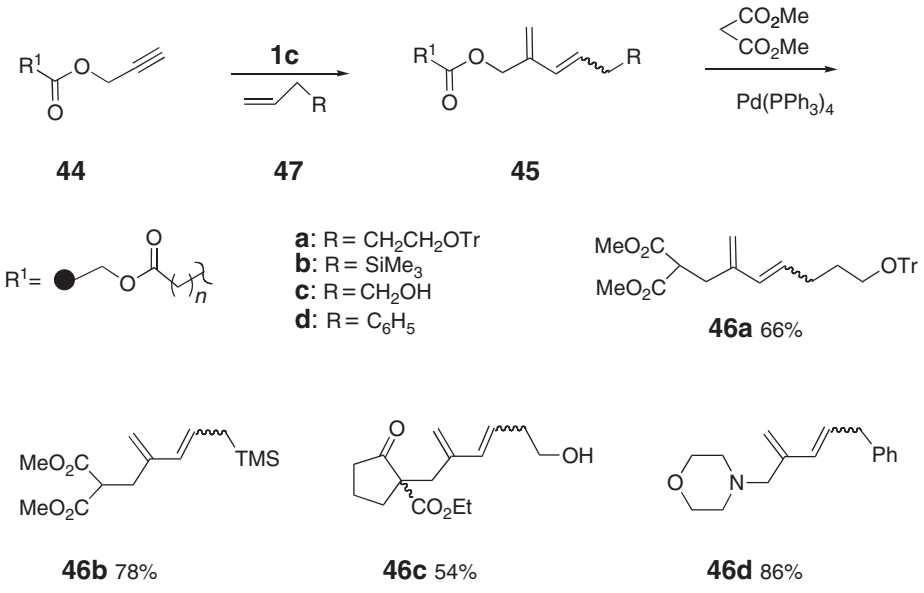


43

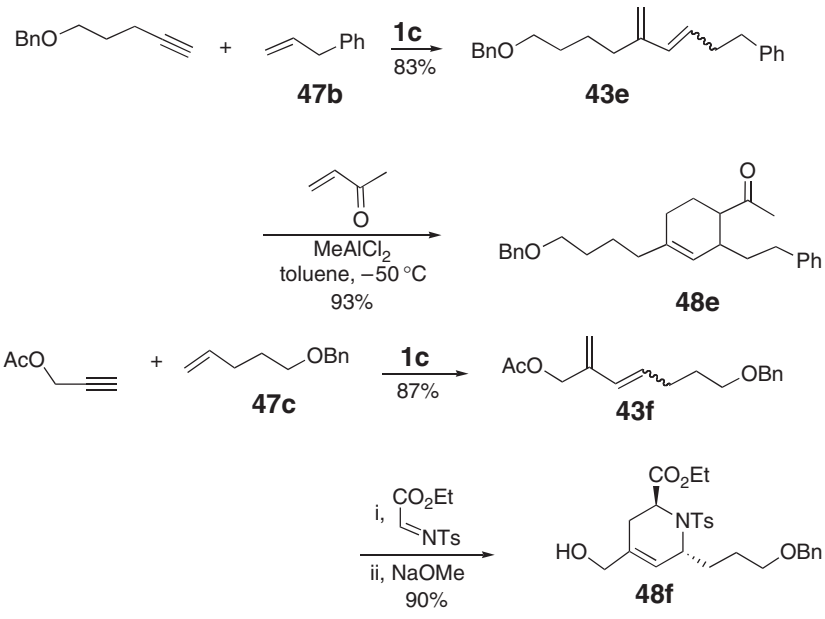
Entry	*Alkyne*	*Alkene*	*1,3-Diene*	*Yield* (%)
1				81
2				90
3				86
4				83

An excellent method for the synthesis of 1,3-diene from polymer-supported alkyne and olefin (Scheme 16) has also been reported.[37] Reaction of polymer-supported alkyne **44** and alkene **47a** in the presence of **1c** gives polymer-supported 1,3-diene **45a**, which is treated with a palladium catalyst in the presence of a nucleophile for cleavage from the polymer to give **46a** in 66% yield. In a similar manner, **46b**, **46c**, and **46d** are obtained from polymer-supported alkyne **44** in high yields. These results indicate that various kinds of nucleophiles are introduced at the diene allylic position corresponding to the propargylic position in **44** (Scheme 16).

Since the CM products have a diene moiety, Diels–Alder reaction is readily applied, and cyclic compounds **48** are available in high yields (Scheme 17).[38,38a]

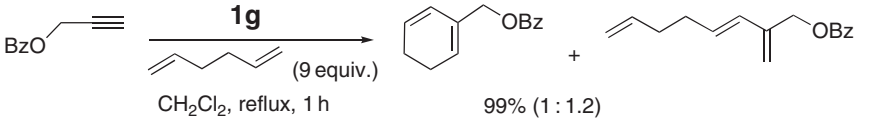


Scheme 16 Synthesis of 1,3-diene from polymer-supported propargyl alcohol and alkenes.



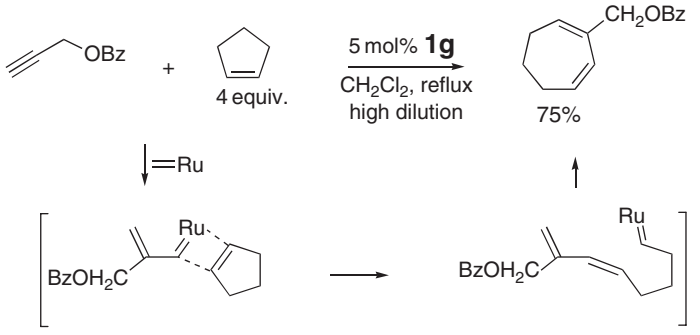
Scheme 17 Diels–Alder reaction of cross-metathesis products.

CM of propynyl benzoate and 1,5-hexadiene is carried out to produce a cyclopentadiene derivative and a triene in 99% yield in a ratio of 1 to 1.2. The former compound is apparently derived from a (*Z*)-isomer of the triene by further metathesis (Equation (14)).[39]



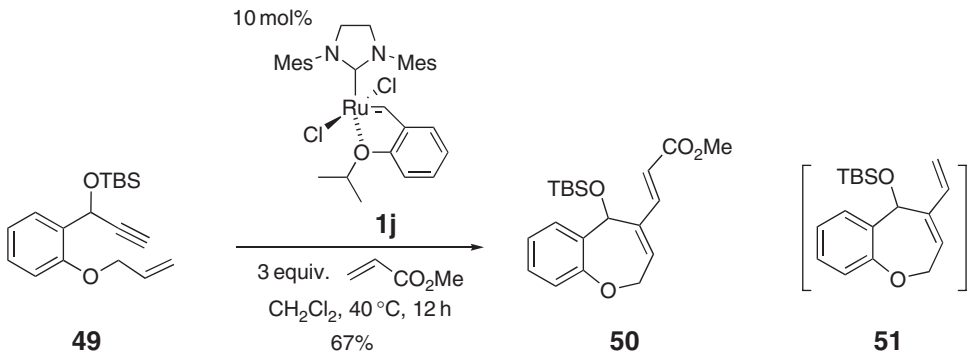
(14)

CM of propynyl benzoate and cyclopentene in excess was carried out by the same group (Equation (15)). Ring opening of cyclopentene with ruthenium carbene complex **1g** followed by intramolecular RCM takes place to give cycloheptadiene in good yield.[40]



(15)

One-pot RCM–CM reaction was carried out by Royer *et al.* (Scheme 18).[41] The RCM of **49** followed by CM with methyl acrylate gives cyclic compound **50** using ruthenium-carbene complex **1j**[42,42a] via CM of intermediate **51** with methyl acrylate.



Scheme 18 RCM followed by CM.

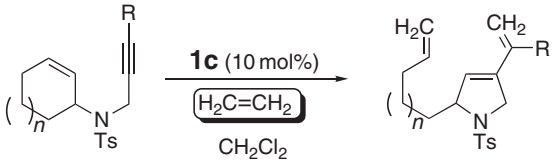
11.08.1.4 Tandem Cyclization (ROM–RCM, ROM–CM)

Tandem cyclization of enyne proceeds via ring-opening metathesis (ROM) followed by RCM and/or CM is a very useful transformation, because different rings are formed from the starting cycloalkene via many steps by a single operation. Mori reported such tandem cyclization of cycloalkene–ynes.[43,43a] When cycloheptene–yne **52a**, whose substituent is placed at the 3-position of cycloalkene, is reacted with the first-generation ruthenium-carbene complex **1c** in CH_2Cl_2 under ethylene gas at RT for 24 h to give pyrrolidine derivative **53a** in 56% yield (Table 3, entry 1). Similarly, various cycloalkene–ynes **52** give pyrrolidine derivatives **53** in high yields by the one-step reaction.

The reaction is considered to proceed via cycloaddition of an alkyne part of **52** with **1h** to afford ruthenacyclobutene **XII** (Scheme 19) and then ring opening of **XII**, giving the ruthenium carbene complex **XIII**, which further reacts with an olefin part of the cycloalkene ring to afford highly strained cyclobutane **XIV**. Ring opening of this gives the ruthenium carbene complex **XV**. CM of **XV** with ethylene gives pyrrolidine derivative **53**. In each case, a pyrrolidine ring is formed and the chain length of the substituent of the pyrrolidine ring depends naturally on the ring size of the original cycloalkene. Formally, the double bonds of ethylene and cycloalkene are cleaved, and carbon–carbon bond formation occurs at the alkyne and cycloalkene carbons, and the two methylene parts derived from ethylene are introduced at the alkene and alkyne carbons, respectively, to give the pyrrolidine derivative **53** (Figure 4).

Cyclopentene–ynes **54a** and **54b** having *cis*- or *trans*-substituents on the cyclopentene are reacted with **1c** under ethylene gas to give pyrrolidine derivatives **55a** and **55b**, respectively, in high yields. The reaction proceeds in a highly stereoselective manner. However, under similar reaction conditions, cyclohexene–yne **54c** having *cis*-substituents on the cyclohexene ring gives selectively triene **56**, which is a CM product of an alkyne part and

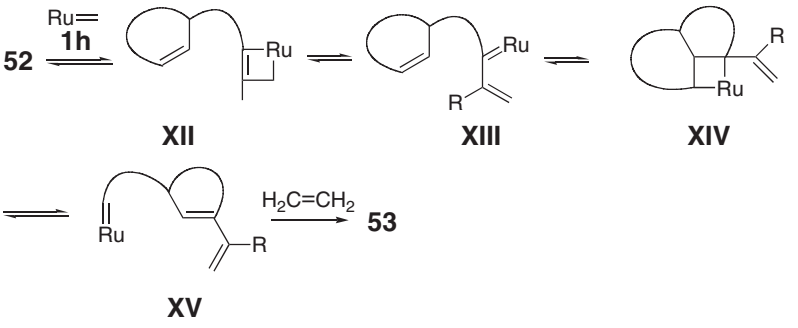
Table 3 ROM–RCM of Cycloalkene–yne



52 53

Entry		*R*	*Ring size*	*n*	*Time* (h)		*Yield* (%)[a]
1	**52a**	Me	7	2	24	**53a**	56[b]
2	**52b**	H	6	1	4	**53b**	78
3	**52c**	H	7	2	1	**53c**	70
4	**52d**	H	8	3	1	**53d**	75

[a]Yields were calculated from ^{1}H NMR.
[b]**52a** was recovered in 36% yield.



Scheme 19 Reaction course of ROM–RCM of cycloalkene–yne.

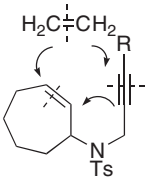
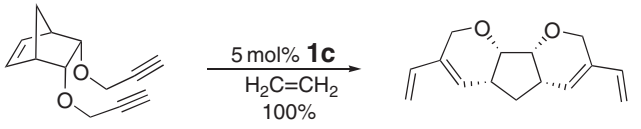


Figure 4 Formal reaction course.

ethylene. Presumably, the double bond in the cyclohexene moiety cannot approach the ruthenium carbene site due to steric hindrance (Figure 5). On the other hand, cycloalkene–yne **54d** having *trans*-substituents affords pyrrolidine derivative **55d** via ROM–RCM and then CM with ethylene. Deprotection of the silyl group followed by the Dess–Martin oxidation gives tricyclic compound **57** via the Diels–Alder reaction (Scheme 20).

Blechert carried out a tandem reaction of enynes in the presence of olefins instead of ethylene (Scheme 21).[44,44a] Treatment of cyclopentenol derivative **58a** with **1c** in the presence of an alkene affords **59a**. The five-membered ring in estrone **58b** is cleaved by **1c** to give **59** and an alkene part is introduced on the six-membered C ring. However, cycloalkenyl amine derivative **60** is treated in a similar manner in the presence of an allyl alcohol derivative to give pyrrolidine derivative **61**, and in this case, an alkene part is introduced on the diene moiety. Presumably, ruthenium carbene complex **XVI** reacts with an alkyne part to produce the pyrrolidine ring with a regioselectivity opposite to the other cases.

North and Banti observed double-ring-opening metathesis of dialkynylcycloalkenes and obtained a tricyclic compound from a norbornene derivative shown in Equation (16).[45,45a]

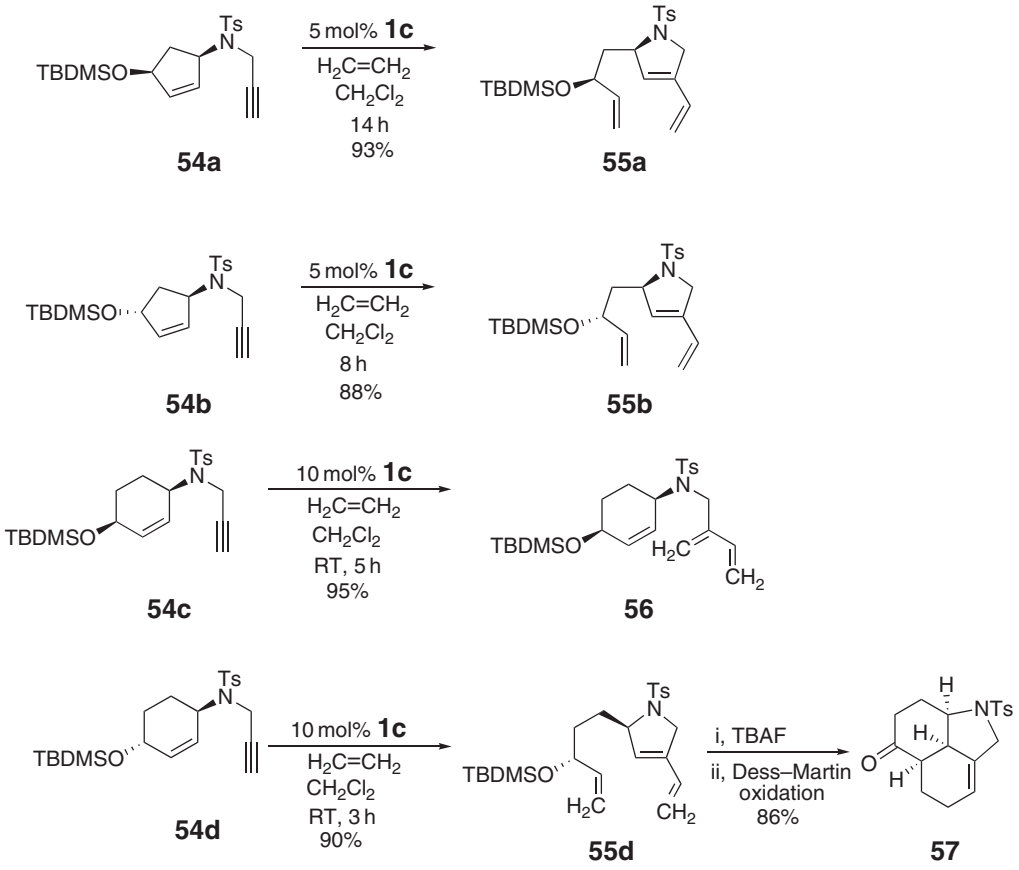


(16)

Plumet *et al.* described domino metathesis of propargyl (2-endo-7-oxanorborn-5-enyl) ethers **62a–62c** with allyl acetate in the presence of Grubbs' ruthenium catalyst **1c** (Scheme 22). The reaction proceeds stereoselectively to produce substituted *cis*-fused bicyclic ethers **63a–63c**.[46,46a] In a similar manner, indolizidinone derivative **64** is obtained from compound **62d** instead of pyrrolizidine derivative **63d**.[46a]

If cycloalkene–yne **65** having an ω-alkynyl substituent at an olefinic position in a cycloalkene is treated with a ruthenium catalyst, what kinds of products are produced? In this reaction, ruthenium mono-substituted carbene complex **XVII** is anticipated to be formed from a highly strained ruthenacyclobutane intermediate. If it then reacts with ethylene, triene **67** should be formed, but if **XVII** reacts with an alkene part intramolecularly, bicyclic compound **66** should be formed via ruthenacyclobutane (Scheme 23).

In fact, when a cyclohexene–yne **65a** is treated with **1g** under an ethylene gas atmosphere, three products are produced. An expected bicyclic compound **66a** is obtained in only 14% yield, and a major product (57%) is an unexpected bicyclic compound which turned out to be **66b**. In addition, dimeric compound **68** is formed in 26%



Scheme 20 ROM–RCM of cycloalkene–ynes.

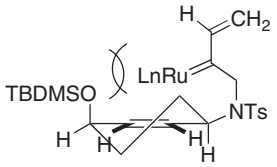
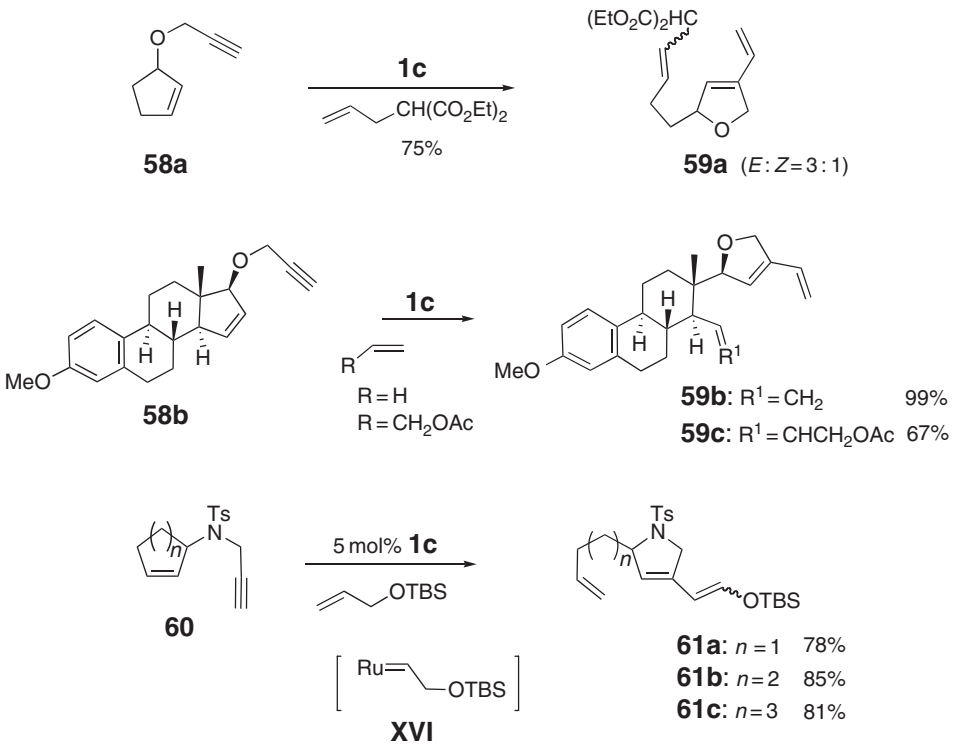


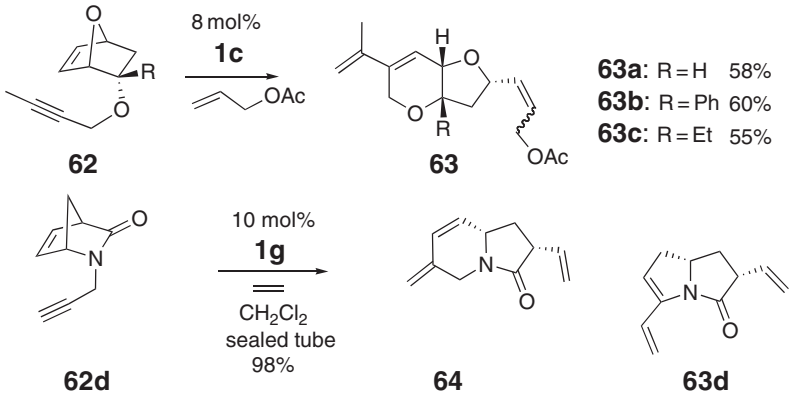
Figure 5 Steric repulsion between ruthenium–carbene complex with the silyloxy group in trans-substituents.

yield. When the dimeric compound **68** is further treated with **1g** under ethylene gas, bicyclic compounds **66b** and **66a** are obtained in 39% and 21% yields, respectively, along with **67a** in 9% yield. In this reaction, the two double bonds in 16-membered ring of **68** must be cleaved by **1g** to give bicyclic compounds **66a** and triene **67a**. On the other hand, isomerization of the double bond of **67a** followed by RCM gives **66b**, which should be a thermodynamic product under these reaction conditions. Cyclopentene analog **65b** is found to give only bicyclic compound **66b** in a quantitative yield (Scheme 24).[47,43a] In this reaction, bicyclic compound **66b** is formed from cycloalkene–yne **65b**. This means that, formally, the cyclopentene ring in **65b** is cleaved and two carbon–carbon bonds are formed between the double and triple bonds, respectively, to produce **66b** (Figure 6). Ring size of the cycloalkene formed in this reaction corresponds to the carbon number of the original cycloalkene plus two carbons.

If quinoline derivatives are expected to be synthesized by this procedure, the starting cycloalkene should contain a cyclobutene ring. When cyclobutene derivative **65c** is reacted with **1g** under ethylene gas, isoquinoline derivative **66c** is obtained in 60% yield. Furthermore, cyclic amino acid ester **66d** is obtained from glycine derivative **65d** in 75% yield by a one-step reaction. Various isoquinolone derivatives **66e–66i** are also synthesized from cyclobutenyl amides



Scheme 21 Mechanism switch in ROM–RCM followed by CM.

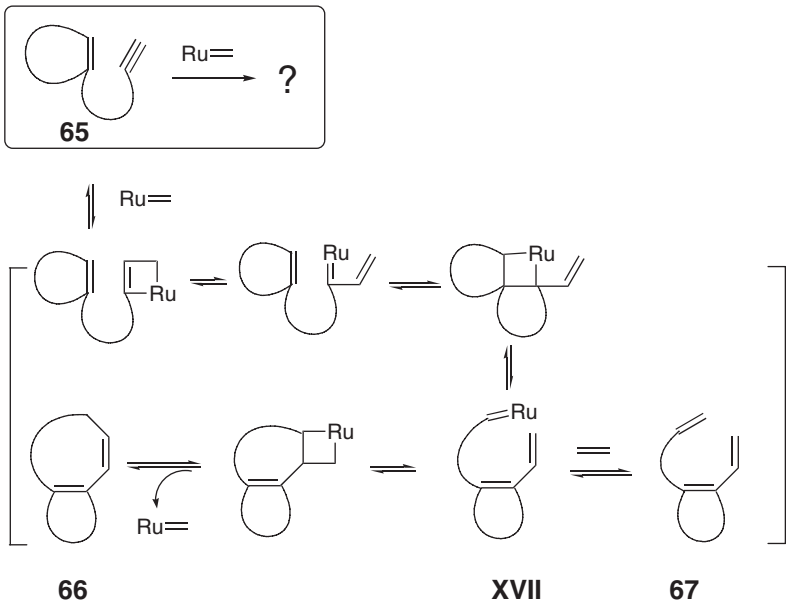


Scheme 22 ROM–RCM followed by CM of cycloalkene–yne.

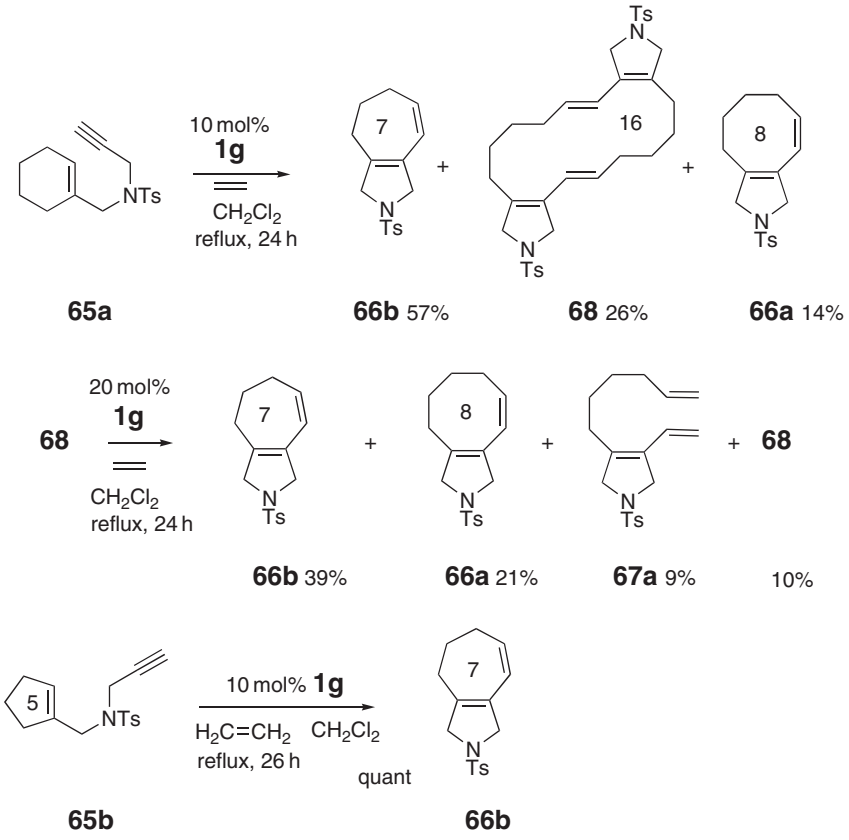
65g–65i including those having an aromatic ring at the terminal alkyne in high yields. The aryl group is placed at C-5 of isoquinolone (Scheme 25).[48]

11.08.1.5 Skeletal Reorganization with Metal Complex

Trost reported the first example of skeletal reorganization using palladium and platinum complexes.[13,14] In 1994, Murai and Chatani reported skeletal reorganization of 1,6-enynes using $[RuCl_2(CO)_3]_2$ as a catalyst (Scheme 26).[49] When the reaction of (*E*)-69a (*E*/*Z* = 80/20) is carried out in the presence of $[RuCl_2(CO)_3]_2$ under carbon monoxide, the (*E*)-isomer 70a is produced predominantly. It is interesting that from (*Z*)-69a (*E*/*Z* = 11/89) also gives (*E*)-70a. Similarly an *E*/*Z* mixture of 1,7-enyne 69b affords only (*E*)-isomer of 70b in 86% yield.



Scheme 23 Plan for ROM–RCM of cycloalkene–yne having a substituent at the 1-position.



Scheme 24 ROM–RCM of cycloalkene-ynes.

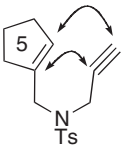
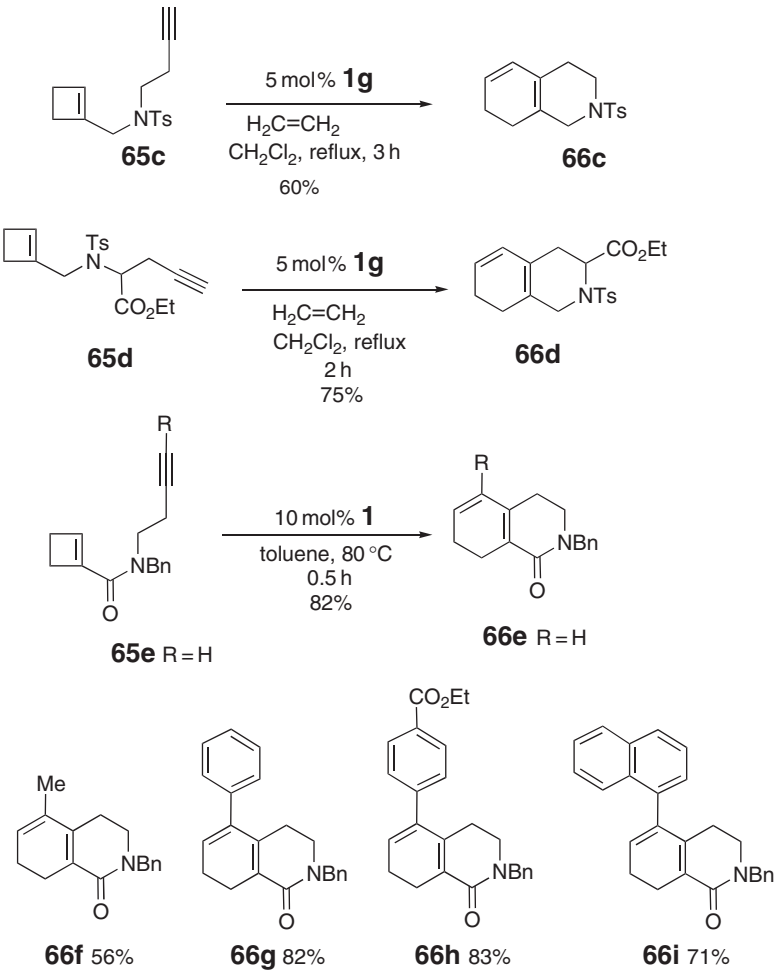


Figure 6 Formal reaction course in ROM–RCM of cycloalkene–yne.

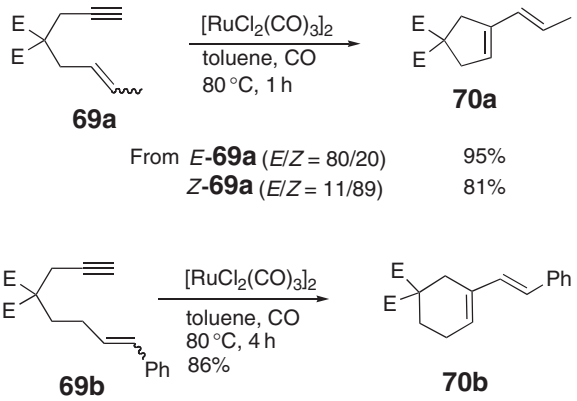


Scheme 25 Synthesis of isoquinoline derivatives.

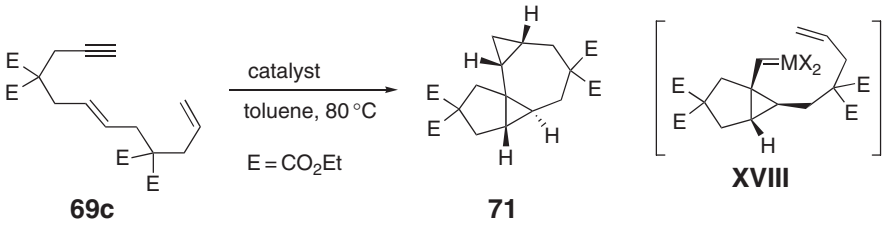
Murai and Chatani speculated that the two acetylene carbons should be converted into two carbene equivalents to give **XVIII** during the reaction.[49a] To trap this intermediate, the reaction of 6,11-dien-1-yne **69c**, which has an olefin moiety in a tether, is carried out in the presence of $[RuCl_2(CO)_3]_2$ in toluene at 80 °C for 4 h to give tetracyclic compound **71** in 84% yield. It is interesting to note that other transition metal complexes, such as $PtCl_2$, $[Rh(OOCCF_3)_2]_2$, $[IrCl(CO)_3]_n$, and $ReCl(CO)_5$ also show catalytic activity for this very complex transformation (Scheme 27).

Dixneuf used $[RuCl_2(p\text{-cymene})]_2$ as a catalyst for the reaction of enyne **72a** in the presence of imidazolium salt and Cs_2CO_3 and obtained the enyne metathesis product **73a** in a high yield.[50,50a] The enyne silyl ether **72b** is converted under similar reaction conditions into *spiro*-compound **73b** which after the Tamao oxidation gives diol **74** (Scheme 28). In this reaction, *N*-heterocyclic carbene should be generated to coordinate to the ruthenium metal, but the actual species for this reaction is not well documented.

$PtCl_2$ constitutes an efficient and practical catalyst for skeletal rearrangement reaction of enynes. This includes a formal enyne metathesis reaction delivering 1,3-dienes. Skeletal reorganization of enyne **75a** having a carbon chain in

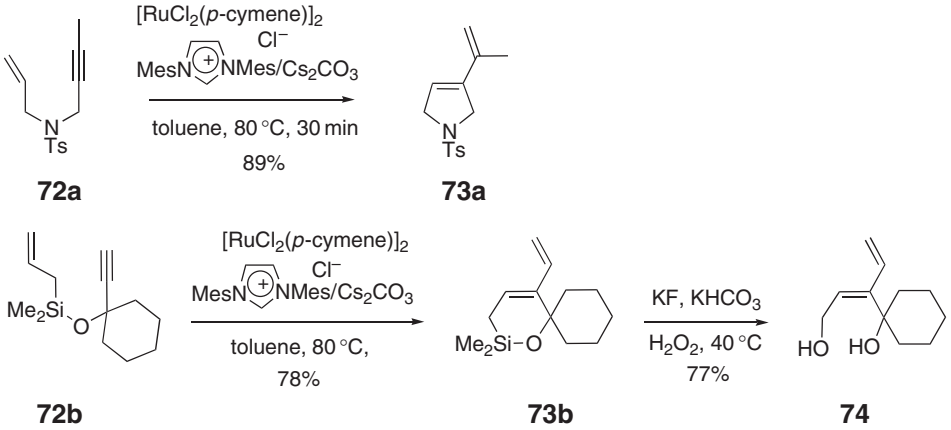


Scheme 26 Ruthenium-catalyzed skeletal reorganization.



Compound	*Time*	*Yield* (%)
$[RuCl_2(CO)_3]_2$	4 h	84
$PtCl_2$	4 h	75
$[Rh(OCOCCF_3)_2]_2$	1 h	72
$[IrCl(CO)_3]_n$	4 d	54
$ReCl(CO)_5$	1 d	74

Scheme 27 Trapping of carbenoid intermediate.

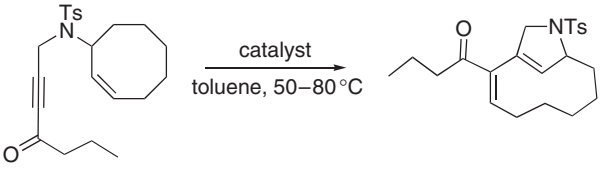


Scheme 28 Enyne metathesis using $[RuCl_2(p\text{-cymene})]_2$.

a tether takes place in the presence of $PtCl_2$ to give formal metathesis product **76a** in high yield.[51,51a,51b] However, enyne **75b** containing a nitrogen atom in a tether between the alkene and alkyne moieties leads to the formation of bicyclo[4.1.0] heptene **77b** and a small amount of 1,3-diene **76b** originating from simple CM. Furthermore, enyne **75c** having cycloheptene in a tether containing a nitrogen atom gives tricyclic compound **77c** and standard CM product **76c** in 32% and 59% yields, respectively. Enyne **75d** containing an oxygen atom in a tether gives only **77d** in moderate yield (Scheme 29).

The reaction is considered to be initiated by π-complexation of Pt(II) onto an alkyne unit in substrates (Scheme 30).[51a] A strong experimental support for the proposed mechanism comes from deuterium labeling. When geminally D-labeled **75e-2D** is treated with $PtCl_2$, **77e-2D** and **77e-D** are obtained. Formation of **77e-2D** indicates that the reaction proceeds through **XX** and then **XXI** by hydrogen migration.

Surprisingly, in some cases, simple Lewis or Brönsted acids as the catalysts can replace the $PtCl_2$ catalyst (Equation (17)).[51a]

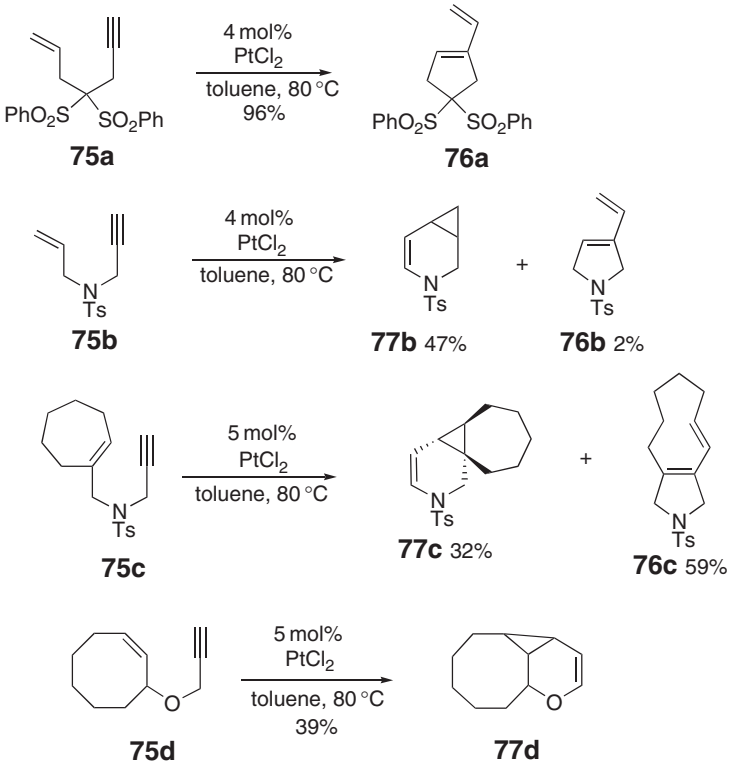


Catalyst	*Yield* (%)
$PtCl_2$	79
$BF_3{\cdot}Et_2O$	64
HBF_4	57

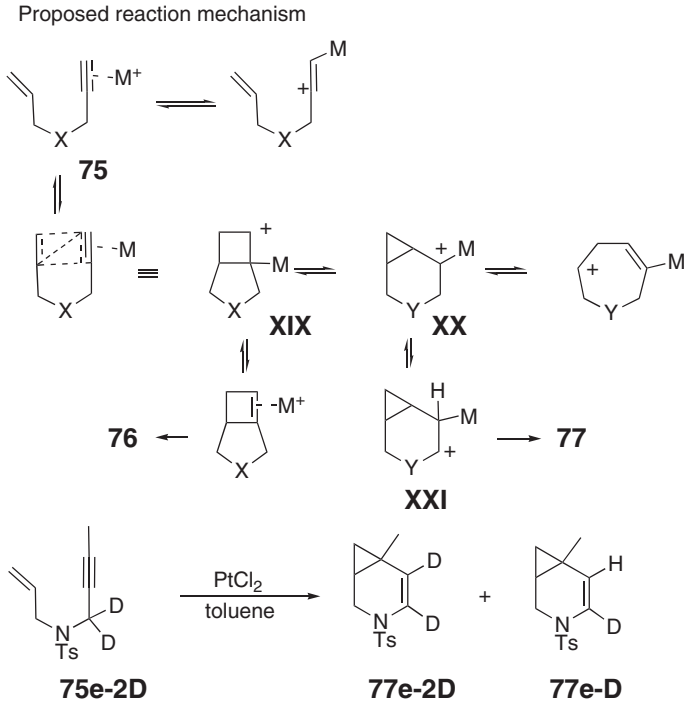
(17)

Murai *et al.* also reported a platinum-catalyzed skeletal reorganization of 1,6-enyne **78** to 1-vinycyclolalkene **79**.[52] The reaction of **78b** with $PtCl_2$ gives **79b** and **80b** (ratio of 8 to 1). Formation of **80b** is intriguing with respect to reaction mechanism, because it should involve an unusual reorganization in bond connection. An anomalous C–C bond formation is suggested in the reaction of **78a-D**. Formation of **80a-D** indicates the occurrence of unusual bond fission. The platinum-catalyzed reaction of **78c** gives exclusively bicyclic compound **79c** in 97% yield (Scheme 31).

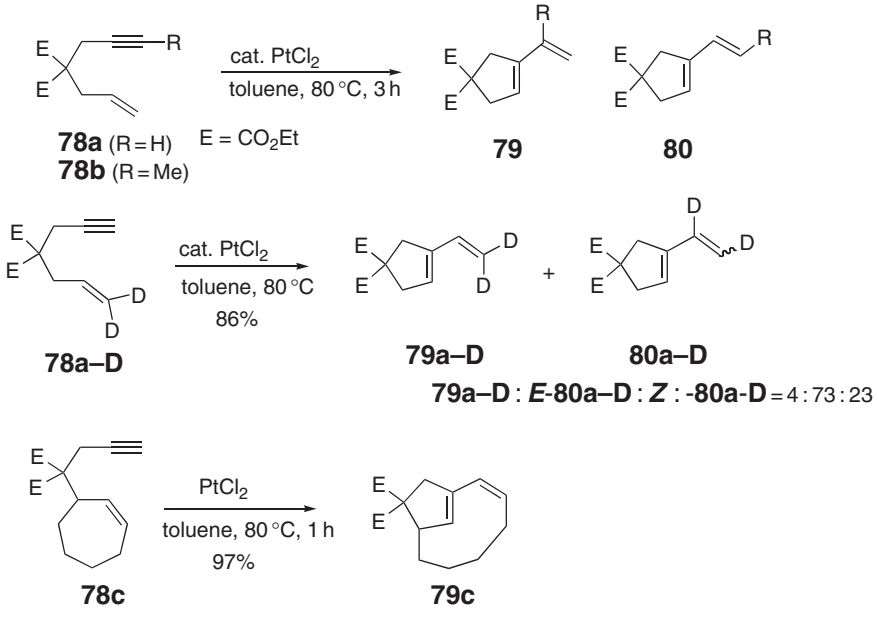
Iridium complex $[IrCl(CO)_3]_n$ also catalyzes skeletal reorganization of enyne **78d** to **79d** (Scheme 32).[53] In contrast, enyne **78e** having a methyl group on an alkyne terminal fails to give any products under the same reaction. Use of



Scheme 29 Formation of cyclopropane derivatives catalyzed by $PtCl_2$.



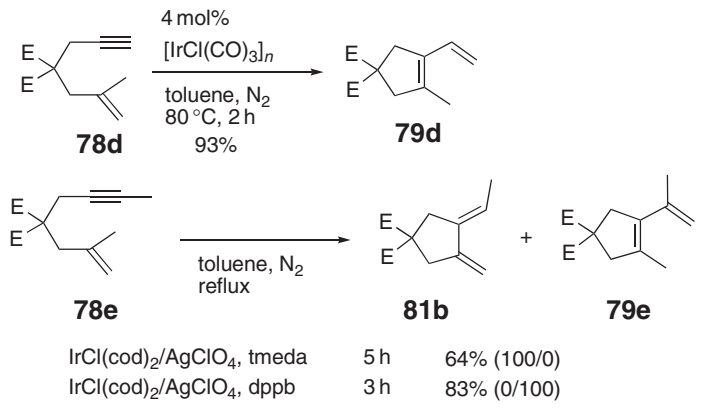
Scheme 30 Deuterium labeling experiment.



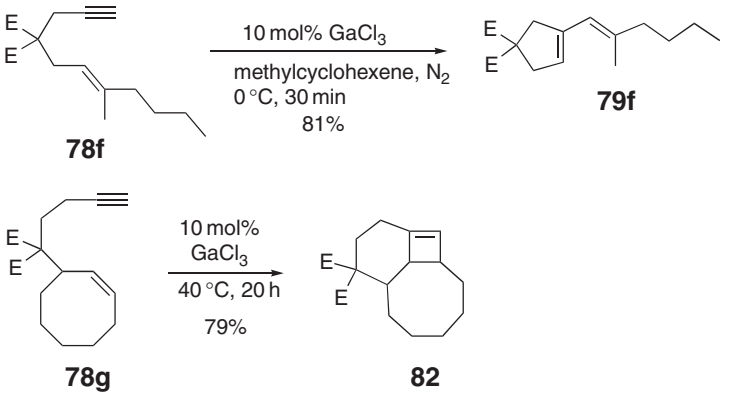
Scheme 31 Platinum-catalyzed skeletal reorganization.

such an additive as $AgClO_4$/tmeda or dppb drastically improves the reaction efficiency to give **81b**, whereas use of dppb gives only metathesis product **79e**.

Very recently, the same group reported skeletal reorganization of enynes to 1-vinylcycloalkene by $GaCl_3$.[54] Reaction of **78f**, for example, proceeds in toluene at 0 °C and is completed within 1 h to give **79f**. It is interesting that highly strained cyclobutene derivative **82** is obtained from 1,7-enyne **78g** (Scheme 33).



Scheme 32 Iridium-catalyzed skeletal reorganization.



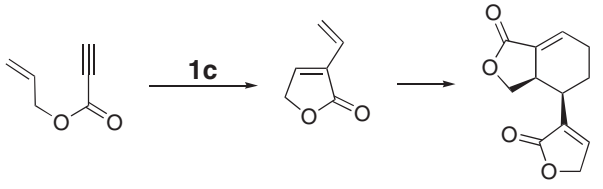
Scheme 33 Skeletal reorganization by $GaCl_3$.

Presumably, these skeletal reorganization reactions start by coordination of a metal ion to an alkyne part in **78** to allow an alkene part to attack the resulting electrophilic alkyne carbon coordinated by the metal. However, the reaction mechanism remains yet to be clarified, and it is thought that each reaction mechanism differs depending on the metal used.

11.08.1.6 Enyne Metathesis for Synthesis of Natural Products and Biologically Active Substances

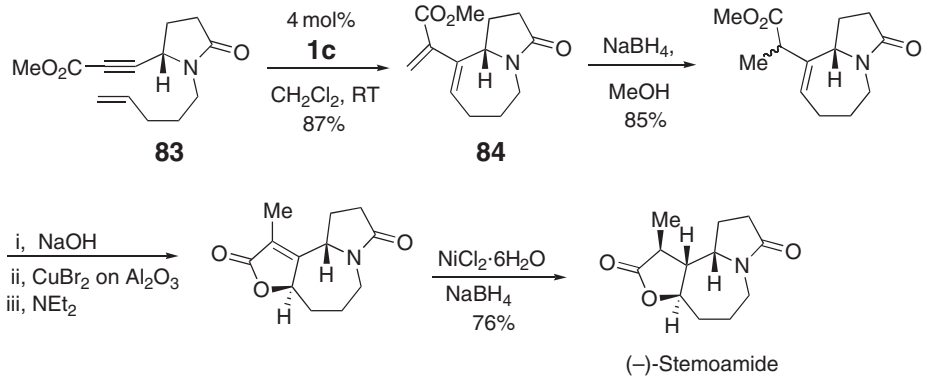
In 1996, Mori reported the total synthesis of (−)-stemoamide through a ruthenium-catalyzed enyne metathesis developed by their group (Scheme 34).[55,55a] Enyne **83** prepared from (−)-pyroglutamic acid is reacted with **1c** in CH_2Cl_2 at RT to give **84**, which is converted into (−)-stemoamide via halolactonization.

(±)-Differolide is synthesized by dimerization of the enyne metathesis product of allyl propiolate (Equation (18)).[56]

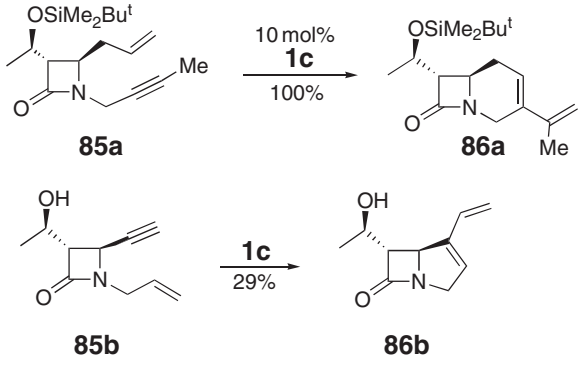


(18)

Carbacephem skeleton **86a** can be constructed using enyne metathesis.[57] Synthesis of carbapenem **86b** has been reported, although the yield is moderate due possibly to high strain in the product (Scheme 35).[57a]



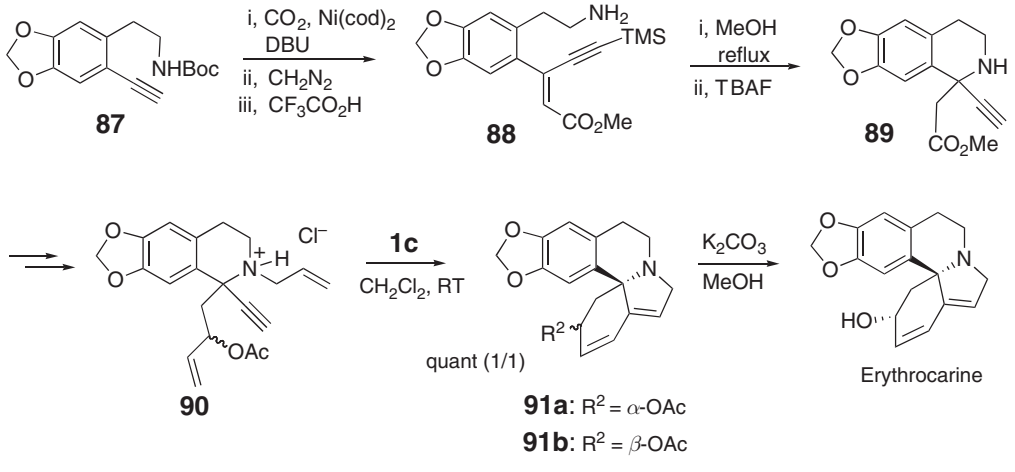
Scheme 34 Total synthesis of (–)-stemoamide.



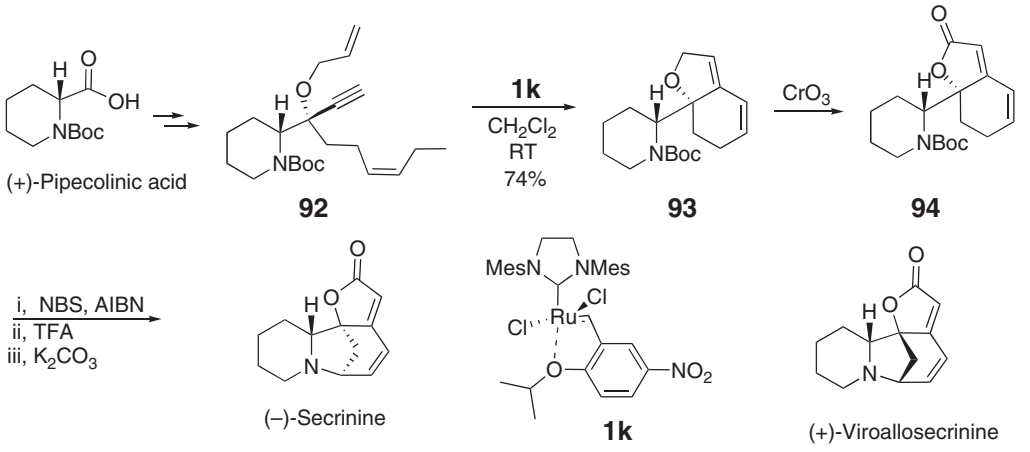
Scheme 35 Construction of carbacephem and carbapenem skeleton.

Total synthesis of (±)-erythrocarine has been achieved by Mori, who employed dienyne metathesis.[58] Isoquinoline derivative **89** is synthesized by nickel-mediated carboxylation of alkyne **87** followed by Michael-type reaction developed by their group. Metathesis of dienyne **90**·HCl derived from **89** is carried out using ruthenium catalyst **1c** to give tetracyclic compounds **91a** and **91b** in a quantitative yield in a ratio of 1 to 1. From α-isomer **91a**, erythrocarine is synthesized (Scheme 36). Taking advantage of the procedure, Hatakeyama succeeded in total synthesis of erythravine.[58a]

Honda *et al.* succeeded in the diastereoselective total synthesis of securinine in an optically pure form by employing RCM of the corresponding dienyne **92** as a key step (Scheme 37).[59] They used the ruthenium catalyst



Scheme 36 Total synthesis of erythrocarine.



Scheme 37 Total synthesis of (−)-secrinine.

1k[60] and obtained the bicyclic compound **93**, which was oxidized with CrO_3 and then treated with *N*-bromosuccinimide (NBS) to afford (−)-secrinine. They also synthesized viroallosecurinine in a similar manner.[59a]

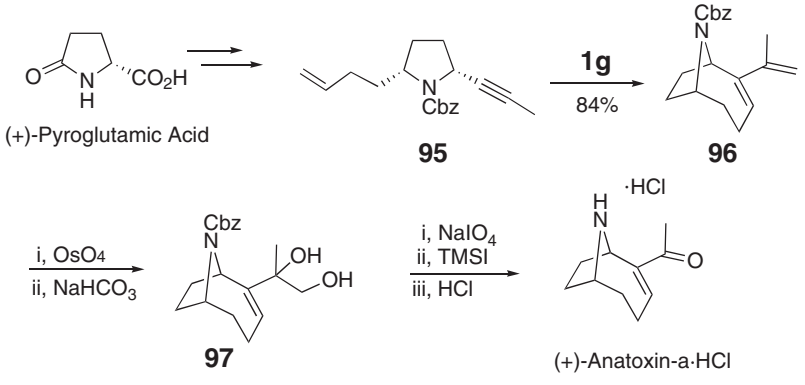
Total synthesis of anatoxin-a was achieved by Martin and Mori through the same strategy (Scheme 38).[61,61a,61b] The key step is the construction of a bicyclo[4.2.1] system. To this end, pyrrolidine derivative **95** having *cis*-substituents is synthesized from (+)-pyroglutamic acid and subjected to enyne metathesis using **1g** to result in formation of **96** in 84% yield. From **96**, synthesis of (+)-anatoxin-a is straightforward and successfully achieved.[61,61a]

Synthesis of pyrrolo-1,4-benzodiazepinone **101a** is achieved using RCM as a key step (Scheme 39).[62] The starting enyne **98** is synthesized from L-methionine, and RCM of **98** using **1c** gives pyrrolidine derivative **99**, which is converted into **100**. Reductive cyclization of **100** using Zn-AcOH followed by treatment with dil. HCl gives pyrrolobenzodiazepinone **101a**. In a similar manner, pyrrolobenzodiazepinone **101b** is synthesized and then CM for **101b** with methyl acrylate is carried out. The reaction smoothly proceeds using ruthenium catalyst **1l**[63]to give **102a**. Amide **102b** is successfully converted into (+)-anthramycin by Stille.

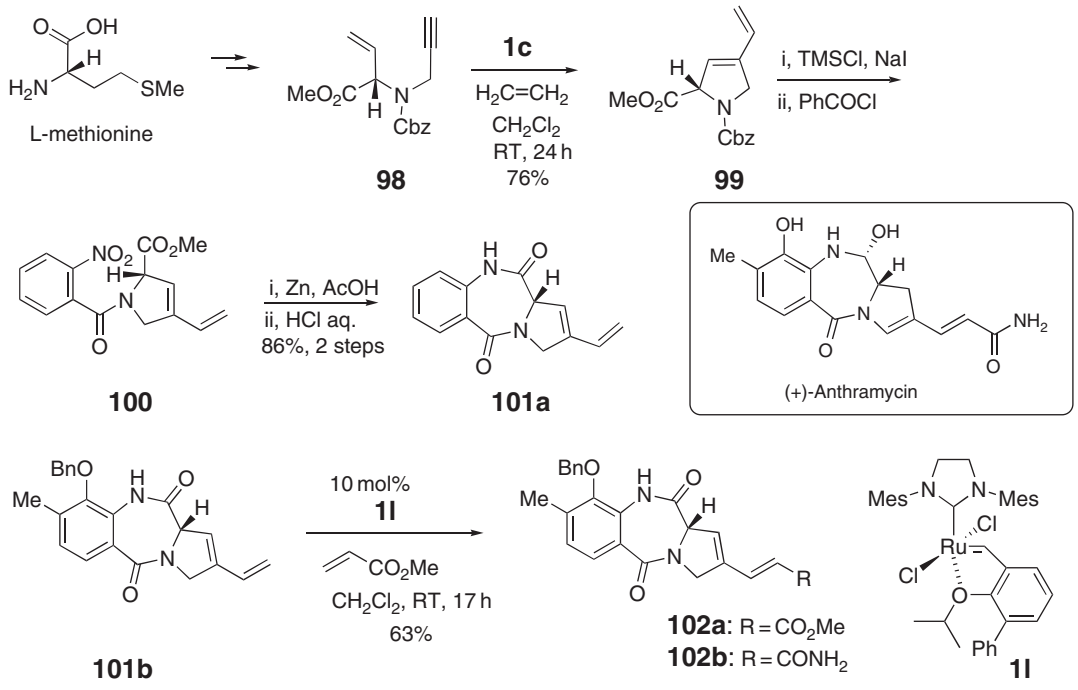
An enantioselective biomimetic synthesis of longithorone A was accomplished on the basis of proposed biosynthesis.[64] The syntheses of two [12]-paracyclophanes **105** and **107** are realized by applying ene–yne metatheses macrocyclization to **104** and **106**, which are synthesized from the common substrate **103**. Longtholone A is constructed using intermolecular and transannular Diels–Alder reactions followed by oxidation (Scheme 40).

Construction of 1,3-diene moieties from alkynes and ethylene is a unique methodology for the synthesis of 1,3-dienes. Mori used this strategy for the synthesis of anolignan A. Two methylene groups from ethylene are introduced onto the alkyne carbon of **109** using **1g** to give 1,3-diene **110**. From this compound, short-step synthesis of anolignan A is achieved (Scheme 41).[65]

Skeletal reorganization is a useful tool for the synthesis of complicated natural products. Fürstner achieved formal total syntheses of antibiotics metacycloprodigiosin and streptorubin B by platinum-catalyzed skeletal reorganization



Scheme 38 Total synthesis of (+)-anatoxin-a•HCl.



Scheme 39 Synthesis of anthramycin derivative.

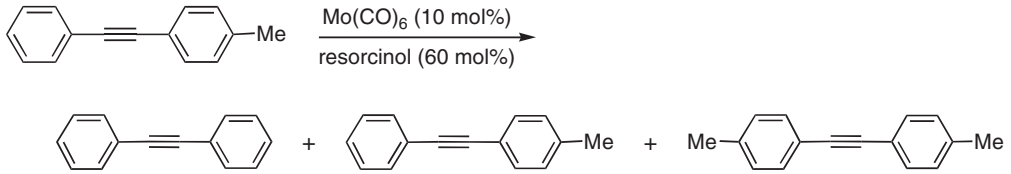
reaction (Scheme 42).[66] The key step leading to the *meta*-bridged pyrrole core structures consists of a metathesis reaction of electron-deficient enynes **111a** and **111b** catalyzed by $PtCl_2$. The skeletal reorganization products **112a** and **112b** are converted into the respective target molecules.

Trost succeeded in formal total synthesis of roseophilin. Macrocyclic compound **118** is synthesized from enyne **117** by platinum-catalyzed skeletal reorganization reaction and is converted into **119**, which is further converted into pyrrole derivative **120** (Scheme 43).[67]

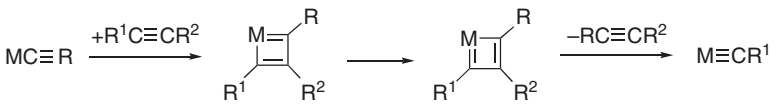
11.08.2 Alkyne Metathesis

11.08.2.1 Introduction

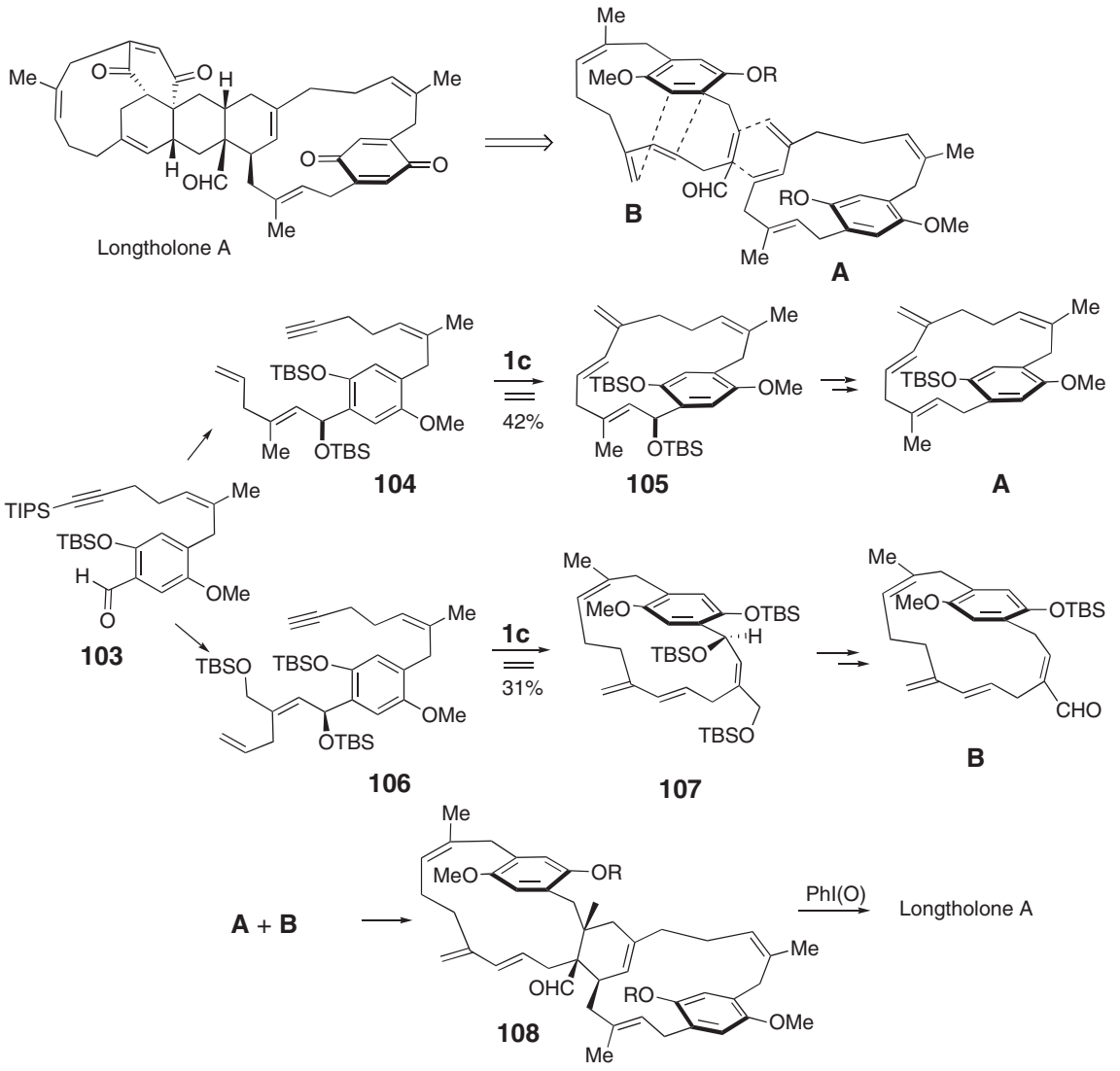
Alkyne metathesis is a curious reaction in view of the fact that two alkyne triple bonds are cleaved and reconstructed simultaneously leading to different triple bonds.[68,68a] The first reported effective catalyst is a heterogeneous mixture of tungsten oxide and silica.[69] Then Mortreux found that a catalytic system that consisted of $Mo(CO)_6$ and resorcinol was effective for alkyne metathesis. As reported, the added alkynes come into equilibrium with different product alkynes at higher reaction temperatures (Equation (19)).[70,70a] The reaction is understood to proceed by [2 + 2]-cycloaddition of the metal alkylidyne complex and the alkyne. (Equation (20)).[71]



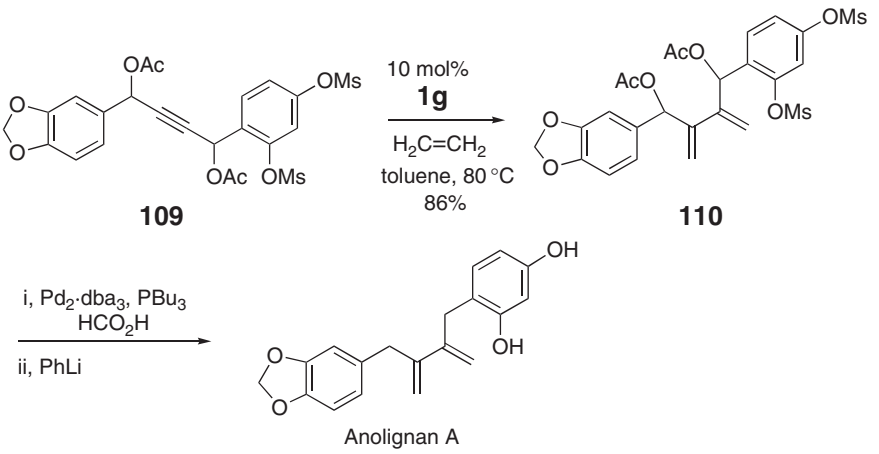
(19)



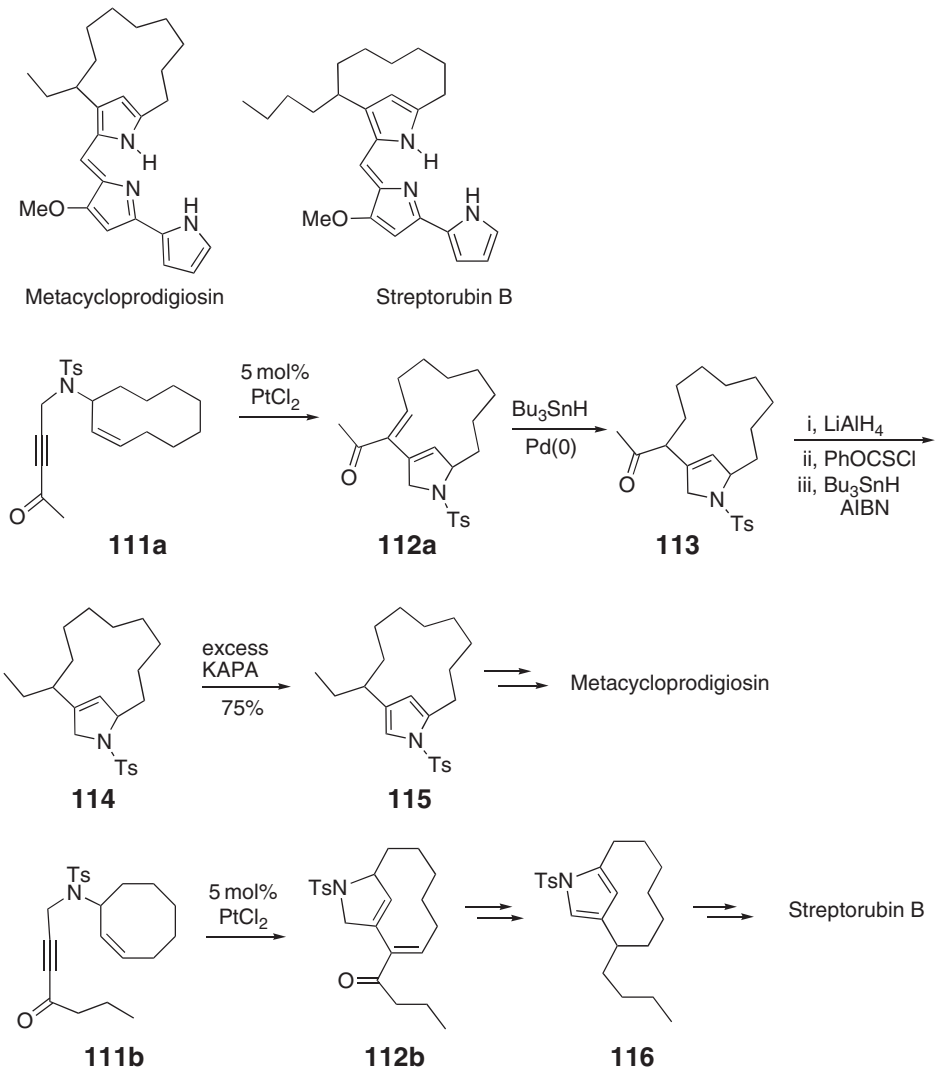
(20)



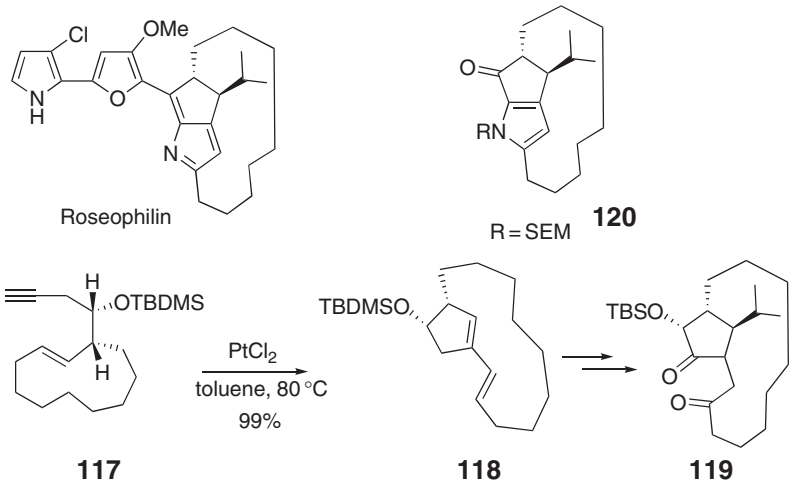
Scheme 40 Total synthesis of (–)-longtholone A.



Scheme 41 Synthesis of anolignan A using cross enyne metathesis.



Scheme 42 Formal total syntheses of streptorubin B and metacycloprodigiosin.



Scheme 43 Formal total synthesis of roseophilin.

This mechanism was later confirmed experimentally in 1981 by Schrock and others,[72,72a] who reported the first example of alkyne metathesis by tungsten(VI)-alkylidyne complex. They have prepared tungsten alkylidyne complex **120** (Equation (21)) and found that it reacts with diphenylacetylende to give tungsten alkylidyne complex **121** and another alkyne **122** (1 equiv.) (Equation (22)). Furthermore, complex **121** works as a catalyst for the alkyne metathesis reaction.

$$W(CCMe_3)(CH_2CMe_3)_3 + 3HCl + NEt_4^+Cl^- \longrightarrow [Et_4N]^+[W(CCMe_3)Cl_4]^-$$
$$[Et_4N]^+[W(CCMe_3)Cl_4]^- + 3LiO^tBu \xrightarrow{THF} (^tBuO)_3W{\equiv}C{-}CMe_3 \quad \textbf{120} \qquad (21)$$

$$\textbf{1} + Ph{-}{\equiv}{-}Ph \longrightarrow (^tBuO)_3W{\equiv}C{-}Ph \quad \textbf{121} + Ph{-}{\equiv}{-}{}^tBu \quad \textbf{122} \qquad (22)$$

Alkyne metathesis is now shown to be extremely useful in synthetic organic chemistry and growing to be applied extensively.

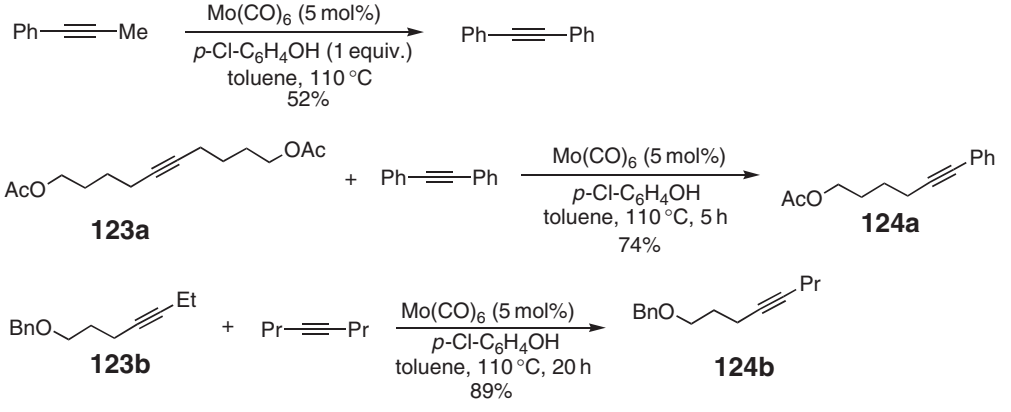
11.08.2.2 Alkyne Metathesis with $Mo(CO)_6$-Phenol System

Although the real species of alkyne metathesis using $Mo(CO)_6$-phenol is not clear at present, the catalytic system for alkyne metathesis is attractive from the viewpoint that the catalyst is commercially available and strict reaction conditions are not required. A novel method for synthesis of alkynes is developed.[73,73a] When alkyne **123a** is heated with diphenylacetylene in excess (3 equiv.) in the presence of a catalytic amount of $Mo(CO)_6$ (5 mol%) and *p*-Cl-C_6H_4OH (1 equiv.) in toluene, alkyne **124a** is obtained in 74% yield. In a similar manner, the reaction of **123b** and 4-octyne gives **124b** in 89% yield (Scheme 44).

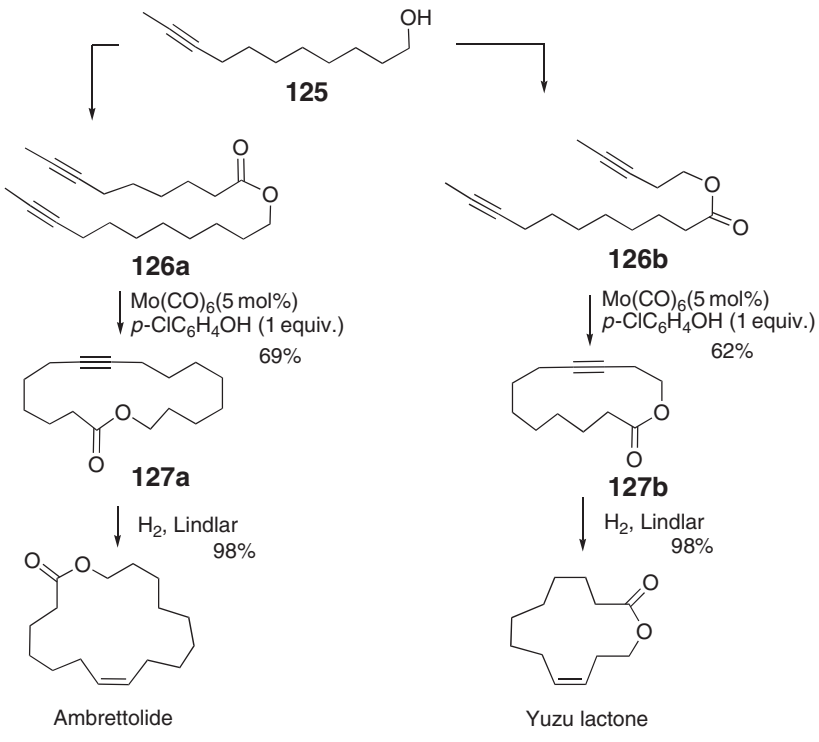
Using this catalyst system for ring-closing alkyne metathesis, Fürstner successfully synthesized ambrettolide and yuzu lactone from alcohol **125**.[74,74a] Treatment of diyne **126a** with $Mo(CO)_6$ (5 mol%) and *p*-chlorophenol (1 equiv.) in chlorobenzene at 140 °C leads to cycloalkyne **127a** in 69% yield. Subsequent Lindlar reduction proceeds smoothly in a stereoselective manner to afford ambrettolide. Similarly, **126b** affords cycloalkyne **127b** in 62% yield. From this compound, yuzu lactone has been synthesized (Scheme 45).[74,74a]

11.08.2.3 Alkyne Metathesis with Tungsten Alkylidyne Complex

At the same time, Fürstner and others used Schrock's tungsten alkylidyne complex **120** for ring-closing alkyne metathesis. They compared **120** with the $Mo(CO)_6$-*p*-ClC_6H_4OH system (Table 4) in reactivity and found that



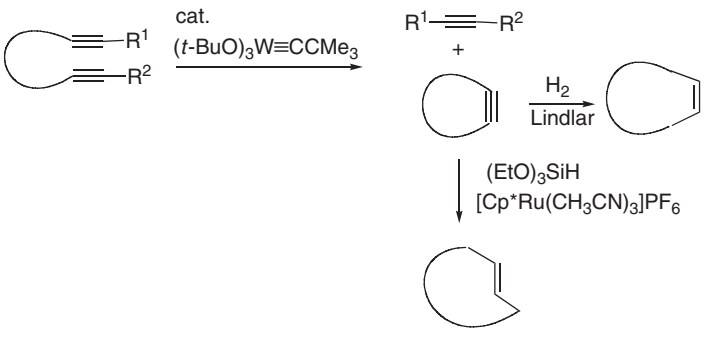
Scheme 44 Synthesis of disubstituted alkyne from alkyne.



Scheme 45 Synthesis of macrolactone using $Mo(CO)_6$/*p*-ClC_6H_4OH.

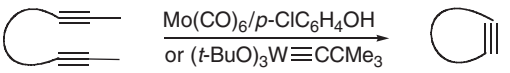
both catalysts worked well, although higher reaction temperatures were required for the $Mo(CO)_6$-*p*-chlorophenol system.[74,74a] A common remarkable feature of these catalysts is that the catalysts tolerate various functional groups, but a secondary amide having an acidic proton does not give the desired cyclized compound **129c** with $Mo(CO)_6$-*p*-ClC_6H_4OH (entry 3). Interestingly, these catalysts rigorously distinguish between alkyne and alkene groups (entry 4).

RCM of dienes to cycloalkenes provides a useful method for the syntheses of carbo- and heterocycles and thus has been proved to be extremely effective in total synthesis of various natural products. Usually, however, mixtures of (*E*)- and (*Z*)-olefins result. In contrast, ring-closing alkyne metathesis provides a reliable route for synthesis of both (*E*)- and (*Z*)-macrocycloalkenes in a stereoslective manner taking advantage of stereoselective partial reduction of resulting cycloalkynes. A Lindlar reduction gives (*Z*)-cycloalkenes, whereas a hydroboration/protonation sequence afford (*E*)-cycloalkenes (Equation (23)). Recently, Trost reported an alternative procedure for the synthesis of (*E*)-olefins from alkynes through hydrosilylation by a ruthenium catalyst.[75] This procedure converts cycloalkyne **130**, for example, to vinylsilane **131** and then to (*E*)-cycloalkene **132** in a stereoselective manner (Scheme 46).[75a]

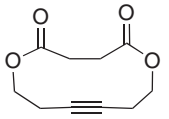
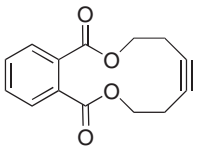
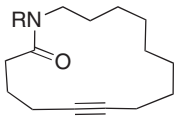
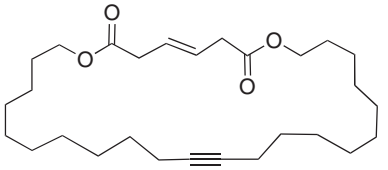


(23)

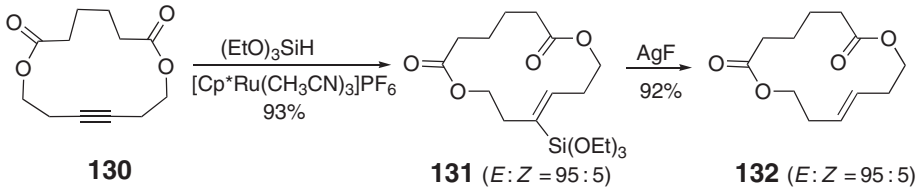
Table 4 Cyclization using $Mo(CO)_6/p\text{-}ClC_6H_4OH$ or $(t\text{-}BuO)_3W{\equiv}CCMe_3$



128 **129**

Entry	*Product*		$(t\text{-}BuO)_3W{\equiv}CCMe_3$[a]	$Mo(CO)_6/p\text{-}ClC_6H_4OH$[b]
1		**129a**	73%	64%
2		**129b**	68%	0%
3		**129c** **129d**	R═H 62% R═Me 72%	0% 64%
4		**129e**	53%	70%

[a]Using **120** (5 mol%) in chlorobenzene at 80 °C.
[b]$Mo(CO)_6$ (5 mol%) and *p*-chlorophenol (1 equiv.) at 140 °C.

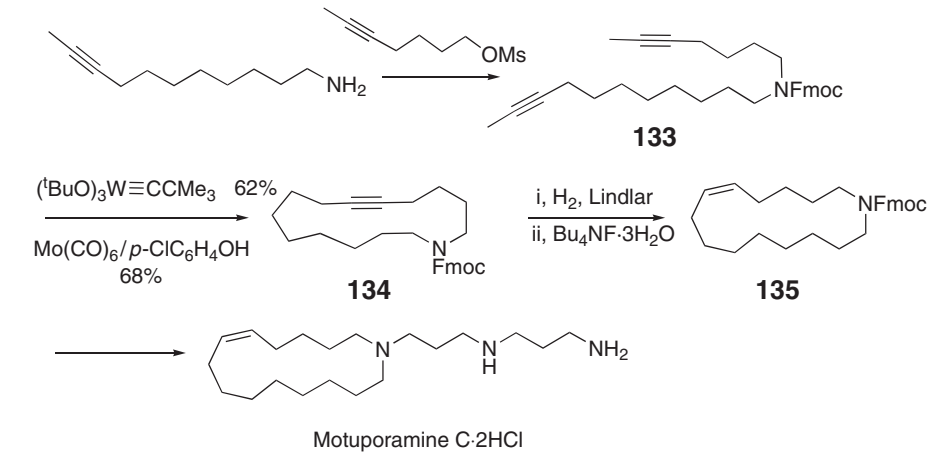


130 **131** (*E*:*Z* = 95:5) **132** (*E*:*Z* = 95:5)

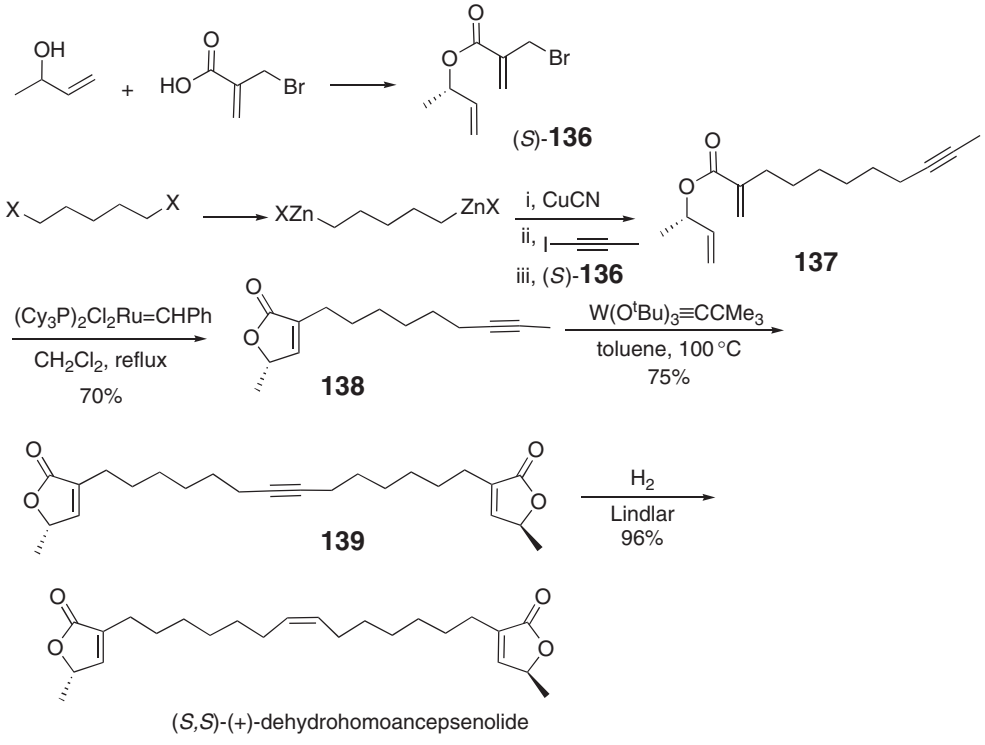
Scheme 46 Synthesis of *E*-cycloalkenes from cycloalkyne.

Total synthesis of motuporamide C is achieved by alkyne metathesis as a key step.[76] Diyne **133** is readily transformed into macrocyclic alkyne **134** with either catalyst. Lindlar reduction of **134** gives cycloalkene **135**, which is further derivatized to motuporamine C·2HCl (Scheme 47).

A concise total synthesis of dehydrohomoancepsenolide is achieved in an optically active form.[77] The key steps are alkene metathesis and alkyne metathesis. A three-component coupling reaction affords dienyne **137**, which undergoes ring-closing alkene metathesis in the presence of the first-generation ruthenium carbene complex to give **138**,



Scheme 47 Synthesis of motuporamine C•2HCl.



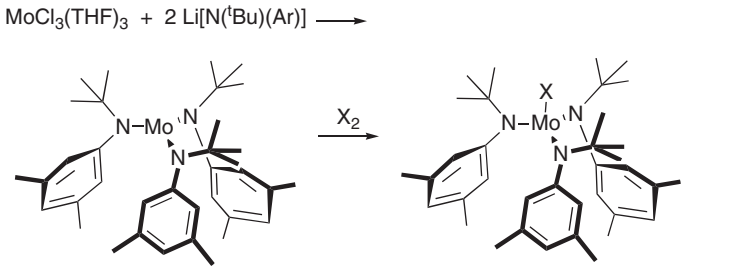
Scheme 48 Concise synthesis of dehydrohomoancepsenolide.

which is subjected to alkyne metathesis and converted into butenolide **139**. Subsequent Lindlar reduction of **139** gives (*S*,*S*)-dehydrohomoancepsenolide (Scheme 48).

11.08.2.4 Alkyne Metathesis Using Molybdenum Alkylidyne Complex

A novel complex, Mo[N(^{t}Bu) (Ar)]$_3$ **140**, was prepared and shown to activate the triple bond in molecular nitrogen in a stoichiometric fashion.[78,78a] However, the complex, when used for alkyne metathesis,[79] does not affect the expected transformation, but undergoes a vigorous endothermic process in a CH_2Cl_2 solution. The resultant solution

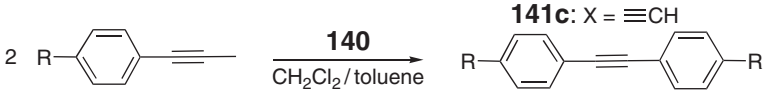
is demonstrated to catalyze the metathesis coupling of a variety of different aliphatic and aromatic alkynes (Equations (24)–(26)).



140

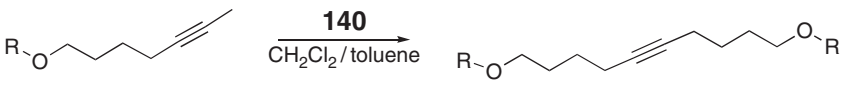
141a: X = Cl
141b: X = Br
141c: X = ≡CH

(24)



R	*Yield* (%)
H	60
CN	58

(25)

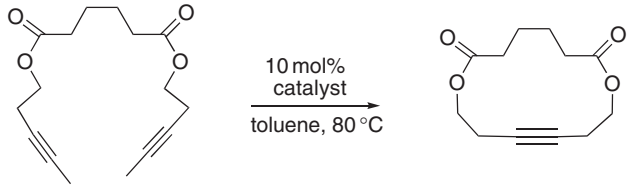


R	*Yield* (%)
Me	59
THP	55

(26)

To identify the truly active species for the alkyne metathesis, various experiments are carried out for ring-closing alkyne metathesis of diynes (Table 5). Activation of complex **140** with CH_2Cl_2 and evaporation of all the volatiles is shown to yield $Mo[N(Ar)(^tBu)]_3Cl$ **141a** and alkylidyne complex **141c** as major components. The former complex **141a**, that is also accessible by treatment of **140** with Cl_2 (Equation (24)), had an equal catalytic activity (entry 6), but

Table 5 Reactivities of molybdenum complex



Entry	*Catalyst*	*Yield* (%)
1	**140**/CH_2Cl_2 (*in situ*)	81
2	**140**/CH_2Br_2 (*in situ*)	84
3	**140**/TMSCl (*in situ*)	75
4	**140**/$PhCHCl_2$ (*in situ*)	78
5	**141c**	38[a]
6	**141a**	70
7	**141b**	79

[a]Using 35 mol% of **141c**.

the latter complex **141c** was not so effective (entry 5). Examination of the reaction of **140** in toluene with various halogen-containing substrates has led to the discovery that CH_2Br_2, TMSCl, and $PhCHCl_2$ work almost equally (entries 2, 3, and 4).

Although the real species of this solution for alkyne metathesis is not clear, this complex is an excellent tool from a preparative point of view. It is very active for the formation of cycloalkynes of different ring sizes from diynes. In contrast to tungsten alkylidyne complex **1**, catalyst **140**/CH_2Cl_2 is sensitive toward acidic protons such as amide proton and exhibited remarkable tolerance toward many polar functional groups (Table 6).[79]

The catalyst system is applicable to synthesis of 15-epiprostagrandin E_2-1,15-lactone. The crucial cyclization of diyne **142** to cycloalkyne **143** is carried out with different alkyne metathesis catalysts; the catalyst formed from **140** and CH_2Cl_2 gives an excellent results (Table 4, entry 1). Schrock's tungsten catalyst **120** also gives similar results (entry 2), but the conversion of **142** into **143** using the $Mo(CO)_6$-*p*-Cl–C_6H_4OH system turned out futile (entry 3). Lindlar reduction of **143** followed by deprotection affords 15-epi-prostagrandin E_2-1,15 lactone.[80,80a]

Alkyne CM is also achieved using the **140**/CH_2Cl_2 catalyst system. Even with a 1 : 1 mixture of two different alkynes, the desired metathesized alkyne is obtained in 71% yield (Equation (27)).[80,80a]

Table 6 Diyne metathesis using tungsten and molybdenum complexes

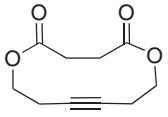
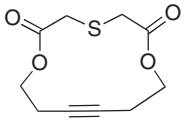
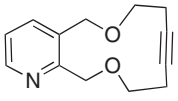
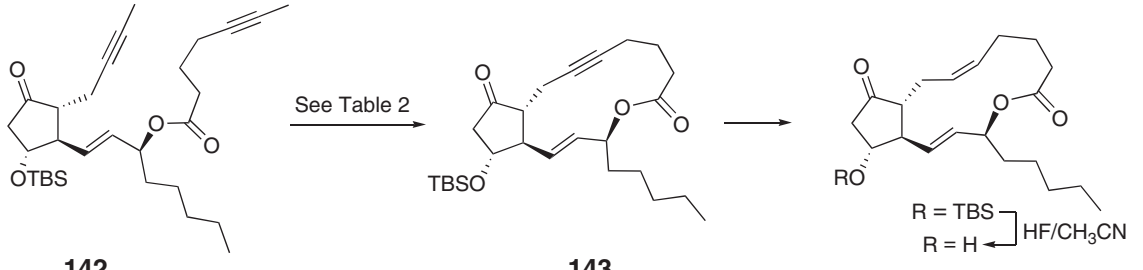
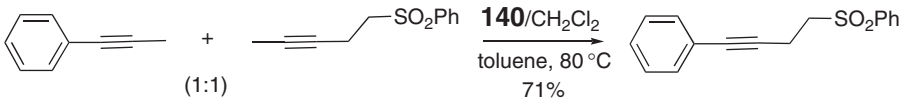
Entry	*Product*	$(^tBuO)_3W\equiv$	**140**/CH_2Cl_2
1		73%	91%
2		0%	84%
3		0%	88%

Table 7 Comparison of the reactivities on ring-closing alkyne metathesis



142 **143** 15-Epi-prostagrandin E_2-1, 15-lactone

Entry	*Catalyst*	*Conditions*	*Yield* (%)
1	**140**/CH_2Cl_2	toluene, 80 °C, 8 h	81
2	$(^tBuO)W\equiv CCMe_3$	toluene, 80 °C, 8 h	65
3	$Mo(CO)_6$/*p*-ClC_6H_4OH	Cl–C_6H_5, 130 °C, 24 h	0

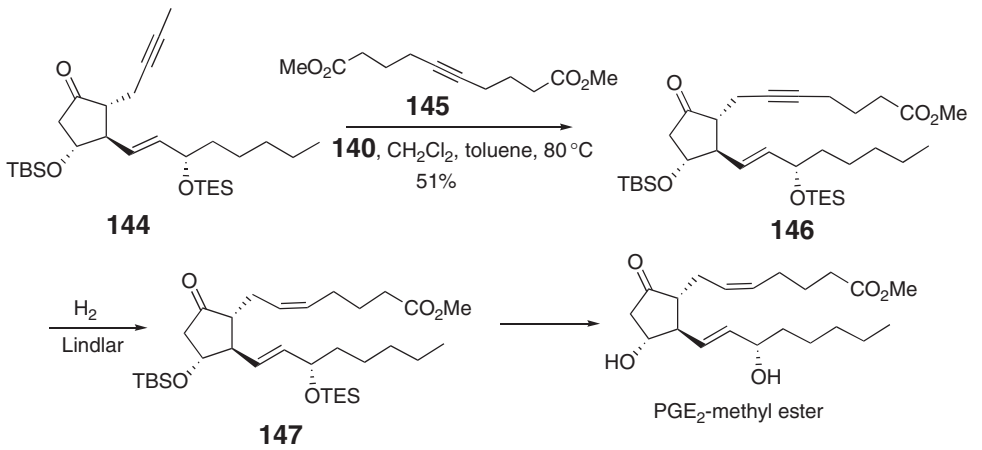


(27)

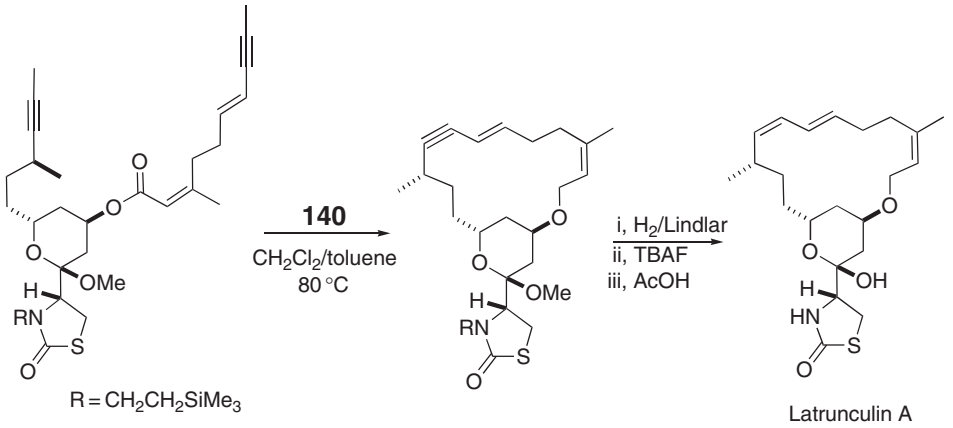
Alkyne metathesis is employed for constructing the α-chain of PGE_2-methyl ester. Reaction of alkyne **144** and symmetrical alkyne **145** in a slight excess in the presence of the **140**/CH_2Cl_2 catalyst produces the desired CM product **146** in 51% yield, which is then converted to PGE_2-methyl ester by partial reduction with a Lindlar catalyst leading to (*Z*)-olefin **147** and subsequent deprotection (Scheme 49).[81]

Concise and practical synthesis of latrunculin A is achieved by ring-closing enyne–yne metathesis. Cyclization of the enyne–yne shown in Scheme 50 is carried out smoothly with **140** in CH_2Cl_2/toluene upon heating to give a macrocyclic enyne, which is then transformed to the target molecule by a sequence of Lindlar reduction and deprotection.[82]

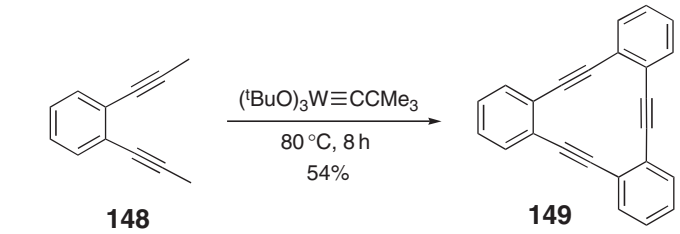
Tribenzocyclynes **149** is synthesized by alkyne metathesis of *o*-dipropynylated arenes **148** using tungsten alkylidiyne complex **120** (Equation (28)).[83] Interest has recently been focused on super-persistent arylene ethynylene macrocycles in the fields of supermolecular chemistry and material sciences. Phenylene ethynylene macrocycles **151** are obtained from monomers **150** in good yields using molybdenum catalyst **152**. Particularly, it is noteworthy that multi-gram synthesis of **151b** is accomplished from **150b** in one step (Equation (29)).[84,84a]



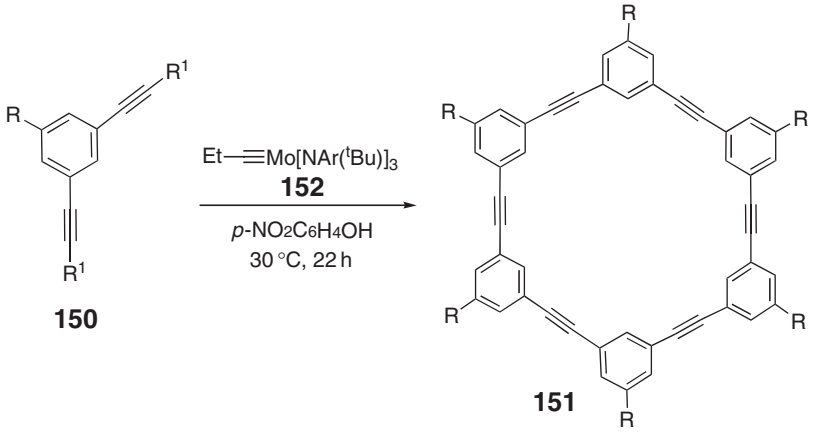
Scheme 49 Synthesis of PGE_2-methyl ester using cross-metathesis of alkyne.



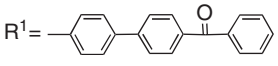
Scheme 50 Synthesis of latrunculin A.



148 **149** (28)



150 **151** (29)

		mg-Scale	g-Scale
R^1 = Me	R = ^{t}Bu	**151a** 61%	—
R^1 = 	R = $COO(CH_2CH_2O)_3CH_3$	**151b** 81%	77%

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11.09
Sequential Formation of More than One C–C and Other Bonds by Multiple Heck-type Reactions

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11.09.1 Introduction

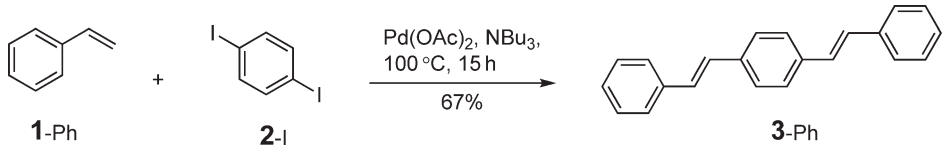
The development of processes in which several new bonds are formed in a single synthetic operation plays an important role and is an active field in modern synthetic organic chemistry. In this context, transition metal-catalyzed bond-forming processes have attracted particular attention, since they usually proceed under mild reaction conditions and can tolerate a variety of functional groups. During the last two decades, Heck reactions, originally discovered by Mizoroki and Heck simultaneously, have especially frequently been used as key steps and applied in a repetitive manner toward the construction of complex organic molecules. In this context, multiple Heck reactions are defined as palladium-catalyzed cross-coupling reactions involving the sequential formation of several C–C bonds by carbopalladations of alkenes and alkynes. Quite a few reviews on this topic have appeared in the literature within the last 12 years,[1–8] and the most comprehensive coverage has been presented in two recent handbooks.[9,10] Therefore, this chapter is being restrained to summarizing the various reaction modes involving the sequential formation of more than one C–C and other bonds by multiple Heck-type reactions, and presenting some representative examples for each reaction mode.

11.09.2 Multiple Heck Couplings of Oligohaloarenes with Alkenes

11.09.2.1 Intermolecular Couplings

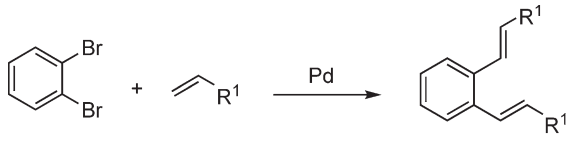
Heck in one of his first papers already demonstrated the feasibility of applying the palladium-catalyzed cross-coupling of aryl and alkenyl halides with alkenes repetitively on appropriate oligofunctional substrates. For example, twofold coupling of 1,4-diiodobenzene with styrene furnished 1,4-distyrylbenzene in 67% yield (Scheme 1).[11] Since then, a large number of *ortho*-, *meta*-, and *para*-dihaloarenes and -heteroarenes have been subjected to twofold Heck reactions with various alkenes (Schemes 2–4).

With the original protocol, attempted threefold couplings of even a 4-nitro-substituted 1,2,3-triiodobenzene derivative failed.[12] However, under the modified conditions of Jeffery, that is, with a base like potassium carbonate in the presence of a tetrabutylammonium halide,[13,13a] multifold Heck couplings of oligohaloarenes are brought about in very good yields (Schemes 5 and 6).[14–16]



1-Ph **2**-I **3**-Ph

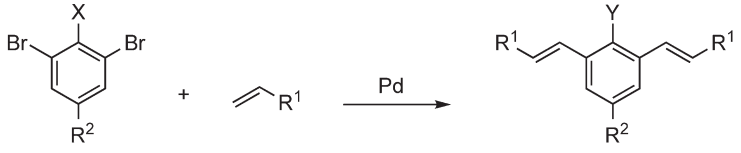
Scheme 1 Twofold Heck reaction of 1,4-diiodobenzene.[11]



4 **1**-R^1 **5**-R^1

R^1	*Conditions*	*Yield* (%)	*References*
Ph	$Pd(OAc)_2$, Bu_4NBr, K_2CO_3, DMF, 100 °C	92	14
Ph	$Pd(OAc)_2$, P(*o*-tol)$_3$, NEt_3, THF/MeCN, 55 °C, 10 kbar	59	15
CO_2Me	$Pd(OAc)_2$, P(*o*-tol)$_3$, NEt_3, 150 °C (microwave)	65	16
CO_2Me	$Pd(OAc)_2$, NBu_4Cl, LiCl, K_2CO_3, DMF, 100 °C	86	17
Me (5 bar)	$Pd(OAc)_2$, NBu_4Cl, LiCl, $KHCO_3$, NMP, 100 °C	79	18
H (13.8 bar)	$Pd(OAc)_2$, P(*o*-tol)$_3$, NEt_3, MeCN, 125 °C	78	19
P(O)MePh	$Pd(OAc)_2$, PPh_3, NEt_3, DMF, 135 °C	65	20
4-Py	$Pd(OAc)_2$, PPh_3, NEt_3, 100 °C	80	21

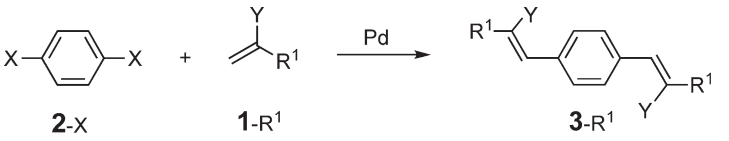
Scheme 2 Twofold Heck reactions of 1,2-dibromobenzene.[14,21]



6-R^2 **1**-R^1 **7**-R^2

R^2	R^1	*X*	*Conditions*	*Y*	*Yield* (%)	*References*
CH_2OH	CO_2Et	H	$Pd(OAc)_2$, P(*o*-tol)$_3$, NEt_3, MeCN, 90 °C	H	94	22
CO_2Et	CN	H	$Pd(OAc)_2$, PPh_3, NEt_3, MeCN, 120 °C	H	56	23
H	P(O)MePh	H	$Pd(OAc)_2$, PPh_3, NEt_3, DMF, 135 °C	H	92	20
H	4-Py	H	$Pd(OAc)_2$, PPh_3, NEt_3, 100 °C	H	77	21
H	Ph	Br	$Pd(OAc)_2$, NBu_4Br, K_2CO_3, DMF, 100 °C	CHCHPh	56	14
H	CO_2tBu	Br	$Pd(OAc)_2$, NBu_4Br, K_2CO_3, DMF, 90 °C	$CHCHCO_2Bu^t$	58	17

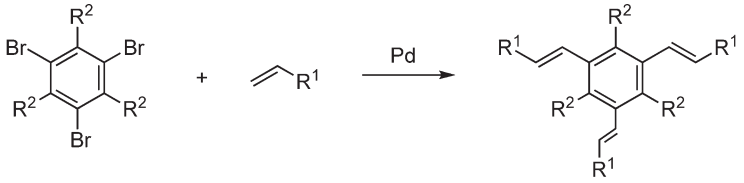
Scheme 3 Two- and threefold Heck reactions of 1,3-dibromo- and 1,2,3-tribromobenzene.[14,17,20–23]



2-X **1**-R^1 **3**-R^1

X	R^1	Y	Conditions	Yield (%)	References
I	CO_2Bn	NHBn	$Pd(OAc)_2$, NBu_4Cl, $NaHCO_3$, DMF, 85 °C	55	24
I	CO_2Me	H	$Pd(OAc)_2$, PPh_3, NEt_3, 100 °C	32	12
I	$O(CH_2)_2NMe_2$	H	$Pd(OAc)_2$, NBu_4Cl, K_2CO_3, DMF, 80 °C	76	25
Br	Ph	H	$Pd(o\text{-tol})_2Cl$, NBu_3, K_2CO_3/H_2O, 100 °C	85	26

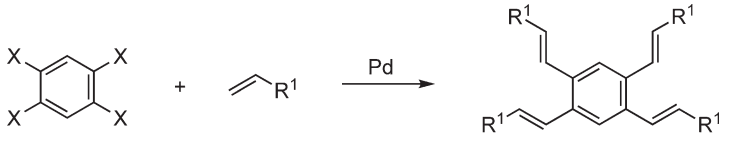
Scheme 4 Twofold Heck reactions of 1,4-dihalobenzenes.[12,24–26]



8-R^2 **1**-R^1 **9**-R^1,R^2

R^2	R^1	Conditions	Yield (%)	References
H	4-$MeOC_6H_4$	$Pd(OAc)_2$, PPh_3, NEt_3, 100 °C, 3 d	>40	27
H	4-Py	as above	70	27
H	4-Py	$Pd(OAc)_2$, NBu_4Br, K_2CO_3, DMF, 100 °C, 5 d	92	28
H	2-Py	as above	92	28
Me	Ph	$Pd(OAc)_2$, $P(o\text{-tol})_3$, NEt_3, DMF, 80 °C	51	29

Scheme 5 Threefold Heck reactions of 1,3,5-tribromobenzene derivatives.[27,29]



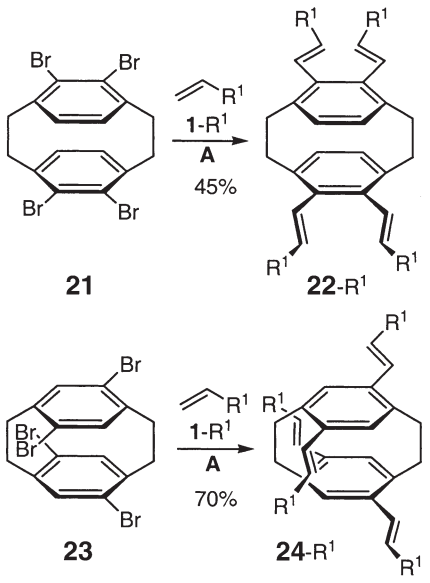
10-X **1**-R^1 **11**-R^1

X	R^1	Conditions	Yield (%)	References
Br	Ph	$Pd(OAc)_2$, NEt_4Cl, K_2CO_3, LiCl, DMF, 110 °C, 3 d	62	14
I	CO_2Me	$Pd(OAc)_2$, PPh_3, NEt_3, 100 °C, 48 h	16	12

Scheme 6 Fourfold Heck reactions of 1,2,4,5-tetrabromobenzene.[12,14]

Fourfold Heck coupling (twofold on each dibromobenzene moiety) and Jeffery conditions has been applied on the two easily accessible tetrabromo[2.2]paracyclophane isomers **21** and **23**, respectively, to prepare new double-layered 1,2- and 1,4-distyrylbenzene chromophoric systems **22**-R^1 and **24**-R^1, respectively, to enable studies of intramolecular charge-transfer phenomena in such systems (Scheme 7).[30,31]

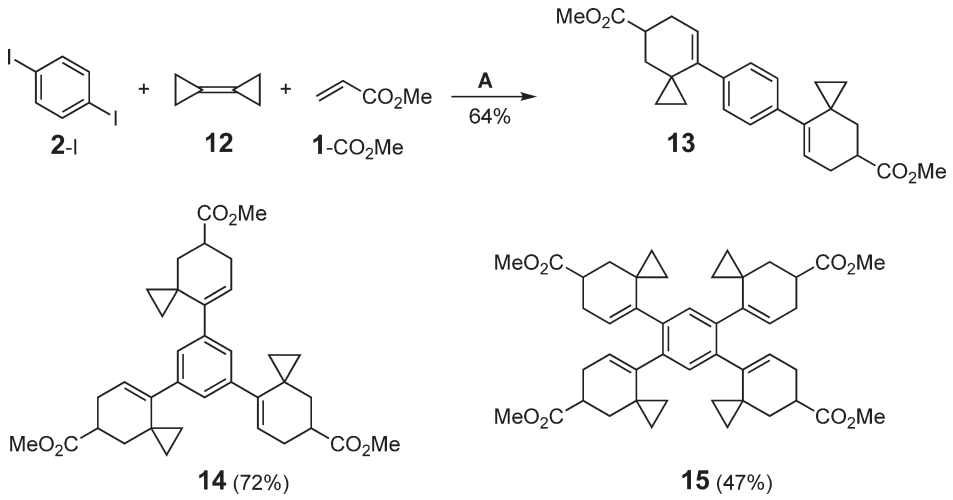
The domino Heck–Diels–Alder reaction of an aryl iodide, bicyclopropylidene **12**, and a dienophile such as methyl acrylate **1**-CO_2Me, leading to 4-arylspiro[2.5]oct-4-ene derivatives in high yields,[32,32a,33] has also been accomplished in a two-, three- and even fourfold manner (Scheme 8).[33] In these sequences, the carbopalladation across the highly strained double bond of bicyclopropylidene **12** is succeeded by a cyclopropylmethylpalladium to homoallylpalladium halide rearrangement to yield, after β-hydride elimination, an allylidenecyclopropane, which subsequently undergoes a smooth [4 + 2] cycloaddition to furnish the spiro[2.5]octene moiety. With 1,4-diiodobenzene **2**-I, a single diastereomer **13** was obtained in 64% yield, 1,3,5-triiodobenzene gave the threefold coupling–rearrangement–cycloaddition product **14** in 72% yield, and ultimately, 1,2,4,5-tetraiodobenzene provided the fourfold domino reaction product **15** in 47% yield in a single operation, in which 12 new carbon–carbon bonds were formed.



R^1	*Product*	*Yield* (%)
Ph	**22**-Ph	45[a]
Ph	**24**-Ph	70
CO_2Me	**24**-CO_2Me	56
2-MeC_6H_4	**24**-2-MeC_6H_4	41[a]
3-MeC_6H_4	**24**-3-MeC_6H_4	30[a]
4-MeC_6H_4	**24**-4-MeC_6H_4	44[a]
4-$MeOC_6H_4$	**24**-4-$MeOC_6H_4$	46[a]
4-$MeO_2CC_6H_4$	**24**-4-$MeO_2CC_6H_4$	7[a]

[a] Yield after recrystallization, yields of the crude coupling products were 10–15% higher.

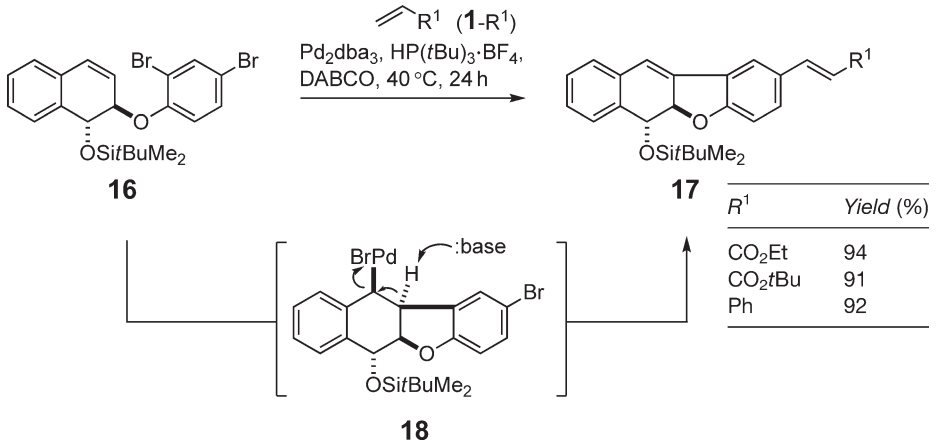
Scheme 7 New double-layered 1,2- and 1,4-distyrylbenzene chromophores by fourfold Heck couplings. **A**: $Pd(OAc)_2$, NBu_4Br, K_2CO_3, DMF.[30,31]



Scheme 8 Two-, three-, and fourfold domino Heck–Diels–Alder reactions involving bicyclopropylidene **12** and methyl acrylate **1**-CO_2Me. **A**: $Pd(OAc)_2$, PPh_3, Bu_4NCl, K_2CO_3, MeCN, 80 °C, 2 days.[32,32a,33]

11.09.2.2 Intra-intermolecular Couplings

The main steps in the currently accepted catalytic cycle of the Heck reaction are oxidative addition, carbopalladation (C═C insertion), and β-hydride elimination. It is well established that both, the insertion as well as the elimination step, are *cis*-stereospecific. Only in some cases has formal *trans*-elimination been observed. For example, exposure of the 1,3-dibromo-4-(dihydronaphthyloxy)benzene derivative **16** and an alkene **1**-R^1 to a palladium source in the presence of a base led to a sequential intra-intermolecular twofold Heck reaction furnishing the alkenylated tetracyclic products **17** in good to excellent yields (Scheme 9).[34] In the rate-determining step, the base removes a proton in an antiperiplanar orientation from the benzylic palladium intermediate. The best amine base was found to be 1,4-diazabicyclo[2.2.2]octane, which apparently has an optimal shape for this proton abstraction.



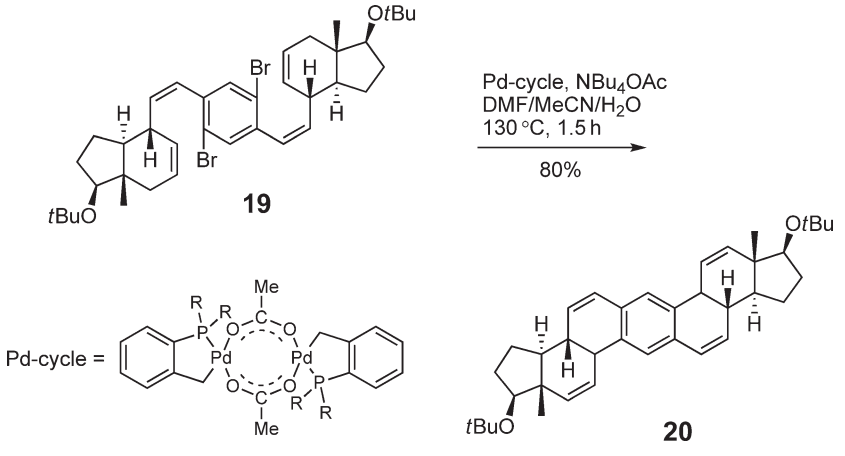
Scheme 9 Sequential intra-intermolecular twofold Heck reaction involving a *trans*-β-hydride elimination.[34]

11.09.2.3 Intramolecular Couplings

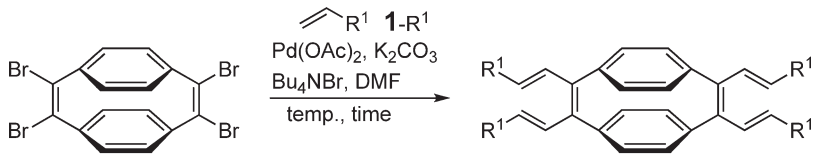
A twofold intramolecular Heck reaction of the dibromobenzene derivative **19** has been used to construct the heptacyclic skeleton **20** of cephalostatin analogs. This reaction required a precise control of the reaction time and temperature. The conversion proceeded best with a catalytic amount of the palladacycle from tris(*o*-tolyl)phosphine and palladium acetate, and gave exclusively (in 80% yield) the heptacycle **20** with an unusual *cis*-annelation of the two newly formed rings (Scheme 10).[35]

11.09.3 Twofold Heck Couplings of 1,2-Dihalocycloalkenes and Related Compounds

Twofold Heck reactions of vicinal *cis*-1,2-dihaloalkenes constitute an easy access to (*E*,*Z*,*E*)-1,3,5-hexatrienes, which are perfectly set up to undergo 6π-electrocyclizations to yield cyclohexa-1,3-dienes. Thus, the synthesis of several 7 : 8,15 : 16-dibenzo[2.2]paracyclophane-7,15-dienes was accomplished by fourfold Heck coupling, in 7,8,15,16-tetrabromo[2.2]paracyclophane-7,15-diene **25**, as a key step (Scheme 11).[36] The Heck reaction proceeds cleanly under Jeffery's conditions[13,13a] to give the tetraalkenylated products **26** in moderate to good yields. The latter upon heating at 150 °C undergo clean twofold 6π-electrocyclizations and after subsequent dehydrogenation yield the bisbenzoannelated [2.2]paracyclophanediene derivatives.[36]



Scheme 10 A twofold intramolecular Heck reaction of a 1,4-dibromobenzene derivative leading to a heptacyclic skeleton.[35]

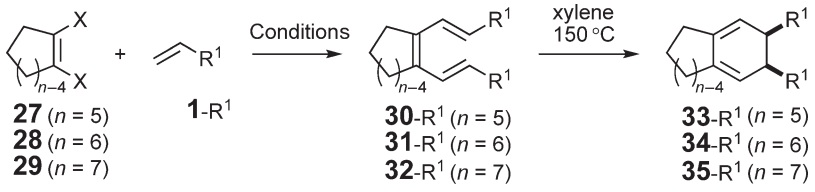


25 **26**-R^1

R^1	*Temp.* (°C)	*Time* (h)	*Yield* (%)
Ph	100	72	58
4-*t*BuC_6H_4	100	48	55
4-$MeO_2CC_6H_4$	70	36	58
4-PhC_6H_4	100	96	15
H	100	48	24
$SiMe_3$	40	120	55
CO_2Me	70	12	48
CHO	40	48	38

Scheme 11 Two twofold Heck couplings of 7,8,15,16-tetrabromo[2.2]paracyclophane-7,15-diene **25**.[36]

Starting from easily accessible 1,2-dihalocycloalkenes **27**–**29**, ring-attached (*E*,*Z*,*E*)-1,3,5-hexatrienes **30**-R^1, **31**-R^1, **32**-R^1, with various substituents in the 1,6-positions, are available by twofold Heck reactions with the correspondingly substituted alkenes. Most of these hexatrienes undergo 6π-electrocyclizations reasonably cleanly upon heating in an inert solvent in the absence of oxygen to give the ring-anellated *cis*-5,6-disubstituted 1,3-cyclohexadienes **33**-R^1, **34**-R^1, **35**-R^1 (Scheme 12),[33] and the latter can be employed in stereocontrolled intermolecular [4 + 2]-cycloadditions.[28] The tri(organosilyl)-substituted 1,3,5-hexatrienes, however, neither undergo thermal[37] nor photochemical[38] 6π-electrocyclization.



27 (*n* = 5)
28 (*n* = 6)
29 (*n* = 7)

1-R^1

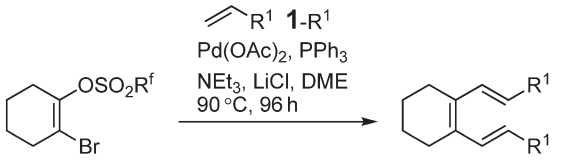
30-R^1 (*n* = 5)
31-R^1 (*n* = 6)
32-R^1 (*n* = 7)

33-R^1 (*n* = 5)
34-R^1 (*n* = 6)
35-R^1 (*n* = 7)

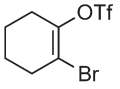
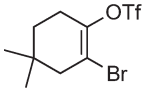
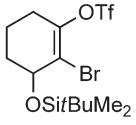
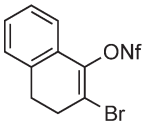
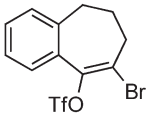
n	*X*	R^1	*Conditions*	*Yield* (%)[a]	*References*
5	Br	CO_2Me	**A**	81	37
5	Br	CO_2Et	**A**	59	38
5	Br	CO_2tBu	**A**	56	37
5	Br	Ph	**A**	73	37
6	Br	CO_2Me	**A**	55	37
6	Br	CO_2Et	**A**	62	38
6	Br	CO_2tBu	**A**	57	37
6	Br	Ph	**A**	69	37
5	I	$SiMe_3$	**B**	80[b]	37
5	I	$SiEt_3$	**B**	81[b]	37
5	I	$SiMe_2Ph$	**B**	53[b]	37
5	I	Si(*n*Bu)$_3$	**B**	71[b]	37
6	I	$SiMe_3$	**B**	78[b]	37
6	I	$SiEt_3$	**C**	80[b]	37
6	I	$SiMe_2Ph$	**C**	52[b]	37
7	Br	CO_2Me	**D**	66	38
7	Br	CO_2tBu	**E**	52	39

[a]Yield for the first step only.
[b]No 6π-electrocyclization upon heating.

Scheme 12 Twofold Heck couplings on 1,2-dihalocycloalkenes. **A**: $Pd(OAc)_2$, PPh_3, NEt_3, DMF, 90–100 °C. **B**: $Pd(OAc)_2$, $AgNO_3$, NEt_3, DMSO, 25 °C, 2 days. **C**: As in **B**, but under 5 bar argon pressure. **D**: $[Pd_2(dba)_3]\bullet CHCl_3$, (*n*Bu)$_4$NBr, K_2CO_3, DMF, 90 °C, 7 h. **E**: $Pd(OAc)_2$, K_2CO_3, (*n*Bu)$_4$NBr, LiCl, DMF, 90 °C, 8 h.



36 **37**

Starting material	*Alkene* **1**-R^1	*Conditions*	*Yield* (%)	*References*
	CO_2tBu	**A**	73	37
	CO_2tBu	**A**	86	37
	CO_2tBu	**A**	64	40, 5b
	CO_2Me	**A**	71	37
	CO_2Me	**B**	51	38

Scheme 13 Twofold Heck couplings on 2-bromocycloalkenyl perfluoroalkanesulfonates. **A**: $Pd(OAc)_2$, PPh_3, NEt_3, LiCl, DMF, 60–90 °C, 24–96 h. **B**: As in **A**, but without LiCl. Tf = SO_2CF_3, Nf = $SO_2C_4F_9$.

As alternatives to the 1,2-dihalocycloalkenes, 1-halo-2-perfluoroalkanesulfonyloxycycloalkenes can also be favorably employed for twofold Heck reactions. Since they can be easily prepared from the corresponding ketones via the α-haloketones and subsequent sulfonylation of the enolate, this sequence provides a straightforward access to variously substituted 1,3,5-hexatrienes and cyclohexadiene-annelated cycloalkanes, essentially from cycloalkanones (Scheme 13).[37–40]

11.09.4 Twofold Heck Couplings on the Same Alkene

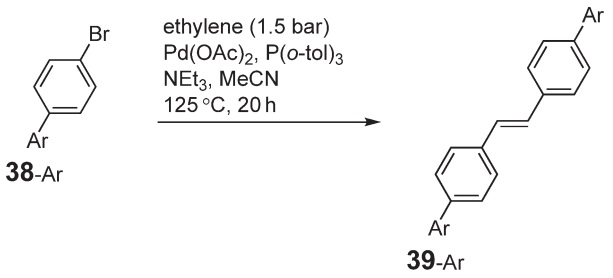
11.09.4.1 Ethylene

The twofold Heck arylation of ethylene and ethylene equivalents, initially investigated by Heck himself,[19,41] provides an easy access to stilbene derivatives **39**-Ar (Scheme 14).[42] The pressure of ethylene has to be carefully controlled, otherwise styrene derivatives, which are initially formed in this process, will be found as major products. In general, a slightly elevated pressure (1–5 bar) of ethylene is favorable for the vicinal twofold coupling leading to stilbenes in up to 69% yield.[42]

11.09.4.2 Other Alkenes

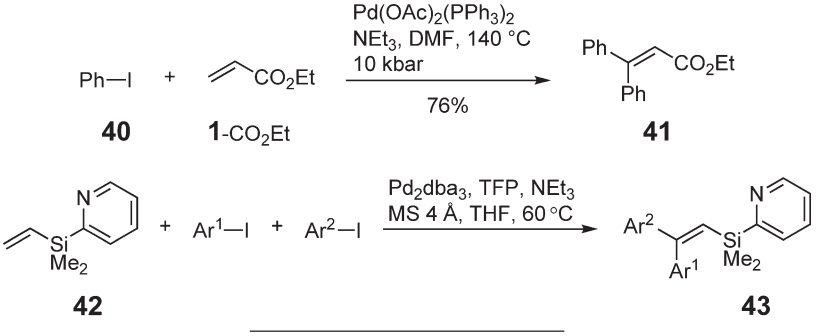
In general, the Heck coupling of aryl halides with terminal alkenes yields styrene derivatives. However, under certain conditions, such as with an excess of the aryl halide, and at elevated temperatures and/or under high pressure, electron-deficient alkenes like ethyl acrylate **1**-CO_2Et can undergo a geminal twofold coupling at the terminal methylene group to yield 1,1-diarylalkene derivatives like **41** (Scheme 15).[43,44]

The one-pot twofold Heck coupling of 2-pyridyldimethyl(vinyl)silane **42** was also carried out with two different aryl iodides to afford 2′,2′-diaryl(vinyl)silanes **43** in good yields (Scheme 15).[44] A coordination of the pyridyl group to



Ar	*Yield* (%)
Ph	69
$Et_3\overset{+}{N}H\ C_6H_4\text{-}4\text{-}SO_3^-$	64

Scheme 14 Twofold Heck coupling on ethylene.[42]



Ar^1	Ar^2	*Yield* (%)
Ph	Ph	74
Ph		68
	Ph	65

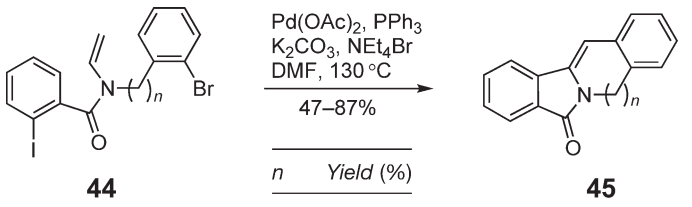
Scheme 15 Twofold Heck couplings on acceptor-substituted terminal alkenes to yield geminally diarylated alkenes.[43,44]

palladium might render the carbopalladation event kinetically and/or thermodynamically favorable. A subsequent Hiyama-type cross-coupling of the thus obtained (2′,2′-diarylvinyl)silanes **43** produced triarylethylene derivatives with three different aryl groups, in high yields.[44]

Some tetracyclic nitrogen heterocycles **45** were elegantly obtained by twofold intramolecular Heck arylation of the vinyl group in *N*-vinylbenzamides **44** (Scheme 16).[45] This palladium-catalyzed twofold Heck reaction takes advantage of the differences in reactivity between an aryl iodide and an aryl bromide. Specifically, the sequence of events starts with a chemoselective oxidative addition of the more reactive aryl iodide to the palladium(0) species, with subsequent carbopalladation of the vinyl group in a 5-*exo-trig* mode, eventually (after β-hydride elimination) to a methyleneisoindolinone intermediate, which then undergoes a second Heck coupling with cyclization.

11.09.4.3 Dienes and Trienes

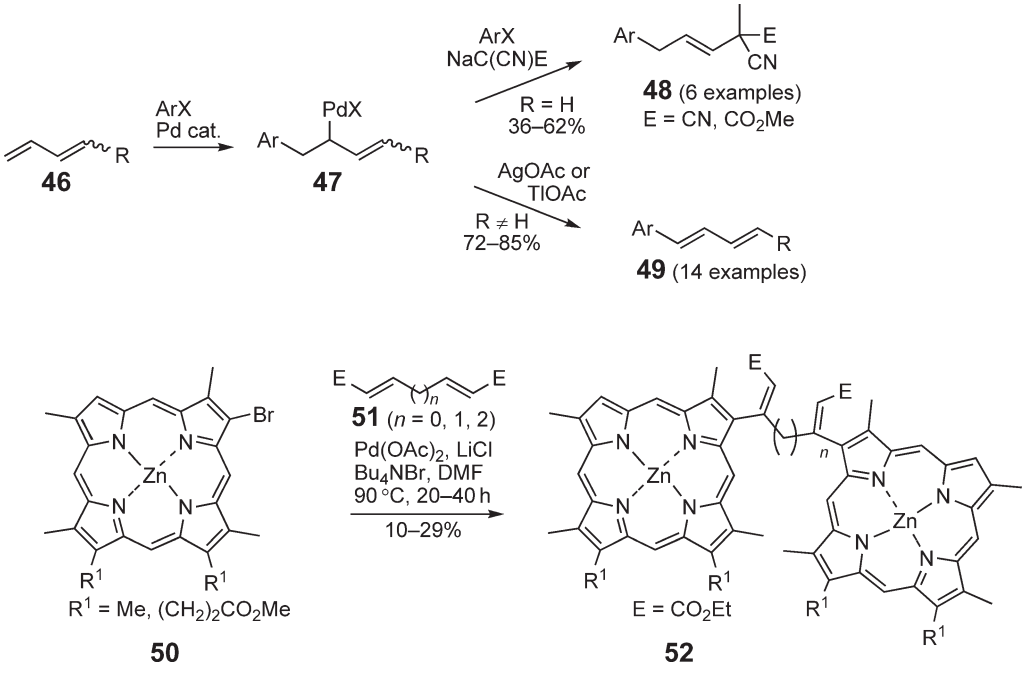
A clean twofold Heck coupling of unsubstituted butadiene **46** (R = H) in the 1- and 4-positions has not been reported. However, the initial carbopalladation product from **46** (R = H) and an *in situ* formed arylpalladium halide, the σ-allylpalladium halide **47** equilibrating with the corresponding π-allylpalladium halide, can efficiently be trapped with the anion formed by arylation of malononitrile or cyanoacetate to give **48**, a product of reductive 1,4-arylation–alkylation of 1,3-butadiene **46** (R = H).[46] β-Hydride elimination from the intermediate **47** (R ≠ H) can be accomplished when the reaction is carried out in the presence of silver acetate or thallium acetate, leading to the



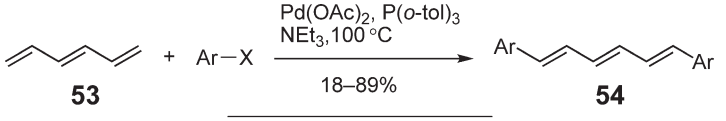
n	*Yield* (%)
0	81
1	87
2	47

Scheme 16 Construction of a heterotetracyclic skeleton by a twofold intramolecular Heck arylation of an alkenyl group.[45]

terminally arylated conjugated dienes **49** (R ≠ H). A twofold Heck coupling of conjugated and non-conjugated diethyl 1,(4 + *n*)-alka-1,(3 + *n*)-dienedicarboxylates **51** with brominated zinc-porphyrin complexes **50** has been used to prepare bisacrylate-tethered bismetalloporphyrins **52** (Scheme 17).[47] In contrast to the unsubstituted 1,3-butadiene **46** (R = H), *trans*-1,3,5-hexatriene **53** underwent clean 1,6-bisarylation to give 1,6-diarylhexa-1,3,5-trienes **54** (Scheme 18).[48] In general, electron-acceptor-substituted haloarenes give higher yields than donor-substituted ones. Similarly, bromoalkenes such as *β*-bromostyrene can be coupled with 1,3,5-hexatriene **53** to furnish 1,10-



Scheme 17 Twofold Heck coupling reactions with conjugated and non-conjugated dienes.[46,47,49]



Ar—X	*Yield* (%)
4-OHCC$_6$H$_4$Br	89
4-O$_2$NC$_6$H$_4$Br	65
4-AcOC$_6$H$_4$Br	30
PhI	18

Scheme 18 Twofold Heck reactions with *trans*-1,3,5-hexatriene.[48]

diphenyldecapentaene, albeit in low yield (14%). Thus, this twofold coupling provides a facile access to conjugated oligoene hydrocarbon skeletons. As byproducts, Diels–Alder adducts of the newly formed oligoene derivatives onto the starting material **53** were observed.[48]

11.09.5 Twofold Heck Couplings Involving Cyclizations

11.09.5.1 Intra-intramolecular Couplings

A twofold intramolecular Heck reaction has been employed as a key step for the synthesis of the skeleton of the natural product (−)-chimonanthine **58** (Scheme 19).[50] The synthetically most challenging structural features of this bispyrroloindoline alkaloid are its two adjacent quaternary centers. They were both built up by intramolecular double-bond carbopalladations, which stereoselectively produced the pentacycle **57** from the C_2-symmetrical bis[*N*-(2-iodophenyl)-cyclohexane-1,2-dicarboxamide **55** via the intermediate **56**. The key intermediate **57** was thus obtained as a single enantiomer in 90% yield.

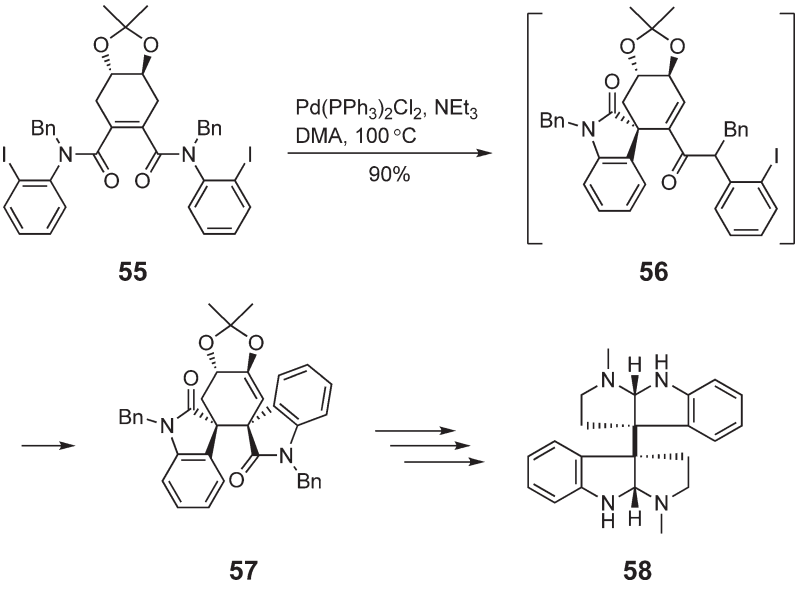
11.09.5.2 Inter-intramolecular Couplings

A sequence of an inter- and an intramolecular Heck coupling has been used to construct the 26-membered carbocyclic compound **60** from an acyclic precursor **59**, which presents half of the target molecule (Scheme 20).[51] The first step of this twofold coupling is favored to occur inter- rather than intramolecularly, because the latter would lead to a highly strained 13-membered ring system with a biaryl unit and a *trans*-configured double bond. In the cyclizing second step, polymerization is disfavored by the orientation of the two side arms in the 3- and 3′-positions of the initially formed 1,1′-biaryl derivative.

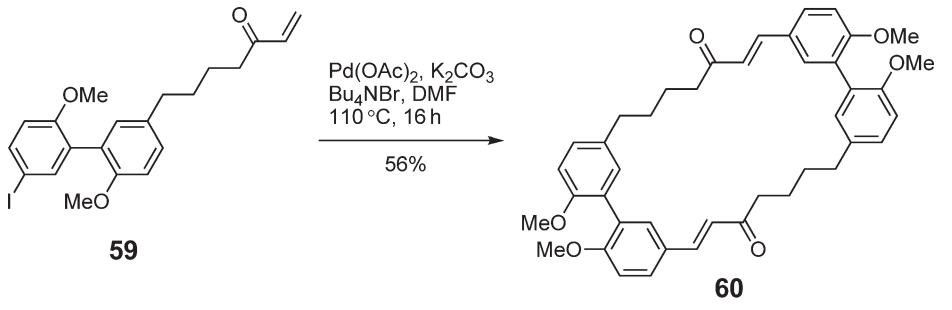
Surprisingly, *o*-bromostilbenes **61**, under Jeffery conditions, also undergo reductive dimerization by an inter-intramolecular coupling sequence to give 9,10-bis(arylmethylene)dihydroanthracenes **62** in high yields (Scheme 20).[52]

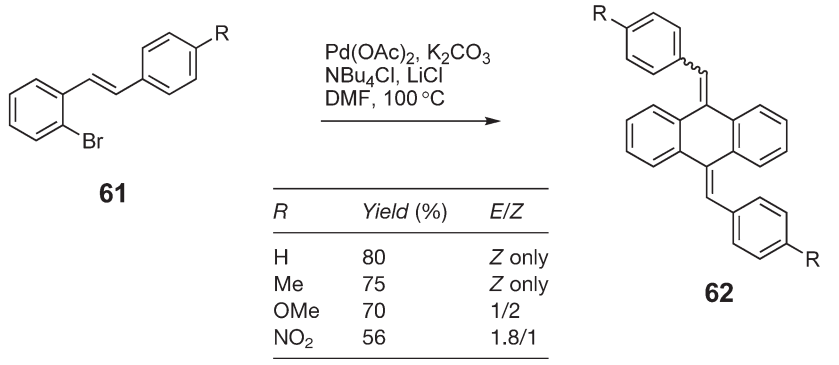
The relatively simple mold alkaloid arcyriacyanin A also has rapidly been assembled employing an inter-intramolecular Heck reaction sequence (Scheme 21). Treatment of the bromo(indolyl)maleimide **63** and 4-bromoindole **64** with palladium acetate in the presence of triphenylphosphine and triethylamine, that is, classical Heck conditions, in acetonitrile at 80 °C gave the hexacyclic natural product in up to 30% yield.[53]

A similar sequence has been utilized for an elegant assembly of the estrone derivative **68**.[54] Under modified Heck conditions, the dibromomethoxystyrene **66** was coupled with the enantiomerically pure hexahydroindene derivative **67**, prepared from an established C,D-ring building block of previously developed steroid total syntheses, under



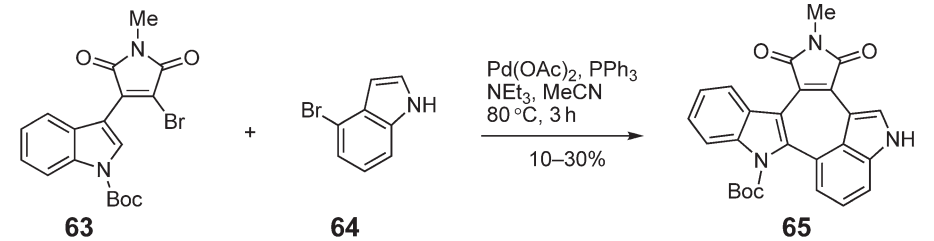
Scheme 19 A twofold intramolecular Heck reaction en route to the bispyrroloindoline alkaloid (−)-chimonanthine **58**.[50]

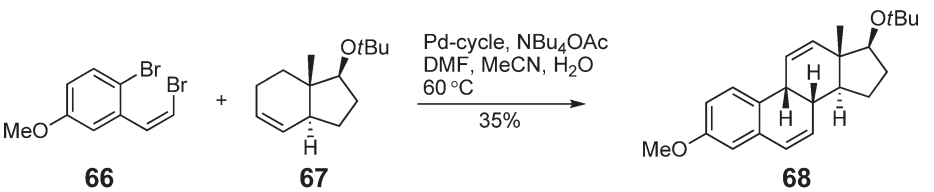


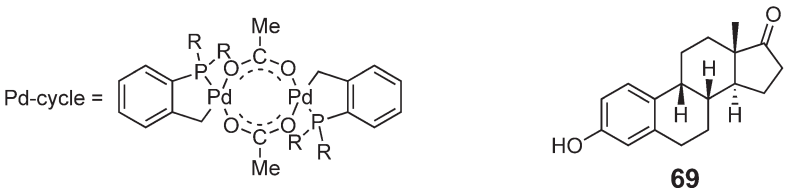


R	*Yield* (%)	*E*/*Z*
H	80	*Z* only
Me	75	*Z* only
OMe	70	1/2
NO_2	56	1.8/1

Scheme 20 Inter-intramolecular Heck coupling sequences with cyclizations leading to a macrocycle and to 9,10-dihydroanthracene derivatives.[51,52]







Scheme 21 Rapid assembly of the mold alkaloid arcyriacyanin A **65** and the skeleton **68** of estrone **69** by inter-intramolecular Heck coupling sequences.[53,54]

palladium catalysis, to furnish **68** in moderate yield (35%). The methyl group in **67** controls the stereochemistry of this process by forcing the initial carbopalladation of the double bond in **67** to occur from the opposite side, and the subsequent debromopalladation with cyclization must occur from the same side resulting in a *cis*-junction between the B- and C-rings. Due to the regioselectivity of the first coupling step, the newly formed six-membered ring is attached to **67** in the right position, and with a high degree of diastereoselectivity for the two stereogenic centers at the ring junction. The success of this transformation heavily relies on the proper choice of the catalyst. As it turned out, only the palladacycle from tris-*o*-tolylphosphine and palladium acetate[33,55,55a] brought about the second, the intramolecular, coupling.

11.09.6 Co-Cyclizations and Cascade Oligocyclizations by Multiple Heck-type Reactions

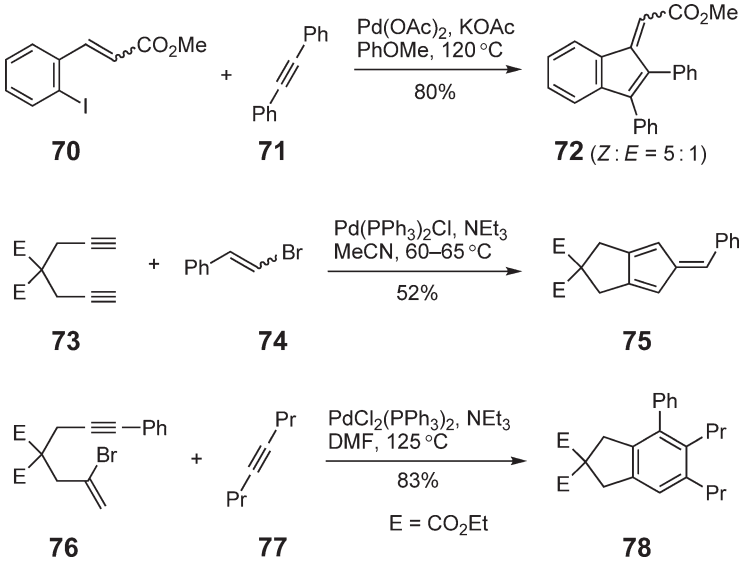
11.09.6.1 Oligocyclizations Succeeding Inter- and Intramolecular Carbopalladations of Alkyne Triple Bonds

Highly efficient cascade cyclizations consisting of Heck-type reactions can be designed especially for the construction of various oligocyclic systems. Starting with an oxidative addition of an aryl or alkenyl halide to a palladium(0) species, the resulting organopalladium halide can undergo carbopalladation of a carbon–carbon triple or double bond without immediate β-dehydropalladation, and the σ-alkenyl- or σ-alkylpalladium intermediate can undergo a further carbopalladation of a carbon–carbon triple or double bond, etc., before the sequence is terminated by β-dehydropalladation.

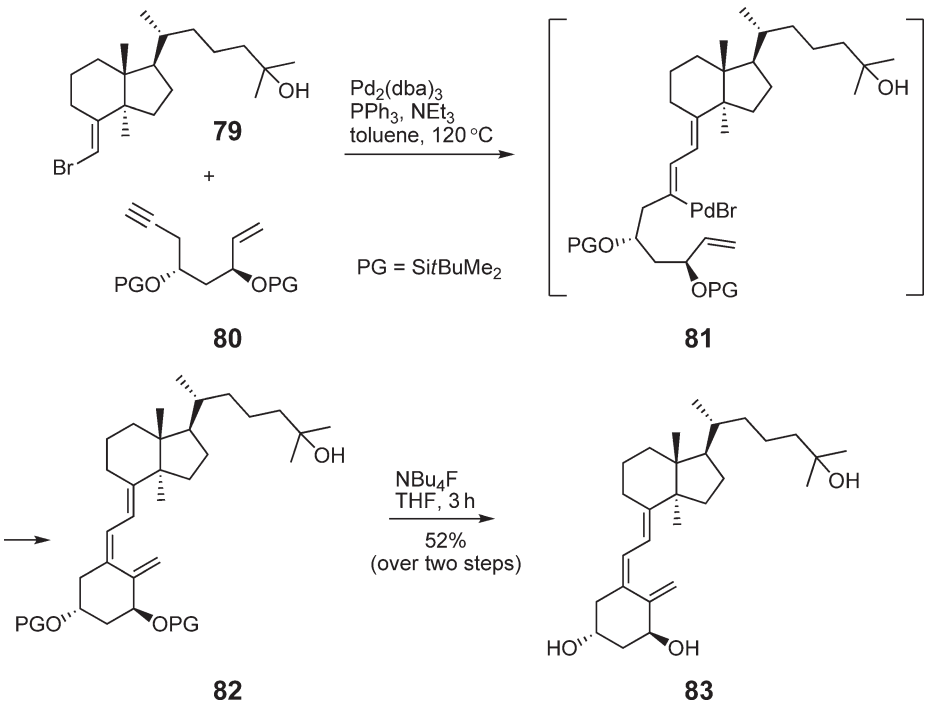
The alkyne relay, in particular, has frequently been used for cascade carbopalladations with ring formation, because a carbon–carbon triple bond is more reactive toward carbopalladation than a carbon–carbon double bond. Thus, methyl *o*-iodocinnamate **70** reacts with diphenylacetylene **71** to yield the methylenediphenylindene derivative **72** (Scheme 22).[56]

An inter-intra-intramolecular carbopalladation cascade, initiated by the alkenylpalladium bromide intermediate from β-bromostyrene **74** inserting into one of the triple bonds of the diyne **73**, yields the ring-annelated fulvene derivative **75** (Scheme 22).[57]

A different reaction mode was observed in the Pd-catalyzed co-cyclization of the 2-bromo-1-en-6-yne **76** and 4-octyne **77**. After an intramolecular carbopalladation of the triple bond in **76**, the formed alkenylpalladium bromide carbopalladates **77** and this is followed by another intramolecular carbopalladation or 6π-electrocyclization and dehydropalladation to yield the oligosubstituted indane derivative (Scheme 22).[58]



Scheme 22 Alkyne relays in inter-intramolecular carbopalladation cascades leading to ring-annelated alkylidenecyclopentadienes and cyclopentenes.[56–58]



Scheme 23 Highly convergent assembly of calcitriol **83** employing an alkyne-relayed inter-intramolecular carbopalladation cascade.[59]

One of the most elegant approaches to the clinically important calcitriol **83** has been achieved by a similar alkyne-relayed inter-intramolecular carbopalladation cascade initiated by the alkenylpalladium bromide formed from **79** attacking the 1,7-enyne **80**. The 6-e*xo-trig* cyclizing carbopalladation in the intermediate **81** and β-dehydropalladation leads to the silyl-protected calcitriol **82** in a highly convergent manner. In this one-pot transformation, two new carbon–carbon bonds are formed to yield **82**, and subsequent protiodesilylation gives the final product **83** with a conjugated triene unit in 52% overall yield (Scheme 23).[59]

Tricyclic skeletons such as **85**, **87**, **89** with a central benzene ring are formed in the fully intramolecular Pd-catalyzed cascade cyclization of 2-bromo-1-ene-*n*,*m*-diynes **84**, **86**, **88** and analogs (Scheme 24).[60] This process involves two alkyne relays in a row and a final 6π-electrocyclization or 6-*endo-trig* carbopalladation with ensuing β-dehydropalladation.

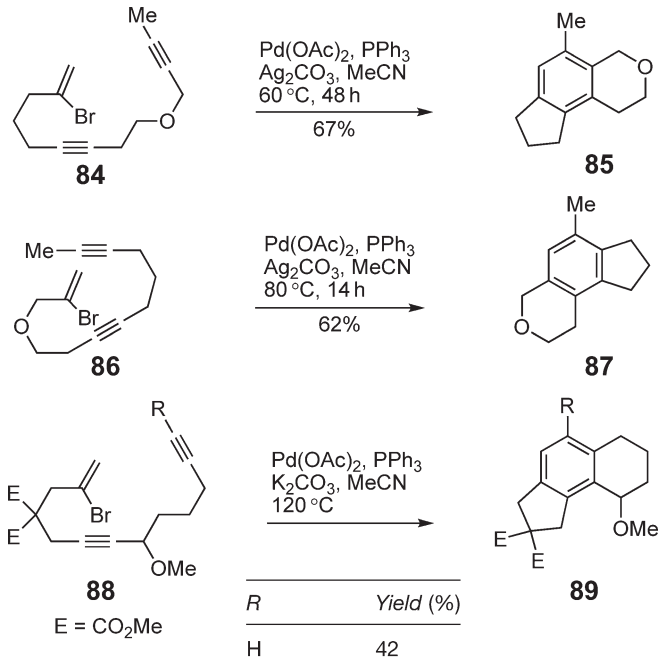
A single alkyne relay is involved in the cascade oligocyclizations of 2-bromoalka-1,*m*-diene-*n*-ynes such as **90**, **92**, **94** and others. Three new rings are formed in these sequences of two intramolecular Heck-type reactions and a 6π-electrocyclization leading to various oligocyclic systems such as **91**, **93**, **95** in a rather elegant way (Scheme 25).[60–63]

These palladium-catalyzed cascade tricyclizations proceed particularly smoothly and with high yields as long as five-membered rings are formed in both intramolecular carbopalladation steps. The overall yields are not as good when one of the carbopalladation steps forms a six-membered ring, especially if this is the second ring-forming step (Scheme 26).[8] The 7,6,5- as well as 5,6,6- and 5,6,7-ring-size combinations are achieved in moderate or poor yields.

However, 2-bromotetradeca-1,13-dien-7-ynes such as **96** ($n = 1$), which were set up to furnish decahydrophenanthrene skeletons (6-6-6-tricycles), gave the interesting tetracyclic compounds **97** ($n = 1$) with a cyclopropane moiety bridging the A- and B-ring junction (Scheme 27).[64,64a]

The tetracyclization is also very efficient for the bromopentadecadienyne **96** ($n = 2$), in which the first cyclization forms a seven-membered ring, and even for **96** ($n = 3$), from which the eight-membered ring-containing tetracycle **97** ($n = 3$) could be isolated in 30% yield from the corresponding precursors.[64,64a]

In these Heck-type cascade tetracyclizations, substituents in the acyclic precursors can play a major role and cause the sequential reaction to proceed in an unprecedented direction. The 2-bromotetradeca-1,13-dien-7-yne **98** with a



R	*Yield* (%)
H	42
CO_2Me	61
COMe	75
$C(OH)Et_2$	67

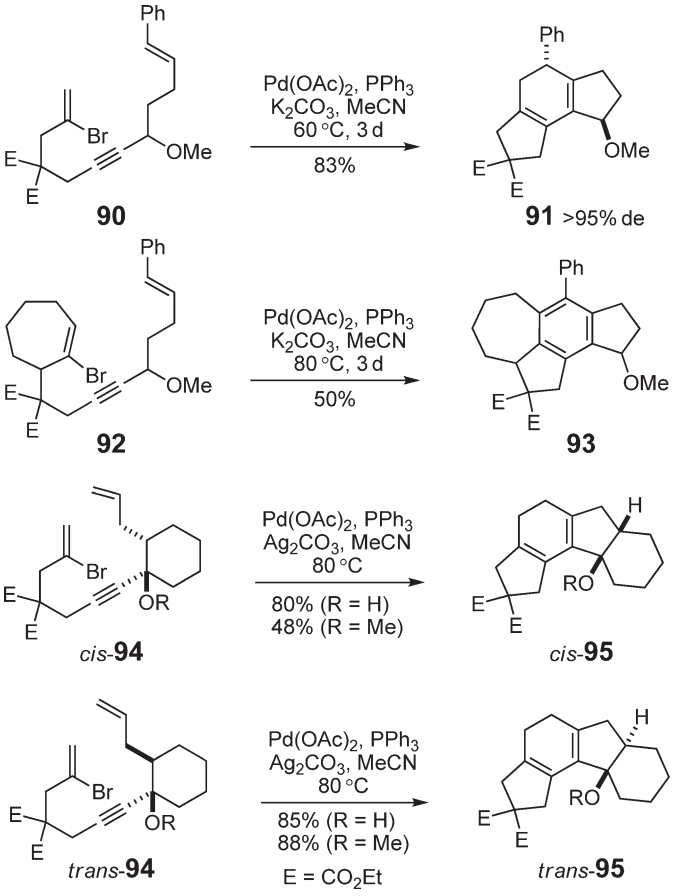
Scheme 24 Two alkyne relays in sequence in intra-intramolecular carbopalladation cascades.[60]

9-methoxy substituent yields the novel tetracyclic system **99** with a cyclopropane ring annelated on the five-membered B-ring. This cascade reaction may involve an unusual γ-hydride elimination in the tricyclic intermediate **100** as the last step, or an unprecedented α-dehydrobromination on an alkylpalladium bromide intermediate to yield a palladiumcarbene species **101** that subsequently undergoes an intramolecular cheletropic addition across the distal double bond to form the cyclopropane ring in **99**.[64,64a]

Regarding efficiency in terms of achieving a maximum increase of molecular complexity in a minimum number of operational steps, the zipper-mode tetracyclization of the open-chain trienediyne **102** leading to the tetracyclic steroidal skeleton **103**, as accomplished by Negishi *et al.*, is particularly impressive (Scheme 28).[65] This transformation involves four intramolecular carbopalladations with two alkyne relays forming four new C,C-bonds with the creation of four rings.

Representative examples of a remarkable increase in molecular complexity by an intra-intermolecular cascade coupling involving an alkyne relay are the Pd-catalyzed co-cyclizations of the 2-bromohept-1-en-6-ynes **104** with bicyclopropylidene **12** leading to spirocyclopropanated bicyclo[4.3.0]nonadiene derivatives **105** (Scheme 29). This sequential transformation involves an intermolecular carbopalladation of the highly reactive alkene **12** by the alkenylpalladium bromide intermediate initially formed by intramolecular carbopalladation of the alkyne relay in **104**, subsequent cyclopropylmethyl- to homoallylpalladium bromide rearrangement turning **106** into **107**, β-dehydropalladation of the latter, and eventual 6π-electrocyclization of the thus formed cross-conjugated tetraene **108**.[66] The tetraenes **108** can be isolated, when the reaction is carried out at 80 °C rather than at 110 °C (Scheme 29). They can also be trapped by an added dienophile, which preferentially [2 + 4]-cycloadds across the allylidenecyclopropane diene moiety leading to a new 1,3,5-hexatriene, and this subsequently undergoes 6π-electrocyclization.[66]

Unfortunately, this process gave good results only with bulky substituents at the acetylenic terminus in **104** and, surprisingly, Jeffery's conditions—but without a quaternary ammonium salt—were found to work best. With an additional alkenyl substituent at the acetylenic terminus as in the cyclohexenyl-substituted 2-bromonona-1,8-dien-6-yne **109**, the co-cyclization with bicyclopropylidene **12**, under these conditions, leads to **110**. This transformation involves two consecutive 6π-electrocyclizations of the initially formed cross-conjugated pentaene **111**, which was not isolated (Scheme 30).[66]



Scheme 25 Formation of three new rings from 2-bromoalka-1,*m*-dien-*n*-ynes in a domino sequence of two intramolecular Heck-type reactions and 6π-electrocyclization.[60–63]

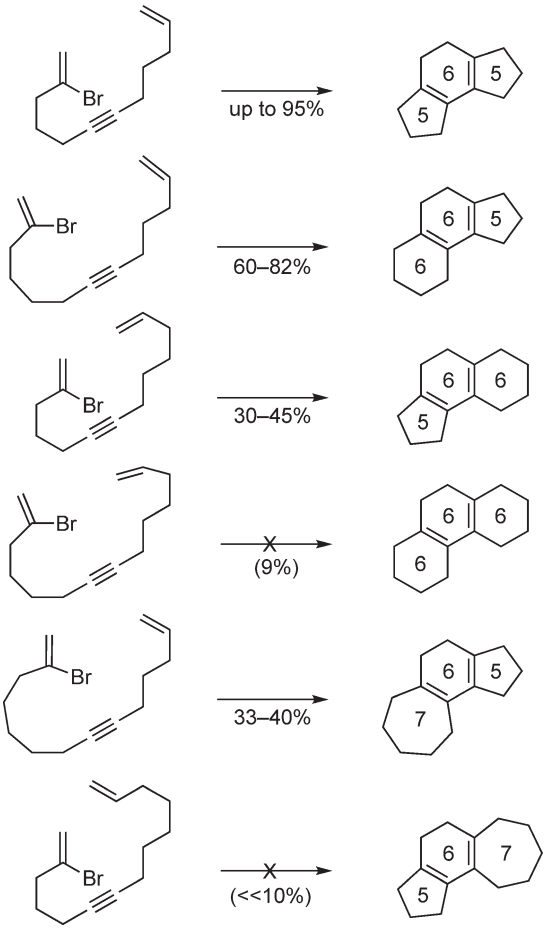
11.09.6.2 Oligocyclizations Succeeding Inter- and Intramolecular Carbopalladations of Alkene Double Bonds

Five-membered ring closures have been observed when *o*-halostyrene derivatives such as **113** were coupled with alkenes under palladium catalysis. Apparently, an intramolecular carbopalladation with 5-*exo-trig* ring closure to give **114**-R[1] can favorably compete with β-hydride elimination in the first-formed intermediate to yield **115**-R[1]. This reaction mode for the halostyrene is observed especially under Jeffery conditions, when the alkene is ethene or propene (Scheme 31). Under the same conditions, however, *o*-dibromobenzene gives very high yields of *o*-dialkenylbenzene derivatives (see Scheme 2).[18]

When β-hydride elimination in the carbopalladation relay is completely blocked as in norbornene **116** and norbornadiene **117**, the coupling with *o*-bromostyrene **113** furnished the respective cyclopentannelation products **118** and **119** exclusively and in good yields.[67]

Two molecules of norbornene **116** are incorporated in its coupling with β-bromostyrene to yield the bisnorbornane-annelated methylenecyclopentane derivative **120**.[67] But under different conditions, the reaction proceeds with the reverse 2:1 stoichiometry to give the cyclohexadiene-annelated norbornane derivative **121** (Scheme 32).[68]

Cascade carbopalladation sequences after attack on an alkene are most commonly terminated by dehydropalladation, if a β-hydride is available in a *syn*-orientation. The intramolecular carbopalladation starting from the monocyclic diene **122** with a geminally disubstituted alkene terminator leads to a neopentylpalladium intermediate **123**, which cannot undergo β-dehydropalladation, but continue the cascade by a 3-*exo-trig* carbopalladation to eventually form the tricycloalkene **124** (Scheme 33).[69] This sequential bicyclization proceeds equally well for ring sizes 5, 6, and 7 in the first-formed ring.



Scheme 26 Achievable ring-size combinations in the palladium-catalyzed cascade tricyclizations of 2-bromoalka-1,*m*-dien-*n*-ynes.[8]

For such cascades with intramolecular carbopalladations, smaller ring sizes (5 and 6) are preferred due to the entropic term; thus, 1,1-disubstituted alkenes suitably located in the substrate preferably serve as the relay without formation of the larger ring size resulting from insertion into the terminal alkene moiety.

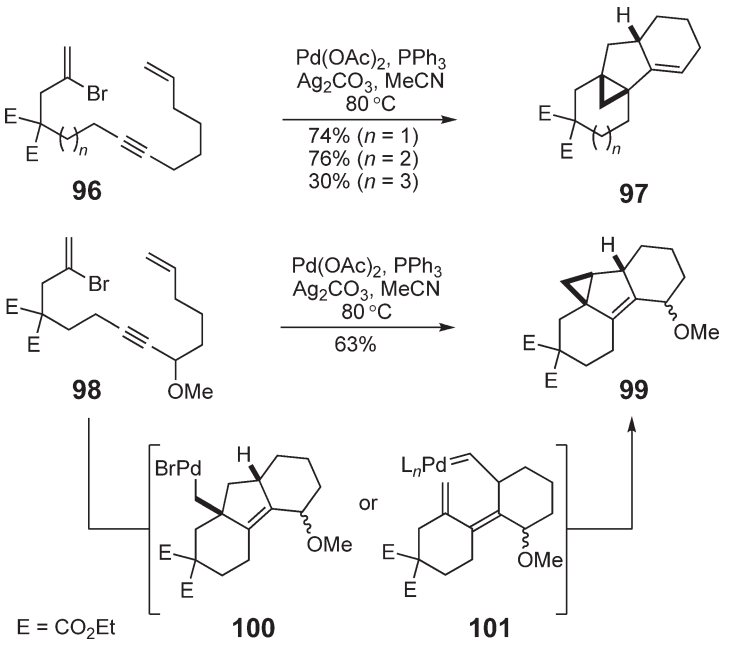
This principle has been exploited in the pioneering application of a cascade oligocyclization by Overman *et al.* toward the total synthesis of the natural product scopadulcic acid A.[70] Treatment of the iodoalkenyl-substituted methylenecycloheptene derivative **125** with a suitable palladium catalyst cocktail first induces a 6-*exo-trig* carbopalladation of the exomethylene group. The resulting neopentylpalladium intermediate then undergoes a second 5-*exo-trig* carbopalladation, this time of the endocyclic double bond in **125**, and the sequence is terminated by β-hydride elimination furnishing the tetracycle **126**, which was further elaborated to the natural product (Scheme 33).[70] It is remarkable that all three quaternary carbon centers in **126** can be assembled by intramolecular Heck-type reactions.

Adhering to the same principle, the (*o*-iodophenyl)diene **129** undergoes a sequence of two intramolecular 5-*exo-trig* carbopalladations (Scheme 34) to yield the benzoannelated spiro[4.4]nonane derivative **129**.[71]

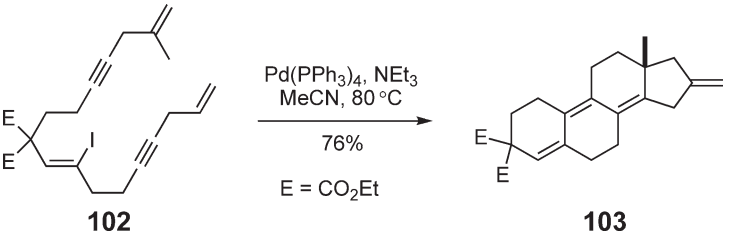
The ultimate in the so-called zipper-mode carbopalladations has been demonstrated by Trost and Shi with the oligocyclization of the heptaenyne **130c** to the heptacyclic hexaspirane **131c**.[72,72a]

Such oligocyclizations have also been carried out on prochiral substrates such as **132** with asymmetric induction by chiral ligands on palladium. With (*S*,*S*)-DIOP, the spirocyclic system **133** was obtained in good yield with an enantiomeric excess (ee) of 45% (Scheme 35).[71]

With (*R*,*R*)-BINAP as the ligand, Keay and Lau have been able to achieve the cascade cyclizations of the dienyl-substituted aryl triflates **134** toward the total synthesis of the natural product (+)-halenaquinone with ee's of up to 96% (Scheme 35). For these substrates, they observed an interesting influence of the remote substituent R^2 in **134**.[73]



Scheme 27 Cascade tetracyclizations of 2-bromoalka-1,*m*-dien-*n*-ynes.[64,64a]



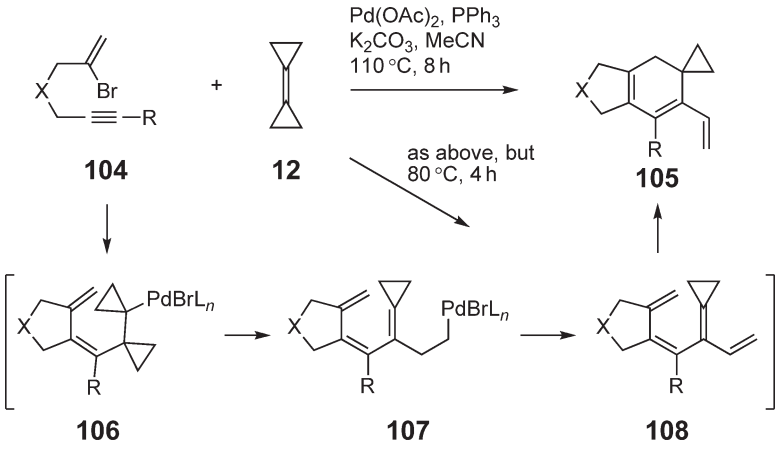
Scheme 28 Construction of a tetracyclic steroid skeleton by a crochet-mode cyclization.[65]

Narasaka *et al*. have extended these crochet-mode cascade cyclizations to di- and trienyl-substituted *o*-pentafluorobenzoyloximes **136** and **140**, to furnish spirofused cyclic imines **139** and **141**, respectively (Scheme 36).[74] The latter structure has been found in some bioactive natural products such as cephalotaxine.

The transformations of **136** proceed cleanly upon treatment with a catalytic amount of $Pd(PPh_3)_4$, in the presence of triethylamine and molecular sieve (MS) 4 Å; it apparently is initiated by oxidative addition of the N(sp^2)–O bond of **136** to the Pd(0) complex, and this is succeeded by two or even three intramolecular carbopalladations followed by β-hydride elimination. This Heck-type reaction is not affected by the configuration of the oxime derivatives probably due to a facile enough *E*/*Z*-isomerization of the alkylideneaminopalladium intermediate.

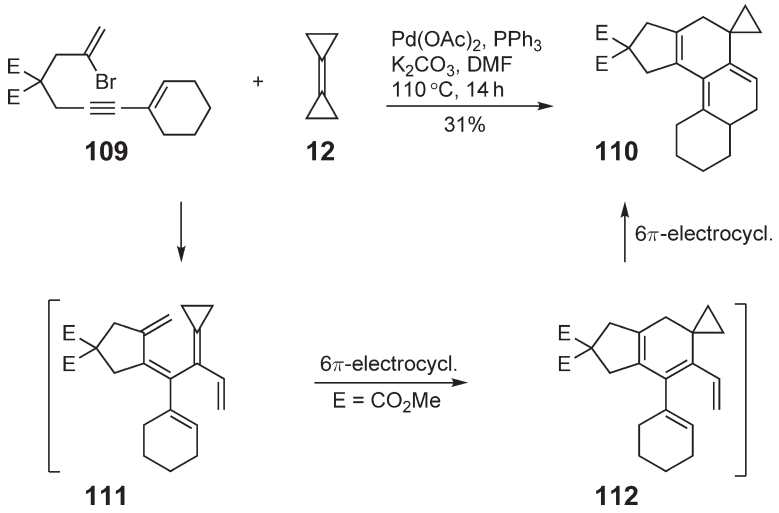
11.09.6.3 Cyclizations Proceeding with Inter- and Intramolecular Carbopalladations of Allenes

Grigg and Xu have developed a variety of so-called queuing cascades involving allenes. The intra-intermolecular carbopalladation sequence of the *o*-iodo-*N*-methyl-*N*-(methylallyl)aniline **142** and 1,1-dimethylallene **143** with subsequent β-dehydropalladation leads to the 1,3-dienyl-substituted indole derivative **144**, which is immediately trapped by an added dienophile (e.g., *N*-methylmaleimide) in a Diels–Alder reaction to yield **145** (Scheme 37).[75]



	X	R	108 (%)	105 (%)
a	$C(CO_2Me)_2$	*t*Bu	66	56
b	$C(CO_2Me)_2$	*t*$BuMe_2Si$	72	65
c	O	Ph	64	71
d	NTs	Ph	35	44

Scheme 29 Palladium-catalyzed co-cyclizations of 2-bromohept-1-en-6-ynes **104** with bicyclopropylidene **12**.[66]

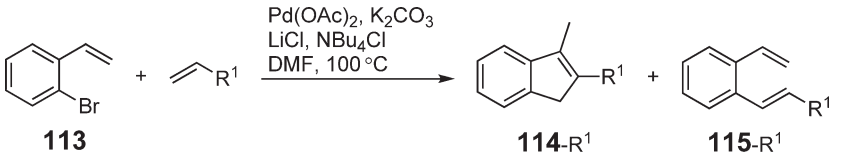


Scheme 30 Palladium-catalyzed co-cyclization of a 2-bromonona-1,8-dien-6-yne with bicyclopropylidene **12** involving two consecutive 6π-electrocyclizations.[66]

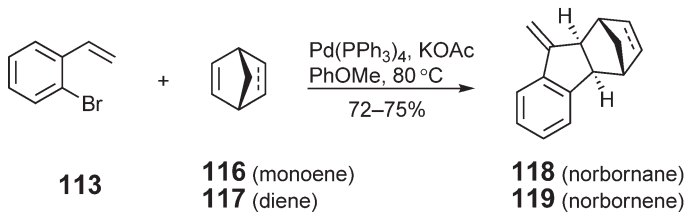
Under palladium catalysis, the *o*-iodoallenylbenzene **146** first undergoes an intermolecular carbopalladation of the double bond in the added norbornene **116**, and only then follows an intramolecular carbopalladation of the allene moiety in **146**; ensuing β-hydride elimination finally provides the tricyclic compound **147** (Scheme 37).[76]

11.09.6.4 Cascade Cyclizations Involving C–H Bond Activation of an Arene

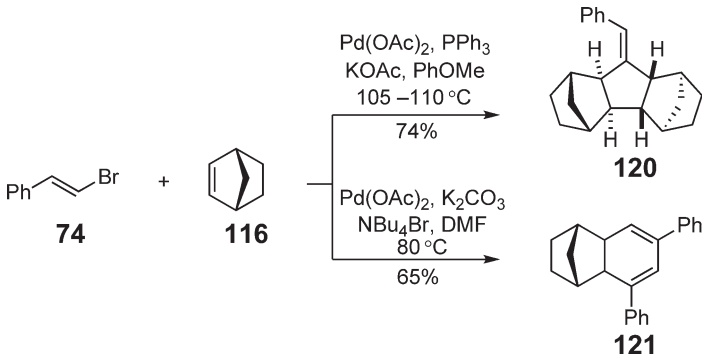
Termination of cascade carbopalladation sequences by arylation can play a major role in systems that form a reasonably long-lived palladium intermediate and contain a suitably functionalized arene moiety in the vicinity of the organopalladium function. In particular, neopentylpalladium intermediates have been found to intramolecularly attack an adjacent arene moiety. For example, iodoarenes **149** with electron-withdrawing substituents in the



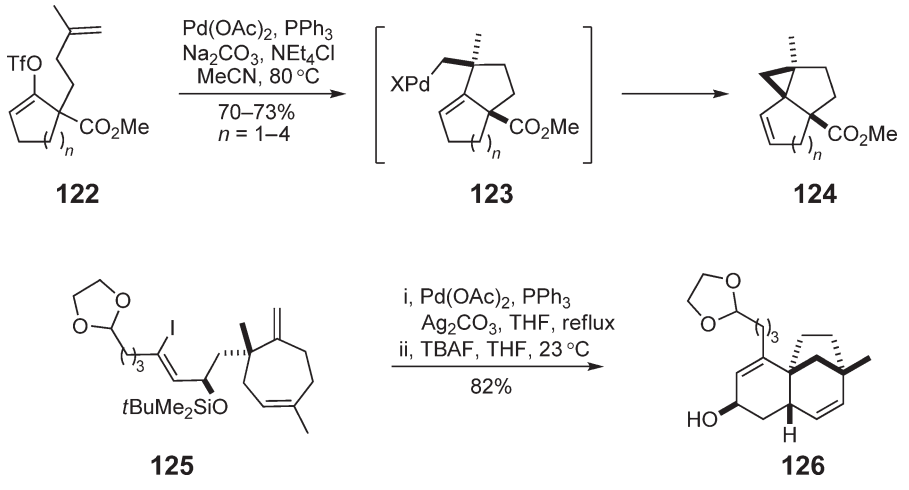
R^1	*Yield* (%)	*Ratio* **114 : 115**
H	71	5 : 1
Me	51	1 : 3



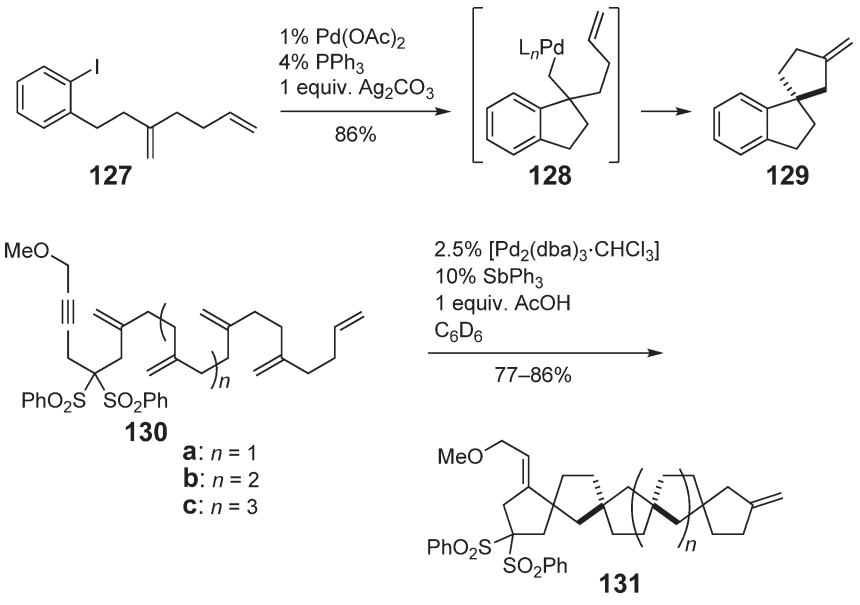
Scheme 31 Cyclopentannelation succeeding intermolecular carbopalladation of an alkene double bond.[67]



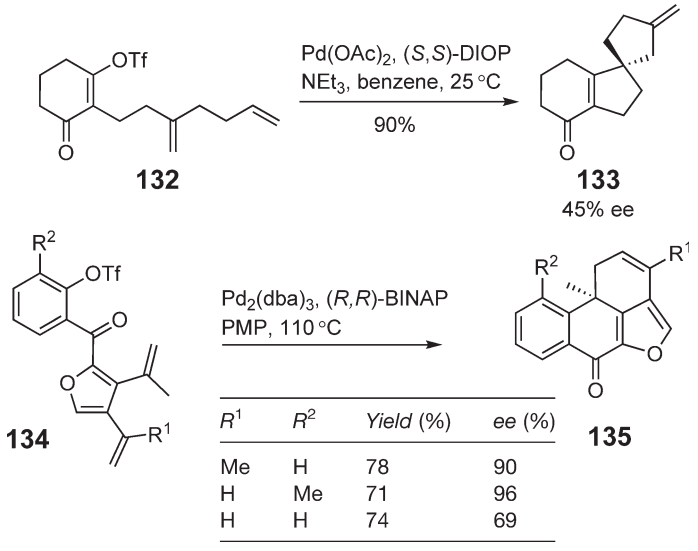
Scheme 32 Two different reaction modes in the cross-coupling of β-bromostyrene with norbornene.[67,68]



Scheme 33 All-intramolecular double-bond carbopalladation cascades leading to tricyclic skeletons.[69,70]



Scheme 34 Zipper-mode cascade carbopalladations leading to spirocyclic skeletons.[71,72,72a]

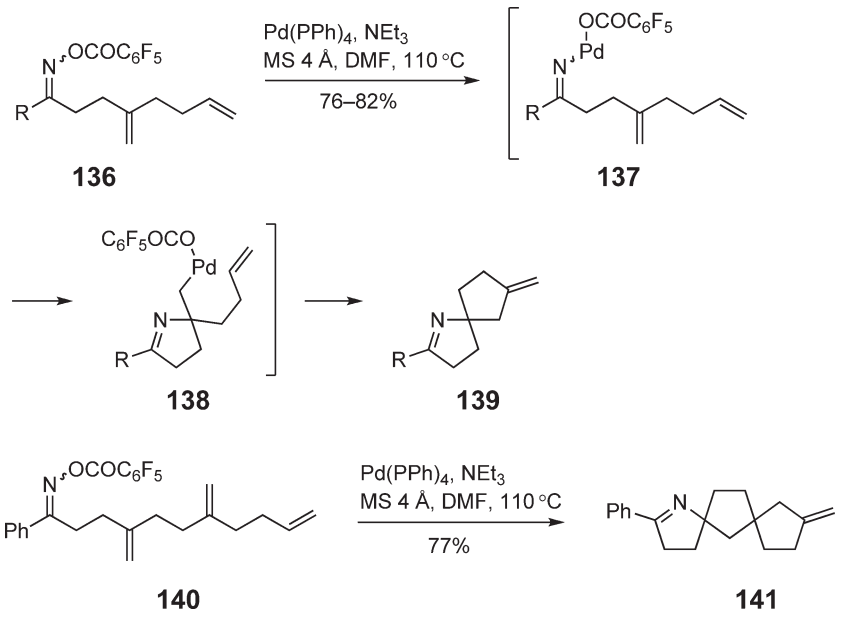


Scheme 35 Ligand-induced enantioselective crochet-mode oligocyclizations. PMP = pentamethylpiperidine.[71,73]

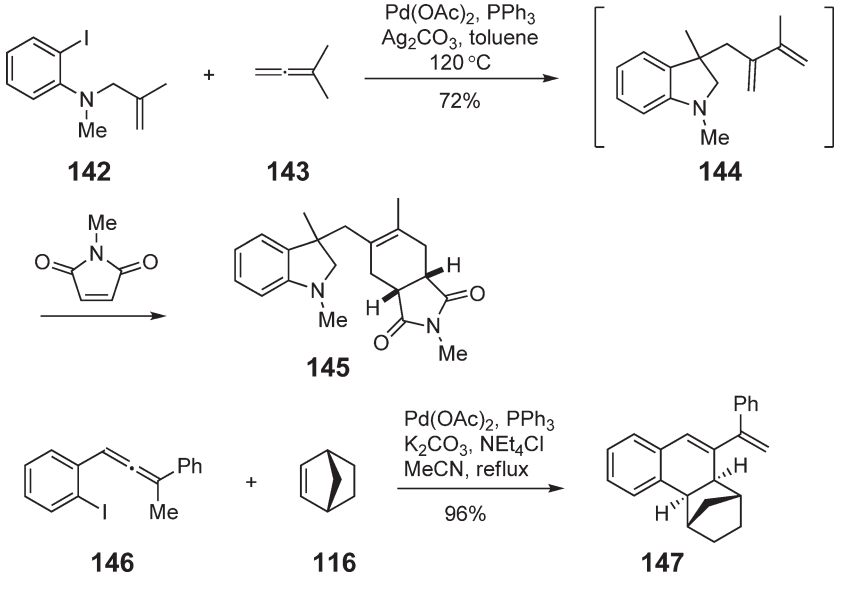
ortho-position react with the 1,6-enyne **148** with *ortho*-C–H activation and cyclization to yield the tricyclic systems **151** incorporating the aromatic ring (Scheme 38).[77]

The intermolecular carbopalladation of a triple bond can be faster than that of an intramolecular double bond as, for example, in the *o*-iodo(1-methylallyl)benzene **152**. The arylpalladium iodide initially formed from **152** and a palladium(0) species intermolecularly carbopalladates diphenylacetylene **71**, and only the thus formed alkenylpalladium intermediate **153** undergoes insertion into the internal double bond to furnish the neopentylpalladium species **154** which, by *ortho*-attack on the adjacent phenyl group, finally forms the tetracyclic system **155**.[78]

With its *ortho*-(ω-phenylalkynyl) group, the iodoarene **156** in the presence of a palladium catalyst initiates the cascade process with an intramolecular carbopalladation; this is followed by an intermolecular insertion, for example, into the double bond of the 3-azanorborn-5-en-1-one **157** and terminated by *ortho*-attack of the norbornyl-type σ-palladium intermediate on the previously terminal aryl group to yield the two regioisomeric hexacyclic systems **158** and **159** in a ratio of 1 : 1 (Scheme 39).[79]



Scheme 36 Crochet-mode oligocyclizations of di- and trienyl-substituted *o*-pentafluorobenzoyloximes.[74]

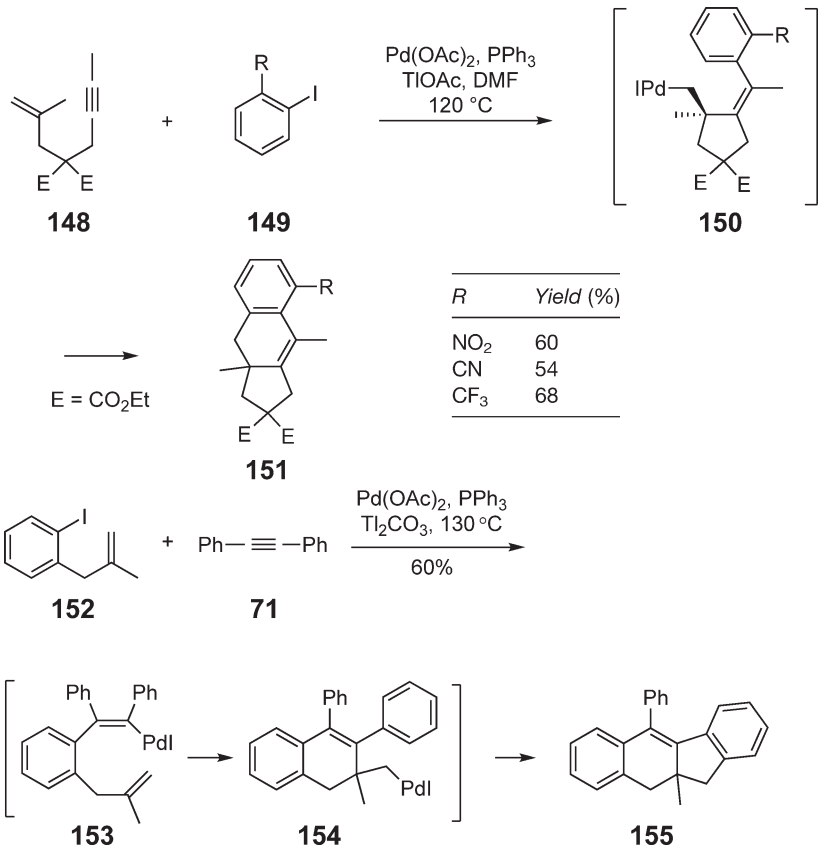


Scheme 37 Two cascade cyclizations involving inter- or intramolecular carbopalladations of allenes.[75,76]

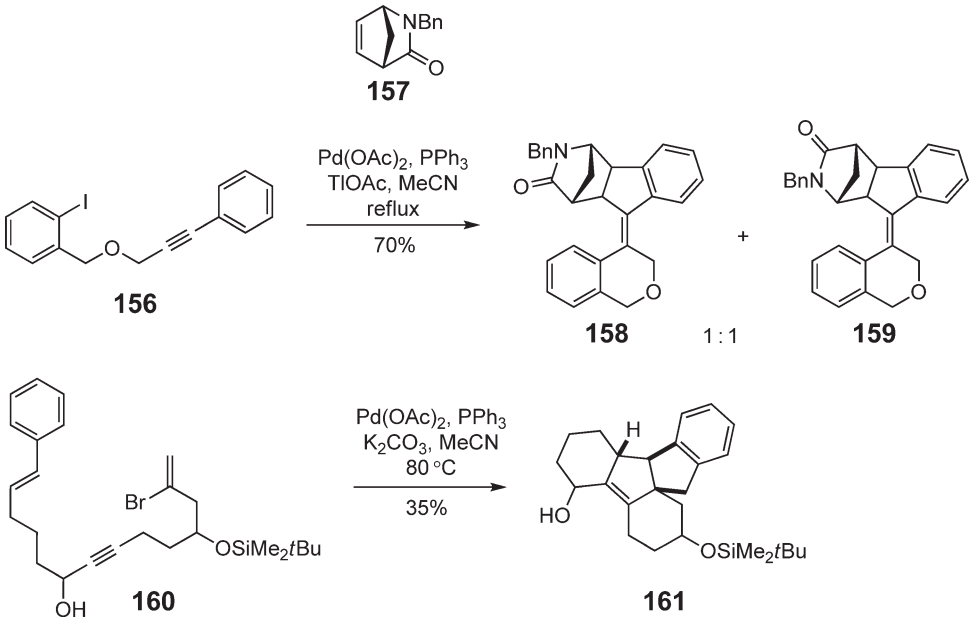
The 2-bromotetradeca-1,13-diene-7-yne **160** with its terminal phenyl group apparently also prefers to undergo a cascade cyclization via a neopentylpalladium intermediate with attack on the eventually proximal phenyl group to yield the pentacyclic system **161** (Scheme 39).[62]

11.09.7 Oligo- and Polymerizations by Heck Couplings

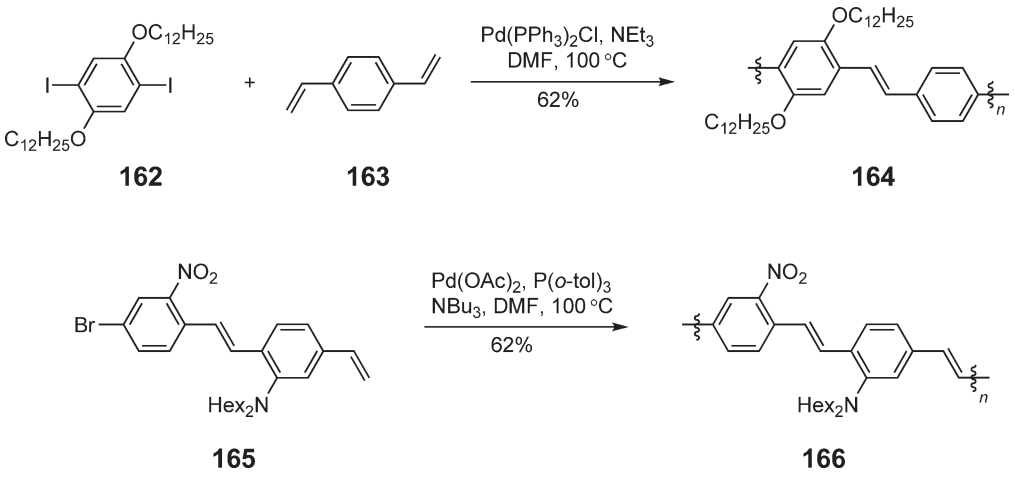
Multiple Heck reactions have also been applied in a number of ways to prepare polymers (Scheme 40).[9,10] One-dimensionally π-conjugated polymers are attractive materials because of their optical and electrical properties resulting from π-electron delocalization along their main chains. Among these, poly(*p*-phenylenevinylene) (PPV) shows high electrical conductivity, large non-linear optical responses, and electroluminescent activity. One approach



Scheme 38 Inter-intramolecular carbopalladations involving formal C–H bond activation of an arene moiety.[77,78]



Scheme 39 An intra-inter- and an intra-intramolecular carbopalladation with *ortho* C–H activation terminating the sequence.[62,62a,79]



Scheme 40 Two ways of forming substituted PPVs by multiple Heck reactions.[80–82]

to PPVs is by multiple coupling of a 2,6-dialkyloxy-substituted 1,4-diiodobenzene like **162** with *p*-divinylbenzene **163**.[80,81] Another way of achieving the same goal is by multiple coupling of an appropriately substituted 4-bromo-4′-vinylstilbene (Scheme 40).[82] Careful design of the monomers can lead to success in the synthesis of custom-tailored polymers. The Heck reaction has a high potential for the synthesis of novel materials, because the two essential functional groups (vinyl and halide substituents) are incorporated in the substrates, and the Heck reaction is quite tolerant to a variety of other functional groups.

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11.10
Pauson–Khand Reaction

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11.10.1 Introduction to Pauson–Khand (PK) Reaction

The preparation of five-membered rings has been the subject of extensive studies, which may be attributed to the ubiquity of this building block in biologically relevant natural products. The three-component transition metal-mediated [2 + 2 + 1]-carbocyclization of an alkyne, an olefin, and carbon monoxide, which is known as Pauson–Khand reaction (hereafter, PKR or PK-type reaction) when dicobalt octacarbonyl is used,[1] has attracted a great amount of interest over the last three decades. However, since the seminal work first reported during the early 1970s by Pauson and Khand, progress was at a relatively steady pace until the late 1980s. Since then, development has been explosive and the progress is exhaustively reviewed. One may find a tremendous number of publications and easily refer to them to discover more details about the specific aspects of the reaction.[2,2a–2i] The purpose of this chapter is to update and highlight the recent advances with critical comments instead of duplicating the previous review articles, and the main emphasis will be on the developments since 1993.

Owing to the efforts of Pauson and co-workers, and many others in the 1970s and 1980s, the fundamental issues with respect to regiochemistry, stereochemistry, and substrate compatibility are well established.

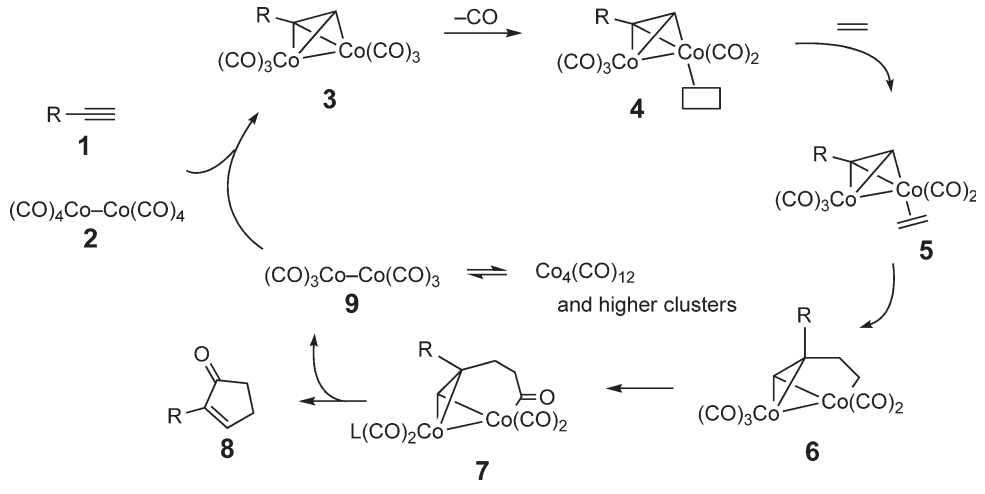
However, from the outset of this field, the limitations as well as the potentials of this cycloaddition were also apparent. For instance, the efficiency of this cycloaddition in an intermolecular manner was typically low unless strained olefins were used. Moreover, the use of unsymmetrical alkenes led to a mixture of the cyclopentenone regioisomers. Synthetic utility of this reaction is considerably expanded by the emergency of the intramolecular reaction. Schore introduced the first intramolecular version forming several rings simultaneously,[3,3a] which is now the most popular synthetic strategy in natural product synthesis because of its conceptual and operational simplicity. Additionally, the regiochemistry is no longer the problem in this variation.

11.10.2 Development and Variations in Stoichiometric Pauson–Khand Reactions

11.10.2.1 Problems in Association with the Proposed Mechanism

In spite of its simplicity and conceptual clearances, the original protocol has suffered from many intrinsic problems in a practical sense. For example, the reaction with the alkyne–cobalt complexes provided low chemical yields and required harsh reaction conditions. In addition, it was also difficult to extract the obtained product from the sticky metallic residue. Those problems can be accounted for based on the widely accepted mechanism given in Scheme 1, which, as proposed by Magnus,[4] is supported by many theoretical studies.[5,5a–5c]

The alkyne–cobalt carbonyl complex **3** formed from the alkyne **1** and dicobalt octacarbonyl **2** should lose at least one of the COs on the metal to provide the vacancy for the incoming olefins. Subsequently, an olefin-bound complex **5** rearranged oxidatively to yield a metallacyclic intermediate **6**. Migratory insertion of CO of **6** would provide the homologated ring intermediate **7**, and the following two successive reductive eliminations afford the cyclopentenone



Scheme 1

product **8** and the unsaturated dicobalt carbonyl species **9**. In this multi-step process, the decarbonylation from the complex **3** is thought to be the rate-determining step of the overall process. In fact, none of the proposed intermediates beyond **3** has been isolated and characterized except only very special cases.[6]

11.10.2.2 Promoter-assisted PKR with Dicobalt Octacarbonyl

The requirement of the harsh reaction condition is mainly related to the first decarbonylation of the complex **3**, as previously mentioned. The first practical and significant rate acceleration had been achieved by the dry support adsorption method on silica gel or alumina. Smit and Caple[7,7a] used the cobalt-complexed enynes **1** adsorbed on silica gel, and afforded the cyclopentenones in good yields by heating mildly over several hours (Table 1).

11.10.2.2.1 Oxidative promoters

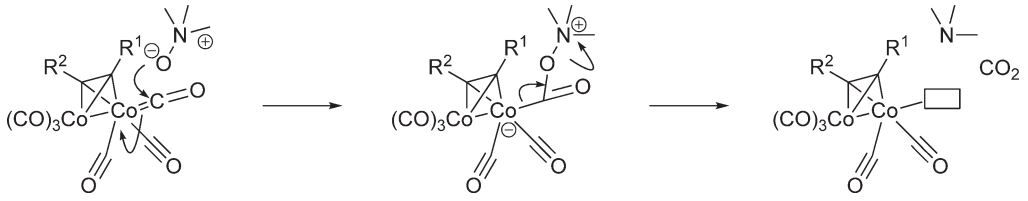
Subsequent to this success, Schreiber[8] and Jeong[8a] independently reported that amine oxides such as *N*-methylmorpholin *N*-oxide (NMO) and trimethylamine *N*-oxide (TMANO) could promote the reaction substantially, affording high yields in short reaction times. It is thought that these amine *N*-oxides act as oxidants to make at least one of the COs to CO_2, which is a much weaker binder to metal, and then provide the required vacancy for the incoming olefins. As a result, the activation energy for this rate-determining step decreased considerably to make the reaction proceed even at ambient temperatures (Scheme 2). This general approach has become the primary choice of the methods.

The beneficial effects of amine *N*-oxide promoters are well documented in the example given in Equation (1).[9] While the aromatized product **12** instead of the PKR product was obtained from the reaction of diethylacetylene **10** and compound **11** under thermal conditions, the desired PKR product **13** was formed only by the aid of amine *N*-oxide.

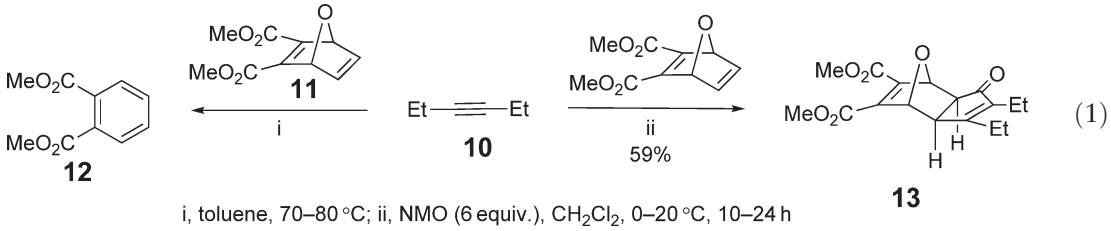
Table 1 The promoter-assisted Pauson–Khand reaction

Promoter-assisted condition				*Yield (%)*	*References*
Promoters	*Solvent*	*T* (°C)	*t*		
With Cobalt					
SiO_2		60			7,7a
By oxidative promoters					
N-methylmorpholin *N*-oxide	CH_2Cl_2	0–RT	3–20 h	95	8
Trimethylamine *N*-oxide	CH_2Cl_2	0–RT	3 h	95	8a
TMANO with 4A MS	CH_2Cl_2	−10 to RT	3 h	45–90	10
Dimethylsulfoxide	Benzene	40–50	3–20 h	83–92	11
Amine *N*-oxide on solid	THF	RT	0.5 h	91[a]	14
By non-oxidative promoters					
CH_3CN	CH_3CN	80	16 h	53	11
$RSCH_3$	1,2-DCE	80	0.5–2 h	22–99	12
Cyclohexylamine	1,2-DCE	83	5 min	99	13
NH_4OH	H_2O	100	15 min	95	13
Sulfide on solid	1,2-DCE	83	0.5 h	76[a]	15
Microwave	Toluene	90	5 min	97[a,b]	20
With Molybdenum					
DMSO	Toluene	100	8 h	76	17
$Mo(CO)_3(DMF)$	CH_2Cl_2	RT	15 min	83	18

[a] The yields were taken from the intermolecular reaction.
[b] The *exo* and *endo* ratio is 95 : 5.



Scheme 2



i, toluene, 70–80 °C; ii, NMO (6 equiv.), CH_2Cl_2, 0–20 °C, 10–24 h

(1)

Later, Perez-Castells has shown that the addition of molecular sieves to the amine *N*-oxide-promoted cycloaddition results in improved yields of cycloadducts (Equation (2)).[10]

i, TMANO, 4 Å molecular sieve, 85% ii, TMANO only, 40%

(2)

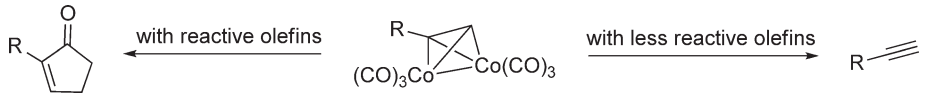
Jeong and Pauson revealed that sulfoxides are milder but excellent promoters for the reaction, albeit slight warming (50 °C) of the reaction mixture was required.[11]

11.10.2.2.2 Non-oxidative promoters

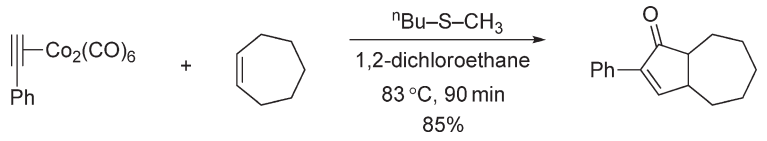
Although the oxidative promoters have been quite effective, the reaction with less reactive olefins is still troublesome. Under the conditions with the oxidative promoter, the PKR is inevitably competing with the demetallation of the alkyne–cobalt carbonyl complex to give the metal-free alkynes. This competition is insignificant when the reactive olefins are employed, but it is prone to give more demetallated alkynes when the less reactive olefins are used (Scheme 3). This is reasoned by the fact that it is hard to expect from those promoters to oxidize only one of the COs on metal, and, in other words, the decarbonylation is not discriminative. As a result, the finding of the optimum condition is critical to favor the desired PKR product.

Sugihara reported that dialkylsulfides were effective for this stoichiometric reaction as a non-oxidative promoter.[12]

This finding is rooted in the DMSO promoter[11] and Krafft's demonstration[6] that a suitably positioned sulfur moiety tethered to the PK precursor increases the reaction efficiency. The reaction conditions with these promoters generally require much higher reaction temperatures than that with oxidative promoters, and complete the reaction in substantially shorter periods to give high chemical yields. Moreover, the sulfur additive promotes the intermolecular PKR with even unstrained and less reactive olefins. A prominent example is the reaction between phenylacetylene and cycloheptene (Equation (3)).[12]



Scheme 3 The oxidative promoter-assisted reactions.



(3)

Otherwise, only phenylacetylene was obtained as a major product with an NMO promoter, and the PKR product was obtained in only 23% yield under the thermal conditions after 3 days.

Sugihara and co-workers have demonstrated a rate enhancement by the use of primary amines as a solvent.[13] Trials to find the conditions that use amines as an additive in more conventional solvent were unsuccessful, but use of 3.5 equiv. of cyclohexylamine as an additive in 1,2-dichloromethane (1,2-DCM) turned out to be the choice of conditions to give the high conversion and chemical yield (99%). Ammonia can serve as a promoter in a biphasic system of an aqueous solution of ammonium hydroxide. The reaction provided nearly quantitative yield in less than 1 h under optimized conditions.[13]

11.10.2.2.3 Solid-supported promoters

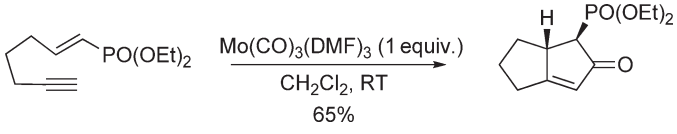
Recently, Kerr introduced a promoter anchored to a solid support to facilitate workup after the reaction. For example, the PKR proceeds to completion by use of the amine *N*-oxide anchored on solid support **14**, and then the polymeric amine is recovered by simple filtration. The recovered polymer is cleaned by washing with a THF–aqueous 2 M HCl mixture (2 : 1 mixture), followed by washing of hydrochloride salt with a 10% solution of $^{i}Pr_2NEt$ in DMF. The resultant resin is oxidized again and then used without loss of activities.[14] Kerr and Pauson also successfully employed sulfide promoters anchored on the solid support **15** for this cycloaddition (Figure 1).[15]

11.10.2.2.4 Other metals coupled with promoter

Group 16 metal carbonyls are also effective in the PKR. Hoye prepared a pre-activated tungsten catalyst ($W(CO)_5THF$) by replacing one of the COs on tungsten with THF photochemically, and successfully applied it to PKR. This semicatalytic system constitutes one of the early examples useful even for the substrates bearing electron-withdrawing groups.[16]

Jeong and co-workers reported the activation of molybdenum hexacarbonyl *in situ* by the aid of dimethylsulfoxide.[17] A mixture of the substrate and $Mo(CO)_6$ (1.0 equiv.) together with the excess of DMSO (10 equiv.) in toluene and/or benzene was heated to give the corresponding products.

Recently, Carretero showed that $Mo(CO)_3(DMF)_3$ obtained by mixing of molybdenum hexacarbonyl with DMF for several months efficiently promotes the PKR. In particular, the phosphonate-conjugated olefin works nicely to give the corresponding product (Equation (4)).[18]



(4)

11.10.2.2.5 Promotion by physical means

Physical means including irradiation with ultraviolet light and ultrasound have also been tested and shown positive effects.[19] Most noticeably, Evans and co-workers introduced an interesting promotion by microwave to expedite the reaction to complete in a minute. Nevertheless, the beneficial effect in terms of chemical yield is not spectacular (Equation (5)).[20]

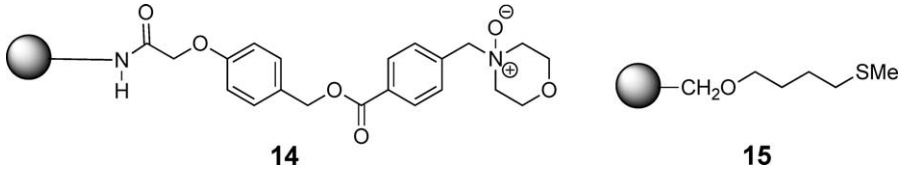
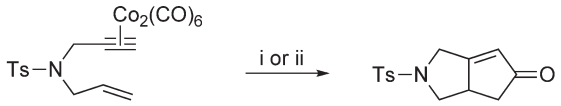


Figure 1 The solid-supported promoters.



(5)

i, microwave, DCE (0.05 M), 90 °C, 100 s, 72% ii, DCM, NMO (5 equiv.), 25 °C, 16 h, 95%

11.10.3 Catalytic PKR

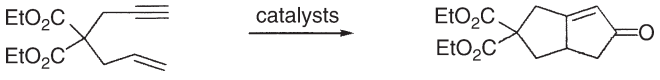
11.10.3.1 Homogeneous Catalysts Based on Cobalt Metal

11.10.3.1.1 Based on dicobalt octacarbonyl

Since the very first report of PKR, the catalytic version of the PKR had been envisioned. In fact, Pauson reported early success in the intermolecular version employing a continuous supply of ethylene.[1] However, it was not until 1990 that Rautenstrauch and co-workers reported the first reliable example using cobalt in the literature (Table 2).[21]

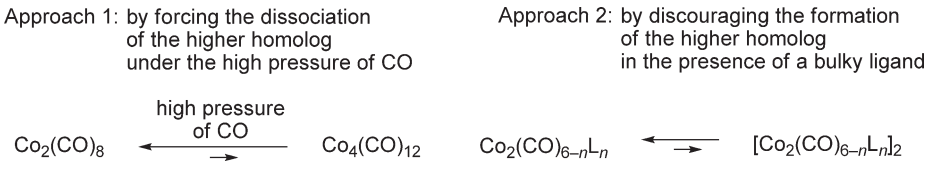
It has been suggested that the difficulty in realizing the catalytic reaction is mainly associated with the formation of the higher homolog of cobalt clusters (Scheme 1), which are presumed to be formed from the unsaturated cobalt carbonyl species after the reductive elimination to deliver the cyclopentenones. For instance, $[Co_4(CO)_{12}]$ might be derived by dimerization of $[Co_2(CO)_6]$. Once this is formed, high pressure of CO is required to dissociate it to give $[Co_2(CO)_8]$. However, the dilemma is the very first step of this catalytic cycle, that is, the formation of unsaturated

Table 2 The catalytic Pauson–Khand reaction



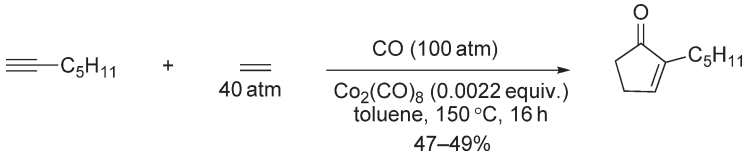
Catalytic condition				*Yield (%)*	*References*
Catalysts	*Solvent*	P_{CO} (atm)	T(°C)		
Based on cobalt					
$Co_2(CO)_8$	Toluene	40	50–55	83	21
	DME	1	90	82	22,22a,22b
	Scf CO_2	30	90	82	34
$Co_2(CO)_8$ + light	DME	1	50	95	22,22a,22b
$Co_2(CO)_8 + P(OPh_3)_3$ or	DME	1–3	120	82	24
PAr_3	DME	1.05	70	80	25
$Co_2(CO)_8$ + DME	Toluene	7	120	94	27
$Co_2(CO)_8 + R_3PS$	Benzene	1	70	90	29
$Co_4(CO)_{11}P(OPh_3)_3$	Scf ethylene	5	120	94	35
$Co_4(CO)_{12}$	CH_2Cl_2	10	150	92	23
	Scf ethylene	5	150	92[a]	35
$Co_4(CO)_{12} + C_6H_{11}NH_2$	Toluene	1	65–70	94	28
$Co_3(CO)_9(\mu^3\text{-CH})$	Toluene	7	120	98	30,30a
Co(II)salts	CH_2Cl_2	30–40	100	98	33
+reducing agent	Tol/*t*-BuOH	1	110	88	33a
Indenyl cobalt(I) **20**	DME	15	100	64	31
Co═NHC **21**	DME	1.05	75	73	32
Based on metals other than cobalt					
$Ru_3(CO)_{12}$	Dioxane of DMAC	10–15	140–150	86	41
				78	42
$Cp_2Ti(CO)_2$	Toluene	1.5	90	90	39,39a
$[RhCl(CO)_2]_2$	Dibutyl ether	1	130	94	44,44a
$[RhCl(CO)dppp]_2$	THF	1	110	99	44b,44c
RhCl(CO)dppe	Toluene	1	110	94	44b,44c

[a]The yield was based on the used alkynes during the intermolecular reaction.



Scheme 4

cobalt carbonyl [$Co_2(CO)_{8-n}$] ($n = 1$ or 2) under the presence of CO, which will be retarded by the pressure of CO. As a result, many early attempts at simple use of the catalytic amount of dicobalt octacarbonyl have been prone to give erratic results. The first success was the reaction between ethylene (40 bar) and 1-heptyne in toluene under pressure of carbon monoxide (100 bar),[21] and this constitutes truly the first catalytic reaction; the turnover number is very high (>220). This result was not always reproducible, and the reported chemical yield was not high enough (<50%) because of the competition of the trimerization of 1-heptyne Equation (6).



(6)

Livinghouse and co-workers finally refined the catalytic PKR employing $Co_2(CO)_8$ (5 mol%) and expanded the scope of the reaction. They first reported the protocol, in which the photoactivated $Co_2(CO)_8$ was used under the atmospheric pressure of carbon monoxide. Next, they revealed the thermal condition, keeping the reaction temperature in a very narrow range (50–55 °C).[22,22a,22b] The high purity of $Co_2(CO)_8$ is another provision to ensure reproducible results for the both studies.

Meantime, several independent modifications have been introduced to circumvent this inconvenience. The bottom line in devising the catalytic PKR is to develop the way to discourage the formation of higher cobalt clusters, and allow enough time to the unsaturated cobalt carbonyl species for binding the new substrates before making aggregated clusters (Scheme 4).

Chung provided one of the simple solutions based on this line of concept.[23] Under the high pressure of carbon monoxide, the higher homolog of cobalt carbonyls including $Co_4(CO)_{12}$ is depressed, and the considerable amount of $Co_2(CO)_8$ becomes available. This is now used for the catalytic reaction at high temperature of 150 °C.

11.10.3.1.2 Phosphorus ligand-modified cobalt catalysts

More practically, the catalytic PKR is realized by introduction of a sterically bulky external ligand. Highly congested environment around a cobalt metal was considered to discourage the dimerization or oligomerization of the unsaturated metal carbonyls.

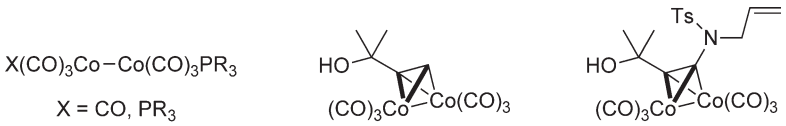
Jeong and co-workers devised the method by using a phosphite-modified cobalt catalyst, which was obtained *in situ* by mixing of dicobalt octacarbonyl (3 mol%) and triphenylphosphite (10 mol%) prior to the addition of reactants. Best results were obtained under mild pressure of CO (3 atm).[24]

This condition is so practical that the reaction can be carried out up to 2 kg scale as long as the proper equipment is available. Although the phosphites were used in the original work, any phosphorus ligands including phosphanes are also effective as long as their solubility in the reacting solvent is guaranteed. Subsequently, it was shown that use of robust pre-made catalysts **16** together with phosphanes and phosphites is effective under a 1 atm carbon monoxide atmosphere.[25]

As reported previously,[22,22a,22b] preparation and handling of highly purified [$Co_2(CO)_8$] required tiresome and careful operations because it ignites spontaneously upon contact with air. Some modified ways to use stable cobalt precursors appeared in the literature. Early attempts of Billington to use ethyne–[$Co_2(CO)_6$][26] and recent examples using **17** and **18** are representative examples in this category (Figure 2).[26a,26b]

11.10.3.1.3 "Hard" Lewis base-modified cobalt catalysts

The phosphorus ligand-modified catalysts have provided reliable transformations, but one of the problems is the substantial deceleration of the reaction rate. It is mainly attributed to the electron flow from the ligands to metal, now



16 **17** **18**

Figure 2 The stable precursors of cobalt(0)–carbonyl complexes.

making the π-backbonding of metal–CO much stronger, and thus the removal of CO more difficult. Use of "hard Lewis bases" would be the solution to detour this hurdle, because these kinds of ligands are known to make carbon monoxide of low-valent organotransition metal complexes more labile.

Among various candidates, 1,2-dimethoxyethane (DME) in toluene was found to be the best promoter providing the cycloaddition products in high yields, but required a higher pressure of CO (7 atm).[27] Water was less efficient under the same conditions, but provided the comparable yield at higher concentrations. Nevertheless, use of DME as the solvent instead is detrimental to the reaction under the conditions. Once again, one should notice that there must be a competition between the demetallation from the alkyne–cobalt complex and the catalytic cycle for the PKR products.

Cyclohexylamine, which was one of the best promoters for the stoichiometric reaction, failed to give the catalytic version under the pressure of CO (7 atm).[13] However, Krafft and co-workers used cyclohexylamine coupled with dicobalt octacarbonyl and/or even tetracobalt dodecacarbonyl in DME for a catalytic cyclization. Cyclohexylamine is a relatively sterically bulky amine and is presumed to leave the unsaturated dicobalt species intact and to make CO more labile.[28]

Hashimoto has shown that the addition of phosphane sulfides results in higher yields and faster conversions for PKR under atmospheric pressure of CO. This mild promoter provided high TONs, and can be applied to catalyze an intermolecular PKR under 1 atm of CO.[29]

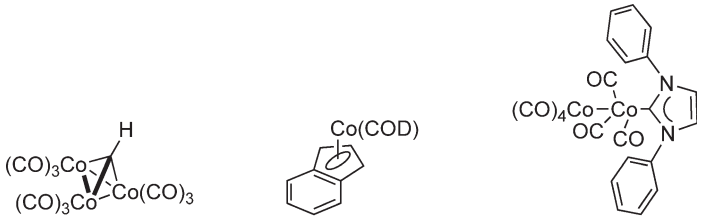
11.10.3.1.4 Miscellaneous cobalt catalysts

Interestingly, cobalt clusters, for example, alkylidynetricobalt nonacarbonyl **19**, which are easily prepared by the reaction of dicobalt octacarbonyl with trihaloalkane, were utilized for the PKR.[30,30a] Among the clusters investigated, the one having a relatively small substituent on the bridging carbon, $Co_3(CO)_9(\mu^3\text{-CH})$ **19**, turned out to be the best choice. However, relatively high pressure of CO (7 atm) is required. In another study, a monocobalt(I) species proved its utility for the catalytic PKR successfully. Chung and Jeong reported the conditions that employed a catalytic amount of [(indenyl)(COD)cobalt(I)] **20** to promote the reaction (Figure 3). Although this catalyst required high pressure of CO (15 atm) to obtain excellent results, TON was as high as 97.[31]

Robust NHC carbene-bound cobalt **21** has been used albeit with a little inferior efficiency, which might be attributed to the highly electron-donating character of NHC ligands.[32]

Studies using alternative sources of cobalt have been a subject of the research also because of the relative instability of $Co_2(CO)_8$.

Generation of Co(0) can be effected either by reduction of $Co(acac)_2$ by $NaBH_4$ in CH_2Cl_2 or by reduction of $CoBr_2$ by Zn in toluene/*t*-BuOH.[33,33a] With cobalt particles, the reaction requires rather forcing conditions, CO (30–40 atm), 100 °C, or high dose of cobalt (0.4 equiv.) under the atmospheric pressure of CO.

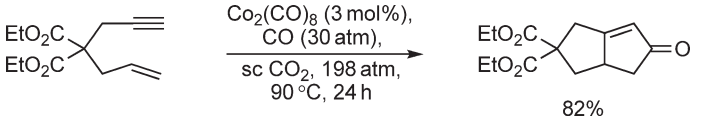


19 **20** **21**

Figure 3 More variations of cobalt-based catalysts for PKR.

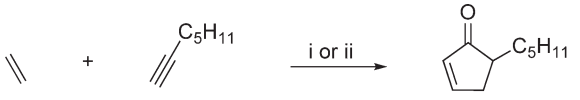
11.10.3.1.5 Cobalt-mediated catalytic PKR in unconventional media

Jeong *et al.* have demonstrated that the efficiency of PKR is substantially improved in a supercritical CO_2 fluid.[34] Advantages may be attributed to the high solubility of gaseous reactants including CO, rapid diffusion of solutes, and weakening of the solvation around the reacting species (Equation (7)).



(7)

In a subsequent study, they used ethylene for a dual purpose, as a substrate as well as a supercritical fluid solvent.[35] This notoriously unreactive olefin to PKR served nicely to give 2-substituted cyclopentenones. Reaction efficiency of each alkyne substrate can be tuned by changing catalyst precursors. Not only $Co_2(CO)_8$ but also the two cobalt clusters $[Co_4(CO)_{12}]$ and $[Co_4(CO)_{11}\{P(OPh)_3\}]$ work well for some substrates (Equation (8)). The comparison with Rautenstrauch's result[21] clearly shows the beneficial effect of this approach.



(8)

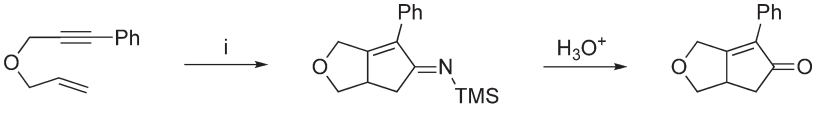
i, CO (100 atm), ethene (40 atm), $Co_2(CO)_8$ (0.0022 equiv.), toluene, 150 °C, 16 h, 47–49%;
ii, CO (5 atm), ethene (110 atm) at 34 °C, $[Co_4(CO)_{11}\{P(OPh)_3\}]$ (3 mol%), 42 h, 85 °C, 70%

Ionic liquids are a versatile class of solvents in transition metal-mediated reactions because of many projected advantages compared with conventional media, including their non-volatility. The catalytic PKR was also tested in this media, but only a narrow range of substrates provided reasonable chemical yields.[36]

11.10.3.2 Homogeneous Catalysts Based on Metals Other than Cobalt

The use of other metals for PKR has attracted much attention recently in the search for new possibilities.

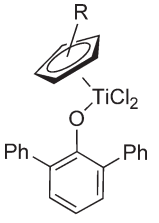
The initial success with early transition metals, such as zirconium and titanium, reported by the Buchwald group, included an indirect cycloaddition between an enyne and isocyanides. The first protocol that used $[Cp_2Ti(PMe_3)_2]$ or Ni(COD) together with triphenylphosphine failed to cyclize the enynes under the pressure of CO, but provided the cyclic imines with trialkylsilyl isocyanides, and bicyclic enones were obtained by hydrolysis of the resultant imine products (Equation (9)).[37–38]



(9)

i, $Cp_2Ti(PMe_3)_2$ (0.1 equiv.), or Cp_2TiCl_2/nBuLi, (0.1 equiv.), or $Ni(COD)_2/PPh_3$, Me_3SiCN, benzene, 45 °C

Subsequently, direct incorporation of CO by titanocene(II) catalyst, $Cp_2Ti(CO)_2$, under a CO atmosphere was reported.[39,39a] This catalytic system showed substantially higher TON and broader functional group compatibility. However, this catalyst fails to react with sterically hindered olefins and alkynes. In a recent contribution from the same group, a series of aryloxide titanium complexes **22** (Figure 4) are prepared and shown to promote PKR with some sterically hindered enynes.[40]



22

Figure 4 The precursor of titanium-based catalyst bearing aryloxide.

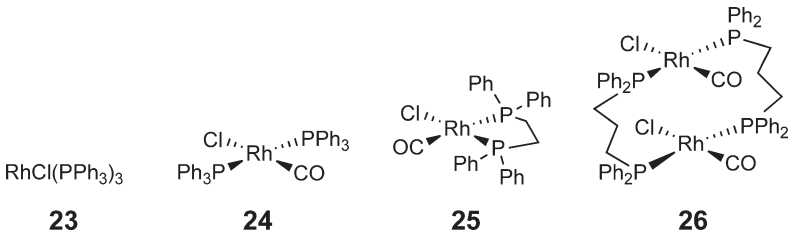
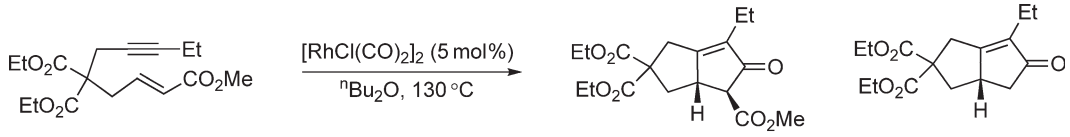


Figure 5 Examples of rhodium-based catalysts for PKR.

In addition to these examples, the late transition metals such as ruthenium, rhodium, and iridium have shown their effectiveness in catalyzing the PKR. In 1997, two groups independently showed that $[Ru_3(CO)_{12}]$ can catalyze the PKR. The group led by Murai reported the conditions that employ dioxane as a solvent;[41] another group led by Mitsudo employed DMAC as a solvent.[42] Both conditions required high pressure of CO (10–15 atm) and the scope is limited to the disubstituted alkynes.

Rhodium-catalyzed PKR was also revealed by two groups simultaneously and has attracted much more attention.[43] Early studies by Narasaka and co-workers employed $[RhCl(CO)_2]_2$ as a catalyst in dibutyl ether,[44,44a] and the report by Jeong and co-workers employed various phosphine ligand-modified Rh(I) catalysts in non-coordinating solvents like toluene.[44b,44c] The latter has an implication for further development toward the enantioselective version. Requirements for efficient transformation, when phosphane-ligated catalysts are used, are well defined. For example, while complexes such as $RhCl(PPh_3)_3$ **23** and *trans*-$RhCl(CO)(PPh_3)_2$ **24** require co-use of silver(I) salts for faster reaction, *trans*-$[RhCl(CO)(dppp)]_2$ **26** efficiently promotes the reaction without any additives (Figure 5).

Rhodium catalysts demonstrate some additional unique features, effective for electron-deficient alkenes and alkynes, the previously formidable substrates (Equation (10)). Moreover, the reaction rate increases when pressure of CO is decreased down to 0.1 atm without loss of chemical yield.



1 atm CO	18 h	19%	68%
0.1 atm CO and 0.9 atm Ar	4 h	59%	31%

(10)

A catalyst based on iridium(I) has also been discovered and will be discussed later in Section 11.10.4.1.

11.10.3.3 Heterogenous (Immobilized) Catalysts

In view of the environmental issues and operational simplicity, heterogeneous catalytic systems have been suggested to be advantageous. Gibson and co-workers first introduced polymer-bound cobalts **27** and **28** to this end.[45] Subsequently, Portnoy and Dahan immobilized cobalt on dendrimeric phosphane ligands, which have a partial structure of **29** (Figure 6).[45a]

Chung and Hyeon developed a variety of heterogeneous catalysts, using cobalt metal immobilized on mesoporous silica[46] or charcoal (Table 3).[46a] Although these catalysts generally require harsh conditions (high CO pressure and high catalyst loading) to effect the reaction, reuse of the catalysts many more times without loss of activity may compensate such drawbacks.

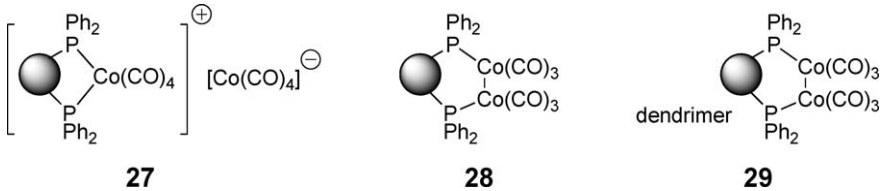
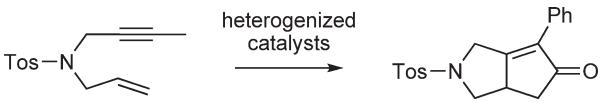


Figure 6 The immobilized phosphorus-ligated cobalt catalysts.

Table 3 Heterogeneous catalysts for the Pauson–Khand reactions developed by Chung and Hyeon group



Catalyst (mol.%)	*Solvent*	P_{CO} (atm)	*Yield (%)*	*References*
Co/silica	DCM	20	92	46
Co/charcoal	THF	20	98	46a
Colloidal Co	THF or H_2O	5–20	90	46b,46c
Entrapped Rh	THF	5	90	46d,46e
RuCNC[a]	THF	b		46f

[a]RuCNC; heterobimetallic ruthenium/cobalt nanoparticle immobilized on charcoal.
[b]2-Pyridylmethyl formate is used.

Substantial improvements are made by using the cobalt nanoparticles. Contrary to the previous cases, much lower CO pressure (5 atm) is enough for the completion of the reaction. However, high loading of catalysts (45 mol%) seems to be a drawback. Nevertheless, this system can be reused, and one of them is compatible with water solvent.[46,46a–46f]

Rh and cobalt bimetallic nanoparticles can effect the reaction even at 1 atm pressure of CO.[46,46a–46f]

11.10.3.4 Alternative Sources of CO

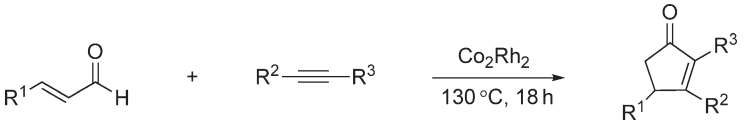
Facile formation of metal carbonyl complexes makes rhodium a very useful catalyst for both the hydroformylation of multiple bonds and the decarbonylation of the aldehydes. Two groups have independently utilized rhodium carbonyl complex obtained from decarbonylation of aldehydes in PKR (Scheme 5).

Kakiuchi and co-workers found that aromatic aldehydes bearing electron-withdrawing substituents were able to serve as a carbon monoxide source.[47] A stoichiometric amount of pentafluorobenzaldehyde in refluxing xylene is generally enough to perform this transformation (Table 4).

In a subsequent study, they have also developed the condition using formaldehyde in water.[47b]

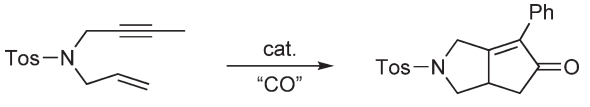
Shibata and co-workers used an excess of cinnamaldehyde, which was employed as a CO source without solvent to furnish the corresponding PKR product in almost quantitative yield.[47a]

Chung successfully used cinnamaldehyde not only as a CO but also as a reactant styrene source. The PKR was achieved using Rh/Co colloidal nanoparticles (Equation (11)).[46d]

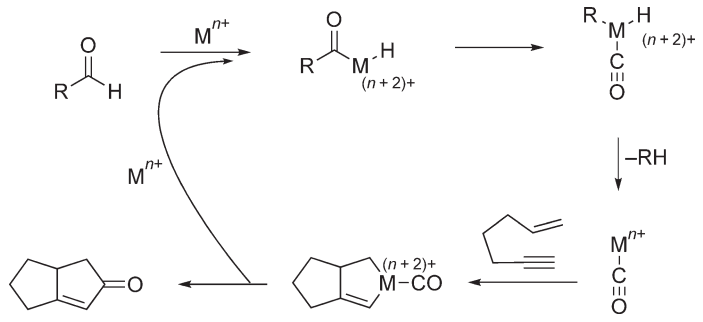


(11)

Table 4 The catalytic Pauson–Khand reaction using aldehydes as CO source

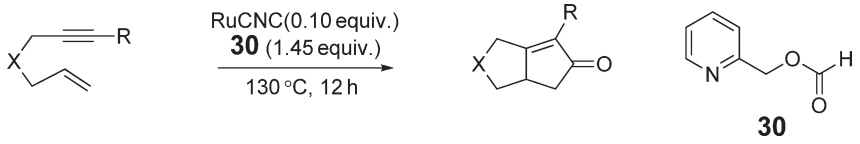


Catalyst (mol.%)	*Additive* (mol.%)	*RCHO*	*References*
$RhCl(cod)_2$ (5)	Dppp	C_6F_5CHO	47
$Rh(dppp)_2Cl$ (5)		Cinnamaldehyde (20 equiv.)	47a
$RhCl(cod)_2$ (5)	Dppp (10) TPPTS (10) SDS (200)	HCHO in H_2O	47b



Scheme 5

More recently, Chung introduced a combination of a well-designed CO surrogate **30** and ruthenium colloidal particles (RuCNC) (Equation (12)).[46e]



(12)

30

11.10.4 Enantioselective PKR and Related Cycloadditions

In recent decades, there have been extensive efforts made toward asymmetric PKRs . These efforts include the following categories: (i) substrate-controlled asymmetric reactions and (ii) reagent-controlled asymmetric reaction.

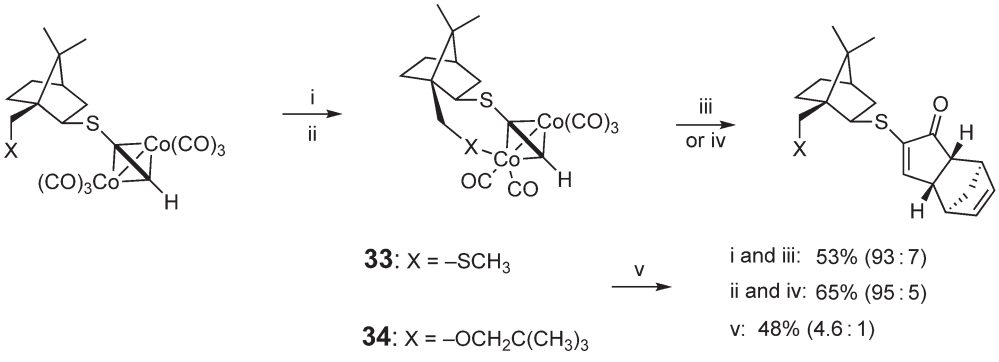
11.10.4.1 Substrate-controlled Asymmetric Reactions

11.10.4.1.1 Use of chiral auxiliary

Early efforts using a chiral auxiliary, such as a chiral acetal or 2-phenylcyclohexanol, resulted in modest diastereoselectivity.[48,48a–48c]

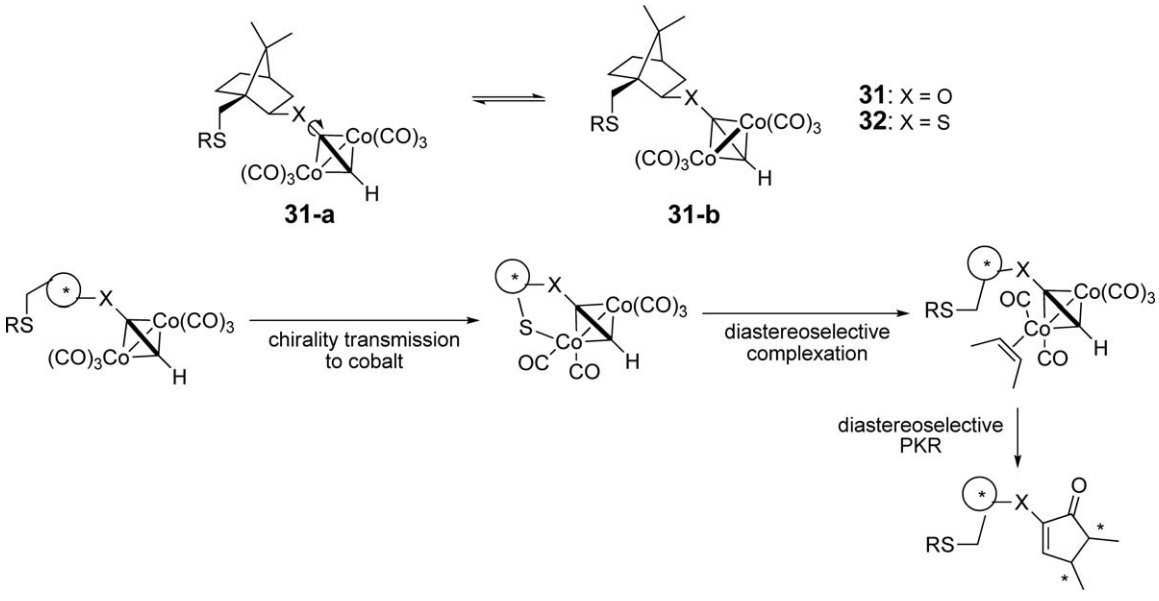
A major breakthrough was provided by Moyano and Pericas. They used chiral alcohols **31** or sulfides **32** bearing a suitably positioned extra sulfur appendage. The extra sulfide is able to coordinate to the cobalt–alkyne complex to prevent free rotation of the alkyne–cobalt complex moiety along the axis between the alkyne carbon and the heteroatoms. To ensure the high diastereoselectivity, the portion of one conformer **31-a** in the equilibrium should be maximized before the PKR (Scheme 6).[49] This can be done either by thermal conditions, or by addition of NMO (6 equiv.) under a nitrogen atmosphere. In addition, it is still required to use highly strained reactive olefins like norbonadiene. Otherwise, in the case of the reaction with the less reactive olefin, cyclopentene, only a 1 : 1 mixture of diasteromers was obtained in 14% yield.[49]

The significance of the pre-chelation is again supported by the fact that compounds **33** and **34** gave a big difference in diastereoselectivity (Equation (13)).[49a,49b]



(13)

i, (a) $Co_2(CO)_8$ (b) heating at 55 °C; ii, (a) $Co_2(CO)_8$ (b) NMO (3 equiv.) in CH_2Cl_2; iii, norbonadiene, –20 °C; iv, norbonadiene, –10 °C; v, (a) $Co_2(CO)_8$ (b) NMO (6 equiv.), –20 °C, CH_2Cl_2



Scheme 6

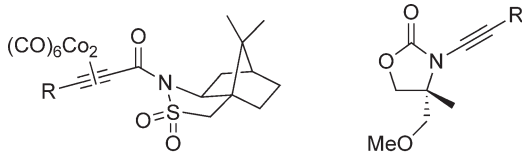
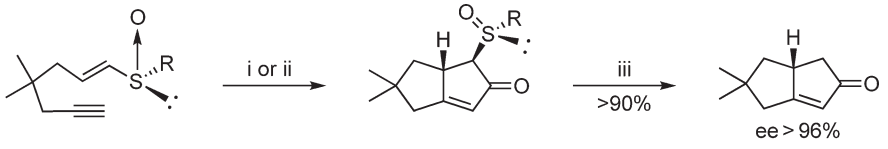


Figure 7 The alkyne substrates with chiral auxiliaries.

Other chiral auxiliaries like Oppolzer's bornanesultam **35** or chiral oxazolidinone **36** gave excellent results in stereocontrol and yield (Figure 7).[49c]

Carretero has demonstrated the feasibility of the reaction of electron-deficient vinylsulfoxides. Details will be discussed in Section 11.10.5.1.3. The chiral sulfoxide group next to an olefinic moiety controls the reaction pathway efficiently and provides high diastereoselectivity. In addition, a mixture of (*E*)- and (*Z*)-vinylsulfoxides gives only one isomer of products, which was treated under reductive condition with zinc to remove the sulfoxide moiety (Equation (14)).[50,50a,50b]



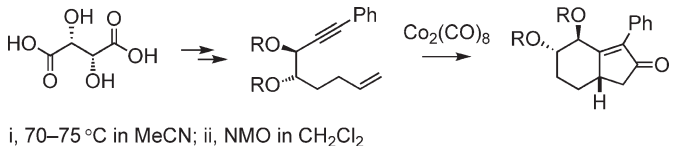
(14)

i, (a) $Co_2(CO)_8$ (b) CH_3CN, 80 °C, 65%; ii, (a) $Co_2(CO)_8$ (b) NMO-H_2O (6 equiv.), CH_2Cl_2, RT;
iii, Zn, NH_4Cl, H_2O–THF, RT

11.10.4.1.2 Chirality transfer from the substrates

Relative stereocontrol of the substrates with pre-existing stereogenic centers during PKR has been extensively studied, and the outcome of the reaction is now expected with high probability. Many fundamental factors for obtaining high degrees of stereoselectivity are defined in the course of early studies directed to the natural product synthesis.[51]

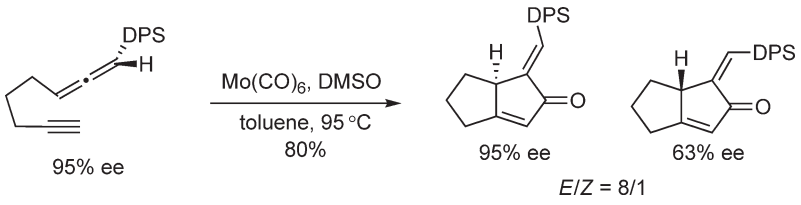
More recently, Mukai and Hanaoka have demonstrated that a variety of optically active bicyclo[4.3.0]-nones are prepared from the substrates possessing pre-existing stereogenic centers. The precursors are prepared from such a natural chiral pool as dimethyl L-tartarate or L-ascorbic acid (Equation (15)).[52,52a,52b]



R,R	*Condition*	*Ratio*	*Yield* (%)
2TBDMSO	i	100	99
2HO	ii	1 : 99	94
$OC(CH_3)_2O$	i	0 : 100	56

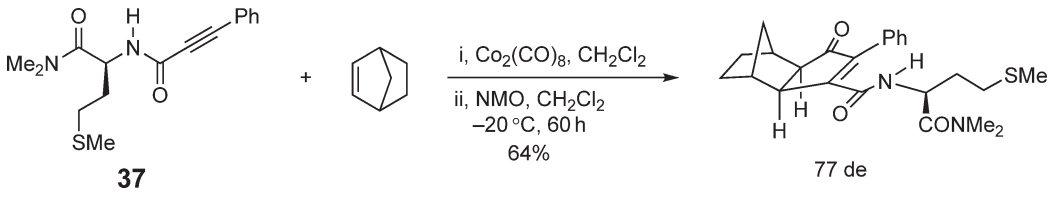
(15)

Brummond's example of successful chirality transfer from a chiral allene is noteworthy (Equation (16)).[53]



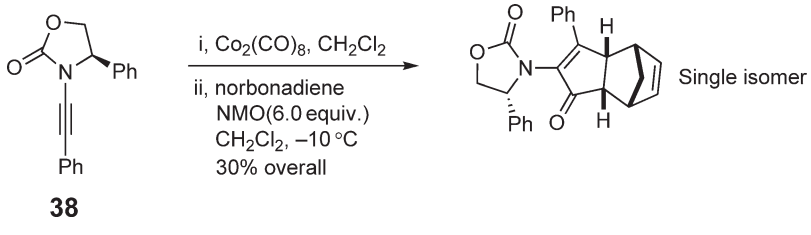
(16)

Hiroi and co-workers employed alkynamide **37** derived from methionine for the regio- and stereoselective PKR (Equation (17)).[54]



(17)

A chiral imidate **38** is successfully employed for the intermolecular PKR to provide a single diastereomeric product, albeit in low yield (Equation (18)).[55]



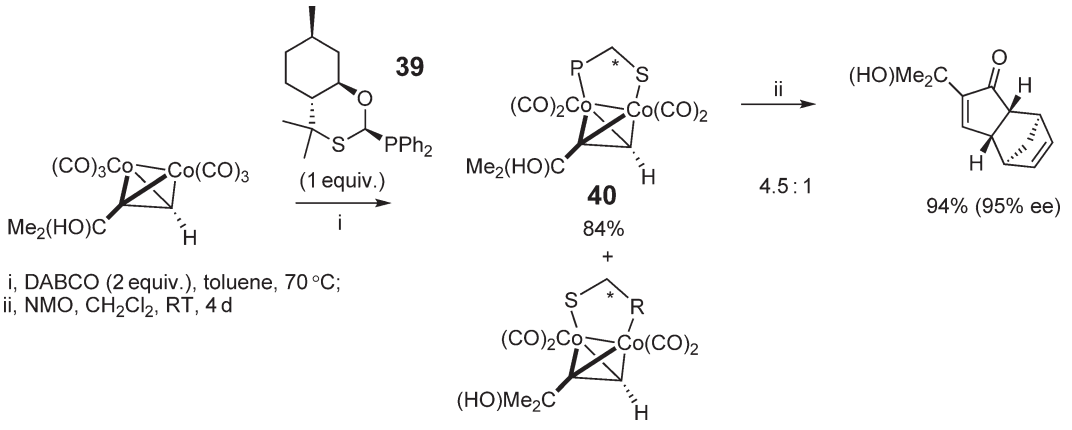
(18)

11.10.4.2 Reagent-controlled Asymmetric Reactions

11.10.4.2.1 Use of chiral metal complexes

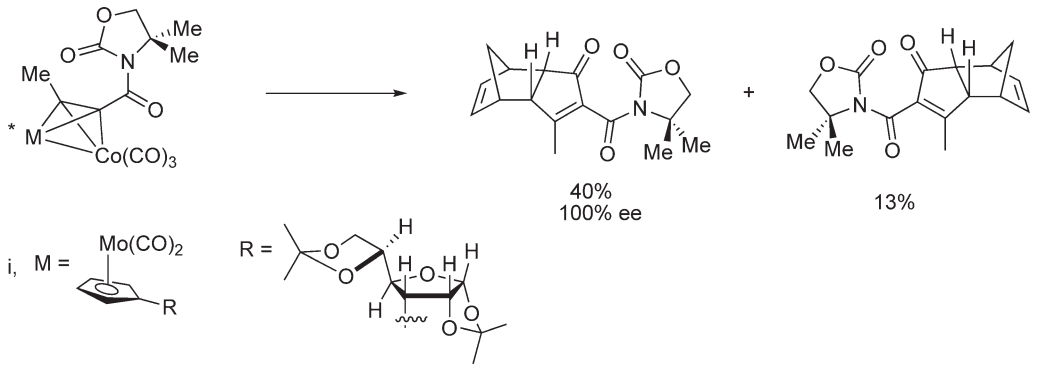
In fact, this approach constituted one of the earliest trials. One is introduction of a chiral ligand like glyphos on cobalt by replacing one of the carbon monoxides to obtain an enantiomerically enriched new metal–alkyne complex. The second approach is use of the propargyl alcohol bearing a chiral auxiliary. Replacement of only one carbon monoxide would lead to a mixture of diastereomers. In both cases, a 1 : 1 mixture of products was obtained, and each diastereomer was separated before the PKR.[56,56a]

After the first report by Greene, Pericas and Moyano prepared a complex between the cobalt–alkyne and PuPHOS **39**, which was readily obtained from (+)-pulegone. Diastereomers, obtained in a 4.5 : 1 ratio, were separated. The major diastereomer **40** reacted with norbonadiene by the assistance of a promoter NMO to give the PKR product in excellent yield as well as enantioselectivity (Equation (19)).[57]



(19)

Pericas and Moyano reported an interesting observation that the heterobimetallic (Mo–Co) complex provided the intermolecular PKR products in favor for *endo*-stereochemistry. Based on this, they prepared the enantiomerically pure complexes with the aid of the chiral auxiliaries, and effected PKR to attain high enantioselectivity (Equation (20)).[57a]



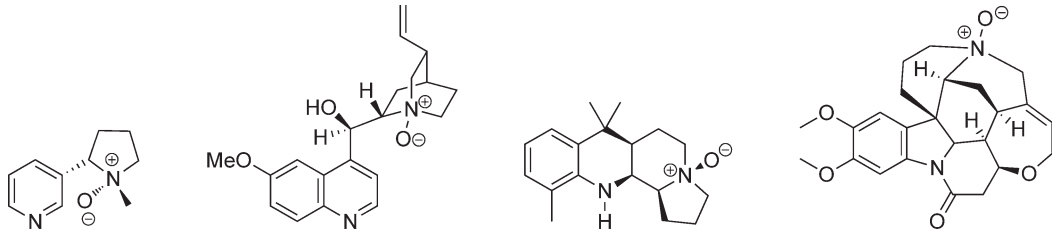
(20)

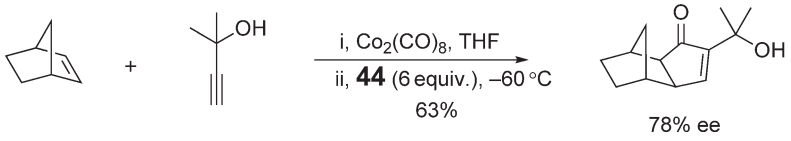
11.10.4.2.2 Use of chiral promoters

One of the conceptually appealing approaches for enantioselective PKR with cobalt–alkyne complexes is the use of chiral promoters. It is expected that a sterically biased promoter can approach to one of the two equivalent cobalts preferentially, and effect oxidation of CO to make a vacant coordination site. Early attempts were marginally successful, and there remained much room for improvement. Recently, enhanced enantioselectivity has been obtained by using a bulky amine *N*-oxides like brucine *N*-oxide **44** under carefully controlled conditions (Scheme 7).[58,58a–58c]

11.10.4.2.3 Use of chiral catalysts

Despite impressive advances in the catalytic PKR, development of an enantioselective version could not parallel the pace of other successes (Table 5). External ligand-assisted catalytic reaction was extended to use the chiral phosphane or phosphate ligands, but with little success. Hiroi and co-workers reported the first example of the asymmetric cobalt-catalyzed PKR. They employed chiral phosphanes as ligands. Of them all, diphosphane (*S*)-Binap induced the highest enantioselectivity.[59] However, limitations of this approach, such as narrow scope of substrates and high catalyst loading, are also apparent. Furthermore, the conditions are only applicable to intramolecular reactions.[59a] More recently, Buchwald and Sturla studied the influence of a chiral phosphite on the cobalt-catalyzed PKR.[60] Only modest ee values (64–75%) were reported for only two substrates, using a mixture of $Co_2(CO)_8$ (0.06 equiv.) and the chiral biaryl phosphate **45** (0.1 equiv.) (Figure 8).





Scheme 7

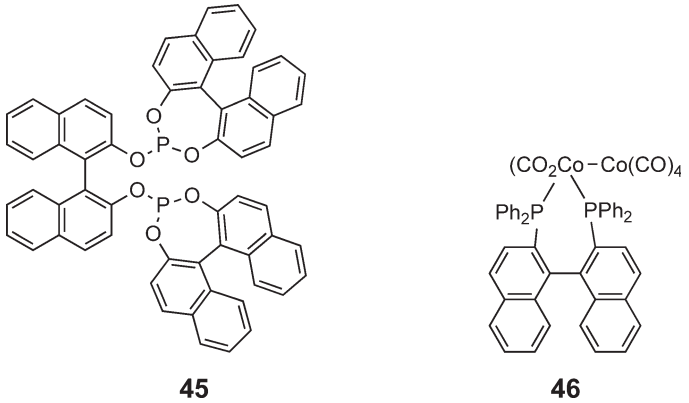
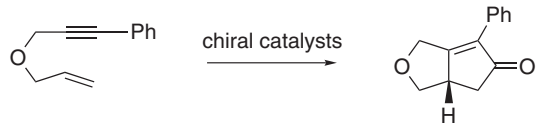


Figure 8

Table 5 The catalytic enantioselective Pauson–Khand reaction



Enantioselective catalytic condition						
Catalytic system	*Solvent*	*CO* (atm)	*T* (°C), *t* (h)	*Yield* (%)	*Range of ee* (%)	*Authors*
With cobalt						
$Co_2(CO)_8$ + BINAP	DCE	1	Reflux, 17	64	90	Hiroi[59]
$Co_2(CO)_8$ + phosphites **45**	Toluene	1	120, 24	75	75	Buchwald[60]
Pre-formed alkyne-BINAP Co(CO)-$Co(CO)_3$	DME	1–3	75, 5	70	89	Gibson[61]
With other metals						
(*S*,*S*)-(ebth)$TiMe_2$ (0.05 eq)	Tolune	1	90, 12	96	85	Buchwald[62]
$[RhCl(CO)_2]_2$ (0.03 eq) + (*S*)-BINAP (0.09 eq) + AgOTf(0.12 eq)	THF	1	100, 5	88	81	Jeong[63a]
$[RhCl(cod)_2]_2$ (0.03 eq) + (*S*)-BINAP (0.09 eq)	Cinnam aldehyde	0	100, 3–4	89	82	Shibata[63b]
$[IrCl(cod)]_2$ (0.1–0.15 eq) + (*S*) tol-BINAP	Tolune	1	130, 36	80	96	Shibata[64]
$[Rh(cod)Cl]_2$ (0.05 eq) + (*S*)-tolBINAP, TPPTS, SDS	H_2O	HCHO	100, 5	61	93	Kakiuchi[63c]

These disappointing initial results can be explained by the fact that this reaction is the ligand-decelerated reaction. Under this circumstance, the only way to achieve high enantioselectivity is to employ a tightly ligand-bound catalyst, in which the metal–ligand bonds should be strong enough not to be dissociated even under the carbon monoxide pressure. Gibson and co-workers have identified one of such catalysts **46** and realized high enantioselectivity.[61]

11.10.4.2.4 Other metals

It was 1996 when Buchwald and Hicks reported the first example of an asymmetric PKR involving a catalytic amount of a chiral titanocene complex. The titanium catalyst (*S*,*S*)-(EBTHI)Ti(CO)$_2$ (EBTHI = ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)) obtained *in situ* by treatment of (*S*,*S*)-(EBTHI)TiMe$_2$ under CO pressure was efficient for the formation of enantiomerically enriched carbocyclization adducts.[62,62a]

Following on the successful application of a rhodium(I) catalyst bearing tunable bidentate phosphine ligands such as **25**, Jeong and co-workers reported a rhodium-based enantioselective PKR.[63]

Asymmetric catalytic version with Rh(I) under solvent-free conditions have also been reported by Shibata. Contrary to the previous results, a neutral rhodium(I) complex provided comparable enantioselectivities with high chemical yields.[63a]

With the success of PKR with formaldehyde in water, Kakiuchi developed asymmetric PKR under the same conditions using chiral ligands. They were able to obtain evenly high enantioselectivity over a broad range of substrates.[63b]

Following the success with cobalt and rhodium, Shibata reported Ir(I)-based enantioselective catalytic reaction. Right after their observation that the efficiency of [IrCl(COD)]$_2$-catalyzed PKR substantially increased by addition of a phosphane co-ligand, they moved directly to use chiral phosphanes and examined the enantioselectivity.[64] TON and TOF of the reaction were low and the number of examples was limited. Typically, the reaction required a fair amount of Ir(I) catalyst [IrCl(COD)]$_2$ (0.1–0.15 equiv.) and (*S*)-Tol–Binap (0.3 equiv.)] and prolonged reaction time. However, this has remained as the best in terms of enantioselectivity to date. Moreover, this catalytic system provided the first asymmetric intermolecular reaction as well.

11.10.5 Applications

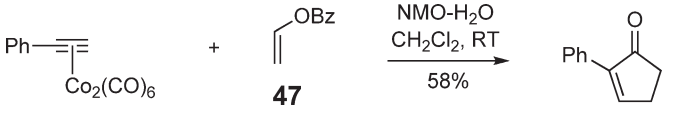
The potential of the PKR in synthesis of natural products and biologically and theoretically interesting compounds has been proved, as discussed above. This section will sort previous achievements according to the class which they might belong to and highlight some selected examples.

11.10.5.1 Substrate Scope

11.10.5.1.1 Surrogates for previously formidable olefins in PKR

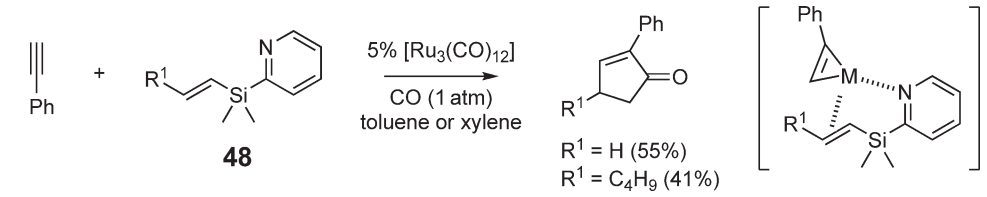
11.10.5.1.1.(i) Ethylene

Kerr and Pauson successfully employed vinyl ester **47** as an ethylene substitute. The reaction can be carried out at ambient pressure and temperature (Equation (21)).[65]



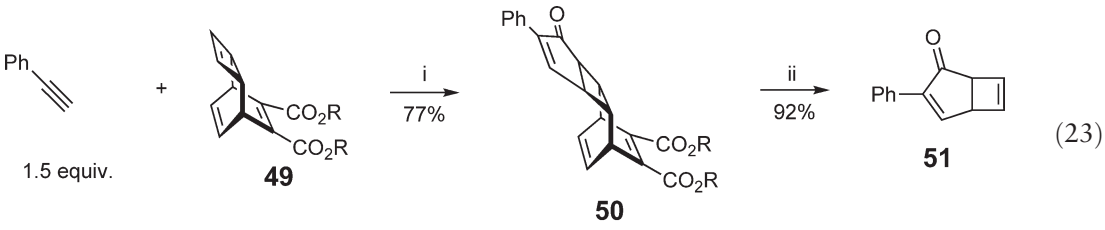
(21)

Itami and Yoshida reported an elegant surrogate for terminal olefins, dimethyl(2′pyridyl)–vinylsilane **48**. Since the reaction proceeds through a pre-complexation of Ru with the pyridine moiety, the outcome is regioslective to provide the products with the R^1 locating at the β-positon from carbonyl (Equation (22)). This approach allows us to obtain products from any terminal olefins with well-defined regiochemistry.[66,66a]



11.10.5.1.1.(ii) Cyclobutene

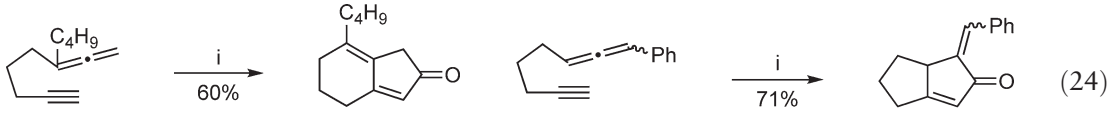
Gibson and co-workers have introduced a well-designed latent cyclobutadiene moiety. Compound **49** reacts with a phenylethyne–cobalt complex to give PKR product **50** as a single diastereomer that resulted from the reaction at the less sterically hindered site, and **50** was subjected to the retro-Diels–Alder reaction at 205 °C under a vacuum of 6 torr to give **51** (Equation (23)).[67]



i, $Co_2(CO)_8$ (5 mol%), CO (1 atm), DME, 75 °C, 4 h; ii, 205 °C, 6 torr, 1 h

11.10.5.1.2 Allenic substrates

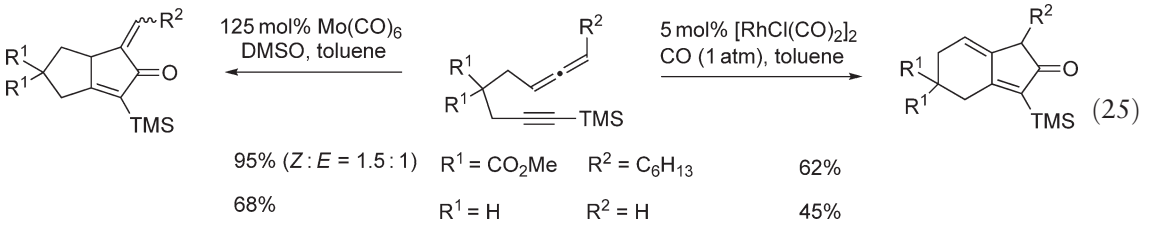
An allene moiety is an interesting substitute for an olefinic moiety. Thus, PKR with allenes has been flourishing in recent years. Since some earlier frustration and successes with this functionality employing cobalt metal is well summarized in a review written by Alcaide and Almendrous;[68] this section will be limited to only recent progresses. Most notably, a system with a stoichiometric amount of molybdenum carbonyl with dimethylsulfoxide and the rhodium catalysts was found to give the desired products nicely. Employing the combination of molybdenum carbonyl and DMSO originally developed by Jeong,[17] Brummond demonstrated the efficiency of the reaction. They also showed that the regioselectivity of the reaction could be controlled by changing the substitution pattern because more substituted olefin is less reactive.[69,69a] For example, when they employed 1,3-disubstituted allenes, they obtained products resulting from the reaction with the internal double bond of the allene. On the other hand, 3-monosubstituted allene forced the reaction to occur at the terminal double bond, and 1,1-disubstituted allenes led the reaction at the internal double bond (Equation (24)).



i, $[Mo(CO)_6]$/DMSO, toluene, 100 °C

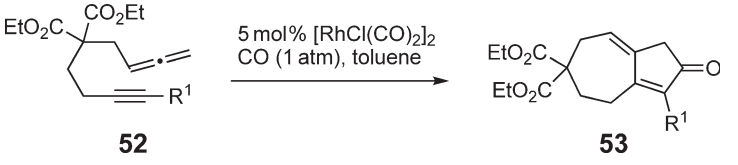
The regioselectivity is dependent not only on the substitution patterns of the substrates, but also on catalysts used. Rhodium can also catalyze the reaction efficiently with allenes, and it complements molybdenum in terms of

regioselectivity.[70,70a] While the internal olefin in allene takes part in the reaction with molybdenum, as previously mentioned, the terminal olefin in allene reacts with rhodium catalyst to give a larger ring (Equation (25)).



(25)

Preparation of a bicyclo[5,3,0]-decenone system by PKR was a big challenge for a long time in PKR. The breakthrough came with Rh catalysts, thanks to their unique regioselectivities mentioned above. Treatment of **52** with either $[RhCl(CO)_2]_2$ or $[RhCl(CO)dppp]_2$ in toluene in the presence of 1 atm of CO furnished bicyclo[5,3,0] compounds **53** in excellent yields (Equation (26)).[70,70a]

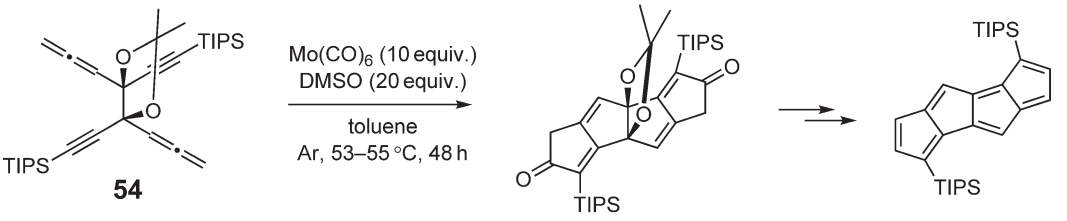


52 **53**

R^1	*Compound*	*Yield* (%)
i-Pr	**53a**	76
Ph	**53b**	77

(26)

Cook and co-workers took advantage of the molybdenum-based methodology and reported one of the most graceful applications of the allenic PKR. They intended to use PKR to synthesize a theoretically interesting tetracyclic compound **55**, which has 14 π-electrons and is supposed to be aromatic in principle. To this end, they have applied PKR to various alkynyl allenes, and finally employed a diyne–diallene substrate **54** successfully (Equation (27)). Double PKR by employing molybdenum hexacarbonyl in excess and DMSO afforded the requisite intermediate in a high yield.[71,71a,71b]



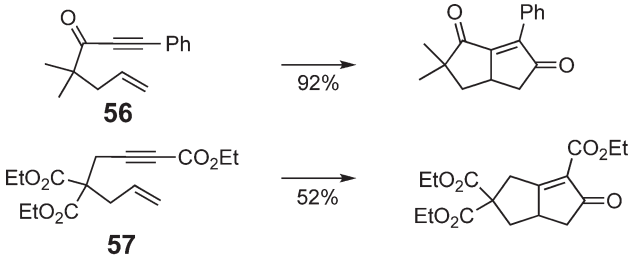
54 **55**

(27)

11.10.5.1.3 Electron-deficient substrates

Efforts with electron-deficient substrates and early marginal successes are well reviewed elsewhere.[72]

The situation is now turned to favorable direction in two ways. First, since the inherently electron-rich rhodium(I) is able to donate electrons from the metal center, and thus make π-backbonding with the electron-deficient multiple bonds much stronger, it initiates the reaction to furnish the cycloaddition products in a highly facile and efficient manner. In addition to the example given below, alkynone **56** and alkynoate **57** also give PKR products in moderate to excellent yields (Equation (28)).[44]



56 **57**

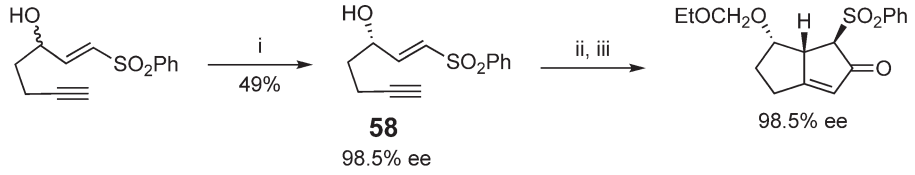
(28)

$[RhCl(CO)_2]_2$ (5 mol%), CO (1 atm), dibutyl ether, 130 °C, 3 h

Second, Carretero and his co-workers introduced 1,6-enynes bearing a sulfoxide group at C-1 position. The cobalt-complexed enynes readily afford the desired PKR products either by heating in CH_3CN at 80 °C or by using amine *N*-oxide promoters (NMO) in CH_2Cl_2 at room temperature.

Since the sulfur atom in sulfoxides is inherently a stereogenic center, the resultant products are a mixture of diastereomers. Proper choice of an R group on sulfur increases the diastereomeric ratio up to >98 : 2.[50–51] The examples have been given already in Section 11.10.4.1.1.

The complication by formation of unwanted diasteromeric mixtures can be avoided by use of sulfones in lieu of sulfoxides. Sulfonyl-substituted substrate **58** affords the corresponding PKR product in high yield with high stereoselectivity (Equation (29)).[73,73a]



(29)

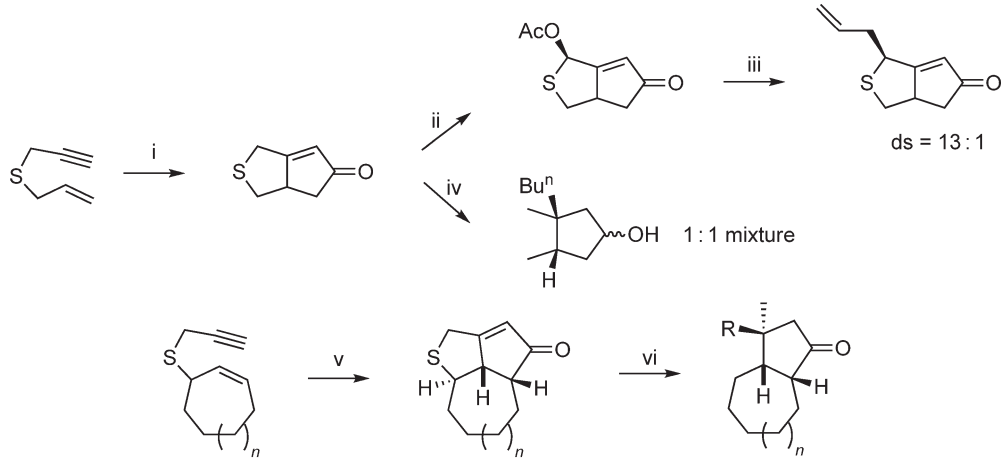
i, Lipase PS, vinyl acetate, toluene, RT; ii, $EtOCH_2Cl$, DIPEA, CH_2Cl_2; iii, (a) $Co_2(CO)_8$, (b) TMANO, RT

11.10.5.1.4 Substrates having removable tethers

Despite the significant progress in PKR, the success in its intermolecular version is still largely restricted to strained olefins. As a result, the access to monocyclic products is extremely limited.

An alternative way to make such monocyclic products is to take an advantage of intramolecular reaction with substrates bearing removable functional group after the cycloaddition is performed.

Pericas and Jeong demonstrated independently that sulfur-tethered substrates, when subjected to the PKR conditions, afforded the desired bicyclic products. The sulfur tether is removed cleanly by Pummerer reaction after oxidation of sulfur to sulfoxide or 1,4-addition of bisalkyl cuprate followed by hydrogenolysis of sulfide with Raney nickel. It is worth mentioning that the regioselectivity regarding the acetylene part is opposite to that of the intermolecular version (Equation (30)).[74,74a]

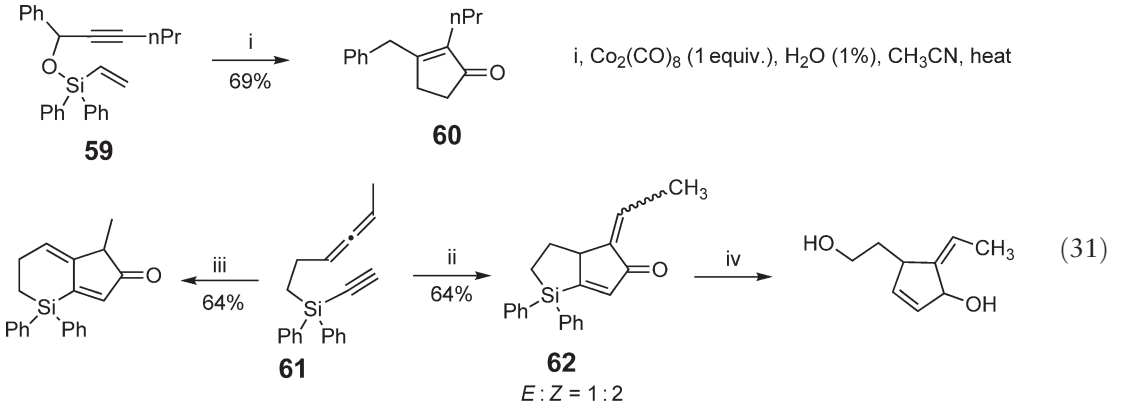


(30)

i, DMSO (10 equiv.), DMS (10 equiv.), benzene, 60 °C, 6 h, 65%;
ii, (a) H_2O_2, acetone, 76% (b) Ac_2O, reflux, 81%; iii, allyl TMS, TMS triflate, CH_2Cl_2, –78 °C, 65%;
iv, (a) ^nBuLi (3 equiv.), CuCN (1.5 equiv.), Et_2O, –10 to 0 °C, 10 min, then enone, RT, 12 h
(b) Raney Nickel, EtOH, reflux, 2 h;
v, (a) $Co_2(CO)_8$ (1.1 equiv.), CH_2Cl_2, RT (b) NMO (6 equiv.), RT, 12 h (85%);
vi, (a) PhLi (3 equiv.), CuCN (1.5 equiv.), Et_2O, –10 to 0 °C, 10 min, then enone, RT, 12 h

An alternative approach involves the use of a silicon atom as a removable tether. Since silicon is more versatile in further functionalization like photodesilylation and Tamao–Fleming oxidation, much effort has been directed to realize PKR of silicon-tethered substrates. However, the outcome in the beginning was far from the expected.[75]

Upon optimization for this particular PKR, propargyl vinylsilyl ether **59** always afforded monocyclic products **60** after loss of silicon atom (Equation (31)). The yield was moderate, and it was possibly due to the formation of the presumed hydrido–cobalt species again. However, Pagenkopf optimized this transformation intensively to find that a small portion of water substantially improved the yield.[76,76a]



(31)

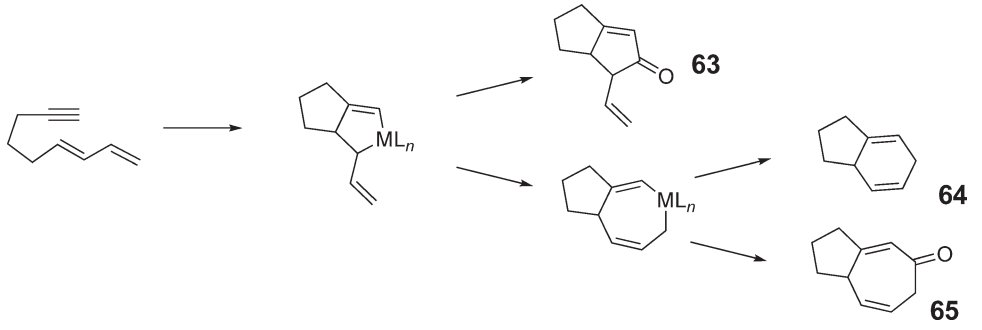
Brummond reported the silicon-bound products **62** were obtained from the (allenylethyl)alkynylsilane **61** (Equation (31)). Either molybdenum/DMSO or rhodium(I) catalysts affords the desired products, but the regioselectivity is dependent on the catalysts used. The trend is in line with what is mentioned previously.[77]

11.10.5.1.5 1,3-Dienes

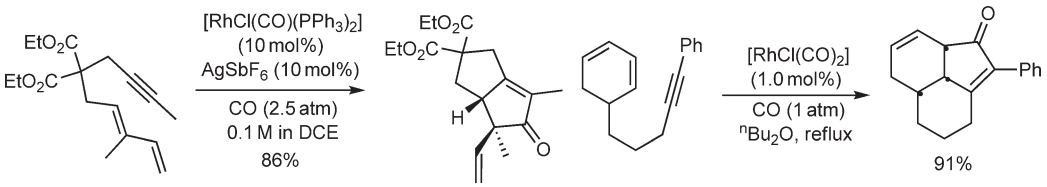
The PKR with 1,3-dienes implicates much more interesting features. First, there must be competitive pathways in the formation of PK product **63**, Diels–Alder product **64**, and homologous PKR product of bicyclo[5,3,0]-decadienone **65** (Scheme 8).

Wender and co-workers focused their attention on the selectivity of the reaction with dienynes mediated by rhodium catalysts. Disubstituted alkynes give excellent yields of PK products, whereas terminal alkynes react less efficiently. Substituents at 2- and 3-positions in the diene moiety tolerate well. The stereochemistry of alkenes is well conserved during the transformation.[78]

Yeh and co-workers employed conformationally rigid dienes and successfully obtained PKR products in high yields (Equation (32)).[78a]



Scheme 8

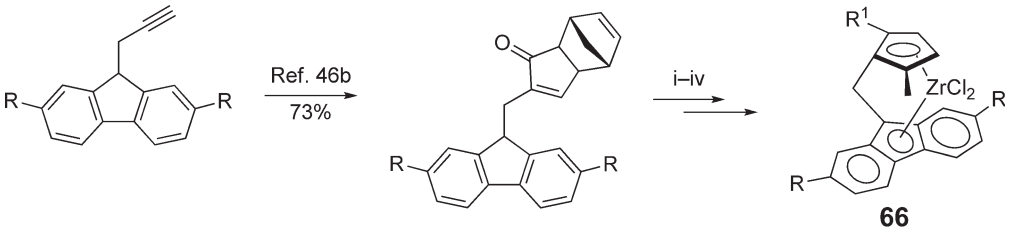


(32)

Later, Wender and co-workers showed that an intermolecular reaction with disubstituted alkynes and 2,3-dimethylbutadiene provided PKR products in high yields under similar conditions.[78b]

11.10.5.1.6 Preparations of Cp derivatives

Since the cyclopentenones obtained by PKR can be subjected to further chemical transformations, there are plenty of chances to prepare various kinds of Cp-type ligands. The efforts are summarized thoroughly by Chung.[2e] Only a couple of examples are mentioned here. A nice demonstration is the synthesis of **66**, which clearly shows that a combination of various reaction sequences opens an access to cyclopentadienes (Equation (33)).[79]



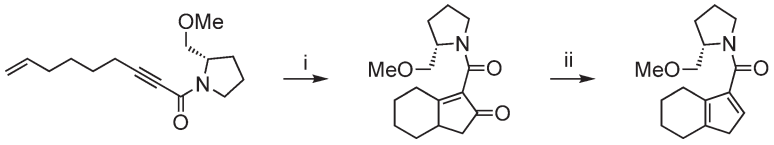
66

(33)

i, 1,4-addition of R^1; ii, retro Diels–Alder reaction; iii, 1,2-addition of Me followed by treatment with acid; iv, treatment with base followed by the addition of zirconium precursor

These catalysts were used in combination with methylaluminoxane (MAO) for ethylene–norbornene co-polymerization and compared with isopropylidene[9-fluorenylcyclopentadienyl]zirconium dichloride catalyst activity under identical conditions.

Moyano and Pericas prepared cyclopentadiene **67** having a chiral appendage (Equation (34)).[79a]



67

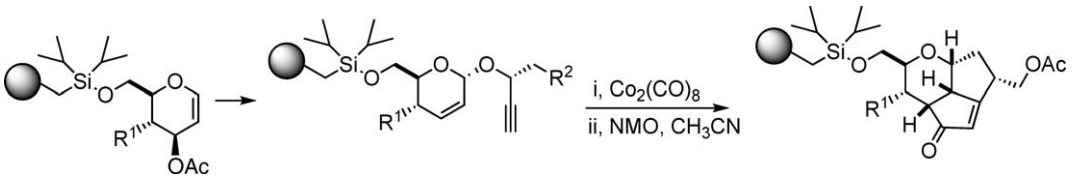
(34)

i, (a) 1.1 equiv. $Co_2(CO)_8$ (b) 10 equiv. DMSO, toluene, 75 °C, 6 h, 71%; ii, (a) 1.1 equiv. $CeCl_3 \cdot 7H_2O$ 2 equiv. $NaBH_4$, MeOH, RT, 30 min, 80% (b) 0.2 equiv. *p*-TsOH, benzene, RT, 4 h, 73%

11.10.5.1.7 Substrates on solid support

The PKR with substrates attached on solid was introduced by Schore and Kurth to improve the chemical yield of an intermolecular reaction of low molecular weight alkynol and norbornadienes by anchoring the alcohol on silica gel.[80] Later, Bolton extended this approach to an intramolecular reaction to form bicyclic α-amino acids.[80a,80b]

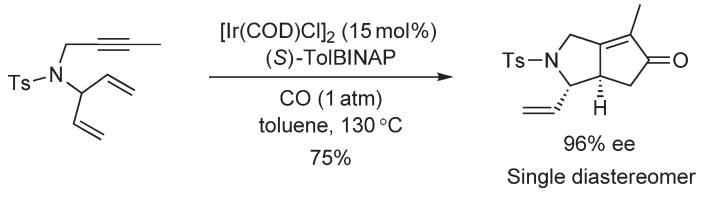
Schreiber and co-workers have shown that this approach is useful in the preparation of compound libraries. One of their examples is a diversity-oriented synthesis of polycyclic scaffolds through the Ferrier reaction followed by the PKR of a glycal template on solid support (Equation (35)).[80c]



(35)

11.10.5.1.8 Desymmetrization by asymmetric PKR catalysts

Jeong described desymmetrization of dienynes, such as *N*-propargyl-*N*-(penta-1,4-dien-3-yl) tosylamides, by the asymmetric Ir(I)-based PK-type reaction. The corresponding vinyl-substituted bicyclo[3,3,0]-octenones were obtained with high diastereoselectivity and enantioselectivity (Equation (36)).[81]

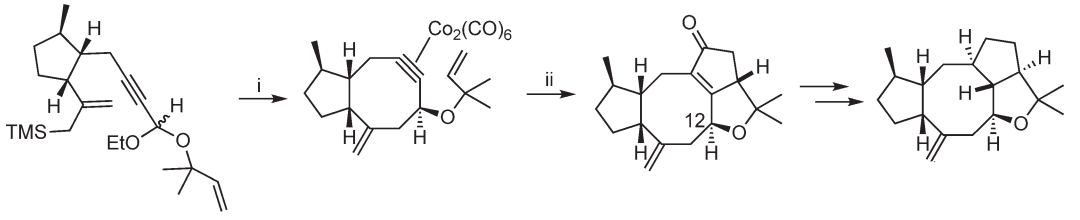


(36)

11.10.5.2 Tandem Approaches Coupled with Other Reactions

Tandem reaction generally attracts much interest because it allows us to effect multiple transformations, all in one pot. Two types are known at present. The most popular approach is a combination of several reactions with PKR. Properly functionalized 1,6- or 1,7-enynes are readily obtained from the propargyl alcohol–dicobalt hexacarbonyl complexes and a properly nucleophilic allylic moiety in the presence of a Lewis acid. The resultant enynes are subjected to the promoter-assisted PKR without purification to afford the desired PKR products (Scheme 9).[82,82a–82e]

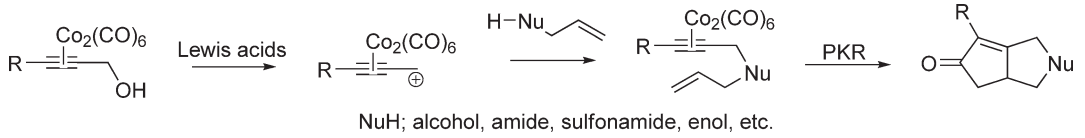
Schreiber and co-workers provide one of the most stylish examples of this approach. The successful synthesis of (+)-epoxydictymene relies on selective activation of an ethoxy group compared with an allyloxy group in the Nicholas reaction (selectivity 8.5 : 1) and the stereoselective PKR (Equation (37)).[82a,82b]



(37)

i, (a) $Co_2(CO)_8$ (b) Me_3SiOTf, Et_2O, –78 °C, 82% (8.5 : 1); ii, heat, CH_3CN, 5 : 1 at C-12

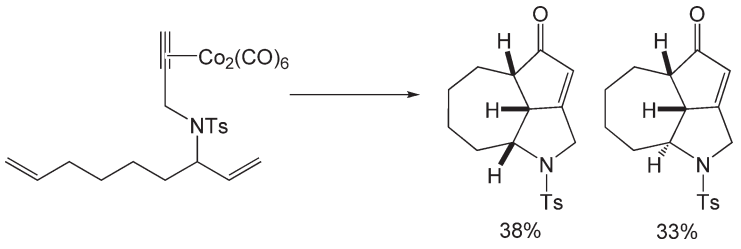
More examples in this line can be found in the reports of Shea[82c] and Carbery.[82d] Perez-Castells and co-workers combined ring-closure metathesis and PKR for the synthesis of tricyclic compounds in one batch. In this approach, a



NuH; alcohol, amide, sulfonamide, enol, etc.

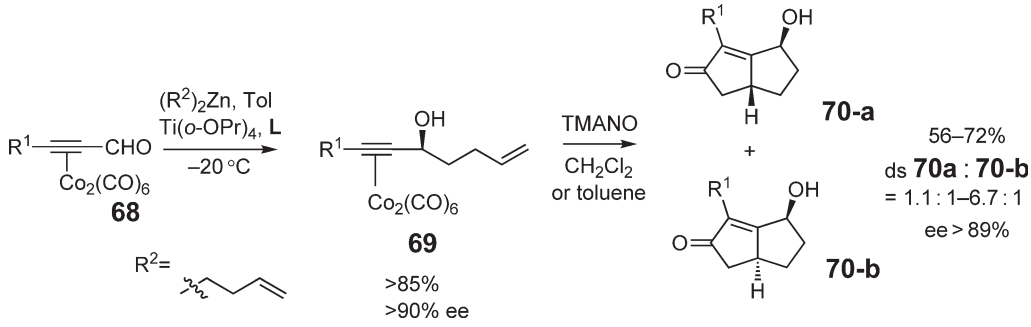
Scheme 9

cobalt complex was used as a PKR precursor for a later stage, and as an alkyne-protecting group for the metathesis stage (Equation (38)).[82e]



(38)

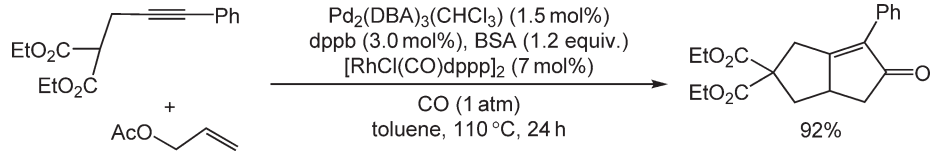
Jeong and co-workers utilized a cobalt–alkyne complex to enhance enantioselectivity of the addition of bis (homoallyl)zinc to propargyl aldehydes **68** by the exaggeration of steric environment. The reaction provided optically enriched propargyl alcohol **69** in the presence of a chiral ligand and titanium tetra(isopropoxide) in excess. Adduct **69** was subjected to PKR to yield optically enriched bicyclic compounds **70** (Equation (39)).[83]



(39)

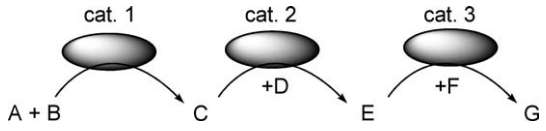
One of the most desirable tandem processes is a mimic of a multi-enzymatic process. It is well known that most of the metabolites in living cells are synthesized by a programmed sequence of enzymes that show high specificity toward different intermediates involved (Scheme 10).

In particular, Jeong was the first to demonstrate that this concept was feasible with the combination of π-allylic substitution (by a palladium catalyst) and PKR (by a rhodium catalyst). This two-step transformation is achieved by mixing all ingredients and heating the mixture in toluene at 110 °C (Equation (40)).[84]

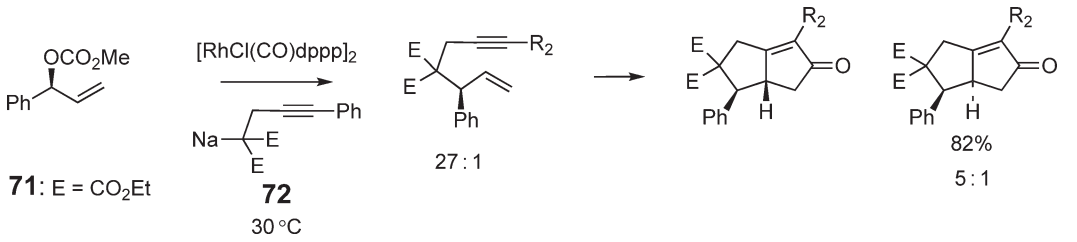


(40)

Regio- and diastereoselective rhodium-catalyzed tandem allylic alkylation of **71** with stabilized carbon and heteroatom nucleophiles **72** followed by the PK annulation by the same catalyst was described by Evans and co-workers. Alkylation of an optically active allylic alcohol carbonate **71** proceeds in a regio- and stereospecific manner successfully at 30 °C by π-acidic Rh(I) catalysts (Equation (41)). The resultant product then undergoes the PKR with the aid of the pre-existing catalyst under CO pressure at elevated temperature.[85]



Scheme 10



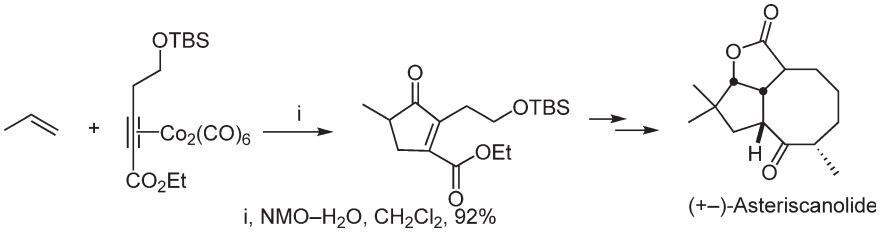
(41)

The moderate diastereoselectivity common with PKR is substantially increased by introduction of bulkier substituents (Equation (41)).

11.10.5.3 Natural Product Synthesis

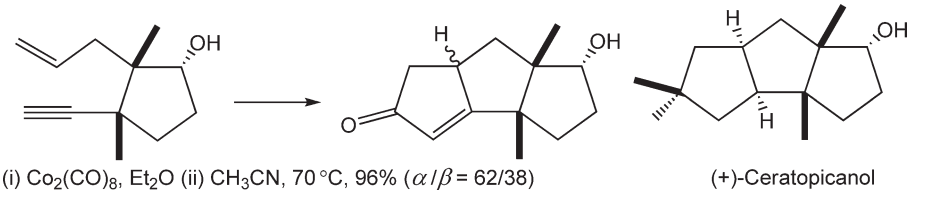
One of the most prominent features of PKR is a quick access to relatively complex multicyclic compounds. Specially, the intramolecular PKR with properly functionalized precursors allows preparation of highly functionalized cyclic intermediates with complete control of the regioselectivity as well as a relatively high degree of the steroselectivity. Early examples including synthesis of furanether B, coriolin, quadron, hirsutic acid, carbaprostacyclin, kainic acid, loganin and brefeldin A are discussed in the previous reviews.[2a] Here, we highlight the more recent examples.

Intermolecular PKR is not widely applied. Krafft and co-workers reported the synthesis of asteriscanolide. In their approach, regioslective intermolecular PKR with propene is used for the construction of the cyclopentane backbone of the target molecule (Equation (42)).[86]



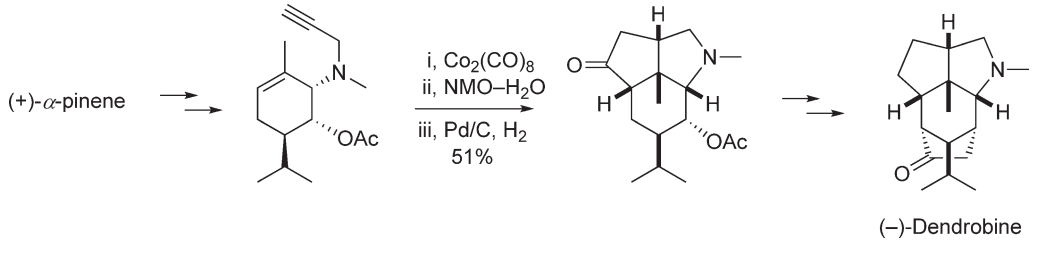
(42)

Persistent synthetic efforts toward the triquinane skeleton through the intramolecular PKR have appeared in the literature. These include synthesis of (+)-ceratopicanol by Mukai,[87] synthesis of the tricyclic moiety in kalmanol by Paquette,[88] asymmetric synthesis of 15-nor-pentalene by Pericas and Moyano, and the synthesis of the D/E ring in pentacyclic steroid xestoergsterol as described by Krafft (Equation (43)).[89]



(43)

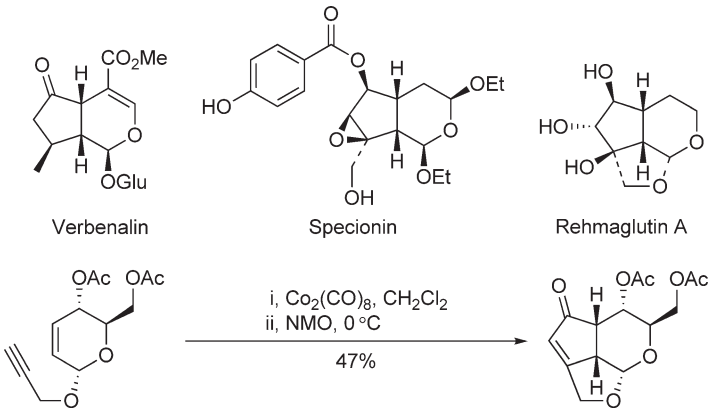
Introduction of a quaternary carbon center is readily achieved by PKR. Takano and Zard independently employed this methodology for the synthesis of (−)-dendrobin (Equation (44)).[90]



(44)

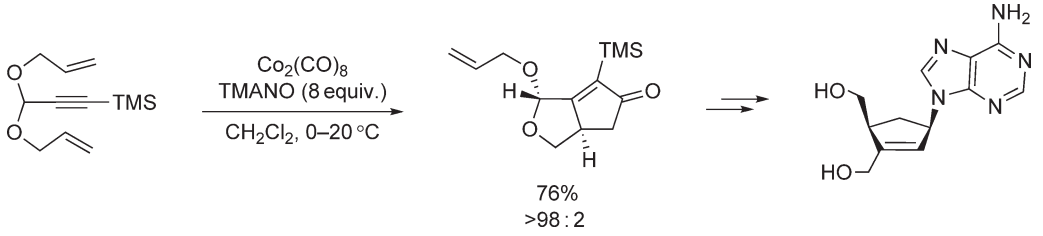
A number of methods for formation of a quaternary carbon are given below: synthesis of α-cedrene and β-cedrene by Kerr and Pauson,[91] synthesis of the core of (−)-tricycloillicinone,[92] and synthetic efforts toward the synthesis of partial structures of magellani,[93] nakadomarin,[94] and conessin.[95]

It is well documented already that the cobalt-mediated PKR is tolerant to the various functional groups, especially oxygen functionality. Iridoids are among the challenging synthetic targets, because of the plethora of oxygen functionality present in a relatively small backbone. Utilizing the carbohydrate-based precursors for PKR, synthesis of this class of target turned out to be efficient (Equation (45)).[96,96a,96b]



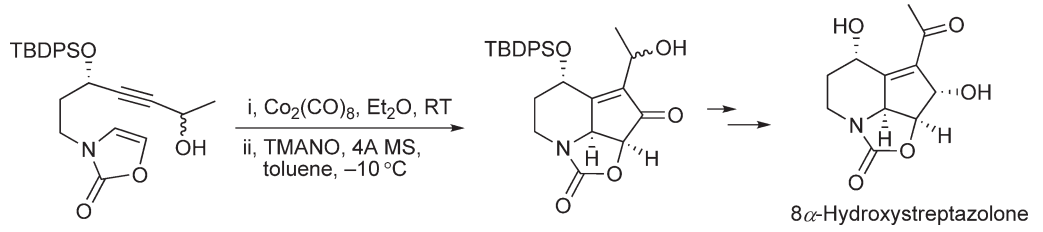
(45)

In conjunction with this, Jeong reported the cycloadditions of bis(allyl) and bis(homoallyl) acetals of alkynals leading to bicyclic lactols.[97] Smaltz extended its utility to the synthesis of carbocyclic nucleoside by coupling with nucleophilic substitution of a π-allylic palladium complex (Equation (46)).[97a]



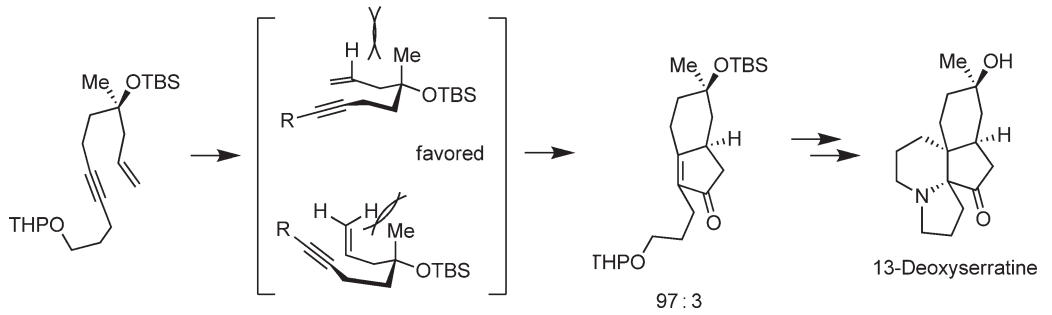
(46)

Mukai's synthesis of 8α-hydroxystreptazolone represents an excellent example of using the oxazolone derivative in PKR. This implies the possibility of use of an enamine as the olefinic part of the reaction (Equation (47)).[98]



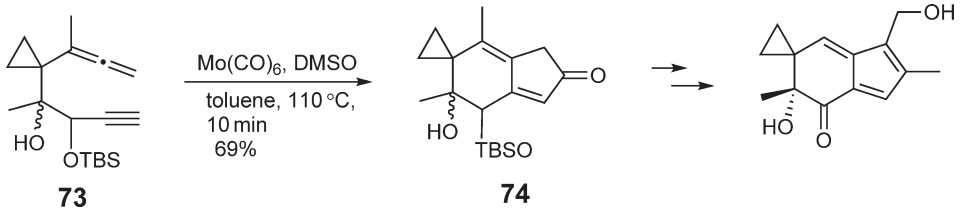
(47)

Zard and co-workers recently reported a synthesis of 13-deoxyserratine. This synthesis includes a highly diastereoselective PKR (Equation (48)).[99]



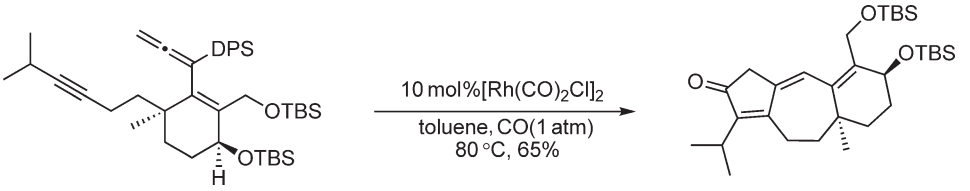
(48)

As seen in the previous section, the PKR of the alleneynes opens new horizons for the applications. One of the rewards of this approach is the synthesis of highly functionalized compact bicyclic compound-like illudins. Brummond and co-workers performed PKR with the properly functionalized allenyne **73** to afford compound **74**, which is transformed into HMAF (Equation (49)).[100,100a]



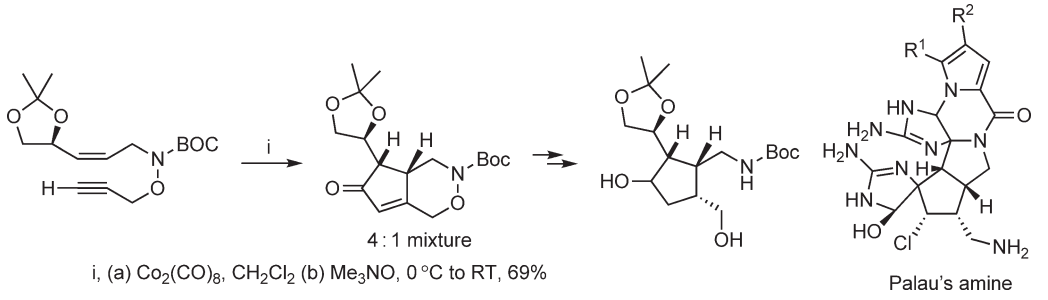
(49)

A synthesis of the highly functionalized tricyclic core of guanacasterpene represents an example of the Rh(I)-catalyzed intramolecular PKR leading to bicyclo[5,3,0]-decanes from the allenynes (Equation (50)).[101]



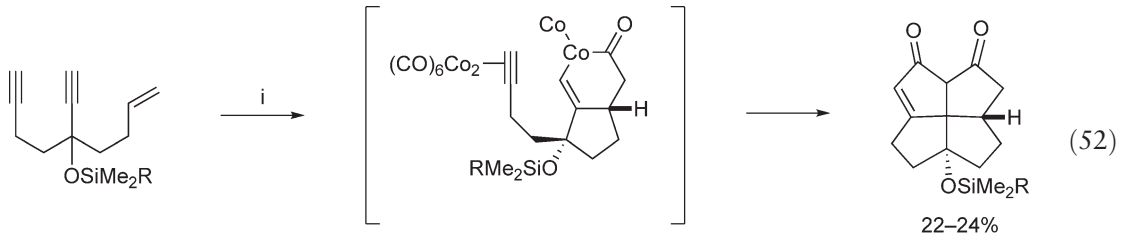
(50)

Koenig employed N–O-linked substrates in PKR to synthesize the fully functionalized bottom core of Palau's amine and styloguanidine (Equation (51)).[102,102a]



(51)

Keese's elegant synthesis of farnestane [5,5,5,5]-ring system through PKR was upgraded by Chung and co-workers armed with the improved protocols (Equation (52)).[103,103a–103c]



(52)

i, (a) $Co_2(CO)_8$ (2 equiv.) (b) NMO, THF–CH_2Cl_2, RT

11.10.6 Conclusions

The PKR is a truly remarkable synthetic method in several aspects. It creates much molecular complexity in one step along with retaining original functionality in substrate. Every carbon on the pentagon corner can further be functionalized to lead to products decorated with various functional groups.

The progress made over the last decade widens the horizon of the reaction. More specifically, the development of catalytic versions including heterogeneous as well as the enantioselective ones clearly demonstrates its application in industry is more tangible. We also have witnessed rapid expandsion of the substrate scope and are expecting further possibilities for this method. With understanding of the reaction mechanism and accumulated knowledge for the regio- and stereoselectivities, this reaction has become undoubtedly an indispensable tool in organic synthesis.

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11.11
Silane-initiated Carbocyclization Catalyzed by Transition Metal Complexes

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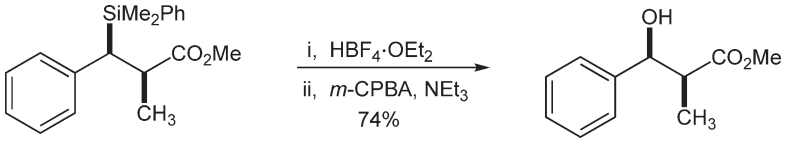
11.11.1 Introduction

The transition metal-catalyzed addition of the Si–H bond of a hydrosilane across a C═C or C≡C bond is a transformation of considerable importance in both large-scale industrial processes and in small-scale organic synthesis.[1–6] Perhaps the most common industrial application of catalytic hydrosilylation is the platinum-catalyzed cross-linking of vinylsilane polymers with hydrosilanes.[2] The interest in catalytic hydrosilylation in organic synthesis

stems primarily from the ability of a functionalized silyl group to serve as a latent hydroxyl group that can be unmasked via oxidation (Equation (1)).[3–5] In this regard, functionalized organosilanes are oftentimes more versatile than organoboranes due to the greater stability of organosilanes, which allows an organosilane to be carried through a number of synthetic steps prior to the eventual unmasking step. The utility of catalytic hydrosilylation in organic synthesis has been further enhanced through the development of a number of effective procedures for asymmetric hydrosilylation.[6,6a]



(1)

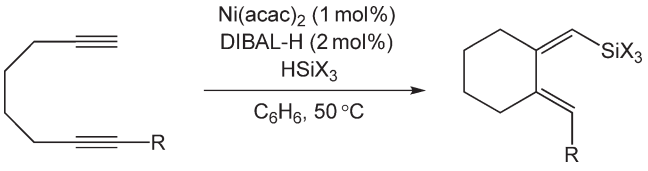
Although a number of mechanisms for the transition metal-catalyzed hydrosilylation of C–C multiple bonds have been proposed,[7] these mechanisms typically invoke formation of a reactive M–C intermediate. Because many of these M–C complexes are potentially reactive with respect to olefin and alkyne β-migratory insertion, the development of silane-initiated carbocyclization processes represents a natural extension of the catalytic hydrosilylation of C–C multiple bonds. Indeed, since the 1989 report of Tamao and Ito describing the nickel-catalyzed cyclization/hydrosilylation of 1,7-diynes,[8,8a] numerous silane-initiated carbocyclization reactions involving diynes, enynes, dienes, and related substrates have been described. These transformations are catalyzed by a diverse range of transition metal complexes including electron-rich Rh(I) carbonyl complexes, unsupported Ni(0) complexes, cationic Pd, Pt, and Rh complexes, and highly electrophilic d^0-metallocene complexes. The synthetic utility of silane-initiated carbocyclization has been further extended through the development of carbonylative processes, asymmetric processes, and processes that employ bimetallic reagents. This review provides a comprehensive overview of the transition metal-catalyzed, silane-initiated carbocyclization of diynes, enynes, dienes, and related substrates.

11.11.2 Cyclization/Hydrosilylation of Diynes

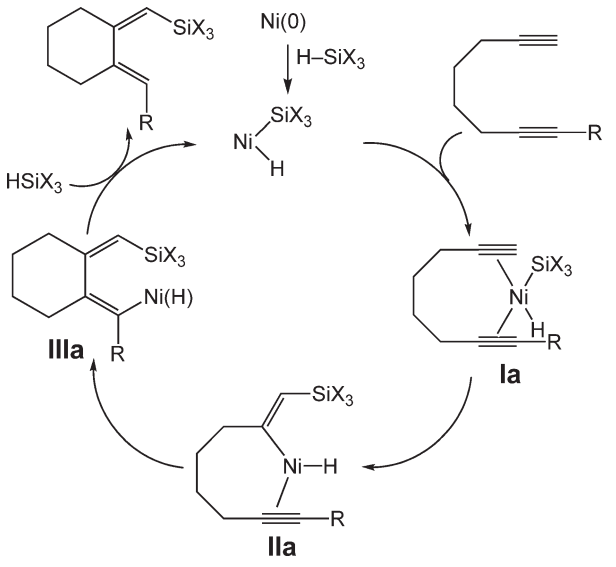
11.11.2.1 Nickel Catalysts

Tamao and Ito have reported a nickel-catalyzed protocol for the cyclization/hydrosilylation of 1,7-diynes to form (*Z*)-silylated dialkylidene cyclohexane derivatives.[8,8a] For example, reaction of 1,7-octadiyne with triethoxysilane catalyzed by a mixture of $Ni(acac)_2$ (1 mol%) and DIBAL-H (2 mol%) in benzene at 50 °C for 6 h gave the corresponding silylated dialkylidene cyclohexane in 70% yield as a single isomer (Table 1). The reaction of 1,7-octadiyne was also realized with mono- and dialkoxysilanes, trialkylsilanes, and dialkylaminosilanes (Table 1). Diynes that possessed an internal alkyne also underwent nickel-catalyzed reaction, albeit with diminished efficiency (Table 1), while 1,6- and 1,8-diynes failed to undergo nickel-catalyzed cyclization/hydrosilylation.

Table 1 Nickel-catalyzed diyne cyclization/hydrosilylation



SiX_3	*R*	*Yield* (%)
$Si(OEt)_3$	H	70
$SiMe(OEt)_2$	H	68
$SiMe_2(OPr^i)$	H	67
$SiMeEt_2$	H	55
$SiMe_2(NEt_2)$	H	52 ($Z/E = 94/6$)
$SiMe_2(OPr^i)$	Bu^n	36

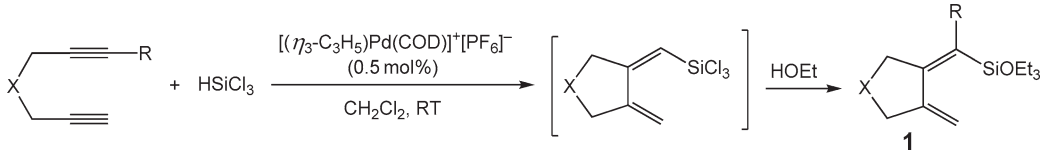


Scheme 1

Tamao and Ito proposed a mechanism for the nickel-catalyzed cyclization/hydrosilylation of 1,7-diynes initiated by oxidative addition of the silane to an Ni(0) species to form an Ni(II) silyl hydride complex. Complexation of the diyne could then form the nickel(II) diyne complex **Ia** (Scheme 1). Silylmetallation of the less-substituted C≡C bond of **Ia**, followed by intramolecular β-migratory insertion of the coordinated C≡C bond into the Ni–C bond of alkenyl alkyne intermediate **IIa**, could form dienylnickel hydride intermediate **IIIa**. Sequential C–H reductive elimination and Si–H oxidative addition would release the silylated dialkylidene cyclohexane and regenerate the silylnickel hydride catalyst (Scheme 1).

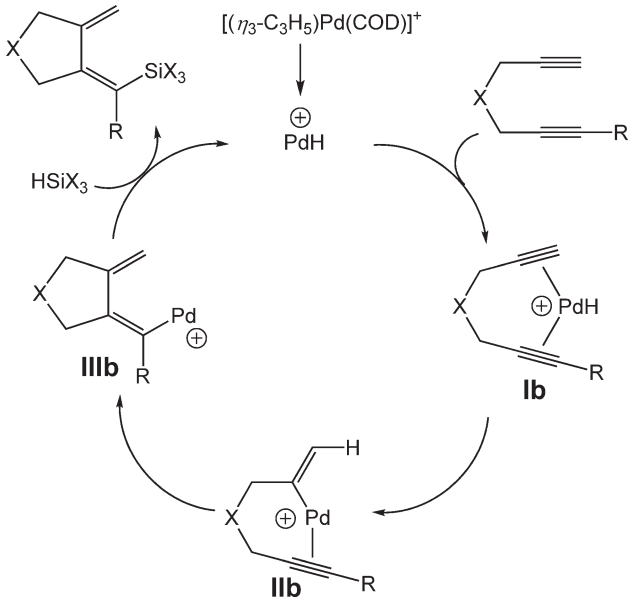
11.11.2.2 Palladium Catalysts

Yamamoto has reported a palladium-catalyzed protocol for the cyclization/hydrosilylation of 1,6- and 1,7-diynes to form silylated dialkylidene cycloalkanes.[9,9a] For example, reaction of dimethyl dipropargylmalonate and trichlorosilane catalyzed by the cationic (π-allyl)palladium complex $[(\eta^3\text{-}C_3H_5)Pd(COD)]^+[PF_6]^-$ in dichloromethane at room temperature followed by *in situ* alcoholysis with ethanol gave the silylated dialkylidene cyclopentane **1** [X = $C(CO_2Me)_2$, R = H] in 56% yield as a 92 : 8 mixture of *Z* : *E* isomers (Equation (2)). Dichloromethylsilane and chlorodimethylsilane provided comparable results. Dipropargyl ethers, dipropargylamides, and 1,7-diynes also underwent palladium-catalyzed cyclization/hydrosilylation to form the corresponding silylated dialkylidene derivatives **1** in moderate yield with good stereoselectivity (Equation (2)). Also noteworthy was that 1,6-diynes which possessed one internal and one terminal C≡C bond underwent palladium-catalyzed reaction to form the silylated dialkylidene cyclopentane resulting from exclusive delivery of the silane to the internal C≡C bond (Equation (2), R = Me).



X	*R*	*Yield* (%)	*Ratio Z : E*
$C(CO_2Me)_2$	H	56	92 : 8
$C(CO_2Me)_2$	Me	53	93 : 7
O	H	33	93 : 7
O	Me	40	100 : 0
NTs	H	53	100 : 0
$(CH_2)_2$	H	68	84 : 16

(2)

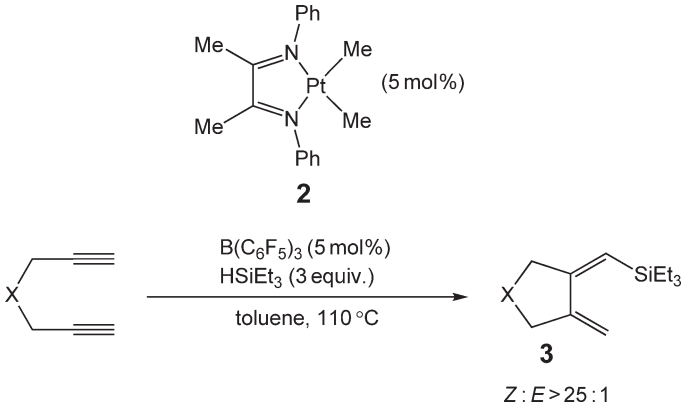


Scheme 2

Yamamoto has proposed a mechanism for the palladium-catalyzed cyclization/hydrosilylation of enynes that accounts for the selective delivery of the silane to the more substituted C≡C bond. Initial conversion of $[(\eta^3\text{-}C_3H_5)Pd(COD)]^+[PF_6]^-$ to a cationic palladium hydride species followed by complexation of the diyne could form the cationic diynylpalladium hydride intermediate **Ib** (Scheme 2). Hydrometallation of the less-substituted alkyne would form the palladium alkenyl alkyne complex **IIb** that could undergo intramolecular carbometallation to form the palladium dienyl complex **IIIb**. Silylative cleavage of the Pd–C bond, perhaps via σ-bond metathesis, would then release the silylated diene with regeneration of a palladium hydride species (Scheme 2).

11.11.2.3 Platinum Catalysts

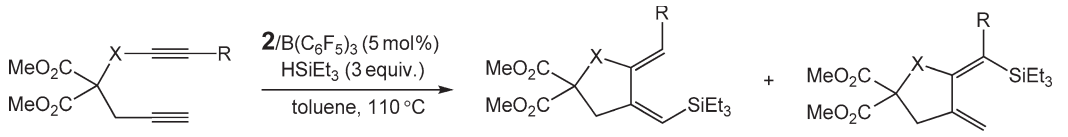
Widenhoefer and co-workers have developed an effective platinum-catalyzed protocol for the cyclization/hydrosilylation of 1,6-diynes that possess terminal C≡C bonds.[10,10a] As an example, reaction of dimethyl dipropargylmalonate with $HSiEt_3$ catalyzed by a 1 : 1 mixture of the platinum diimine complex [PhN=C(Me)C(Me)=NPh]$PtMe_2$ **2** and the strong Lewis acid $B(C_6F_5)_3$ at 110 °C for 10 min gave silylated dialkylidene cyclopentane **3** [X = $C(CO_2Me)_2$] in 82% yield as a 26 : 1 mixture of *Z* : *E* stereoisomers (Equation (3)). A 1 : 1 mixture of the platinum phenanthroline complex (phen)$PtMe_2$ and $B(C_6F_5)_3$ also catalyzed the reaction of dimethyldipropargylmalonate, although longer reaction times were required.[10,10a]



X	*Yield* (%)
$C(CO_2Me)_2$	82
$C(CH_2OP_{iv})_2$	76
$C[CH_2OCMe_2OCH_2]$	77
$C(CH_2OBn)_2$	86
$C(CH_2OTBDMS)_2$	80
$C(CO_2Me)(Ph)$	84
$C(CO_2Me)(SO_2Me)$	74
$C(CO_2Me)(CONMe_2)$	80
$C(CO_2Me)(COMe)$	65
$C(CO_2Me)(H)$	72
$C_2(CO_2Et)_4$	77

(3)

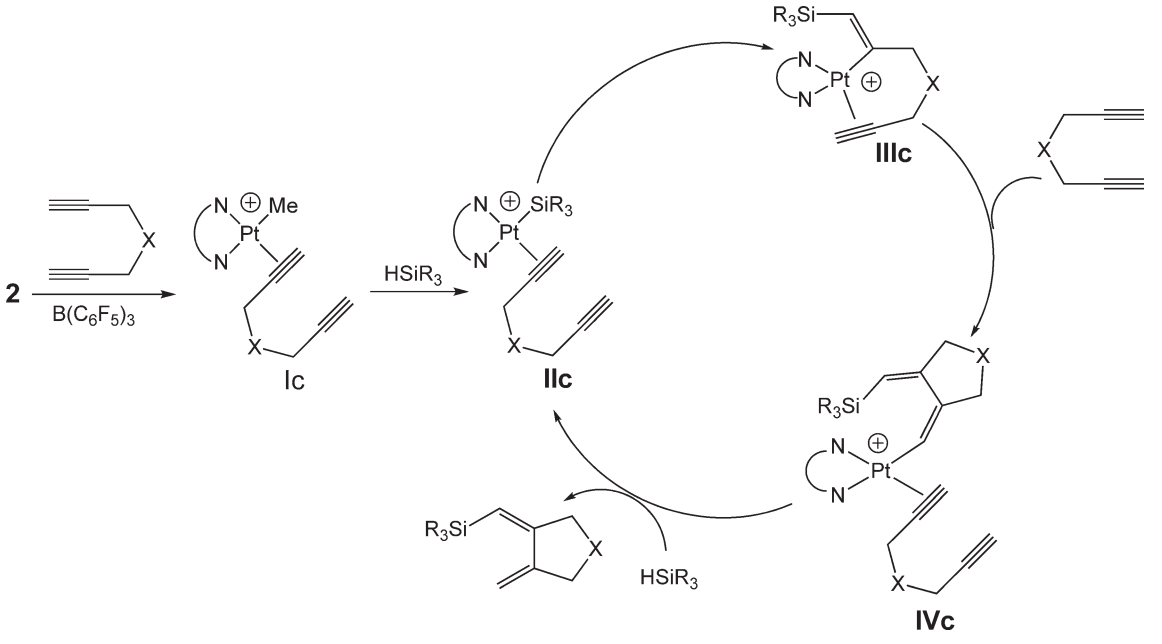
Platinum-catalyzed diyne cyclization/hydrosilylation tolerated a range of polar functional groups, including esters, ketones, sulfonates, carboxamides, ethers, silyl ethers, and acetals (Equation (3)). *gem*-Dialkyl substitution at the homoallylic position appeared to facilitate reaction but was not required (Equation (3), X = C(CO_2Me)(H)). Diynes that possessed mono- or *gem*-disubstitution at one of the propargylic positions underwent reaction in good yield with modest regioselectivity (Equation (4); X = CHMe, X = C(Me)(CO_2Me)). Diynes that possessed a single internal C≡C bond underwent cyclization/hydrosilylation in moderate yield with high selectivity for delivery of the silane to the less substituted C≡C bond (Equation (4); X = CH_2, R = CO_2Me). Diynes that possessed two internal C≡C bonds did not undergo reaction. 1,7-Diynes also underwent Pt-catalyzed cyclization/hydrosilylation to form dialkylidene cyclohexanes in good yield with good stereoselectivity (Equation (3); X = $C_2(CO_2Et)_4$).



(4)

X	*R*	*Yield* (%)	*Ratio Z : E*
CHMe	H	80	1 : 1.2
C(Me)(CO_2Me)	H	82	1 : 2.3
CH_2	CO_2Me	43	>30 : 1

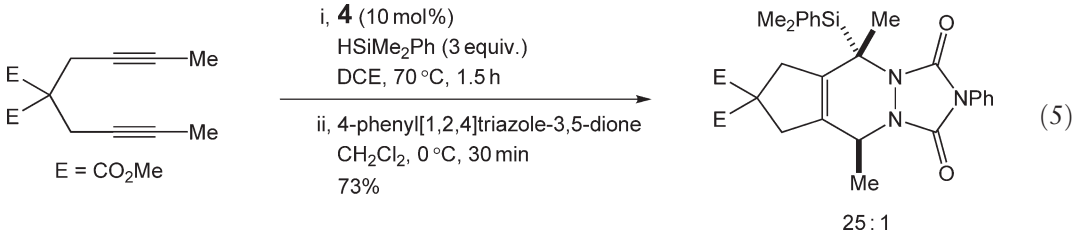
On the basis of a number of precedents,[11,11b–d] a plausible mechanism for the platinum-catalyzed cyclization/hydrosilylation of 1,6-diynes was constructed. Abstraction of a methyl group from **2** with B(C_6F_5)$_3$ in the presence of diyne could form the four-coordinate cationic platinum methyl alkyne complex **Ic** (Scheme 3).[11] Silylation of the Pt–C bond of **Ic**,[11a] presumably via an oxidative addition/reductive elimination sequence,[11b–11d] would form platinum silyl complex **IIc**. Silylmetallation of the complexed C≡C bond followed by intramolecular carbometallation of the resulting alkenylplatinum alkyne complex **IIIc** could form the dienylplatinum alkyne species **IVc**. Silylation of the Pt–C bond of **IVc** could release the silylated diene with regeneration of **IIc** (Scheme 3).



Scheme 3

11.11.2.4 Rhodium Catalysts

Widenhoefer and Liu have reported an effective rhodium-catalyzed protocol for the cyclization/hydrosilylation of functionalized 1,6-diynes that possessed internal C≡C bonds to form silylated (*Z*)-1,2-dialkylidene cyclopentanes.[12] For example, reaction of 5,5-bis(methoxycarbonyl)-2,7-nonadiyne and triethylsilane catalyzed by $[(BINAP)Rh(COD)]^+$-$[BF_4]^-$ **4** (10 mol%) in DCE at 70 °C for 1 h gave the corresponding silylated dialkylidene cyclopentane in 77% yield as a single isomer (Table 2, entry 1). The reaction catalyzed by **4** tolerated a number of functional groups including pivaloyl esters, benzyl ethers, and carboxamides, and was applicable to the synthesis of silylated dialkylidene heterocyclic compounds (Table 2, entries 2–6). Furthermore, the protocol was not restricted to diynes that possessed terminal methyl groups (Table 2, entries 7–9). It was noteworthy that differentially substituted diynes reacted with selective transfer of the silane to the less hindered alkyne moiety (Table 2, entry 9). Functionalized silanes such as dimethylphenylsilane were also effective for rhodium-catalyzed diyne cyclization/hydrosilylation, although *in situ* trapping of the silylated (*Z*)-1,2-dialkylidene cyclopentane was required to separate the cyclization/hydrosilylation product from the corresponding silylated uncyclized byproduct (Equation (5)).

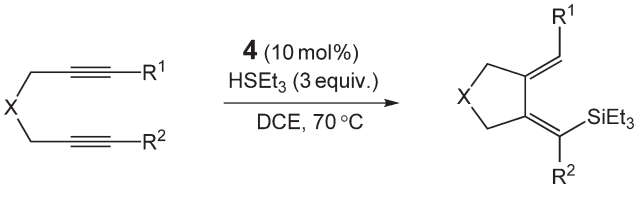


(5)

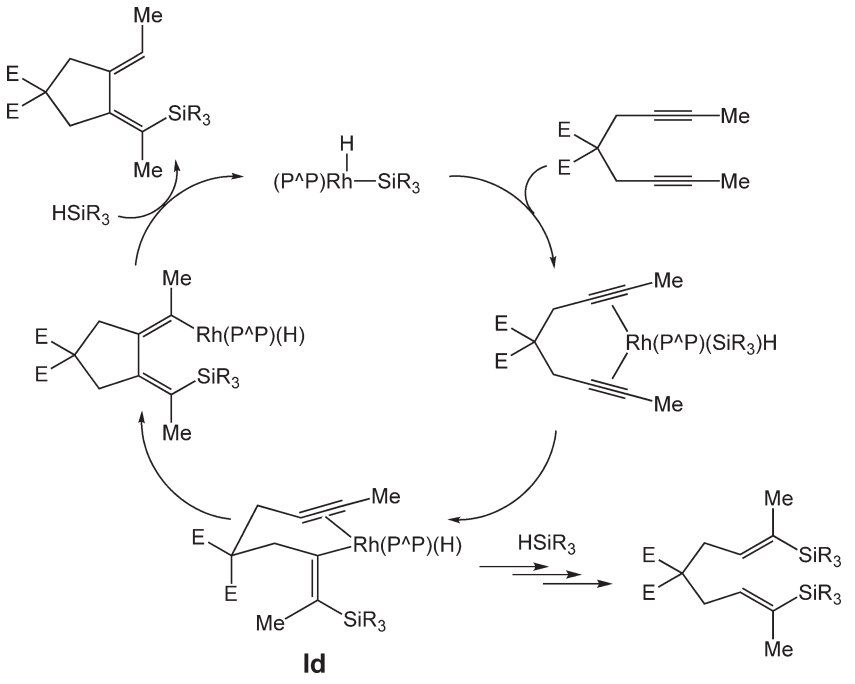
Diyne cyclization/hydrosilylation catalyzed by **4** was proposed to occur via a mechanism analogous to that proposed for nickel-catalyzed diyne cyclization/hydrosilylation (Scheme 4). It was worth noting that experimental evidence pointed to a silane-promoted reductive elimination pathway. In particular, reaction of dimethyl dipropargylmalonate with $HSiMe_2Et$ (3 equiv.) catalyzed by **4** led to predominant formation of the disilylated uncyclized compound **5** in 51% yield, whereas slow addition of $HSiMe_2Et$ to a mixture of the diyne and **4** led to predominant formation of silylated 1,2-dialkylidene cyclopentane **6** (Scheme 5). This and related observations were consistent with a mechanism involving silane-promoted C–H reductive elimination from alkenylrhodium hydride species **Id** to form silylated uncyclized products in competition with intramolecular carbometallation of **Id** to form cyclization/hydrosilylation products (Scheme 4). Silane-promoted reductive elimination could occur either via an oxidative addition/reductive elimination sequence involving an Rh(V) intermediate, or via a σ-bond metathesis pathway.

Matsuda reported a protocol for the cyclization/hydrosilylation of diynes to form silylated (*E*)-1,2-dialkylidene cyclopentanes catalyzed by neutral Rh(I) and Rh(III) complexes.[13,13a] For example, reaction of dimethyl dipropargylmalonate with dimethylphenylsilane catalyzed by $Rh(H)(SiMe_2Ph)Cl(PPh_3)_2$ **7** in dichloromethane at room temperature gave

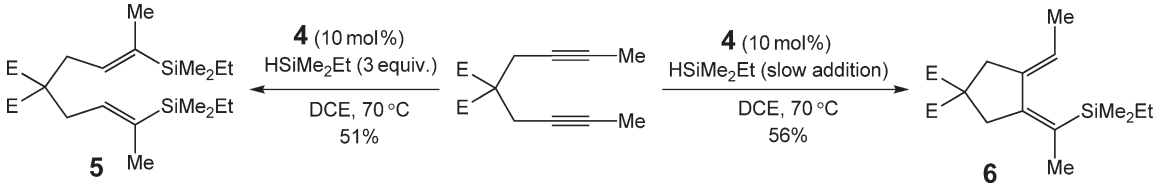
Table 2 Rhodium-catalyzed diyne cyclization/hydrosilylation



Entry	*X*	R^1	R^2	*Yield* (%)	*Isomer ratio*
1	$C(CO_2Me)_2$	Me	Me	77	>25 : 1
2	$C(CH_2OBn)_2$	Me	Me	62	>25 : 1
3	$C(CH_2OPiv)_2$	Me	Me	72	>25 : 1
4	$C(CO_2Me)(CONMe_2)$	Me	Me	70	>25 : 1
5	NTs	Me	Me	70	10 : 1
6	O	Me	Me	40	>25 : 1
7	$C(CO_2Me)_2$	Et	Et	56	>25 : 1
8	$C(CO_2Me)_2$	*n*-pentyl	*n*-pentyl	60	>25 : 1
9	$C(CO_2Me)_2$	Et	Me	65	15 : 1

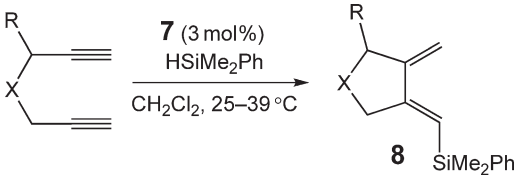


Scheme 4



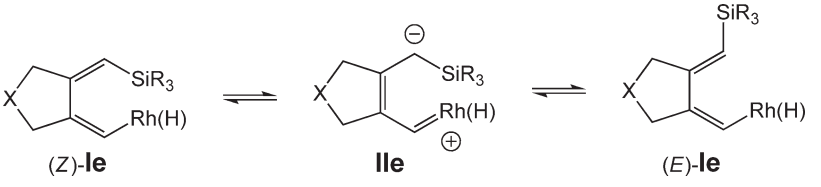
Scheme 5

silylated dialkylidene cyclopentane (*E*)-**8** (X = $C(CO_2Me)_2$) in 61% yield as a single diastereomer (Equation (6)). Although the yields were modest, the protocol was also effective for the synthesis of silylated nitrogen heterocycles. Also noteworthy was that diynes that possessed a propargylic substituent underwent reaction with selective transfer of the silyl group to the less substituted alkyne moiety (Equation (6); X = CMe_2, R = OTBDMS). Selective formation of the (*E*)-dialkylidene cyclopentane in preference to the (*Z*)-dialkylidene cyclopentane was attributed to secondary isomerization of the initially formed rhodium dialkylidene species (*Z*)-**Ie** to (*E*)-**Ie** via zwitterionic intermediate **IIe** (Scheme 6).



X	*R*	*Yield* (%)
$C(CO_2Me)_2$	H	61
CH_2	H	53
NBn	H	53
N(allyl)	H	52
CMe_2	OTBDMS	67

(6)



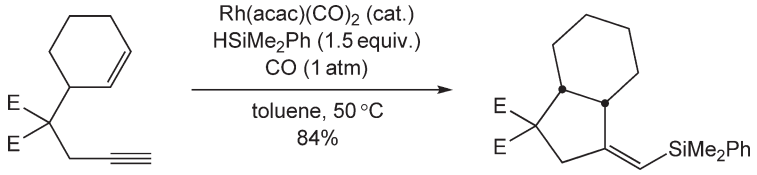
Scheme 6

11.11.3 Cyclization/Hydrosilylation of Enynes and Eneallenes

11.11.3.1 Rhodium Catalysts

Ojima has reported that a number of mono- and polynuclear rhodium carbonyl complexes catalyze the cyclization/hydrosilylation of functionalized enynes to form silylated alkylidene cyclopentanes.[14,14a] For example, reaction of diethyl 2-allyl-2-(2-propynyl)malonate with dimethylphenylsilane catalyzed by $Rh_4(CO)_{12}$ in hexane at room temperature under an atmosphere of CO led to rapid (<1 min) cyclization/hydrosilylation to form the corresponding (*Z*)-silylated alkylidene cyclopentane in 94% isolated yield with exclusive delivery of the silyl group to the alkyne moiety of the enyne (Table 3, entry 1). In addition to diphenylmethylsilane, dialkoxysilanes and trialkoxysilanes were effective in the reaction of 1,6-enynes catalyzed by rhodium carbonyl complexes (Table 3, entries 2–4).

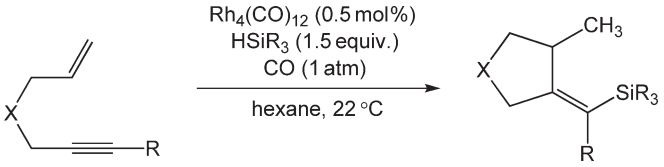
Cyclization/hydrosilylation of enynes catalyzed by rhodium carbonyl complexes tolerated a number of functional groups, including acetate esters, benzyl ethers, acetals, tosylamides, and allyl- and benzylamines (Table 3, entries 6–14). The reaction of diallyl-2-propynylamine is noteworthy as this transformation displayed high selectivity for cyclization of the enyne moiety rather than the diene moiety (Table 3, entry 9). Rhodium-catalyzed enyne cyclization/hydrosilylation tolerated substitution at the alkyne carbon (Table 3, entry 5) and, in some cases, at both the allylic and terminal alkenyl carbon atoms (Equation (7)).



(7)

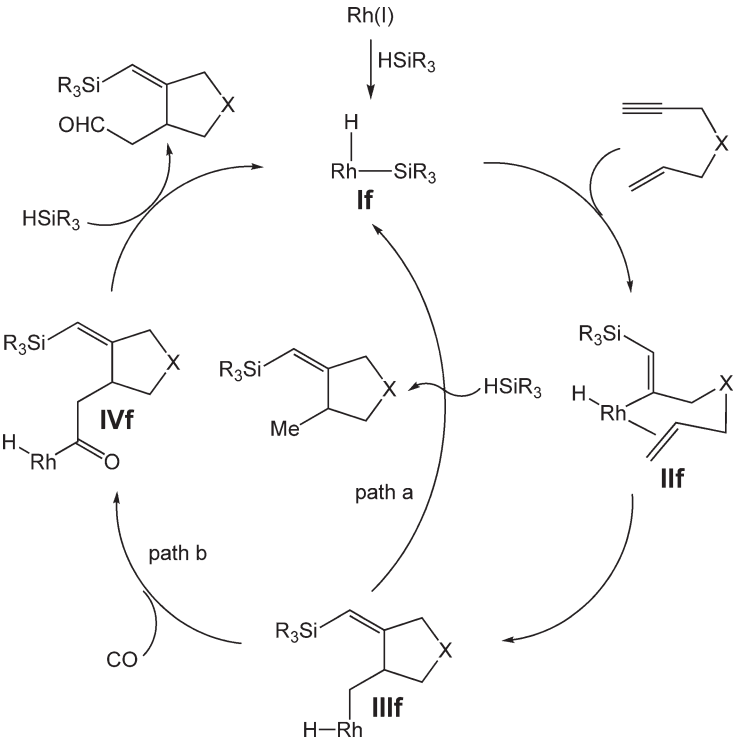
Ojima has proposed a mechanism for the rhodium-catalyzed cyclization/hydrosilylation of enynes initiated by oxidative addition of the H–Si bond of the hydrosilane to form the Rh(III) silyl hydride complex **If** (Scheme 7). Silylmetallation of the C≡C bond of the enyne coupled with coordination of the pendant C=C bond could form

Table 3 Rhodium-catalyzed enyne cyclization/hydrosilylation



Entry	*X*	*SiR*$_3$	*R*	*Yield* (%)
1	$C(CO_2Me)_2$	$SiMePh_2$	H	94
2	$C(CO_2Me)_2$	$SiMe(OEt)_2$	H	>99
3	$C(CO_2Me)_2$	$Si(OEt)_3$	H	99
4	$C(CO_2Me)_2$	$Si(OMe)_3$	H	>99
5	$C(CO_2Me)_2$	$SiMe_2Ph$	Me	89
6	NTs	$SiMe_2Ph$	H	86
7	NBn	$SiMe_2Ph$	H	83
8	NCH(Me)Ph	$SiMe_2Ph$	H	89
9	N(allyl)	$SiMe_2Ph$	H	74
10	O	$SiMe_2Ph$	H	82[a]
11	$C(CH_2OH)_2$	$SiMe_2Ph$	H	52
12	$C(CH_2OAc)_2$	$SiMe_2Ph$	H	90
13	$C(CH_2OMe)_2$	$SiMe_2Ph$	H	96[b]
14	$C[CH_2OC(Me)_2OCH_2]$	$SiMe_2Ph$	H	92[b]

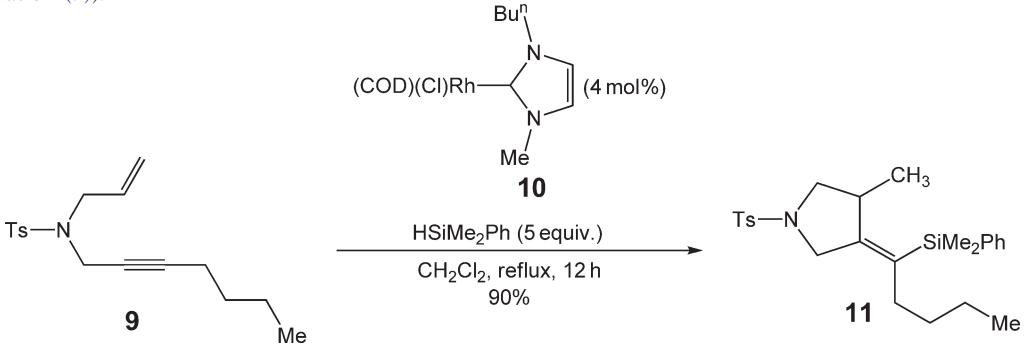
[a]$Rh_2CO_2(CO)_{12}$ (0.5 mol%) employed as catalyst.
[b]Reaction performed at 70 °C in toluene using $Rh(acac)(CO)_2$ (1 mol%) as catalyst.



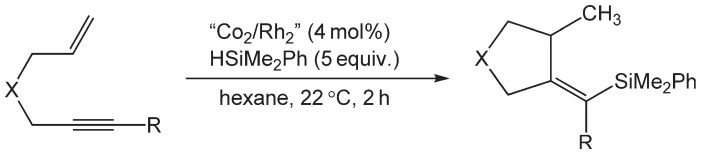
Scheme 7

alkenylrhodium alkene complex **IIf**. *β*-Migratory insertion of the C═C bond into the Rh–C bond of **IIf** could then form cyclopentylmethylrhodium complex **IIIf**. Silane-promoted reductive elimination from **IIIf** would release the alkylidene cyclopentane with regeneration of **If** (Scheme 7, path a).

Chung has demonstrated that, in addition to rhodium carbonyl complexes, rhodium complexes that contain *N*-heterocyclic carbene ligands and cobalt/rhodium nanoparticles (Co_2/Rh_2) catalyze the cyclization/hydrosilylation of 1,6-enynes.[15,16] As an example of the former transformation, reaction of enyne **9** with dimethylphenylsilane catalyzed by rhodium carbene complex **10** (4 mol%) in refluxing dichloromethane formed pyrrolidine **11** in 90% yield (Equation (8)). As an example of the latter procedure, reaction of diethyl allylpropargylmalonate with dimethylphenylsilane catalyzed by Co_2/Rh_2 in hexane at ambient temperature for 2 h gave the corresponding silylated alkylidene cyclopentane in 97% yield (Equation (9), X = $C(CO_2Et)_2$, R = H). The cobalt/rhodium nanoparticle-catalyzed reaction was compatible with a range of functional groups including esters, free hydroxyl groups, tosylamides, and ethers, and the protocol was effective with both internal and terminal alkyne moieties (Equation (9)).



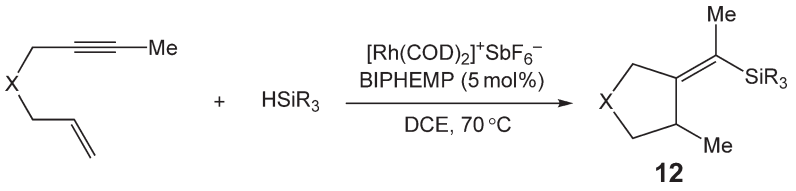
(8)



X	R	Yield (%)
$C(CO_2Et)_2$	H	97
$C(CH_2OH)_2$	H	83
NTs	H	90
$C(CO_2Me)_2$	Me	87
NTs	*n*-Bu	92

(9)

Table 4 Rhodium-catalyzed asymmetric enyne cyclization/hydrosilylation

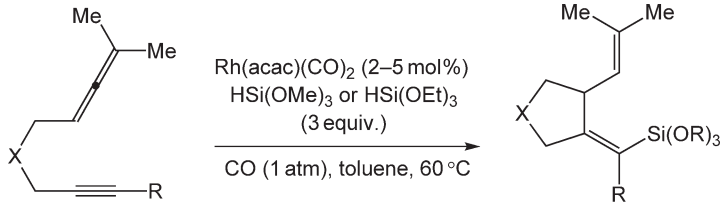


12

Entry	*X*	*HSiR*$_3$	*Yield* (%)	*ee* (%)
1	$C(CO_2Me)_2$	$HSiEt_3$	81	92
2	$C(CO_2Me)_2$	$HSiMePh_2$	71	77
3	$C(CO_2Me)_2$	$HSiMe_2Ph$	77	77
4	$C(CO_2Me)_2$	$HSiMe_2$*n*-octyl	74	82
5	$C(CO_2Me)_2$	$HSiMeEt_2$	76	88
6	NTs	$HSiMePh_2$	73	80
7	$C(CH_2OCH_3)_2$	$HSiEt_3$	65	80
8	$C(CH_2OAc)_2$	$HSiEt_3$	58	83

Widenhoefer and co-workers have developed an effective protocol for the asymmetric cyclization/hydrosilylation of functionalized 1,6-enynes catalyzed by enantiomerically enriched cationic rhodium bis(phosphine) complexes.[17] For example, treatment of dimethyl allyl(2-butynyl)malonate with triethylsilane (5 equiv.) and a catalytic 1 : 1 mixture of $[Rh(COD)_2]^+SbF_6^-$ and (*R*)-BIPHEMP (5 mol%) at 70 °C for 90 min gave the silylated alkylidene cyclopentane **12** in 81% yield with 98% de and 92% ee (Table 4, entry 1). A number of tertiary silanes were effective for the rhodium-catalyzed asymmetric cyclization/hydrosilylation of dimethyl allyl(2-butynyl)malonate with yields ranging from 71% to 81% and with 77–92% ee (Table 4, entries 1–5). Although the scope of the protocol was limited, a small number of functionalized 1,6-enynes including *N*-allyl-*N*-(2-butynyl)-4-methylbenzenesulfonamide underwent reaction in moderate yield with ≥80% ee (Table 4, entries 6–8).

Shibata and co-workers have reported an effective protocol for the cyclization/hydrosilylation of functionalized eneallenes catalyzed by mononuclear rhodium carbonyl complexes.[18] For example, reaction of tosylamide **13** (X = NTs, R = Me) with triethoxysilane catalyzed by $Rh(acac)(CO)_2$ in toluene at 60 °C gave protected pyrrolidine **14** in 82% yield with ≥20 : 1 diastereoselectivity and with exclusive delivery of the silane to the C≡C bond of the eneallene (Equation (10)). Whereas trimethoxysilane gave results comparable to those obtained with triethoxysilane, employment of dimethylphenylsilane or a trialkylsilane led to significantly diminished yields of **14**. Although effective rhodium-catalyzed cyclization/hydrosilylation was restricted to eneallenes that possessed terminal disubstitution of the allene moiety, the protocol tolerated both alkyl and aryl substitution on the terminal alkyne carbon atom and was applicable to the synthesis of cyclopentanes, pyrrolidines, and tetrahydrofurans (Equation (10)).



13 **14**

X	R	Yield (%)
NTs	Me	82
NTs	*n*-Bu	79
NTs	Ph	52
O	Me	73
O	Ph	54
$C(CO_2Et)_2$	Ph	61

(10)

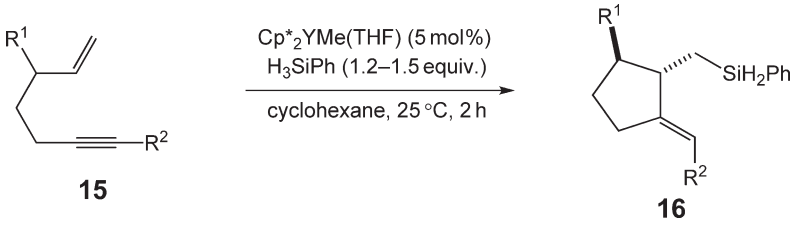
11.11.3.2 Lanthanide Catalysts

Molander has developed effective protocols for the cyclization/hydrosilylation of 1,6-enynes catalyzed by lanthanide metallocene complexes.[19] For example, reaction of cyclohexyl-substituted 1,6-enyne **15a** with phenylsilane catalyzed by $Cp^*_2YMe(THF)$ in cyclohexane at room temperature for 2 h gave silylated alkylidene cyclopentane **16a** as a 6.5 : 1 mixture of *trans* : *cis* isomers (Table 5, entry 1). The diastereoselectivity of the reaction depended strongly on the nature of the allylic substituent. For example, yttrium-catalyzed cyclization/hydrosilylation of the ethyl-substituted enyne **15b** gave silylated cyclopentane **16b** in 88% yield as a single diastereomer (Table 5, entry 2).

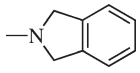
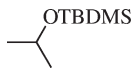
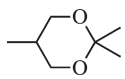
Yttrium-catalyzed enyne cyclization/hydrosilylation was proposed to occur via σ-bond metathesis of the Y–C bond of pre-catalyst $Cp^*_2YMe(THF)$ with the Si–H bond of the silane to form the yttrium hydride complex **Ig** (Scheme 8). Hydrometallation of the C≡C bond of the enyne coupled with complexation of the pendant C=C bond could form the alkenylyttrium alkyl complex **IIg**. Subsequent β-migratory insertion of the alkene moiety into the Y–C bond of **IIg** could form cyclopentylmethyl complex **IIIg**. Silylation of the resulting Y–C bond via σ-bond metathesis could release the silylated cycloalkane and regenerate the active yttrium hydride catalyst. Predominant formation of the *trans*-cyclopentane presumably results from preferential orientation of the allylic substituent in a pseudo-equatorial position in a chairlike transition state for intramolecular carbometallation (**IIg** → **IIIg**).

Although the highly oxophilic yttrium metallocene pre-catalyst and the corresponding intermediates are highly air and moisture sensitive, the protocol tolerated several functional groups including tertiary amines, ethers, and silyl ethers (Table 5). However, the presence of sterically unhindered oxygenated functionality significantly decreased the rate of reaction (Table 5, entry 5), presumably due to complexation of the oxygen atom to the electrophilic yttrium atom. Furthermore, the protocol was incompatible with polar unsaturated functionality such as esters, ketones, and nitriles, and both a branched alkyl substituent on the terminal alkyne carbon and a substituent at the allylic position of the enyne were required to achieve regio- and chemoselective hydrometallation of the C≡C bond (Scheme 8).

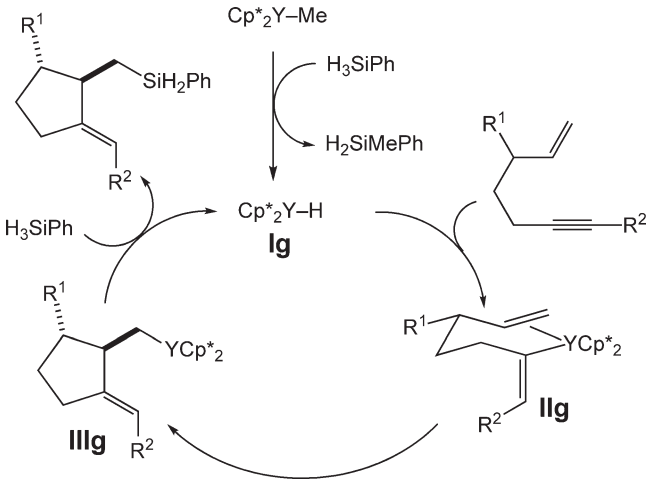
Table 5 Yttrium-catalyzed enyne cyclization/hydrosilylation



15 **16**

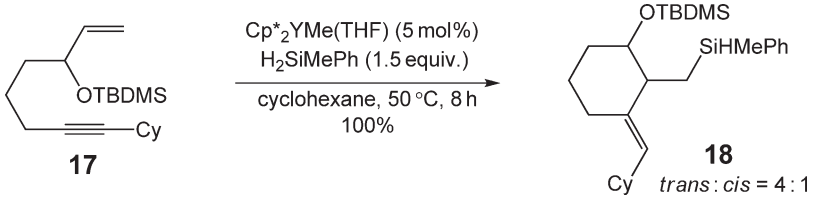
Entry	*Compound*	R^1	R^2	*Yield* (%)	*dr*
1	**a**	OTBDMS	Cy	93	6.5 : 1
2	**b**	Et	Cy	88	>50 : 1
3	**c**	OTIPS	Cy	93	12 : 1
4	**d**	OTr	Cy	84	24 : 1
5	**e**	CH_2OMe	Cy	80	20 : 1
6	**f**	$CH_2OTBDMS$	Cy	76	>50 : 1
7	**g**		Cy	91	40 : 1
8	**h**	OTr		77	
9	**i**	OTr		88	35 : 1

[a]Reaction run at 100 °C in a sealed tube.
[b]Reaction performed in d_6-benzene for 0.5 h employing 2 mol% $Cp^*_2YMe(THF)$.



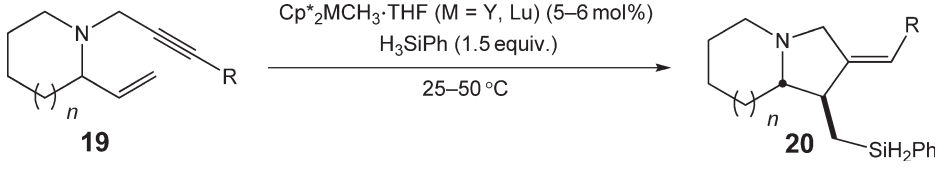
Scheme 8

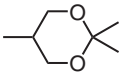
Lanthanide-catalyzed enyne cyclization/hydrosilylation was also applied to the synthesis of silylated alkylidene cyclohexane derivatives. For example, reaction of the 3-silyloxy-1,7-enyne **17** with methylphenylsilane catalyzed by $Cp^*_2YMe(THF)$ at 50 °C for 8 h gave **18** in quantitative yield as a 4 : 1 mixture of *trans* : *cis* isomers (Equation (11)). Employment of methylphenylsilane in place of phenylsilane was required to inhibit silylation of the initially formed yttrium alkenyl complex, prior to intramolecular carbometallation (see Scheme 8).



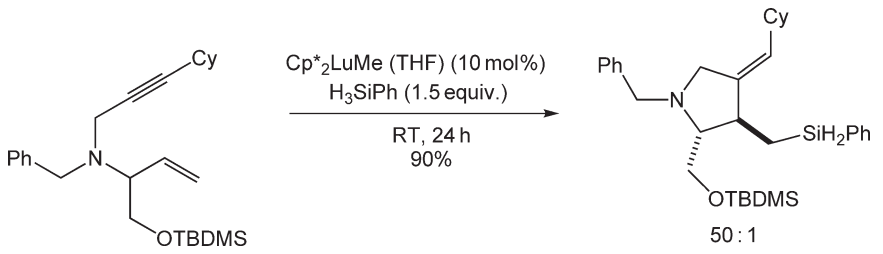
(11)

Lanthanide-catalyzed enyne cyclization/hydrosilylation was also applied to the synthesis of silylated nitrogen heterocycles.[20] For these transformations, the smaller and presumably less Lewis-acidic lutetium complex $Cp^*_2LuMe(THF)$ generally proved superior to $Cp^*_2YMe(THF)$. As an example, reaction of the 1-propargyl-2-vinylpiperidine derivative **19** ($n = 1$, R = Cy) with phenylsilane catalyzed by $Cp^*_2LuMe(THF)$ at room temperature for 6 h gave the indolizidine derivative **20** in 92% yield as a single diastereomer (Equation (12)). The protocol also proved effective for the cyclization/hydrosilylation of 2-vinyl-1-propargylazepanes (Equation (12), $n = 2$), acyclic allyl propargyl amines (Equation (13)), and 2-vinyl-1-homopropargylpiperidines (Equation (14)).

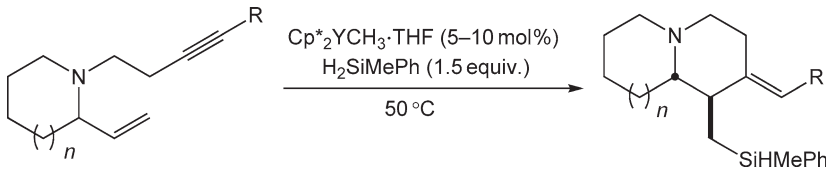


n	*R*	*Yield* (%)	*Ratio*
0	Cy	92	>50 : 1
1		78	>50 : 1
2	Cy	82	8 : 1

(12)



(13)



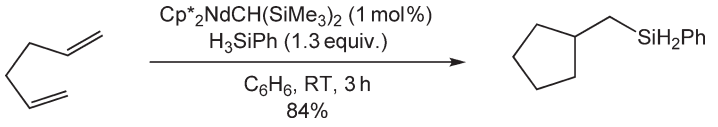
n	*R*	*Yield* (%)
0	Cy	100
1	Cy	94
1	Pr^i	100

(14)

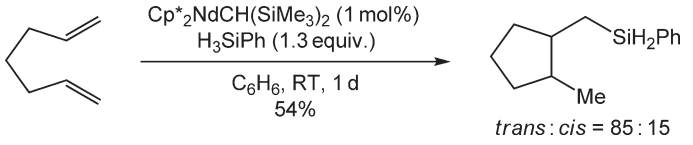
11.11.4 Cyclization/Hydrosilylation of Dienes

11.11.4.1 Lanthanide Metallocene Catalysts

Dienes are less reactive toward transition metals than enynes and diynes, and perhaps for this reason, the development of effective catalyst systems for the cyclization/hydrosilylation of dienes lagged behind development of the corresponding procedures for enynes and diynes. The transition metal-catalyzed cyclization/hydrosilylation of dienes was first demonstrated by Tanaka and co-workers in 1994.[21] Reaction of 1,5-hexadiene with phenylsilane catalyzed by the highly electrophilic neodymium metallocene complex $Cp^*_2NdCH(SiMe_2)_3$ (1 mol%) in benzene at room temperature for 3 h led to 5-*endo*-cyclization and isolation of (cyclopentylmethyl)phenylsilane in 84% yield (Equation (15)). In comparison, neodymium-catalyzed reaction of 1,6-heptadiene with phenylsilane led to 5-*exo*-cyclization to form (2-methylcyclopentylmethyl)phenylsilane in 54% yield as an 85 : 15 mixture of *trans* : *cis* isomers (Equation (16)).



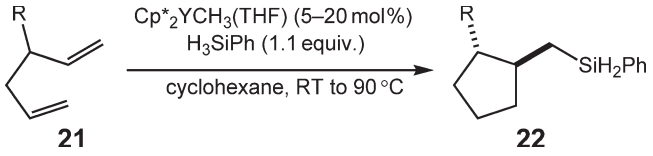
(15)



(16)

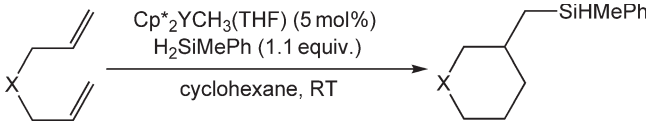
More general and more effective methods for diene cyclization/hydrosilylation were developed by Molander employing methyl yttrocene complexes as catalysts.[22] For example, reaction of the trityl-protected 1,5-hexadien-3-ol **21** (R = $OCPh_3$) with phenylsilane (1.1 equiv.) catalyzed by $Cp^*_2YCH_3(THF)$ (5 mol%) in cyclohexane at room temperature for 1 h gave silylated cyclopentane **22** in 71% yield as a 24 : 1 mixture of *trans* : *cis* isomers with exclusive delivery of silane to the more hindered C═C bond (Equation (17)). 1,6-Heptadienes also underwent efficient reaction provided that methylphenylsilane was employed in place of phenylsilane, as was also required for the effective yttrium-catalyzed cyclization/hydrosilylation of 1,6-enynes. It was noteworthy that the yttrium-catalyzed cyclization/hydrosilylation of 1,6-heptadienes occurred with 6-*endo*-regioselectivity (Equation (18)), in contrast to the 5-*exo*-regioselectivity observed for the reaction of 1,6-heptadienes catalyzed by $Cp^*_2NdCH(SiMe_3)_2$.[21] In addition to sterically hindered ethers, yttrium-catalyzed diene cyclization/hydrosilylation tolerated hindered silyl ethers, thiols, and tertiary amines (Equations (17) and (18)).[23] Conversely, the protocol was incompatible with polar unsaturated

functionality, and sterically unhindered ethers significantly decreased the rate of reaction, as was observed for the Y-catalyzed cyclization/hydrosilylation of enynes.



R	*Yield* (%)	*Ratio*
$OCPh_3$	71	24 : 1
H	100	
OBn	76	3.5 : 1
OTBDMS	75	4 : 1

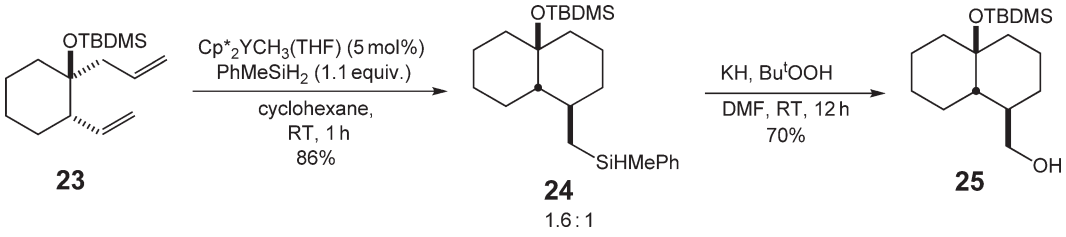
(17)



X	*Yield* (%)	*Ratio*
N-*t*-Bu	97	
CH_2	98	
CHOTBDMS	99	1.5 : 1
$CHOCPh_3$	99	2 : 1
$C(SCH_2CH_2CH_2S)$	99	

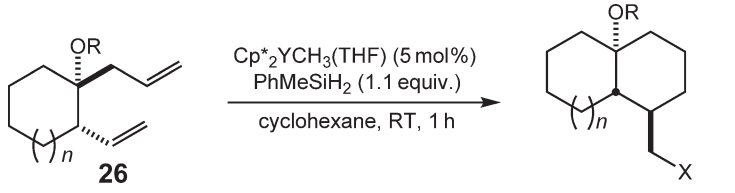
(18)

Yttrium-catalyzed diene cyclization/hydrosilylation was applied to the synthesis of a number of polycyclic compounds.[24] For example, reaction of the *cis*-1-allyl-2-vinylcyclohexane derivative **23** with methylphenylsilane catalyzed by $Cp^*_2YMe(THF)$ gave *cis*-decalin **24** in 86% yield as a 1.6 : 1 mixture of diastereomers due to the presence of the stereogenic silicon atom (Equation (19)). Subsequent oxidation of **24** gave monoprotected diol **25** in 70% isolated yield as a single diastereomer (Equation (19)). The reaction of the *trans*-1-allyl-2-vinylcyclohexane derivative **26a** gave the *trans*-decalin **27a** in 93% yield. Subsequent oxidation gave monoprotected diol **28a** in 53% yield as a single diastereomer (Scheme 9). In comparison, yttrium-catalyzed cyclization/hydrosilylation of the *trans*-1-allyl-2-vinylcyclopentane derivative **26b** followed by oxidation formed monoprotected diol **28b** in 86% overall yield as a 1 : 1 mixture of diastereomers (Scheme 9).



(19)

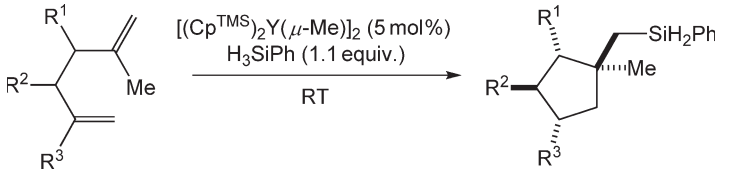
Cyclization/hydrosilylation catalyzed by $Cp^*_2YCH(SiMe_3)_2$ failed in the case of dienes that possessed substitution on the alkenyl carbon atoms, presumably due to the excessive steric crowding about the yttrium center. In contrast, the less sterically hindered metallocene complex $[(Cp^{TMS})_2Y(\mu\text{-Me})]_2$ ($Cp^{TMS} = \eta^5\text{-}C_5H_4SiMe_3$) catalyzed the



n	*R*	*Compound*	*Yield* **27** (%)	*Yield* **28** (%)	*dr of* **28**
1	TMS	**a**	89	53	Single isomer
0	TBDMS	**b**	92	86	1 : 1

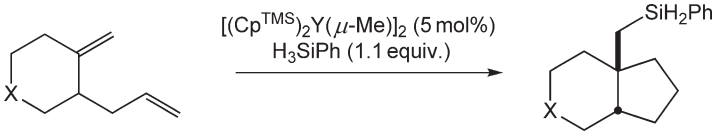
Scheme 9

cyclization/hydrosilylation of dienes that possessed one or more 1,1-disubstituted alkenyl groups.[25] For example, reaction of 2-methyl-3-phenyl-1,5-hexadiene with phenylsilane catalyzed by $[(Cp^{TMS})_2Y(\mu\text{-Me})]_2$ at room temperature for 16 h gave the corresponding silylated cyclopentane in 92% yield as a single isomer (Equation (20)). Reaction of 2-methyl-1,5-hexadienes catalyzed by $[(Cp^{TMS})_2Y(\mu\text{-Me})]_2$ also tolerated substitution at either the C(4) or C(5) position and tolerated ethers, silyl ethers, tertiary amines, and dithianes (Equation (20)). The protocol was also effective for the synthesis of *O*- and *N*-heterocycles (Equations (20) and (21)). The silyl-bridged yttrocene complex $Me_2Si(C_5H_3SiMe_3)_2YCH(SiMe_3)_2$ also catalyzed reaction of 1,5-dienes that possessed 1,1-disubstituted alkenyl groups but was generally inferior to $[(Cp^{TMS})_2Y(\mu\text{-Me})]_2$.



(20)

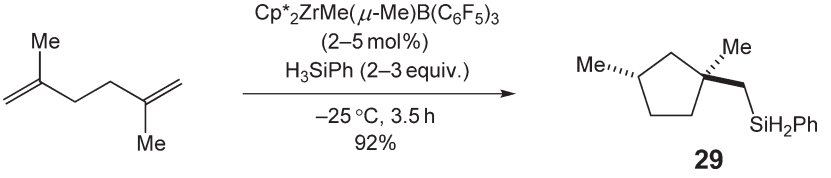
R^1	R^2	R^3	*Yield* (%)
Ph	H	H	92
OTBDPS	H	H	74
H	Ph	H	95
H	H	Me	92



X	*Yield* (%)
CH_2	95
NBn	77
O	57
$CSCH_2CH_2S$	98

(21)

The zwitterionic zirconocene complex $Cp^*_2ZrMe(\mu\text{-Me})B(C_6F_5)_3$, generated from reaction of $Cp^*_2ZrMe_2$ with $B(C_6F_5)_3$, also catalyzed the cyclization/hydrosilylation of dienes that possessed one or more 1,1-disubstituted alkenyl groups.[26] For example, reaction of 2,5-dimethyl-1,5-hexadiene with phenylsilane catalyzed by $Cp^*_2ZrMe(\mu\text{-Me})B(C_6F_5)_3$ at −25 °C for 3.5 h gave the silylated dimethylcyclopentane **29** in 92% yield as a single diastereomer (Equation (22)). Dienes that did not possess at least one 1,1-disubstituted alkenyl group gave low yields of silylated carbocycle, presumably due to competitive polymerization of the diene. More problematic, however, was that the highly electrophilic zirconocene complex was incompatible with most functional groups, including protected alcohols and amines, alkyl halides, and arenes.

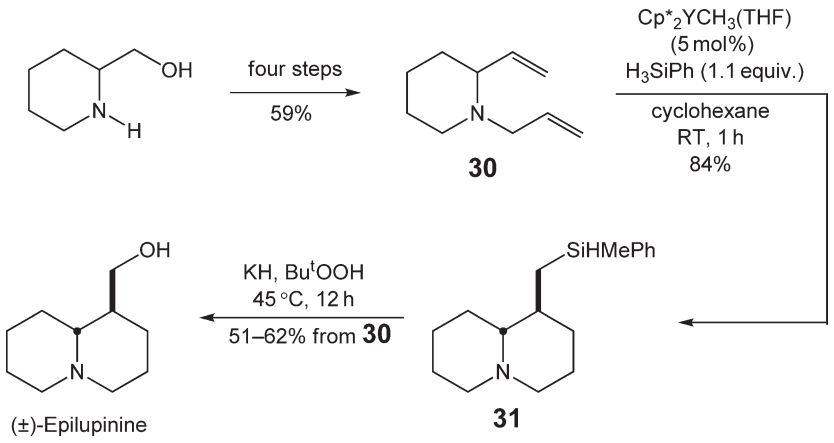


29

(22)

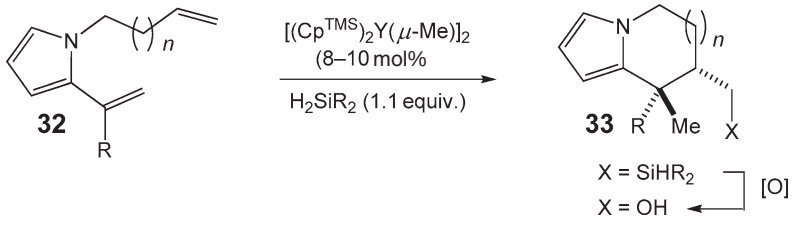
Yttrium-catalyzed diene cyclization/hydrosilylation was applied to the synthesis of aliphatic nitrogen heterocycles such as the indolizidine alkaloid (±)-epilupinine.[27] 1-Allyl-2-vinylpiperidine **30** was synthesized in four steps in 59% overall yield from commercially available (±)-2-piperidinemethanol (Scheme 10). Treatment of **30** with phenylsilane and a catalytic amount of $Cp^*_2YCH_3(THF)$ gave silylated quinolizidine derivative **31** in 84% yield, resulting from selective hydrometallation of the *N*–allyl C═C bond in preference to the exocyclic vinylic C═C bond. Oxidation of the crude reaction mixture with *tert*-butyl hydrogen peroxide and potassium hydride gave (±)-epilupinine in 51–62% yield from **30** (Scheme 10).

Yttrium-catalyzed cyclization/hydrosilylation was also applied to the synthesis of silylated heteroaromatic bicyclic compounds. Reaction of 1-allyl-2-vinyl pyrrole (**32**, $n = 0$, R = H) with phenylsilane catalyzed by $[(Cp^{TMS})_2YMe]_2$ at room temperature for 6 h followed by oxidation gave the corresponding heterobicycle amine **33** in 90% yield as a 98 : 2 mixture of isomers (Equation (23)).[28] It was noteworthy that selective conversion of **32** to **33** required initial



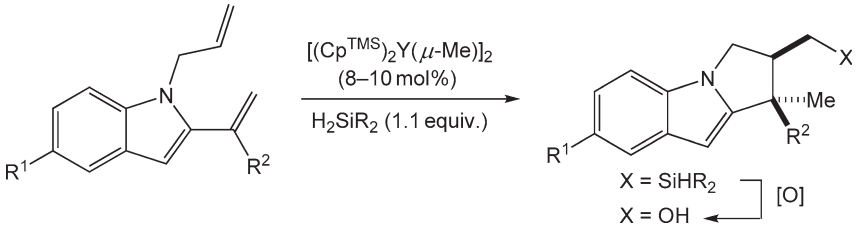
Scheme 10

hydrometallation of the more substituted vinyl group in preference to the less hindered allyl group. As was initially suggested by Marks,[29] this selectivity presumably results from directed delivery of the Lewis-acidic yttrocene catalyst to the vinyl group by the weakly Lewis-basic aryl group. Yttrium-catalyzed cyclization/hydrosilylation of allyl vinyl pyrroles tolerated substitution at the internal vinylic carbon atom and was applicable to the formation of six-membered rings and polycyclic indole derivatives (Equations (23) and (24)).



(23)

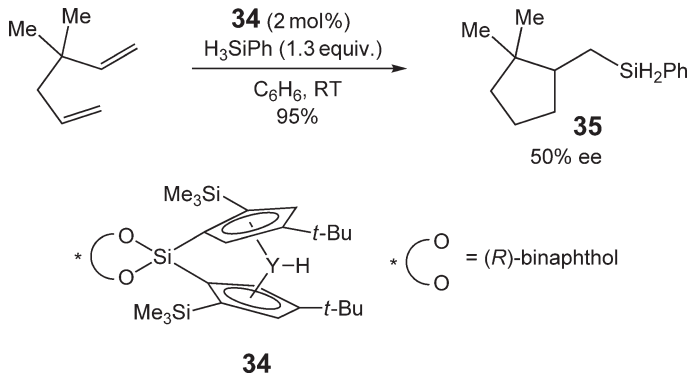
n	*R*	*X*	*Yield* (%)	*Ratio of isomers*
0	H	OH	90	98 : 2
0	Me	SiH_2Ph	94	
1	H	OH	60	98 : 2



(24)

R^1	R^2	*X*	*Yield* (%)	*Ratio*
H	H	SiH_2Ph	85	98 : 2
OMe	H	SiH_2Ph	80	98 : 2
H	Me	OH	68	

Bercaw has investigated the application of the C_2-symmetric, enantiomerically pure lanthanide metallocene derivative (*R*,*S*)-BnBpYH **34** as a catalyst for the asymmetric cyclization/hydrosilylation of 1,5- and 1,6-dienes.[30] Although **34** displayed high activity for the reaction of a number of dienes, asymmetric induction was low. In the best case, reaction of 3,3-dimethyl-1,5-hexadiene with phenylsilane catalyzed by **34** gave silylated cyclopentene **35** in 95% yield with 50% ee (Equation (25)).

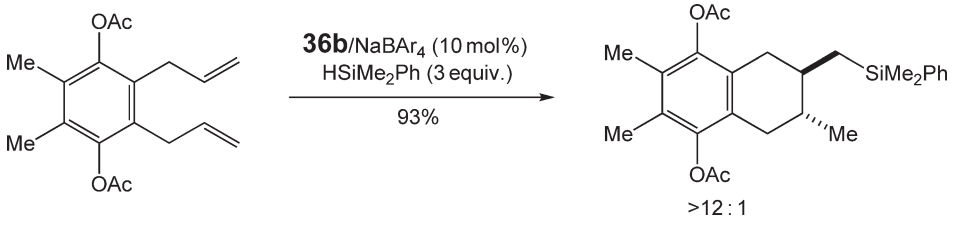


(25)

11.11.4.2 Palladium Catalysts

Widenhoefer and DeCarli have developed effective protocols for the cyclization/hydrosilylation of functionalized dienes catalyzed by cationic palladium complexes that contained bidentate nitrogen ligands.[31,31a] Brookhart had previously employed these electrophilic complexes as catalysts for olefin polymerization,[32] ethylene/CO copolymerization,[32] and olefin hydrosilylation.[33,33a] As an example of palladium-catalyzed diene cyclization/hydrosilylation, reaction of dimethyl diallylmalonate and triethylsilane (3 equiv.) catalyzed by (phen)Pd(Me)$(OEt_2)^+BAr_4^-$ [phen = 1,1-phenanthroline, Ar = 3,5-$C_6H_3(CF_3)_2$] **36a** (5 mol%) in dichloromethane at 0 °C for 5 min gave *trans*-silylated cyclopentane **37** in 92% yield with ≥50 : 1 diastereoselectivity (Table 6, entry 1). The active cationic catalyst was more conveniently generated *in situ* via halide abstraction from (phen)Pd(Me)Cl **36b** with $NaBAr_4$.[34]

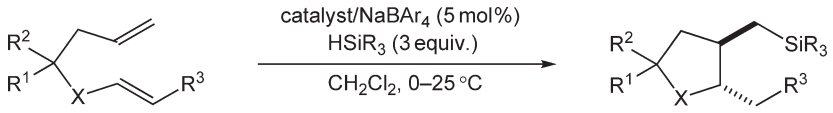
Palladium-catalyzed diene cyclization/hydrosilylation was compatible with a number of functionalized silanes, including dimethylphenylsilane, dimethylbenzylsilane, dimethylbenzhydrylsilane, and pentamethyldisiloxane (Table 6, entries 2–7).[34–37] The tetramethylphenanthroline complex (N–N)Pd(Me)Cl (**36c**; N–N = 3,4,7,8-tetramethyl-1,10-phenanthroline) proved a particularly active catalyst for cyclization/hydrosilylation with $HSiMe_2Ph$ (Table 6, entries 8–14).[37] The protocol was compatible with a range of polar functional groups, including pivaloyl, sulfonyl, carbamoyl, acyl, cyano, and alkoxy- and benzyloxymethyl groups (Table 6, entries 8–14), and tolerated substitution at one of the allylic positions or at one of the *trans*-terminal olefinic positions to form silylated cyclopentanes resulting from exclusive delivery of the silyl group to the less hindered C═C bond (Table 6, entries 15–22).[34–37] Palladium-catalyzed cyclization/hydrosilylation was also effective for the reaction of 1,7-dienes to form silylated cyclohexane derivatives (Equation (26)).[34,36,37]



(26)

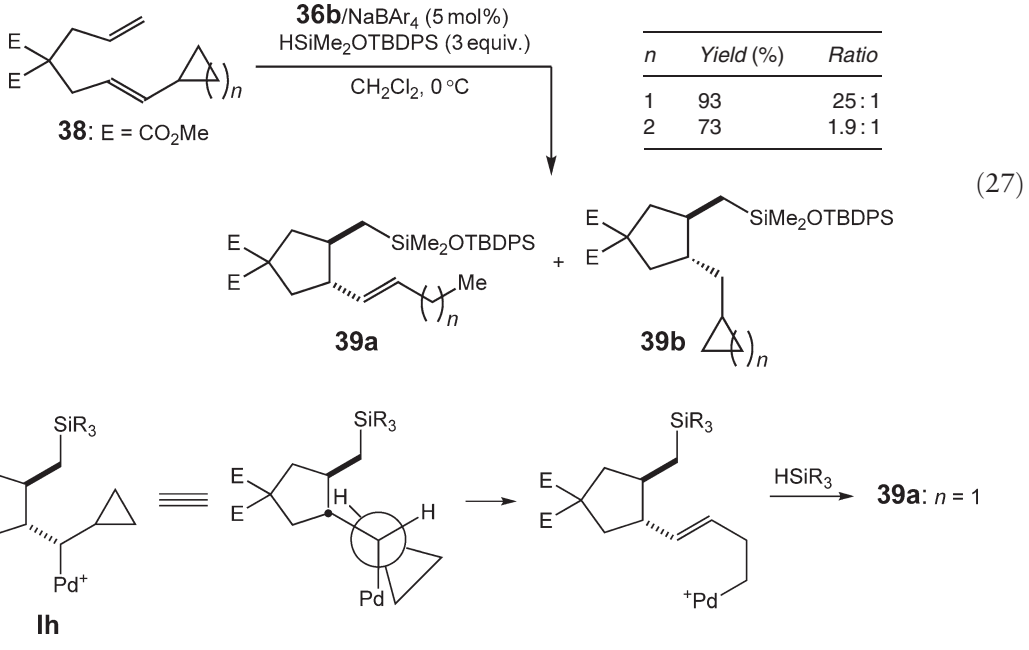
1-Cyclopropyl-1,6-hexadienes and 1-cyclobutyl-1,6-hexadienes underwent palladium-catalyzed ring-opening cyclization/hydrosilylation to form (*E*)-(1-alkenyl)cyclopentanes.[38] For example, reaction of the 1-cyclopropyl-1,6-heptadiene **38** ($n = 1$) and $HSiMe_2OSiPh_2Bu^t$ catalyzed by a 1 : 1 mixture of (phen)Pd(Me)Cl and $NaBAr_4$ (5 mol%) in dichloromethane at 0 °C for 12 h gave (*E*)-(1-butenyl)cyclopentane (*E*)-**39a** in 93% yield without formation of the corresponding cyclopropylcyclopentane **39b** (Equation (27)). In comparison, palladium-catalyzed cyclization/hydrosilylation of the 1-cyclobutyl-1,6-heptadiene **38** ($n = 2$) gave a 1.9 : 1 mixture of (*E*)-(1-pentenylenyl)cyclopentane (*E*)-**39a** and (cyclobutylmethyl)cyclopentane **39b** in 73% combined yield (Equation (27)). Formation of ring-opened products (*E*)-**39a** was proposed to occur via β-alkyl elimination from the initially formed cyclopropylmethylpalladium intermediate **Ih** followed by silylation (Scheme 11). The stereoselective formation of (*E*)-**39a** is in accord with β-alkyl elimination from the more stable rotamer of **Ih** (Scheme 11).

Table 6 Palladium-catalyzed cyclization/hydrosilylation of functionalized 1,6-dienes



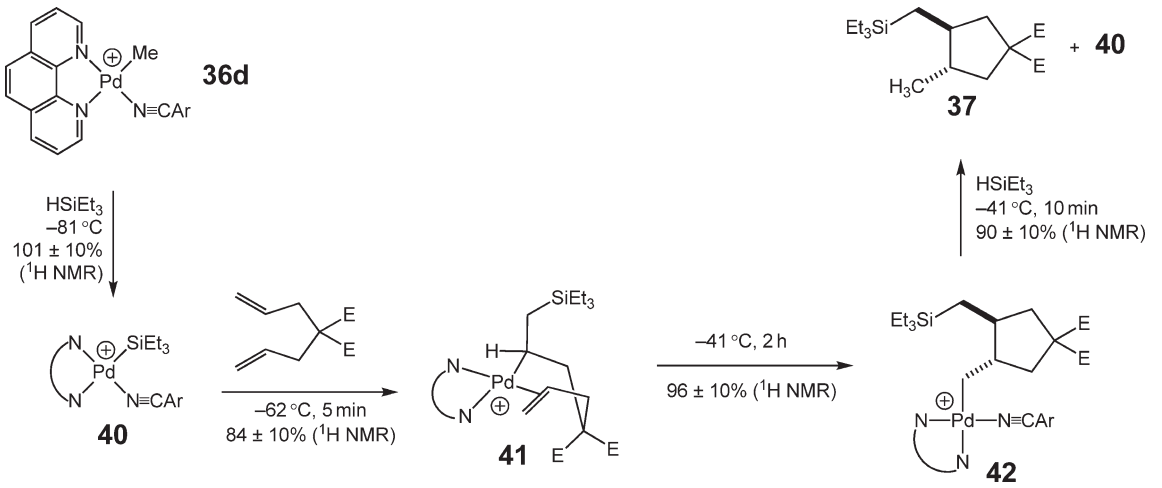
37

Entry	*Cat.*	R^1	R^2	R^3	*X*	SiR_3	*Yield* (%)	*dr*
1	**36a**	CO_2Me	CO_2Me	H	CH_2	$SiEt_3$	92	50 : 1
2						$SiMe_2Ph$	93	50 : 1
3						$SiMe_2OSiMe_3$	98	50 : 1
4	**36b**					$SiMe_2OSiPh_2t$-Bu	98	50 : 1
5	**36a**					$SiPh_3$	84	25 : 1
6	**36b**					$SiMe_2Bn$	89	50 : 1
7						$SiMe_2CHPh_2$	98	50 : 1
8	**36c**		COMe			$SiMe_2Ph$	74	2.1 : 1
9			SO_2Me				77	1.7 : 1
10			CN				86	2.2 : 1
11			$CONMe_2$				62	4.8 : 1
12		CH_2OAc	CH_2OAc				69	50 : 1
13		CH_2OBn	CH_2OBn				77	50 : 1
14		CH_2OMe	CH_2OMe				91	50 : 1
15	**36b**	CO_2Me	CO_2Me	Me		$SiMe_2OSiMe_3$	82	25 : 1
16				Bu^n			76	31 : 1
17				CH_2OPh			84	22 : 1
18				Ph			71	8 : 1
19				CH_2(phthalimde)			70	15 : 1
20				H	$C(CH_2CH_2CH_2)$	$SiMe_2Bn$	83	50 : 1
21					$C(CH_2CH_2CH_2CH_2)$	$SiMe_2Bn$	95	50 : 1
22					$C(CH_2CH_2CH_2CH_2CH_2)$	$SiMe_2OSiPh_2Bu^t$	92	50 : 1



(27)

Scheme 11



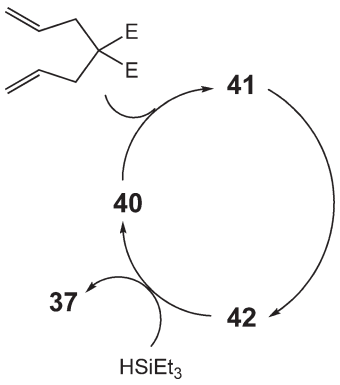
Scheme 12

Perch and Widenhoefer have investigated the mechanism of the cyclization/hydrosilylation of dimethyl diallylmalonate with triethylsilane to form **37** catalyzed by the cationic palladium phenanthroline complex $[(phen)Pd(Me)(NCAr)]^+[BAr_4]^-$ [Ar = 3,5-$C_6H_3(CF_3)_2$] **36d**, relying heavily on low-temperature ^1H NMR spectroscopy.[39,39a] Reaction of an equimolar mixture of $HSiEt_3$ and **36d** in CD_2Cl_2 at −81 °C formed the thermally sensitive palladium silyl complex **40** in quantitative yield (Scheme 12). Reaction of dimethyl diallylmalonate (1 equiv.) with **40** at −62 °C led to rapid ($t_{1/2} \leq 5$ min) formation of the 5-hexenylpalladium chelate complex **41** in 84 ± 10% yield (^1H NMR) as a single diastereomer. Low-temperature ^1H-^1H NOESY analysis of **41** established orientation of the C═C bond approximately perpendicular to the coordination plane, with the triethylsilylmethyl group adopting an axial or pseudo-axial position about the hexenyl chelate. Complex **41** presumably adopts a boat-like conformation to avoid unfavorable 1,3-diaxial interaction between the triethylsilylmethyl group and one of the methoxycarbonyl groups.

Warming an equimolar solution of **41** and NCAr at −41 °C for 2 h led to β-migratory insertion and formation of the cyclopentylmethylpalladium complex **42** in 96 ± 10% yield (^1H NMR) as a single diastereomer. Disappearance of **41** at −41 °C obeyed first-order kinetics to >3 half-lives with the following activation parameters: $\Delta G^{\ddagger} = 16.9 \pm 0.1$ kcal mol^{-1}; $\Delta H^{\ddagger} = 13.5 \pm 0.6$ kcal mol^{-1}; $\Delta S^{\ddagger} = -15 \pm 2$ eu. Treatment of **42** with $HSiEt_3$ (50 mM) at −41 °C for 10 min led to complete consumption of **42** to form a 1 : 1 mixture of **37** and **40** as the sole products in quantitative yield (Scheme 12).

The low-temperature NMR studies described in the preceding paragraphs, in conjunction with additional kinetic and deuterium labeling studies, were in accord with a mechanism for the palladium-catalyzed cyclization/hydrosilylation of dimethyl diallylmalonate initiated by silylpalladation of one of the C═C bonds of dimethyl diallylmalonate, with **40** coupled with coordination of the pendant C═C bond to form **41**. β-Migratory insertion of the coordinated C═C bond into the Pd–C bond of **41** would form **42**, which could react with silane to release **37** with regeneration of **40**. The magnitudes of the first-order rate constant for intramolecular carbometallation of **41** → **42** ($k_1 = 7.7 \times 10^{-4}$ s^{-1}) and the second-order rate constant for the silylation of **42** ($k_1 = 0.12$ M^{-1} s^{-1}) were such that at moderate to high silane concentration ([$HSiEt_3$] > 85 mM), silylation of palladium alkyl complex **42** was fast relative to intramolecular carbometallation, rendering conversion of **41** to **42** turnover limiting. At lower silane concentrations ([$HSiEt_3$] < 85 mM), the rate of silylation of **42** was competitive with the rate of intramolecular carbometallation, and the rate of catalytic cyclization/hydrosilylation depended on silane concentration under these conditions (Scheme 13).

Widenhoefer and co-workers have developed an effective Pd-catalyzed protocol for the asymmetric cyclization/hydrosilylation of functionalized 1,6-dienes that employed chiral, non-racemic pyridine–oxazoline ligands.[40,40a–40c] Optimization studies probed the effect of both the C(4) substituent of the pyridine–oxazoline ligand (Table 7, entries 1–6) and the nature of the silane (Table 7, entries 6–15) on the yield and enantioselectivity of the cyclization/hydrosilylation of dimethyl diallylmalonate. These studies revealed that employment of isopropyl-substituted catalyst (N–N)Pd(Me)Cl [N–N = (*R*)-(+)-4-isopropyl-2-(2-pyridinyl)-2-oxazoline] [(*R*)-**43f**] and a stoichiometric amount of benzhydryldimethylsilane provided the best combination of asymmetric induction and chemical yield, giving the corresponding silylated cyclopentane in 98% yield as a single diastereomer with 93% ee (Table 7, entry 15).

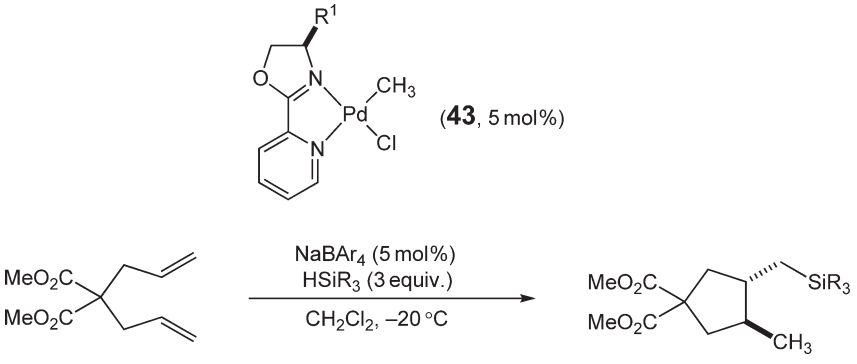


Scheme 13

The effectiveness of dimethylbenzhydrylsilane in the asymmetric reaction was fortuitous as the resulting silylated cyclopentanes underwent efficient oxidation under mild conditions.[41]

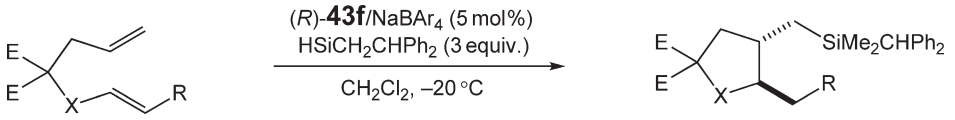
Palladium-catalyzed asymmetric cyclization/hydrosilylation tolerated a number of functional groups including benzyl and pivaloyl ethers as well as benzyl and methyl esters (Table 8, entries 1–4). Furthermore, the protocol tolerated substitution at one of the two *trans*-terminal alkenyl positions and at one of the two allylic positions of the 1,6-diene (Table 8). As was the case with diene cyclization/hydrosilylation catalyzed by achiral palladium

Table 7 Asymmetric cyclization/hydrosilylation of dimethyl diallyl malonate catalyzed by palladium pyridine–oxazoline complexes



Entry	*SiR*$_3$	*R*^{1}	*Cat.*	*Yield* (%)	*ee* (%)
1	$SiEt_3$	Me	**43a**	89	76
2	$SiEt_3$	Ph	**43b**	82	49
3	$SiEt_3$	Cy	**43c**	96	80
4	$SiEt_3$	CH_2Cy	**43d**	74	77
5	$SiEt_3$	(*S*)-Bu^s	**43e**	91	79
6	$SiEt_3$	Pr^i	**43f**	89	84
7	$SiMe_2Et$	Pr^i	**43f**	71	82
8	$SiMe_2Bu^t$	Pr^i	**43f**	87	89
9	$SiMe_2Ph$	Pr^i	**43f**	38	80
10	$SiMe_2OSiMe_2Bu^t$	Pr^i	**43f**	99	80
11	$Si(Pr^i)_2OSiMe_3$	Pr^i	**43f**	99	86
12	$SiMe_2OSi(Pr^i)_3$	Pr^i	**43f**	99	89
13	$SiMe_2OSiPh_2Bu^t$	Pr^i	**43f**	100	91
14	$SiMe_2CH_2Ph$	Pr^i	**43f**	91	86
15	$SiMe_2CHPh_2$	Pr^i	**43f**	98	93

Table 8 Asymmetric cyclization/hydrosilylation of functionalized dienes catalyzed by (*R*)-**43f**/$NaBAr_4$



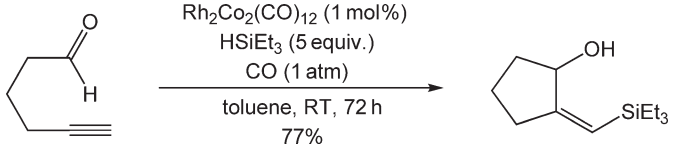
Entry	*E*	*X*	*R*	*Yield* (%)	*ee* (%)
1	CO_2Bn	CH_2	H	87	94
2	CH_2OPiv	CH_2	H	96	95
3	CH_2OBn	CH_2	H	89	95
4	CH_2OMe	CH_2	H	81	88
5	CO_2Me	CH_2	Me	87	90
6	CO_2Me	Me_2	H	89	87
7	CO_2Me	$C(CH_2CH_2CH_2)$	H	100	86
8	CO_2Me	$C(CH_2CH_2CH_2CH_2)$	H	98	88

phenanthroline complexes, the reaction of these substituted dienes catalyzed by (*R*)-**43f** led to exclusive delivery of the silane to the less hindered alkene moiety (Table 8, entries 5–8).

11.11.5 Silylative Cyclization Involving Addition to C═X (X = O, N) Bonds

11.11.5.1 Cyclization with C–Si Bond Formation

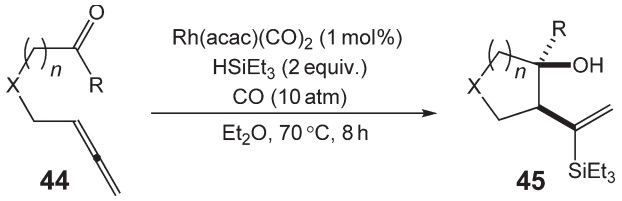
Ojima has reported the catalytic cyclization/hydrosilylation of ynals to form silylated alkylidene cyclopentanols.[42] For example, reaction of 5-hexynal with triethylsilane catalyzed by $Rh_2Co_2(CO)_{12}$ under CO (1 atm) at room temperature for 72 h gave (*Z*)-2-(*exo*-triethylsilylmethylene)-1-cyclopentanol in 77% yield (Equation (28)). Unfortunately, Rh-catalyzed cyclization/hydrosilylation of ynals was intolerant of substitution at the alkyne or carbonyl carbon atom and was restricted to the formation of cyclopentanols. The Rh-catalyzed cyclization/hydrosilylation of ynals was proposed to occur via initial silylmetallation of the C≡C bond followed by intramolecular carbometallation and O–H reductive elimination.



(28)

Yu and co-workers have expanded upon Ojima's work through development of an effective Rh-catalyzed protocol for the cyclization/hydrosilylation of allenyl carbonyl compounds to form silylated vinylcycloalkanols and heterocyclic alcohols.[43] For example, reaction of tosylamide **44** (X = NTs, R = H, *n* = 1) and triethylsilane catalyzed by $Rh(acac)(CO)_2$ (1 mol%) under CO (10 atm) at 70 °C for 8 h gave the silylated vinyl pyrrolidinol **45** (X = NTs, R = H, *n* = 1) in 74% yield with exclusive formation of the *cis*-diastereomer (Equation (29)). The rhodium-catalyzed reaction was also effective for the cyclization of alleneones and for the formation of carbocycles, oxygen heterocycles, and six-membered cyclic alcohols (Equation (29)). However, Rh-catalyzed cyclization/hydrosilylation of allenyl carbonyl compounds that possessed substitution on an allenyl carbon atom was not established (Equation (29)). The efficiency of the Rh-catalyzed reaction of allenyl carbonyl compounds depended strongly on CO pressure. Reactions run under 10 atm CO were more efficient than were

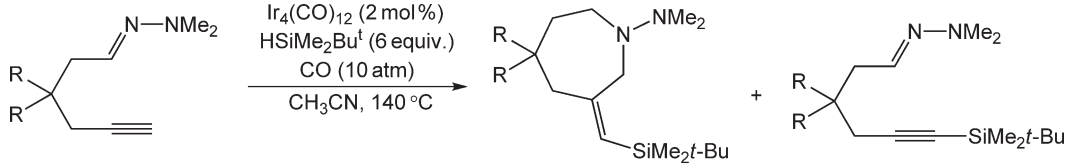
transformations run under either 5 or 20 atm CO, whereas no conversion was observed for reactions run at ambient CO pressure.



X	R	n	Yield (%)
NTs	H	1	74
NTs	H	2	61
NTs	Me	1	64
NTs	Et	1	56
$C(CO_2Et)_2$	H	1	68
$C(CO_2Et)_2$	Me	1	56
O	H	2	68

(29)

Murai has reported an unusual iridium-catalyzed silylative cyclization of alkynyl hydrazones to form nitrogen heterocycles that involves cyclization with incorporation and reduction of one molecule of CO.[44] For example, reaction of alkynyl hydrazone **46a** with *tert*-butyldimethylsilane catalyzed by tetrairidiumdodecacarbonyl in acetonitrile under CO (10 atm) led to formation of the seven-membered nitrogen heterocycle **47a** in 53% yield by GC analysis along with the acyclic silylated alkyne in 18% yield (Equation (30)). Unfortunately, the scope of the reaction was narrow. Alkynyl hydrazones that possessed an internal C≡C bond failed to undergo silylative cyclization, and Ir-catalyzed reaction of alkynyl hydrazones such as **46b** that did not possess geminal substitution along the backbone, with silane and CO, led to predominant formation of the corresponding acyclic silylated alkyne (Equation (30)).



46a: R = CO_2Et
46b: R = H

47a: 53%
47b: 16%

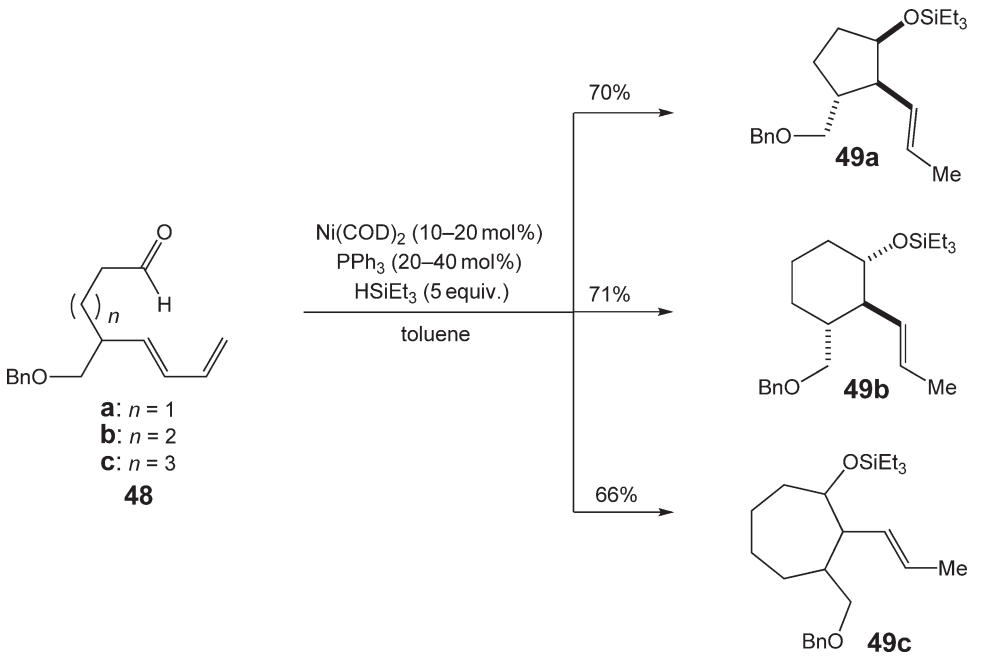
18%
42%

(30)

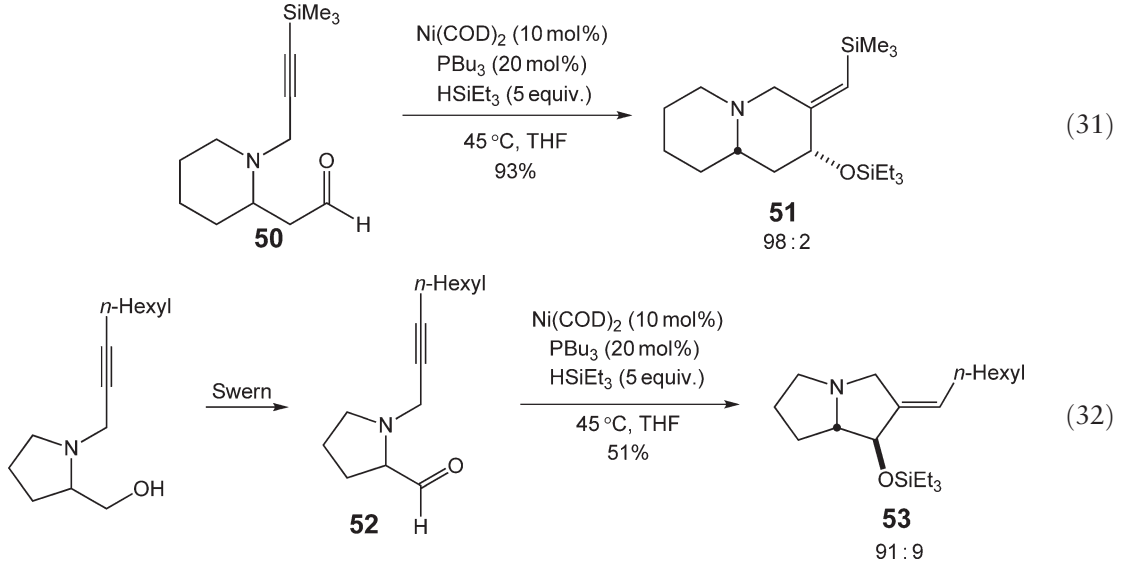
11.11.5.2 Cyclization with Si–O Bond Formation

Mori has reported the nickel-catalyzed cyclization/hydrosilylation of dienals to form protected alkenylcycloalkanols.[45] For example, reaction of 4-benzyloxymethyl-5,7-octadienal **48a** and triethylsilane catalyzed by a 1:2 mixture of $Ni(COD)_2$ and PPh_3 in toluene at room temperature gave the silyloxycyclopentane **49a** in 70% yield with exclusive formation of the *cis*,*trans*-diastereomer (Scheme 14). In a similar manner, the 6,8-nonadienal **48b** underwent nickel-catalyzed reaction to form silyloxycyclohexane **49b** in 71% yield with exclusive formation of the *trans*,*trans*-diastereomer, and the 7,9-decadienal **48c** underwent reaction to form silyloxycycloheptane **49c** in 66% yield with undetermined stereochemistry (Scheme 14). On the basis of related stoichiometric experiments, Mori proposed a mechanism for the nickel-catalyzed cyclization/hydrosilylation of dienals involving initial insertion of the diene moiety into the Ni–H bond of a silylnickel hydride complex to form the (π-allyl)nickel silyl complex **Ii** (Scheme 15). Intramolecular carbometallation followed by O–Si reductive elimination and H–Si oxidative addition would release the silyloxycycloalkane with regeneration of the active silylnickel hydride catalyst.

Montgomery has developed an effective nickel-catalyzed protocol for the cyclization/hydrosilylation of ynals and has applied the method to the synthesis of nitrogen heterobicycles.[46] For example, reaction of propargyl piperidine carboxaldehyde derivative **50** with triethylsilane catalyzed by a 1:2 mixture of $Ni(COD)_2$ and PBu_3 in THF at 45 °C gave silyl-protected alkylidene quinolizidine **51** in 93% yield as a 98:2 mixture of diastereomers (Equation (31)). In a similar manner, the reaction of propargyl pyrrolidine carboxaldehyde **52**, generated *in situ* via Swern oxidation of the corresponding alcohol, gave silylated pyrrolizidine **53** in modest yield and with modest diastereoselectivity (Equation (32)).



Scheme 14



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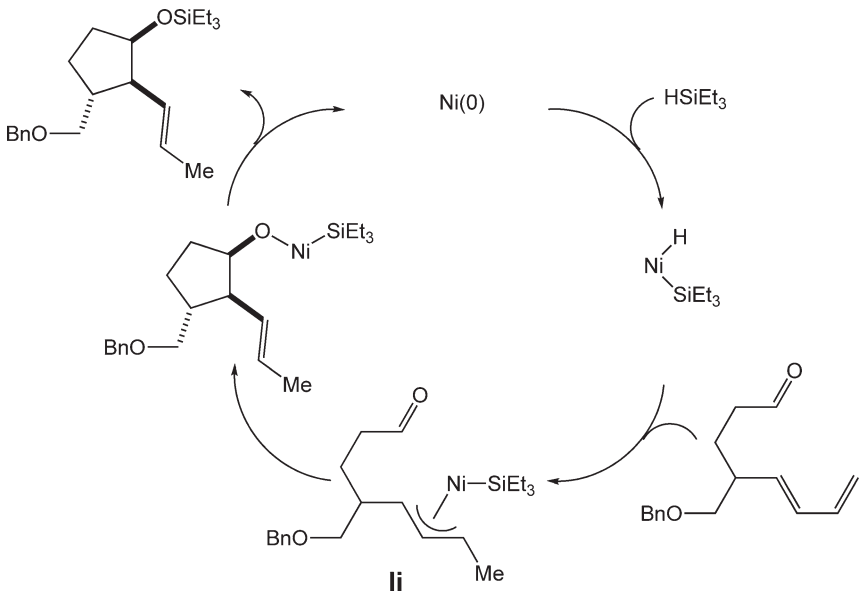
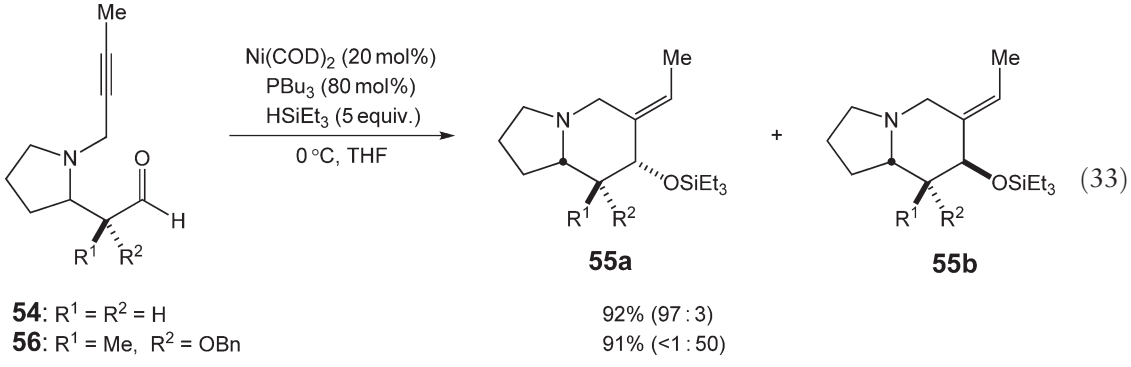
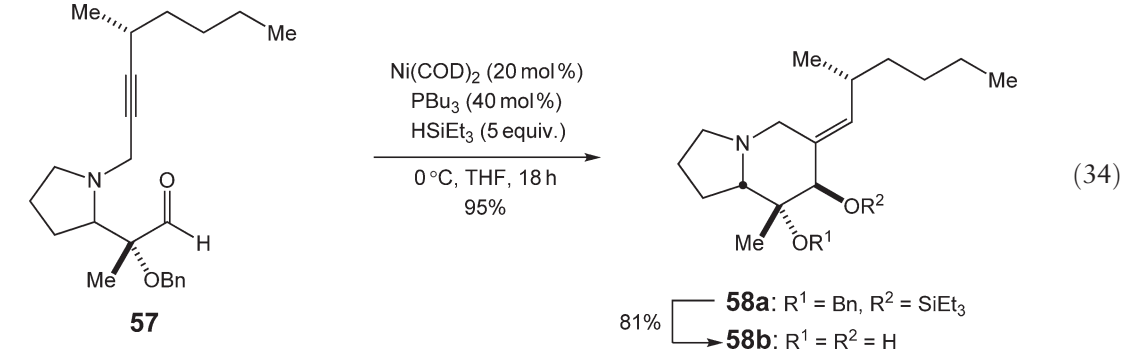
Nickel-catalyzed cyclization/hydrosilylation of propargyl pyrrolidine carboxaldehyde **54** formed indolizidine **55** ($R^1 = R^2 = H$) in 92% yield with 97% selectivity for the diastereomer possessing a *trans*-relationship between the bridgehead hydrogen atom and the exocyclic silyloxy group (**55a**; Equation (33)). In comparison, the reaction of propargyl pyrrolidine carboxaldehyde **56** that possessed a tetra-substituted atom α- to the carbonyl group formed indolizidine **55** ($R^1 = Me$, $R^2 = OBn$) in 91% yield with >98% selectivity for the diastereomer possessing a *cis*-relationship between the bridgehead hydrogen atom, the exocyclic methyl group, and the exocyclic silyloxy group (**55b**; Equation (33)). The relative stereochemistry of **55b** mirrored that found in the allopumiliotoxin alkaloids, isolated from the skin of dendrobatid frogs. For this reason, nickel-catalyzed cyclization/hydrosilylation was applied to



Scheme 15

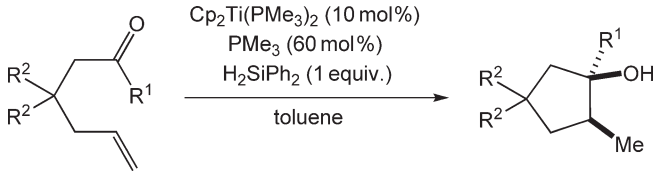
the synthesis of (+)-allopumiliotoxin 267A, 339A, and 339B. To this end, the reaction of the enantiomerically pure ynal **57** gave indolizidine **58a** in 95% yield as a single diastereomer (Equation (34)). Subsequent deprotection of the triethylsilyl and benzyl groups gave (+)-allopumiliotoxin 267A **58b** in 81% yield. A similar strategy was applied to the syntheses of allopumiliotoxins 339A and 339B.





Buchwald has reported the titanium-catalyzed cyclization/hydrosilylation of 6-hepten-2-ones and 5-heptenals to form silylated cyclopentanols.[47] As an example, reaction of 6-hepten-2-one and diphenylsilane catalyzed by $Cp_2Ti(PMe_3)_2$ in the presence of PMe_3 (0.6 equiv.) in toluene at −20 °C followed by acidic workup gave

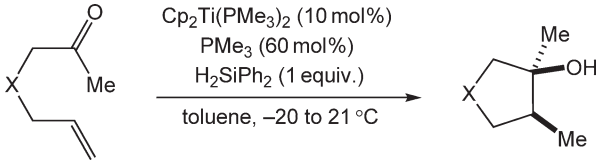
1,2-dimethylcyclopentanol in 64% yield with 98% selectivity for the diastereomer that possessed a *cis*-relationship between the hydroxyl group and the vicinal methyl group (Equation (35); $R^1 = Me$, $R^2 = H$). Similarly, titanocene-catalyzed cyclization/hydrosilylation of 3,3-bis(ethoxycarbonyl)-5-pentenal followed by acidic workup gave 2,2-bis(ethoxycarbonyl)-4-methylcyclopentanol in 65% yield with 99% selectivity for the *cis*-diastereomer (Equation (35); $R^1 = H$, $R^2 = CO_2Et$).



R^1	R^2	Yield (%)	Ratio
Me	H	64	43 : 1
H	CO_2Et	65	99 : 1

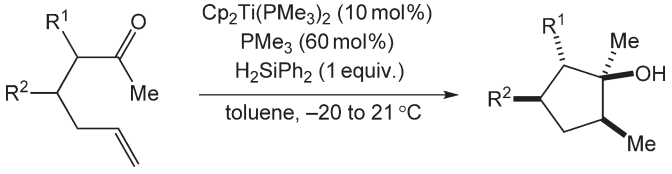
(35)

The diastereoselectivity of the titanium-catalyzed cyclization/hydrosilylation of 6-hepten-2-ones was sensitive to substitution along the backbone of the enone. 4,4-Disubstituted 6-hepten-2-ones cyclized with diminished diastereoselectivity (≥10 : 1) relative to their unsubstituted counterparts (Equation (36); $X = C(CO_2Me)_2$, CMe_2). Enones that possessed a heteroatom *β*- to the carbonyl group cyclized with negligible diastereoselectivity (Equation (36); X = NPh, O). 6-Hepten-2-ones that possessed a single C(4) substituent underwent cyclization with low diastereoselectivity (Equation (37); $R^2 = Ph$). Conversely, 6-hepten-2-ones that possessed a single C(3) substituent underwent cyclization with good selectivity for the diastereomer that possessed a trans-relationship between the hydroxyl group and the C(3) substituent (Equation (37); $R^1 = CO_2Et$, Bn). The protocol failed to tolerate substitution at the alkenyl positions and was restricted to the formation of five-membered rings.



X	Yield (%)	Ratio
$C(CO_2Me)_2$	68	10 : 1
CMe_2	56	13 : 1
NPh	75	1 : 1
O	72	1.5 : 1

(36)

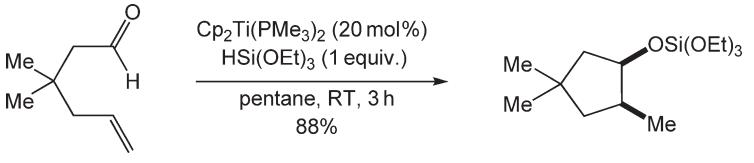


R^1	R^2	Yield (%)	Ratio
H	Ph	63	2.5 : 1
CO_2Et	H	78	90 : 1
Bn	H	71	20 : 1

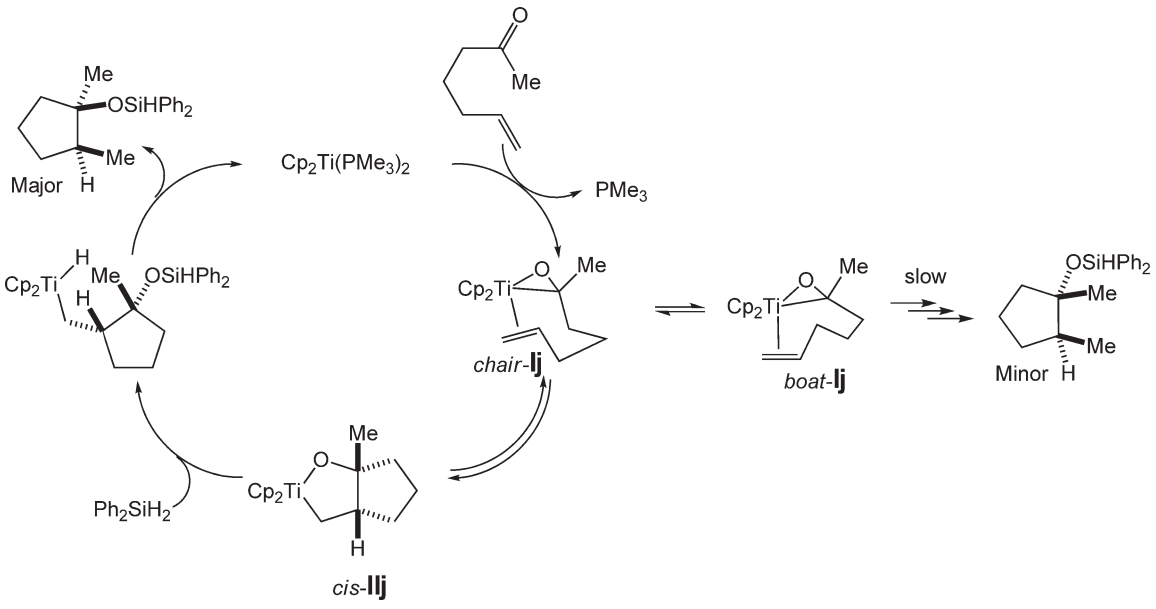
(37)

Titanium-catalyzed cyclization/hydrosilylation of 6-hepten-2-one was proposed to occur via *β*-migratory insertion of the C=C bond into the titanium–carbon bond of the η^2-ketone olefin complex *chair*-**Ij** to form titanacycle *cis*-**IIj** (Scheme 16). *σ*-Bond metathesis of the Ti–O bond of *cis*-**IIj** with the Si–H bond of the silane followed by C–H reductive elimination would release the silylated cyclopentanol and regenerate the Ti(0) catalyst. Under stoichiometric conditions, each of the steps that converts the enone to the titanacycle is reversible, leading to selective formation of the more stable *cis*-fused metallacycle.[48] For this reason, the diastereoselective cyclization of 6-hepten-2-one under catalytic conditions was proposed to occur via non-selective, reversible formation of η^2-ketotitanium olefin complexes *chair*-**Ij** and *boat*-**Ij**, followed by preferential cyclization of *chair*-**Ij** to form *cis*-**IIj** (Scheme 16).

Crowe and co-workers independently reported a procedure for the cyclization/hydrosilylation of enones and enals similar to that reported by Buchwald.[49] As an example, reaction of a 1 : 1 mixture of 3,3-dimethyl-5-hexenal and triethoxysilane catalyzed by $Cp_2Ti(PMe_3)_2$ (20 mol%) in pentane at room temperature for 3 h gave *cis*-1,1,3-trimethyl-4-triethoxysilyloxycyclopentane in 88% yield as a single diastereomer (Equation (38)).



(38)



Scheme 16

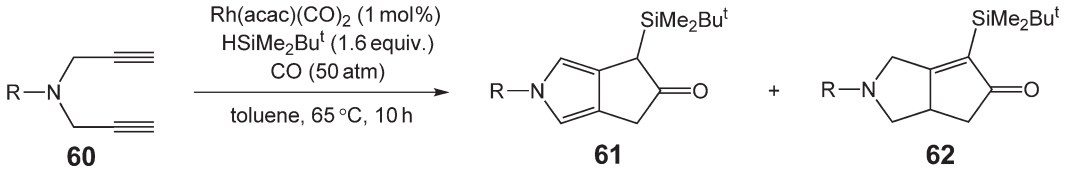
11.11.6 Carbonylative Processes

11.11.6.1 Cyclization/Silylation/Carbonylation of Diynes

Ojima has reported the rhodium-catalyzed cyclization/silylation/carbonylation of 1,6-diynes to form bicyclo[3.3.0] octenones and/or bicyclo[3.3.0]octadien-3-ones.[50,51,51a] For example, reaction of dimethyl dipropargylmalonate and *tert*-butyldimethylsilane catalyzed by $Rh_2Co_2(CO)_{12}$ or Rh(acac)$(CO)_2$ under CO gave 2-silylbicyclo[3.3.0]oct-$\Delta^{1,5}$-en-3-one **59a** in ≥90% yield. Compound **59a** isomerized to the corresponding conjugate enone **59b** upon treatment with a catalytic amount of rhodium trichloride hydrate in ethanol (Equation (39)). Product distribution in the rhodium-catalyzed cyclization/silylation/carbonylation of 1,6-diynes depended strongly on the nature of the homoallylic groups of the diyne. Rhodium-catalyzed reaction of dipropargylamine derivatives **60** formed 2-silyl-7-azabicyclo[3.3.0]octa-5,8-dien-3-ones **61** in preference to 2-silylbicyclo[3.3.0]oct-1-en-3-ones **62** (Equation (40)). Conversely, the reaction of 1,6-diynes derived from 2,2-dipropargyl-1,3-propanediol led to exclusive formation of 2-silylbicyclo[3.3.0]octa-1,5-dien-3-ones **63** (Equation (41)).

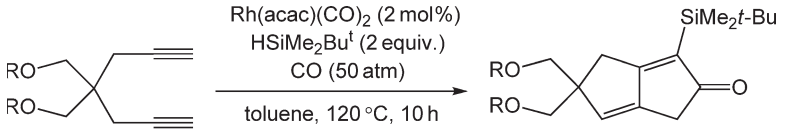
(39)

R^1	R^2	*Yield* (%)	*Ratio*
CO_2Et	CO_2Et	92	100 : 0
CO_2Et	Me	70	100 : 0
CO_2Et	H	65	74 : 24
CH_2OAc	H	73	100 : 0



60 **61** **62** (40)

R = Bn	70%	18%
R = *n*-hexyl	58%	0%
R = allyl	56%	22%

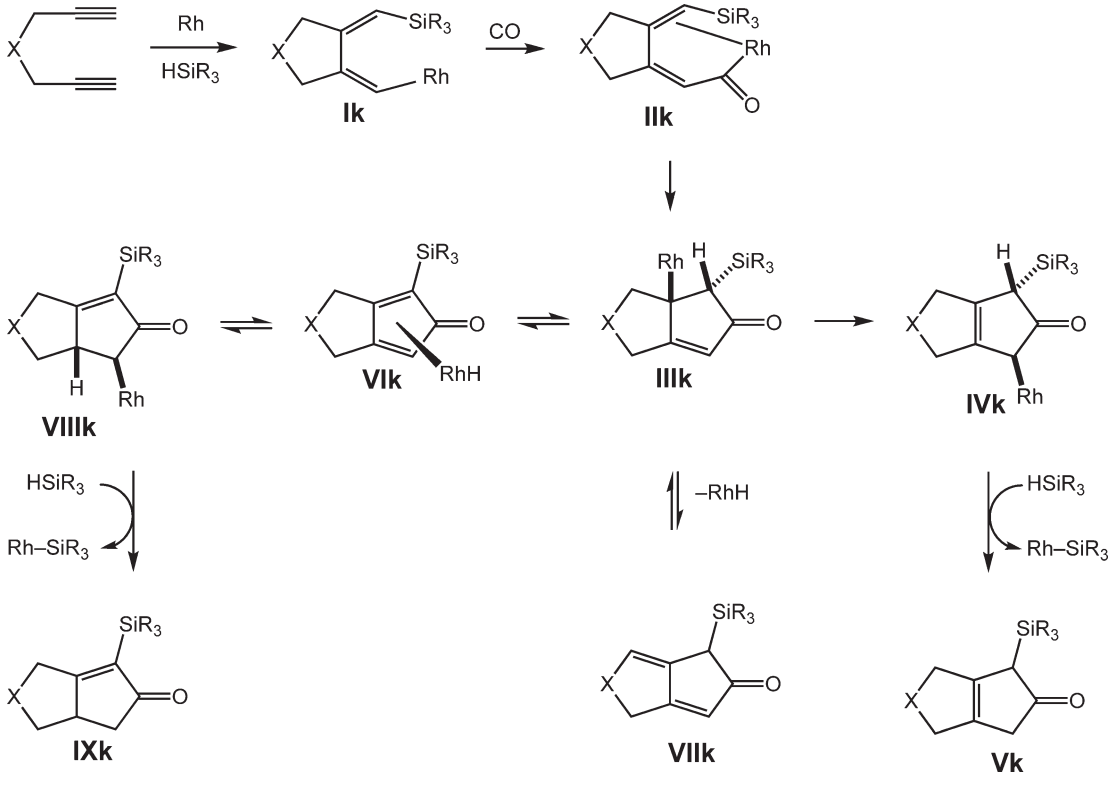


63 (41)

(TIPS = $SiPr^i_3$ = triisopropylsilyl)

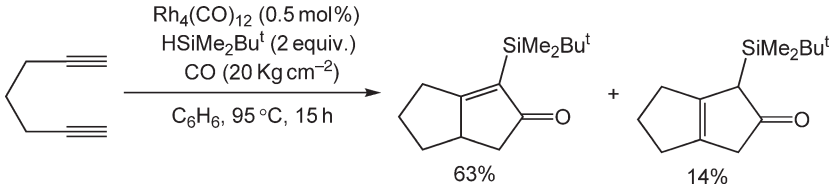
R	*Yield* (%)
TBDMS	95
TIPS	72
Ac	72
H	71

Rhodium-catalyzed cyclization/silylation/carbonylation of 1,6-diynes was proposed to occur via α-migratory insertion of CO into the Rh–C bond of dialkylidene cyclopentane intermediate **Ik** to form acylrhodium alkene intermediate **IIk** (Scheme 17).[50,51,51a] 5-*endo*-β-Migratory insertion of the silylated alkylidene moiety into the Rh–C bond of **IIk** would form the silylbicyclo[3.3.0]octenonerhodium intermediate **IIIk**, which could undergo 1,3-migration via a π-allyl intermediate to form rhodium enolate **IVk**. Silane-promoted C–H reductive elimination from **IVk** would form the 2-silylbicyclo[3.3.0]oct-$\Delta^{1,5}$-en-3-one product **Vk**. Alternatively, **IIIk** could undergo β-elimination of a secondary or tertiary hydrogen atom to form the dienylrhodium hydride intermediate **VIk** or the 4-silylbicyclo[3.3.0]octa-1,5-dien-3-one product **VIIk**, respectively. β-Addition of the Rh–H bond across the trisubstituted C=C bond of **VIk** could then form **VIIIk**, which could undergo silane-promoted C–H reductive elimination to form the 2-silylbicyclo[3.3.0]oct-1-en-3-one product **IXk**.



Scheme 17

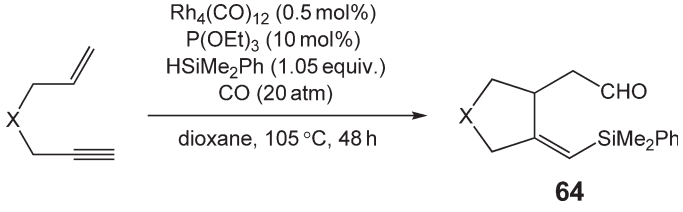
A procedure for the cyclization/silylation/carbonylation of diynes similar to that developed by Ojima was developed independently by Matsuda.[52] For example, reaction of 1,6-heptadiyne and *tert*-butyldimethylsilane catalyzed by $Rh_4(CO)_{12}$ in benzene under CO at 95 °C for 15 h gave 2-*tert*-butyldimethylsilylbicyclo[3.3.0]oct-1-en-3-one in 63% yield and 2-*tert*-butyldimethylsilylbicyclo[3.3.0]oct-$\Delta^{1,5}$-en-3-one in 14% yield (Equation (42)).



(42)

11.11.6.2 Cyclization/Silylformylation of Enynes

Ojima has developed an effective protocol for the cyclization/silylformylation of enynes to form silylated cyclopentane carboxaldehydes.[14a] For example, treatment of a dilute solution of *N*-allyl-*N*-propargyltosylamide (0.02 M) and dimethylphenylsilane with a catalytic mixture of $Rh_4(CO)_{12}$ (0.5 mol%) and $P(OEt)_3$ (10 mol%) in dioxane at 105 °C for 48 h under CO (20 atm) gave the silylated alkylidene pyrrolidine carboxaldehyde **64** (X = NTs) in 85% yield (Equation (43)). High dilution of the reaction medium was avoided by pressurizing a frozen mixture of the enyne, silane, and catalyst with CO followed by heating the resulting mixture in an autoclave. The protocol tolerated a range of functionality including esters, acetals, and silyl ethers. Substitution at the allylic and alkynic positions was likewise tolerated, and the reaction was effective for the synthesis of oxygen heterocycles and carbocycles (Equation (43)). Conversely, the protocol did not tolerate substitution on the C=C bond and was not effective for the formation of six-membered rings.

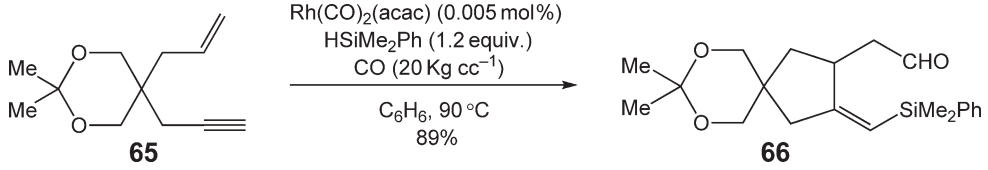


X	*Yield* (%)
NTs	85
NMs	56
$C(CO_2Et)_2$	91
$C(CH_2OMe)_2$	83
$C(CH_2OAc)_2$	91
$C[CH_2OC(Me)_2OCH_2]$	89

(43)

Ojima has proposed a mechanism for the rhodium-catalyzed cyclization/silylformylation of enynes that invokes several of the same intermediates proposed for the rhodium-catalyzed cyclization/hydrosilylation of enynes (Scheme 7). Silylmetallation of the C≡C bond of the enyne followed by β-migratory insertion of the pendant C=C bond into the resulting Rh–C bond could form rhodium cyclopentyl complex **IIIf**. α-Migratory insertion of CO into the Rh–C bond of **IIIf** followed by silane-promoted reductive elimination from the resulting rhodium formyl complex **IVf** could release the silylated cyclopentane carboxaldehyde with regeneration of silylrhodium hydride complex **If** (Scheme 7).

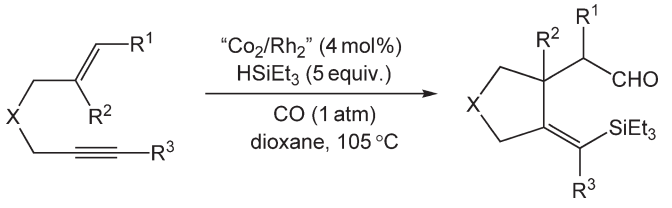
Matsuda independently developed an alternative procedure for the cyclization/silylformylation of enynes that did not require the use of phosphite ligand, and which was effective with low catalyst loading.[53] As an example, reaction of a benzene solution of acetal **65** (0.1 M) and dimethylphenylsilane catalyzed by $Rh(acac)(CO)_2$ (0.005 mol%) under CO (20 bar) at 90 °C for 14 h formed silylated alkylidene carboxaldehyde **66** in 89% yield (Equation (44)).



(44)

Chung has developed an effective protocol for the cyclization/silylformylation of 1,6-enynes catalyzed by cobalt/rhodium nanoparticles (Co_2/Rh_2).[16] For example, reaction of dimethyl allylpropargylmalonate and triethylsilane catalyzed by Co_2/Rh_2 in dioxane at 105 °C under CO formed the corresponding silylated cyclopentane

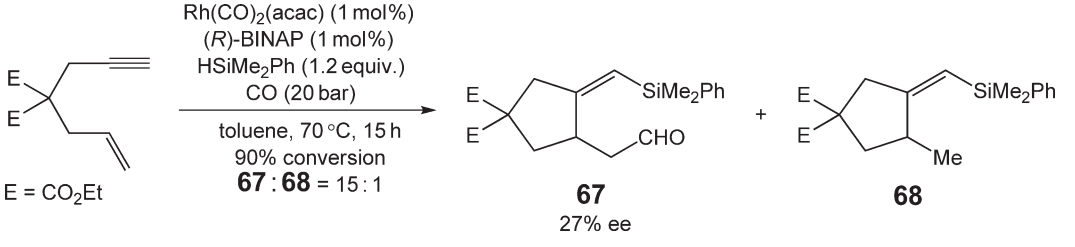
carboxaldehyde in 93% yield (Equation (45); X = $C(CO_2Me)_2$, $R^1 = R^2 = R^3 = H$). It was noteworthy that cyclization/silylformylation of 1,6-enynes catalyzed by Co_2/Rh_2 required only 1 atm of CO. Rhodium/cobalt nanoparticle-catalyzed enyne cyclization/silylformylation displayed good generality and tolerated esters, free alcohols, tosylamides, and ethers (Equation (45)), and the protocol tolerated substitution at either the *trans*-terminal alkenyl position ($R^1 = CH_3$) or the alkyne carbon atom (R^3 = Ph). 1,6-Enynes that possessed internal alkenyl substitution also underwent reaction, albeit with diminished yields (Equation (45); R^2 = Me).



(45)

X	R^1	R^2	R^3	*Yield* (%)
$C(CO_2Me)_2$	H	H	H	93
$C(CH_2OH)_2$	H	H	H	52
NTs	H	H	H	93
O	H	H	Ph	87
O	CH_3	H	Ph	58
O	H	CH_3	Ph	23

Suisse and co-workers have studied the asymmetric cyclization/silylformylation of enynes employing catalytic mixtures of a rhodium(I) carbonyl complex and a chiral, non-racemic phosphine ligand. Unfortunately, only modest enantioselectivities were realized.[54] For example, reaction of diethyl allylpropargylmalonate with dimethylphenylsilane (1.2 equiv.) catalyzed by a 1 : 1 mixture of Rh(acac)$(CO)_2$ and (*R*)-BINAP in toluene at 70 °C for 15 h under CO (20 bar) led to 90% conversion to form a 15 : 1 mixture of cyclization/silylformylation product **67** and cyclization/hydrosilylation product **68**. Aldehyde **67** was formed with 27% ee (Equation (46)).



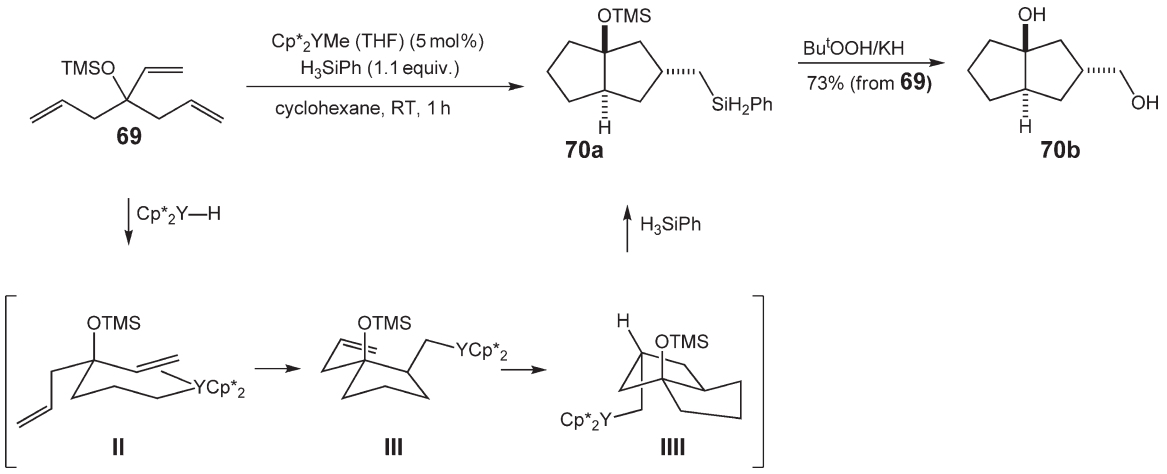
(46)

11.11.7 Multiple Ring Forming Processes

11.11.7.1 Cascade Cyclization/Hydrosilylation of Trienes

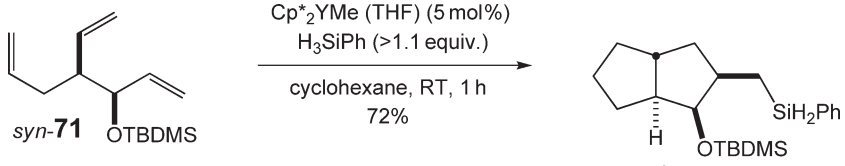
Yttrocene complexes catalyze the cascade cyclization/hydrosilylation of trienes to form saturated silylated bicyclic compounds.[24] For example, reaction of the 4-silyloxy-4-vinyl-1,6-hexadiene **69** and phenylsilane catalyzed by $Cp^*_2YMe(THF)$ at room temperature for 1 h followed by oxidation of crude **70a** gave *trans*-[3.3.0]bicyclic diol **70b** in 73% yield over two steps as a single diastereomer (Scheme 18). Selective conversion of **69** to **70a** presumably requires initial 1,2-hydrometallation of one of the less-hindered C═C bonds to form alkylyttrium alkene complex **II** (Scheme 18). Selective 5-*exo* carbometallation of **II** in preference to 6-*exo* carbometallation would form cyclopentylmethylyttrium complex **III** (Scheme 18). Cyclization of **III** via a chairlike transition state would form the strained *trans*-fused alkylyttrium complex **IIII**, which could undergo silylation to form **70a**.

Yttrium-catalyzed cascade cyclization/hydrosilylation was also applied to 3-substituted 4-vinyl-1,6-hexadienes. For example, reaction of *syn*-3-(*tert*-butyldimethylsiloxy)-4-ethenyl-1,6-heptadiene (*syn*-**71**) with phenylsilane catalyzed by $Cp^*_2YMe(THF)$ gave **72a** in 72% yield as a 2.1 : 1 mixture of diastereomers (Equation (47)). Yttrium-catalyzed cascade reaction of the corresponding diastereomer *anti*-**71** was more effective and gave **72b** in 78% yield as a 7.2 : 1

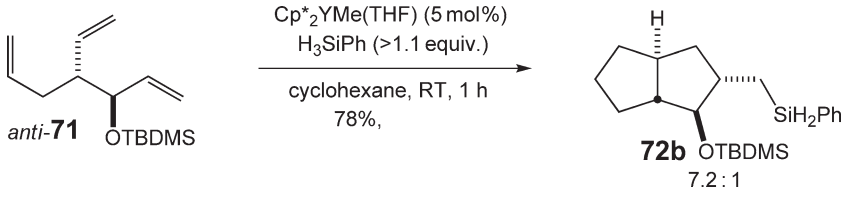


Scheme 18

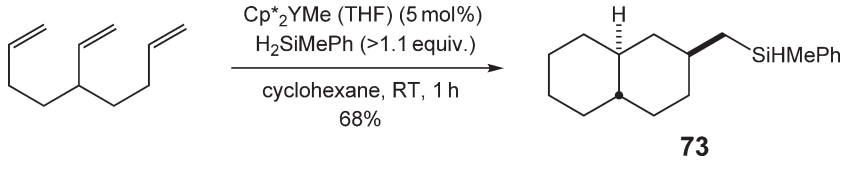
mixture of diastereomers (Equation (48)). The reaction was also applied to the synthesis of silylated decalins. As an example, reaction of 5-vinyl-1,8-nonadiene with methylphenylsilane catalyzed by $Cp^*_2YMe(THF)$ gave the *trans*-fused decalin **73** in 68% yield as a single diastereomer with respect to the stereogenic carbon atoms (Equation (49)).



(47)

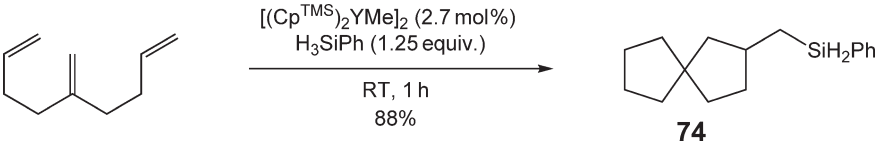


(48)

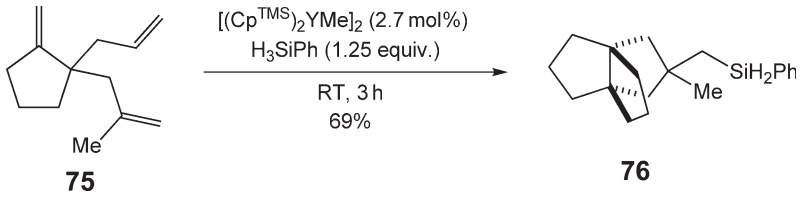


(49)

Employment of the less sterically hindered yttrocene catalyst $[(Cp^{TMS})_2YMe]_2$[25] or the more reactive zwitterionic zirconocene catalyst $Cp^*_2ZrMe(\mu\text{-}Me)B(C_6F_5)_3$[26] allowed cascade cyclization/hydrosilylation of trienes that possessed one or more 1,1-disubstituted alkene. As examples, reaction of 2-(3-butenyl)-1,6-hexadiene and phenylsilane catalyzed by $[(Cp^{TMS})_2YMe]_2$ gave silylated spirocycle **74** in 88% yield. Likewise, the reaction of the dialkenyl alkylidene cyclopentane **75** gave silylated propellane **76** in good yield (Equations (50) and (51)).

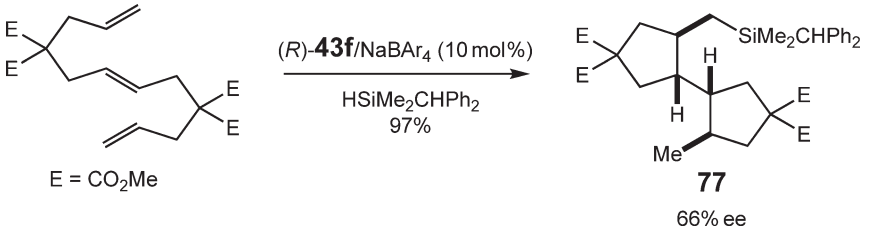


(50)

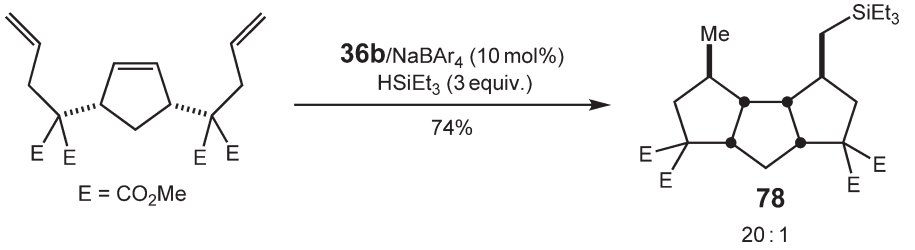


75 **76** (51)

Cationic palladium complexes catalyze the cascade cyclization/hydrosilylation of 1,6,11-trienes to form tethered and fused polycycles.[35,40c] For example, reaction of 4,4,9,9-tetrakis(methoxycarbonyl)-1,6,11-dodecatriene and benzhydryldimethylsilane catalyzed by a 1:1 mixture of the enantiomerically pure palladium pyridine–oxazoline complex (*R*)-**43f** (10 mol%) and $NaBAr_4$ [$Ar = C_6H_3(CF_3)_2$] led to cascade cyclization/hydrosilylation with isolation of bicyclopentane **77** in 97% yield as a single diastereomer with 66% ee (Equation (52)). In a second example, reaction of di(3-butenyl)cyclopentene and triethylsilane catalyzed by a 1:1 mixture of **36b** (10 mol%) and $NaBAr_4$ [$Ar = C_6H_3(CF_3)_2$] gave **78** in 74% yield as a 20:1 mixture of isomers (Equation (53)).



77
66% ee (52)



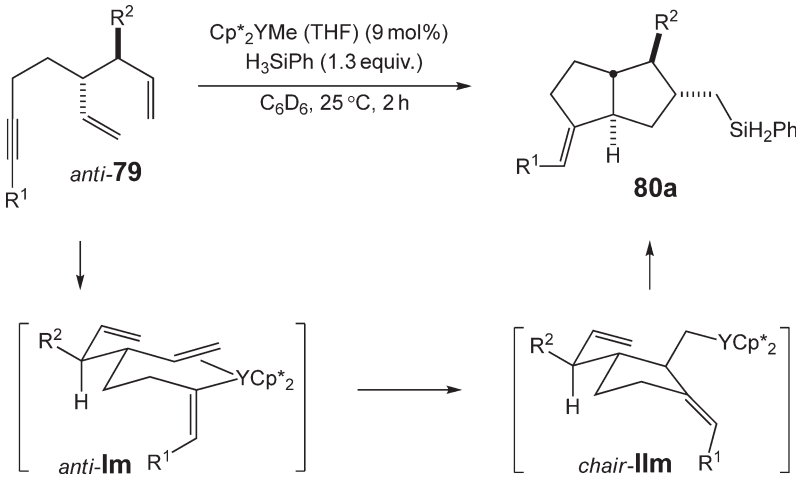
78
20:1 (53)

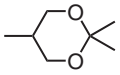
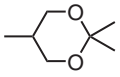
11.11.7.2 Cascade Cyclization/Hydrosilylation of Dieneynes

The yttrocene methyl complex $Cp^*_2YMe(THF)$ is also an effective catalyst for the cascade cyclization/hydrosilylation of 3-(3-butynyl)-1,5-hexadienes to form silylated [3.3.0] fused bicyclic ring systems.[55] For example, reaction of *anti*-**79** ($R^1 = Cy$, $R^2 = OCPh_3$) with phenylsilane catalyzed by $Cp^*_2YMe(THF)$ in cyclohexane at room temperature for 2 h gave the silylated [3.3.0]bicyclic compound **80a** ($R^1 = Cy$, $R^2 = OCPh_3$) in 86% yield as a ≥30:1 mixture of diastereomers (Scheme 19). The regio- and stereoselective conversion of *anti*-**79** to **80a** was proposed to occur through two successive 5-*exo*-intramolecular carbometallations via chairlike transition states that resemble intermediates *anti*-**Im** and *chair*-**IIm** (Scheme 19).

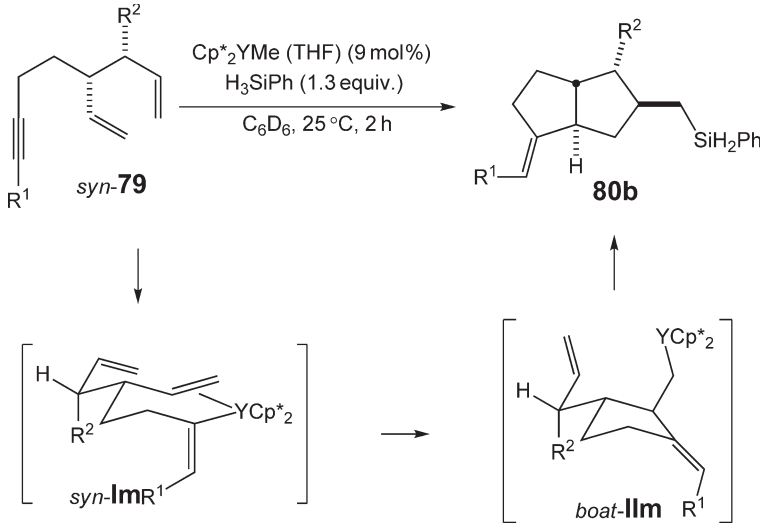
Yttrium-catalyzed cascade cyclization/hydrosilylation of 3-(3-butynyl)-1,5-hexadienes was stereospecific, and *syn*-**79** ($R^1 = Cy$, $R^2 = OCPh_3$) underwent cascade cyclization/hydrosilylation to form **80b** ($R^1 = Cy$, $R^2 = OCPh_3$) in 97% yield as a single diastereomer (Scheme 20). The regio- and stereoselective conversion of *syn*-**79** to **80b** was proposed to occur through an initial 5-*exo*-intramolecular carbometallation via a chairlike transition state that resembles alkenyl olefin complex *syn*-**Im** followed by 5-*exo* intramolecular carbometallation via a boatlike transition state that resembles alkyl olefin complex *boat*-**IIm**. The second intramolecular carbometallation presumably occurs via a boatlike transition state to avoid the unfavorable 1,3-interaction present in the corresponding chairlike transition state (Scheme 20).

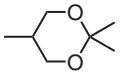
Several additional points regarding the yttrium-catalyzed cascade cyclization/hydrosilylation of dienynes are worth noting. First, substitution at the 4-position of the 3-(3-butynyl)-1,5-hexadiene and a branched substituent on the terminal alkyne carbon atom were required to achieve high chemo- and regioselectivity,



R^1	R^2	*Yield* (%)	*Ratio*
Cy	$OCPH_3$	86	30 : 1
Cy	OTBDMS	93	7 : 1
	$OCPh_3$	98	40 : 1
	OTBDPS	90	14 : 1

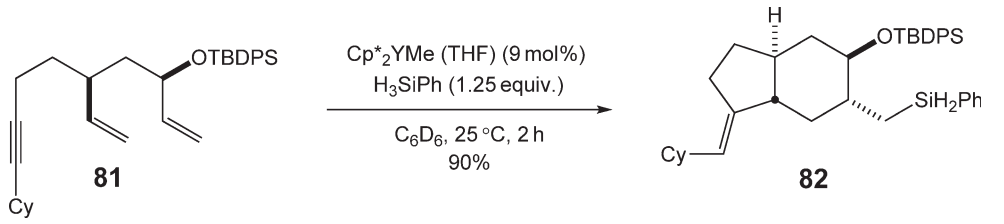
Scheme 19



R^1	R^2	*Yield* (%)	*Ratio*
Cy	$OCPh_3$	97	>60 : 1
	benzyl	89	30 : 1

Scheme 20

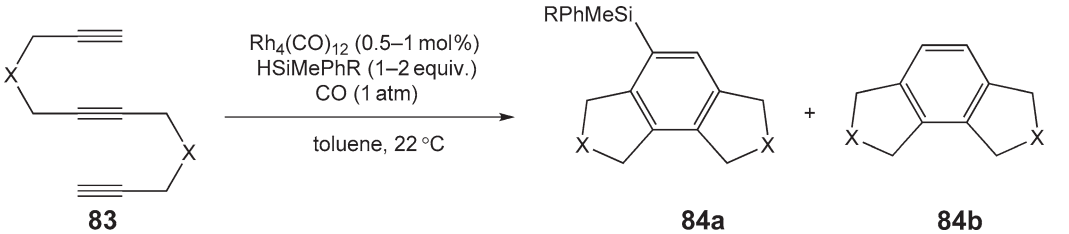
respectively, of the initial hydrometallation. Second, although substitution at the C(5)-alkenyl carbon also served as direct hydrometallation to the C≡C bond, the reaction of these substrates led to formation of mixtures of mono- and bicyclic silylated products. Third, the diastereoselectivity of cascade cyclization/hydrosilylation was sensitive to the nature of the allylic substituent (Scheme 19; R^1 = Cy, R^2 = OTBDMS). Fourth, yttrium-catalyzed cascade cyclization/hydrosilylation was also effective for the formation of silylated [4.3.0] fused bicyclic ring systems. For example, reaction of the 3-(3-butynyl)-1,6-heptadiene **81** with phenylsilane led to cascade cyclization/hydrosilylation to form **82** in 90% yield as a single diastereomer (Equation (54)).



(54)

11.11.7.3 Silane-initiated Cascade Cyclization of Triynes

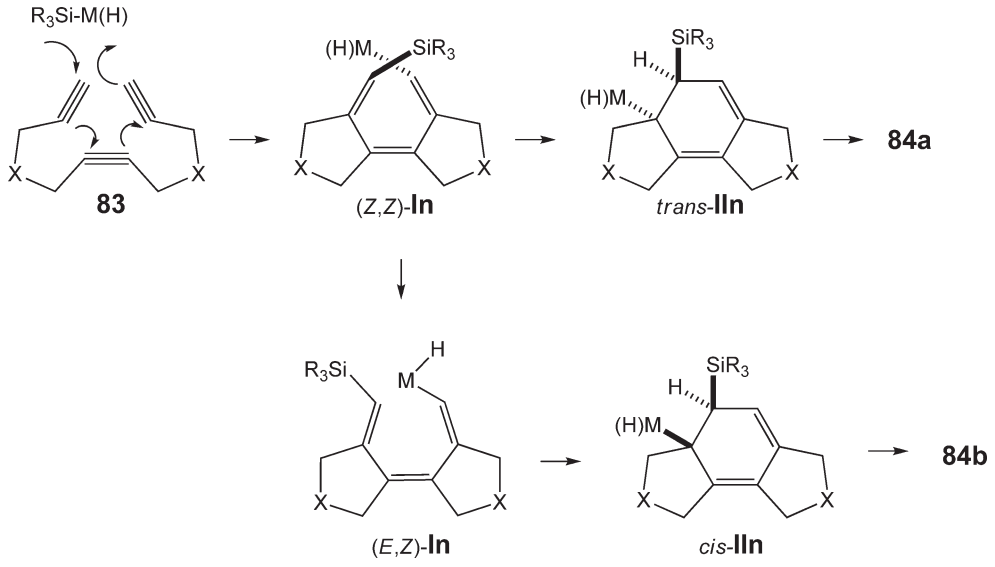
Rhodium carbonyl complexes catalyze the silane-initiated cascade cyclization of 1,6,11-triynes to form fused aromatic tricyclic compounds. For example, reaction of **83** [X = $C(CO_2Et)_2$] with methyldiphenylsilane catalyzed by the tetrarhodium carbonyl cluster $Rh_4(CO)_{12}$ in toluene at room temperature gave an 88 : 12 mixture of the silylated and unsilylated fused tricycles **84a** and **84b** [X = $C(CO_2Et)_2$] in 85% combined yield (Equation (55)).[56] The ratio of silylated to unsilylated tricyclic product formed in the reaction of 1,6,11-triynes was dependent on the nature of the substrate (Equation (55)). For example, $Rh_4(CO)_{12}$-catalyzed reaction of diaminotriyne **83** (X = NBn) with methyldiphenylsilane gave unsilylated tricycle **84b** (X = NBn) in 92% yield as the exclusive product (Equation (55)).



(55)

X	*R*	*Yield* (%)	*Ratio*
$C(CO_2Et)_2$	Ph	85	88 : 12
NBn	Me	92 (^{1}H NMR)	0 : 100
NTs	Me	99 (^{1}H NMR)	15 : 85
$C(CH_2OMe)_2$	Me	69	92 : 8
$C(CH_2OBn)_2$	Me	76	100 : 0
O	Me	75 (^{1}H NMR)	24 : 76

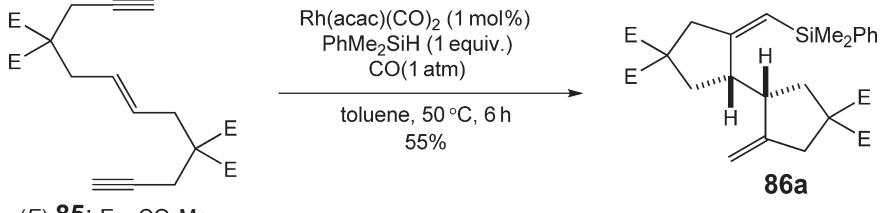
Rhodium-catalyzed, silane-initiated cascade cyclization of 1,6,11-triynes **83** was proposed to occur via a silane-initiated cascade carbocyclization to form the silylated bicyclic triene (*Z*,*Z*)-**In**. *β*-Migratory insertion of the silylated C═C bond into the Rh–C bond of (*Z*,*Z*)-**In** followed by *β*-hydride elimination from *trans*-**IIn** could then form **84a**. Alternatively, *cis*/*trans* isomerization of (*Z*,*Z*)-**In** followed by *β*-migratory insertion of the silylated C═C bond into the Rh–C bond of resulting isomer (*E*,*Z*)-**In** could form *cis*-**IIn**. Subsequent *β*-silyl elimination from *cis*-**IIn** would form unsilylated tricycle **84b** (Scheme 21).



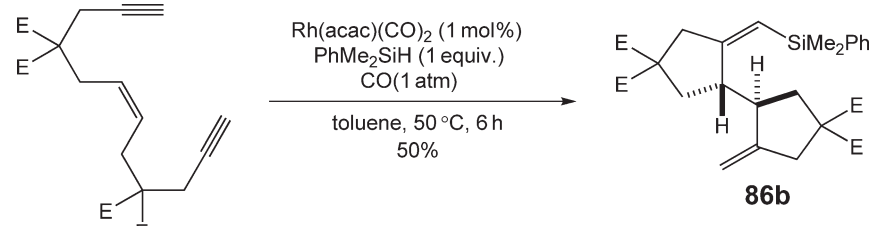
Scheme 21

11.11.7.4 Silane-initiated Cascade Cyclization of Enediynes

Rhodium carbonyl complexes also catalyze the cascade cyclization/hydrosilylation of 6-dodecene-1,11-diynes to form silylated tethered 2,2′-dimethylenebicyclopentanes.[57,57a] For example, reaction of (*E*)-**85** with dimethylphenylsilane catalyzed by Rh(acac)$(CO)_2$ in toluene at 50 °C under CO (1 atm) gave **86a** in 55% yield as a single diastereomer (Equation (56)). Rhodium-catalyzed cascade cyclization/hydrosilylation of enediynes was stereospecific, and reaction of (*Z*)-**85** under the conditions noted above gave **86b** in 50% yield as a single diastereomer (Equation (57)). Rhodium(I)-catalyzed cascade cyclization/hydrosilylation of 6-dodecene-1,11-diynes was proposed to occur via silylmetallation of one of the terminal C≡C bonds of the enediyne with a silyl–Rh(III) hydride complex, followed by two sequential intramolecular carbometallations and C–H reductive elimination.[57,57a]

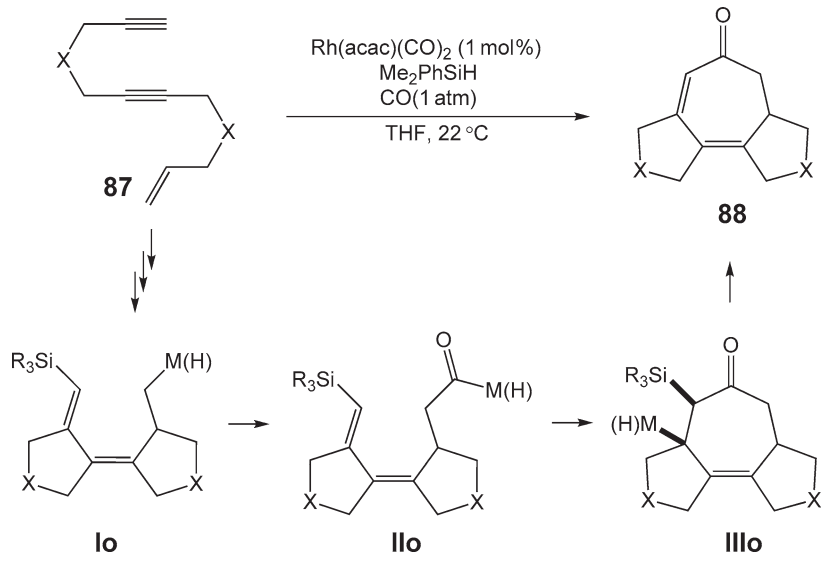


(56)



(57)

In contrast to the reactivity of 6-dodecene-1,11-diynes, rhodium-catalyzed reaction of 1-dodecene-6,11-diynes with silane led not to cascade cyclization/hydrosilylation but rather to carbonylative tricyclization. For example, reaction of **87** [X = $C(CO_2Me)_2$] and dimethylphenylsilane catalyzed by Rh(acac)$(CO)_2$ in THF at room temperature under CO gave the cyclopenta[e]azulene **88** in 92% yield as the exclusive product (Scheme 22). Although the protocol was



X	Yield (%)
$C(CO_2Et)_2$	92
NTs	85
O	50
$C(CH_2OMe)_2$	89
$C(CH_2OBn)_2$	87
$C(CH_2OAc)_2$	81
$C(CH_2OH)_2$	62

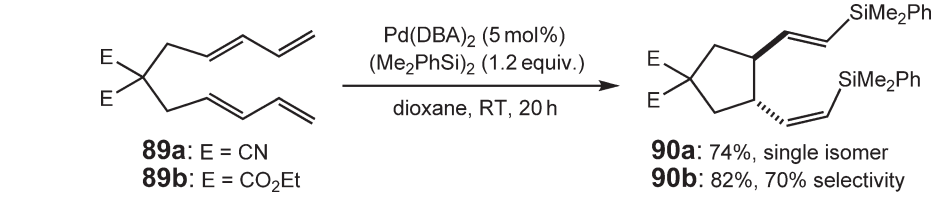
Scheme 22

intolerant of substitution at the C(1) or C(11) positions of the enediyne, a number of 1-dodecene-6,11-diynes underwent rhodium-catalyzed carbonylative tricyclization to form the corresponding cyclopenta[e]azulenes in moderate to good yield (Scheme 22). Rhodium-catalyzed carbonylative tricyclization of **87** was proposed to occur via initial silylative bicyclization to form **Io**. α-Migratory insertion of CO into the Rh–C bond of **Io** could form acylrhodium intermediate **IIo** (Scheme 22). β-Migratory insertion of the silylated C═C bond into the Rh–C bond of **IIo** to form the tricyclic rhodium silyl intermediate **IIIo**, followed by β-silyl elimination, would then release **88** (Scheme 22).

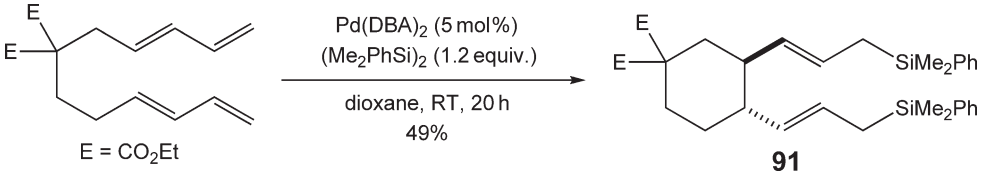
11.11.8 Silylative Cyclization to Form Bis(functionalized) Carbocycles

11.11.8.1 Cyclization/Disilylation

Tsuji has reported the palladium-catalyzed cyclization/disilylation of bis(1,3-dienes) with disilanes to form disilylated divinylcycloalkanes.[58] For example, reaction of (*E*,*E*)-6,6-dicyano-1,3,8,10-undecatetraene **89a** and diphenyltetramethyldisilane (1.2 equiv.) catalyzed by $Pd(DBA)_2$ gave **90a** in 74% yield with exclusive formation of the *trans*-*E*,*Z*-diastereomer (Equation (58)). The stereoselectivity of the palladium-catalyzed cyclization/disilylation of bis(dienes) was substrate dependent, and the Pd-catalyzed reaction of **89b** gave the bis(silylated) cyclopentane **90b** in 82% yield with 70% selectivity for the *trans*-*E*,*Z*-diastereomer (Equation (58)). In comparison, the reaction of (*E*,*E*)-6,6-bis(ethoxycarbonyl)-1,3,9,11-dodecatetraene gave the bis(silylated)cyclohexane **91** in 49% yield with exclusive formation of the *trans*-*E*,*E*-diastereomer (Equation (59)).

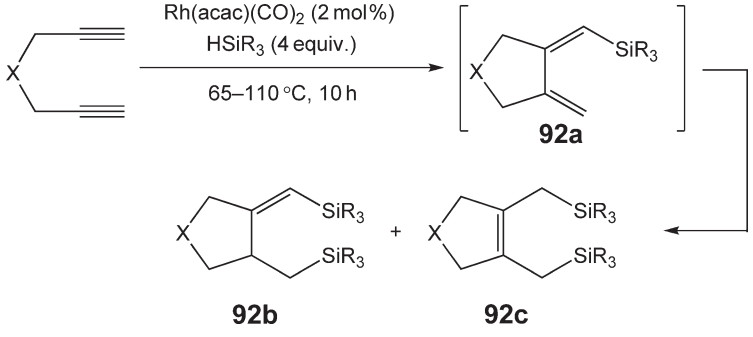


(58)



(59)

Ojima has reported a rhodium-catalyzed protocol for the disilylative cyclization of diynes with hydrosilanes to form alkylidene cyclopentanes and/or cyclopentenes.[50] As an example, reaction of dipropargylhexylamine with triethylsilane catalyzed by $Rh(acac)(CO)_2$ under an atmosphere of CO at 65 °C for 10 h gave an 83 : 17 mixture of the disilylated alkylidene pyrrolidine derivative **92b** (X = N-*n*-hexyl) and the disilylated dihydro-1*H*-pyrrole **92c** (X = N-*n*-hexyl) in 76% combined yield (Equation (60)). Compounds **92b** and **92c** were presumably formed via hydrosilylation and hydrosilylation/isomerization, respectively, of the initially formed silylated dialkylidene cyclopentane **92a** (Equation (60)). The **92b** : **92c** ratio was substrate dependent. Rhodium-catalyzed disilylative cyclization of dipropargyl ether formed the disilylated alkylidene tetrahydrofuran **92b** (X = O) as the exclusive product in low yield, whereas the reaction of dimethyl dipropargylmalonate formed cyclopentene **92c** [$X = C(CO_2Et)_2$] as the exclusive product in 74% isolated yield (Equation (60)).



(60)

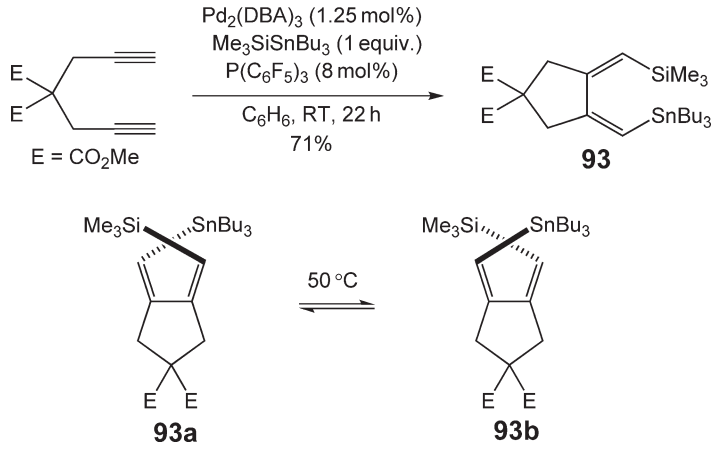
X	*SiR*$_3$	*Yield* (%)	*Ratio* **92b : 92c**
N-*n*-hexyl	$SiEt_3$	76	83 : 17
O	$SiMe_2Bu^t$	21	100 : 0
$C(CO_2Et)_2$	$SiMe_2Bu^t$	74	0 : 100

11.11.8.2 Cyclization/Stannylsilylation

RajanBabu has reported the palladium(0)-catalyzed cyclization/stannylsilylation of 1,6-diynes to form bis(functionalized) dialkylidene cyclopentanes.[59] Reaction of dimethyl dipropargylmalonate with trimethylsilyltributylstannane catalyzed by a mixture of $Pd_2(DBA)_3$ (1.25 mol%) and $P(C_6F_5)_3$ (8 mol%) gave cyclopentane **93** in 71% yield with (*Z*)-stereochemistry about each of the exocyclic C═C bonds (Scheme 23). Compound **93** displayed unusual fluxional behavior due to the helical-chiral arrangement of the exocyclic trialkylsilyl and trialkylstannylalkylidene groups. The ^1H NMR spectrum of **93** at 50 °C displayed two broad singlets at $\delta = 2.97$ and 3.01, which resolved into two sets of AB quartets at $\delta = 3.12$ ($J_{AB} = 9$ Hz) and $\delta = 2.72$ ($J_{AB} = 14$ Hz) at −40 °C. These data are in accord with the existence of two enantiomeric forms of **93** (**93a** and **93b**) that interconvert rapidly on the NMR timescale at 50 °C but slowly at −40 °C. The non-planar orientation of the exocyclic dienyl substituents of **93** was also evidenced by the failure of **93** to undergo [4 + 2]-cycloaddition with maleic anhydride at 150 °C. Palladium-catalyzed cyclization/silylstannylation of 1,6-diynes was compatible with a range of functional groups including tosylamides, tertiary amines, and carbonyl groups, and the procedure displayed low sensitivity to air and moisture.

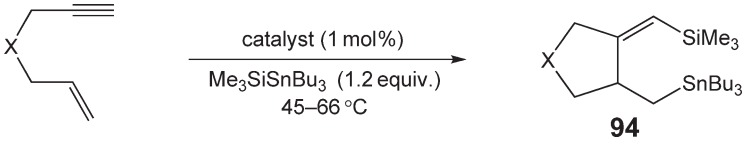
Lautens has developed an effective palladium-catalyzed protocol for the cyclization/stannylsilylation of 1,6-enynes to form bis(functionalized) alkylidenecyclopentanes.[60] For example, reaction of dimethyl allylpropargylmalonate and trimethylsilyltributylstannane (1.2 equiv.) catalyzed by a 1 : 1 mixture of $PdBr_2$(dmmdiy)

and $NaBAr_4$ [Ar = 3,5-$C_6H_3(CF_3)_2$] (1 mol%) in toluene at 45 °C for 42 h gave **94** in 81% yield with selective delivery of the silane to the alkyne moiety of the enyne (Table 9, entry 1). Comparable results (71% yield) were obtained employing a 1 : 1 mixture of $Pd_2(DBA)_3$ and dicyclohexyl(*o*-biphenyl)phosphine as the catalyst system (Table 9, entry 2). Palladium-catalyzed cyclization/stannylsilylation of 1,6-enynes tolerated a number of functional groups including free hydroxyl groups, acetals, ethers, and silyl ethers, and the protocol was effective for the synthesis of



Scheme 23

Table 9 Palladium-catalyzed cyclization/stannylsilylation of 1,6-enynes

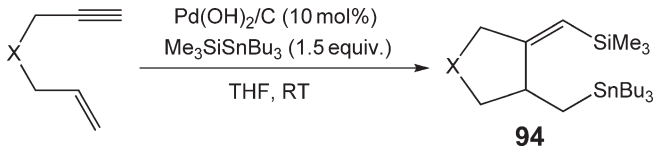


Entry	*X*	*Catalyst*[a]	*Yield* (%)
1	$C(CO_2Et)_2$	A	81
2	$C(CO_2Et)_2$	B	71[b]
3	$C(CH_2OH)_2$	B	62
4	$C[CH_2OC(Me_2)OCH_2]$	B	76
5	$C(CH_2OTIPS)_2$	B	55
6	$C(CH_2OBz)_2$	B	61
7	NTs	A	80
8	NBoc	A	41

[a]Catalyst A: $PdBr_2$(dmmdiy)/$NaBAr_4$ [Ar = 3,5-$C_6H_3(CF_3)_2$]. Catalyst B: $Pd_2(DBA)_3/PCy_2$(*o*-biphenyl).
[b]5% catalyst loading.

bis(functionalized) pyrrolidine derivatives (Table 9, entries 3–8). Conversely, the protocol of 1,6-enynes tolerated neither internal alkynes nor 1,6-enynes that possessed allylic substitution.

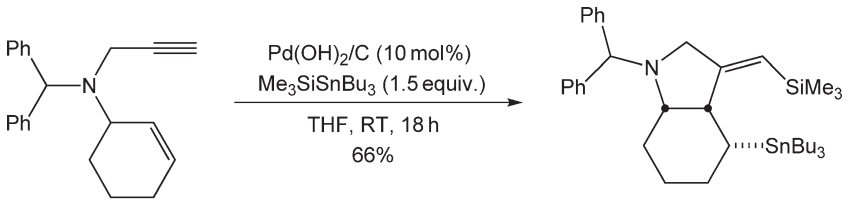
Mori has independently developed a procedure for the cyclization/stannylsilylation of enynes similar to that developed by Lautens.[61] As an example of Mori's procedure, reaction of dimethyl allylpropargylmalonate with trimethylsilyltributylstannane catalyzed by Pearlman's catalyst [$Pd(OH)_2$/C] in THF at room temperature for 20 h formed cyclopentane **94** [X = $C(CO_2Me)_2$] in 90% yield (Equation (61)). The transformation was compatible with a number of functional groups, tolerated limited substitution of the C═C bond, and was applicable to the synthesis of nitrogen heterocycles. In a notable example, reaction of the benzhydryl-protected allylpropargylamine **95** with $Me_3SiSnBu_3$ catalyzed by $Pd(OH)_2$/C formed the bis(functionalized) octahydroindole **96** in 66% yield as a single diastereomer (Equation (62)).



94

X	*Yield* (%)
$C(CO_2Et)_2$	90
$C(CH_2OBz)_2$	52
$C[CH_2OC(Me)_2OCH_2]$	65
$C(CH_2OBn)_2$	78
NTs	82

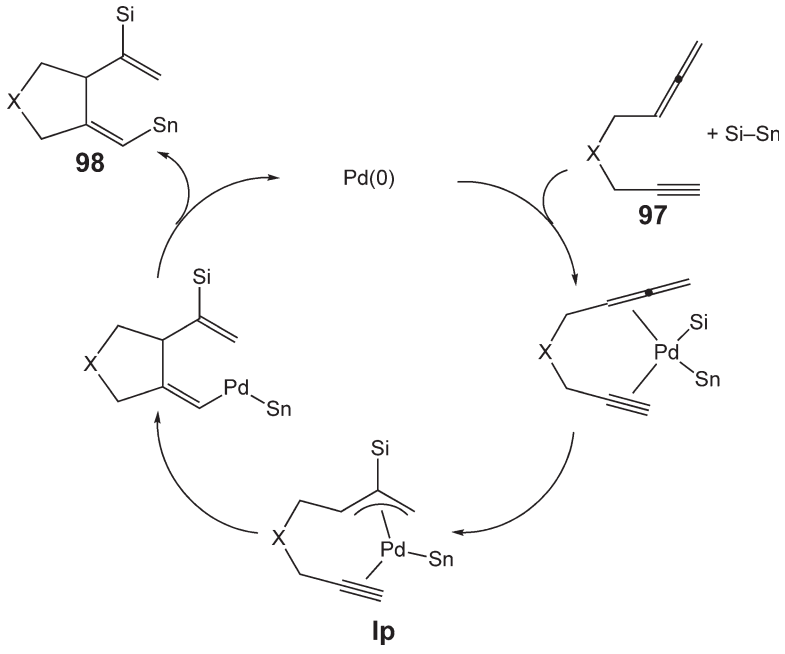
(61)



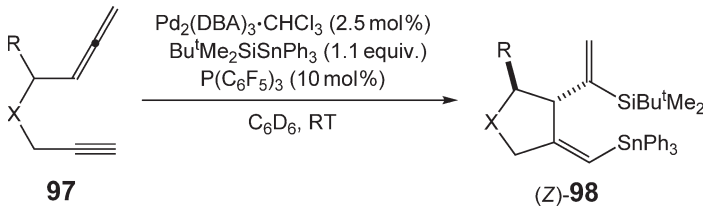
95 96

(62)

RajanBabu has reported a procedure for the cyclization/stannylsilylation of allenynes to form bis(functionalized) alkenyl alkylidene cyclopentanes.[62] For example, reaction of allenyne **97** [X = $C(CO_2Me)_2$, R = H] with *tert*-butyldimethylsilyltriphenylstannane catalyzed by a mixture of $Pd_2(DBA)_3{\cdot}CHCl_3$ and $P(C_6F_5)_3$ led to 5-*exo*-cyclization with isolation of alkenyl alkylidene cyclopentane (*Z*)-**98** (X = $C(CO_2Me)_2$, R = H) in 80% yield, with exclusive delivery of the silane to the central carbon atom of the allenyl moiety (Equation (63)). Although the scope of the reaction was limited, the transformation was also applicable to the synthesis of bis(functionalized) alkylidene tetrahydrofuran and pyrrolidine derivatives (Equation (63); X = O, NTs). Palladium-catalyzed cyclization/stannylsilylation of **97** was proposed to occur via silylmetallation of the allene moiety to form the (π-allyl)palladium intermediate **Ip**, followed by sequential intramolecular carbometallation and C–Sn reductive elimination to release **98** with regeneration of Pd(0) (Scheme 24).



Scheme 24

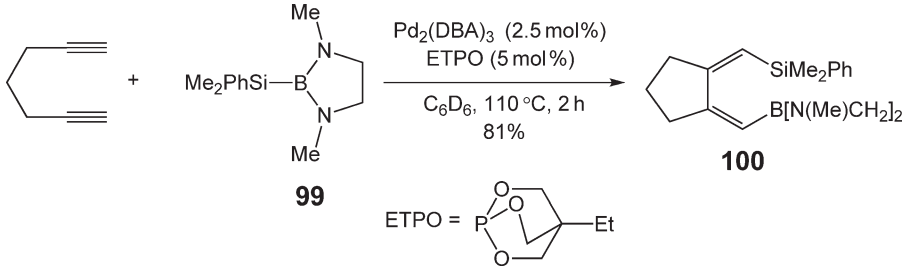


X	*R*	*Yield* (%)
$C(CO_2Me)_2$	H	80
NTs	H	41
O	Ph	61

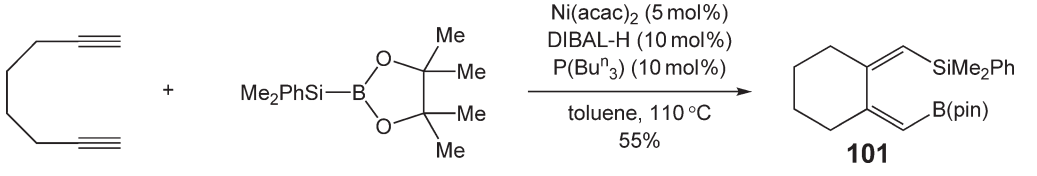
(63)

11.11.8.3 Cyclization/Borylsilylation

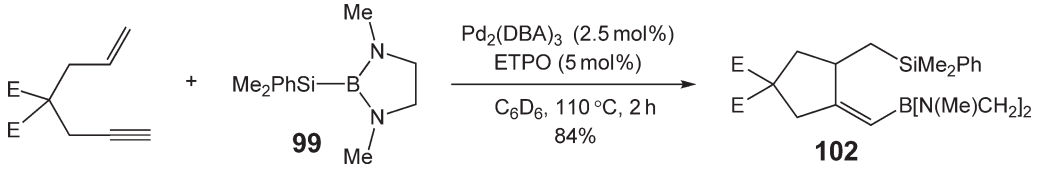
Tanaka[63] and Ito[64] have independently developed effective protocols for the catalytic cyclization/borylsilylation of diynes to form bis(functionalized) dialkylidene cyclopentanes.[63] As an example of the Tanaka procedure, reaction of 1,6-heptadiyne with borylsilane **99** catalyzed by a 1 : 2 mixture of $Pd_2(DBA)_3$ and ETPO (ETPO = 4-ethyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane) at 110 °C for 2 h gave **100** in 81% yield (Equation (64)).[63] As an example of the Ito procedure, reaction of 1,7-octadiyne with dimethylphenylsilylpinacolborane, catalyzed by the Ni(0) complex generated *in situ* from a 1 : 2 : 2 mixture of $Ni(acac)_2$, DIBAL-H, and P(*n*-Bu)$_3$ in toluene at 110 °C, gave the bis(functionalized) dialkylidene cyclohexane **101** in 55% yield (Equation (65)).[64] Tanaka's protocol was also effective for the cyclization/borylsilylation of 1,6-enynes. As an example, reaction of dimethyl allylpropargylmalonate with **99** catalyzed by $Pd_2(DBA)_3$/ETPO gave the bis(functionalized) alkylidene cyclopentane **102** in 84% yield with exclusive delivery of the borane to the alkyne moiety of the enyne (Equation (66)).[63]



(64)



(65)



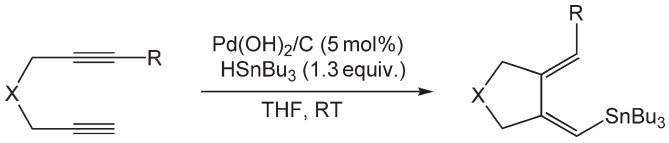
(66)

11.11.9 Related Cyclization/Metallation Processes

11.11.9.1 Stannylative Cyclization

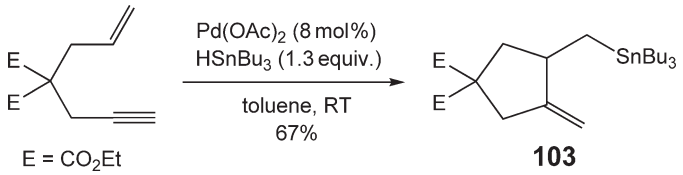
Lautens has developed effective palladium-catalyzed protocols for the cyclization/hydrostannylation of diynes to form stannylated dialkylidene cyclopentanes.[65] For example, slow addition of tributylstannane to a suspension of dimethyl dipropargylmalonate and a catalytic amount of $Pd(OH)_2$ on carbon (5 mol%) in THF at room temperature gave the corresponding stannylated cyclopentane in 95% yield as a single isomer (Table 10, entry 1). It was

Table 10 Pd-catalyzed cyclization/hydrostannylation of diynes



Entry	*X*	*R*	*Yield* (%)
1	$C(CO_2Me)_2$	H	95
2	$C[CH_2OC(Me_2)OCH_2]$	H	70
3	O	H	68
4	NBn	H	85
5	S	H	58
6	SO_2	H	77
7	$C(CH_2OH)_2$	H	61
8	$C(CH_2OBz)$	H	60
9	NBn	C(O)Et	64

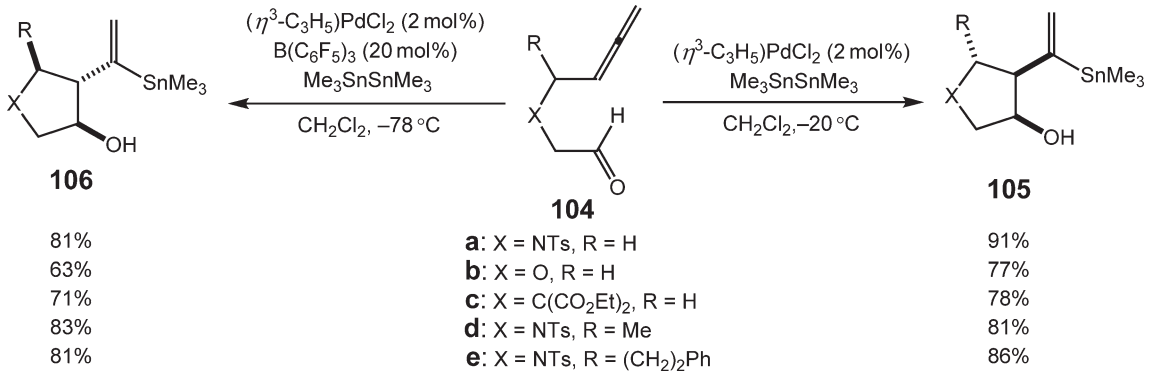
noteworthy that the presence of phosphine ligands led to a significant decrease in the efficiency of the transformation. Palladium-catalyzed diyne cyclization/hydrostannylation was compatible with protected and unprotected alcohols, acetals, sulfides, and sulfones, and the protocol tolerated limited substitution on the alkyne carbon atom (Table 10, entries 2–8). Enynes also underwent reaction, although this transformation was less general than was the cyclization/hydrostannylation of diynes.[66] In one example, slow addition of tributylstannane to a solution of diethyl allylpropargylmalonate and a catalytic amount of palladium acetate gave stannylated alkylidene cyclopentane **103** in 67% yield (Equation (67)).



(67)

Yu and co-workers have developed a pair of complementary palladium-catalyzed protocols for the stannylative cyclization of allenals to form functionalized five-membered alcohols that possess either *cis*- or *trans*-stereochemistry about the newly formed C–C bond.[67] In one procedure, reaction of allenal **104a** with hexamethyldistannane and a catalytic amount of $(\eta^3\text{-}C_3H_5)PdCl_2$ in dichloromethane at −20 °C for 30 min gave the pyrrolidine derivative **105a** in 91% yield with exclusive formation of the *cis*-diastereomer (Scheme 25). The protocol was also amenable to the synthesis of functionalized tetrahydrofuran and cyclopentane derivatives **105b** and **105c** (Scheme 25). It was noteworthy that the reaction of allenals which possessed a single substituent α- to the allene moiety such as **104d** and **104e** gave heterocycles **105d** and **105e**, respectively, with exclusive formation of the *cis*,*trans*-diastereomer (Scheme 25).

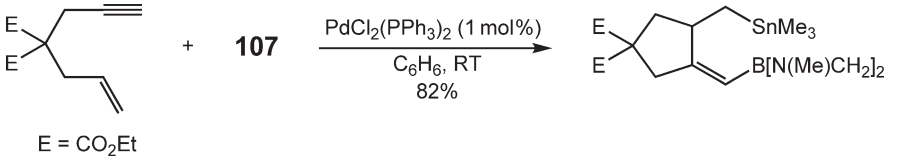
In the complementary protocol, reaction of **104a** with hexamethyldistannane catalyzed by a 1 : 10 mixture of $(\eta^3\text{-}C_3H_5)PdCl_2$ and $B(C_6F_5)_3$ in dichloromethane at −78 °C for 20 min, followed by aqueous workup, gave the corresponding pyrrolidine derivative **106a** in 81% yield with exclusive formation of the *trans*-diastereomer (Scheme 25).[67] The $Pd^{II}/B(C_6F_5)_3$-catalyzed stannylative cyclization of allenals was also effective for the synthesis of functionalized tetrahydrofuran and cyclopentane derivatives **106b** and **106c** (Scheme 25). The reaction of allenals that possessed a single substituent α- to the allene moiety such as **104d** and **104e** gave heterocycles **106d** and **106e**, respectively, with exclusive formation of the *trans*,*trans*-diastereomer (Scheme 25). The mechanisms of both the Pd and $Pd/B(C_6F_5)_3$-catalyzed stannylative cyclization of allenals have not been elucidated.



Scheme 25

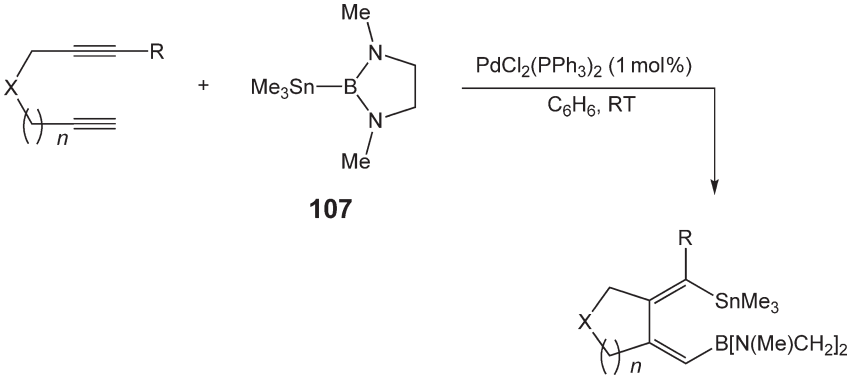
11.11.9.2 Additional Processes Involving Tin, Boron, and Germanium

Tanaka has reported the palladium-catalyzed cyclization/borylstannylation of diynes that form bis(functionalized) dialkylidene cyclopentanes.[68] Reaction of 1,6-heptadiyne with **107** catalyzed by $PdCl_2(PPh_3)_2$ in benzene at room temperature for 1 h gave the corresponding bis(functionalized) dialkylidene cyclopentane in 79% yield (Table 11, entry 1). The protocol was also effective for the synthesis of dialkylidene cyclobutanes, dialkylidene cyclohexanes, as well as oxygen and nitrogen heterocycles (Table 11, entries 2–5). Diynes that possessed an internal alkyne underwent cyclization/borylstannylation in good yield with exclusive delivery of the boryl group to the less-substituted C≡C bond (Table 11, entry 6). Likewise, the Pd-catalyzed reaction of diethyl allylpropargylmalonate with **107** formed the corresponding bis(functionalized) alkylidene cyclopentane with exclusive delivery of the boryl group to the C≡C bond of the enyne (Equation (68)).



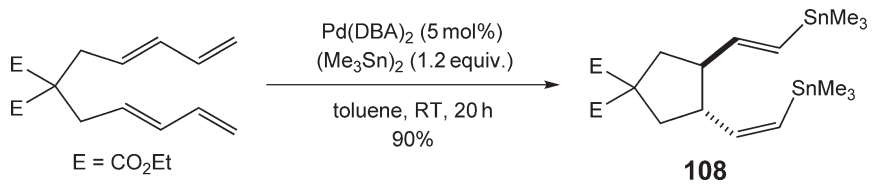
(68)

Table 11 Pd-catalyzed borylstannylation of diynes



Entry	*X*	*n*	*R*	*Yield* (%)
1	CH_2	1	H	79
2	CH_2	0	H	64
3	CH_2	2	H	74
4	O	1	H	83
5	NTs	1	H	82
6	$C(CO_2Et)_2$	1	Et	86

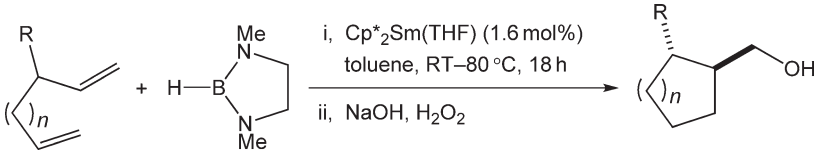
Tsuji has reported the cyclization/distannylation of bis(1,3-dienes) that form bis(functionalized) 1,2-dialkenylcycloalkanes, although the scope of the transformation was quite limited.[58] In one example, reaction of (*E*,*E*)-6,6-bis(ethoxycarbonyl)-1,3,8,10-undecatetraene and hexamethyldistannane (1.2 equiv.) catalyzed by $Pd(DBA)_2$ in toluene at room temperature for 20 h gave *trans*-(*E*,*Z*)-1,2-bis-[2-(trimethylstannyl)vinyl]cyclopentane [*trans*-(*E*,*Z*)-**108**] in 90% yield as a single regioisomer and diastereomer (Equation (69)).



(69)

Widenhoefer has developed a palladium-catalyzed procedure for the cyclization/hydrogermylation of functionalized 1,6-dienes to form functionalized cyclopentanes.[69] For example, reaction of dimethyl diallylmalonate and triethylgermane (1.2 equiv.) catalyzed by a 1 : 1 mixture of **36b** and $NaBAr_4$ (5 mol%) in DCE at 80 °C gave **109** in 77% yield with exclusive formation of the *trans*-diastereomer (Table 12, entry 1). Palladium-catalyzed cyclization/hydrogermylation tolerated a number of functional groups including benzyl and methyl ethers as well as benzyl and pivaloyl esters (Table 12, entries 2–4). The protocol tolerated substitution at one of the two allylic carbon atoms with exclusive delivery of the germyl group to the less hindered C═C bond (Table 12, entries 5 and 6). Conversely, the protocol failed to tolerate substitution on the alkenyl carbon atoms and was restricted to the formation of cyclopentanes.

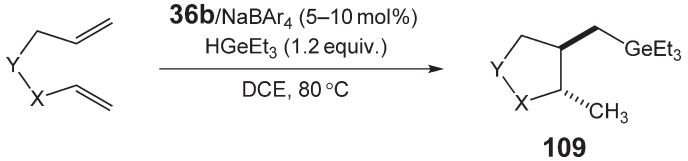
Guided by Marks's report of the samarium-catalyzed hydroboration of alkenes,[70] Molander has developed a samarium-catalyzed protocol for the cyclization/hydroboration of unfunctionalized 1,6-dienes.[71] In an optimized procedure, reaction of 1,5-hexadiene and 1,3-dimethyl-1,3-diaza-2-boracyclopentane catalyzed by $Cp^*_2Sm(THF)$ in toluene at room temperature for 18 h followed by oxidation gave hydroxymethylcyclopentane in 86% yield (Equation (70); R = H, *n* = 0). The transformation was stereoselective, and Sm-catalyzed cyclization/hydroboration of 2-phenyl-1,5-hexadiene followed by oxidation formed *trans*-1-hydroxymethyl-2-phenylcyclopentane in 64% yield (Equation (70); R = Ph, *n* = 0). The samarium-catalyzed reactions was also applicable to the synthesis of hydroxymethylcyclohexanes (Equation (70), *n* = 1) but tolerated neither polar functionality nor substitution on the alkenyl carbon atoms.



R	*n*	*Yield* (%)
H	0	86
Ph	0	64
H	1	55
Ph	1	52

(70)

Table 12 Pd-catalyzed cyclization/hydrogermylation of dienes



Entry	*X*	*Y*	*Yield* (%)
1	CH_2	$C(CO_2Me)_2$	77
2	CH_2	$C(CO_2Bn)_2$	77
3	CH_2	$C(CH_2OMe)_2$	84
4	CH_2	$C(CH_2OPiv)_2$	73
5	CHMe	$C(CO_2Et)_2$	69 (1 : 1)
6	CMe_2	$C(CO_2Et)_2$	62

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11.12 Carbonylative Cross-coupling and Carbocyclization

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11.12.1 Carbonylative Cross-coupling

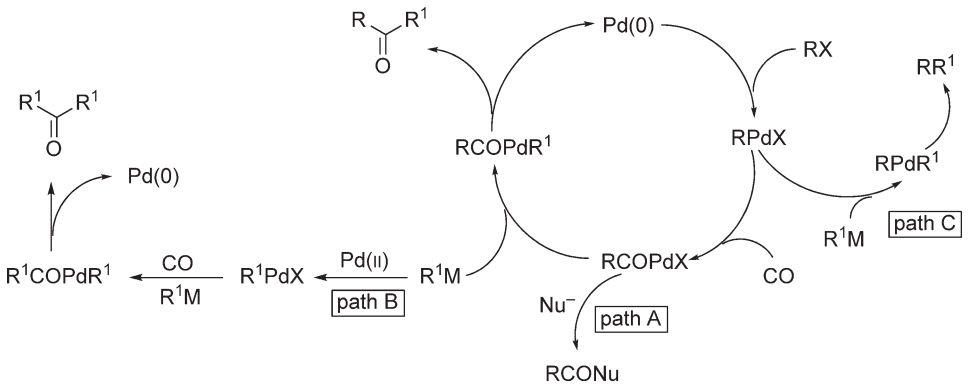
Three-component reactions between organic electrophile (halide, ester, etc.), carbon monooxide, and organic nucleophile (organometallic compound) (Equation (1)) catalyzed by transition metal complexes afford a powerful method for the synthesis of various ketones. The pioneering works in this area appeared in the early 1980s.[1–3]

$$\mathrm{RX + CO + R^1M \xrightarrow{Pd(0)} RCOR^1} \quad (1)$$

R = Ar, heteroaryl, alkenyl, alkynyl
X = I, Br, OTf, N_2^+

The catalytic cycle involves the oxidative addition of RX to Pd(0), coordination and migratory insertion of CO leading to σ-acylpalladium complexes, transmetallation of the latter by organometallic compounds, followed by reductive elimination (Scheme 1).

Three competitive pathways may interfere with carbonylative cross-coupling—the cleavage of acylpalladium complex RCOPdX by nucleophiles to yield carboxylic acids or their derivatives (path A), carbonylative homo-coupling of organometallic compound to yield symmetrical ketones (path B), and non-carbonylative cross-coupling (path C). The formation of symmetrical ketones requires Pd(II), and is not a catalytic process in the absence of external oxidant.[4] Therefore, this process rarely presents real problems, while the other two (paths A and C) are both truly catalytic and often compete dramatically with carbonylative cross-coupling reaction. This competition is the main reason why carbonylative cross-coupling, which seemingly is a very powerful method of ketone synthesis, is not usually regarded as a viable tool in complex synthetic tasks. The organometallic compounds (Hg, Sn, B, Al, etc.), useful in this reaction, should not be too reactive to suppress competitive cross-coupling leading to $R–R^1$ products. Several smaller tricks may in some cases help carbonylative cross-coupling winning the competition. Thus, it has been noted that not only oxidative addition, but also the migratory insertion of CO is facilitated if X = I. The latter accounts for strong positive effect of added alkali metal or tetraalkylammonium iodides on the yields of reactions involving aryl bromides or triflates:[5] The literature before 1994 has been discussed in COMC (1995), and here receives only a brief mention for the sake of comprehensiveness.

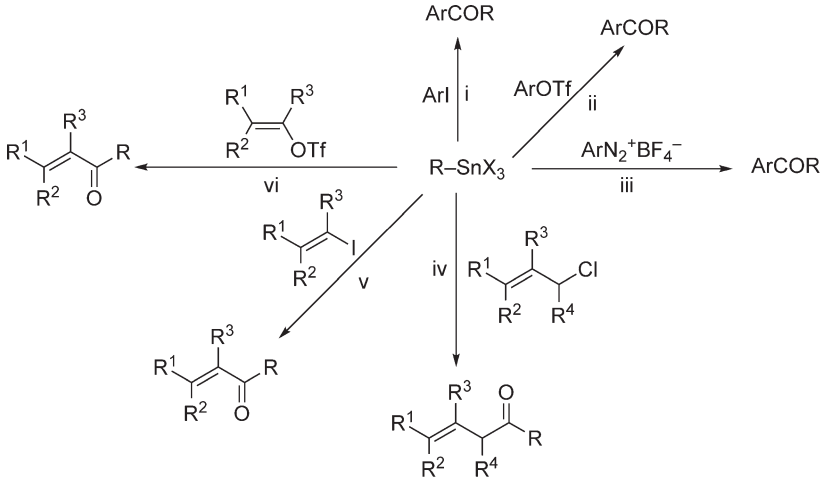


Scheme 1

11.12.1.1 Organotin Compounds

Carbonylative cross-coupling has been first realized using organotins,[1] which so far remain the most useful reagents for this method. The method was first introduced by Tanaka as cross-coupling of iodoarenes with tetraalkylstannane requiring $PhPdI(PPh_3)_2$ catalyst at 120 °C and elevated CO pressure; the method has been further elaborated into general approach to unsymmetrical ketones. This method has been fully elaborated before 1994. Major achievements are enumerated in Scheme 2.

Carbonylative cross-coupling of aryl iodides and aryltrimethylstannane can be performed under mild conditions (1 atm CO, RT) in highly polar solvent hexamethylphosphorus triamide (HMPA).[6] Carbonylative cross-coupling of aryl iodides and alkenylstannanes can be performed under elevated CO pressure in the presence of $PdCl_2(PPh_3)_2$.[7] Aryl triflates are useful if $PdCl_2$(dppf) (dppf = 1,1-bis-(diphenylphosphino)ferrocene) is used as catalyst, and reaction is run in the presence of LiCl. This method is applicable to a wide range of stannanes including alkyl, aryl, alkenyl, and alkynyl groups, and tolerates various functional groups.[8] Arenediazonium salts are useful in carbonylative cross-coupling with alkyl- or arylstannanes in a phosphine-free catalytic system (9 atm CO, $Pd(OAc)_2$, MeCN, RT).[9,10]

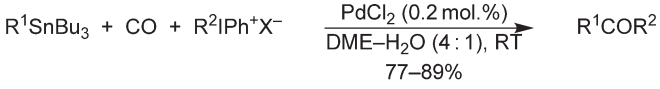


i, CO (1 atm), (η^3-$C_3H_5PdCl)_2$, HMPA, RT (R = aryl);
ii, CO (1 atm), $PdCl_2$(dppf), LiCl, DMF, 70–110 °C (R = alkyl, aryl, alkenyl, alkynyl);
iii, CO (9 atm), $Pd(OAc)_2$, MeCN–ether (R = Me, Et, Ph);
iv, CO (3–4 atm), $Pd_2(dba)_3$, PPh_3, THF, 50 °C (R = allyl, Ph, 3-furyl, etc.);
v, CO (3 atm), $BnPdCl(PPh_3)_2$, THF, 50 °C (R = alkenyl);
vi, CO (1 atm), $Pd(PPh_3)_4$, LiCl, THF, 55 °C (R = alkenyl), the same + $ZnCl_2$ (R = alkyl, aryl)

Scheme 2

Alkyl halides possessing β-hydrogens are usually poor substrates for carbonylative cross-coupling due to competitive β-hydride elimination.[11] Allyl chlorides can be used in carbonylative cross-coupling with allylstannanes,[12] phenyl-, 3-furyl,[13] or vinylstannanes[14,15] to afford allylketones in modest to good yields. Divinylketones can be accessed through the reaction of vinylstannanes with vinyl iodides[16] or vinyl triflates,[17,18] with the latter requiring the addition of LiCl. Synthetic potential of this method has been proved in the formation of macrocyclic ketone jatrophone.[19] In the reaction of vinyl triflates with tetramethyltin or aryltrimethylstannanes the additional activation by $ZnCl_2$ is required.[17]

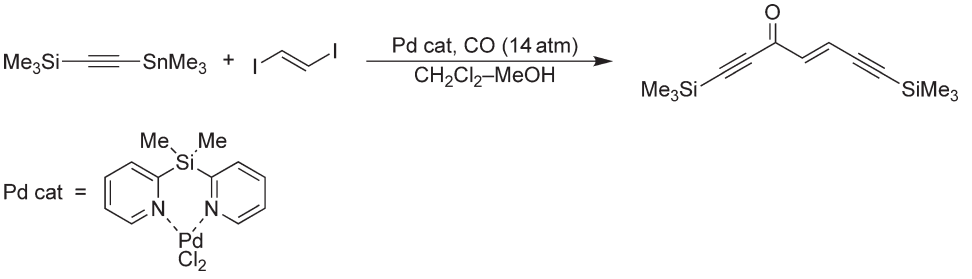
Several important improvements of this methodology have been reported since 1994. A broad range of organotins were used in the reactions with aryl-, heteroaryl-, or alkenyliodonium salts in aqueous organic solvents. This reaction (Equation (2)) takes place at room temperature in the presence of phosphine-free palladium catalysts.[20]



(2)

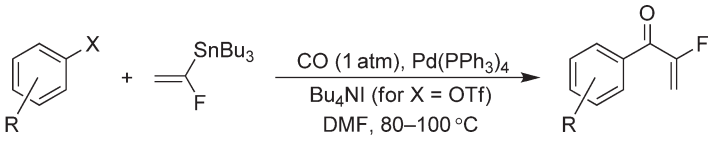
R^1 = Ph, 2-thienyl, 2-furyl, $CH{=}CH_2$, $PhC{\equiv}C$
R^2 = Ph, *p*-$MeOC_6H_4$, 2-thienyl, *trans*-PhCH=CH

A unique example of selective combination of cross-coupling and carbonylative cross-coupling in the presence of chelated Pd complex was described (Equation (3)).[21]



(3)

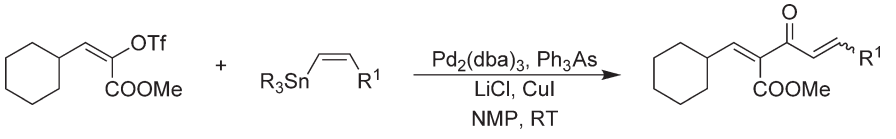
Carbonylative cross-coupling of iodoarenes and aryl triflates with *gem*-fluorovinyltributylstannane takes place smoothly in a standard system, with triflate substrates requiring the addition of tetrabutylammonium iodide (Equation (4)).[22]



(4)

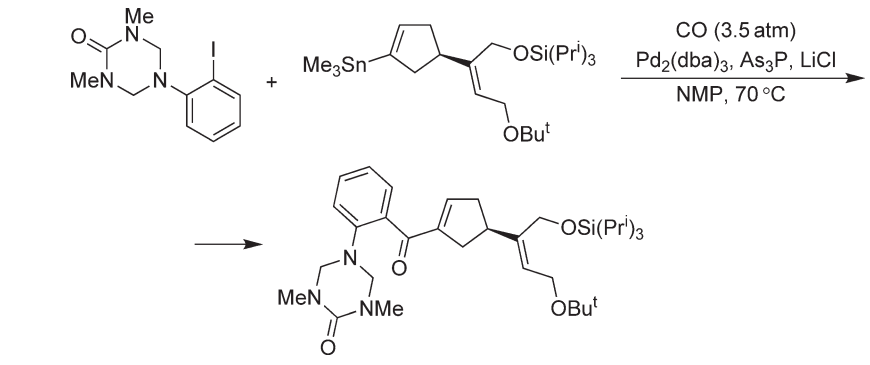
X = I, OTf
R = *p*-Ac, COOEt, NO_2, MeO, $MeOCH_2$, *m*-MeO, *o*-COOMe, Et, Cl, etc.

The addition of LiCl and CuI, and triphenylarsine as ligand are required to suppress side-reactions in the carbonylative cross-coupling of geminally substituted alkenyl triflate in the synthesis of sarcodictyin. Stereochemical configuration of the double bond of organotin compound was completely lost in this reaction (Equation (5)).[23,24]

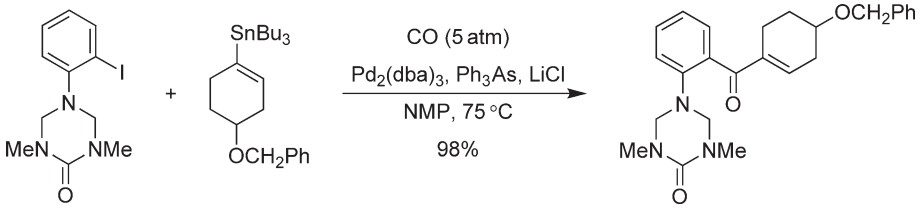


(5)

The application of triphenylarsine ligand and LiCl as promoter allows for realization of carbonylative cross-coupling in complex synthetic tasks, as shown, for example, in Equations (6)[25] and (7).[26,27]

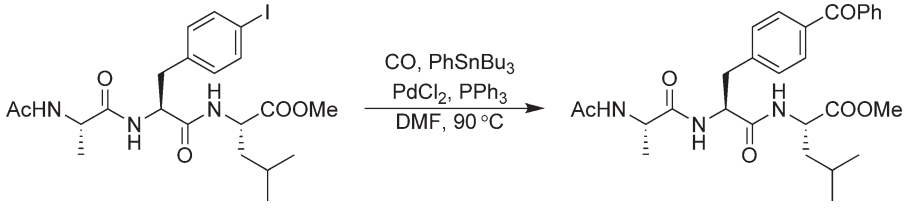


(6)



(7)

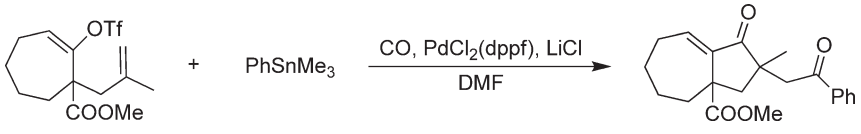
Introduction of acyl groups into protected amino acids or even short peptides can be effected through *p*-iodophenylalanine residues (Equation (8)), though triflate of tyrosine failed in this protocol.[28]



(8)

Carbonylative Stille reaction has been successfully used for the preparation of radiolabeled ketones using [^{11}C]CO as label source. Because of fast radioactive decay of ^{11}C the reactions should be fast and reliable. Among the methods reported are catalytic systems based on $Pd(PPh_3)_4$ in dry dimethyl sulfoxide (DMSO) at 100 °C for 10 min,[29] and $Pd(AsPh_3)_4$ in *N*-methylpyrrolidone (NMP) at 130 °C for 5 min.[30] The latter system is the most versatile, allowing to prepare labeled ketones from aryl iodides or enone triflates and aryl-, alkyl-, and alkenylstannanes in good radiochemical yields.[30] On the other hand, a phosphine-free system with $PdCl_2$ as a catalyst in aqueous 1,2-dimethoxyethane (DME) allows for effective carbonylative cross-coupling of either aryl iodides[31] or diaryliodonium salts[32] with arylstannanes within the reaction of 1 min time at room temperature.

The organotin compounds were used in the termination of cascade processes, as shown, for example, in Equation (9).[33]

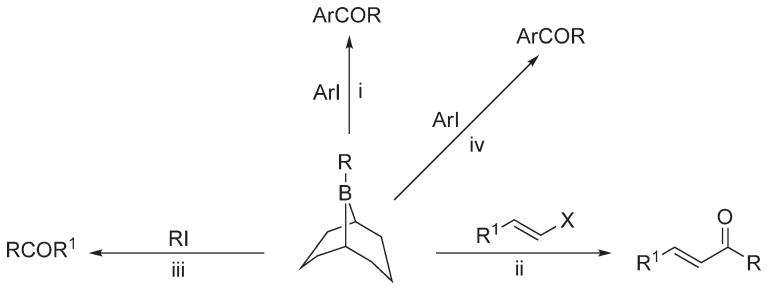


(9)

11.12.1.2 Organoboron Compounds

Transfer of alkyl groups from the readily available 9-alkyl-BBN derivatives or simple trialkylboranes was the subject of earlier studies (Scheme 3) (where BBN = borabicyclo[3.3.1]nonane). Aryl iodides,[34] benzyl bromide,[34] alkenyl iodides or bromides,[35] or alkyl iodides[36] can be used as coupling partners. Various promoting factors, such as special Lewis acids or irradiation, are required in these protocols to achieve good yields of ketones. *tert*-Butyl isocyanide can be used as synthic equivalent of CO in carbonylative cross-coupling of aryl iodides with 9-alkyl-BBN derivatives.[37]

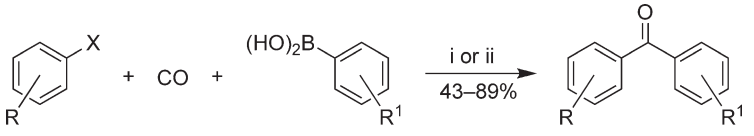
Aryl iodides and arylboronic acids have been shown to give diaryl ketones under 1 atm CO in the presence of $PdCl_2(PPh_3)_2$ and K_2CO_3 in anisole at 80 °C.[38] The scope of method has been extended to include aryl bromides,



i, CO (1 atm), $PdCl_2(PPh_3)_2$, $Zn(acac)_2$, THF–HMPA, 50–55 °C;
ii, CO (1–3 atm), $Pd(PPh_3)_4$, K_3PO_4, benzene, RT;
iii, CO (1–3 atm), $Pd(PPh_3)_4$, K_3PO_4, *hν*, benzene, RT;
iv, (a) *t*-BuNC, $Pd(PPh_3)_4$, K_3PO_4, dioxane, 50 °C (b) H_3O^+

Scheme 3

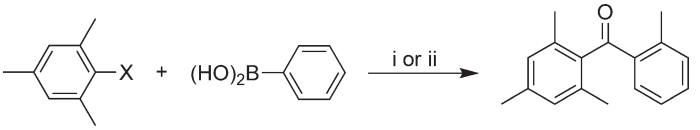
iodides, and triflates. For less reactive aryl bromides and triflates, $PdCl_2$(dppf) complex and the addition of alkali metal iodides were required to achieve high yields and suppress competitive cross-coupling reaction (Equation (10)).[5]



(10)

i, (X = I) $PdCl_2(PPh_3)_2$, K_2CO_3, anisole, 80 °C, 5–24 h;
ii, (X = Br, OTf) $PdCl_2$(dppf), K_2CO_3, MI, anisole, 80 °C, 5–24 h;
R^1 = H, *p*-F, *p*-Br, *p*-Me, *p*-OMe, *o*-Me, 2,4,6-Me_3, etc.;
R = H, *p*-CN, *p*-CHO, *p*-COOMe, *p*-NMe_2, *o*-Me, 2,4,6-Me_3, etc.

Sterically hindered reagents give good yields only if electrophilic coupling partner is aryl iodide (Equation (11)).[5]

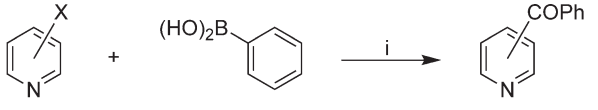


X = I (method i) 63%
X = Br (method ii) traces

(11)

i, (X = I) $PdCl_2(PPh_3)_2$, K_2CO_3, anisole, 80 °C, 5–24 h
ii, (X = Br, OTf) $PdCl_2$(dppf), K_2CO_3, MI, anisole, 80 °C, 5–24 h

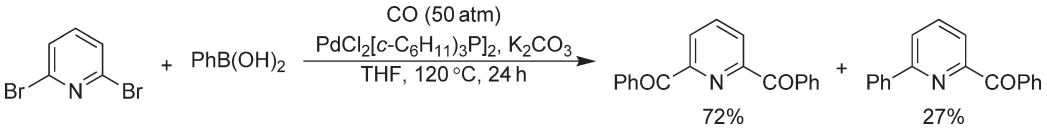
Carbonylative cross-coupling of halopyridines with arylboronic acids suffers from competitive non-carbonylative cross-coupling. Higher selectivity can be achieved under elevated pressures of CO using either $PdCl_2(Ph_3P)_2$ or $PdCl_2[(c\text{-}C_6H_{11})_3P]_2$ catalysts (Equation (12)).[39,40]



(12)

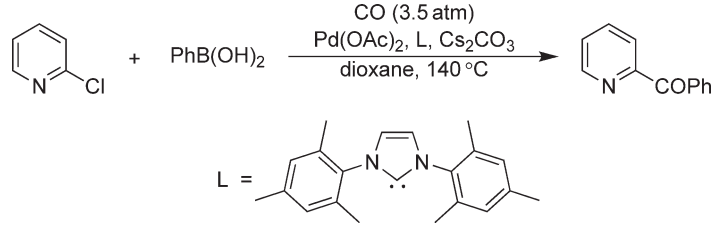
X = 2-, 3-, or 4-I, Br, Cl
i, CO (5–50 atm), $PdCl_2(Ph_3P)_2$ or $PdCl_2[c\text{-}C_6H_{11})_3P]_2$, K_2CO_3, THF, 80–150 °C

The reactions of 2,6-, 3,5-, and 2,5-dibromopyridines were optimized to afford good yields of the respective diketones using $PdCl_2[(c\text{-}C_6H_{11})_3P]_2$ catalyst and 50 atm CO,[40] as shown, for example, in equation (13).



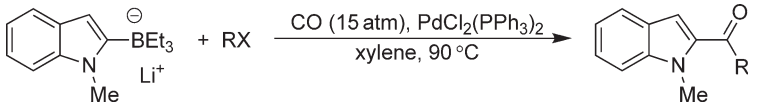
(13)

Under these conditions chloropyridines could not be made to give high yields of ketones.[40] However, good yields of benzoylpyridines can be obtained using bulky heterocyclic carbene ligands (Equation (14)).[41]



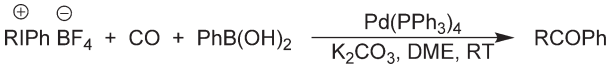
(14)

Lithium triethyl(1-methylindolyl-2)borate has been introduced as a convenient source of indolyl residue for carbonylative cross-coupling with aryl iodides, alkenyl iodides, or triflates. The reaction requires elevated CO pressure and high loading of catalyst (5 mol.%) (Equation (15)). Aryl and alkenyl bromides, as well as aryl iodides with electron-withdrawing substituents, gave poor yields.[42]



(15)

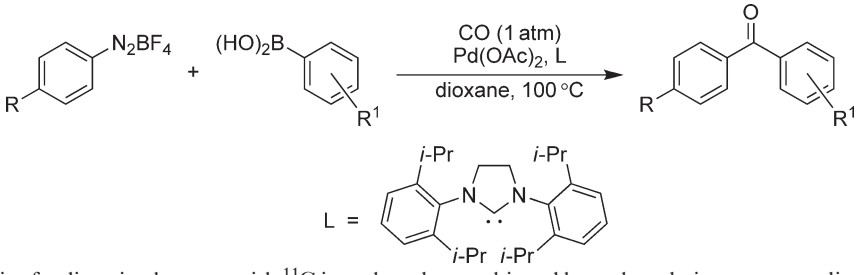
Carbonylative cross-coupling of various iodonium salts bearing transferable aryl, heteroaryl, alkenyl, alkynyl residues with phenylboronic acid takes place under mild conditions giving the respective ketones in high yields (Equation (16)). The yields of competing cross-coupling do not exceed 8%.[43]



(16)

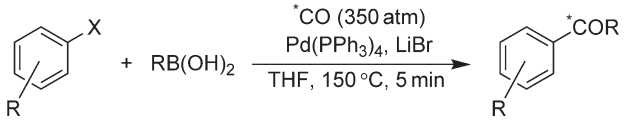
R = Ph (88%), 2-thienyl (82%), β-styryl (87%), 2-phenylethynyl (80%)

Carbonylative cross-coupling of arenediazonium salts with arylboronic or styrylboronic acids was realized using a bulky heterocyclic carbene ligand (Equation (17)).[44]



(17)

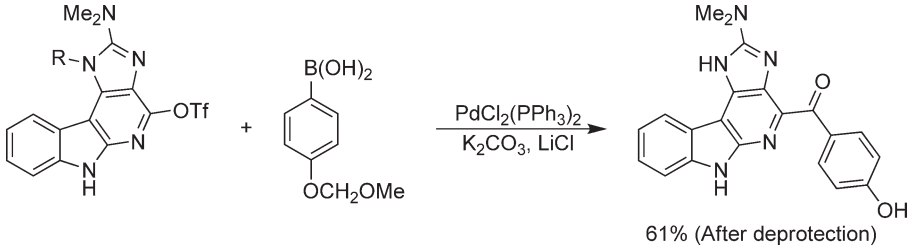
The synthesis of radioactive ketones with ^{11}C in carbonyl was achieved by carbonylative cross-coupling of aryl iodides or triflates with methyl-, phenyl-, or 2-thienylboronic acids under elevated pressure of CO. To ensure fast reaction, harsh conditions were used. Interestingly, under such conditions the addition of a base is not necessary (Equation (18)).[45]



(18)

X = I, OTf

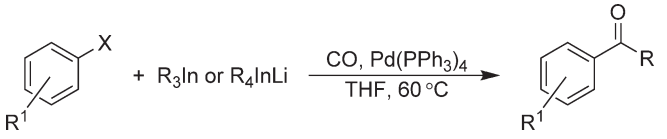
If the reaction is carried out in the presence of solid base (K_2CO_3), a loss of radioactive ketone product takes place due to absorption on the base.[29] The method has been successfully applied in the synthesis of natural compounds, for example, grossularines (Equation (19)).[46]



(19)

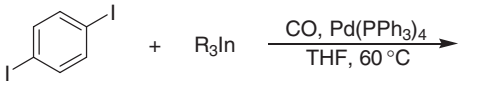
11.12.1.3 Organoindium Compounds

Organoindium compounds R_3In can be used in carbonylative cross-coupling with aryl iodides or triflates, 2-thienyl bromide, alkenyl bromides, iodides, or triflates to transfer all three organic residues. High yields are observed with trialkyl (including secondary alkyls), trialkynyl, and triphenylindiums, while alkenyl, allyl, and propargylindium derivatives give mostly cross-coupling R–R^1 products under 1 atm CO,[47] or slightly elevated pressure (2.5 atm).[48] Similar results can be obtained with tetraorganoindates with all four residues being transferred (Equation (20)).[49]



(20)

Two iodine atoms in diiodobenzene can thus be substituted by acyls (Equation (21)).[47]



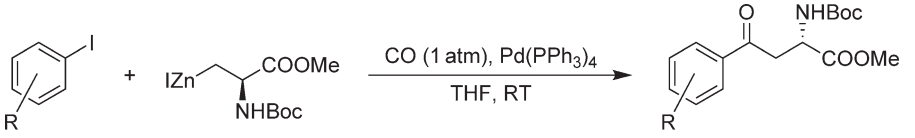
R	*Yield* (%)
Me	68
sec-Bu	54
i-Bu	54
i-Pr	55

(21)

11.12.1.4 Organozinc Compounds

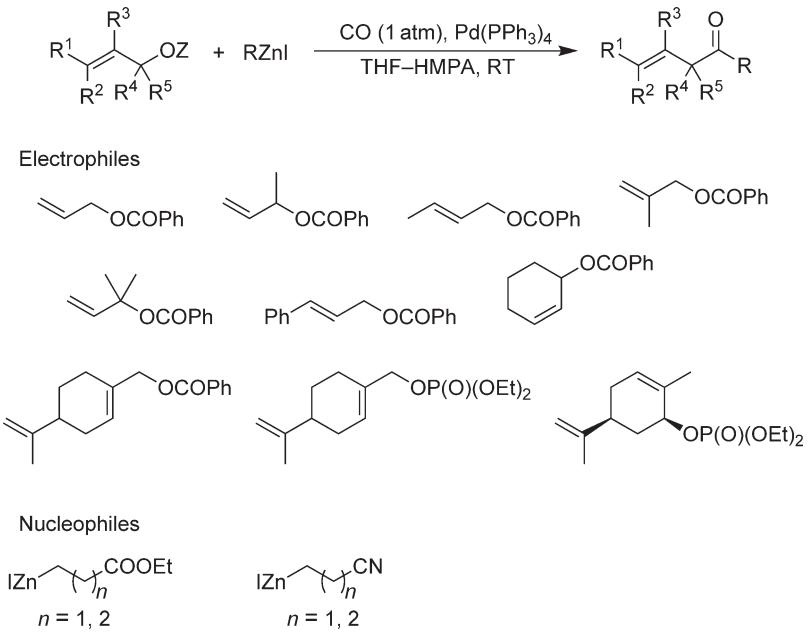
A prototypical study for this section has been obtained as early as in 1983 for carbonylative cross-coupling of the mixture of aryl iodide and alkyl iodide in the presence of Zn metal and palladium catalyst. This system apparently works due to differences of reactivity of aryl versus alkyl iodide toward metallation by Zn.[50] Further studies were rather scarce to involve only preformed functionalized alkylzincs. Carbonylative cross-coupling of functionalized organozinc reagents with allylic esters and CO (1 atm) can be carried out in THF in the presence of HMPA, which suppresses side-reactions (Scheme 4).[51,52]

Similar protocol has been successfully used for the preparation of β-aroylaminoacids (Equation (22)), including protected L-kynurenine. Careful exclusion of air is crucial for the success, as in the presence of oxygen, the formation of symmetrical ketone formed from organozinc reagent competes with carbonylative cross-coupling.[53]



(22)

R = H, *o*-, *m*-, *p*-OMe, Me, NH_2, F, NO_2

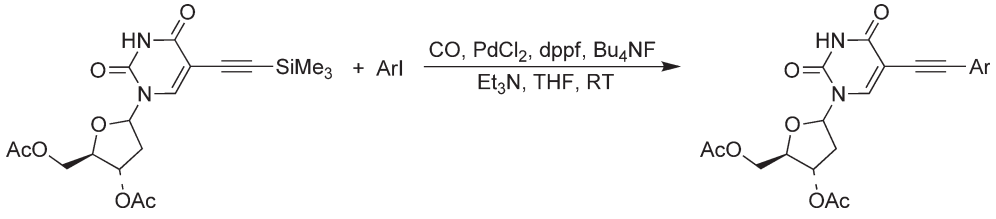


Scheme 4

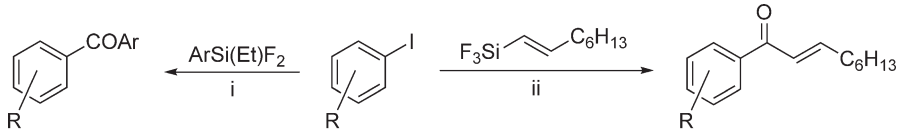
11.12.1.5 Organosilicon Compounds

The application of organosilicon compounds in cross-coupling reactions is a relatively young method in comparison with classical reactions involving organotin, organozinc, or organoboron compounds. It is not surprising therefore that there are only a few papers dealing with carbonylative cross-coupling. Organosilicon compounds are reactive only in the presence of fluorides. Thus, aryl iodides can be reacted with either aryl or alkenylsilanes to give the respective ketones in good yields (Scheme 5).[54,55]

The reaction of trimethylsilylated terminal alkynes with iodoarenes can be performed under 1 atm CO pressure in the presence of dppf complex of palladium, and Bu_4NF at room temperature (Equation (23)).[56] As trimethylsilyl derivatives of terminal acetylenes are known to undergo facile cleavage by fluoride ions, this reaction actually involves not the organosilicon compound, but acetylenide nucleophile. The method has been successfully applied to the modification of uracyl deoxynucleosides.

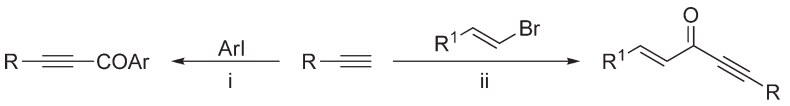


(23)



i, CO (1 atm), (η^3-$C_3H_5PdCl)_2$, KF, *N*,*N*-dimethyl-2-imidazolinedione, 100 °C;
ii, CO (1 atm), (η^3-$C_3H_5PdCl)_2$, TBAF, THF, 50 °C

Scheme 5

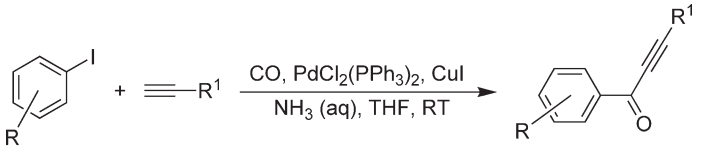


Scheme 6

11.12.1.6 Terminal Acetylenes

Apart from organometallic compounds, terminal acetylenes in the presence of base can also be used as nucleophiles in carbonylative cross-coupling reaction.[57] In earlier studies, aryl iodides and alkenyl bromides were shown to react with terminal acetylenes under elevated CO pressure to yield the respective alkynylketones in high yields (Scheme 6).[58]

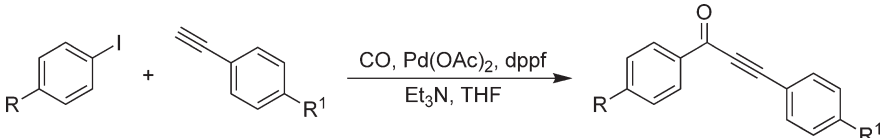
The development of this reaction resulted in more effective and/or milder methods. The use of μ-complex $[(Ph)Pd(Ph_3P)(OH)]_2$ turned out to be advantageous as compared to other pre-catalysts, including phosphine complexes, supported Pd/C, or phosphine-free palladium salts. The reactions are run in Et_3N solution under 17 atm CO at 90 °C with various aryl and alkylacetylenes and iodoarenes to give good to high yields of arylacetylenylketones.[59] Later protocols do not require elevated CO pressures. Thus, aqueous ammonia was reported to promote carbonylative cross-coupling of iodoarenes with aryl or alkylacetylenes. With the latter, the addition of CuI helped to improve yields (Equation (24)).[60]



(24)

R = *p*-OMe, Me, COMe, Cl, *o*-NH_2
R^1 = *n*-C_6H_{13}, Bu^t, CH_2CH_2OH, $CH_2CH_2CH_2OH$

A series of unsymmetrical ketones was obtained from terminal acetylenes and iodoarenes using dppf as ligand (Equation (25)).[61]



(25)

R,R^1 = H, Me, Cl, F, OMe, NO_2

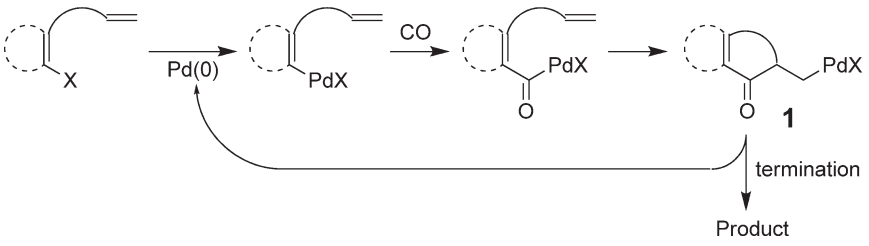
Besides, iodoarenes aryliodonium salts were used as electrophilic coupling partners in the synthesis of ynones. The carbonylative cross-coupling can be run in aqueous DME in the presence of $Pd(OAc)_2$ and CuI as co-catalyst and $NaHCO_3$ as a base at 30 °C.[62]

11.12.2 Carbonylative Carbocyclization

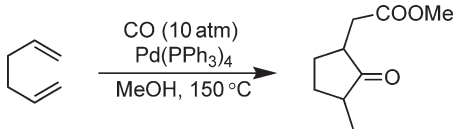
11.12.2.1 Reactions Initiated by Oxidative Addition of C–X Bonds

Acylpalladium intermediates can be involved in intramolecular processes leading to the formation of carbo- or heterocycles. In this chapter we discuss the cyclizations via the attack of acylpalladium intemediates at carbon centers and formation of new C–C bonds. The basic scheme (Scheme 7) of such processes includes the oxidative addition of Pd(0) to C(sp^2)–X bonds (X = halogen or triflate), migratory insertion of CO, and subsequent intramolecular addition of acylpalladium intermediate to double or triple bonds to yield cyclic ketones.

The prototype of this sequence has been discovered by Brewis and Hughes as early as in 1965 in the carbonylation of 1,5-diene (Equation (26)),[63,64] though in this case the process is initiated not by oxidative addition of Pd(0) to C–X bond, but by the addition of hydridopalladium complex to double bond.[65]



Scheme 7



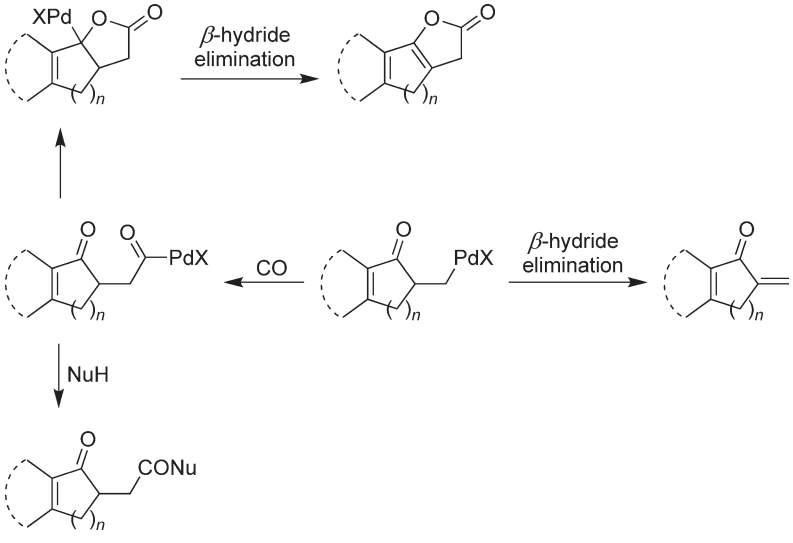
(26)

The detailed investigation of carbonylative cyclization has been performed by Negishi *et al.*, first as a stoichiometric, and then as a catalytic process.[66,67]

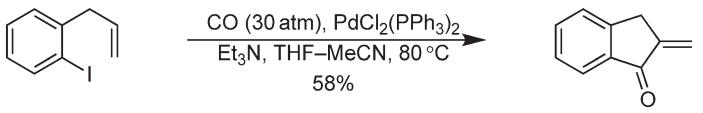
The scope of reaction has been further extended to allylic electrophiles.[68] An extensive investigation of the intramolecular acylpalladation has been performed in a series of *o*-iodoalkenylbenzenes with both terminal and internal double bonds[69] and 1-iodo-substituted 1,4-, 1,5-, or 1,6-dienes.[70]

Termination stages vary depending on substrates and reaction conditions (Scheme 8). Normally, organopalladium intermediates **1** either undergo β-hydride elimination or the second migratory insertion followed by trapping by nucleophile, for example, alcohol used as solvent. The other frequent termination comes from intramolecular attack at carbonyl group (which may be alternatively viewed as acylpalladium cleavage by enolate[71]) leading to lactone ring, often with shifted double bonds.

The transformations of *o*-iodoalkenylbenzenes in the presence of CO and palladium catalysts may involve either carbonylative cylization, or intramolecular Heck reaction, as well as a number of intramolecular pathways leading to oligomeric byproducts. Non-carbonylative pathways can be reasonably suppressed by applying elevated pressures of CO. Under such conditions, the products are formed in good yields, and the predominant termination stage is Pd hydride β-elimination to form *exo*-cyclic double bond (Equation (27)).

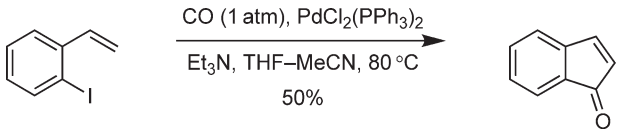


Scheme 8



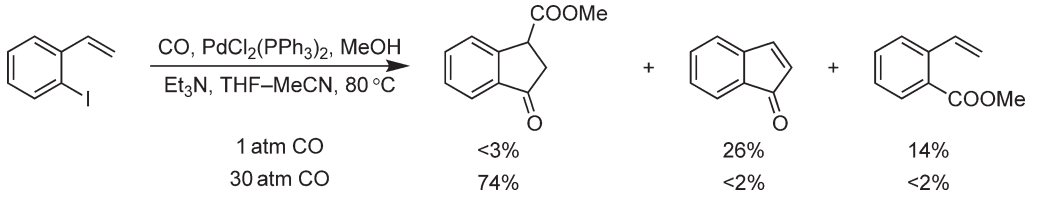
(27)

Five-membered rings are preferentially formed in such cyclizations. Though the *exo*-attack is favored in most cases, *endo*-cyclization takes place instead, particularly, when it would lead to small size rings (Equation (28)).



(28)

In the presence of alcohols, the termination stage changes to nucleophilic cleavage of acylpalladium intermediate. In this case, cyclization competes with premature alkoxycarbonylation (Equation (29)).

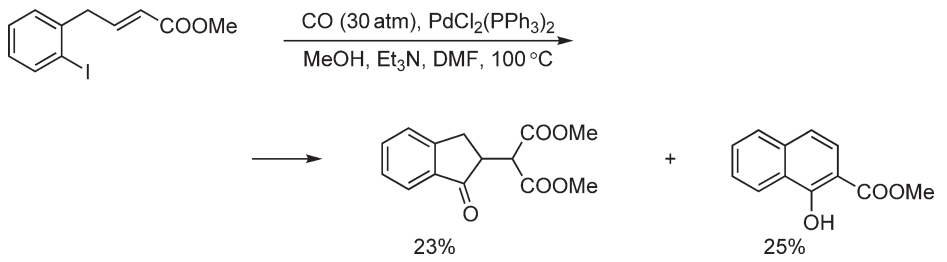


(29)

Six-membered cycles are formed in alcohol-terminated cyclizations in high yields, in contrast to the reaction in the absence of alcohol, as shown, for example, in Scheme 9.[69]

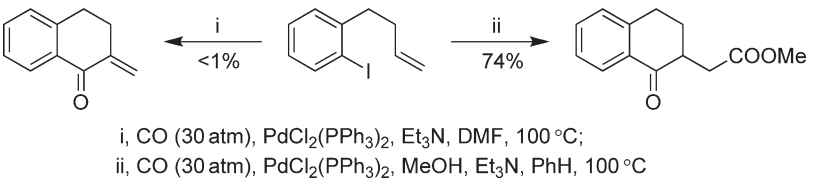
o-Iodoalkenylbenzenes bearing internal double bonds in some cases give better yields, even under less stringent conditions in both modes of carbonylative cyclization reactions. However, in order to obtain the product of nucleophilic cleavage by alcohol in high yields, higher pressures of CO are required (Scheme 10).[69]

However, in the majority of cases, the substrates with substituted double bonds give complex mixtures of products, due to competition of both modes of termination, *exo*- and *endo*-cyclizations, etc. *endo*-Cyclization may be further sophisticated by aromatization of product (Equation (30)).[69]

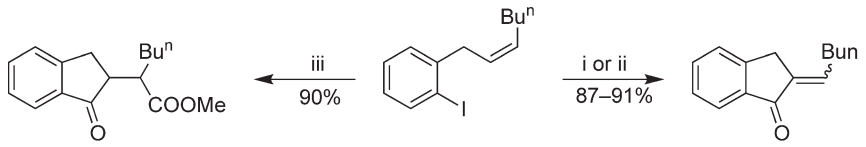


(30)

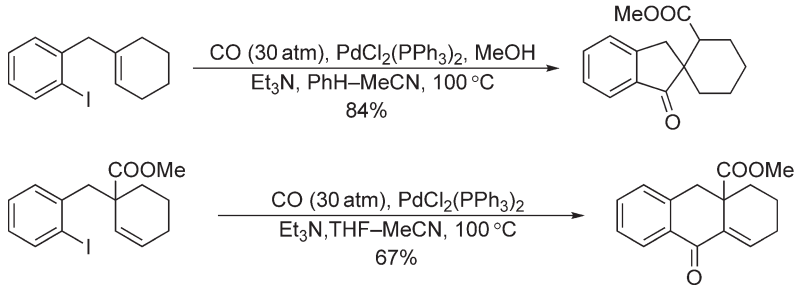
Alkenylsilanes may react via an alternative termination pathway with elimination of silyl group instead of hydride (Equation (31)).



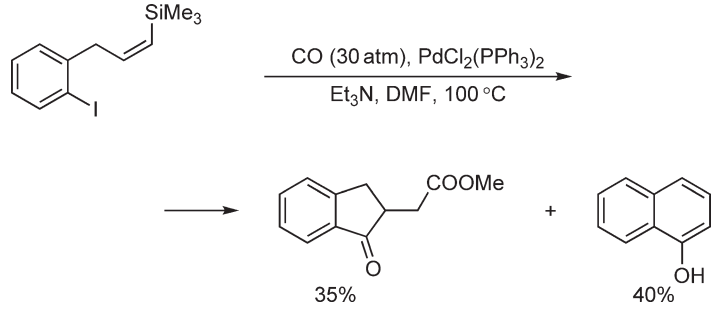
Scheme 9



i, CO (1 atm), $PdCl_2(PPh_3)_2$, Et_3N, DMF, 60 °C; ii, CO (30 atm), $PdCl_2(PPh_3)_2$, Et_3N, DMF, 100 °C; iii, CO (84 atm), $PdCl_2(PPh_3)_2$, MeOH, Et_3N, DMF, 100 °C



Scheme 10



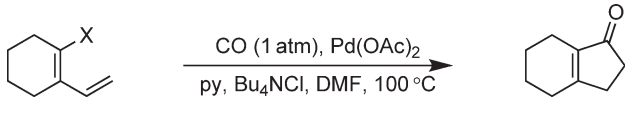
(31)

The transformations of 1-iodo-1,4-dienes and 1,5-dienes are generally similar to the reactions of *o*-iodoalkenylbenzenes. In the absence of external nucleophile, palladium hydride abstraction or intramolecular trapping by enolate take place (Scheme 11).[70]

In the presence of alcohols, nucleophilic cleavage of acylpalladium intermediate becomes the major pathway to give esters (Scheme 12).

An important modification of the initial protocol has been introduced by Larock *et al.* to afford indanones. The saturated ring results from the termination of the process by protonolysis of palladium enolate, which is likely to be generated from reversible palladium hydride elimination–addition. Proton source required for protonolysis hypothetically comes from adventitious water coming with hygroscopic chloride or solvent (Scheme 13).[72]

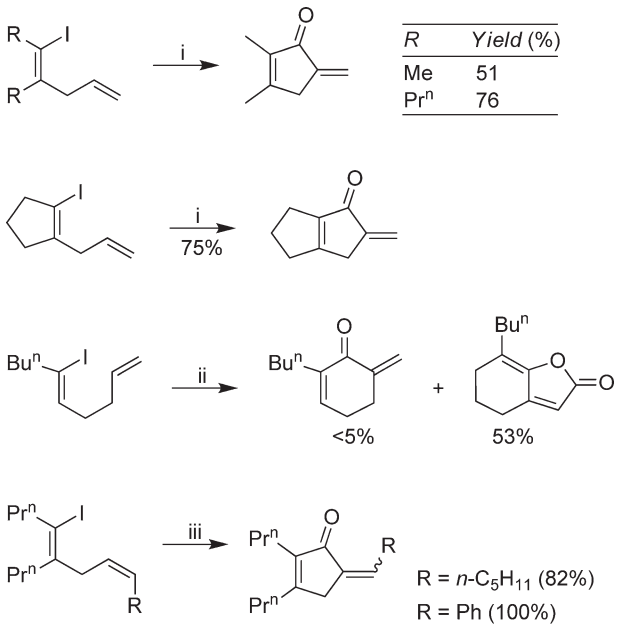
The procedure is also applicable to dienyl iodides, as well as bromides and triflates to afford cyclopentenones in high yields (Equation (32)).[72]



X	*Yield* (%)
I	86
Br	87
OTf	95

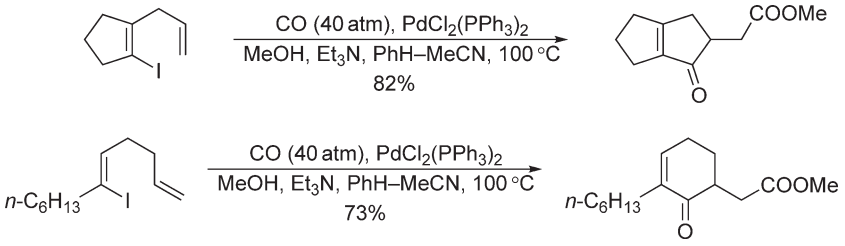
(32)

Further development of this protocol by Larhed *et al.* has led to a procedure useful for *o*-bromo- or *o*-chlorostyrenes, which are made to react using microwave heating and tris-*tert*-butylphosphine (introduced as a salt *t*-Bu_3PHBF_4). Due to instrumental restrictions of microwave setup, CO cannot be used as gas, but $Mo(CO)_6$ has been employed as *in situ* source of CO (Equation (33)).[73] This protocol can be extended to simple substituted styrenes (Equation (34)), which

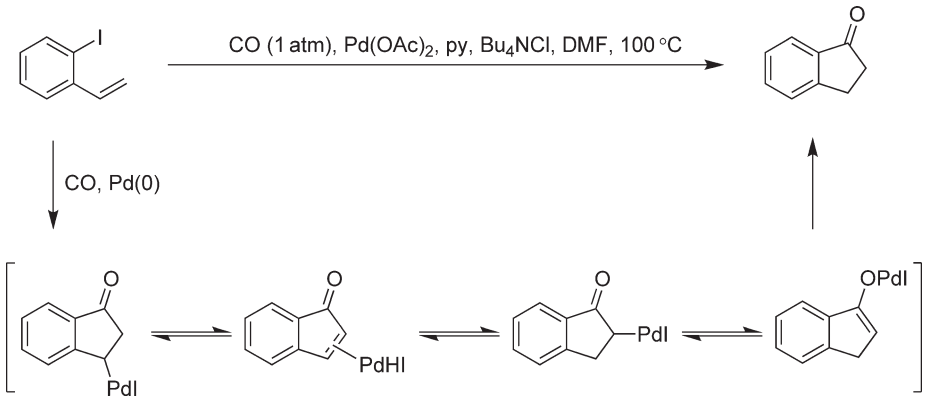


i, CO (1 atm), $Pd(PPh_3)_4$ (10 mol.%), THF, 60 °C, 24 h;
ii, CO (40 atm), $PdCl_2(PPh_3)_2$ (5 mol.%), benzene, 100 °C, 47 h;
iii, CO (40 atm), $PdCl_2(PPh_3)_2$ (5 mol.%), DMF, 100 °C, 12 h

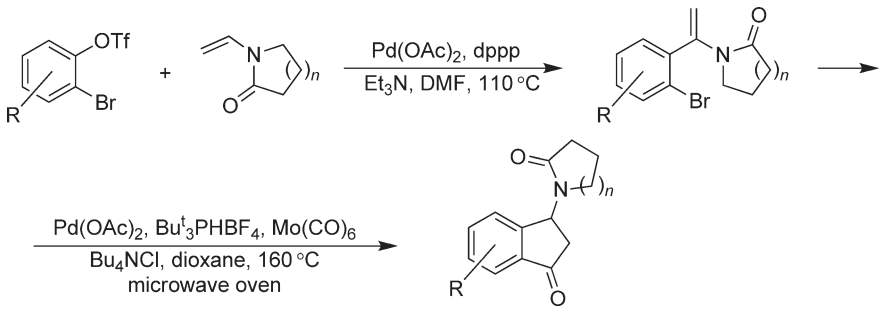
Scheme 11



Scheme 12

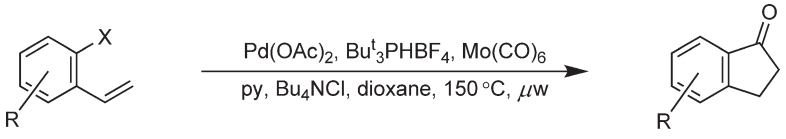


Scheme 13



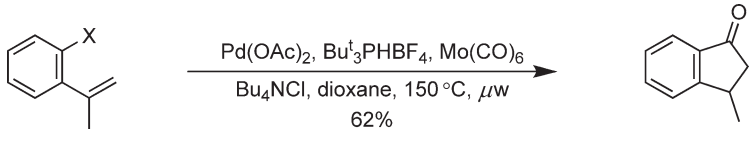
Scheme 14

further enabled an approach to 3-acylaminoindanones through a two-step procedure, using chemoselective substitution of triflate in the Heck reaction followed by carbonylative cyclization of the intermediate (Scheme 14).[73]



(33)

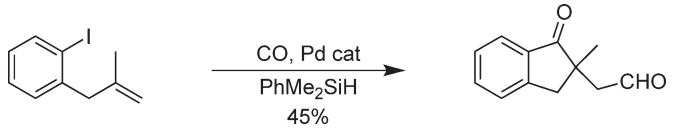
X = Cl (26–51%), Br (59–82%)



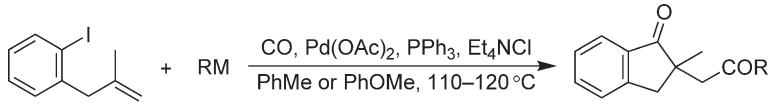
(34)

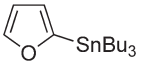
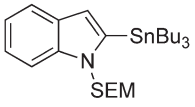
In the presence of appropriate organometallic compounds, the trapping of organopalladium intermediate can be followed by the carbonylative cross-coupling pathway (Scheme 15).[74] The cascade can be applied to the construction of heterocycles (Scheme 16).

Termination by hydride transfer can be achieved using silane to give aldehydes (Equation (35)).[75]

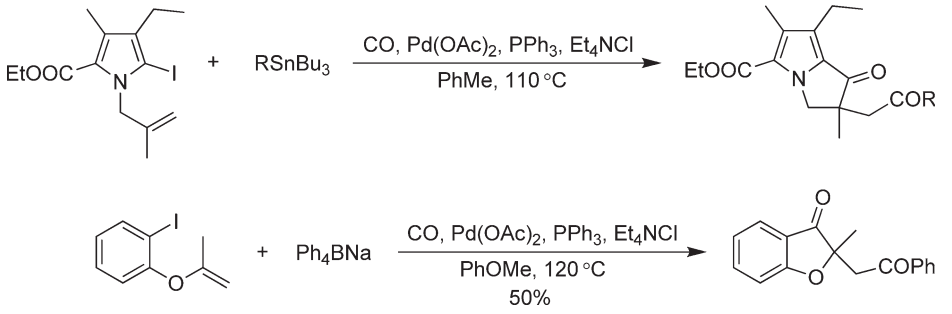


(35)



RM	*Yield* (%)
	76
	58
Ph_4BNa	86

Scheme 15

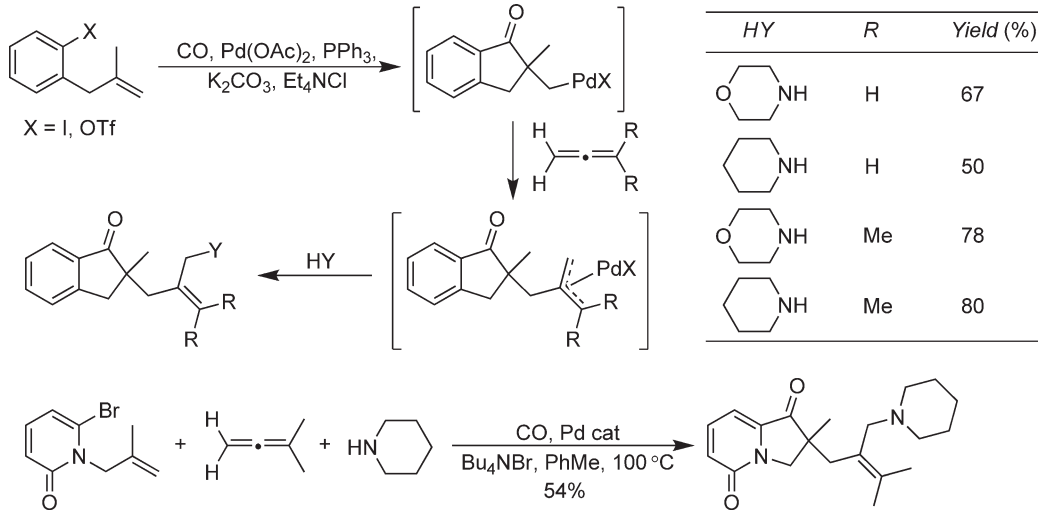


R	*Yield* (%)
Ph	62
2-furyl	68
2-pyridyl	70

Scheme 16

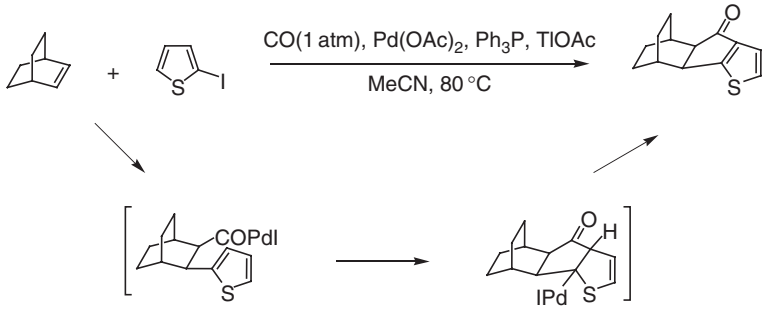
Further development of termination strategies has led to the use of allenes, which trap the organopalladium intermediate to give π-allylic complex. The latter undergoes facile reactions with nucleophiles. The overall process becomes a pentamolecular cascade (Scheme 17).

All these protocols allow us to form a new carbocycle in a bimolecular process. The cyclization involving two different molecules besides CO has been realized, involving carbapalladation of norbornene, migratory insertion of CO, and subsequent intramolecular Heck-like attack at thiophene residue. Thallium acetate is required as electrophilic co-catalyst (Scheme 18).[76]

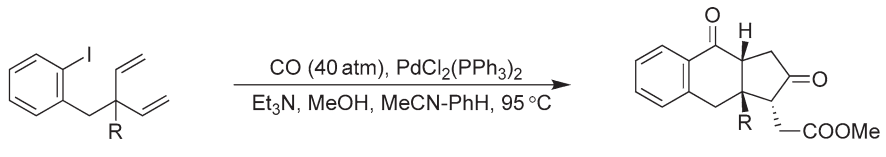


HY	*R*	*Yield* (%)
O, NH	H	67
NH	H	50
O, NH	Me	78
NH	Me	80

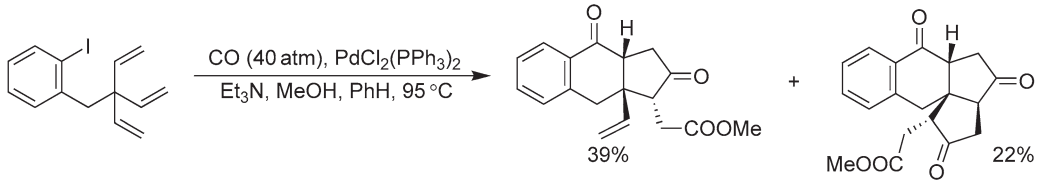
Scheme 17

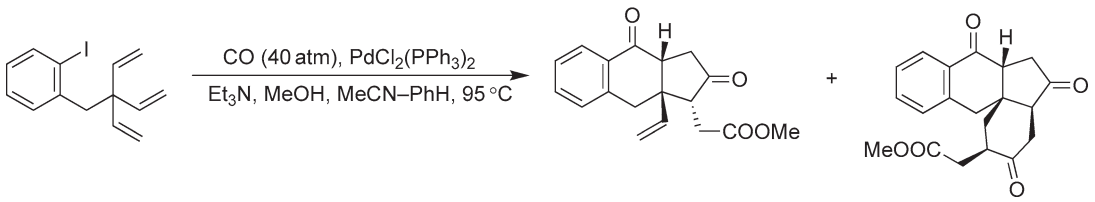


Scheme 18

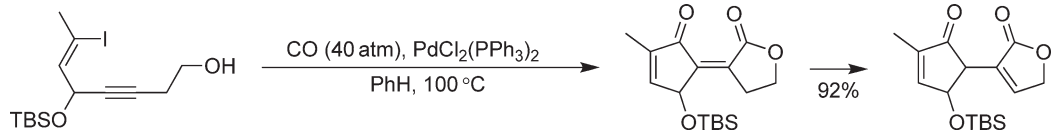


R	*Yield* (%)
Me	70
CH_2OMe	72
$CH_2C{\equiv}CBu^n$	54





Scheme 19



Scheme 20

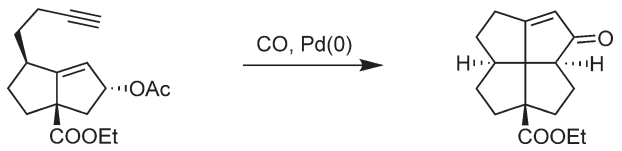
Multiple carbonylative cyclizations can take place with substrates containig several double bonds. Up to three consecutive cyclizations can take place in good overall yields and high diastreoselectivity. All five- and six-membered cycles are formed in *exo*-processes (Scheme 19).[77]

Cyclizations onto triple bonds are rare, and require intramolecular trapping of acylpalladium intermediate (Scheme 20).[78]

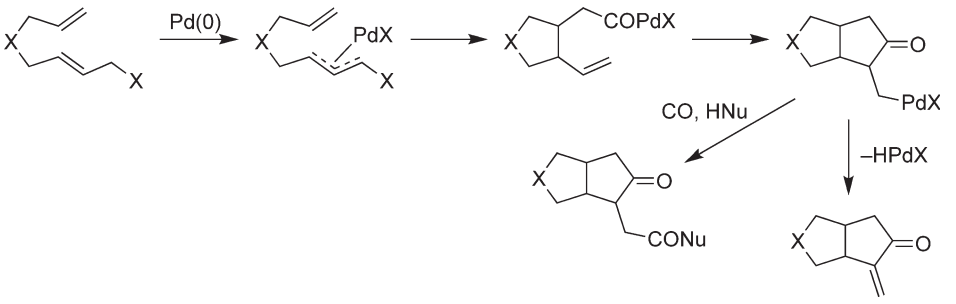
11.12.2.2 Reactions Involving π-Allylic Palladium Complexes

The other strategy requires dienes or enynes containing allylic or propargylic ester fragments. The main pathway in this case involves the formation of allylpalladium intermediates, which perform carbapalladation of double or triple bonds with subsequent acylpalladation forming two cycles, and termination by palladium hydride elimination or other usual trapping pathways (Scheme 21),[79] for example, in the following examples in Scheme 22.[80]

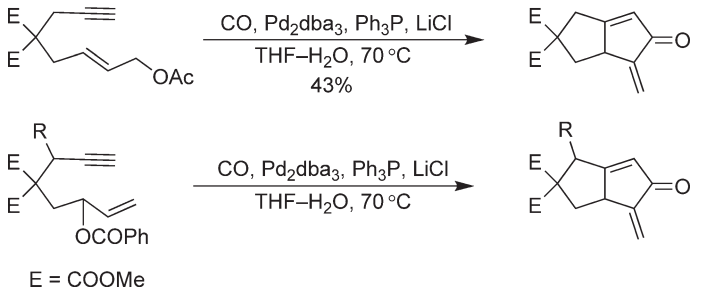
This strategy has been successfully employed for the construction of [5,5,5,5]-fenestranes (Equation (36)),[81,82] as well as for the synthesis of complex natural products such as terpenoids, for example, hirsutene (Equation (37)).[83]



(36)

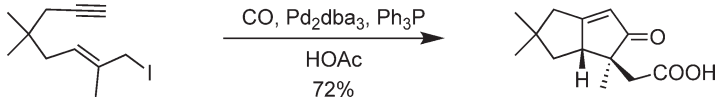


Scheme 21



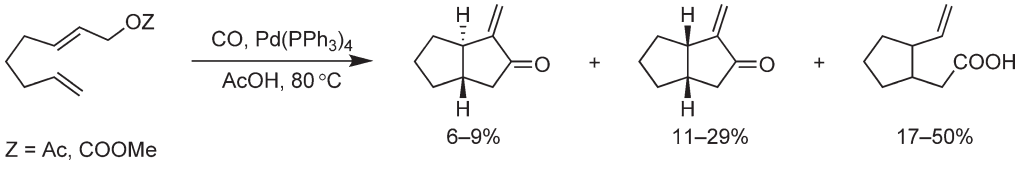
R	*Yield* (%)
H	73
Me	67

Scheme 22



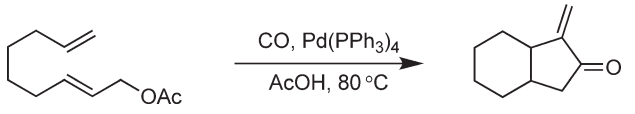
(37)

1,6-Dienylacetates give bicyclo[3.3.0]octanones in reasonable yields and diastereoselectivity, depending on conditions, temperature, and pressure, though the main product of these reactions often results, from premature termination of cascade (Equation (38)).[79]



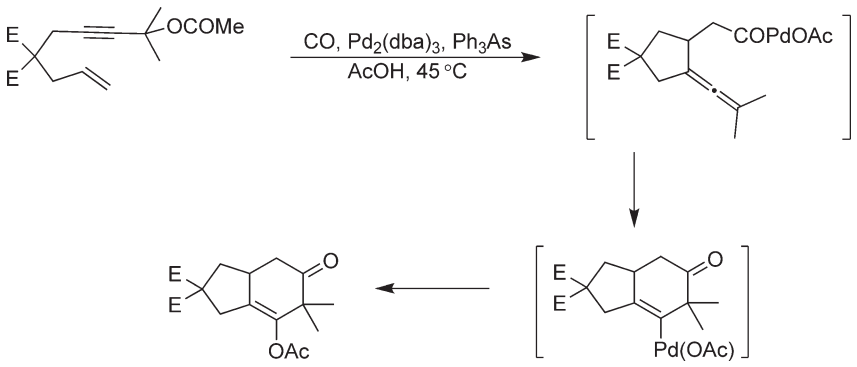
(38)

Similarly, 1,7-dienylacetates afford 7-methylenebicyclo[4.3.0]nonan-8-ones (Equation (39)).



(39)

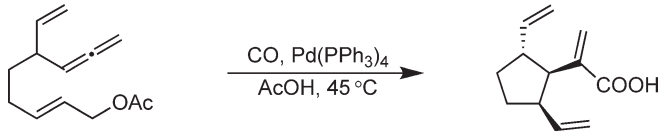
The cyclization of enynes containing propargylic carbonate fragment involves allene intermediate, which takes part in intramolecular acylpalladation by *endo-trig*-mode to give a six-membered ring (Scheme 23).[84]



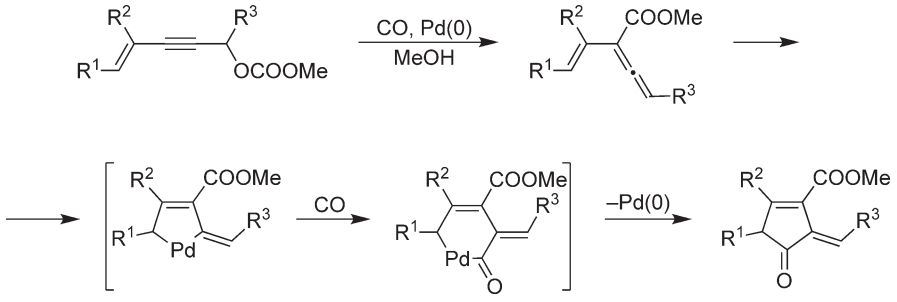
Scheme 23

An interesting mechanism involving palladacycle intermediate has been proposed for carbonylative cyclizations of 4-en-2-ynyl carbonates (Scheme 24).[85] The examples of this transformation are shown in Scheme 25.

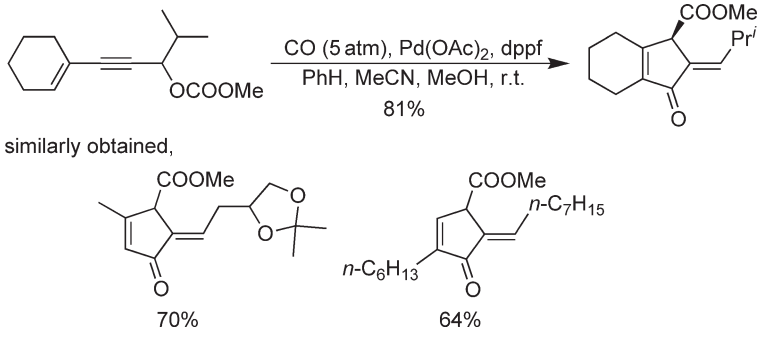
The cyclization onto allenic moiety takes place with high degree of regioselection, with exclusive *exo*-attack at internal double bond and formation of five-membered ring (Equation (40)).[86]



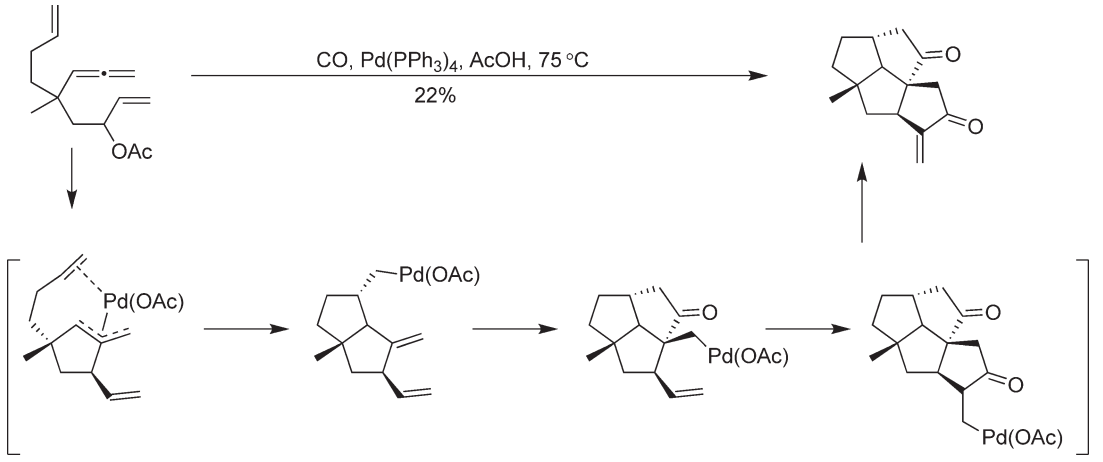
(40)



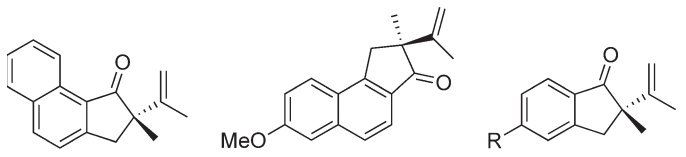
Scheme 24



Scheme 25



Scheme 26

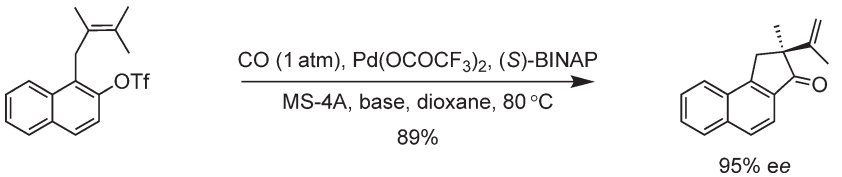


R	*Yield* (%)	*ee* (%)
H	96	72
Me	85	87
OMe	85	97
Cl	93	85
COOMe	75	77
CN	73	79

Scheme 27

A regio- and diastereoselective tandem process involving carbapalladation with two consequtive carbonylative cyclizations has been realized using this strategy (Scheme 26).[86]

Enantioselective carbonylative cyclization has been realized with *o*-alkenylaryl triflates in the presence of 2,2-bis(diphenyl-phosphanyl)-1,1-binaphthyl (BINAP) or TolBINAP ligands in high material yields and enantiomeric excess (Equation (41)).[87]



(41)

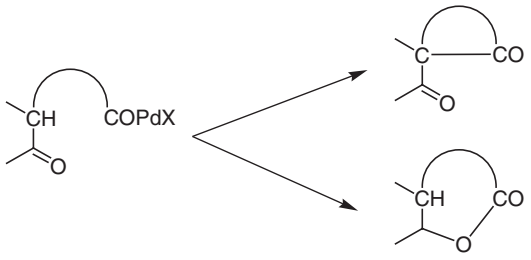
Similarly, the compounds in Scheme 27 were obtained.

11.12.2.3 Carbonylative Cyclizations Involving Enolizable CH-Acids

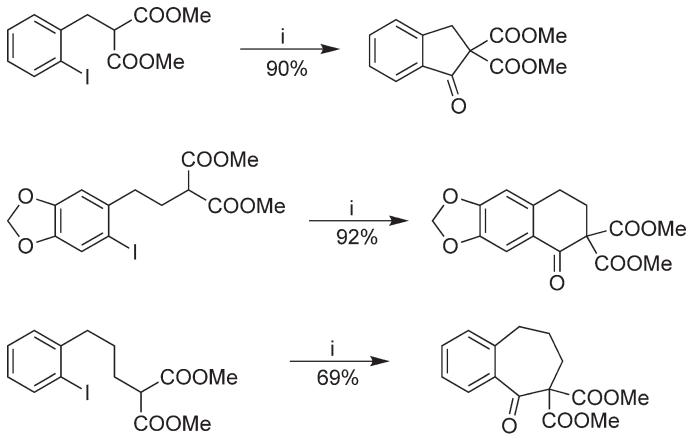
Intramolecular carbonylative cross-coupling involving enolizable CH-acidic fragments has been described by Negishi *et al.* In this case, trapping of acylpalladium intermediate is effected formally by enolate, either with carbon or oxygen center (Scheme 28).

Cyclization at carbon center takes place readily if stronger CH-acids are involved, with five-, six-, and even seven-membered rings being formed in high yields (Scheme 29).[71]

Cyclization at an enolate center can successfully compete with acylpalladation of C═C bonds (Equation (42)).[71]

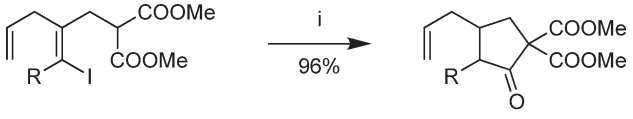


Scheme 28



i, CO (41 atm), $Pd(PPh_3)_4$, Et_3N, THF, MeCN, 100 °C

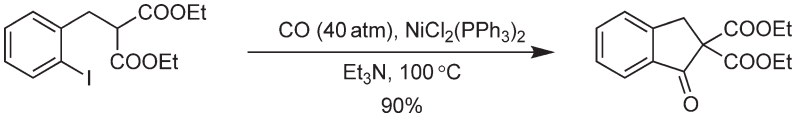
Scheme 29



(42)

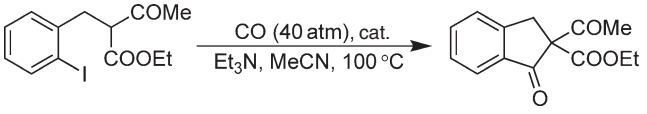
i, CO (41 atm), $Pd(PPh_3)_4$, Et_3N, THF, MeCN, 100 °C

Further studies show that the cyclization can be catalyzed by Ni, Cu, or Pd complexes.[88] Ni complexes perform the best in the majority of cases, such as shown in Equation (43).



(43)

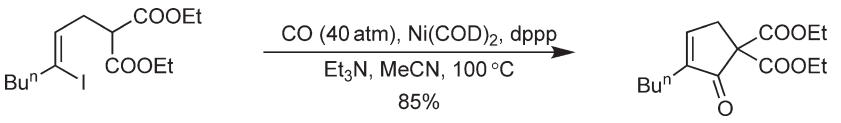
However, in some cases Pd complexes gave better yields (Equation (44)).



cat	*Yield* (%)
$NiCl_2(PPh_3)_2$	<10
Li_2CuCl_4	50
$PdCl_2(PPh_3)_2$	68

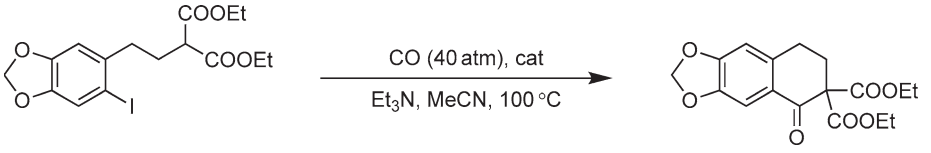
(44)

Similar cyclizations can be performed using iodoalkenes bearing a malonate or similar CH-acidic pendant, though in this case 1,3-bis-(diphenylphosphino)propane (dppp) is required as a ligand (Equation (45)).[88]



(45)

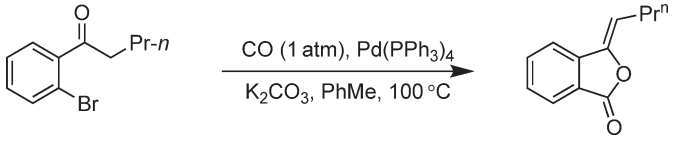
Formation of six-membered cycles is also possible and best achieved using a copper catalyst (Equation (46)).



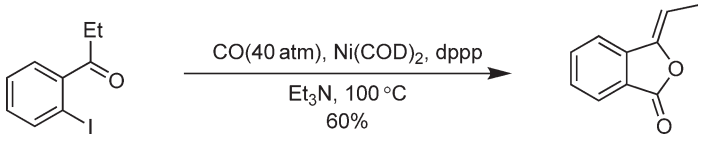
(46)

Cat	*Yield* (%)
$NiCl_2(PPh_3)_2$	92
Li_2CuCl_4	98

However, in many cases the cyclizations at O-center of enolate may become predominant (Equations (47) and (48))[71,88,89]

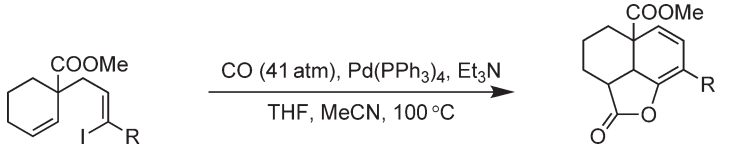


(47)

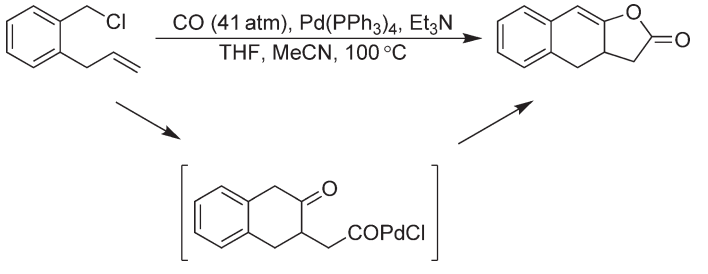


(48)

These reactions may as well occur in the termination stages of cascade reactions, for example, involving intramolecular acylpalladation (Scheme 30)[71] or intramolecular Heck reaction Equation (49).[71]



(49)



Scheme 30

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11.13 Hydroformylation, Other Hydrocarbonylations, and Oxidative Alkoxycarbonylation

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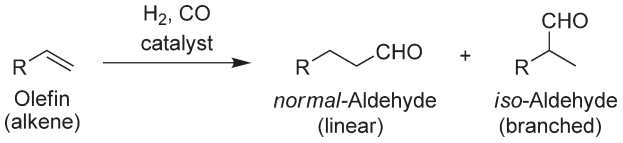
11.13.1 Introduction

This review deals with the recent developments in the transition metal-catalyzed carbonylation reaction, especially hydroformylation, hydrocarbonylation, and oxidative hydrocarbonylation reactions of olefins, referring to literature since 1994. Because of the importance of carbonyl functionality in organic chemistry and the ideal atom efficiency of

these reactions, the field has been extensively studied. The present review focuses on the brief history, mechanisms, and applications of these reactions.

11.13.2 Hydroformylation

Hydroformylation is an addition reaction of a hydrogen atom and a formyl group to an olefin to form two isomeric aldehyde products (Equation (1)). Both the aldehyde products are important chemicals: *normal*-aldehydes are industrially important because they are widely used for detergents and plasticizers; the *iso*-aldehydes can be important intermediates for production of fine chemicals and drugs once the chiral center at the α-carbon to aldehyde is controlled. Progress in hydroformylation exactly traces that in the phosphine ligand chemistry and valuable aldehyde products have become available on an industrial scale.



(1)

This section starts with a history of hydroformylation until 1993 and focuses on the following four topics since 1994: (i) recent advances in the *normal*-selective hydroformylation and asymmetric hydroformylation, (ii) new spectroscopic techniques for understanding details of the reaction, (iii) new reaction media and catalysts for separation which are important for industrial production, and (iv) recent applications to organic syntheses.

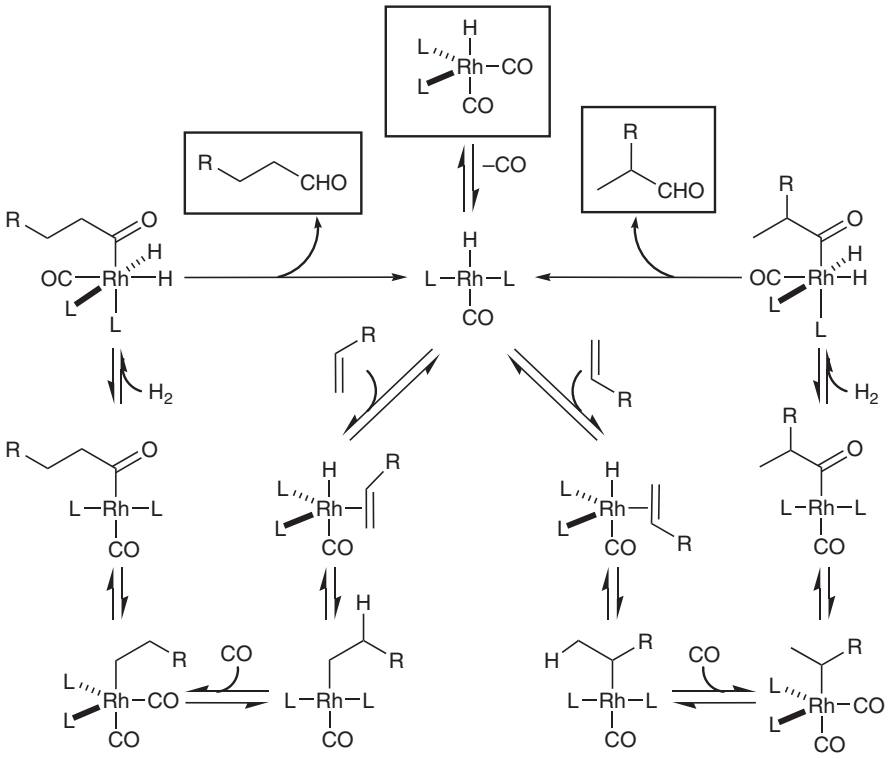
11.13.2.1 A History before 1993

11.13.2.1.1 Brief history before 1993

Since the discovery of hydroformylation by Roelen in 1938,[1] the hydroformylation process had been exclusively based on cobalt as a catalyst metal, until the development of rhodium–phosphine complexes in the late 1960s.[2,3] After the discovery of rhodium catalysts, a low pressure oxo (LPO) process was developed by Union Carbide Corporation and was widely used by many companies. In the mid-1980s, Ruhrchemie established an organic solvent–water two-phase system using trisodium triphenylphosphinetrisulfonate (TPPTS) as a ligand. van Leeuwen's invention[4] of "bulky monophosphite" ligand, which gives very high rate, induced the development of bis-phosphite ligand systems around 1990. Highly selective asymmetric hydroformylation using BINAPHOS ligand reported in 1993[5] has led to further investigation to achieve high enantioselectivity. The following three sections describe the more detailed history of the mechanism of hydroformylation, *normal*-selective hydroformylation, and asymmetric hydroformylation until 1993.

11.13.2.1.2 Mechanism of hydroformylation

Heck and Breslow first reported a general mechanism of the cobalt-catalyzed hydroformylation in 1961,[6] and in 1968 Wilkinson applied the mechanism to the understanding of a PPh_3-ligated rhodium catalyst system. The most commonly accepted mechanism is described in Scheme 1.[2,3] The mechanism consists of five elemental steps: (i) coordination of an olefin to a coordinatively unsaturated rhodium hydride complex, (ii) olefin insertion to a metal–hydride bond to form two isomeric alkyl complexes, (iii) alkyl migration to the carbonyl ligand on the Rh(I) atom to form an acyl complex, (iv) oxidative addition of dihydrogen to Rh(I) to form acyldihydridorhodium(III) complex, and (v) reductive elimination of aldehyde from the Rh(III). Usually, only the last step, reductive elimination, is considered to be a sole irreversible reaction. Discussions here mainly rely on the Wilkinson's dissociative mechanism drawn in Scheme 1. The left and right cycles produce *normal*- and *iso*-aldehydes, respectively.



Scheme 1 Wilkinson's dissociative mechanism for hydroformylation of olefins catalyzed by a phosphine–Rh(I) complex.

11.13.2.1.3 *normal*-Selective hydroformylation before 1993

Industrial efforts have been focused on manufacturing of *normal*-aldehydes ("linear" aldehydes) from olefins. Here, we briefly summarize its history on the development of phosphorus ligands, which are classified as monophosphine, monophosphite, bis-phosphite, and bis-phosphine, all useful for the *normal*-selective hydroformylation.

Regioselectivity with the Rh–PPh_3 system has been extensively studied.[7] The regioselectivity for the *normal*-aldehyde, which is defined as *normal*-aldehyde/sum of *normal*- and *iso*-aldehyde product, in the hydroformylation of 1-alkenes varies from 70% to 96% depending on the CO pressure and PPh_3/Rh ratio. However, a significant amount of internal alkenes resulting from the isomerization of 1-alkenes were obtained as byproducts because these internal alkenes are a less reactive substrate for Rh–PPh_3-catalyzed hydroformylation. The presence of isomerized products made an overall yield for the *normal*-aldehyde decrease, even as the regioselectivity for *normal*-aldehyde remained of high value. Since electron-withdrawing substituents on the ligands make the metal center electron deficient, π-accepting phosphite can be considered to be a better ligand than PPh_3 to accelerate the dissociation of CO ligand due to weaker π-backbonding from the metal center to CO.[8]

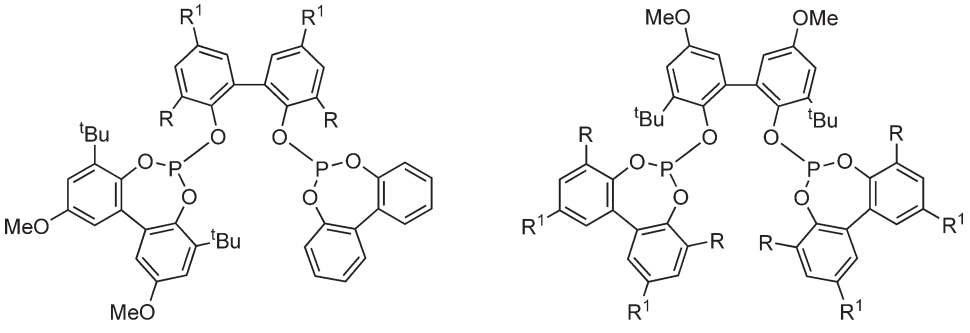
Thus, phosphite ligands are considered to provide higher concentration of the active species for hydroformylation. The first example of the use of phosphite ligands in rhodium-catalyzed hydroformylation of 1-alkenes was reported by Pruett and Smith in 1969.[9] They found a general trend—the lower basicity of the phosphorus ligand makes the higher selectivity for the *normal*-aldehydes. In the early 1980s, van Leeuwen and Roobeek reported a rhodium-bulky monophosphite system which gave moderate *normal*-selectivity and very high reaction rates in hydroformylation due to the exclusive formation of monoligated rhodium–phosphine complexes (Figure 1).[10,11] On the other hand, they also found a remarkable enhancement of the reaction rate by using strongly electron-withdrawing ligands even for the hydroformylation of less reactive internal alkenes.[12]

Since Bryant at Union Carbide Corporation disclosed that a bulky bis-phosphite–Rh system gave very high linearity, that is, a high degree of *normal*-aldehyde formation, even starting from internal alkenes in the late 1980s (Figure 2),[13,14] a number of bis-phosphite–rhodium catalysts have been investigated to produce the *normal*-aldehydes with higher *normal*/*iso*(*n*/*i*) ratio. For example, the catalyst system Rh(I)/**3b** gives a high *n*/*i* ratio of 50.[13] The advantages of the bis-phosphite system for propene hydroformylation as compared to the commercial triphenylphosphine system are that less amount of ligand can be used with higher rates.

1a: R = H
1b: R = Me

2

Figure 1 Bulky phosphite and electron-poor phosphite ligands.



3a: R = R^1 = H
3b: R = ^{t}Bu, R^1 = OMe

3c: R = R^1 = H
3d: R = ^{t}Bu, R^1 = OMe

Figure 2 Union Carbide bis-phosphite ligands for *normal*-selective hydroformylation.

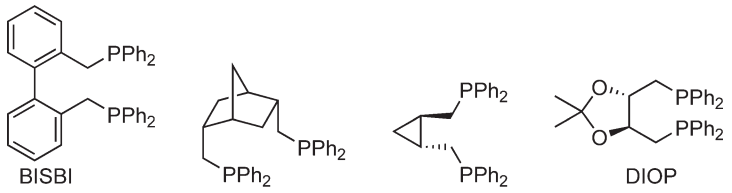
Concerning the ligand structure–catalytic performance relationships, van Leeuwen has summarized the comparison of several patents containing Rh–bis-phosphite system as described in Table 1.[15] It can be seen that the type of bridge in the bis-phosphites plays a significant role, as does the bulkiness of the substituents. There is no single evident factor that controls the linearity of the product. It is noticed that ligands **3b** and **3c** show high selectivity for making linear aldehyde. The presence of a bisphenol bridge seems to be important, but it is not enough, because many ligands containing bisphenol backbones fail to give high selectivities. For instance, ligands **3a** and **3d** give low linearities, even though their structures seem closely related to **3b** and **3c**.

Rhodium catalysts containing particular bis-phosphine ligands show very high selectivity for *normal*-aldehyde formation as was reported by Devon *et al.* in 1987.[16] The new bidentate ligand, 2,2-bis((diphenylphosphino)methyl)-1,1-biphenyl (BISBI), **4**, gives excellent results in the hydroformylation of propene at 125 °C and 18 bar of syn-gas (Figure 3) compared to the other bidentate ligands. A much higher *n*/*i* ratio of 25 was obtained, compared to 3.5 for 1,1′-bis(diphenylphosphino)ferrocene (dppf) and 4 for 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP) (Table 2).[8,16–19] The rate with BISBI is the highest as well (3–4000 TOF), with a ligand-to-metal ratio of 2.4. Later, the organometallic chemistry of Rh–BISBI system was further investigated by Casey.[20] An X-ray structure of BISBI-ligated rhodium hydride complex **8** reveals that three phosphorus atoms are all in the equatorial plane with P–M–P bite angle of 124.8°. A solution structure of the five-coordinate key intermediate (BISBI)Rh$(CO)_2$H **9**, generated by the reaction of **8** with CO at −30 °C in CD_2Cl_2, is assigned to have a trigonal-bipyramidal structure with BISBI in the equatorial plane and the hydride in an apical position by IR and NMR

Table 1 Hydroformylation of 1-alkenes using Union Carbide bisphosphite ligands

Ligand	*Temp*(°C)	*Syn-gas pressure* (bar)	*Ratio of CO*/H_2	*Alkene*	*TOF*[a] (mol mol$^{-1}_{Rh}$ h)	*n*/*i*
3a	70	4.3	1 : 1	Propene	160	6.3
3b	70	2.5	1 : 2	1-Butene	2400	50
3b	71	6.7	1 : 2	1-Butene	730	35
3c	74	4.5	1 : 1	Propene	402	53
3d	70	7	1 : 2	1-Butene	1480	3.2
3d	70	4.3	1 : 1	Propene	20	2.1

[a]Rates were measured in continuous runs or calculated at 30% conversion.



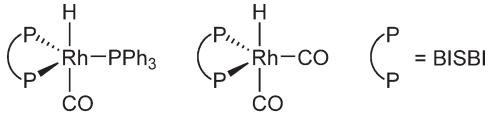
4 5 6 7

Figure 3 Bis-phosphine ligands used for *normal*-selective hydroformylation.

Table 2 Hydroformylation of propene using BISBI and other ligands

Ligand	*Bite angle*	*TOF* (mol mol$^{-1}_{Rh}$ h)	*n/i*
BISBI 4	113/120	3650	25
5	126	2550	2.6–4.3
6	107	3200	4.4–12
DIOP 7	102	3250	4.0–8.5
dppf	99	3800	3.6–5
dppp	91	600	0.8–2.6
dppe	85		2.1
PPh_3[a]		6000	2.4

[a][Rh] = 0.7 mM, L/Rh = 124.
Conditions: 16 bar of syn gas pressure, [Rh] = 1.5 mM, L/Rh 2.4, 95–125 °C, solvent 2,2,4-trimethylpentane–1,3-diolmonoisobutyrate (Texanol), 5 bar of propene pressure.



8 9

Figure 4 Observed rhodium complexes of BISBI.

studies (Figure 4). Casey suggested a wide natural bite angle, which led the diequatorial coordination mode of bis-phosphine ligand to the central rhodium, may be related to the good *n/i* ratio of products. Later, further derivatizations of the BISBI ligand were investigated to give an even higher *n/i* ratio (*vide infra*).

11.13.2.1.4 Asymmetric hydroformylation before 1993

In contrast to the *normal*-selective hydroformylation mainly developed in industry, asymmetric hydroformylation, which requires *iso*-aldehydes ("branched" aldehydes) to be formed from 1-alkenes, was first examined in the early 1970s by four groups independently, using Rh(I) complexes of chiral phosphines as catalysts.[21–24] Since then, a number of chiral ligands have been employed for asymmetric hydroformylation and used in combination with transition metal ions, especially Pt(II) and Rh(I). Asymmetric hydroformylation of 1-alkenes is most extensively studied.

Although the "first-generation" catalysts were Rh(I) complexes of chiral ligands, Pt(II) was considered to be the superior metal in asymmetric hydroformylation until the early 1990s. Using a chiral bis-phosphine–$PtCl_2$ complex as a catalyst, higher activity and improved *i/n* ratio were achieved by addition of a Lewis acid such as $SnCl_2$, which provided a new species, $PtCl(SnCl_3)$(bis-phosphine), as illustrated in Figure 5.[25,26] These "second-generation" catalysts reached the highest level of % ee (up to 96% ee) in the asymmetric hydroformylation of styrene in 1991, as was reported by Stille[27] and Consiglio.[28] They utilized $PtCl_2$ complexes of chiral bis-phosphine ligands, BPPM and BCO-DBP, respectively, in combination with $SnCl_2$. The achievements are summarized in an excellent review article.[29]

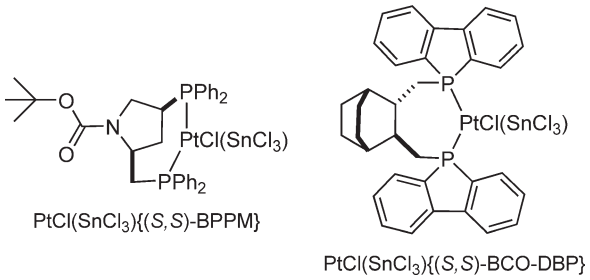
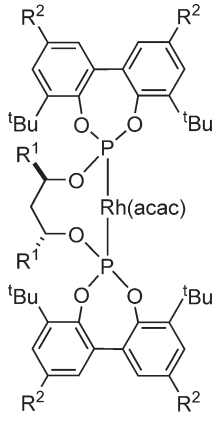


Figure 5 Examples of chiral Pt complexes used as catalysts in asymmetric hydroformylation.

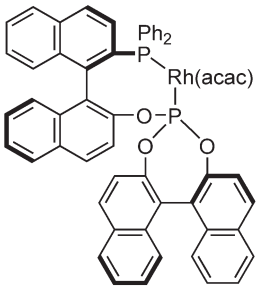
Under these circumstances, the "third-generation" catalysts, Rh(I)–chiral bis-phosphites and Rh(I)–chiral phosphine–phosphites, were developed in 1992–1993. Apart from the asymmetric matter, it was reported in the 1980s that rhodium(I) complexes of phosphites, especially those bearing bulky substituents, showed high activities in the hydroformylation of 1-alkene to give *normal*-aldehydes.[4,10,13,14,30–34] This "phosphite revolution" in the achiral aldehyde synthesis made remarkable advances in the asymmetric hydroformylation area. Thus, the "third-generation" catalysts, Rh(I) complexes of chiral phosphites or related ligands, were developed. Chiral variants of bidentate phosphites first appeared in a patent literature in 1992. Babin and Whiteker reported the hydroformylation of styrene in up to 90% ee using chiral bis-phosphites UC-P_2^* and its derivatives as ligands (Figure 6), although ee's observed for substrates such as 1-hexene and vinyl acetate were not satisfactory yet (50% and 20%, respectively).[35] Similarly, chiral phosphites and phosphinites were employed for the Rh-catalyzed asymmetric hydroformylation by Takaya and van Leeuwen.[36,37]

At this stage, Rh(I) catalysts became the most promising candidates for the asymmetric hydroformylation in comparison with Pt(II) catalysts. In 1993, Takaya and Nozaki developed chiral phosphine–phosphite ligands, (*R,S*)- and (*R,R*)-BINAPHOSes (Figure 7). A Rh(I) complex of one of the two diastereomers, (*R,S*)-BINAPHOS, achieved higher enantioselectivity than the conventional bis-phosphine or bis-phosphite complexes, mostly above 90% ee, for a wide variety of substrates.[5] In most cases, 2.0–2.5 equiv. of phosphine over Rh(I) were high enough to achieve the highest enantioselectivities. One of the characteristic features of the phosphine–phosphite ligand is its unsymmetrical structure. Since the invention of DIPAMP, DIOP, and BINAP as excellent ligands for asymmetric hydrogenation, the ligand design had been shackled by the principle of C_2-symmetry.[38] Rather surprisingly, a chiral phosphine–phosphite ligand (*R,S*)-BINAPHOS, an unsymmetrical bidentate ligand, achieved the highest level of ee's as well as satisfactory regioselectivity and catalytic activity for a wide variety of olefins.



R^1 = Me; R^2 = OMe: UC-P_2*
R^1 = Me; R^2 = ^{t}Bu: UC-P_2*–*t*-butyl
R^1 = Ph; R^2 = OMe: UC-P_2*–1,3-diphenyl

Figure 6 Union Carbide chiral bis-phosphite–rhodium complexes used as catalysts for the asymmetric hydroformylation.



Rh(acac){(*R*,*S*)-BINAPHOS}

Figure 7 A rhodium complex of chiral phosphine–phosphite ligand (*R*,*S*)-BINAPHOS used as a catalyst for asymmetric hydroformylation.

11.13.2.2 Recent Advances in *normal*-Selective and Asymmetric Hydroformylation since 1994

11.13.2.2.1 *normal*-Selective hydroformylation

Synthesis of Xantphos, one of the most effective ligands for *normal*-selective hydroformylation of 1-alkene and that can be structurally and electronically modified with ease, was reported by van Leeuwen in 1995.[39,40] Steric (bite angle) and electronic effects in the hydroformylation using Xantphos or its derivatives (**10–18**, Figure 8) were investigated in detail. The hydroformylation results with Xantphos derivatives **10–18**, which are summarized in Table 3. One can see that the selectivity for *normal*-aldehyde increases with larger bite angles. The *n*/*i* ratio also increases with larger bite angle but the effect diminishes over about 110°. The reaction is accelerated with increasing bite angle (not for **15–17**). They also reported that larger bite angle makes the central rhodium atom become more electron poor as judged by ν_{CO} of (diphosphine)Rh(H)(CO)(PPh_3) in IR spectroscopy.[40,41] Thus, larger bite angle

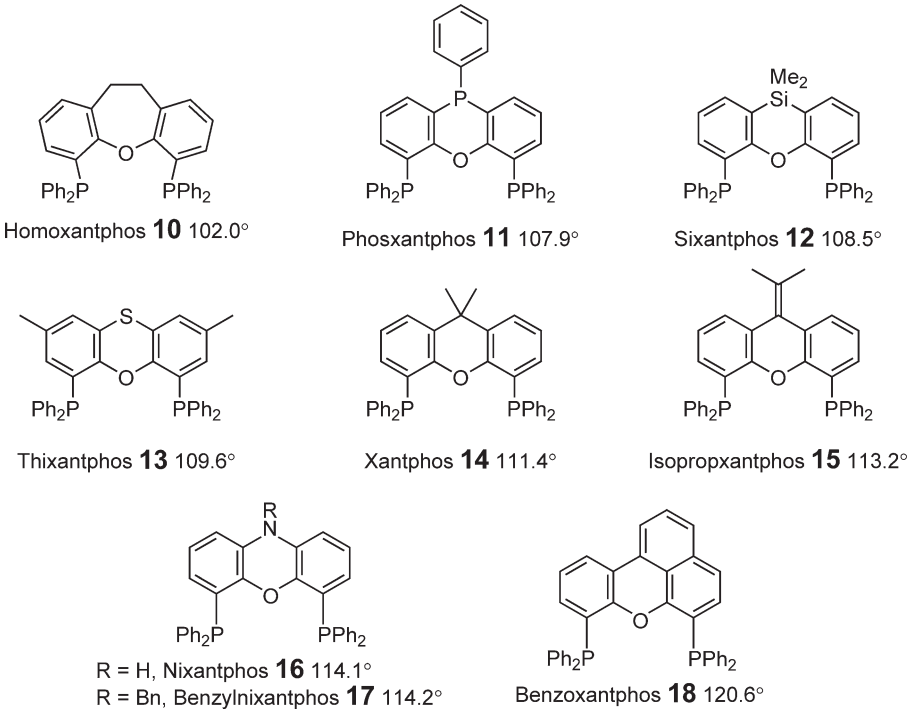


Figure 8 Xantphos derivatives and their natural bite angles.

Table 3 Hydroformylation of 1-octene using Xantphos derivatives **10–18**[a]

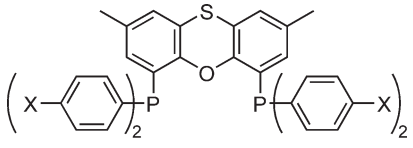
Ligand	$\beta^{b}{}_{n}$ (°)	*ee*:*ae*[b,c]	*n*/*i*[b]	% *n-aldehyde*[b]	% *isomer*[b]	*TOF*[b] (mol mol$^{-1}{}_{Rh}$ h^{-1})
10	102.0	3:7	8.5	88.2	1.4	37
11	107.9	7:3	14.6	89.7	4.2	74
12	108.5	6:4	34.6	94.3	3.0	81
13	109.6	7:3	50.0	93.2	4.9	110
14	111.4	7:3	52.2	94.5	3.6	187
15	113.2	8:2	49.8	94.3	3.8	162
16	114.1	7:3	50.6	94.3	3.9	154
17	114.2	8:2	69.4	94.9	3.7	160
18	120.6	6:4	50.2	96.5	1.6	343

[a]Conditions: $CO/H_2 = 1$, 20 bar of syn gas pressure, L/Rh = 5, s/c = 637, [Rh] = 1.00 mM, no hydrogenation was observed in all experiments.
[b]Natural bite angle, isomeric ratio of $LRh(CO)_2H$, *normal* over *iso* ratio, *normal*-aldehyde product, isomerized product 2-octene, and turnover frequency were determined at 20% alkene conversion.
[c]Calculated from ^{31}P NMR data with $^{2}J_{P-H}$.

ligand makes CO dissociate easily from the central rhodium, resulting in the acceleration of the reaction. Planar ligand **18** bearing a rigid skeleton affords an interesting result of low isomerization rate.

An electronic effect of a series of electronically perturbed thixantphos ligands on the hydroformylation reaction is also investigated (Figure 9 and Table 4).[42] Thixantphos ligands with lower basicity at the phosphorus atoms accelerate reaction similar to that of the electron-withdrawing substituents accelerating the reaction, as described in Section 11.13.2.1.3. They discussed the results based on Tolman's χ-value[43] which is the electronic contribution of each R group on the phosphorus atom toward a donor ability of the phosphine estimated from ν_{CO} value in $R_3PNi(CO)_3$ complex. The *n*/*i* ratio of the product increased along with increasing χ-value but the yields of the *normal*-aldehyde remained almost unchanged. This can be attributed to the acceleration of β-hydrogen elimination from the *iso*-alkylrhodium complex to form 2-alkene (Scheme 2). In the *iso*-alkylrhodium species, steric repulsion between the iso-alkyl group and the coordinated CO causes the easier dissociation of CO, and the coordinatively unsaturated species thus produced easily undergoes β-hydride elimination when compared to the *normal*-alkyl Rh species.

The organometallic chemistry and catalysis of BISBI (**4**, Figure 10) have been studied in detail by Casey and co-workers.[44–46] Deuterioformylation using a rhodium–BISBI system affords an almost complete deuterium labeling at the β- and the formyl positions of the resulting aldehydes (Scheme 3) with a small amount of deuterated olefins and *normal*- and iso-aldehydes via isomerization. The rate of β-elimination from the alkylrhodium complex is very slow as confirmed by the significantly small amount of side-products. This means that the regiochemistry of the product should be kinetically determined at the alkene-insertion step in the current rhodium–BISBI system. Irreversibility of the alkene-insertion step with *trans*-1,2-bis[(diphenylphosphino)methyl]cyclopropane (T-BDCP) **6**, DIOP **7**, and dppe were also confirmed by the same authors. Casey also reported a remarkable acceleration effect (TOF of 62,



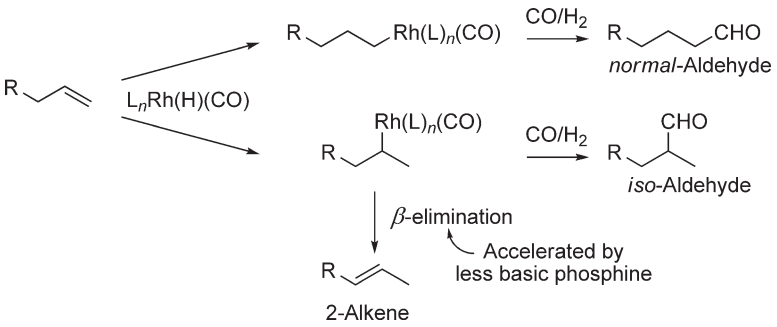
19: X = NMe_2
20: X = OMe
21: X = Me
13: X = H
22: X = F
23: X = Cl
24: X = CF_3

Figure 9 Electronically perturbed thixantphos derivatives.

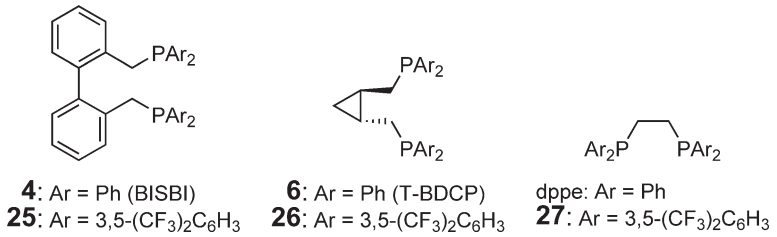
Table 4 Electronic effects in hydroformylation using electronically perturbed thixantphos derivatives[a]

Ligand	χi	*ee*:*ae*[b,c]	*n*/*i*[b]	% *n-aldehyde*[b]	% *isomer*[b]	*TOF*[b] (mol mol$^{-1}_{Rh}$ h^{-1})
19	1.7	47:53	44.6	93.1	4.8	28
20	3.4	59:41	36.9	92.1	5.3	45
21	3.5	66:34	44.4	93.2	4.7	78
13	4.3	72:28	50.0	93.2	4.9	110
22	5.0	79:21	51.5	92.5	5.7	75
23	5.6	85:15	67.5	91.7	6.9	66
24	6.4	92:8	86.5	92.1	6.8	158

[a]Conditions: $CO/H_2 = 1$, 20 bar of syn-gas pressure, L/Rh = 5, [Rh] = 1.00 mM.
[b]Tolman chi value, isomeric ratio of $LRh(CO)_2H$, *normal* over *iso* ratio, *normal*-aldehyde product, isomerized product 2-octene, and turnover frequency.
[c]Calculated from ^{31}P NMR data with $^2J_{P-H}$.



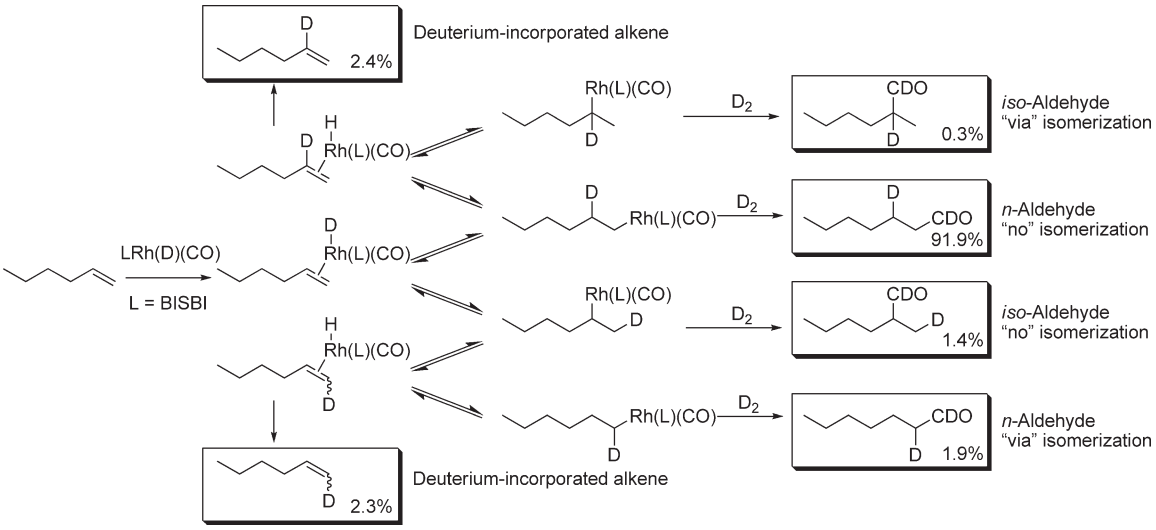
Scheme 2 Competitive β-elimination pathway from *iso*alkylrhodium complex to form 2-alkene instead of *iso*-aldehyde.



4: Ar = Ph (BISBI)
25: Ar = 3,5-$(CF_3)_2C_6H_3$
6: Ar = Ph (T-BDCP)
26: Ar = 3,5-$(CF_3)_2C_6H_3$
dppe: Ar = Ph
27: Ar = 3,5-$(CF_3)_2C_6H_3$

Figure 10 BISBI, T-BDCP, dppe, and their electron-deficient derivatives.

fivefold excess) and higher *n*/*i* selectivity (*n*/*i* ratio of 123, two-fold excess) when the phenyl groups in BISBI were replaced by strongly electron-withdrawing 3,5-$(CF_3)_2C_6H_3$ groups **25**. The high selectivities were attributed to the diequatorial coordination mode of **25** in the catalytic intermediates, as observed in the structure of **25** $Rh(H)(PPh_3)(CO)$ complex by X-ray crystallography. Similar diequatorial coordination mode of a bulky bis-phosphite ligand in $LRh(H)(CO)_2$ complex, which also affords good *n*/*i* ratio and high TOF, was observed in the solid state.[47] In the case of T-BDCP **6**, a slight improvement in *n*/*i* ratio from 12.1 to 17.7 and in TOF from 3.7 to 13.7 was observed by a similar modification of the aryl groups from phenyl to 3,5-$(CF_3)_2C_6H_3$ **26**. These effects of electron-withdrawing substituents for improvement of *n*/*i* ratio and TOF are similar to that discussed above for other types of ligands such as monophosphines, although the reason how the electron-withdrawing group can improve them is not clear so far. In contrast, the *n*/*i* ratio was reduced to half the value of the original ligand when the phenyl groups of dppe were changed into 3,5-$(CF_3)_2C_6H_3$ groups **27**. The dppe-type ligand takes an apical-equatorial coordination mode due to its bite angle nearing 90°.[45] Casey suggested that the electron-poor phosphine ligand at apical position decreases the *n*/*i* ratio based on the results of the modification of dppe ligand, although the reason is not clear.[45,46]



Scheme 3 Deuterioformylation using Rh–BISBI system and its product distribution.

11.13.2.2.2 Asymmteric hydroformylation

11.13.2.2.2.(i) Mechanism in Rh–BINAPHOS catalyst system

Systematic studies on Rh–BINAPHOS catalyst system have been carried out since 1993. To clarify which part of the BINAPHOS skeleton is crucial for enantioselectivity, modifications of BINAPHOS ligands are intensively studied.[48–50] Derivatives **29–31** of (*R*,*S*)-BINAPHOS described in Figure 11 are synthesized. The results for the hydroformylation using these BINAPHOS derivatives are summarized in Table 5. The best combination is realized when the absolute configurations of binaphthyl and binaphthol moieties are opposite. Whereas (*S*,*R*)- or (*R*,*S*)-enantiomer of **28** affords the product in good enantioselectivity, (*R*,*R*)-diastereomer of **28** gives lower enantioselectivity (25%). A comparison of **28**, **29**, and **30b** indicates that the stereocenter at the phosphine moiety plays an important role in the enantiofacial selection step. It is noteworthy that ee obtained with (*R*)-**29** is fairly high, considering a possible exchange between the (*R*,*S*)- and (*R*,*R*)-forms due to rapid isomerization of the phosphite moiety. It may be explained that the binaphthyl rings are fixed to the (*S*)-form upon coordination to the Rh center. Similar discussion is possible for the biphenyl analog **30b**, because ee observed with **30b** is relatively closer to that obtained with (*S*,*R*)-**30a** than that with (*R*,*R*)-**30a**. Based on the hypothesis that the phosphine part is in charge of the enantiofacial selection, modification on the aryl groups of the phosphine moiety is examined. Finally, an introduction of 3-methoxyphenyl groups to (*R*,*S*)-BINAPHOS **31** is most effective for the regio and enantioselective hydroformylation of various olefins.[50]

A complex [(*R*,*S*)-BINAPHOS]Rh(H)$(CO)_2$ was generated by the reaction of Rh(acac)$(CO)_2$ with (*R*,*S*)-BINAPHOS under 1 bar syn-gas atmosphere, and its solution structure was investigated.[49] It is demonstrated that [(*R*,*S*)-BINAPHOS]Rh(H)$(CO)_2$ exists as a single species where the phosphine occupies an equatorial position and the phosphite an apical position by NMR spectroscopies (Figure 12). The existence of a unique single species created by the phosphine–phosphite may be related to the high enantioselectivities of the catalyst.

Effects of CO and H_2 partial pressures on the reaction rate and selectivity of asymmetric hydroformylation of 1-hexene and styrene are examined using (*R*,*S*)-BINAPHOS–Rh catalyst system.[51,52] For both substrates, high CO partial pressure tends to retard the reaction; the partial pressure of H_2 hardly affects the reaction rate (P_{H2}, $P_{CO} = 0.5–5$ MPa). In most cases, the regio- and enantioselectivities are independent of H_2 and CO pressure. Deuterioformylation experiments clearly demonstrate the irreversibility of the olefin-insertion step at total pressures of 2–10 MPa (D_2/CO = 1/1). This fact proves that the regio- and enantioselectivity of the present hydroformylation should be controlled by the olefin-insertion step. Herrmann reported the theoretical calculation of the olefin coordination step, explaining selectivity obtained with (*R*,*S*)-BINAPHOS/Rh system for the hydroformylation of styrene.[53,54]

11.13.2.2.2.(ii) Other catalyst systems giving a high enantioselectivity

A number of papers on asymmetric hydroformylation of olefins using chiral bis-phosphite or bis-phosphine ligand were reported by 2000. Here, we focus on some examples that achieved high enantioselectivities.

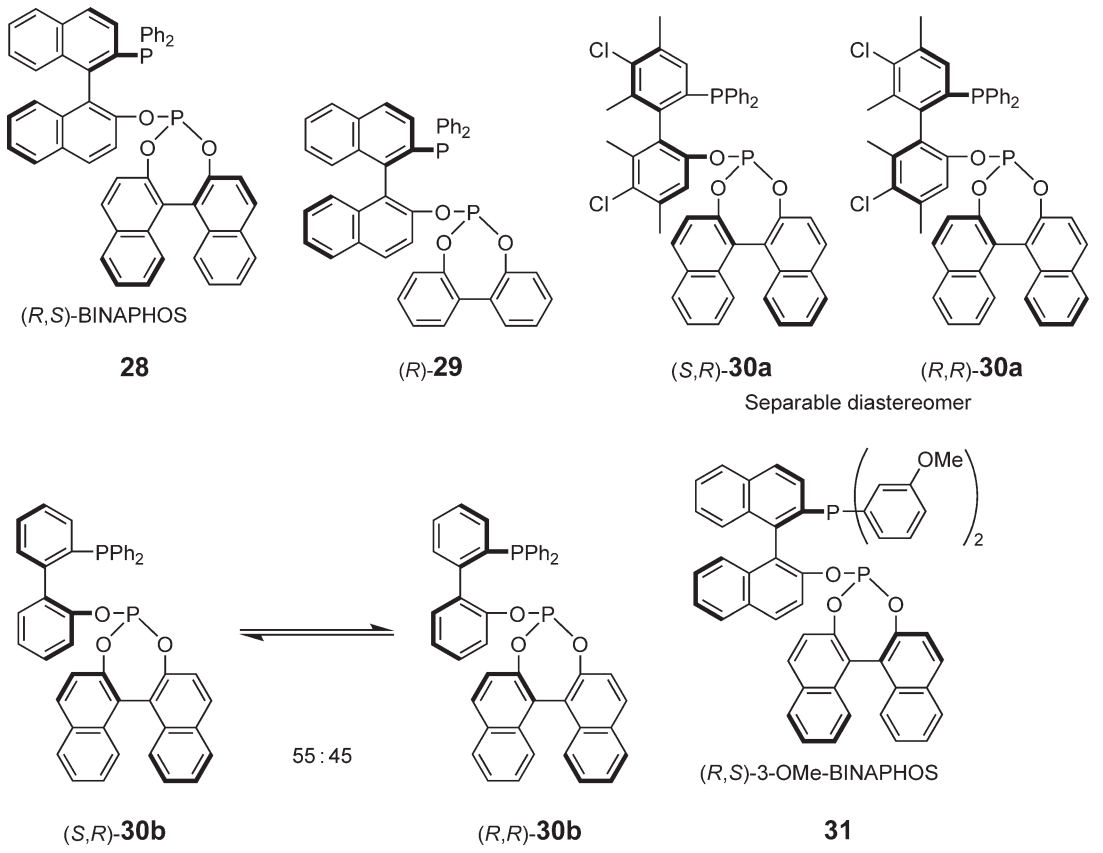


Figure 11 BINAPHOS **28** and its derivatives **29–31**.

Table 5 Results of hydroformylation of styrene using BINAPHOS derivatives **28–31**

Ligand	*CO*/H_2 atm/atm	*Temp* (°C)	*Time* (h)	*conv.* (%)	*i*/*n*	% *ee (absolute configuration)*
(*S*,*R*)-**28**	50/50	60	43	>99	88/12	94 (*S*)
(*R*,*S*)-**28**	50/50	80	16	>99	86/14	89 (*R*)
(*R*,*S*)-**28**	10/90	60	40	>99	88/12	92 (*R*)
(*R*,*R*)-**28**	50/50	60	38	>99	86/14	25 (*R*)
(*R*)-**29**	50/50	60	43	>99	91/9	83 (*R*)
(*S*,*R*)-**30a**	50/50	60	42	>99	90/10	94 (*S*)
(*R*,*R*)-**30a**	50/50	60	40	95	92/8	16 (*R*)
(*R*)-**30b**	50/50	60	40	98	89/11	69 (*S*)
(*R*,*S*)-**31**	50/50	60	20	>99	93/7	95 (*R*)

Styrene 20 mmol in C_6H_6, [Rh] = 0.010 mmol, L/Rh = 4. The ee's were determined by GLC analysis of the corresponding 2-arylpropionic acids derived by Jones oxidation of the products.

Several catalyst systems using pentane-2,4-diyl unit as a backbone of the ligand are used for the platinum- or rhodium-catalyzed asymmetric hydroformylation as a nice extension of the previous report by Babin and Whiteker.[35] Bakos reported asymmetric hydroformylation of styrene using $PtCl_2$/$SnCl_2$–bis-phosphite **32** system which gave high ee values but low aldehyde selectivity and *i*/*n* ratio (Table 6).[55] Ligand **33**, a partially hydrogenated analog of **32**, provided slightly improved aldehyde selectivity and *i*/*n* ratio, retaining high ee values.[56] Similar bis-phosphite ligands **34** and **35** with Me_3Si groups at 3,3′-positions of phosphite moieties (Figure 13) were adopted to Rh-catalyzed hydroformylation of styrene to give high ee values (up to 86% ee). In the rhodium system, variation of the *ortho*-substituents has a large effect on asymmetric induction.[57] Chiral unsymmetrical bis-phosphine–Pt system also afforded high ee values for the hydroformylation of styrene (Table 7).[58]

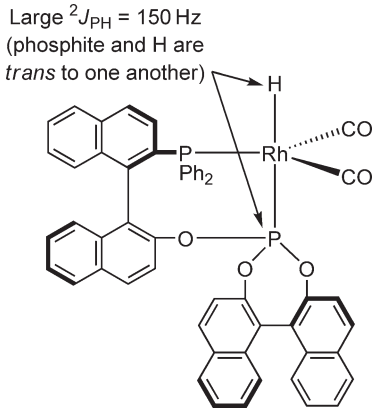
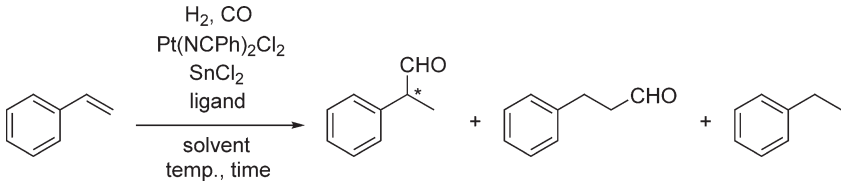


Figure 12 The solution structure of [(*R*,*S*)-BINAPHOS]Rh(H)$(CO)_2$ confirmed by NMR spectroscopies.

Table 6 Hydroformylation of styrene using **32** and **33** as ligands



Ligand	*Solvent*	*Substrate/Pt*	*Time* (h)	*Temp* (°C)	*Conv.*[a] (%)	% ald.[b]	*i*/*n*[a]	*%ee (absolute configuration)*[a]
32[c]	CH_2Cl_2	5,000	70	17	90	46	60/40	91 (*R*)
32[c]	toluene	2,000	67	17	76	45	58/42	88 (*R*)
33	CH_2Cl_2	2,000	20	23	62	71	85/15	86 (*R*)
33	toluene	2,000	20	23	83	62	84/16	88 (*R*)

[a]Determined by GC.
[b]Aldehydes/(aldehydes + ethylbenzene).
[c]H_2 and CO (1 : 1) at 100 atm d H_2 and CO (1 : 1) at 100 atm.

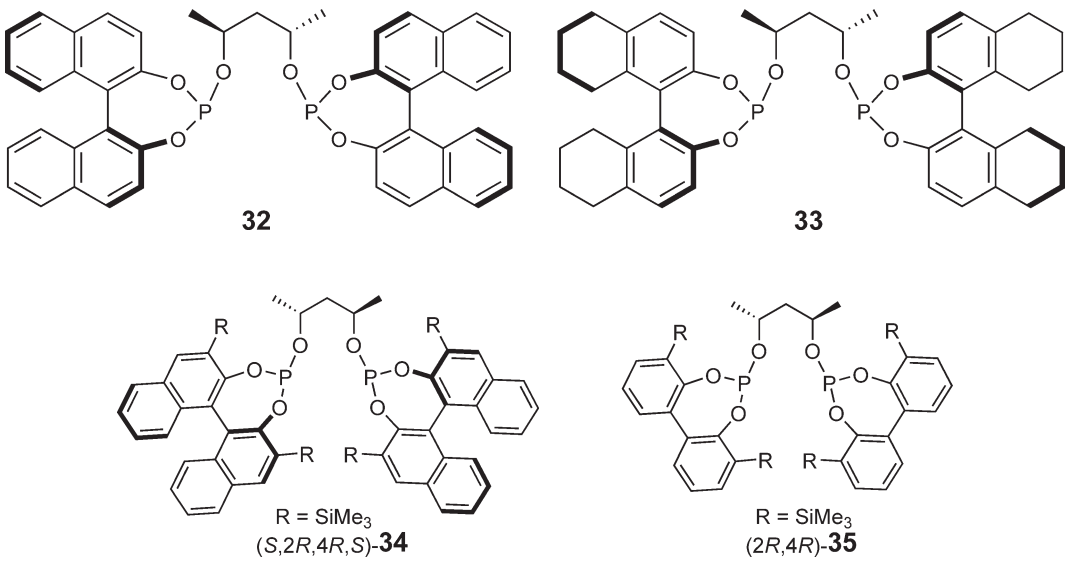
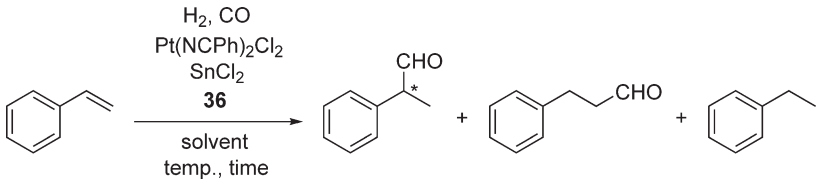


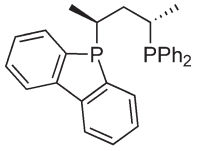
Figure 13 Chiral ligands for asymmetric hydroformylation of styrene.

Table 7 Hydroformylation of styrene using bisphosphine **36** as a ligand



Time (h)	*Temp* (°C)	*Conv.*[a] (%)	*TOF* (mol mol$^{-1}_{Rh}$ h^{-1})	*Percent aldehyde*[b]	*i*/*n*[a]	*Percent ee (absolute configuration)*[a]
45	24	70	29	94	85/15	89 (*S*)
27	24	43	27	84	89/11	88 (*S*)
8	70	64	139	87	56/44	43 (*S*)

[a]Determined by GC.
[b]Aldehydes/(aldehydes + ethylbenzene).



36

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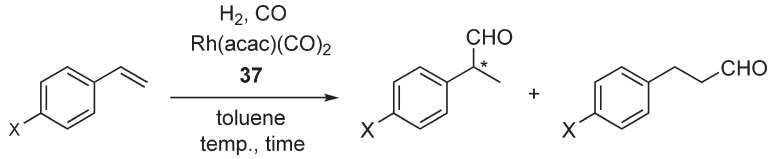
Asymmetric hydroformylation of styrene using sugar-based bis-phosphite ligand–Rh systems, reported by Diéguez and Claver in 2000, gave ee values up to 91 and regioselectivities up to 98.8% (Table 8).[59] Later, systematic studies on the varying configuration at the C3 and C5 positions of the sugar-based ligand system showed that **37** has the best combination of stereogenic centers to give the highest ee values.[60] Introduction of Me_3Si group to the biphenyl moiety also resulted in high ee values.[61]

Hydroformylation of functionalized ethenes has been considered more difficult than that of arylethenes because of the low reactivity of the substrates and possible undesired side-reactions. Here, we focus on the recent progress of asymmetric hydroformylation of such functionalized alkenes. With (*R*,*S*)-BINAPHOS–Rh(I), vinyl acetate is converted into (*S*)-2-acetoxypropanal (86% yield, 92% ee) along with 3-acetoxypropanal (14% yield).[49] It should be noted that high syn-gas pressure of a total of 10 MPa was required to achieve the highest performance. The catalyst system (*R*,*S*)-BINAPHOS–Rh(I) is also suitable for other polar substrates, such as vinyl phthalimide, *p*-tolyl vinyl sulfide, and 3,3,3-trifluoro-1-propene.[49,62] A sugar-based bis-phosphine ligand **38**–Rh system gives a high yield (96%), high enantioselectivity (92% ee), and high regioselectivity (*i*/*n* = 95/5) in the hydroformylation of vinyl acetate (Figure 14), but not of styrene and norbornene.[63] This specificity for vinyl acetate is explained by a transition state structure with a hydrogen bond at the olefin-insertion step. Asymmetric hydroformylation of vinyl acetate using bis(diazaphospholidine) **39**–Rh catalyst system (Figure 14) affords a highly enantioenriched aldehyde product (90.3% yield, 89% ee, *i*/*n* = 94.5/5.5).[64] Prolonged reaction time in the **39**/Rh system sometimes affords the corresponding 2-acetoxypropan-1-ol and acetyl-migrated 1-acetoxypropan-2-ol through an overreduction. Asymmetric hydroformylation of methyl acrylate is also performed by using an Rh–**40** system to give an enantioenriched aldehyde (95% conv., *i*/*n* = 97/3, 92% ee).[65] Recently Klosin reported that two types of ligands **41** and **42** are suitable for asymmetric hydroformylation of allyl cyanide (96% conv., *i*/*n* = 7.1/1, 90% ee for **41**; 100% conv., *i*/*n* = 4.1/1, 87% ee for **42**).[66–68] In paticular, **42**/Rh shows an exceptionally high activity (TOF = up to 9,000 mol mol$_{Rh}^{-1}$ h^{-1}) without decreasing ee values.[67] The resulting chiral, branched *β*-cyanoaldehyde product can be converted into important chiral building blocks for potent non-peptide gonadotropin releasing hormone antagonist[69] and novel tachykinin NK_1 receptor antagonist,[70,71] both disclosed by Takeda.

11.13.2.3 New Reaction Media and Catalysts for Separation

In 1976, water-soluble triarylphosphine, TPPTS (**43**, Figure 15), was synthesized and used for two-phase hydroformylation system. Here the rhodium catalyst is soluble in water, whereas the substrate and the product remain in organic solvents. The catalytic performance of the rhodium–TPPTS complexes is similar to the ordinary

Table 8 Asymmetric hydroformylation of styrene derivatives using a sugar-based ligand **37**



X	*Temp.* (°C)	*Time* (h)	*Conv.*[a] (%)	*TOF*[b] (mol mol$^{-1}_{Rh}$ h^{-1})	*Percent regio*[c]	*Percent ee (absolute configuration)*[a]
H	40	6	100	174	97.9	78 (*S*)
H	20	48	83	18	98.6	90 (*S*)
F	20	48	80	17	98.8	89 (+)
OMe	20	48	81	16	98.6	91 (−)

[a]Determined by GC.
[b]determined after 1 h.
[c]Percent regio defined as $i/(j+n)$.

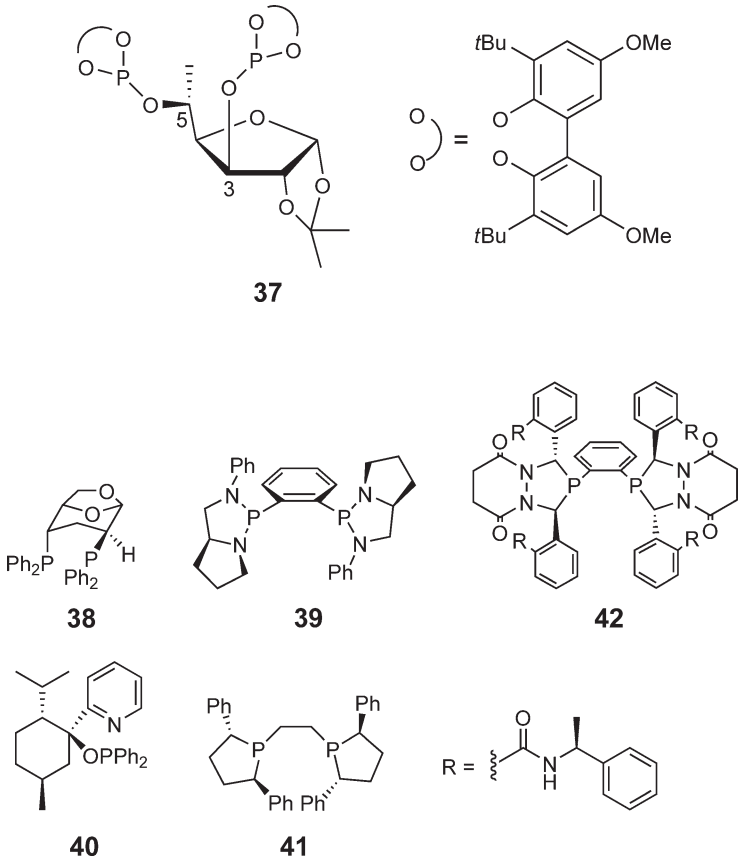


Figure 14 Bidentate ligands for asymmetric hydroformylation of olefins bearing a polar substituent.

triarylphosphine complexes.[72] The soluble phosphine makes the separation step easier, so that the TPPTS processes are commercialized by Ruhrchemie following the initial work conducted by workers at Rhône-Poulenc[73] for the production of butanal from propene. After the discovery of TPPTS, many types of heterogeneous catalyst systems have been designed for better separation. The catalyst systems can be classified into two types: (i) a biphasic catalyst system using non-organic solvent to dissolve the catalyst, and (ii) an immobilized catalyst system where the catalyst is fixed on the solid surface. The following are recent examples of these catalyst systems for easier separation.

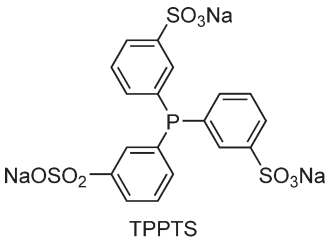


Figure 15 Water-soluble derivative of PPh_3, TPPTS.

11.13.2.3.1 Water

History of the water/organic solvent biphasic catalyst system starts with the invention of water-soluble ligands. The aldehyde selectivity and regioselectivity of the hydroformylation using water-soluble ligands are almost similar to those in traditional homogeneous phase catalyst systems. Here, we focus on some examples of water-soluble catalyst systems, which give high selectivities.

As Herrmann reported, hydroformylation of propene using a polysulfonated bis-phosphine ligand BINAS–Na (**44a**, Figure 16) proceeds efficiently and regioselectively ($n/i = 98/2$) in a water–organic solvent biphasic system.[74,75] The catalyst activity is improved [TOF = 178 $mol_{aldehyde}/(mol_{Rh} \cdot min)$] by use of the binaphthyl skeleton, whereas BISBIS ligand **44b**, a sulfonated analog of BISBI **4** that gives high n/i ratio in the homogeneous system, affords lower activity (TOF = 64) than that of BINAS–Na.[76,77] Hanson synthesized a new sulfonated BISBI derivative **44c** that bears pendant alkyl chains (Figure 16) and applied it to hydroformylation of 1-octene to find out whether the activity is improved [TOF = 12.3 $mol_{aldehyde}/(mol_{Rh} \cdot h)$; six times to shorter alkyl chain (three methylenes) derivative] while retaining a high n/i ratio (up to 91/9).[78] Later, Beller showed that pH and CO partial pressure significantly affected the regioselectivity in BINAS/Rh-catalyzed hydroformylation.[79] Under the optimized conditions, *n*-aldehyde is selectively produced ($n/i > 99$) from not only 1-alkenes but also from 2-alkenes via the isomerization of 2-alkenes to 1-alkenes prior to the hydroformylation.

Xantphos, one of the best ligands for *normal*-selective hydroformylation, can also be sulfonated to form 2,7-bis(SO_3Na)–Xantphos (**45**, Figure 17), which is applied to the hydroformylation of propene and 1-hexene in aqueous/organic biphasic media. The high activity, selectivity for aldehyde, and regioselectivity ($n/i = 30$ for propene, 35 for 1-hexene) are comparable to those obtained with Xantphos under homogeneous conditions.[80] Derivatives of Xantphos with surface-active pendant groups have been synthesized **46a–46c**.[81] Electron microscopy experiments show that **46a–46c** and their complexes form vesicles in water, if the hydrophobic part of the ligand is large enough ($n = 3, 6$). The presence of the vesicles makes solubilities of organic substrates better and enhances the reaction rate in the rhodium-catalyzed hydroformylation of 1-octene.

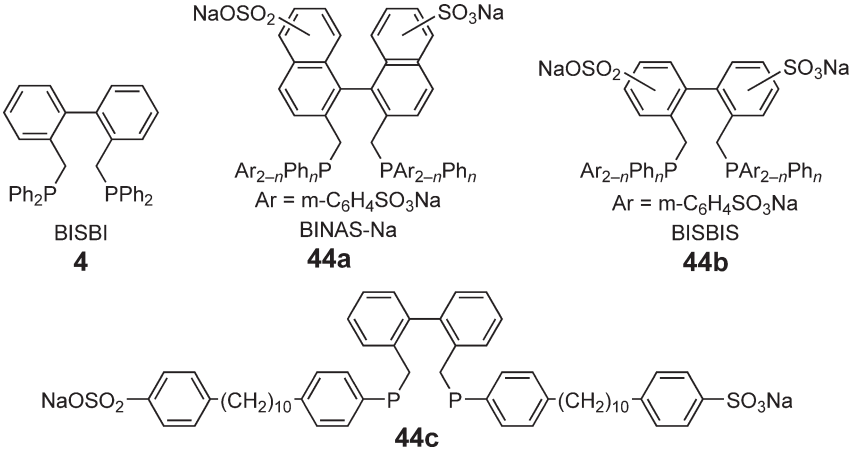


Figure 16 BISBI **4** and its sulfonated derivatives **44a–c** for *normal*-selective hydroformylation in aqueous/organic biphasic media.

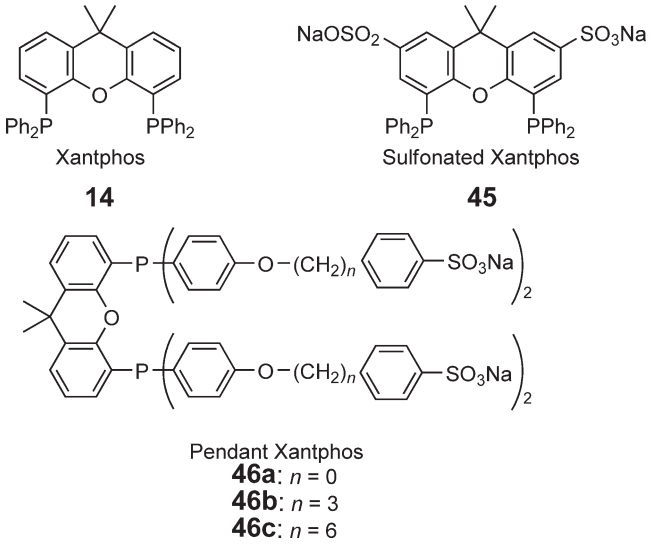


Figure 17 Xantphos **14** and its sulfonated derivatives for *normal*-selective hydroformylation in aqueous/organic biphasic media.

11.13.2.3.2 Fluorous solvent

The temperature-dependent miscibility of highly fluorinated solvents and organic solvents was applied to catalyst/product separation by Horváth and Rábai in 1994.[82] Donor ability of the phosphorus atom of triarylphosphines is retained even by an introduction of fluorinated substituents with some spacers such as $–OCH_2–$ or $–C_2H_4–$ between the aromatic ring and the perfluoroalkyl group. The donor ability is judged by $^1J_{PSe}$ of the corresponding triarylphosphine selenide in ^{31}P NMR spectroscopy.[83,84] Accordingly, it is possible to introduce perfluoroalkyl groups to conventional ligands for regio- or enantioselective hydroformylation without causing any electronic perturbation. Syntheses of perfluoroalkylated Xantphos derivatives have been reported only recently.[85] The *normal*-selective hydroformylation in fluorous media is anticipated to be disclosed.

11.13.2.3.3 Ionic liquid

Currently, two-phase industrial processes deal only with short-chain olefins (less than six carbon), because higher olefins are insufficiently soluble in water for an effective reaction to occur.[86] Ionic liquids exhibit better solubilities for higher olefins and thus offer the possibility of replacing the water layer to extend the usefulness of the biphasic technique. Chauvin was the first to apply this specific solvent to hydroformylation in 1996.[87] The reaction rate of Rh/TPPMS **47**-catalyzed hydroformylation of 1-hexene (Figure 18) in ionic liquid/organic solvent system is found

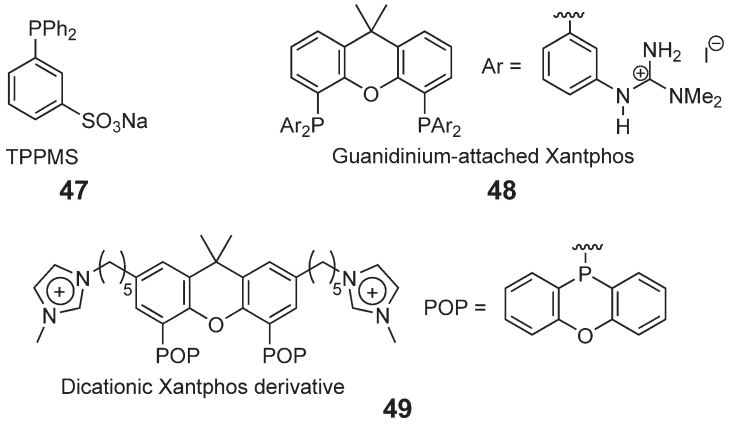


Figure 18 Ligands for hydroformylation in ionic liquid/organic solvent biphasic system.

to depend on the solubility of 1-hexene in various ionic liquids.[88] The kinds of ionic liquid also strongly affect the selectivity in the hydroformylation using Rh-sulfonated-Xantphos **45** system.[89] Guanidinium-attached Xantphos derivatives **48** are synthesized and applied to the rhodium-catalyzed hydroformylation of 1-octene. Regioselectivity (up to $n/i = 21$) in the reaction is comparable to that in common organic solvents without detectable Rh leaching by inductively coupled plasma (ICP) analysis.[90] Rh-dicationic Xantphos-derivative **49** system shows very high activity (up to 8,900 mol mol_{Rh}^{-1} h^{-1}) and a high n/i ratio (up to 54) at a stirring rate of 900 rpm under high H_2 partial pressure and low catalyst concentration ([Rh] = 1.7 mM, [**49**] = 27 mM). High concentration retards the reaction by forming a CO-bridged Rh dimer via loss of H_2.

11.13.2.3.4 Polymer-supported catalyst

Anchoring the catalyst to polymeric materials has some advantages[91] in easy product separation and catalyst recovery for recycling. The first example of a polymer-supported rhodium catalyst for hydroformylation was reported in 1975.[92] Since then, many reports have been published on polymer-supported catalysts; here, we focus on examples of *normal*-selective or enantioselective hydroformylation.

Several silica-supported Xantphos derivatives (Figure 19) are prepared using trialkoxysilyl-tethered Xantphos **50**, **51** through two approaches (Scheme 4): (i) simultaneous condensation with $Si(OMe)_4$ (sol–gel method) and (ii) direct reaction with commercially available silica gel (direct anchoring method).[93–97] The rhodium species on silica is identified as a cationic species $[LRh(CO)]^+$ by comparing with the corresponding complex for the homogeneous phase reaction. Exposure of the silica-supported cationic rhodium complex to CO/H_2 (1 : 1) produces a key complex, $LRh(H)(CO)_2$, as confirmed by ^{31}P NMR and IR spectrometries.[93] Although the activity is relatively low compared to the standard homogeneous catalysis, comparable activity and regioselectivity can be achieved under solvent-free

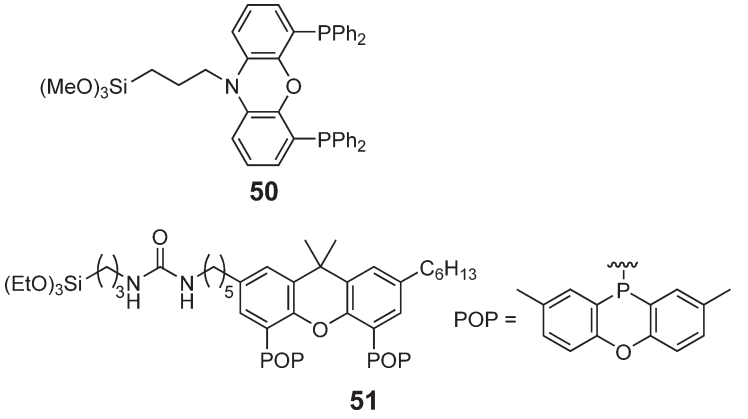
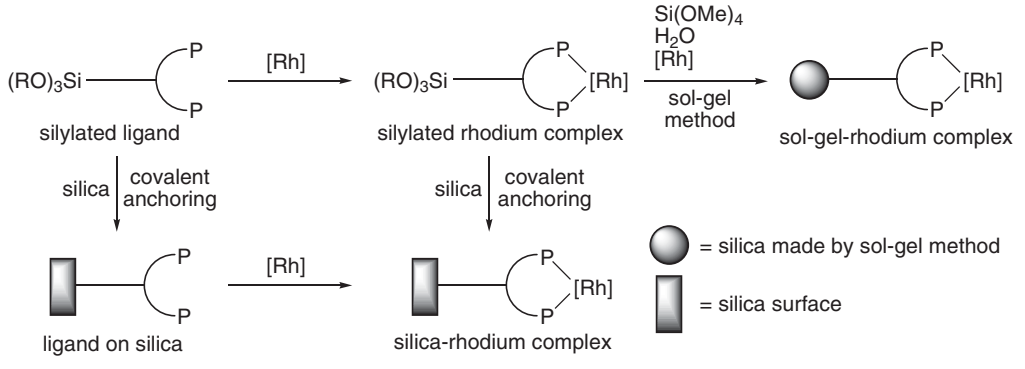


Figure 19 Xantphos derivatives for immobilization into silica-based solid.



Scheme 4 Methods for immobilization of rhodium complex to silica.

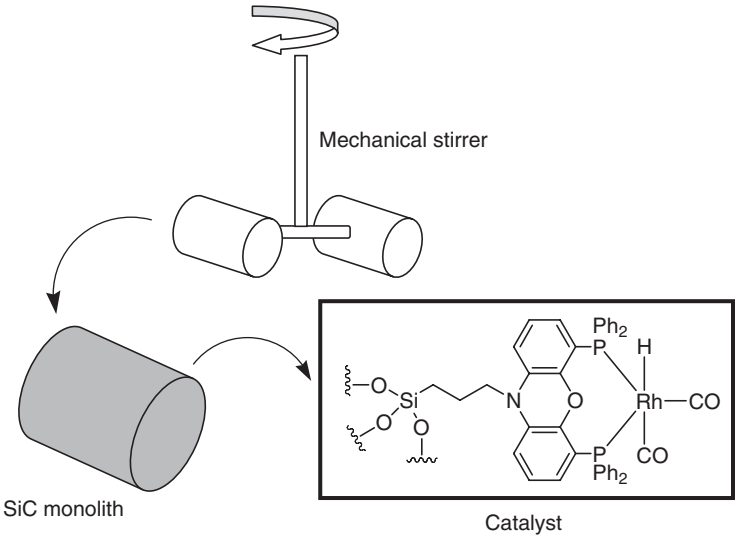


Figure 20 Xantphos derivative on the blade of stirrer made from silicon carbide, ''ROTACAT.''

conditions. The control of the conditions for the preparation of catalyst can afford *n*-aldehyde together with *n*-alcohol (up to 29.6%) via the reduction of *n*-aldehyde.[94] Silica-supported Xantphos system is also anchored to the blade of mechanical stirrer (ROTACAT, Figure 20).[97] The catalyst-containing device is used for hydroformylation of propene and 1-octene, and the activity and the regioselectivity are shown to be comparable to the previous silica-based catalyst system.

The ligand (*R*,*S*)-BINAPHOS **28** is also anchored to the polymer matrix (Figure 21).[98–103] Vinyl-substitued BINAPHOSes **52a–52c** are subjected to a radical co-polymerization with styrene derivatives to form the corresponding co-polymers PS-**52a**.[98,99] Hydroformylation of styrene, vinyl acetate, (*Z*)-2-butene, and CH_2═CH–CF_3 using a catalyst (Rh–PS-**52a**) made by complexation of the ligand with [Rh(acac)$(CO)_2$] gives *iso*-rich aldehyde products with high ee values (up to 92% ee). Since *m*-OMe substitution at PPh_2 moiety of BINAPHOS showed higher activity and selectivities in the asymmetric hydroformylation, rhodium complex of alkoxy-substituted vinyl–BINAPHOS **53** was polymerized to form catalyst PS-[Rh(acac)**53**].[101] The Rh–PS-**52a** system is also effective for the vapor-phase asymmetric hydroformylation of gaseous substrates, such as styrene, (*Z*)-2-butene, and CH_2═CH–CF_3, without any solvents.[100] In the case of CH_2═CH–CF_3, catalytic activity [TOF = 156 $mol_{aldehyde}/(mol_{Rh}\cdot h)$] is higher than that of the solution-phase reaction using **28** (TOF = 64).

11.13.2.3.5 Dendritic catalyst

Since dendritic molecules retain shape and size during reactions, isolation of dendritic catalysts by nanofiltration through a suitable membrane has been attempted. Two types of dendrimer structures are employed so far: (i) periphery-functionalized dendrimer containing many coordinating atoms as ligands at the periphery of a dendrimer molecule and (ii) core-functionalized dendrimer that contains a single coordinating ligand moiety at the center of a dendrimer molecule. These structural features bring about two types of special effects, such as, concentration effect and isolation effect.

Alper reported *iso*-selective hydroformylation (up to *i*/*n* = 36) of styrene and vinyl esters using silica- and resin-supported polyamide dendrimers (Figure 22, **54a–54c**, **55a**, **55b**) bearing PPh_2 groups on the periphery of the dendrimer molecules.[104–107] These catalysts are easily recyclable without significant loss of selectivity and activity. Cole–Hamilton reported that a dendritic catalyst system **56a**, **56b** connected to a silsesquioxane-core was efficient for *normal*-selective hydroformylation of 1-alkene in even higher regioselectivity (up to *n*/*i* = 15) than that in monomeric catalyst system.[108–113] In both cases, the chain length of the partial structure of dendrimer molecules affects the selectivity and activity. Xantphos, the ligand for highly *normal*-selective hydroformylation, was also incorporated into the core of carbosilanedendrimer by van Leeuwen **57a–57c**. High regioselectivity (up to *n*/*i* = 56) and activity (up to TOF of 180 $mol\,mol_{Rh}^{-1}\,h$) were obtained in a manner similar to the non-dendritic catalyst system.

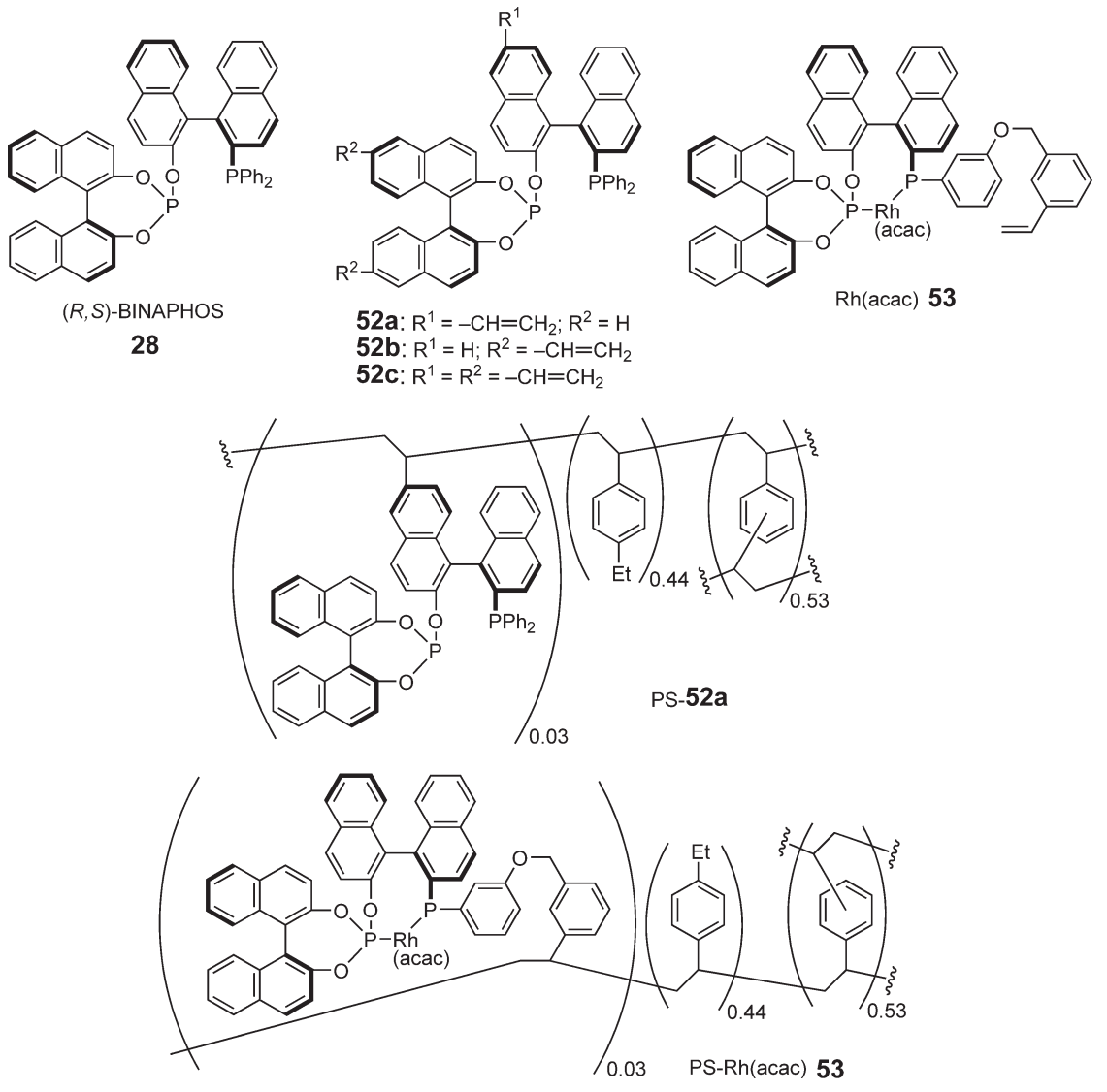


Figure 21 Vinyl–BINAPHOS derivatives and its co-polymer with ethylstyrene and divinylbenzene.

11.13.2.3.6 Supercritical carbon dioxide

Because of miscibility of supercritical carbon dioxide ($scCO_2$) with both reactant gases and organic substrates, Rathke and Klingler originally introduced $scCO_2$ as a reaction media of hydroformylation with a $[Co_2(CO)_8]$ catalyst system.[114,115] Later, fluorinated triarylphosphine ligands were shown to improve the catalyst activity and selectivity (n/i = up to 6) in $scCO_2$, although the selectivity did not reach the highest values as was observed in organic solvents.[116–118] In order to improve the separation efficiency, $scCO_2$ has begun to be used as a reaction media in combination with supported catalysts, such as polymer-supported, dendritic, and ionic liquid-supported ones. Described here are some examples containing typical ligands, which work well for the *normal*-selective or asymmetric hydroformylation.

Solvent-free asymmetric hydroformylation of an olefin library using a polymer-supported (*R*,*S*)-BINAPHOS catalyst system (PS-**52a**/[Rh(acac)$(CO)_2$]) in an $scCO_2$-flowing reactor gives a chiral aldehyde library.[102] An immobilized Xantphos–silica catalyst system (silica–**50**/[Rh(acac)$(CO)_2$]) is successfully applied to a continuous process of hydroformylation with flowing $scCO_2$ to achieve a high regioselectivity (up to $n/i = 50$, similar to that of unmodified catalyst).[96,119]

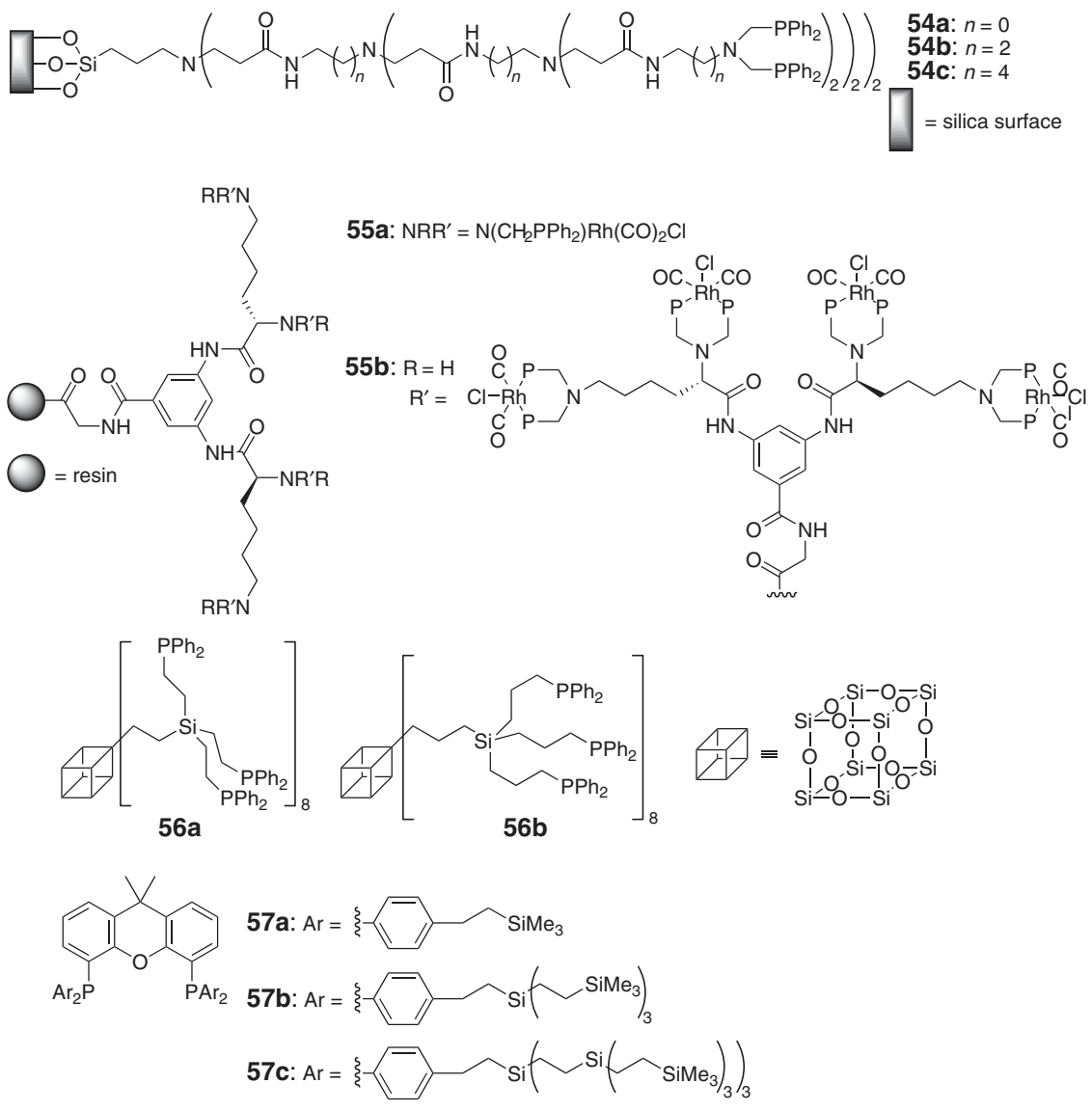


Figure 22 Dendritic catalysts for hydroformylation.

11.13.2.4 New Techniques for Mechanism Understanding

Because hydroformylation is a gas–liquid two-phase reaction under mostly high pressure, various special methods have been used for direct observation of the catalytic reactions. Here, we focus on the techniques recently developed for this purpose.

11.13.2.4.1 *In situ* observation by high-pressure IR spectroscopy

Historically, high-pressure IR spectroscopy has been one of the most important methods to measure intermediates or resting-state species in catalytic cycles. In 1968, Wilkinson observed $HRh(PPh_3)_2(CO)_2$ in the Rh/PPh_3 catalyst system by IR spectroscopy where an IR cell was connected via a tube to the autoclave. A related study was performed more recently by Moser *et al.*,[120,121] who applied their cylindrical internal reflectance IR cell. They determined the rate-limiting step of the reaction and identified some inactive rhodium dimers as a result of decomposition of the active hydrido species. A very extensive and careful study was carried out by Garland on phosphine-free systems.[122–125] *In situ*

IR spectroscopy has revealed that an acylrhodium complex, Rh(acyl)$(CO)_4$, is a resting state of the catalytic cycle. On the other hand, van Leeuwen, using a rhodium complex of a monodentate bulky phosphite, reported that the rate-determining step varies depending on the olefins employed, that is, hydrogenolysis for 1-octene and olefin coordination for cyclohexene,[11] whereas the styrene coordination step is a candidate for the rate-determining step when the hydroformylation is carried out at high pressure of syn-gas (up to $H_2CO = 12$ atm/18 atm) using the bidentate ligand (2,4-bis-diphenylphosphino)pentane (BDPP).[126] van Leeuwen has also reported that several steps may contribute to the reaction rate in the 1-octene hydroformylation catalyzed by Rh and a monodentate phosphorus diamide as a ligand.[127] Thus, even with the same catalyst system, the rate-determining step can vary depending on the substrates or reaction conditions.[128]

Recently, IR monitoring of asymmetric hydroformylation and *normal*-selective hydroformylation are performed to identify the catalytic intermediates in detail. Nozaki reported mechanistic studies on hydroformylation catalyzed by Rh–(*R*,*S*)-BINAPHOS **28** or its 3-methoxy derivative (**31**, Figure 23, see also Section 11.13.2.2.1). The following two features are disclosed: (i) olefin insertion into the Rh–H bond is irreversible, and (ii) the reaction rate is dependent on the styrene concentration and is independent on hydrogen pressure.[51] To investigate the origin of the very high activity of Xantphos-type ligands **58** and **59** for hydroformylation and isomerization, van Leeuwen measured the rate of CO dissociation from the (bis-phosphine)Rh$(CO)_2$H complex using ^{13}CO labeling in rapid-scan IR experiments at 40 °C.[129] The CO dissociation is found to obey simple first-order kinetics. The (bis-phosphine)Rh$(^{13}CO)_2$H complexes, prepared *in situ* from Rh(acac)$(CO)_2$ and bis-phosphine under an atmosphere of $^{13}CO/H_2$ (1 : 4), allow the observation of rate constants k_1 listed in Table 9. The CO dissociation rate for ligand **58** is in the same range as the other ligands. The CO dissociation rate for ligand **59**, however, proves to be four to six times higher. Furthermore, independency of the concentration of (bis-phosphine)Rh$(^{13}CO)_2$H complex toward k_1 can conclude that the CO dissociation for these complexes proceeds by a purely dissociative mechanism and follows a first-order rate law. Later, the rates of hydroformylation using sterically varied Xantphos derivatives (**10–18**, Figure 8, see above) as a ligand were measured by the high-pressure IR spectroscopy.[40] The observed CO dissociation rates do not correlate with the natural bite angle of the ligand. These findings indicate that the bite angle effect on hydroformylation activity is dominated by the relative rate of coordination of CO versus an alkene to the unsaturated (bis-phosphine)Rh(CO)H. The bite angle affects the selectivity in the steps of alkene coordination and hydride migration; the structure of the saturated (bis-phosphine)Rh$(CO)_2$H complex has only some circumstantial relevance to the selectivity.

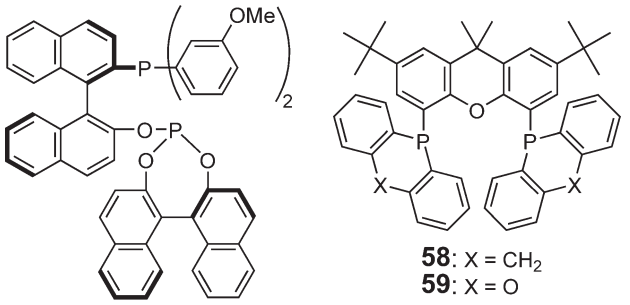


Figure 23 Bidentate ligands used for *in situ* IR monitoring.

Table 9 Rate constants for the CO dissociation from an LRh(H)$(CO)_2$ complex[a]

Ligand	R^2	k_1 (h^{-1})[b]
58	0.987	-288 ± 8
58	0.987	-266 ± 7
59	0.992	-1188 ± 29
59	0.990	-1171 ± 23

[a]Reaction conditions: [Rh] = 2.00 mM in *c*-C_6H_{12}, $P(CO) = 2.5$ MPa, $P(^{13}CO) = 0.1$ MPa, $P(H_2) = 0.4$ MPa, $T = 40$ °C, diphosphine/Rh = 5.
[b]Values of k_1 are least-square fit of lines from ln[Rh] versus time over the first 15 s for **58** or 4 s for **59**.

11.13.2.4.2 *In situ* observation by high-pressure NMR spectroscopy

As in the previous section, this section deals with two topics: (i) high-pressure NMR study on unmodified catalyst system and (ii) high-pressure NMR study on *normal*-selective or asymmetric hydroformylation.

As discussed in the Sections 11.13.2.2.1 and 11.13.2.2.2, the regio- and/or enantioselectivity is determined in the alkene-insertion step, which is virtually irreversible at moderate temperatures and sufficiently high pressures of CO, when phosphine or phosphite ligands are employed. Therefore, the structure of the five-coordinate alkene complex is thought to play a crucial role in controlling the regioselectivity of the reaction. Previously, the $[HRh(PPh_3)_2(CO)_2]$ complex was characterized as an equilibrium mixture between equatorial–equatorial (ee) and equatorial–apical (ea) complex isomers by Brown and Kent using ambient-pressure NMR study.[131] Bianchini *et al.* have recently used high-pressure NMR spectroscopy to evaluate the influence of CO/H_2 pressure on the equilibria of all the Rh–PPh_3 species that are visible on the NMR timescale during the hydroformylation of 1-hexene by $[HRh(CO)(PPh_3)_3]$.[132] As many as four rhodium resting states are identified and some factors are found to control their formation/interconversion/inhibition. Upon introduction of CO/H_2 gas to the reaction mixture, several new signals are observed in the NMR spectrum: the $[HRh(CO)(PPh_3)_3]$ complex is converted into the five-coordinate $[HRh(PPh_3)_2(CO)_2]$ complex and a signal corresponding to the $[Rh(acyl)(CO)_2(PPh_3)_2]$ complex is also assigned. The stability and composition of the rhodium–hydride complexes are found to be dependent on the CO/H_2 pressure. In the absence of H_2, the loss of a H_2 molecule from 2 equiv. of five-coordinate $[HRh(PPh_3)_2(CO)_2]$ complex made most of the existing rhodium species become a Rh(0) dinuclear complex, $[(PPh_3)_2Rh(CO)(\mu\text{-}CO)]_2$, that is five-coordinate acyl complex $[Rh(acyl)(CO)_2(PPh_3)_2]$ cannot accumulate during the carbonylation reaction in the absence of H_2. Upon venting the NMR cell, several resting states including Rh dimeric species are formed whose equilibrium concentrations are dependent on the pressure of carbon monoxide and hydrogen.

For *normal*-selective hydroformylation, electronically perturbed Xantphos-based ligand system is extensively studied by high-pressure NMR spectroscopy[42] to reveal that $[HRh(L)(CO)_2]$ complexes in solutions consist of isomeric mixtures (ee and ea). Details are described in Figure 9 and Table 4 in Section 11.13.2.2.1. Rhodium-catalyzed hydroformylation of 1-octene using bis(phosphite) ligand **3b** (Figure 2) is monitored *in situ* by high-pressure ^1H and ^{31}P NMR and Fourier transform infrared (FTIR) spectroscopies.[133] Four species, [Rh(acac)**3b**], $[HRh(CO)_2$**3b**], and two dimeric complexes are found to appear sequentially during different stages of the catalysis when $[Rh(acac)(CO)_2]$ is used as the catalyst precursor. The former two complexes [Rh(acac)**3b**] and $[HRh(CO)_2$**3b**] are independently synthesized, and their stoichiometric and catalytic reactivity is evaluated. The major species present during the catalysis is $[HRh(CO)_2$**3b**]. Any ligand degradation via hydrolysis or reaction with the aldehyde is not observed by means of ^{31}P NMR spectroscopy. Furthermore, poor mass transfer of reactive gases from the headspace of the NMR tube is also found to lead to rapid depletion of CO and H_2 from the solution, thereby resulting in favored alkene isomerization.

11.13.2.4.3 ^{103}Rh NMR spectroscopy

^{103}Rh NMR spectroscopy is also considered to be an important tool for the characterization of catalytic intermediates. In 1999, Elsevier focused on the bite angle and electronic effect of the Xantphos-based bis-phosphine ligands (**11–16** in Figure 8 and **19–24** in Figure 9) toward ^{103}Rh NMR chemical shift obtained from ^1H-^{103}Rh heteronuclear multiple quantum correlation (HMQC) technique in the $HRh(CO)_2$(ligand) complexes (Table 10).[134] A rough negative correlation ($R = 0.793$) is observed between bite angle of bis-phosphine ligand and ^{103}Rh NMR chemical shift, whereas a positive correlation ($R = 0.980$) is noticed between Hammett parameter of the *para*-substituent and ^{103}Rh chemical shift in the substituted thixantphos complexes **13** and **19–24**. In 2001, van Leeuwen used the ^{13}C–^{103}Rh HMQC technique to characterize a major complex as an acyl complex $[L_2Rh(acyl)(CO)_2]$ (**61**, L = **60** in Scheme 5) where both ligands were located at equatorial position with the observation of isomeric complexes in the reaction mixture. The same reports noted that four inequivalent doublets observed by low-temperature ^{31}P NMR spectroscopy indicate that the ee–ea (equatorial–equatorial–apical–equatorial) isomerization is slowed down upon cooling to 193 K. Additionally, ^{13}CO labeling study has revealed that CO ligands exchange with dissolved ^{13}CO, and the insertion–desorption equilibrium between $[L_2Rh(acyl)(CO)_2]$ and $[L_2Rh(alkyl)(CO)_2]$ complexes exists above 223 K. The exchange rate k_1 is larger than k_2 which is similar to k_3.

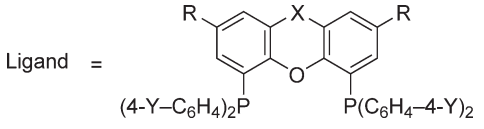
11.13.2.4.4 EXAFS (extended X-ray absorption fine structure)

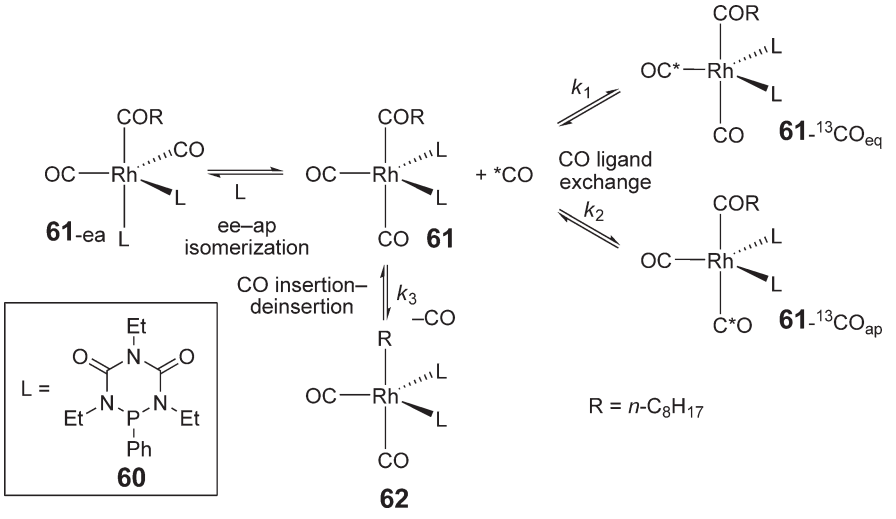
Due to the heterogeneity of the recently advanced solid-support catalyst for the hydroformylation, direct structural information on catalyst surface has been collected by extended X-ray absorption fine structure (EXAFS). Iwasawa is the first to directly characterize the structure of dimeric rhodium complexes supported on

Table 10 Natural bite angles, ^{103}Rh NMR chemical shifts, and Hammett parameter of Y in HRh(ligand)(CO)$_2$[a]

Ligand	*R*	*X*	*Y*	β_n[b]	$\delta(^{103}Rh)$[c]	σ_P[d] of Y
11	H	PPh	H	ca. 103	−828.2	
12	H	$SiMe_2$	H	106.2	−817.4	
13	Me	S	H	106.4	−840.8	0.00
14	H	CMe_2	H	109.8	−800.8	
15	H	$C{=}CMe_2$	H	ca. 110	−821.2	
16	H	NH	H	115–120	−785.3	
24	Me	S	CF_3	109.3	−850.9	0.54
23	Me	S	Cl	107.8	−840.7	0.23
22	Me	S	F	106.6	−835.6	0.26
21	Me	S	Me	106.7	−831.5	−0.17
20	Me	S	OMe	106.9	−825.3	−0.27
19	Me	S	NMe_2	109.1	−814.3	−0.83

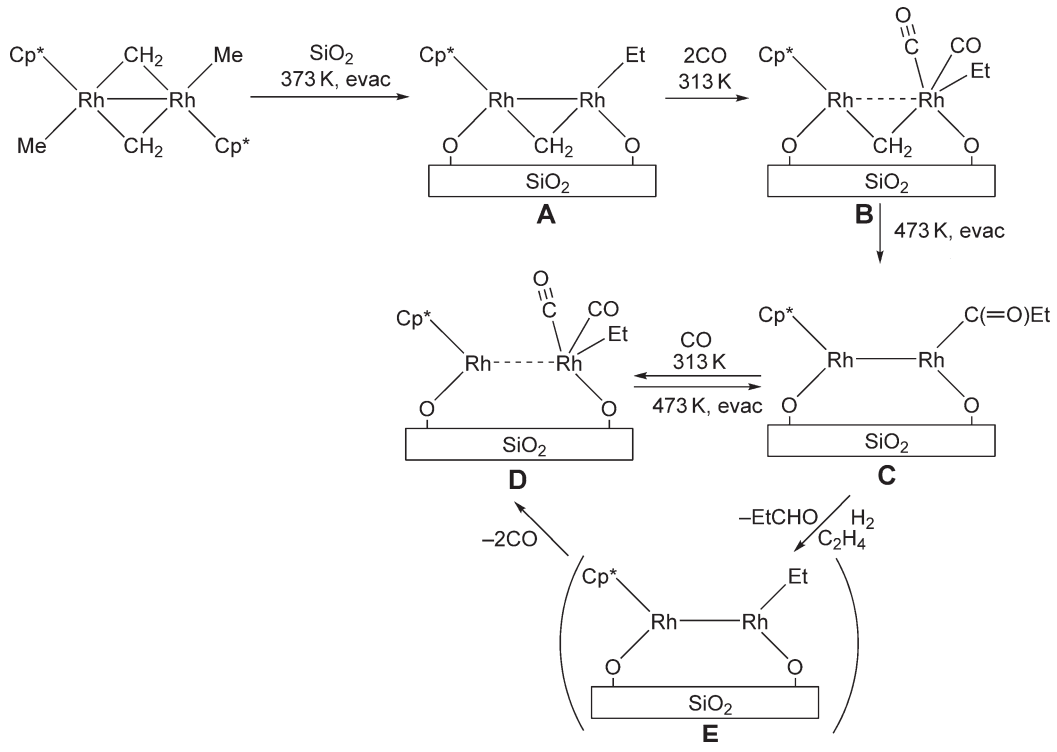
[a]At $T = 298$ K, solvent C_6D_6.
[b]Natural bite angle.
[c]Estimated from ^{1}H–^{103}Rh HMQC.
[d]Hammett parameter.





Scheme 5 Equilibrium contains acylrhodium complex **61**.

SiO_2 surface using EXAFS and IR spectroscopy and compare the data with those of reference compounds.[135,136] The Rh–Rh bond in the attached Rh dimer **A** (Scheme 6, Rh–Rh = 0.262 nm) is shown to be cleaved by CO adsorption to form a monomer pair **B** [$Rh(C_2H_5)(CO)_2$(O–Si) + $Rh(C_5Me_5)$(O–Si)]. Heating the monomer pair (**B**) to 473 K under vacuum results in CO insertion with new peaks exhibiting at 1,710 and 1,394 cm^{-1} due to the acyl ligand in **C**. The insertion is promoted by rebonding of the two adjacent Rh atoms observed at 0.270 nm. The Rh–acyl dimers are reversibly converted into the previous monomer pair **D** without Rh–Rh bonding by CO admission. The formation of acyl ligand in the species **C** is also confirmed by the reaction with H_2 at 473 K, where propanal is produced, showing a decrease in the peak at 1,710 cm^{-1} with an appearance of Rh–Rh bond in the species **E**.



Scheme 6 Structural change of Rh dimers attached on SiO_2 surface.

11.13.2.5 Applications to Organic Synthesis

One of the goals of homogeneous asymmetric catalysis is its application to manufacture fine chemicals such as pharmaceuticals, agrochemicals, flavors, and fragrances.[137] When hydroformylation is applied to such a purpose, substrate olefins often possess one or more chiral centers. Meanwhile, sequential, cascade, and tandem reactions to construct a complex structure of organic molecules are also important to make such products. Here, we focus on the following two topics: (i) diastereoselective hydroformylation of chiral substrates to make products possessing two or more stereocenters in a diastereoselective manner and (ii) sequential, cascade, and tandem reactions consisting of hydroformylation and other reactions.

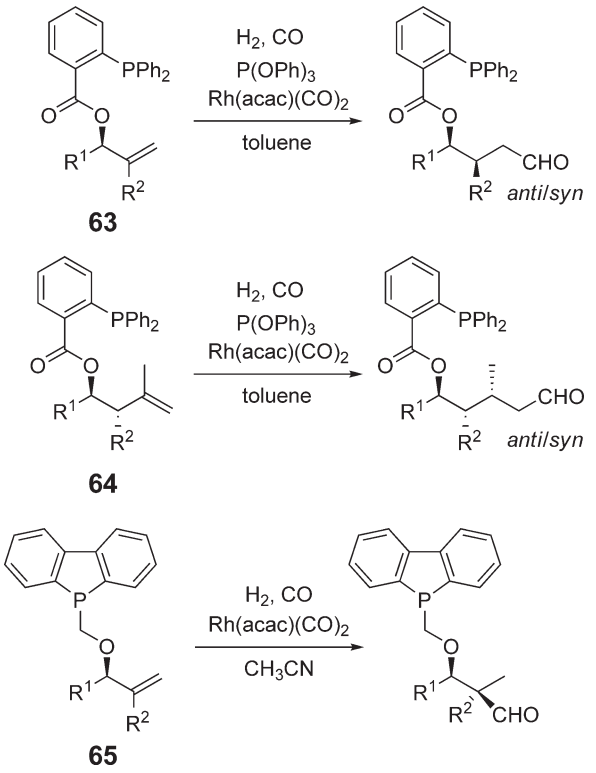
11.13.2.5.1 Diastereoselective hydroformylation for synthesis of natural products and pharmaceuticals

Breit reported a substrate-directed diastereoselective hydroformylation of acyclic methallylic and homomethallylic alcohols protected by 2-(diphenylphosphanyl)benzoyl group (**63** and **64**) using a $P(OPh)_3/Rh(acac)(CO)_2$ system and isolated the corresponding *anti*-aldehydes in good diastereoselectivity (Table 11, up to 96/4 = *anti*/*syn*).[138–142] They carefully characterized two conformational isomers of the $[P(OPh)_3]Rh(H)(CO)$(substrate) complex containing an olefin coordination to the rhodium metal by comparison between the structures generated from molecular mechanics calculations and results from nuclear Overhauser enhancement spectroscopy (NOESY) experiments. The equilibrium ratio of these isomeric complexes nicely explained the diastereoselectivity in the intramolecular carbonylation.[140,142] Introduction of a bulky substituent to the substrate improves the diastereoselectivity up to 99/1 = *anti*/*syn*.[142] The resulting products, benzoyl-protected γ- or δ-hydroxyaldehydes, can be converted into the corresponding hemiacetals after deprotection.[140,141] Leighton also reported a similar catalyst system containing dibenzophosphol-5-ylmethyl ether as a protecting group for allylic alcohol **65**.[143] The protecting group, dibenzophosphol-5-ylmethyl ether, can be selectively cleaved at a C–P or O–P bond by lithium di-*tert*-butylbiphenylide or $LiAlH_4$ to form the corresponding methyl ether or diol, respectively. Diastereoselectivity in this system is up to 94/6 = *anti*/*syn*.

Table 11 Diastereoselective hydroformylation of methallylic and homomethallylic alcohols protected by diphenylphosphanyl benzoyl group

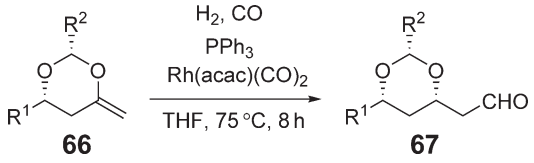
Ester	R^1	R^2	*T* (°C)	*t* (h)	*Yield* (%)[a]	*anti/syn*[b]
63	^{i}Pr	H	90	24	97	96/4
63	Ph	H	90	24	99	92/8
63	Ph	^{i}Pr	60	33	97	99/1
63	Bn	^{t}Bu	60	40	95	99/1
64	^{i}Pr	H	50	72	93	91/9
64	^{i}Pr	H	70	24	99	87/13
64	^{i}Pr	H	90	24	99	70/30
64	^{i}Pr	Me	50	168	91	96/4
64	Ph	H	30	120	72	90/10
64	^{n}Hex	H	30	168	81	90/10
65	Me	H	65	24	92[c]	81/19
65	Ph	H	65	24	96[c]	86/14
65	^{i}Pr	H	65	24	94[c]	94/6

[a]Isolated yield after column chromatgraphy.
[b]Determined by ^{1}H NMR of the crude product.
[c]Regioselectivity was determined as *i*/*n* > 98/2.



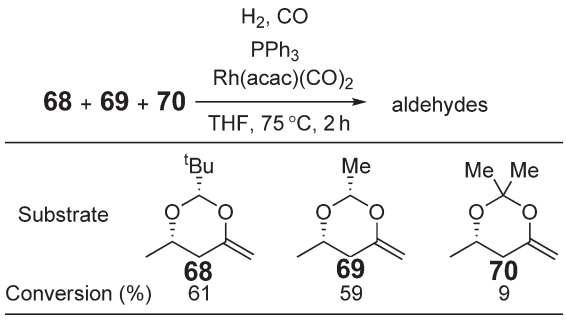
Leighton demonstrated that 4-methylene-1,3-dioxanes can be converted into the corresponding protected 3,5-dihydroxyaldehyde in a highly diastereoselective fashion (Table 12, no C3 diastereomer is detected).[143,144] It was also revealed that the axial methyl group decelerates the reaction as evidenced by a competition experiment possibly because of a 1,3-diaxial repulsion during an attack of rhodium hydride to the olefin (Equation (2)). This system is applied by Breit to the hydroformylation of 4-vinyl-1,3-dioxane to construct a building block (Scheme 7, **72**) for the natural product bafilomycin A_1 **71**.[145,146]

Table 12 Diastereoselective hydroformylation of 4-methylene-1,3-dioxane derivatives



R^1	R^2	*Yield*[a] (%)	*n*/*i*[b]
H	^{t}Bu	81	12
Me	^{t}Bu	72	13
Me	Me	75	13

[a]Isolated yield after column chromatgraphy.
[b]Determined by GC analysis.



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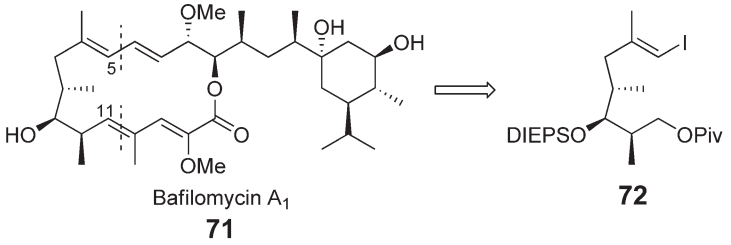
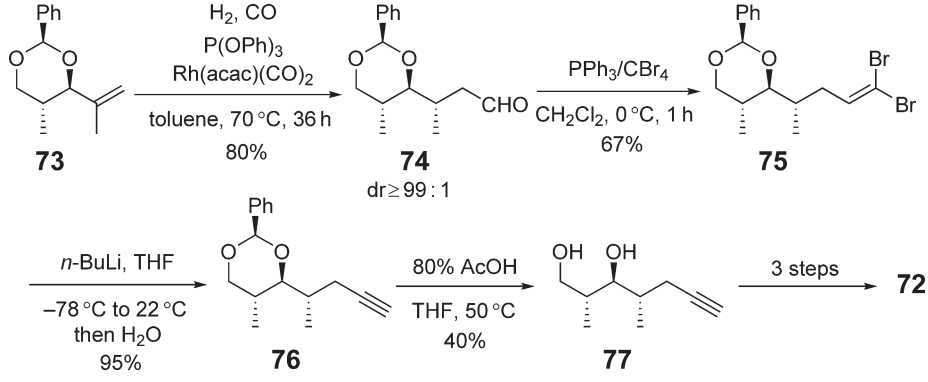
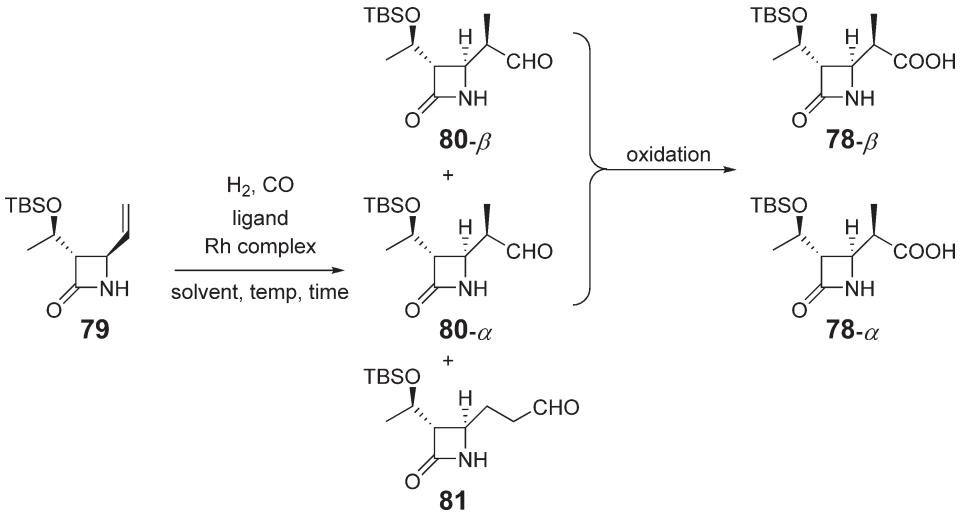




Scheme 7 Synthesis of **72**, a synthetic intermediate for Bafilomycin A_1 **71**, using the diastereoselective hydroformylation.

Takasago group and Nozaki reported the synthesis of the 1-methylcarbapenem intermediate **78** by hydroformylation of the 4-vinyl β-lactam, (3*S*,4*R*)-3-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-vinyl-2-azetidinone **79** using Rh/BINAPHOS system followed by oxidation (Scheme 8, Table 13, entry 1).[147] Slightly better selectivities are

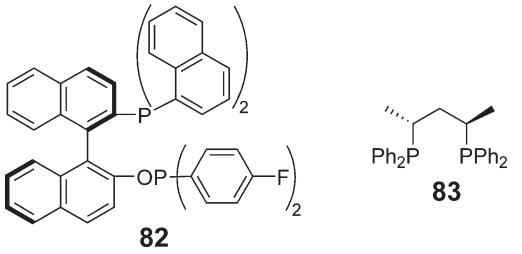


Scheme 8 Hydroformylation of vinyl–β-lactam **79** followed by oxidation.

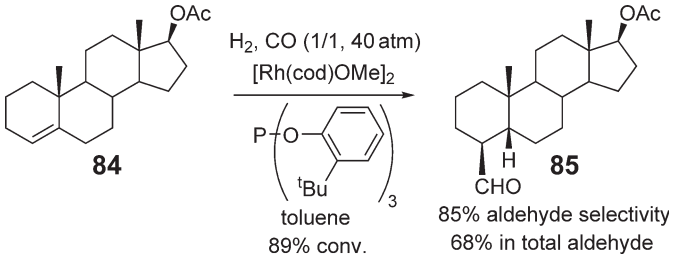
Table 13 Results of hydroformylation of **79**

Ligand	*Rh complex*	*Solvent*	P_{CO} (atm)	*Temp* (°C)	*Time* (h)	*Yield*[a] (%)	**80/81**[a]	α/β in **80**[a]
82	$Rh(acac)(CO)_2$	decane	50	60	6	95	74/26	96/4
83	$Rh(nbd)^+BPh_4^-$	DME	82	70	48	70[b]	93/7	92/8
83	$Rh(nbd)^+BPh_4^-$	decane	60	60	24	100	97/3	91/9

[a]Determined by NMR or GC.
[b]Conversion.



reported by two groups with a ligand system containing **83** (Table 13, entries *2* and *3*).[148,149] The Rh/BINAPHOS-catalyzed asymmetric hydroformylation has been successfully applied to the total synthesis of (+)-ambruticin by Jacobsen (Scheme 9).[150] A steroid skeleton could also be hydroformylated by Rh/phosphite system in a moderate yield (Equation (3)).[151] The reaction occurs preferentially at the β-face of the steroid framework forming a new steroid with *cis*-fusion of A and B rings.



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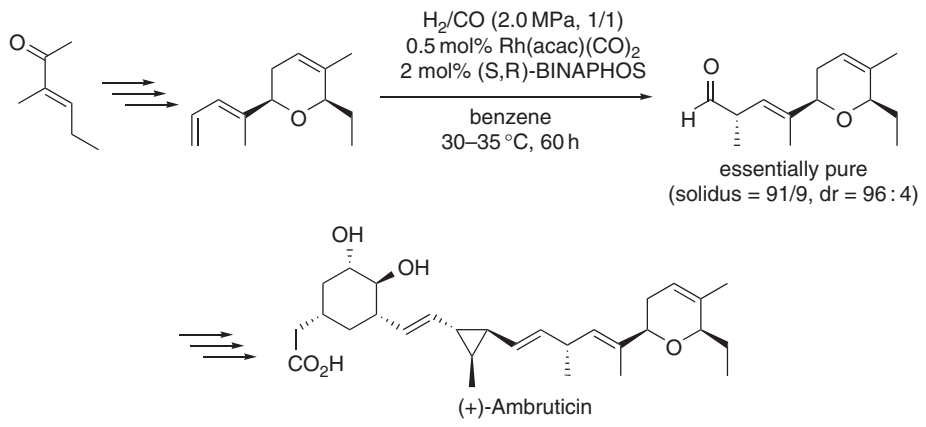


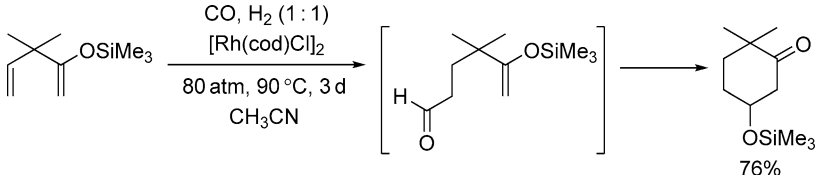
Scheme 9 Total synthesis of (+)-ambruticin via asymmetric hydroformylation.

11.13.2.5.2 Sequential, cascade, and tandem reactions to construct complex structures

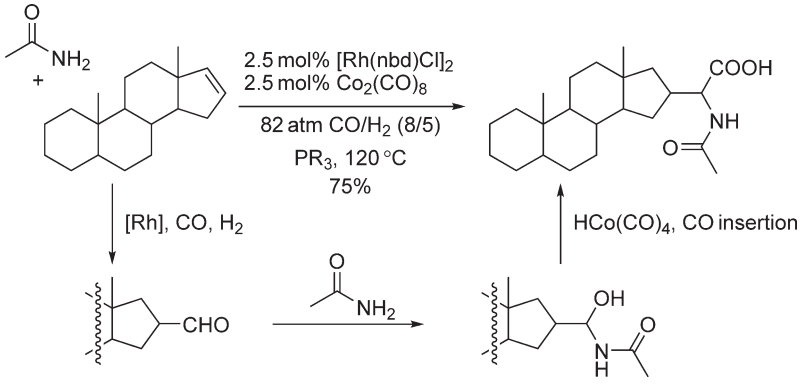
Because of the high and versatile reactivity of aldehyde in the organic transformations, hydroformylation reaction was often combined with other sequential reactions to perform several reactions in one pot. Here, we focus on such tandem reactions containing hydroformylation.

Auto-tandem hydroformylation–cyclization, catalyzed by $[RhCl(cod)]_2$, enables expansion of the organic skeleton of unsaturated silyl enol ethers (Scheme 10).[152] Linear aldehydes generated in the hydroformylation step subsequently undergo Rh-catalyzed, intramolecular Mukaiyama aldol addition. Bicyclic ketones are also accessible from cyclic silyl enol ethers.

Derivatives of the steroids androstene and pregnene have been transformed directly into *N*-acyl amino acids by an orthogonal catalysis procedure, utilizing $[RhCl(nbd)]_2$ and $Co_2(CO)_8$ (Scheme 11).[153] The rhodium phosphine catalyst (generated *in situ* in the presence of syn-gas and phosphine) affects hydroformylation of the internal olefin to generate aldehyde. In the presence of $Co_2(CO)_8$, *N*-acyl amino acids are obtained as the major products. An unstable amido alcohol intermediate, formed by reaction of the amide with aldehyde, is proposed to undergo cobalt-catalyzed CO insertion to yield the desired *N*-acyl amino acid.



Scheme 10 Hydroformylation–Mukaiyama aldol reaction.

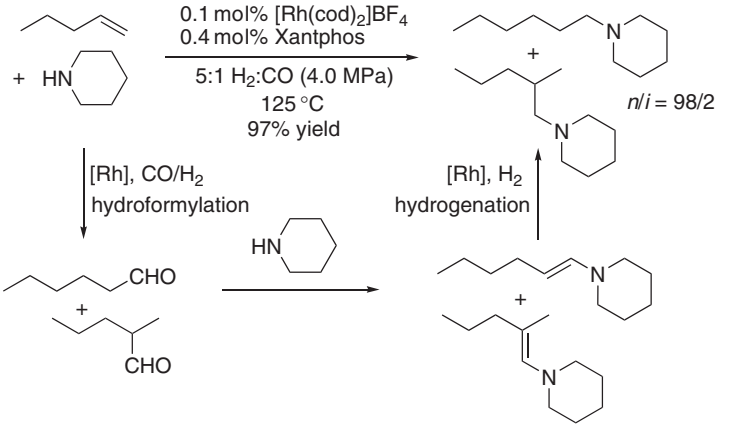


Scheme 11 Hydroformylation–amidocarbonylation.

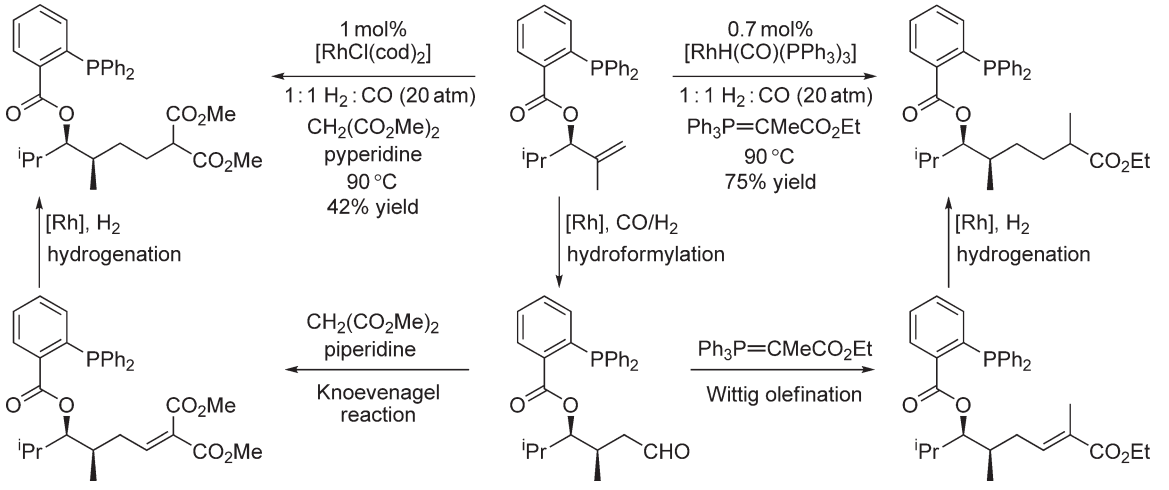
Most of the manufactured *normal*-aldehydes are converted into *normal*-alcohol via hydrogenation in a separate reactor after purification of aldehydes. This two-step process causes high cost and large fuel-energy consumption in manufacture of *normal*-alcohol. Accordingly, sequential hydroformylation–hydrogenation to afford *normal*-alcohols is one of the most important issues to be solved. As described in Section 11.13.2.3.4, some hydroformylation reactions co-produce *normal*-alcohol, as a result of hydrogenation of *normal*-aldehyde.[94] This process may be improved for future manufacturing.

Transformation of olefins to homologous amines can be achieved by sequential processes of catalytic hydroformylation, stoichiometric trapping with amine or ammonia to form imines or enamines, and their catalytic reduction (Scheme 12).[154] Once the catalytic process becomes efficient enough, such auto-tandem catalysis should offer an attractive alternative to the classical syntheses of amines via ammonolysis of alcohols, reductive amination of aldehydes, or hydrogenation of nitriles. Good to excellent yields of linear amines are obtained in a tandem catalysis protocol applicable to a wide range of olefins and amines, using an Rh–phosphine catalyst generated *in situ*. Xantphos is found to achieve excellent regioselectivity in the hydroformylation step, as well as superior reactivity in the ensuing enamine hydrogenation.

Extension of the C–C skeleton in methallylic alcohol derivatives has been performed by: (i) Rh-catalyzed hydroformylation, (ii) stoichiometric Wittig olefination of the resulting aldehyde, followed by (iii) Rh-catalyzed reduction of the C═C bond in the product (Scheme 13).[155] The *o*-diphenylphosphinobenzoate directing group used in this reaction promotes *syn*-specificity in the hydroformylation step. In a closely analogous tandem catalysis sequence, the Wittig olefination step is replaced by the base-catalyzed Knoevenagel condensation with malonates, β-keto esters, and β-diketones (Scheme 13).[156] The Knoevenagel route is favorable in view of atom economy: in principle, only water is a byproduct, whereas the Wittig route generates stoichiometric quantities of triphenylphosphine oxide.



Scheme 12 Hydroamination–condensation with amine hydrogenation.

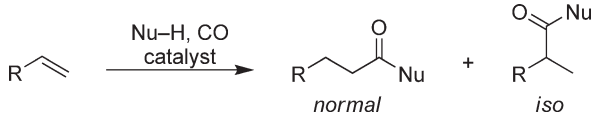


Scheme 13 Hydroformylation–Wittig olefination or Knoevenagel reaction-hydrogenation.

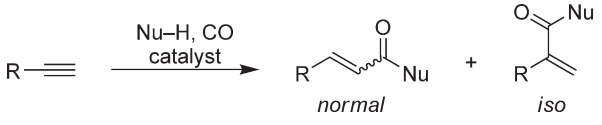
11.13.3 Other Hydrocarbonylation

11.13.3.1 Hydrocarbonylation Reactions

Carboxylic acids and their derivatives like esters, amides, anhydrides, and acyl halides are formally synthesized from olefins, carbon monoxide, and compounds represented by Nu–H such as H_2O, ROH, RNH_2, RCOOH (Equations (4) and (5)). Alkynes also react under similar conditions to afford the corresponding unsaturated carboxylic acid derivatives. These reactions have been named hydrocarboxylation, hydroalkoxycarbonylation, and hydroaminocarbonylation.



(4)



(5)

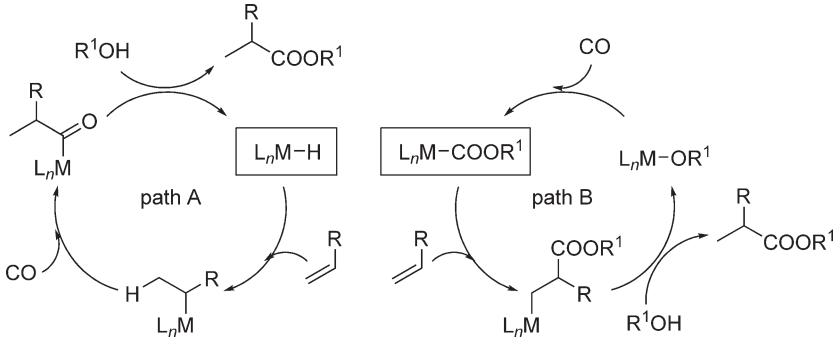
Nu-H = H_2O, ROH, RNH_2, RCOOH...

11.13.3.2 Mechanism of Hydrocarbonylation

Two possible mechanisms are suggested for the hydroalkoxycarbonylation of alkenes.[157–159] One is similar to that of hydroformylation in which a catalytic cycle starts with a hydridometal complex (Scheme 14, path A).[158] Here, olefin insertion takes place into an M–H bond, and then migratory insertion of CO into an alkyl–metal bond takes place to give an acylmetal complex. Alcoholysis of the acylmetal species reproduces the metal hydride and yields the product ester. The other mechanism involves an alkoxycarbonyl complex as an active species (path B).[157] Here, olefin insertion into a metal–carbon bond of the alkoxycarbonylmetal species is followed by alcoholysis to give the product ester and the alkoxymetal complex. Insertion of CO into the alkoxymetal species reproduces the alkoxycarbonyl complex. For other hydrocarbonylation reactions, R^1OH can be replaced by an appropriate nucleophile such as H_2O and R^1NH_2. No details have yet been disclosed on the mechanism of each reaction, which may change depending on catalyst metal and reaction conditions, especially the presence or absence of an acid or base.

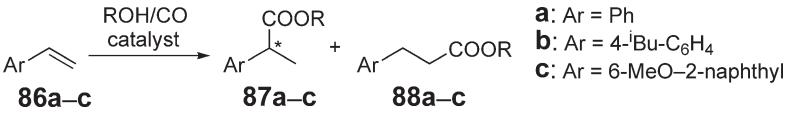
11.13.3.3 Asymmetric Hydrocarbonylation

Considering that the chiral aldehydes obtained by asymmetric hydroformylation of vinylarenes are often oxidized to give the corresponding acids that exhibit biological activities, asymmetric hydrocarboxylation and its related reactions naturally attract much attention. Unfortunately, however, less successful work has not been reported on this subject than on the hydroformylation. Palladium(II) is most commonly used for this purpose. Styrene and other vinylaromatics are most widely examined and the data for representative examples are summarized in Table 14. The products are of



Scheme 14 Two proposed paths for the hydroalkoxycarbonylation of olefins.

Table 14 Hydrocarbonylation of styrene **86a** and its derivatives **86b** and **86c** catalyzed by chiral Pd(II) complexes



Entry	*Substrate*	*R*	*Catalyst*	P_{CO}	*Temp* (°C)	*Time* (h)	*Yield* (%)	*i/n* **87/88**	*% ee of* **87** *(config.)*
1	**86a**	Me	$Pd(dba)_2$, **89**, CF_3CO_2H	1	50	4	94	94/6	52 (nr[a])
2	**86a**	Me	$Pd(OAc)_2$, **90**, TsOH	20	RT	20	17	44/56	86 (*S*)
3	**86a**	Me	$PdCl_2$, $CuCl_2$, **92**	50	80	24	97	96/4	99 (*S*)
4	**86b**	H	$PdCl_2$, (*S*)-**91**, HCl H_2O, $CuCl_2$, O_2	<1	RT	18	89	100/0	83 (*S*)
5	**86c**	H	$PdCl_2$, (*R*)-**91**, HCl H_2O, $CuCl_2$, O_2	<1	RT	18	64	100/0	91 (*R*)
6	**86c**	Me	$Pd(dba)_2$, **89**, CF_3CO_2H	1	50	4	nr[a]	nr[a]	42 (nr[a])
7	**86c**	Me	$PdCl_2$, **93**	30	60	24	21	100/0	53 (*S*)

[a]Not reported.

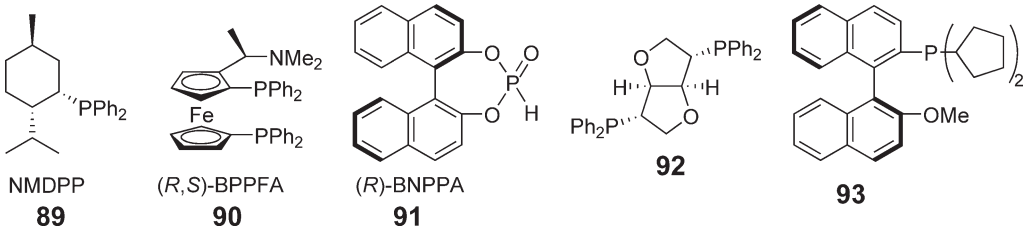
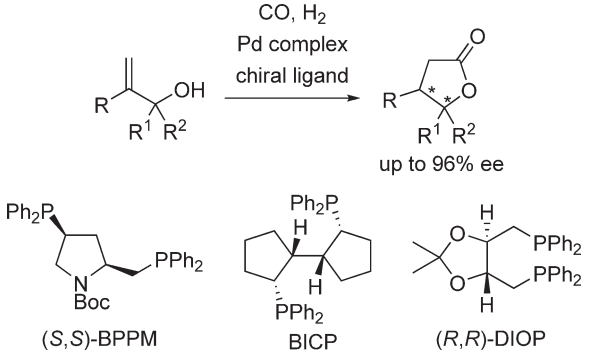


Figure 24 Chiral ligands for asymmetric hydrocarbonylation.

much interest as synthetical intermediates for bioactive compounds. Asymmetric hydrocarboxylation of olefins was first reported in 1973 by Pino using $PdCl_2$ and (−)-DIOP.[160] Asymmetric hydrocarbomethoxylation of styrene was carried out by Chiusoli using neomentyldiphenylphosphine (NMDPP, **89**, Figure 24) as a chiral ligand, and 52% ee was recorded.[161] In 1990, Alper reported high enantioselectivity of 91% ee using 1,1′-binaphthyl-2,2′-diylhydrogen phosphate (BNPPA) **91** for the Pd(II)-catalyzed hydrocarboxylation of 2-vinyl-6-methoxynaphthalene.[162] Several attempts followed that used Pd(II) catalysts in combination with chiral phosphines **90** or **92**.[163,164] Recently, Hiyama and Nozaki also recorded that ligand **93** gave naproxen with 53% ee.[165]

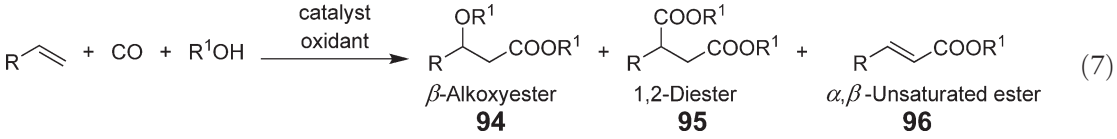
Asymmetric hydroalkoxycarbonylation of α-methylstyrene is also examined, leading to 3-phenyl-butanoic acid, the *normal*-product. The highest ee is at best 60% for this substrate.[166–169] When an allylic alcohol is treated with a chiral Pd complex under CO, cyclohydrocarbonylation takes place to give the corresponding γ-butyrolactone in an asymmetric manner (Equation (6)).[170–175] Similarly, chiral δ-lactones and other lactams can also be synthesized.



(6)

11.13.4 Oxidative Alkoxycarbonylation

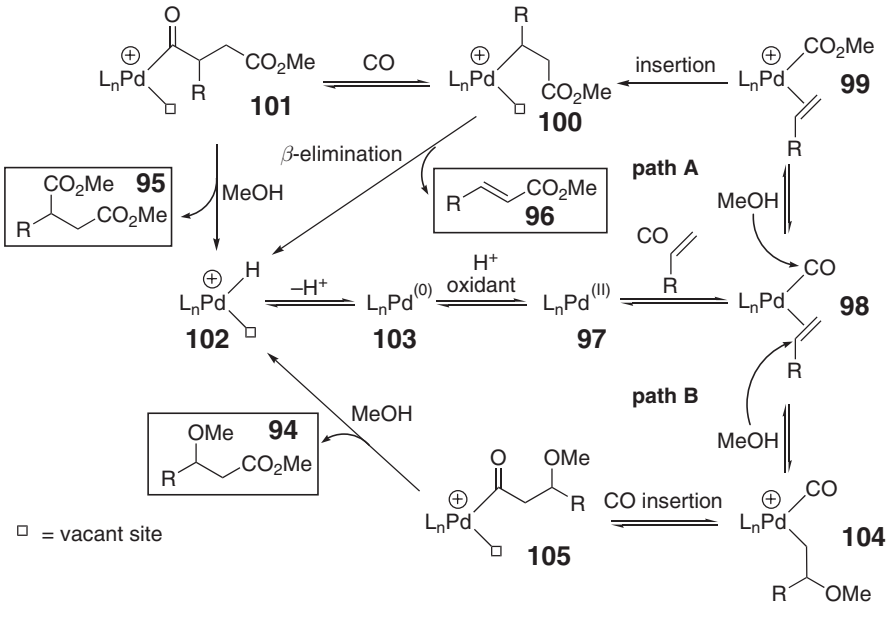
Around 1970, Heck found that olefins reacted with alcohols under a CO atmosphere in the presence of oxidants such as Pd(II) and Cu(II) salts to give β-alkoxy esters **94**, 1,2-diesters **95**, and α,β-unsaturated esters **96**, as described in Equation (7).[176–178] Intensive studies have been carried out, aiming at: (i) seeking an oxidation catalyst using dioxygen from air, (ii) selective formation of the α,β-unsaturated ester product, and (iii) asymmetric synthesis of the 1,2-diester product.



(7)

11.13.4.1 Mechanism of Oxidative Alkoxycarbonylation

A mechanism for the oxidative alkoxycarbonylation is suggested by Heck,[176–178] as illustrated in Scheme 15. The catalytic cycle starts with coordination of CO and olefin to the Pd(II) center **97** to give **98**, which then takes either of the competing pathways A or B. Path A involves an attack of MeOH to the coordinated carbonyl to form alkoxycarbonyl–olefin complex **99**. Path B initiated by an attack of MeOH to the coordinated olefin in a similar manner to the Wacker oxidation to afford the β-alkoxyalkyl complex **104**. In path A, insertion of the coordinated olefin to the alkoxycarbonylpalladium gives a β-alkoxycarbonylalkyl complex **100**. Insertion of CO to **100** leads to the formation of γ-alkoxycarbonyl acyl complex, **101**, which can give diester product **95** and hydridopalladium complex **102** via methanolysis. Loss of proton from **102** gives Pd(0) complex **103**, which is then oxidized to reproduce Pd(II) species **97**. Alkyl complex **100** may also undergo β-hydride elimination to afford α,β-unsaturated ester product **96**, providing with **102**. In path B, a migratory insertion of CO into β-alkoxyalkyl carbonyl complex **104** forms γ-alkoxy acyl complex **105**. Methanolysis of **105** affords β-alkoxy ester **94** and reproduces **102**. Recently, the path A is also suggested to be dominant in the bis-phosphine/Pd catalyst system by Bianchini.[179]



Scheme 15 A proposed mechanism for the oxidative alkoxycarbonylation.

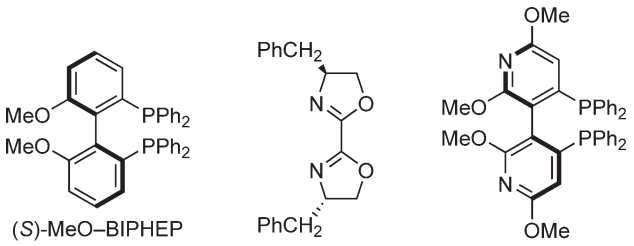


Figure 25 Chiral ligands for asymmetric alkoxycarbonylation.

11.13.4.2 Development of Catalyst in Oxidative Alkoxycarbonylation

As described above, search for an effective oxidation reaction using aerobic oxygen is one of the most important issues in oxidative alkoxycarbonylation. Originally, a stoichiometric amount of Cu(II) salt was used as an oxidant.[176–178] Later, Fenton found that the amount of Cu(II) can be reduced to a catalytic amount in the presence of oxygen.[180] Recently, Ishii reported that molybdovanadophosphate (NPMoV)/hydroquinone/O_2 is an efficient reoxidation system for alkoxycarbonylation.[181]

Selectivity for each product formation may also be controlled by an effective catalyst system. After the discovery of the reaction by Heck, Stille applied the reaction to organic synthesis, as he observed the preferential formation of β-methoxy esters under neutral conditions and 1,2-diesters in the presence of a base.[182] As Bianchini reported in 2001, selective formation of α,β-unsaturated ester product is established by an addition of protic acid such as *p*-TsOH in bis-phosphine/Pd-catalyzed oxidative alkoxycarbonylation.[179]

11.13.4.3 Asymmetric Oxidative Alkoxycarbonylation

In 1993, Consiglio reported an enantioselective bis(alkoxycarbonylation) of styrene to afford dimethyl phenylsuccinate with 93% ee, using $Pd(acac)_2$/(*S*)-MeO–BIPHEP (**106**, Figure 25) as a catalyst, although the chemoselectivity is not high enough for practical use (up to 83%).[183,184] Ukaji and Inomata applied bis(oxazoline) ligand **107** to the same reaction with 66% ee.[185] Recently, Chan disclosed the utilization of axially chiral bipyridine ligand **108** for this reaction to obtain the diester product with 84% ee and 79% chemoselectivity.[186] Thus, asymmetric oxidative alkoxycarbonylation is still halfway to match the industrial requirement.

11.13.5 Summary

As reviewed in this chapter, the hydroformylation reaction now potentially contributes not only to the bulk chemical production but also to fine chemical synthesis. Studies in the last decade have mostly been devoted to obtaining detailed understanding of the ligand-modified rhodium catalysts, which show high performance for regioselective hydroformylation of 1-alkenes to *normal*-aldehydes or asymmetric hydroformylation to produce optically active aldehydes. Aimed at their industrial applications, recovery and recycling of the catalysts have been examined. In contrast to the rather mature research on hydroformylation, several related carbonylation reactions cited here in this chapter are still waiting for further improvement in catalytic activity and seletivities. Regardless of the approach, either rational or combinatorial, ligand design will continue to be one of the most critical issues of new catalyst development. The high functional group tolerance and atom efficiency of the carbonylation reactions will allow them to be applied to the syntheses of a wide variety of organic compounds.

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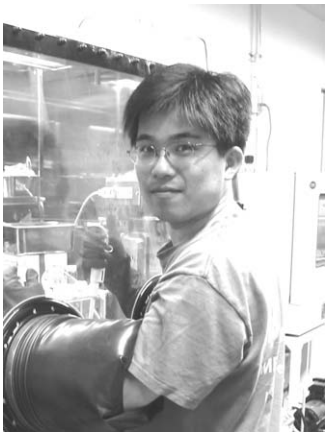
Biographical sketch



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11.14 Silylformylation

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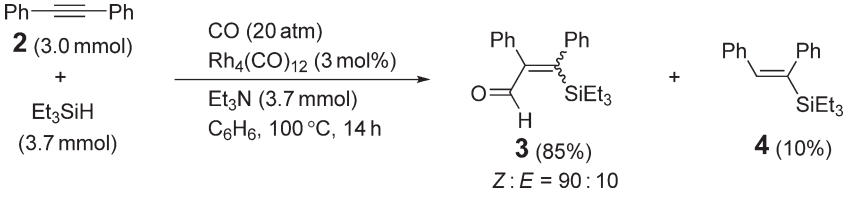
11.14.1 Introduction

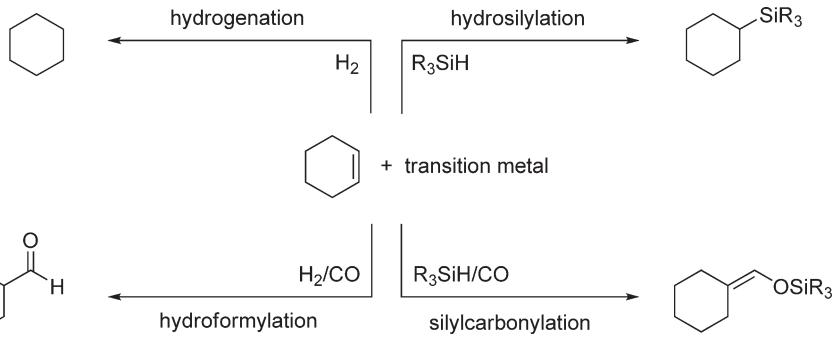
Use of a hydrosilane instead of molecular hydrogen in combination with a transition metal has opened the door leading to hydrosilylation[1] and dehydrogenative silylation of unsaturated bonds.[2–5] Thus, replacement of hydrogen by a hydrosilane is a reasonable strategy to improve serious issues in hydroformylation of alkenes.[6] Along this line, some types of silylcarbonylation were extensively studied by Murai and his co-workers.[7–9] However, the silicon moiety always attaches to the oxygen atom of incorporated CO molecule (Scheme 1).

Although these reactions are quite unusual and useful tools in efficient utilization of CO, it is desirable, from a viewpoint of construction of useful building blocks for synthesis of complex molecules, to retain incorporated CO as a formyl group. Particularly, 3-silylalkenals **1** have gained much interest in synthetic organic chemistry. None of the reported methods leading to **1** did use CO as a source of a formyl group until the mid-1980s.[10–23] The simplest route can be imaged according to the retro-synthetic analysis as shown in Scheme 2.

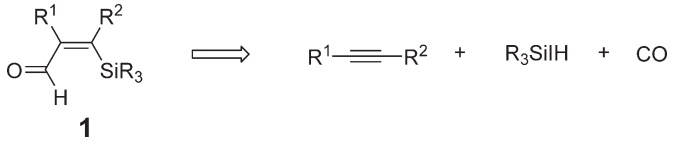
These precedents of silylcarbonylation made Matsuda and his co-workers hesitate to verify this route because intensive financial support for the research of C_1-chemistry in Japan has ended. Fascination to create a new reaction and acquisition of a small fund to purchase a pressure bottle, however, prompted them to embark on exploration of this synthetic plan without any chart. Thus, diphenylacetylene **2** and triethylsilane in almost equal amounts were allowed to interact in the presence of 3 mol% of $Rh_4(CO)_{12}$ and Et_3N under CO pressure (20 atm) as the first trial. The isolated products turned out to be **3** (85%, $Z:E = 90:10$) and **4** (10%) (Equation (1)).



(1)



Scheme 1



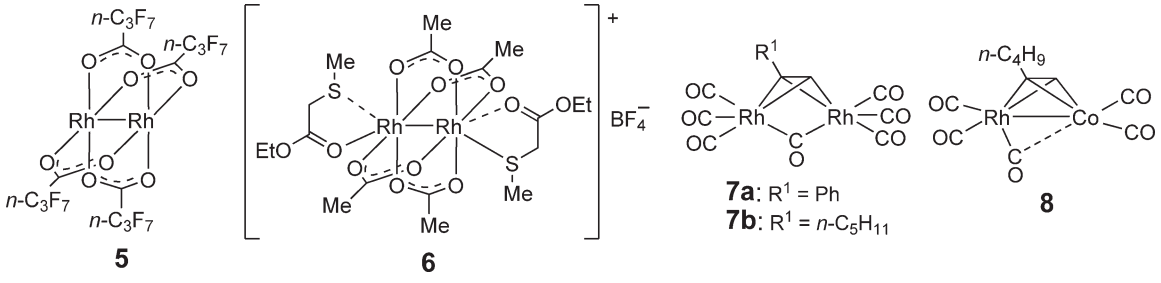
Scheme 2

It should be emphasized that the formyl group remained intact in major product **3** despite the reaction under forcing conditions. This is the first example of "silylformylation" in which a trialkylsilyl group and a formyl group are simultaneously connected to acetylenic carbons to form **1** in a one-pot reaction. Based on this breakthrough, the Matsuda group[24] published refined results and coined the word "silylformylation". The reaction has since been applied to a variety of substrates as described in the following sections.

11.14.2 Scope and Limitation of Silylformylation

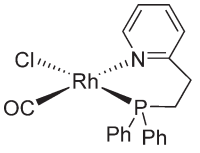
11.14.2.1 Catalyst and Solvents for Silylformylation

Discovery of $Rh_4(CO)_{12}$[24,25] as a catalyst for silylformylation of alkynes stimulated study on similar catalysis using some other types of cluster complexes such as $Rh_6(CO)_{16}$,[26] $Co_2Rh_2(CO)_{12}$,[27] $(Bu^tNC)_4RhCo(CO)_4$,[27,28] $Rh_2(pfb)_4$ (pfb = perfluorobutyrate) **5**,[29,30] **6**,[31] **7**,[25] and **8**.[27]



Although high catalyst activity of some complexes is understood on the basis of examples performed under CO atmosphere below 25 °C,[27,30] CO pressure more than 5 atm is required for selective silylformylation with sufficient reproducibility. Under atmospheric pressure of CO, hydrosilylation becomes the most serious competitive reaction consuming the hydrosilane component. Silylformylation is attained by the catalysis of chloro-bridged dimers, such as $[Rh(CO)_2Cl]_2$,[24] $[Rh(cod)Cl]_2$,[24] $[Rh(\eta^2\text{-methylenecyclopropane})_2Cl]_2$,[32] and $[RhCp^*Cl_2]_2$ (Cp^* = 1,2,3,4,5-pentamethylcyclopentadiene),[25] or monomeric complexes, such as $Rh(acac)(CO)_2$,[33] $RhH(CO)(PPh_3)_3$,[25] $RhCl(PPh_3)_3$,[25] **9**,[34] **10**,[34] $[Rh(cod)(PPh_3)_2]PF_6$,[25] $[Rh(cod)(dppb)]PF_6$,[25] $Rh(CO)_4SiMe_2Ph$ **11a**,[25] $Rh(CO)_4SiEt_2Me$ **11b**,[25] $Rh(CO)_4SiBu^tMe_2$ **11c**,[25] and **12**,[26] though remarkable difference is observed in the catalytic efficiency among these complexes. Rhodium particle co-condensed with mesitylene[35] and its immobilized form on γ-alumina[36] are also

active for silylformylation. In sharp contrast to high performance of Rh complexes, there are no successful examples of silylformylation catalyzed by other metal species, such as $Ru_3(CO)_{12}$, $Co_2(CO)_8$, $Ir_4(CO)_{12}$, $[Ir(cod)(PPh_3)_2]PF_6$, and $Pd(PPh_3)_4$. Thus, the presence of Rh species is crucial for smooth progress of the silylformylation of alkynes regardless of its precursor if reaction temperature is high enough and CO pressure is sufficiently applied.



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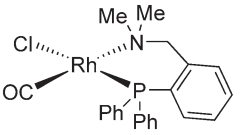

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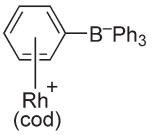


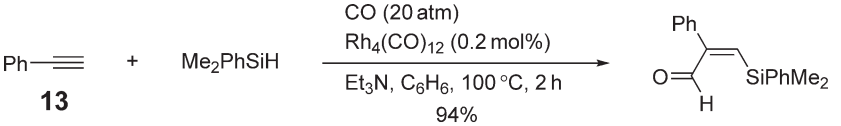
12

Generally speaking, solvent is not a critical factor for practical execution of silylformylation of alkynes, though an adequate selection of catalyst and solvent is required for smooth progress of the reaction in some examples, such as $Rh_2(pfb)_4/CH_2Cl_2$,[29,30] **6**/CH_2Cl_2,[31] rhodium particles/THF,[35] and **12**/an ionic solvent.[37] Any solvents that dissolve all the starting materials are suitable for silylformylation of alkynes. For example, C_6H_6, toluene, hexane, heptane, CH_3Cl, CH_2Cl_2, CH_3CN, THF, EtOAc, and DMF are applicable.[25]

In sharp contrast to silylformylation of alkynes, specific combination{$[Rh(COD)Cl]_2$/THF} of catalyst precursor and solvent is quite important for selective silylformylation of aldehydes.[38,39] Co-use of *N*-methylpyrazole is crucial to perform silylformylation of epoxides ({$[Rh(CO)_2Cl]/CH_2Cl_2$}[40] and oxetanes {$[Rh(CO)_2Cl]_2$/toluene}.[41]

11.14.2.2 1-Alkynes

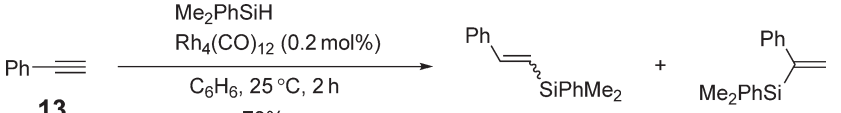
Phenylacetylene **13** readily reacts with Me_2PhSiH under CO pressure to give 3-dimethylphenylsilyl-2-phenylpropenal **14a** in the presence of a catalytic amount of $Rh_4(CO)_{12}$ (Equation (2)). When 10–20 atm of CO pressure and 0.1–0.2 mol% of $Rh_4(CO)_{12}$ are applied, the reaction is completed within 2 h at 100 °C. Silylformylation proceeds smoothly even at room temperature, though the reaction becomes slower (600–700 turnover frequency at room temperature after 17 h). The reaction does proceed in the absence of Et_3N, but its presence improves yield and (*Z*)-selectivity of product **14a**.[25]



14a

Z : *E* = 83 : 17 (2)

The most notable point of this reaction is that the internal *sp*-carbon is selectively carbonylated to form (*Z*)-**14a** predominantly, although the *Z*/*E* ratio is likely to depend on reaction temperature, time, and catalyst precursor. It is revealed that the stereochemistry of the transition metal-catalyzed addition to alkynes is intrinsically *cis*. Isomerization from (*Z*)-**14a** to (*E*)-**14a** proceeds as an independent event from silylformylation. This feature sharply contrasts to the results observed in hydrosilylation of **13** with Me_2PhSiH (Equation (3)).[25]



(3)

Deviation from 1 : 1 mole ratio of **13** to Me_2PhSiH in the vessel results in concomitant formation of **17**, **18**, and **19** or cyclopentenones (*vide infra*).[25]

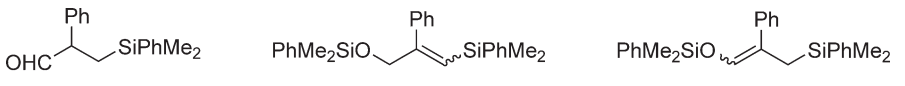
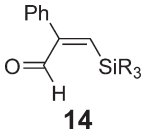


Table 1 Silylformylation of phenylacetylene **13** to give **14**

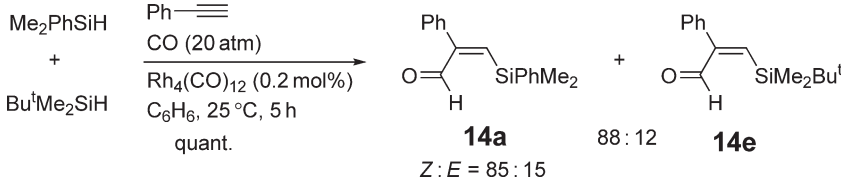
			Product **14**				
Entry	*Hydrosilane*	*Conditions*[a]		SiR_3	*Yield (%)*	*Z : E*	*References*
1	Me_2PhSiH	A	**14a**	$SiMe_2Ph$	89	88 : 12	24,25
2	Me_2PhSiH	B	**14a**	$SiMe_2Ph$	90	98 : 2	25
3	Me_2PhSiH	C	**14a**	$SiMe_2Ph$	73	92 : 8	30
4	Me_2PhSiH	D	**14a**	$SiMe_2Ph$	74	89 : 11	32
5	$MePh_2SiH$	A	**14b**	$SiMePh_2$	94	83 : 17	25
6	$MePh_2SiH$	B	**14b**	$SiMePh_2$	84	97 : 3	25
7	Et_3SiH	A	**14c**	$SiEt_3$	92	91 : 9	25
8	Et_3SiH	B	**14c**	$SiEt_3$	85	98 : 2	25
9	Et_3SiH	C	**14c**	$SiEt_3$	75	96 : 4	29,30
10	Et_3SiH	D	**14c**	$SiEt_3$	90	91 : 9	32
11	Et_3SiH	E	**14c**	$SiEt_3$	87	100 : 0	26
12	Et_2MeSiH	A	**14d**	$SiEt_2Me$	75	79 : 21	25
13	Et_2MeSiH	B	**14d**	$SiEt_2Me$	78	98 : 2	25
14	Bu^tMe_2SiH	B[b]	**14e**	$SiBu^tMe_2$	82	98 : 2	25
15	$Me_2(EtO)SiH$	B	**14f**	$SiMe_2(OEt)$	70	50 : 50	25
16	$(MeO)_3SiH$	B	**14g**	$Si(OMe)_3$	47	14 : 86	25

[a]A: 0.2 mol% of $Rh_4(CO)_{12}$, Et_3N (1 mol), CO (20 atm), C_6H_6, 100 °C, 2 h. B: 0.2 mol% of $Rh_4(CO)_{12}$, Et_3N (1 mol), CO (20 atm), C_6H_6, 25 °C, 15 h. C: 0.3 mol% of $Rh_2(pfb)_4$, CO (10 atm), CH_2Cl_2, 25 °C, 16 h. D: 0.3 mol% of [Rh(η^2-methylenecyclopropane)$_2$Cl]$_2$, CO (30 atm), *n*-C_7H_{16}, 20 °C, 5 h. E: 1 mol% of 12, CO/H_2 (1 : 1, 40 atm), CH_2Cl_2, 40 °C, 24 h.
[b]Reaction time is 65 h.

Other hydrosilanes as well as Me_2PhSiH are suitable for the silylformylation of **13** (Table 1). Rate of the reaction and yield of the product are remarkably affected by substituents on silicon. Relative rate among Me_2PhSiH, $MePh_2SiH$, Et_2MeSiH, and Bu^tMe_2SiH in the silylformylation of **13** is roughly estimated as 38 : 30 : 4 : 1 on the basis of turnover frequencies of $Rh_4(CO)_{12}$. Predominant reactivity of Me_2PhSiH over Bu^tMe_2SiH is also shown by competitive silylformylation using the two hydrosilanes (Equation (4)).[25]



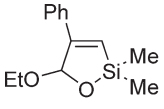
14



(4)

A bulky substituent appears to suppress yield of the silylformylation product under the equal conditions. Pr^i_3SiH is recovered.

$Me_2(EtO)SiH$ and $(MeO)_3SiH$ react readily with **13** to give the corresponding products, **14f** and **14g**, respectively. However, a part of these products is present as cyclic acetals **20** and **21**. Ph_2SiH_2 does not give any products that incorporate CO in the reaction with **13**. Hydrosilylation proceeds selectively even under CO pressure.[25]



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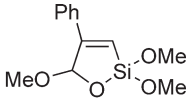
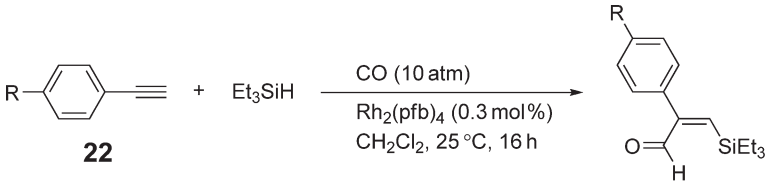


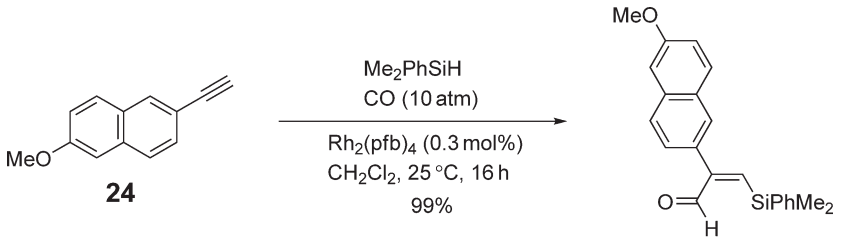
21

Aromatic acetylenes **22** bearing an alkyl substituent on the phenyl ring are also applicable to the silylformylation without any problem (Equation (5)).[30] 6-Methoxy-2-naphthylacetylene **24** gives an excellent yield of the corresponding silylformylation product (Equation (6)).[30]



R	*Yield* (%)	*Z* : *E*
Me	63	94 : 6
Bu^{i}	72	91 : 9

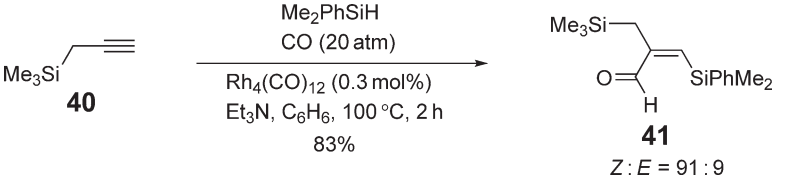
(5)



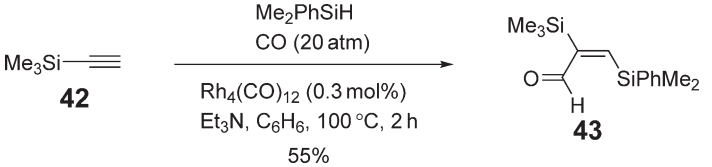
(6)

Aliphatic acetylenes as well as aromatic acetylenes are susceptible to silylformylation under similar conditions. The regiochemistry of the reaction is strictly retained to formylate in the internal *sp*-carbon. Reaction of 1-alkynes **26** generally gives the corresponding 2-substituted 3-silylpropenals **27** in high yields. The substituent R^1 in **26** exerts the stereochemistry in the isolated product **27**. In contrast to the results that ethyne (**26**, $R^1 = H$) forms (*E*)-3-dimethylphenylsilylpropenal (**27**, $R^1 = H$) in the reaction with Me_2PhSiH, other 1-alkynes give (*Z*)-selectively the corresponding products. In particular, (*Z*)-3-silylpropenal (**27**, $R^1 = c\text{-}C_6H_{11}$) is isolated as the sole product in the silylformylation of cyclohexylacetylene (**26**, $R^1 = c\text{-}C_6H_{11}$) under the conditions identical to those of ethyne.[25] A bulky substituent involved in hydrosilane leads to high (*Z*)-selectivity as shown in the reaction of Bu^tMe_2SiH (Table 2).[25] *o*-Tolyldimethylsilane, *p*-tolyldimethylsilane, *p*-anisyldimethylsilane, (4-biphenylyl)dimethylsilane, and thiophen-2-yldimethylsilane react with 1-hexyne under CO pressure to give the corresponding products.[42]

Rhodium-catalyzed silylformylation proceeds smoothly in branched 1-alkynes at 25 °C as shown in Table 3.[35] The stereochemistry at the chiral carbon involved in alkynes is retained intact under the silylformylation conditions. (*S*)-**28**, (*S*)-**30**, and (*S*)-**34** give (*S*)-**29**, (*S*)-**31**, and (*S*)-**35**, respectively, as the sole product of silylformylation catalyzed by rhodium particles co-condensed with mesitylene.[35] 3-Trimethylsilyl-1-propyne **40** reacts similarly to give **41** (Equation (7)).[24,25] *tert*-Butylacetylene does not work as a substrate for the silylformylation because of the bulky *tert*-butyl group on the *sp*-carbon. In contrast to *tert*-butylacetylene, trimethylsilylacetylene **42** gives **43** in a fair yield (Equation (8)).[24,25]



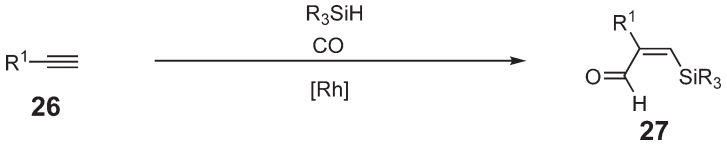
(7)



(8)

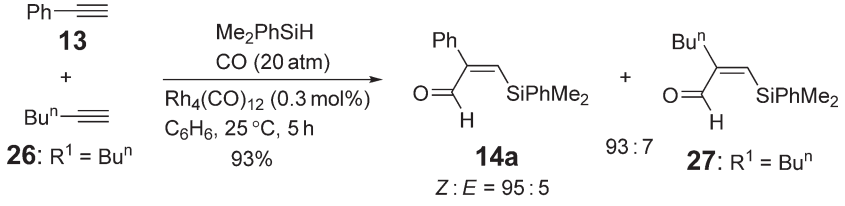
Although aliphatic acetylenes **26** show sufficient reactivity for silylformylation, competitive reaction between **13** and **26** ($R^1 = Bu^n$) clearly demonstrates that **13** overwhelms **26** to react with Me_2PhSiH (Equation (9)).[25]

Table 2 Silylformylation of 1-alkynes **26** to give **27**



				Product **27**		
Entry	*R^1 in* **26**	*Hydrosilane*	*Conditions*[a]	*Yield* (%)	*Z* : *E*	*References*
1	H	Me_2PhSiH	A	73	0 : 100	24,25
2	Me	Me_2PhSiH	A	99	80 : 20	24,25
3	Et	Me_2PhSiH	A	91	94 : 6	24,25
4	Pr^n	Me_2PhSiH	A	93	95 : 5	24,25
5	Pr^n	Et_3SiH	A	91	97 : 3	25
6	Pr^n	Bu^tMe_2SiH	C	91	100 : 0	25
7	Bu^n	Me_2PhSiH	B	86	85 : 15	25,26,27,28,29,30,31
8	Bu^n	$MePh_2SiH$	D	97	100 : 0	27,28
9	Bu^n	Ph_3SiH	D	98	100 : 0	26,27,28
10	Bu^n	Et_3SiH	D	84	100 : 0	26,27,28,32
11	Bu^n	Et_2MeSiH	B	81	89 : 11	25
12	Bu^n	$EtMe_2SiH$	D	84	100 : 0	27,28
13	Bu^n	Bu^tMe_2SiH	C	71	100 : 0	25
14	*n*-C_5H_{11}	Me_2PhSiH	A	71	87 : 13	25,37
15	*n*-C_5H_{11}	Et_3SiH	B	82	95 : 5	25,32
16	*n*-C_6H_{13}	Me_2PhSiH	E	81	97 : 3	25,37
17	*n*-C_6H_{13}	Et_3SiH	B	86	96 : 4	25
18	*c*-C_6H_{11}	Me_2PhSiH	A	96	100 : 0	24,25

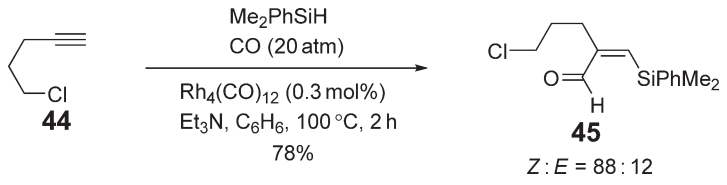
[a]A: 0.2 mol% of $Rh_4(CO)_{12}$, Et_3N (1 mol), CO (20 atm), C_6H_6, 100 °C, 2 h. B: 0.2 mol% of $Rh_4(CO)_{12}$, CO (20 atm), C_6H_6, 100 °C, 2 h. C: 0.2 mol% of $Rh_4(CO)_{12}$, CO (20 atm), CH_3CN, 100 °C, 2 h. D: 0.1 mol% of $Rh_2Co_2(CO)_{12}$, CO (10 atm), toluene, 25 °C, 24 h. E: 0.3 mol% of $Rh_2(pfb)_4$, CO (10 atm), CH_2Cl_2, 25 °C, 16 h.



(9)

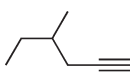
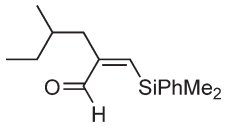
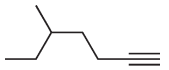
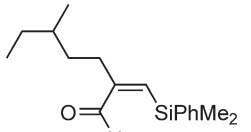
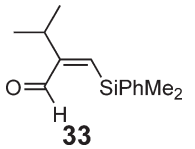
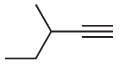
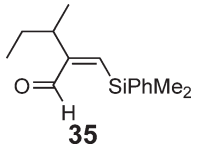
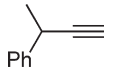
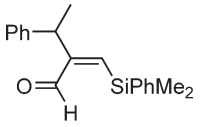
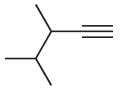
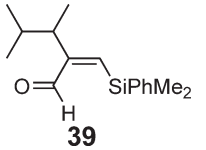
11.14.2.3 Chemoselectivity in Silylformylation of Terminal Acetylenes

Presence of a certain type of functional groups in alkynes does not interfere with silylformylation. For example, the chlorine atom in 5-chloro-1-pentyne **44** and the cyano group in 5-cyano-1-pentyne **46** do not affect the silylformylation to give **45**[25,26] and **47**,[26,28] respectively (Equations (10) and (11)). 4-Bromo-1-butyne and 6-bromo-1-hexyne also give the corresponding silylformylation products.[42]

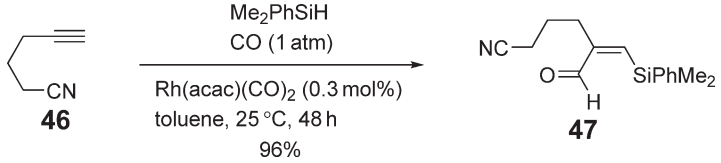


(10)

Table 3 *Z*-Selective silylformylation of branched 1-alkynes with Me_2PhSiH[35]

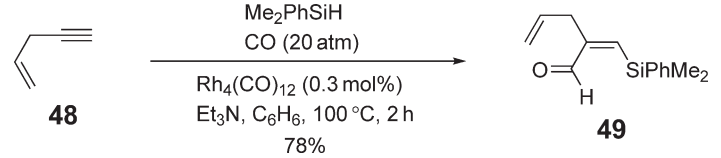
Entry	*Alkyne*	*Product*	*Yield (%)*
1	 **28**	 **29**	94
2	 **30**	 **31**	92
3	 **32**	 **33**	59
4	 **34**	 **35**	94
5	 **36**	 **37**	69
6	 **38**	 **39**	53

Conditions: Rh particle/mesitylene (0.1–1 mol%), CO (10–50 atm), toluene, 25 °C, 24–48 h. Reprinted with permission from Wiley-VCH Verlag GmbH & Co KG by Aronica, L. A.; Terreni, S.; Coporusso, A. M.; Salvadori, P. Silylformylation of chiral 1-alkynes, catalysed by solvated rhodium atoms. *European Journal of Organic Chemistry,* **2001**, *22*, 4321–4329.

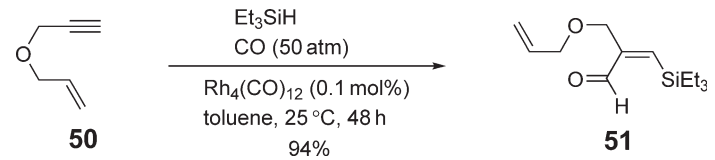


(11)

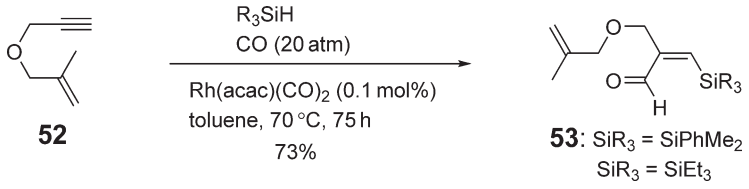
Ethene and 1-hexene do not react with hydrosilane under CO pressure in the presence of an Rh catalyst. Any product is obtained under the conditions similar to the reaction of 1-alkynes. Thus, the alkynyl moiety in pent-1-ene-4-yne **48**, 4-oxahept-1-en-6-yne **50**, and 4-oxa-2-methylhept-1-en-6-yne **52** is solely silylformylated to give **49**,[25] **51**,[28] and **53**,[28] respectively (Equations (12)–(14)).



(12)

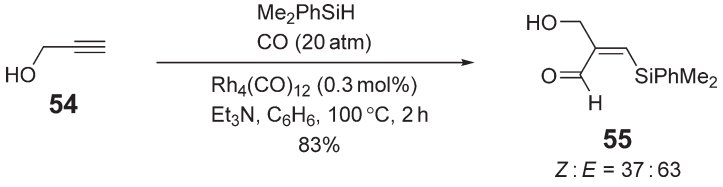


(13)



(14)

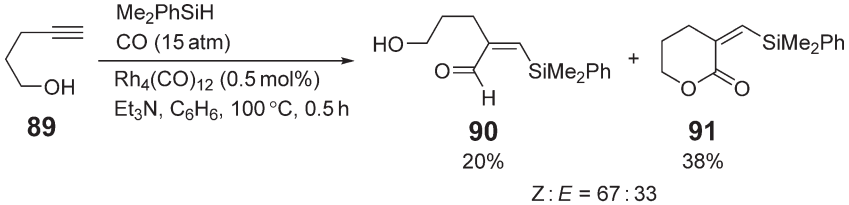
Silylformylation of 1-alkynes is not affected by the presence of small amounts (2 to 3 molar equiv.) of water or methanol in the reaction mixture. The corresponding products are formed in yields similar to the reaction without these additives.[25] This information implies that the silylformylation of alkyne is not affected by the presence of a protic functional group, such as hydroxy and amino groups in alkyne. In fact, 2-propyn-1-ol **54** smoothly gives **55**, in which the hydroxy group remains intact (Equation (15)).[24,25,30] (*Z*)-Selectivity in **55** is drastically improved by the reaction in the absence of Et_3N[25] or by use of $Rh_2(pfb)_4$[30] as the catalyst. The Rh complex is known to work as an active catalyst for alcoholysis of hydrosilane.[43–46] In particular, since $Rh_2(pfb)_4$ shows high activity for alcoholysis of Et_3SiH in the absence of CO,[47] it is quite notable that the product derived from silane alcoholysis is not detected at all in the silylformylation of **54**. Propargylic alcohols, ethers, and esters are uniformly applicable to the silylformylation (Table 4).



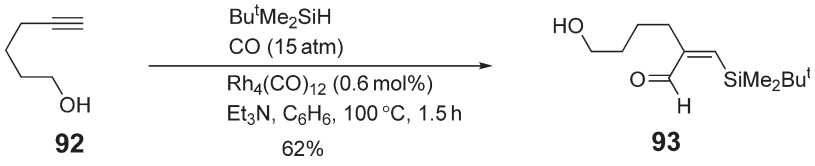
(15)

In the reaction of parent propargyl amine, unidentified intractable materials are formed even under relatively mild conditions. However, selective silylformylation at the alkynyl moiety proceeds by reducing the nucleophilicity of the amino group as tosylamide or carbamate (Table 5).[51]

Although silylformylation of 3-butyn-1-ol **84** gives normal product **85** preferentially in the absence of Et_3N, an appreciable amount (38%) of γ-lactone **86** is formed concomitantly.[49] Protection of the hydroxy group in **84** leads to selective silylformylation of the acetylenic moiety as shown in Scheme 3. Hydrolysis of the silyl ether in **88** gives **85** as a single product. 4-Pentyn-1-ol **89** reacts with Me_2PhSiH under CO pressure to give a mixture of silylformylation product **90** (20%) and δ-lactone **91** (38%) after a short reaction time (0.5 h) (Equation (16)). The unusual lactone formation is not observed in the reaction of 5-hexyn-1-ol **92** in the presence of Et_3N (Equation (17)).[50]



(16)



(17)

Table 4 Silylformylation of propargylic alcohol derivatives

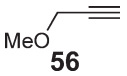
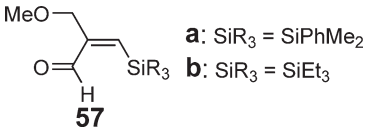
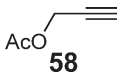
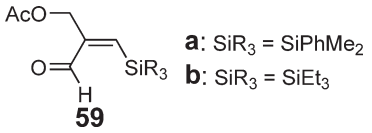
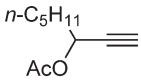
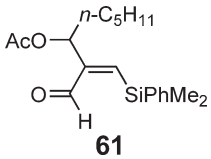
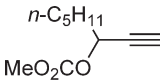
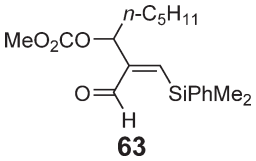
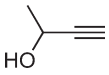
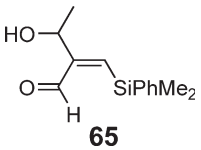
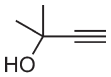
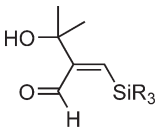
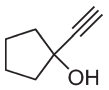
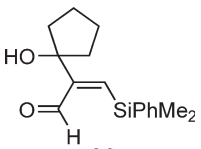
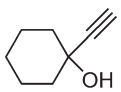
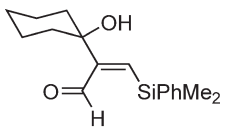
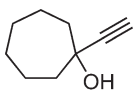
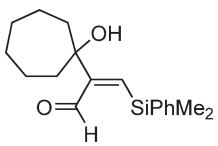
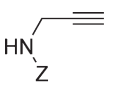
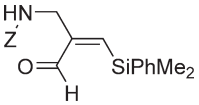
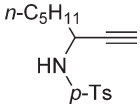
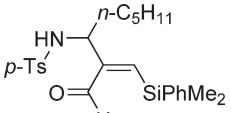
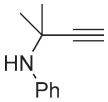
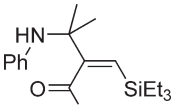
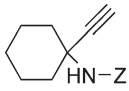
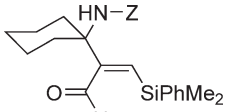
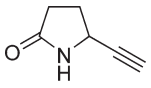
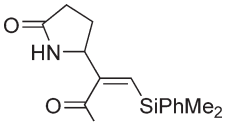
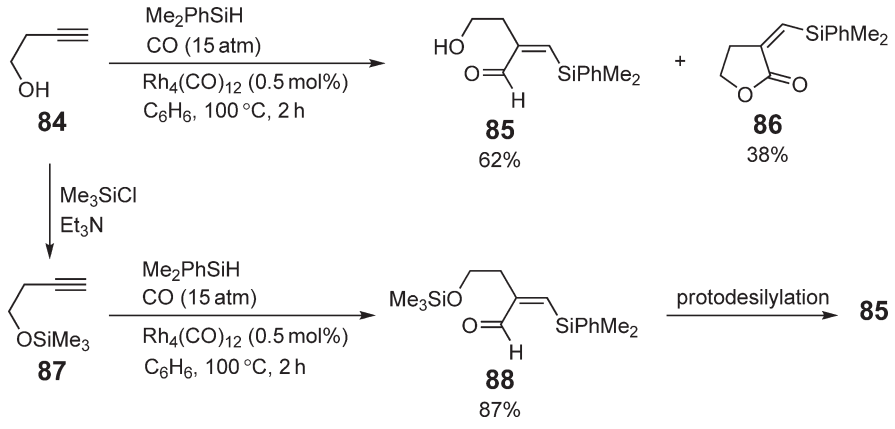
Entry	Propargylic alcohol	Product	Yield (%)	Z : E	References
1	 **56**	 **57** **a**: $SiR_3 = SiPhMe_2$ **b**: $SiR_3 = SiEt_3$	32	88 : 12	25
2			77	97 : 3	29,30
3	 **58**	 **59** **a**: $SiR_3 = SiPhMe_2$ **b**: $SiR_3 = SiEt_3$	58	96 : 4	48
4			51	96 : 4	29,30
5	 **60**	 **61**	88	95 : 5	48
6	 **62**	 **63**	57	100 : 0	48
7	 **64**	 **65**	76	100 : 0	49
8	 **66**	 **67** **a**: $SiR_3 = SiPhMe_2$ **b**: $SiR_3 = SiEt_3$	94	97 : 3	49
9			66	97 : 3	29,30
10	 **68**	 **69**	100	97 : 3	49
11	 **70**	 **71**	94	100 : 0	50
12	 **72**	 **73**	93	97 : 3	50

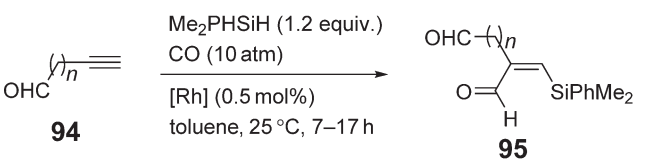
Table 5 Silylformylation of propargylic amine derivatives

Entry	*1-Alkyne*	*Product*	*Yield (%)*	*Z : E*	*References*
1	 **a**: Z = *p*-Ts **b**: Z = CO_2Me **c**: Z = CO_2Bn **74**	 **75**	81	33 : 67	51
2			63	100 : 0	51
3			75	100 : 0	51
4	 **76**	 **77**	65	40 : 60	51
5	 **78**	 **79**	91	100 : 0	26
6	 **a**: Z = *p*-Ts **b**: Z = CO_2Me **80**	 **81**	73	100 : 0	51
7			68	100 : 0	51
8	 **82**	 **83**	97	100 : 0	33



Scheme 3

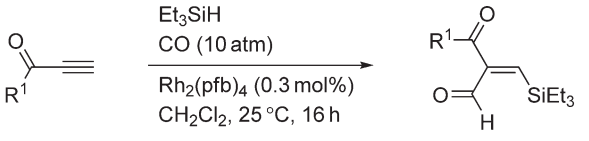
5-Hexynal (**94**, $n = 3$), 6-heptynal (**94**, $n = 4$), and 7-octynal (**94**, $n = 5$) are suitable for the silylformylation to give dials **95** in high yields. The original formyl group in **94** remains intact during the reaction (Equation (18)).[52] The functional group tolerance is in sharp contrast to the hydroxy group intorelance shown in Scheme 3.



n	*Catalyst*	*Yield* (%)
3	$Rh(acac)(CO)_2$	74
3	$Rh_2Co_2(CO)_{12}$	73
4	$Rh(acac)(CO)_2$	81
5	$Rh(acac)(CO)_2$	89
5	$Rh_2Co_2(CO)_{12}$	78

(18)

Electron-deficient acetylenes **96** and **98** form **97** and **99**, respectively, in poor yields with the assistance of $Rh_2(pfb)_4$ (Equation (19)).[30] When $Rh_4(CO)_{12}$ is used as the catalyst, cyclotrimerization of these acetylenes proceeds even in the presence of Me_2PhSiH under CO pressure.[25]



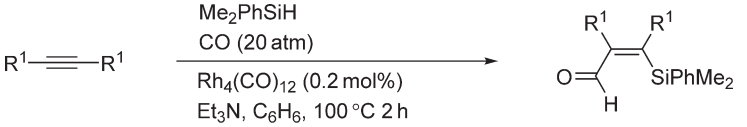
Compound	*Product*	R^1	*Yield* (%)	*Ratio Z : E*
96	**97**	Me	24	52 : 48
98	**99**	OMe	20	42 : 58

(19)

In a manner similar to silylformylation, germylformylation of 1-alkynes catalyzed by **12** proceeds with $Bu^n{}_3GeH$ under CO pressure (20 atm). However, it is difficult to completely suppress hydrogermylation of 1-alkynes as the side-reaction.[53]

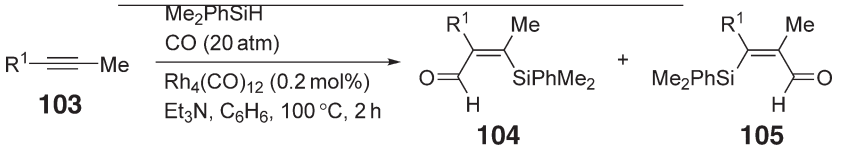
11.14.2.4 Internal Alkynes

Internal alkynes are particularly suitable for silylformylation, and the conditions similar to the reaction of 1-alkynes are applicable. 2-Butyne **100** and diphenylacetylene **2** give corresponding 3-silylalkenals **101** and **102**, respectively, in good yields (Equation (20)).[24,25,32] Unsymmetrically substituted alkynes **103** always give two regioisomers **104** and **105** (Equation (21)). The regioselectivity seems to be controlled by steric bulk of substituents: formyl group is always introduced at the *sp*-carbon bearing a bulkier substituent.



Compound	*Product*	R^1	*Yield* (%)	*Ratio Z : E*
100	**101**	Me	94 (*Z* only)	
2	**102**	Ph	90	95 : 5

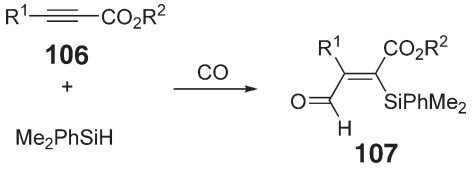
(20)



	Yield (%)		
R^1	**104**	**105**	*References*
Pr^n	60	26	24,25
Pr^i	75	7	71
Ph	74	8	24,25,30

(21)

Regioselectivity for these alkynes cannot be improved any more. In sharp contrast to these alkynes, 1-trimethylsilylpropyne (**103**, $R^1 = SiMe_3$) and 1-phenyl-2-trimethylsilylethyne do not give any product under similar conditions because of the steric hindrance arising from the bulkiness of a trimethylsilyl group.[25] Electronic factor influences the regioselection in some acetylenes. The reaction of propiolate derivative **106** gives 3-alkoxycarbonylalkenal **107** as the sole formylated product (Equation (22)).[25]

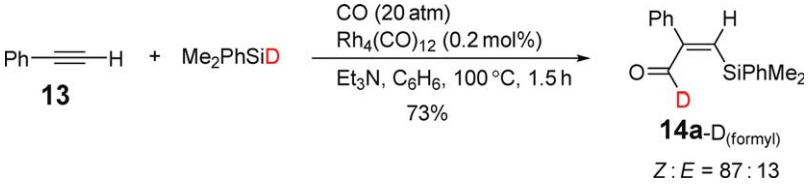


R^1	R^2	*Yield* (%)
Me	Me	67
Ph	Et	43

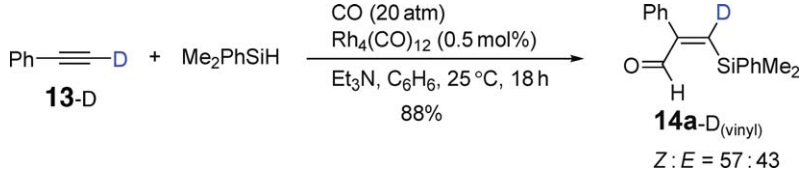
(22)

11.14.3 Mechanism of Silylformylation of Alkynes

The mechanism for silylformylation of alkynes is considered to be closely related to that for hydrosilylation. However, the greatest discrepancy between these reactions is that silylformylation of 1-alkynes is extremely regioselective and stereoselective, whereas hydrosilylation gives a mixture of regio- and stereoisomers (Equation (3)). The presence of CO clearly discriminates between the two reactions. A couple of deuterium-labeling experiments using Me_2PhSiD and deuteriophenylacetylene **13**-D reveal the following facts: (i) the hydrogen atom of the formyl group is derived from hydrosilane used, and (ii) there is minimal scrambling of hydrogen atoms between a hydrosilane and a 1-alkyne in Rh-catalyzed silylformylation. The reaction of **13** with Me_2PhSiD gives alkenal **14a**-$D_{(formyl)}$ deuterated (>98%) at the formyl carbon selectively in 73% yield (Equation (23)). On the contrary, the reaction of **13**-D with Me_2PhSiH under similar conditions gives alkenal **14a**-$D_{(vinyl)}$, selectively deuterated (>94%) at the vinyl carbon (Equation (24)).[25]



(23)



(24)

On the other hand, alkenal **14a** is selectively formed with recovery of $Rh_4(CO)_{12}$ under CO pressure (20 atm) in a stoichiometric reaction {mole ratio = $Rh_4(CO)_{12}$: **13** : Me_2PhSiH = 1 : 4 : 4} as well as a catalytic reaction. When **13** and Me_2PhSiH are mixed at once in a $CDCl_3$ solution of $Rh_4(CO)_{12}$ under CO atmosphere, **14a** is smoothly formed as a major product with concomitant formation of small amounts of **15** and $Me_2PhSiOH$. In the case that **13** and Me_2PhSiH are added separately, it is critical to add **13** to a solution of Me_2PhSiH and $Rh_4(CO)_{12}$ for the production of **14a**. Reverse addition results in hydrosilylation of **13** only.[25] Similar results are observed in the silylformylation catalyzed by $Rh_2(pfb)_4$.[30]

Although any evidence that indicates an interaction between Me_2PhSiH and $Rh_4(CO)_{12}$ under CO atmosphere is not available, $Rh(CO)_4SiMe_2Ph$ **11a** is considered to be the sole species formed in the reaction of $Rh_4(CO)_{12}$ with 4 molar equiv. of Me_2PhSiH under CO pressure (20 atm). Although it cannot be isolated as such because removal of solvent causes decomposition, **11a** is stable in an original solution under CO atmosphere (preferably more than 5 atm of CO pressure) regardless of the solvent (CH_2Cl_2, $CHCl_3$, $CDCl_3$, C_6H_6, and hexane); it is formed almost quantitatively and is characterized on the basis of spectral data of IR ($\nu_{C=O}$ = 2102, 2049, and 2017 cm^{-1}), ^1H NMR (δ = 0.81 ppm, SiMe), and ^{13}C NMR (δ = 189.37 ppm, doublet, J = 66 Hz, C=O). Formation of mononuclear rhodium species **11b** and **11c** are observed in the reaction of Et_2MeSiH or Bu^tMe_2SiH with $Rh_4(CO)_{12}$ under CO pressure (Equation (25)).[25] Cobalt homologs, $Co(CO)_4SiMe_3$ ($\nu_{C=O}$ 2090, 2026, and 1995 cm^{-1}) and $Co(CO)_4SiEt_3$

($\nu_{C\equiv O} = 2089$, 2026, and 1995 cm^{-1}), are actually prepared separately.[54,55] This type of declusterization of carbonyl clusters has been established and used widely as a preparative route for $M(CO)_nSiR_3$ under an inert gas atmosphere (M = Mn, Re, and Co).[56,57] Analogous Rh–Si species, for example, a mixture of $(Me_2PhSi)_2Rh(CO)_nCo(CO)_4$ ($n = 2$ or 3), are reported to form by the reaction of $Rh_2Co_2(CO)_{12}$ with Me_2PhSiH under CO atmosphere. However, neither of them is isolated.[27]

$$Rh_4(CO)_{12} \xrightarrow[CO\ (20\ atm)\\ CH_2Cl_2\\ 25\,^\circ C,\ >8\ h]{4R_3SiH} 4Rh(CO)_4{-}SiR_3 + 2H_2 \quad (25)$$

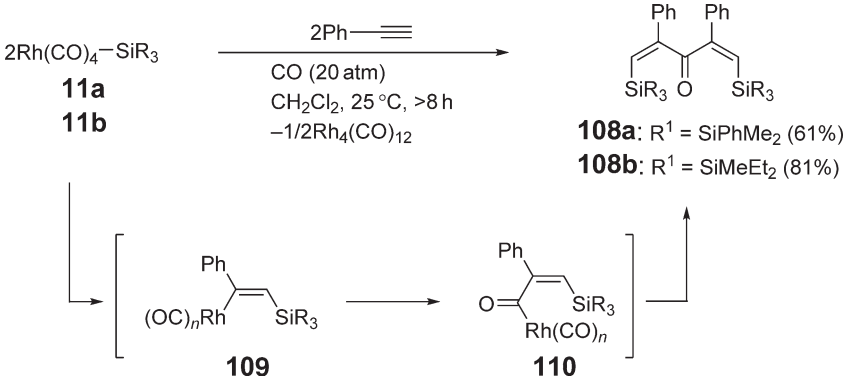
11a: $SiR_3 = SiPhMe_2$
11b: $SiR_3 = SiEt_2Me$
11c: $SiR_3 = SiBu^tMe_2$

Freshly prepared **11** reacts readily with phenylacetylene **13** to give divinyl ketone **108** and $Rh_4(CO)_{12}$ at room temperature under a CO pressure or CO atmosphere. The result strongly suggests that insertion of **13** into an Rh–Si bond in **11** must be involved at the first stage of the conversion of **11** to **108**. The resulting vinyl–rhodium species **109** reacts with CO to form an acyl–rhodium intermediate **108**, coupling of which with another molecule of **109** would afford **108** (Scheme 4).[25]

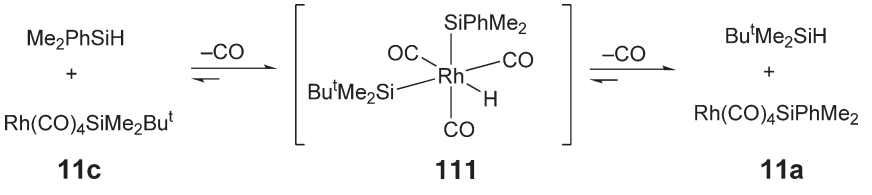
Insertion of unsaturated molecules into a transition metal–silyl bond has been suggested for the catalytic reactions related to hydrosilylation[58–60] and silylcarbonylation.[7–9] However, there is little direct evidence supporting such a process for unsaturated molecules to insert into a metal–silyl bond in organometallic complexes.[61–64] Thus, the fact that **108** is readily derived from **11** and **13** demonstrates the participation of this process in the catalytic cycle of silylformylation.

The triorganosilyl group in **11** is reversibly exchangeable to the triorganosilyl group in a free hydrosilane under CO pressure. In fact, a pair of equimolar mixture, **11c** and Me_2PhSiH or **11a** and $ButMe_2SiH$, shows the identical distribution of the components (**11a** : **11c** ≈ 88 : 12) after 18 h. This suggests strongly that the equilibrium is attained through a common intermediate **111** (Scheme 5).[25]

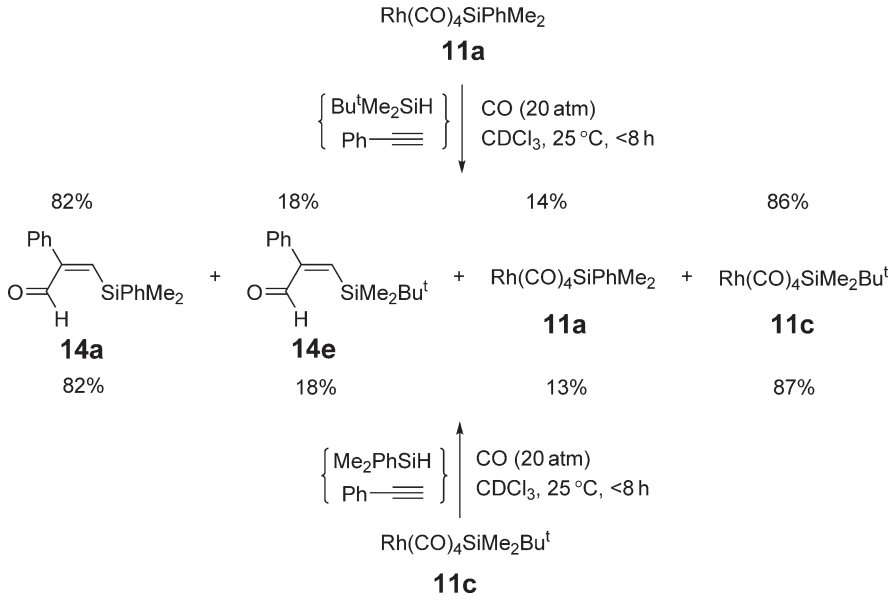
In sharp contrast to the result shown in Scheme 4, complex **11** selectively forms **14** in the presence of an equal amount of phenylacetylene and Me_2PhSiH under CO pressure regardless of a stoichiometric or catalytic reaction. The fact that almost identical results are obtained in a pair of crossover reactions between different triorganosilyl groups suggests the presence of a pre-equilibrium between the hydrosilane and Rh–Si species (Scheme 6).[25]



Scheme 4



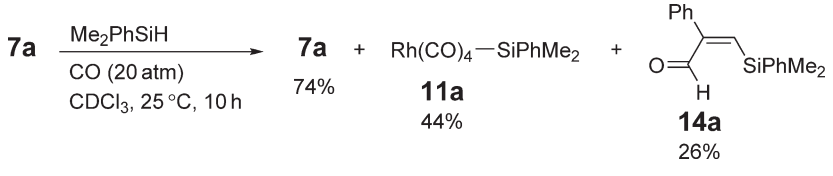
Scheme 5



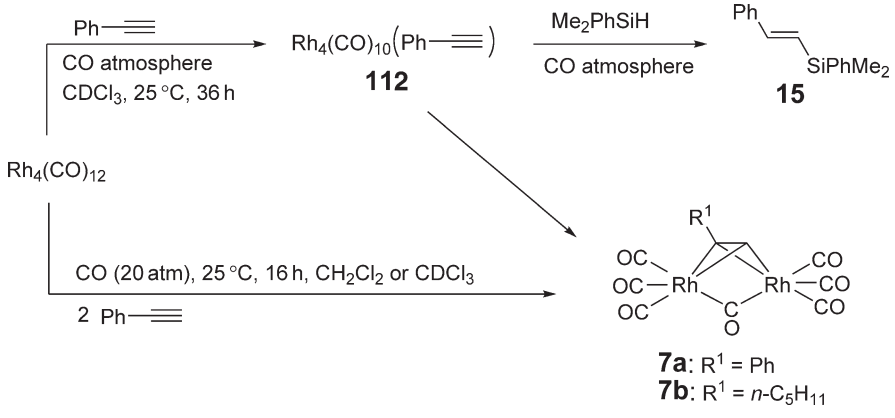
Scheme 6

Phenylacetylene **13** reacts with $Rh_4(CO)_{12}$ to give **112** under an Ar or CO atmosphere. Complex **112** gives (*E*)-**15** as the sole organic product by the reaction with Me_2PhSiH under CO atmosphere. Under CO pressure, **112** is transformed to dinuclear complex **7**, which is directly formed from the reaction of **13** with $Rh_4(CO)_{12}$ under CO pressure, irrespective of the quantity of **13** used (Scheme 7). No specific indication of CO insertion into the Rh–C bond in **7** is observed at this stage. Coordination of **13** to rhodium metal in **7** is relatively stable and the coordinated **13** is not replaced by the free **13** in solution.[25]

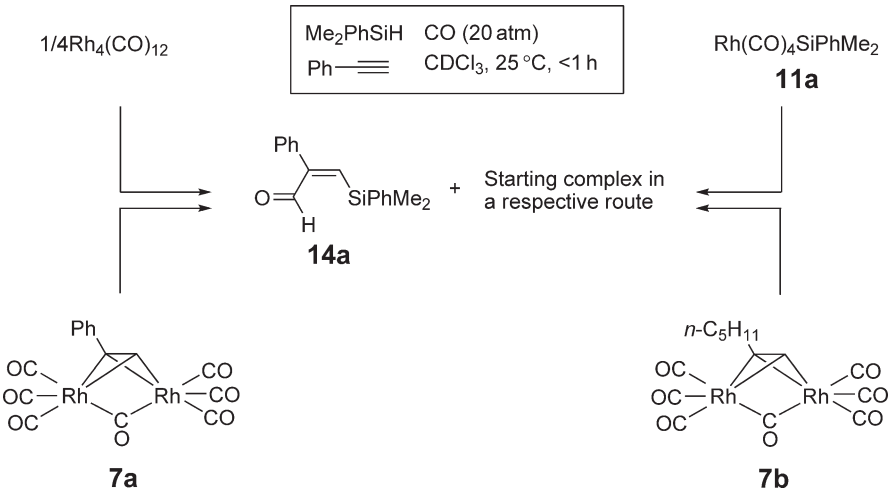
Dinuclear complex **7a** reacts with Me_2PhSiH under CO pressure to give **14a** in a poor yield (26%) along with **11a** (44%). Most of **7a** (74%) is recovered (Equation (26)). The reaction is substantially slower than the formation of **108a**. A slightly different type of dinuclear complex **8** is also characterized in the reaction of $Rh_2Co_2(CO)_{12}$ with 1-hexyne under CO atmosphere.[27,65] Complex **8** reacts with a mixture of Me_2PhSiH and 1-hexyne under CO atmosphere to give **27** ($R^1 = Bu^n$). However, it is ambiguous whether **8** then interacts with hydrosilane or 1-alkyne.[65]



(26)



Scheme 7



Scheme 8

In contrast to the results of Equation (25), Scheme 4, and Scheme 5, four rhodium complexes, $Rh_4(CO)_{12}$, **7a**, **7b**, and **11a**, uniformly interact with a stoichiometric mixture of Me_2PhSiH and phenylacetylene **13** to give **14a** within 1 h under CO pressure. The respective starting complex remains intact after completion of silylformylation (Scheme 8).[25] The results in Equation (26) and the behavior of **7b** in Scheme 8 suggest strongly that the alkyne moiety in **7** is not incorporated directly as a product of silylformylation.

All the starting compounds in Scheme 8 have a sufficient potential for both catalytic and stoichiometric silylformylation, when Me_2PhSiH and 1-alkyne are present in a reaction vessel at the same time. Stable mononuclear complex, $RhH(CO)(PPh_3)_3$, is far inferior in catalyst efficiency at 25 °C, though the efficiency is improved under practical operation at 100 °C (Table 6).[25] Though **7** and **11** are derived from $Rh_4(CO)_{12}$ under controlled conditions and work as an active catalyst of silylformylation, their position in the catalytic cycle is still a precursor of truly active species, because it takes a far longer induction period for activation than that for silylformylation.

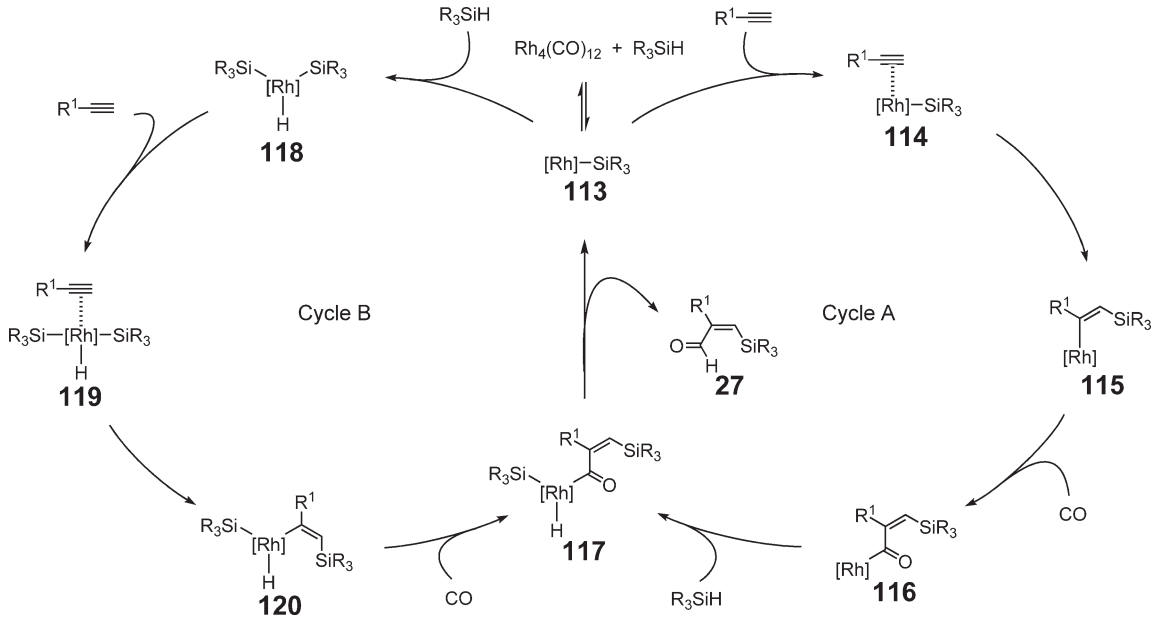
Cumulated results related to $Rh_4(CO)_{12}$, **7**, and **11** give the conclusion that a mononuclear species involving an Rh–Si moiety is an active intermediate. Ojima *et al.* point out a specific role of a heteronuclear framework such as **8** for regioselectivity control in the silylformylation of 1-alkynes on the basis of the results obtained by the catalysis of $Rh_2Co_2(CO)_{12}$.[27,65] Regioselectivity is retained even when stable mononuclear rhodium complexes, $RhH(CO)(PPh_3)_3$, $[Rh(cod)(dppb)]PF_6$, and $Rh(acac)(CO)_2$, are used for the catalyst, though these complexes except $Rh(acac)(CO)_2$ show substantially lower rate than that of $Rh_4(CO)_{12}$.[25] Thus, it is concluded that the presence of Rh species, regardless of nuclearity, is crucial for smooth silylformylation of alkynes. Generation of a mononuclear rhodium carbonyl species such as $Rh(CO)_nSiR_3$ is reasonable rather than the formation of multinuclear metal carbonyl species from $RhH(CO)(PPh_3)_3$, since metal carbonyl clusters have generally been known to decompose to a lower homolog of metal carbonyl clusters under CO pressure.[66]

Accordingly, two possible cycles A and B are proposed for the silylformylation of 1-alkynes (Scheme 9),[25] both starting with oxidative addition of hydrosilane to give an Rh–Si species, **113**. This step is presumably reversible and triggers the degradation of cluster frameworks. In cycle A, **113** is allowed to react with acetylene to form vinyl–Rh

Table 6 Relative efficiency of Rh catalyst precursor in silylformylation of **13**[a]

Entry	*Catalyst precursor*	*Substrate/Rh*	*Yield of* **14a** (%)	*Turnovers per min*
1	$Rh_4(CO)_{12}$	84	82	3.4
2	**11a**	86	88	3.8
3	**11c**	82	70	2.9
4	**7a**	83	65	2.7
5	$RhH(CO)(PPh_3)_3$	83	16[b]	0.2

[a]Reactions were carried out in a C_6H_6 (7 ml) solution containing the fixed mole ratio **13** : Me_2PhSiH : [Rh] = 83 : 83 : 1 at 25 °C for 20 min under CO pressure (20 atm).
[b]Reaction time was increased to 1 h because of the low conversion within the prescribed time.



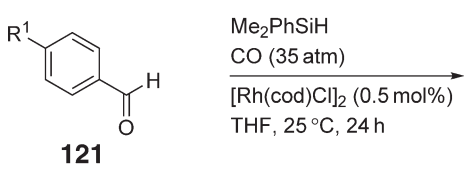
Scheme 9

species **116**. Insertion of CO between the carbon–Rh bond in **115** affords acyl–Rh intermediate **116**. Oxidative addition of an Si–H bond to Rh metal to give **117** is followed by reductive elimination to give rise to a silylformylation product, for example, **14**, and regenerate **113**. When hydrosilane is absent, **116** reacts with another molecule of **115** to afford a divinyl ketone **108** (Scheme 4). Recent demonstration of alkyne insertion into Rh–Si bond[64] allows us to propose the process from **113** to **116**. The final stage of forming **27**, etc., from **116** is also supported by the evidence that a cobalt–acyl complex liberates an aldehyde by the interaction with hydrosilane.[67]

In cycle B, complex **118** is derived from **113** by oxidative addition of R_3SiH and then interacts directly with alkyne to form **119** and then **120**. Insertion of CO into the Rh–vinyl carbon bond in **120** leads to **117**. The rest of the cycle is shared with A. It is difficult to conclude unequivocally which of these cycles dominates silylformylation, because such observable steps as formation of **11** and silyl exchange discussed in Scheme 5 require far longer time than that sufficient for silylformylation.

11.14.4 Silylformylation of Aldehydes, Epoxides, and Oxetanes

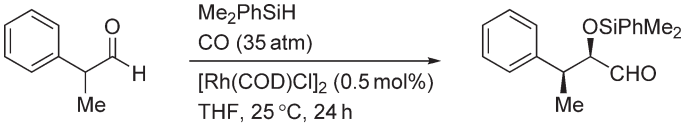
In addition to alkynes, aldehydes can undergo silylformylation (Equation (27)). Although this reaction pattern was previously carried out with cobalt catalysts, the most important merit in the use of $[Rh(cod)Cl]_2$ or $[Rh(CO)_2Cl]_2$ is that the reaction proceeds under far milder conditions. Since such mild conditions make it possible to discriminate starting aldehydes **121** from resultant sterically demanding α-silyloxyaldehydes **122**, adjustment of molar ratios of the starting substrates is unnecessary for isolation of product aldehydes.[38,39]



R^1	*Yield* (%)
H	90
Br	84
Me_2N	80
Me_3SiO	50
$Me_3SiC{\equiv}C$-	80
AcO	70

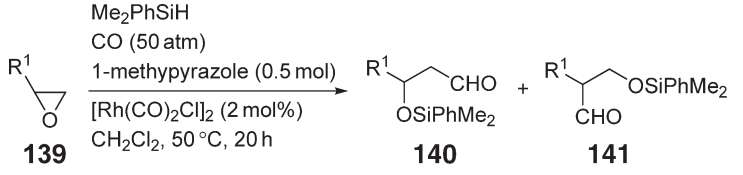
(27)

Choice of THF as the solvent, Me_2PhSiH as the hydrosilane, and operation under anhydrous conditions are critical for selective silylformylation of **121** to give **122**, whereas these regulations are not necessary in the silylformylation of alkynes. Similar silylformylation is applied to 2-(*N*-methylpyrrolidyl)aldehyde (60%), 2-furylaldehyde (90%), 2-thiophenecarboxaldehyde (72%), 2,6-dimethyl-5-heptenal (60%), butanal (60%), 2-methylpropanal (75%), ferrocenecarboxaldehyde (88%), and phenylacetaldehyde (80%)[39] to give the corresponding homologated aldehydes. 2-Phenylpropanal **123** gives predominately *syn*-isomer **124** (*syn: anti* ≈ 10 : 1) under the silylformylation conditions. The stereoselectivity is understood in terms of Cram's rule at the stage of coordination of the catalyst to a least hindered carbonyl face. Subsequent stereospecific and irreversible migratory insertion gives rise to *syn*-aldehyde **124** (Equation (28)).[39]



123 **124** (28)

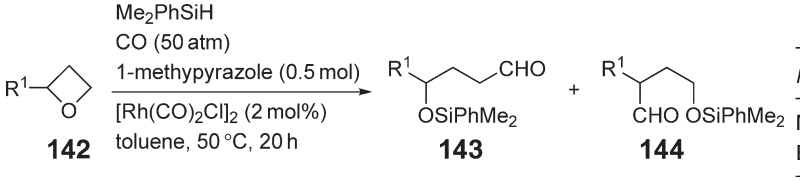
Cyclic ethers such as epoxides and oxetanes are also susceptible to an Rh-catalyzed silylformylation under conditions milder than the $Co_2(CO)_8$-catalyzed reaction (Table 7). Use of 0.5 molar equiv. of 1-methylpyrazole as an additive is crucial for smooth silylformylation of epoxides. Ring opening of epoxides occurs predominantly in a *trans*-manner. Regiochemistry of the epoxy ring opening seems to be controlled by bulkiness of a substituent on the ring carbon. Silylformylation of 1,2-epoxybutane (**139**, $R^1 = Et$) gives a mixture of two regioisomers (**140** : **141** = 77 : 23), whereas **140** ($R^1 = Bu^t$) is the sole product of the reaction with 3,3-dimethyl-1,2-epoxybutane (**139**, $R^1 = Bu^t$) (Equation (29)).[40] Ring opening of **142** occurs regioselectively at a less-substituted carbon atom to give a 95 : 5 mixture of **143** : **144** (Equation (30)).[41]



139 **140** **141**

R^1	*Yield* (%)	**140** : **141**
Et	60	77 : 23
Bu^t	65	100 : 0

(29)

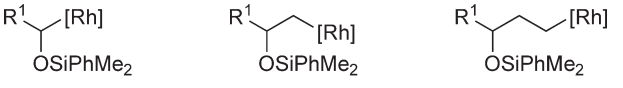


142 **143** **144**

R^1	*Yield* (%)	**143** : **144**
Me	62	95 : 5
Et	64	95 : 5

(30)

Although detailed mechanistic study is not reported on the ring-opening silylformylation, it is elucidated that the respective products are given through continuous steps of CO insertion to the Rh–C(alkyl) bonds in **145**,[39] **146**,[40] and **147**[41] and interaction of the resulting complexes with hydrosilane.

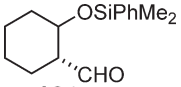
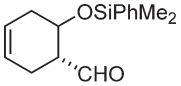
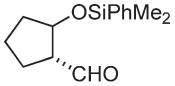
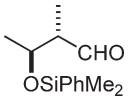
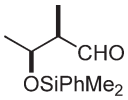
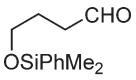
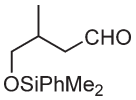
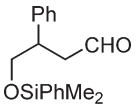


145 **146** **147**

11.14.5 Intramolecular Version of Silylformylation of Alkynes and Alkenes

In contrast to regioselective silylformylation of 1-alkynes, namely, exclusive formylation at an internal *sp*-carbon, silylformylation of internal alkynes results in lower regioselectivity. An *sp*-carbon bearing a bulkier substituent seems to be preferably formylated as seen in the reaction of 2-hexyne (**103**, $R^1 = Pr^n$) and 1-phenylpropyne (**103**, $R^1 = Ph$).[25] On the basis of the mechanisms discussed in Scheme 9 as well as experimental results regarding intramolecular hydrosilylation[68,69] and cyanosilylation,[70] it seems reasonable to assume alkynyldiorganylsilanes can react with CO in an intramolecular fashion. Thus, strict control of formylation site is achieved by an intramolecular version using a starting substrate that contains both an acetylenic bond and a hydrosilyl moiety (Scheme 10). 7-Hydridodimethylsilyl-2-heptyne

Table 7 Silylformylation of epoxides and oxetanes[40,41]

Entry	*Cyclic ethers*	*Solvent*	*Products*	*Yield (%)*
1	 **125**	CH_2Cl_2	 **126**	82
2	 **127**	CH_2Cl_2	 **128**	66
3	 **129**	CH_2Cl_2	 **130**	72
4	 *cis*-**131**	CH_2Cl_2	 *anti*-**132**	70
5	 *trans*-**131**	CH_2Cl_2	 *syn*-**132**	55
6	 **133**	Toluene	 **134**	83
7	 **135**	Toluene	 **136**	80
8	 **137**	Toluene	 **138**	42

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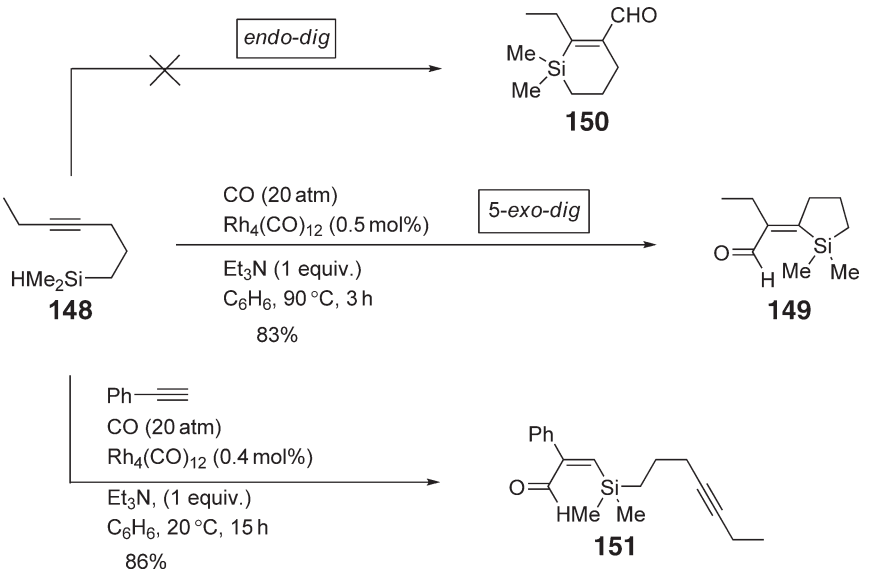
148 readily incorporates CO to give (*Z*)-**149** in 83% yield with the assistance of an $Rh_4(CO)_{12}$ catalyst. Baldwin's rule suggests the cyclization is a 5-*exo-dig*-mode. None of the products derived from an *endo-dig*-mode cyclization **150** or an intermolecular silylformylation of **148** are produced. In the presence of phenylacetylene **13**, alkynylsilane **148** behaves as a hydrosilane and undergoes intermolecular silylformylation to give **151** in 86% yield (Scheme 10). This method provides a vehicle for complete regio- and stereoselective formylation of acetylenic bonds.[71]

Other examples of *exo-dig*-ring closure are summarized in Table 8. Alkynes **152**, **154**, and **156** give **153**, **155**, and **157**, respectively, as the sole product of CO incorporation. Both terminal and internal acetylenes undergo the cyclization to give (*Z*)-*exo-dig*-products.

Intramolecular cyclization is particularly effective to terminal alkynes containing three or four methylene units between acetylenic and silyl moieties such as **158**,[71] **160**,[71] and **162**.[72] But-3-ynylmethylphenylsilane does not give any positive result for CO incorporation. Regioselectivity for the silylformylation is completely reversed from the one in the standard silylformylation discussed in Section 11.14.2.2. A bulky *tert*-butyl group in **162** ($R^1 = Bu^t$) plays an



Scheme 10

Table 8 Intramolecular silylformylation of alkynylsilanes

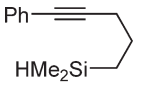
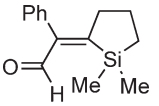
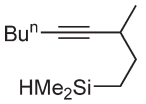
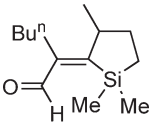
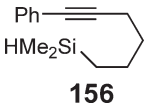
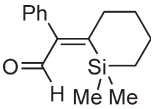
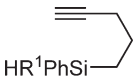
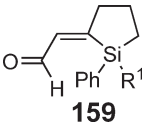
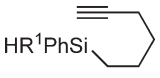
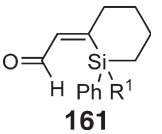
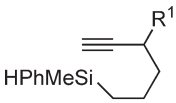
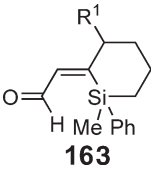
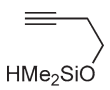
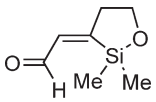
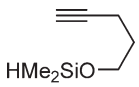
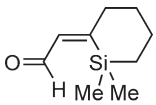
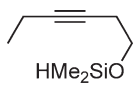
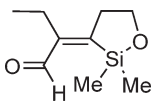
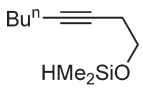
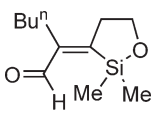
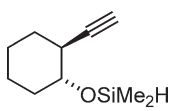
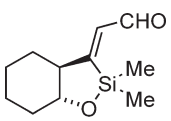
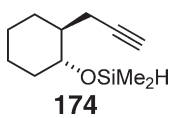
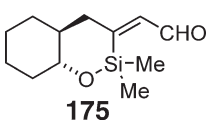
Entry	*Alkynylsilanes*	*Catalyst*	*Products*	*Yield (%)*	*References*
1	 **152**	$Rh_4(CO)_{12}$	 **153**	79	71
2	 **154**	$Rh_4(CO)_{12}$	 **155**	71	71
3	 **156**	$Rh_4(CO)_{12}$	 **157**	69	71
4 5	 R^1 = Me R^1 = Ph **158**	$Rh_4(CO)_{12}$ 12	 **159**	56 37	71 71
6 7	 R^1 = Me R^1 = Ph **160**	12 12	 **161**	56 49	71 71
8 9	 R^1 = Me R^1 = Bu^t **162**	12 12	 **163**	73 70	72 72

Table 9 Intramolecular silylformylation of ω-(hydrodimethylsilyloxy)alkynes[73]

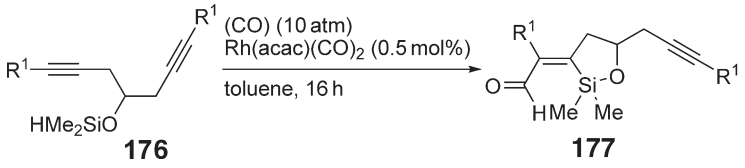
Entry	*Alkynes*	*Catalyst*	*Products*	*Yield*[a] (%)
1	 **164**	$(Bu^tNC)_4RhCo(CO)_4$	 **165**	42
2		$Rh_2Co_2(CO)_{12}$		(46)
3		Rh(acac)$(CO)_2$		(62)
4	 **166**	$(Bu^tNC)_4RhCo(CO)_4$	 **167**	(81)
5		Rh(acac)$(CO)_2$		(73)
6	 **168**	$Rh_4(CO)_{12}$, Et_3N	 **169**	77
7	 **170**	$(Bu^tNC)_4RhCo(CO)_4$	 **171**	66
8		$Rh_2Co_2(CO)_{12}$		(84)
9		Rh(acac)$(CO)_2$		(93)
10		$Rh_4(CO)_{12}$, Et_3N		69
11	 **172**	$(Bu^tNC)_4RhCo(CO)_4$	 **173**	69
12		$Rh_2Co_2(CO)_{12}$		(92)
13		Rh(acac)$(CO)_2$		(94)
14	 **174**	$(Bu^tNC)_4RhCo(CO)_4$	 **175**	73
15		$Rh_2Co_2(CO)_{12}$		(80)
16		Rh(acac)$(CO)_2$		(95)

[a]Isolated yield. The value in parentheses is GC yield.

important role for the diastereoselective formation of **163** with *trans*-geometry between the phenyl(Si) and *tert*-butyl groups, while the methyl group in **162** (R^1 = Me) is a spectator of the diastereomeric discrimination.[72]

A hydrosilyloxy moiety also works as a directing group for the intramolecular silylformylation regardless of terminal and internal alkynes (Table 9).[73]

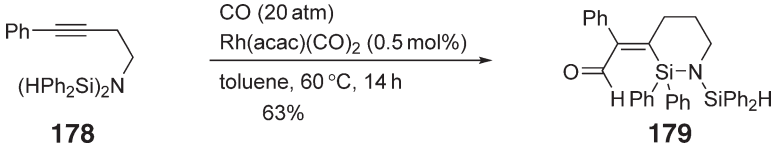
This type of intramolecular silylformylation is applicable to 4-silyloxy-1,6-diyne **176** which gives **177** in good yields (Equation (31)). The remaining alkynyl moiety in **177** can further undergo intermolecular silylformylation.[74]



R^1	*Temperature* (°C)	*Yield* (%)
H	25	98
Me	60	82

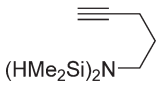
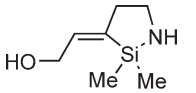
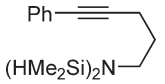
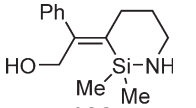
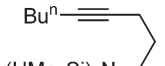
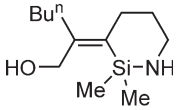
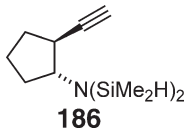
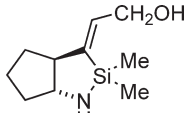
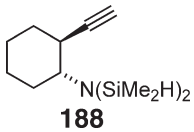
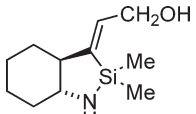
(31)

A similar approach using an aminosilyl directing group is possible. In fact, alkynylamine **178** reacts with CO to give **179** by the catalysis of Rh(acac)$(CO)_2$ (Equation (32)). Since 3-aminosilylalkenals derived from other alkynylamine are unstable to isolate, the corresponding reaction mixture is led to a stable alcohol by reduction with $NaBH_4$ in MeOH without isolation of the silylformylated product (Table 10).[75]



(32)

Table 10 Intramolecular silylformylation of bis(silyl)aminoalkynes[75]

Entry	*Substrates*	*Catalyst*	*Products*	*Yield (%)*
1	 **180**	$Rh(acac)(CO)_2$	 **181**	52
2		$(Bu^tNC)_4RhCo(CO)_4$		80
3		$Rh_2Co_2(CO)_{12}$		75
4	 **182**	$Rh(acac)(CO)_2$	 **183**	71
5		$(Bu^tNC)_4RhCo(CO)_4$		87
6	 **184**	$Rh(acac)(CO)_2$	 **185**	90
7	 **186**	$Rh(acac)(CO)_2$	 **187**	84
8	 **188**	$Rh(acac)(CO)_2$	 **189**	91
9		$(Bu^tNC)_4RhCo(CO)_4$		78

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In sharp contrast to simple alkenes that undergo silylcarbonylation, genuine silylformylation of an olefinic moiety is attained only by an intramolecular technique (Equation (33)). Since the most serious competitive reaction is an intermolecular hydrosilylation reaction to form **192**, the key for the successful transformation depends on an appropriate combination of substituents R^1 and R.[76]

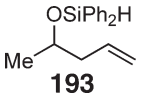
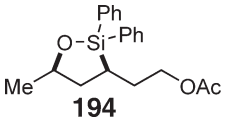
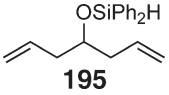
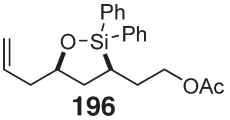
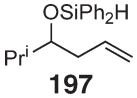
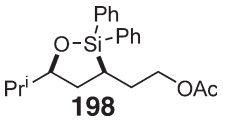
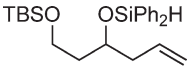
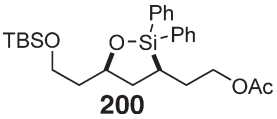
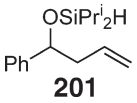
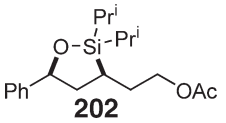
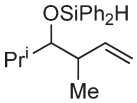
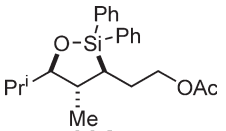
The presence of R^1 (except H) is necessary for the desired silylformylation. Because of the instability of **191**, the formyl group in **191** is immediately converted to the corresponding acetate by sequential reduction and acetylation (Equation 33). An additional feature of this silylformylation is its *cis*-selectivity with respect to the oxasilacyclopentane ring in **191** (Table 11).[76]

(33)

11.14.6 Silylative Lactonization of Alkynyl Alcohols

Silylformylation of 3-butyn-1-ol **84** results in concomitant formation of γ-lactone **86** (Scheme 3). The lactone formation becomes exclusively preferred by use of 1 equiv. of Et_3N (Equation (34)).[49]

Table 11 Intramolecular silylformylation of β-silyloxyalkenes[76]

Entry	*Substrates*	*Products*	*Yield (%)*	*Ratio of diastereomers*
1	 **193**	 **194**	67	4.5 : 1
2	 **195**	 **196**	64	4 : 1
3	 **197**	 **198**	79	6 : 1
4	 **199**	 **200**	60	4 : 1
5	 **201**	 **202**	54	7 : 1
6	 **203**	 **204**	71	10 : 1

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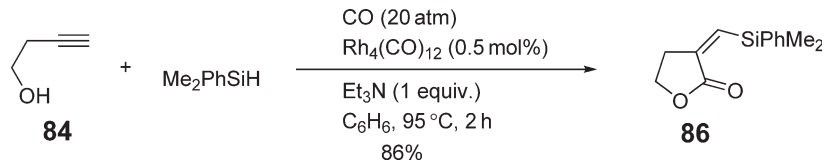
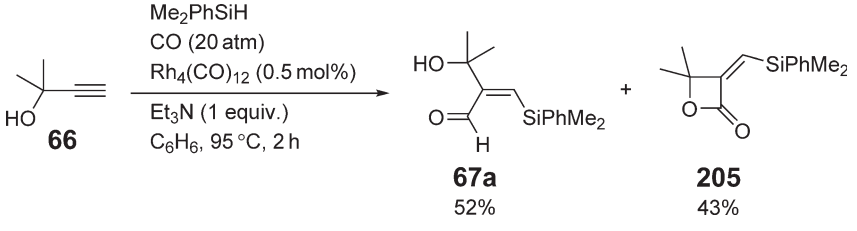


(34)

Homopropargylic alcohols, **210**, **212**, and **214** in Table 12 are carbonylated to form α-silylmethylene-γ-lactones, **211**, **213**, and **215**, respectively, under similar reaction conditions.[49,50]

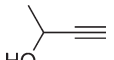
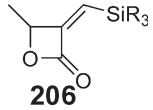
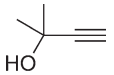
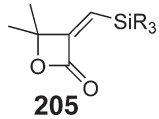
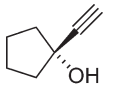
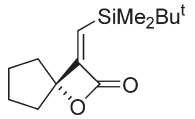
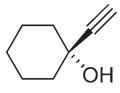
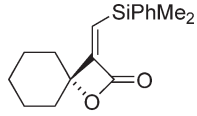
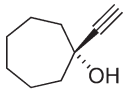
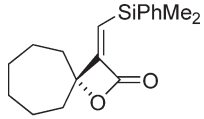
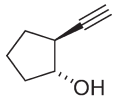
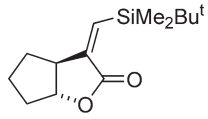
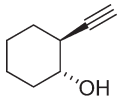
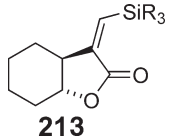
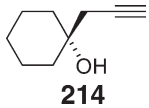
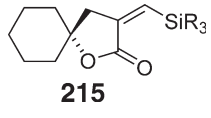
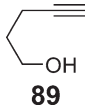
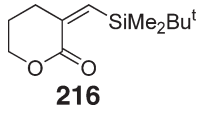
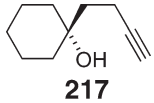
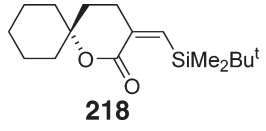
When 2-methyl-3-butyn-2-ol **66** is subjected to the conditions similar to Equation (34), β-lactone **205** ($SiR_3 = SiPhMe_2$) and 3-silylpropenal **67a** are obtained in 43% and 52% yields, respectively (Equation (35)).[49]



(35)

Selectivity for the formation of **207** is dramatically improved by use of either a stronger base, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) instead of Et_3N (0.1 molar equiv. of DBU is sufficient for selective formation of **205**), or a bulkier silane, such as Bu^tMe_2SiH. The *spiro*-type β-lactones **207**, **208**, and **209** are also obtained in good

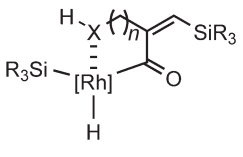
Table 12 Silylative lactonization of alkynylalcohols[49,50]

Entry	*Alkynyl alcohol*	*Hydrosilane*	*Base*	*Product*	*Yield* (%)
1	 **64**	Me_2PhSiH	Et_3N	 **206**	15
2		Me_2PhSiH	DBU		54
3		Bu^tMe_2SiH	DBU		79
4	 **66**	Me_2PhSi	Pyridine	 **205**	0
5		Me_2PhSiH	DABCO		52
6		Me_2PhSiH	DBU		81
7		Et_3SiH	Et_3N		64
8		Pr^i_3SiH	Et_3N		33
9		Bu^tMe_2SiH	Et_3N		86
10	 **68**	Bu^tMe_2SiH	DBU	 **207**	68
11	 **70**	Me_2PhSiH	DBU	 **208**	85
12	 **72**	Me_2PhSiH	DBU	 **209**	86
13	 **210**	Bu^tMe_2SiH	DBU	 **211**	84
14	 **212**	Me_2PhSiH	Et_3N	 **213**	87
15		Bu^tMe_2SiH	DBU		83
16	 **214**	Me_2PhSiH	Et_3N	 **215**	87
17		Bu^tMe_2SiH	DBU		82
18	 **89**	Bu^tMe_2SiH	Et_3N	 **216**	84
19	 **217**	Bu^tMe_2SiH	DBU	 **218**	73

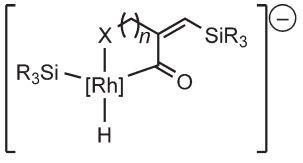
yields by this improved method. In the reaction of less substituted 3-butyn-2-ol **64**, combined use of Bu^tMe_2SiH and 0.1 molar equiv. of DBU is particularly effective for selective formation of β-lactone, **206**.[49]

δ-Lactones **216** and **218** are also selectively constructed from **89** and **217**, respectively, under the similarly modified conditions.[50]

Standard silylformylation is in general robust, as a small amount of water and alcohol do not affect the product selectivity in the standard silylformylation (Section 11.14.2). This applies also to the transformation of **84** to **86**. This fact implies strongly the intermediacy of an intramolecular coordination by a hydroxy group located in an appropriate position to the rhodium center and an additional role of the base in a product determination step. This point is different from the preceding butenolide formation that proceeds through incorporation of 2 equiv. of CO into the acetylenic triple bond in the presence of $Rh_4(CO)_{12}$.[77,78] The results in Table 12 parallel those of the palladium-catalyzed carbonylation of **84** to form α-methylene-γ-butyrolactone, in which alkoxycarbonylpalladium complex is considered to play an important role for the lactone cyclization.[79–81] It is difficult to presume that a similar intermediate controls the lactone formation in this rhodium-catalyzed carbonylation on the basis of the following facts: (i) α-methylene-β-lactone units are not formed by the palladium-catalyzed carbonylation of propargyl type alcohols, and (ii) the presence of R_3SiH as a starting substrate is crucial for smooth carbonylation. Mass spectroscopic analysis of the gas phase recovered from the reaction vessel reveals that hydrogen gas generates concomitantly with the selective formation of **205** ($SiR_3 = SiPhMe_2$). Based on the proposed catalytic cycle for silylformylation (Scheme 9), formation of **86** can be explained by intervention of common intermediate **219** ($n = 2$), which plays a pivotal role in the differentiation between an intramolecular nucleophilic attack of the hydroxy group and reductive elimination of **86**. Thus, addition of base is considered to accelerate the conversion of **219** ($n = 2$) to rhodate anion **220** ($n = 2$). The formation of β-lactone and δ-lactone rings can be explained in a similar way. This working hypothesis is supported by the fact that the presence of such a strong base as DBU is advantageous for selective formation of the lactone framework. Reactivity of Bu^tMe_2SiH and Me_2PhSiH is almost comparable in this lactone formation despite the result of Equation (4). Formation of esters is not observed in the intermolecular silylformylation of a mixture containing 1-alkyne and alcohol.[49] The facts also support that an appreciable energy gain is expected by an intramolecular coordination shown in **219** and **220** in the formation of lactone rings.



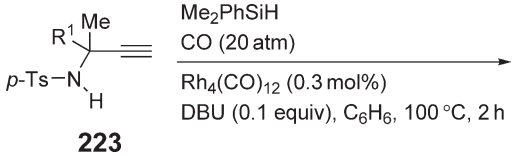
219: X = O (n = 1, 2, and 3)
221: X = NR^1 (n = 1, 2, 3, and 4)



220: X = O (n = 1, 2, and 3)
222: X = NR^1 (n = 1, 2, 3, and 4)

11.14.7 Silylative Carbamoylation of Alkynes

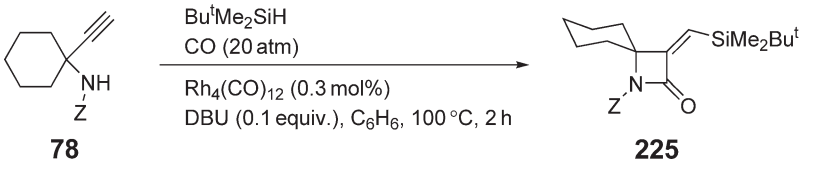
A protocol discussed in the previous section is applicable to selective formation of lactams from alkynylamines, since an amino group involved in alkynylamines is apparently suitable for intramolecular coordination, as shown in **221** and **222**. Propargylic amines **223** with two substituents at the propargyl position react readily with an equimolar amount of Me_2PhSiH to give β-lactam **224** as a sole product in the presence of $Rh_4(CO)_{12}$ (0.3 mol%) and DBU (0.1 equiv.) (Equation (36)).[82] Protection of the amino group as p-tosylamide is essential for selective formation of β-lactam ring. When Bu^tMe_2SiH is used together with DBU, protection of the amino group is not necessary for selective formation of **225** (Equation (37)).[82]



223 **224**

R^1	*Yield* (%)
Me	80
Me_2CHCH_2–	65

(36)

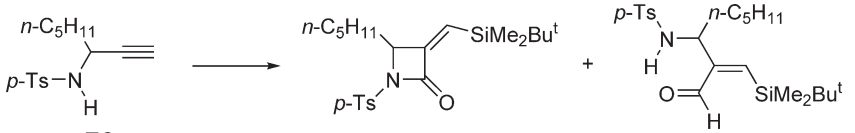


78 225

Z	*Yield* (%)
p-Ts	81
Bn	98
H	64

(37)

In contrast to the above results, less crowded alkynylamide **76** gives **226** in only 18% yield with concomitant formation of **227** under similar conditions (Equation (38)).[82]

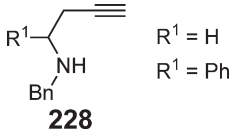
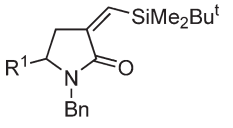
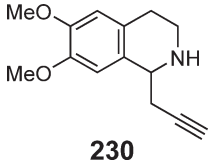
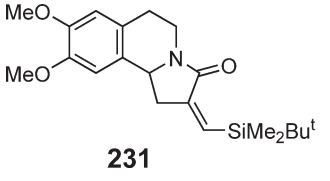
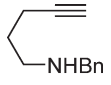
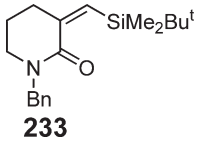
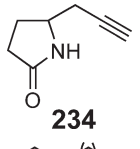
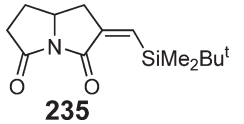
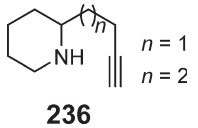
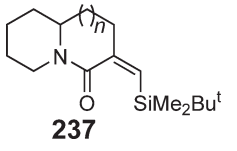


76 **226** 18% **227** 65% *Z* : *E* = 40 : 60

(38)

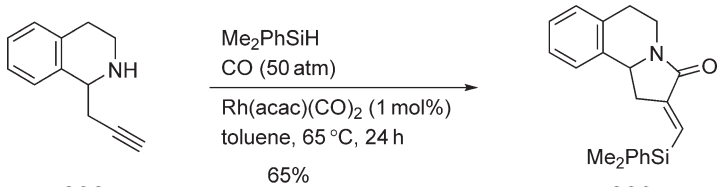
Protection of an amino group by an electron-withdrawing group is not required particularly for energetically favorable lactam ring formation (Table 13).[83]

Table 13 Rh$_4$(CO)$_{12}$-catalyzed construction of lactam frameworks[82,83]

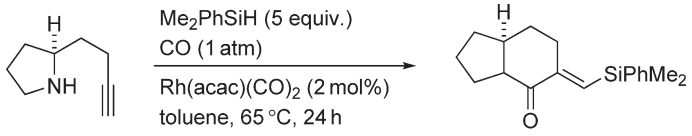
Entry	*Alkynylamine*	*Product*[a]	*Yield* (%)
1	 **228**	 **229**	98
2			84
3	 **230**	 **231**	75
4	 **232**	 **233**	68
5	 **234**	 **235**	97
6	 **236**	 **237**	66
7			55

[a]Reactions were carried out on a 1.6 mmol scale of an alkynylamine and Bu^{t}Me$_2$SiH in C$_6$H$_6$ solution including 0.25 mol% of Rh$_4$(CO)$_{12}$ and 10 mol% of DBU under CO pressure (20 atm) at 100 °C for 2 h.

The lactam ring formation is elucidated by intermediacy of **221** and **222**. In the absence of DBU, the lactam formation suffers from lack of reproducibility in yields and loss of (*Z*)-selectivity at the silylmethylene moiety (Equations (39) and (40)).[84]

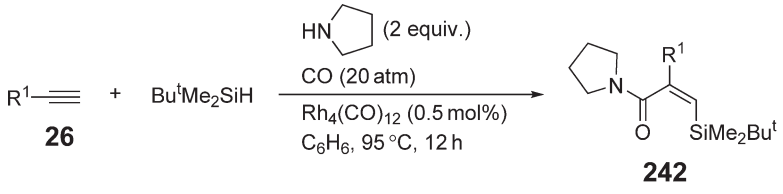


238 **239** (39)



240 **241** (40)

In a similar way, a novel route for synthesis of α,β-unsaturated amide **242** is explored via intermolecular coupling of four components, that is, alkyne, hydrosilane, amine, and CO (Equation (41)).[85] All of these components are assembled in the ordered manner with the assistance of an Rh complex. Pyrrolidine as a nucleophile gives the best results. None of the alcohols can participate in a similar transformation.



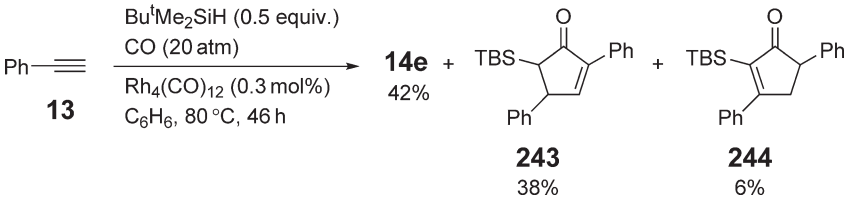
R^1	*Yield* (%)
Bu^n	90
n-C_5H_{11}	82
n-C_6H_{13}	89
c-C_6H_{11}	44
Ph	73

(41)

11.14.8 Annulative Silylcarbonylation

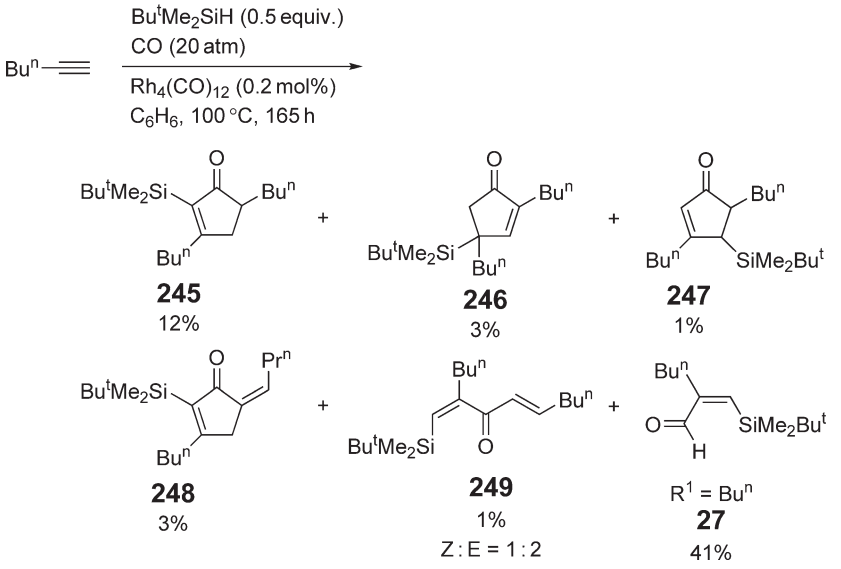
11.14.8.1 1,6-Diynes

Silylformylation of 1-alkynes is a quite reliable tool to selectively introduce both formyl and triorganosilyl groups to carbon–carbon triple bonds as long as 1-alkyne and R_3SiH are employed in a 1 : 1 molar ratio. When less reactive Bu^tMe_2SiH is used in the silylformylation of phenylacetylene **13**, the reaction must be carried out at 25 °C to obtain silylformylation product **14e** in an acceptable yield (entry 14 in Table 1). Operation under forcing conditions (100 °C, 16 h) does not raise the conversion and gives **14e** in 49% yield along with **243** (23%) and **244** (3%). The cyclopentenone formation becomes favored when 2 molar equiv. of **13** are used under high CO pressure (Equation (42)).



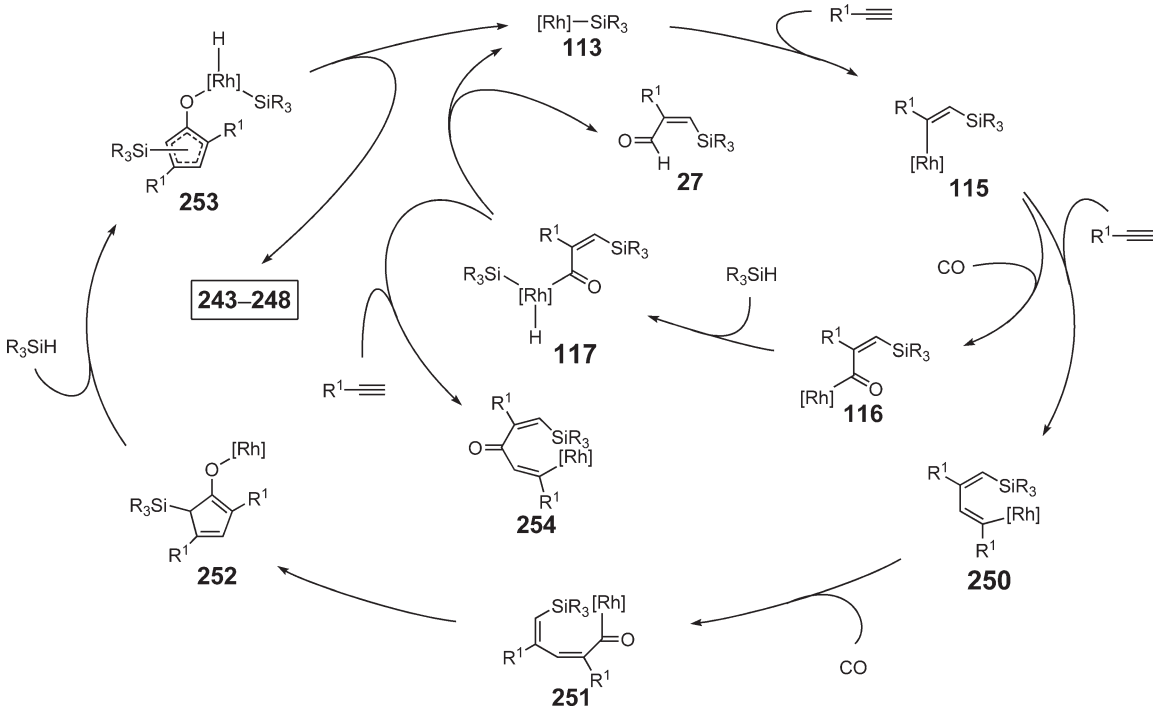
243 38% **244** 6% (42)

The congeners of **243** and **244** are also formed by the reaction with either Me_2PhSiH or Et_2MeSiH (**13** : silane ≈ > 2 : 1); **243** is readily protodesilylated during purification to give 2,4-diphenylcyclopent-2-enone. When **13** is replaced by 1-hexyne, a product akin to **244** is produced as a major cyclocarbonylation product. At higher temperatures, various types of carbonylation products are produced (Equation (43)).[25]



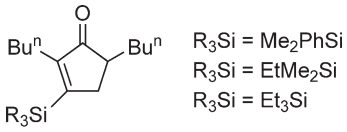
(43)

Formation of such cyclopentenone derivatives is consistently explained in terms of continuous insertion of two alkynes into the Rh–Si bond in **113** to form **250** via **115**. Subsequent insertion of CO into the Rh–C bond in **250** gives **251**, which cyclizes to give **252**. Cyclopentenones **243–248** are all derived from **253**, representing that some isomers are generated from **252** by prototropy or silatropy and the subsequent oxidative addition of R_3SiH to the Rh metal (Scheme 11).[25] The formation of divinyl ketone **249** is ascribed to reverse order of insertion into the Rh–C bond in **115** to give rise to **116**, which is a key intermediate in the silylformylation. Subsequent insertion of 1-alkyne into the Rh–acyl carbon bond in **116** provides **254**, which leads to **249** through interaction with another molecule of R_3SiH (Scheme 11).[25] The rate of this path is apparently far slower than that of the normal silylformylation (Equation (43)).



Scheme 11

Alternative cyclopentenones **255** are suggested for the side-reaction products in the silylformylation of 1-hexyne on the basis of spectral data only,[17,28] and the formation is assumed also by the intermediacy of **116**.

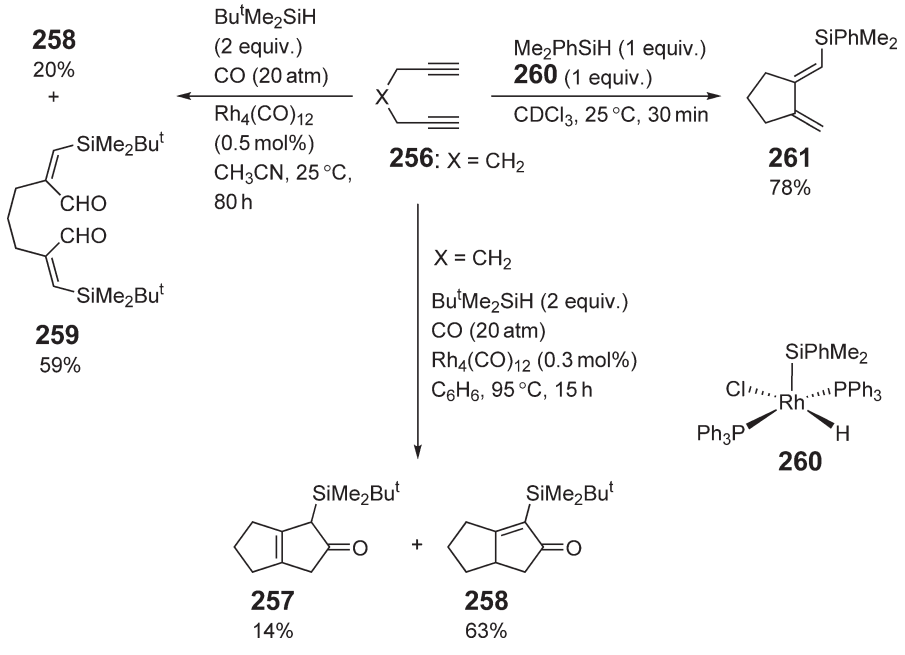


255

Selectivity for the cyclopentenone formation is improved by an intramolecular version. For example, 1,6-heptadiyne (**256**, X = CH_2) reacts in benzene with 2 molar equiv. of Bu^{t}Me$_2$SiH to give two bicyclo[3.3.0]octenones, **257** and **258**, in 14% and 63% yield, respectively, at 95 °C under CO (20 atm) pressure.[86] When benzene is replaced by acetonitrile, **258** becomes a sole product (60% yield). On the other hand, the reaction at 25 °C gives normal silylformylation product **259** as a major component (59%) with the concomitant formation of **258** (20%) (Scheme 12).[86]

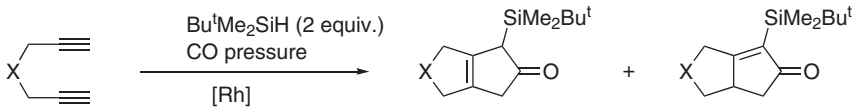
The fact that normal silylformylation product **259** becomes a major product in the reaction at 25 °C suggests that the activation energy to form a bicyclo[3.3.0]-octenone framework is higher than that to form **259**. The formation of **257** and **258** is apparently attributed to the intermediacy of **262** (X = CH_2) and **263** (X = CH_2) on the basis of intermolecular formation of cyclopentenones. This type of ring closing, triggered by silylrhodation of an alkyne moiety, is supported by the fact that **256** reacts with Me$_2$PhSiH to give **264** under a nitrogen atmosphere in the presence of an equimolar amount of complex **260** which is prepared *in situ* by the interaction of RhCl(PPh$_3$)$_3$ with an equimolar amount of Me$_2$PhSiH.[87–89]

This unique [2 + 2 + 1]-cyclocoupling is extended to a variety of 1,6-diyne units. All types of 1,6-diynes **256**, listed in Table 14, react uniformly to give cyclocarbonylation products in moderate to good yields, though product distribution depends on the substrate. It is worth noting that thermodynamically less stable **264** is formed as a major product in the reaction of **256** bearing alkoxycarbonyl groups at the homopropargylic position under the conditions similar to those of 1,6-heptadiyne (**256**, X = CH_2). Isolated **264** {X = $(MeO_2C)_2C$ or $(EtO_2C)_2C$} is readily converted to **265** by treatment with an $RhCl_3 \cdot 3H_2O$ catalyst in ethanol.[86,90] It is quite difficult to isolate **264** in a pure form, since the non-jugative isomerization proceeds partially during purification through a pad of silic gel. Bicylco[3.3.0]-octadienones **266** are isolated as a sole product in the presence of an RhCo mixed cluster catalyst under higher CO pressure. *p*-Tosyl derivative of dipropargylamine preferentially forms **265** as a major



Scheme 12

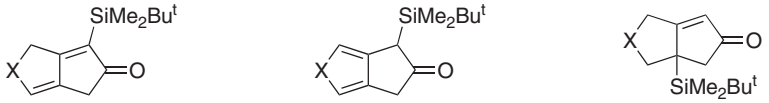
Table 14 Silylative cyclocarbonylation of 1,6-diynes with Bu^tMe_2SiH



256 **264** **265**

Entry	*X in 1,6-diyne*	*Conditions*[a]	*Solvent*	*Percent yield of products* **264**	**265**	*References*
1	$(MeO_2C)_2C$	A	C_6H_6	58	6	86
2	$(MeO_2C)_2C$	A	CH_3CN	70	14	86
3	$(EtO_2C)_2C$	B	Toluene	82	0	90,92
4	$(EtO_2C)(Me)C$	B	Toluene	70	0	92
5	$(EtO_2C)(H)C$	B	Toluene	48	15	92
5	$(HOCH_2)_2C$	C	Toluene	0	71[b]	91
6	$(Bu^tMe_2SiOCH_2)_2C$	C	Toluene	0	95[b]	91
7	$(AcOCH_2)_2C$	C	Toluene	0	72[b]	91
8	$(AcOCH_2)(H)C$	B	Toluene	73	0	92
9	*p*-TsN	A	C_6H_6	18[c]	51	86
10	$PhCH_2N$	A	C_6H_6	31[d]	9	86
11	$PhCH_2N$	A	CH_3CN	72[d]	8	86
12	$PhCH_2N$	D	Toluene	70[d]	18	91,92
13	$CH_2{=}CHCH_2N$	D	Toluene	56[d]	22	92
14	O	A	C_6H_6	0[e]	3	86
15	O	A	CH_3CN	2[f]	35	86
16	O	B	Toluene	27	22	92

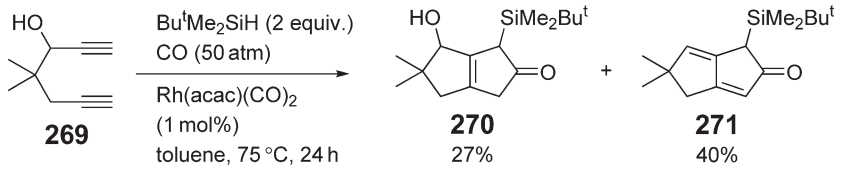
[a]A: CO (20 atm), $Rh_4(CO)_{12}$ (0.5 mol%), 95 °C, 14 h. B: CO (50 atm), $Rh(acac)(CO)_2$ (2 mol%), 120 °C, 5–14 h.C: CO (50 atm), $(Bu^tNC)_4RhCo(CO)_4$, 65 °C, 10 h. D: CO (15 atm), $Rh(acac)(CO)_2$ (2 mol%), 50 °C, 12 h.
[b]This value means the yield of **266**.
[c]A bicyclooctenone, **267**, is isolated as an additional product in 5% yield.
[d]This value means the yield of **267**.
[e]A bicyclooctenone, **268**, is isolated as an additional product in 6% yield.
[f]A bicyclooctenone, **268**, is isolated as an additional product in 2% yield.



266 **267** **268**

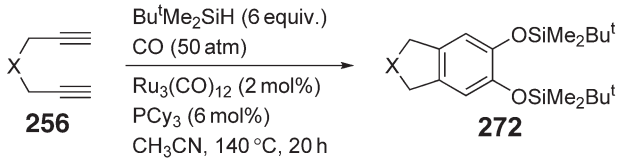
product (entry 9, Table 14),[86] whereas benzyl and allyl groups prefer the formation of **267**.[86,91,92] The products corresponding to **265** ($X = CH_2{=}CHCH_2N$) and **267** ($X = CH_2{=}CHCH_2N$) were ill-defined by speculation on the basis of the structure of **255**.[28,90–93] Bicyclic product **268** (X = O) is also isolated along with **264** (X = O) and **265** (X = O) in the reaction of dipropargyl ether.[86] Formation of **268** (X = O) suggests participation of a process involving silatropy in the catalytic cycle. 2,8-Decadiyne is also carbonylated to give an analog of **264** in 43% yield under relatively low CO pressure (5 atm).[86] Thus, instability of primary product **264** seems to lead to the secondary products by subsequent prototorpy, silatropy, and/or dehydrogenation. Precise control factor on the product distribution is not clear at present.

More complicated results are observed in the reaction of 4,4-dimethyl-1,6-heptadiyn-3-ol **269** with Bu^tMe_2SiH, giving a mixture of **270** and **271** (Equation (44)).[91] Discrimination of the two acetylenic moieties in **269** is hard at the silylrhodation, and thus a complex mixture of regioisomers and diastereomers results.[98] In any event, use of rhodium species as a catalyst is essential for smooth construction of bicyclo[3.3.0]-octenone frameworks.



269 **270** 27% **271** 40% (44)

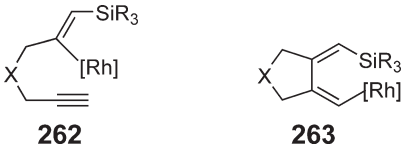
When $Ru_3(CO)_{12}$ is used as the catalyst for the reaction of **256**, quite different products are obtained from identical 1,6-diyne units (Equation (45)).[95]



256 **272**

X	*Yield* (%)
Ac_2C	71
O	40
p-TsN	45

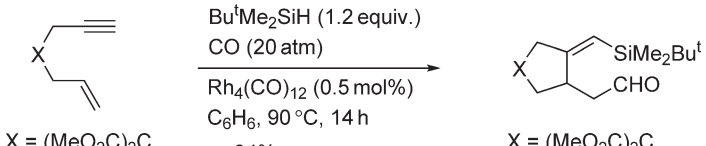
(45)



262 **263**

11.14.8.2 1,6-Enynes

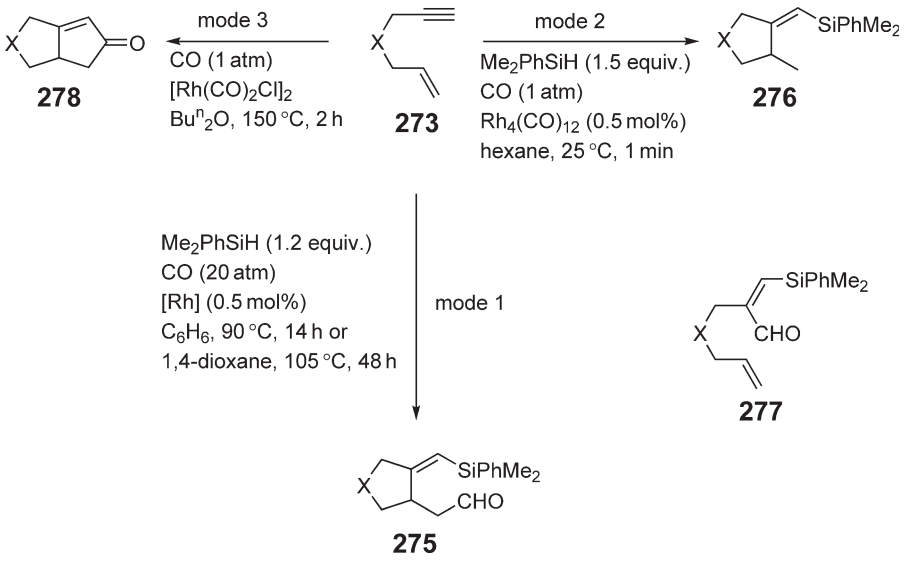
In sharp contrast to 1,6-diyne **256**, which gives a five-membered ring with two *exo*-methylene bonds and then bicyclo[3.3.0]-octenones, 1,6-enyne **273** (X = C(CO$_2$Me)$_2$) gives five-membered product **274** (X = C(CO$_2$Me)$_2$) as a sole product under similar conditions (Equation (46)).[95]



273 **274** (46)

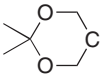
This result clearly shows a possibility of continuous insertion of alkyne into an Rh–Si bond and alkene into an Rh–C double bond. When Me_2PhSiH is used, annulative silylformylation takes place to give **276** as a side-product. This new transformation is optimized in a normal concentration of substrates (0.5 to 0.1 mol l^{-1}) by adopting the following conditions: (i) use of a more reactive hydrosilane Me_2PhSiH, (ii) mixing the starting substrates in a solvent saturated with CO, and (iii) high CO pressure (>20 atm).[95] Additional modification of the reaction conditions provides higher yields and higher selectivity for **275**. The modification involves (i) operation in high dilution of reactants (0.02 mol l^{-1}) and (ii) addition of 10 mol% of P(OEt)$_3$ in a starting mixture.[96] Thus, the annulative silylformylation products **275** are isolated as the sole product in the reaction of 1,6-enyne **273** with an equimolar amount of Me_2PhSiH under high CO pressure (Scheme 13, mode 1) (Table 15).[95,96] *N*-Benzyl-*N*-propargylallylamine (**273**, X = BnN) is exceptional: CO is not incorporated under the same reaction conditions, and pyrrolidine derivative **276** (X = BnN) is the sole product isolated.[95]

When this reaction is carried out under 1 atm of nitrogen or CO atmosphere, a cyclopentane **276** is formed selectively in a minute at 25 °C (Scheme 13, mode 2).[95,96] Although the Pauson–Khand reaction of 1,6-enyne **273** (Scheme 13, mode 3) gives **278**,[97] this transformation is completely suppressed under the conditions of mode 1. Even simple alkyne silylformylation product **277** is not detected at all. This contrasts sharply to the silylformylation of 1-penten-4-yne **48** carried out under similar conditions (Equation (12)). These results can be explained by a pathway similar to the reaction of 1,6-diynes: (i) stepwise insertion of the acetylenic and olefinic moieties into the Rh–Si bond in this order, and (ii) subsequent interaction of CO and Me_2PhSiH with the resultant intermediate to give **275**. The



Scheme 13

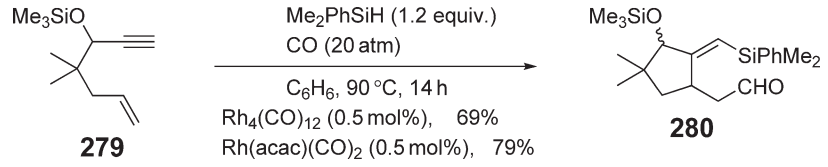
Table 15 Annulative silylformylation of 273 with Me_2PhSiH

Entry	*X in 1,6-enyne*	*Conditions*[a]	*Solvent*	*Percent yield of* **275**	*References*
1	$(MeO_2C)_2C$	A	C_6H_6	85[b]	95
2	$(MeO_2C)_2C$	B	C_6H_6	89	95
3	$(MeO_2C)_2C$	C	1,4-dioxane	98	96
4	$(EtO_2C)_2C$	C	1,4-dioxane	91	96
5		A	C_6H_6	76	95
6		B	C_6H_6	89	95
7		C	1,4-dioxane	89	96
8	$(MeOCH_2)_2C$	C	1,4-dioxane	83	96
9	$(AcOCH_2)_2C$	C	1,4-dioxane	91	96
10	TsN	A	C_6H_6	59	95
11	TsN	B	C_6H_6	74	95
12	TsN	C	1,4-dioxane	85	96
13	MsN	C	1,4-dioxane	56	96
14	BnN	A	C_6H_6	88[c]	95
15	BnN	B	C_6H_6	78[c]	95
16	O	A	C_6H_6	37	95
17	O	B	C_6H_6	37	95

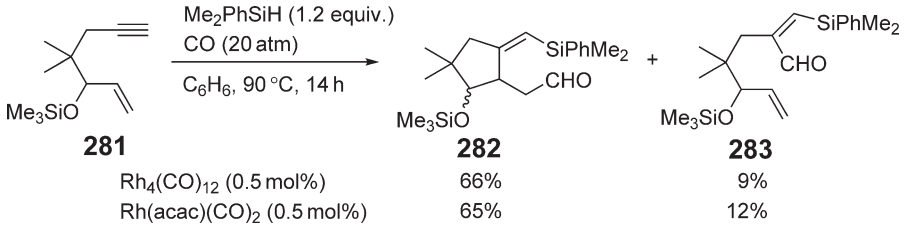
[a]A: $Rh_4(CO)_{12}$ 0.5 mol%, 90 °C, 14 h. B: $Rh(acac)(CO)_2$ 0.5 mol%, 90 °C, 14 h. C: $Rh_4(CO)_{12}$ 0.5 mol%, $P(OEt)_3$ 10 mol%, 105 °C, 45 h.
[b]CO pressure is 36 atm. When the reaction is carried out under 20 atm of CO pressure, 74% of **275** is isolated accompanied with 11% of **276**.
[c]No **275** (X = BnN) is obtained. This value is the yield of **276** (X = BnN).

fact that **276** is formed selectively under CO atmosphere supports elucidation of the stepwise insertion of the acetylenic and olefinic moieties involved in the same molecule into the Rh–Si bond.

The reaction pathway may be supported by the observations with 4,4-dimethyl-5-trimethylsilyloxyhept-1-en-6-yne and its positional isomer 4,4-dimethyl-3-trimethylsilyloxyhept-1-en-6-yne. These react with Me_2PhSiH to give the corresponding aldehydes, **280** and **282**, respectively, as a mixture of two diastereomers under the conditions similar to mode 1 in Scheme 13 (Equations (47) and (48)).[95] In the reaction of **281**, an appreciable amount of **283** is formed concomitantly, which implies that the trimethylsilyloxy group at an allylic position likely retards the cyclopentane annulation step.

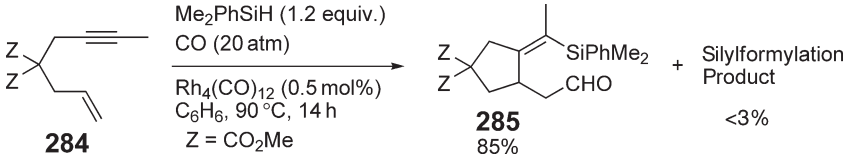


(47)

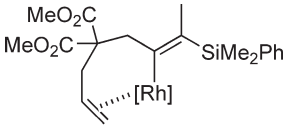


(48)

It is worth noting that the reaction of **284** with Me_2PhSiH gives **285** as a sole cyclic compound; a simple silylformylation product is formed in less than 3% yield (Equation (49)).[95] The outcome is rationalized by intervention of **286** in which intramolecular coordination of an olefinic moiety dominates the orientation of silylrhodation toward the alkyne moiety in **284**.

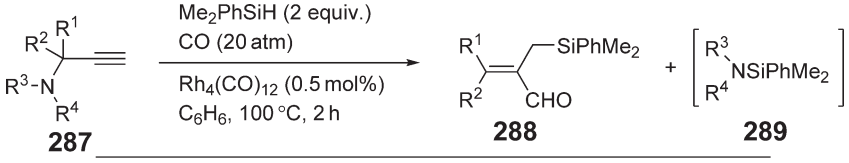


(49)



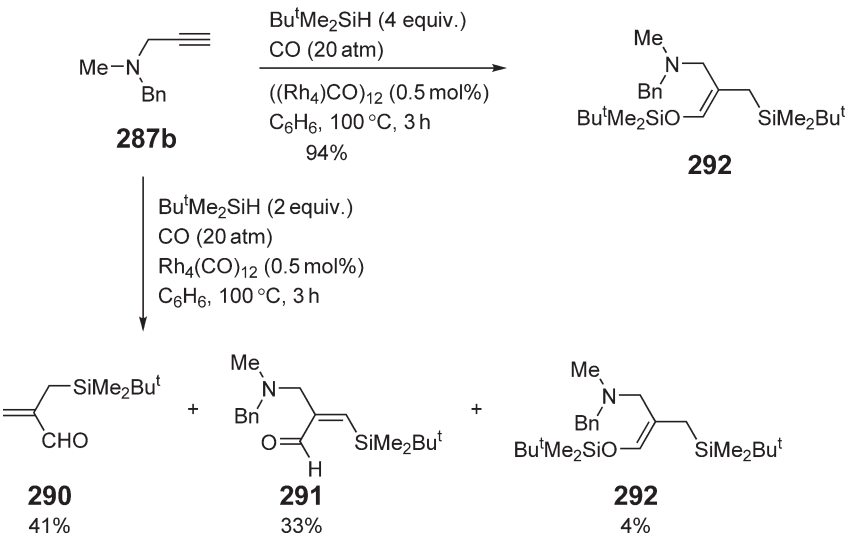
11.14.9 Cascade-Type Reactions in One-Pot Operation

Whereas the reigoselectivity in silylformylation of alkynes is well documented, propargylic amines often give intractable results under the standard conditions. Reaction of **287a** ($R^1 = R^2 = H$; $R^3 = R^4 = Bn$), for example, leads to deaminative silylformylation to give **288a** ($R^1 = R^2 = H$; $R^3 = R^4 = Bn$) (Equation (50)).[99] Use of more than 2 molar equiv. of Me_2PhSiH is a key for this reaction. Propargylic amines **287b–g** are applicable to this type of silylformylation, which is seemingly accelerated by an electron-donating substituent on the amino nitrogen. In contrast, *p*-toluenesulfonyl and methoxycarbonyl groups suppress the transformation (Table 5).



	R^1	R^2	R^3	R^4	*Percent yield of* **288**
a	H	H	Bn	Bn	94
b	H	H	Me	Bn	83
c	Me	H	Bn	Bn	90 ($Z > 98\%$)
d	n-C_5H_{11}	Me	$-(CH_2)_5-$		93 ($Z > 98\%$)
e	Me		$-(CH_2)_5-$		65
f	$-(CH_2)_5-$		$-(CH_2)_5-$		80
g	$-(CH_2)_5-$		H	Bn	88

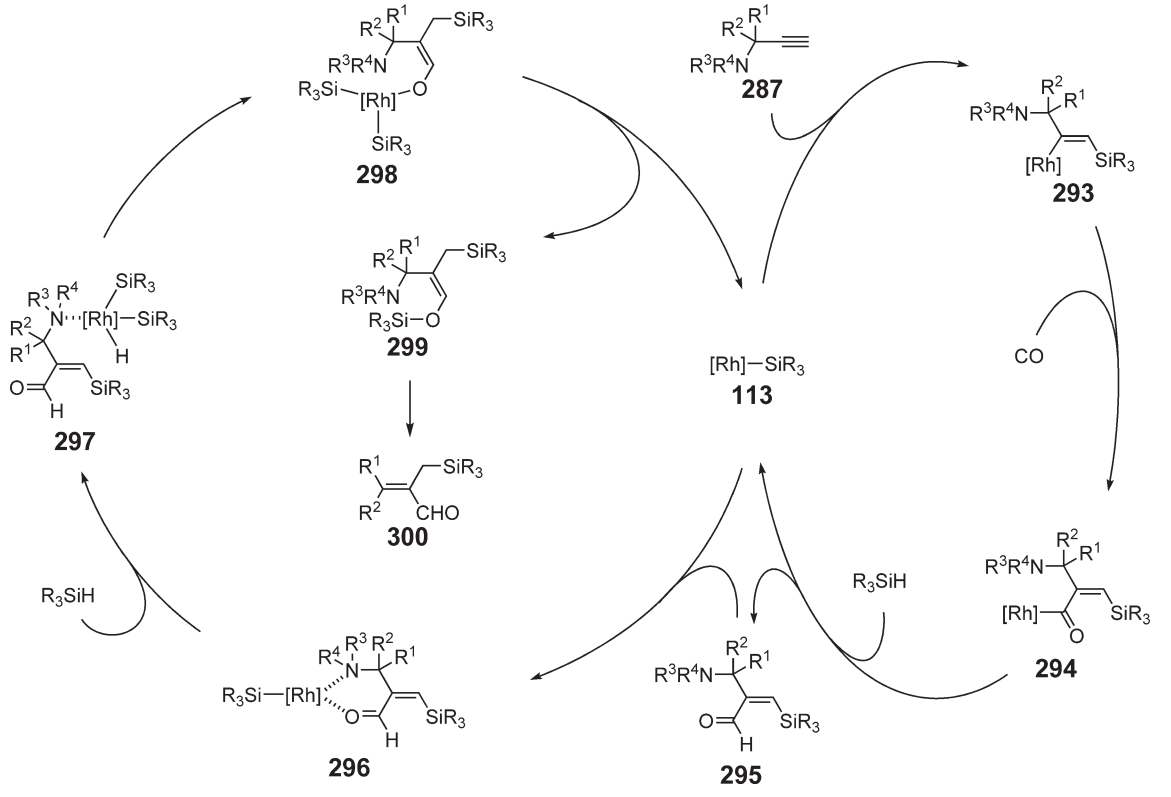
(50)



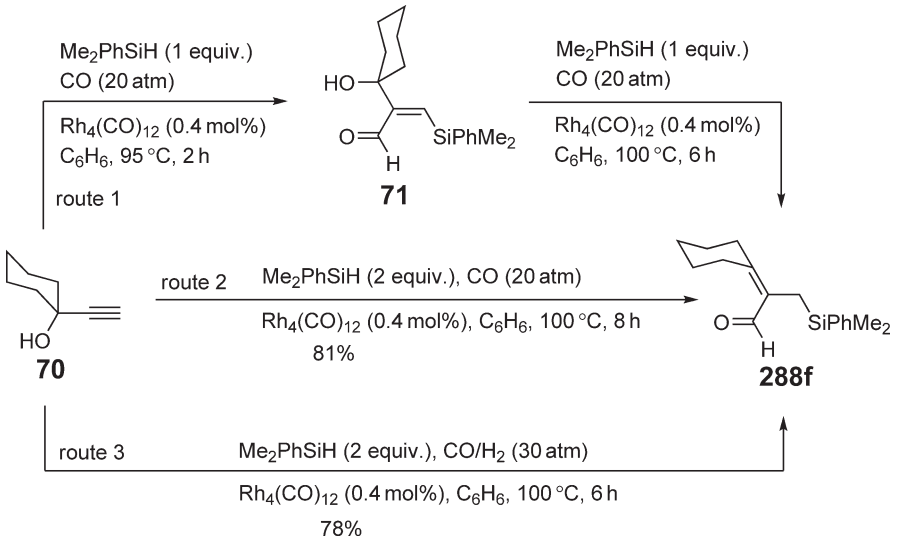
Scheme 14

When 2 molar equiv. of Bu^tMe_2SiH are used for the reaction of **287b** under the conditions similar to Equation (44), three types of products, **290**, **291**, and **292**, are isolated (Scheme 14).[100] Use of more Bu^tMe_2SiH (up to 4 molar equiv.) furnishes **292** as the sole product, which upon treatment with silica gel suspended in benzene decomposes to **290**. These results suggest that formation of **290** can be explained by sequential reactions of **287b** → **291** → **292** → **290**.

Thus, the formation of 2-silylmethylalkenals **288** from **287** can be explained by the intervention of a silylformylation product **295** and its consecutive reaction with another molecule of R_3SiH under CO pressure as shown in Scheme 15.[100]



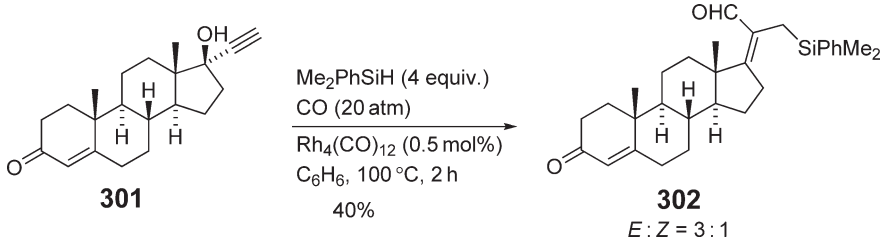
Scheme 15



Scheme 16

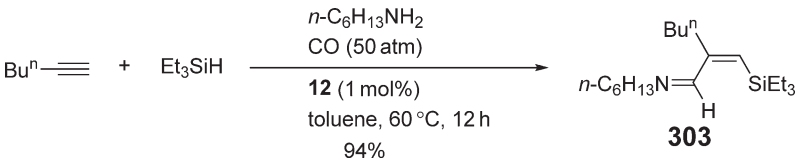
This mechanism suggests that **288** may be constructed by a similar sequential reaction starting from propargylic alcohols, **70**. Under the standard conditions, **70** is silylformylated to give **71**, which upon treatment with 1 molar equiv. of Me_2PhSiH under CO in the presence of a catalytic amount of $Rh_4(CO)_{12}$ may be converted into an expected **288f**. This product is indeed obtained in high yield (route 1 in Scheme 16).[48,101] The identical transformation is actually attained by a one-pot reaction of **70** with >2 molar equiv. of Me_2PhSiH under CO (route 2 in Scheme 11).[48] Propargylic carboxylates and carbonates are also suitable for the one-pot procedure. The transformation of **71** to **288** may be regarded as a formal S_N2' reaction by a hydride as a nucleophile. If this is the case, molecular hydrogen could play the role of Me_2PhSiH in the last step. In fact, the third route for the conversion of **70** to **288** is realized by the reaction of **70** with Me_2PhSiH, CO, and H_2.[102] When silylformylation of 1-hexyne and 4-phenyl-1-butyne is carried out under the pressure (40 atm) of CO/H_2 (1/1), using **12** as a catalyst, **288** ($R^1 = Bu^n$, $R^2 = H$ and $R^1 = PhCH_2CH_2$, $R^2 = H$) is formed in one-pot operation. However, this reaction depends heavily on the structure of 1-alkynes used.[26]

Despite the rich chemistry of **288** that may be anticipated,[14,103,104] synthetic methods for this type of compounds are limited to the one involving oxidation of the corresponding alcohols. In contrast, **288** is readily derived from **287** by a simple and one-pot operation. Since propargylic alcohols are readily accessible from ketones or aldehydes, the straightforward transformation from **70** to **288f** provides a novel method for carbonyl olefination of ketones and aldehydes. For example, ethisterone, **301**, is tolerable to this transformation (route 2, Scheme 16) without any protection of the functional groups to give **302** (Equation (51)).[48]



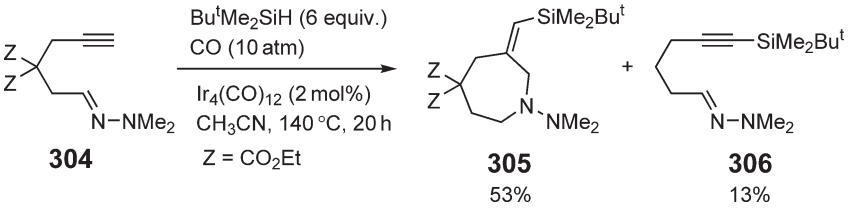
(51)

Silylformylation of 1-alkynes proceeds smoothly even in the presence of a base or a protic reagent. This feature makes it possible to design a cascade-type condensation using the resultant 3-silylalkenals as a component in one-pot operation during the silylformylation. Aza-1,3-dienes **303** are formed with sufficient selectivity by the reaction of 1-alkyne, a hydrosilane, primary amine, and CO under the silylformylation conditions (Equation (52)).[105]



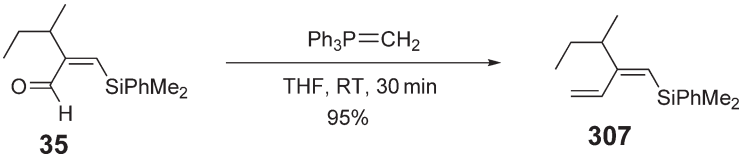
(52)

A novel hydrazepine formation is observed in the iridium-catalyzed reaction of alkynyl hydrazone **304** with Bu^tMe_2SiH in excess under slightly forcing conditions (Equation (53)).[106] The transformation leading to **305** can be explained by continuous interaction of Bu^tMe_2SiH with a silylformylation product of **304** under the reaction conditions.[106]

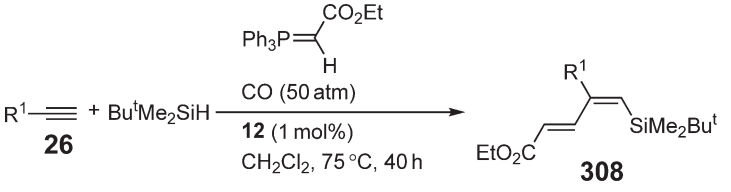


(53)

It is demonstrated that the formyl group in **35**, prepared by silylformylation of 3-methyl-1-pentyne **34**, reacts with methylenetriphenylphosphorane to give the corresponding 1,3-diene **307** (Equation (54)).[35] This two-step transformation can be performed in one pot by carrying out the silylformylation in the presence of a stabilized Wittig reagent (Equation (55)).[107] Trialkylsilanes are conveniently used here, as Me_2PhSiH does not work well under these conditions.



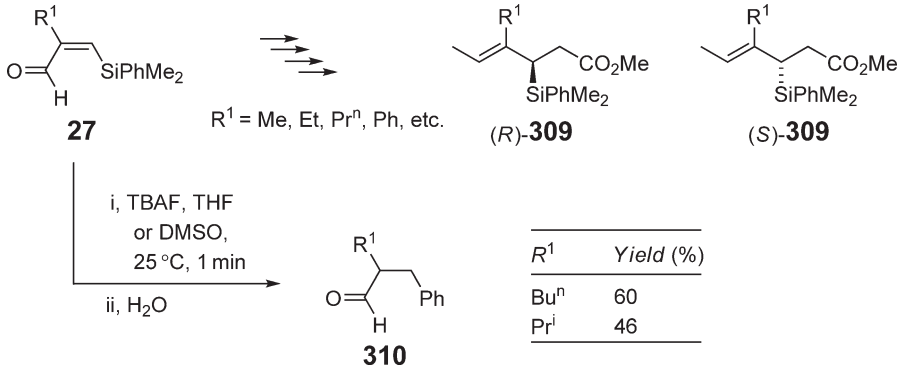
(54)



R^1	*Yield* (%)
Bu^n	91
Ph	84
$EtOCH_2$	89

(55)

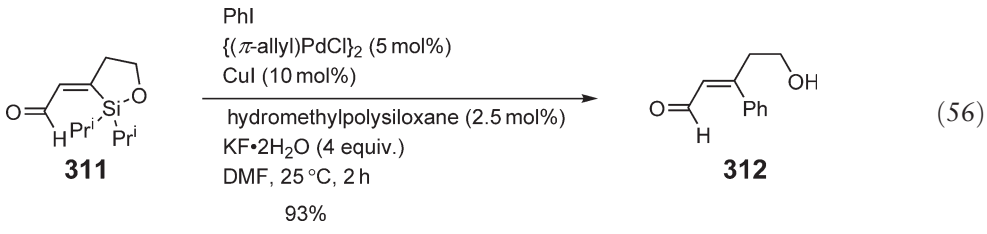
The silylformylation products can undergo various synthetic transformations, taking advantage of either the formyl or silyl group as a clue. For example, **27** is derivatized to optically pure allylsilane **309** through multiple operations including resolution.[108] Treatment of **27** with TBAF (tetrabutylammonium fluoride) in THF assists migration of the phenyl group to give 2-benzylalkanal, **310**, in moderate yields after aqueous workup (Scheme 17).[42,109]



R^1	*Yield* (%)
Bu^n	60
Pr^i	46

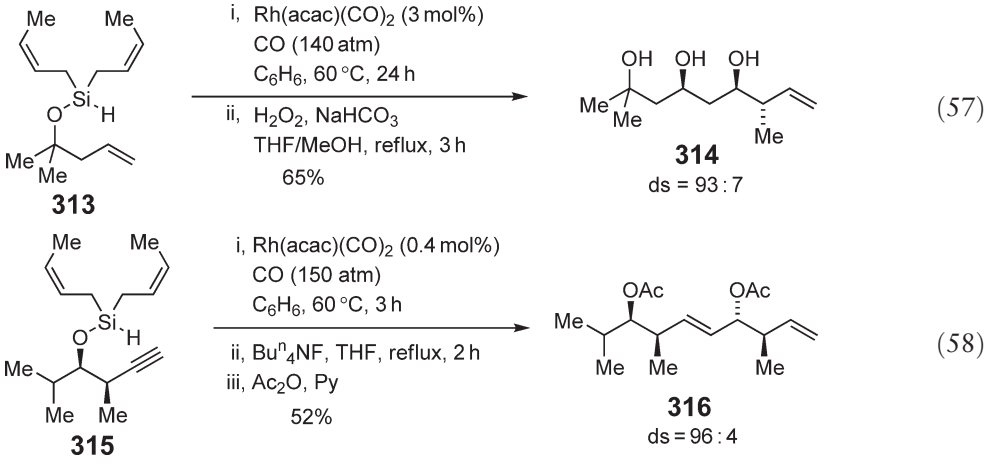
Scheme 17

The silyl group in **311**, prepared by intramolecular silylformylation, is intermolecularly substituted by a phenyl group by a palladium-catalyzed reaction with PhI to give coupled product **312** (Equation (56)).[110]



(56)

Allylic substituents on silyl (e.g., **313** and **315**) can work as a good nucleophile toward a formyl group newly formed by the silylformylation. This merit is clearly brought to realization by construction of versatile synthetic blocks (**314** and **316**) for synthesis of myticin A and dolabelides (Equations (57) and (58)).[111–116]



(57)

(58)

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11.15 Amidocarbonylation, Cyclohydrocarbonylation, and Related Reactions

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11.15.1 Introduction

Carbonylations of olefins, acetylenes, halides, alcohols, amines, nitro compounds, etc., promoted by transition metal complexes are very important in both industrial and laboratory organic syntheses.[1–4] The mechanisms of those reactions have been studied extensively, especially for those associated with commercial processes.[2,4] The research

on the utilization of carbon monoxide was substantially promoted by the "C1 Chemistry" projects with regard to the establishment of chemical technology, which enables us to produce gasoline, ethylene glycol, acetic acid, ethanol, methanol, etc., directly from carbon monoxide and hydrogen in the presence of appropriate catalysts.[1,2] The use of carbon monoxide as "one-carbon unit" has a high potential in modern organic synthesis as well.[3,4] Accordingly, a variety of new carbonylations have been explored, which may eventually become commercial processes.

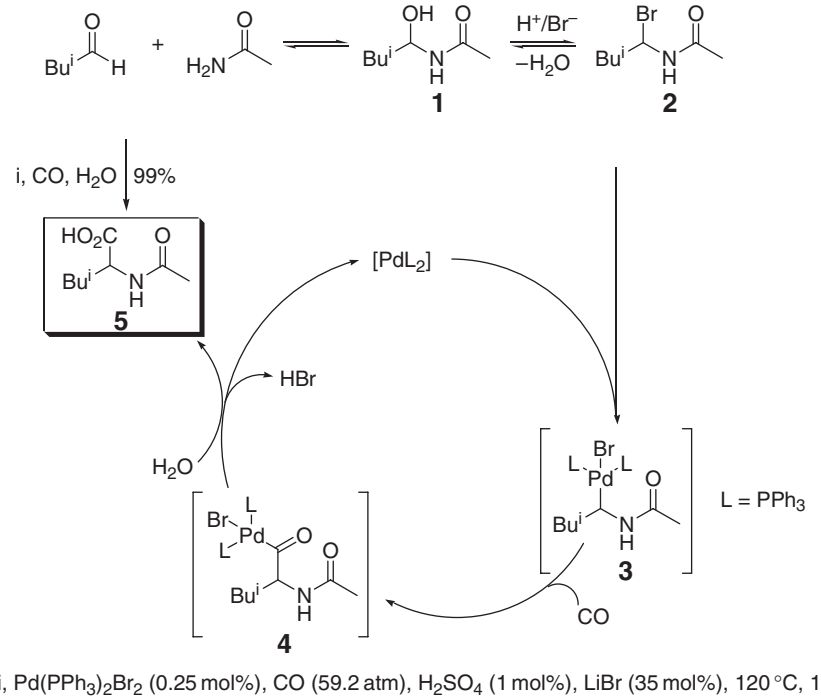
This chapter covers the recent advances in amidocarbonylations, cyclohydrocarbonylations, aminocarbonylations, cascade carbonylative cyclizations, carbonylative ring-expansion reactions, thiocarbonylations, and related reactions from 1993 to early 2005. In addition, technical development in carbonylation processes with the use of microwave irradiation as well as new reaction media such as supercritical carbon dioxide and ionic liquids are also discussed. These carbonylation reactions provide efficient and powerful methods for the syntheses of a variety of carbonyl compounds, amino acids, heterocycles, and carbocycles.

11.15.2 Amidocarbonylation Reactions

Since Wakamatsu serendipitously discovered amidocarbonylation while performing the cobalt-catalyzed hydroformylation of olefins in 1971,[5,6] this unique carbonylation reaction, affording α-amino acids directly from aldehydes, has been extensively studied.[7–11] More recently, palladium-catalyzed processes have been developed to expand the scope of this reaction.[12–19] The Pd-catalyzed amidocarbonylation has been applied to aldehydes,[12–15,17,19,20] aryl halides,[21] and imines.[18] As a related reaction, lactamization[21] of aryl halides catalyzed by a rhodium complex has also been developed.

11.15.2.1 Amidocarbonylation of Aldehydes

The original amidocarbonylation reaction catalyzed by $HCo(CO)_4$, generated *in situ* from $Co_2(CO)_8$, required very high pressures (>200 atm) of CO and H_2, which made the scope of this process rather limited.[8,10,11] However, the use of palladium catalysts for this process has substantially expanded the scope of the reaction. The Pd-catalyzed amidocarbonylation of aldehydes proceeds under CO pressure (60 atm) in the presence of water, a catalytic amount of acid, and a substoichiometric amount of lithium bromide, giving the corresponding *N*-acyl-α-amino acids (Scheme 1).[12,15,17,22,23]

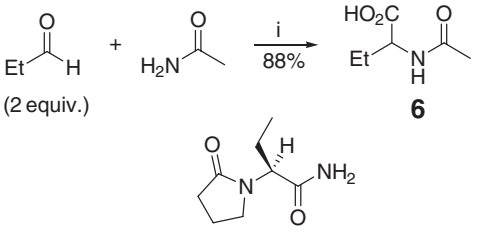


Scheme 1 Reproduced from Beller, M.; Eckert, M.; Vollmüller, F.; Bogdanovic, S.; Geissler, H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1494–1496, with permission from Wiley-VCH.

This process does not require molecular hydrogen to generate an active catalyst species in contrast to the original Co-catalyzed process. Moreover, the pressure of CO to run the reaction is much lower than that necessary for the Co-catalyzed process.

As Scheme 1 illustrates,[22] the Pd-catalyzed process includes the formation of hemiamidal **1** in the same manner as that in the Co-catalyzed process. However, the unique feature in this process is that hemiamidal **1** is converted to α-bromoamide **2**, which is the key intermediate in this process. Then, the oxidative addition of **2** to the Pd(0) species forms alkyl-Pd complex **3**. Subsequent insertion of CO to the carbon–Pd bond of **3** gives the acyl-Pd complex **4**, which leads to the formation of the *N*-acyl-α-amino acid **5** through reductive elimination and hydrolysis.

The Pd-catalyzed amidocarbonylation was used for the synthesis of α-arylglycines that are antimicrobial agents and enzyme inhibitors.[16] Thus, *N*-acyl-α-arylglycines and other *N*-acyl-α-amino acids were synthesized in highly efficient and economical manner under the standard conditions. In a similar manner, an advanced intermediate for the synthesis of antiepileptic Levetiracetam® **7**, *N*-acetyl-α-aminobutyric acid **6**, was synthesized in high yield from propanal and acetamide (Equation (1)).[12]



Levetiracetam® **7**

(1)

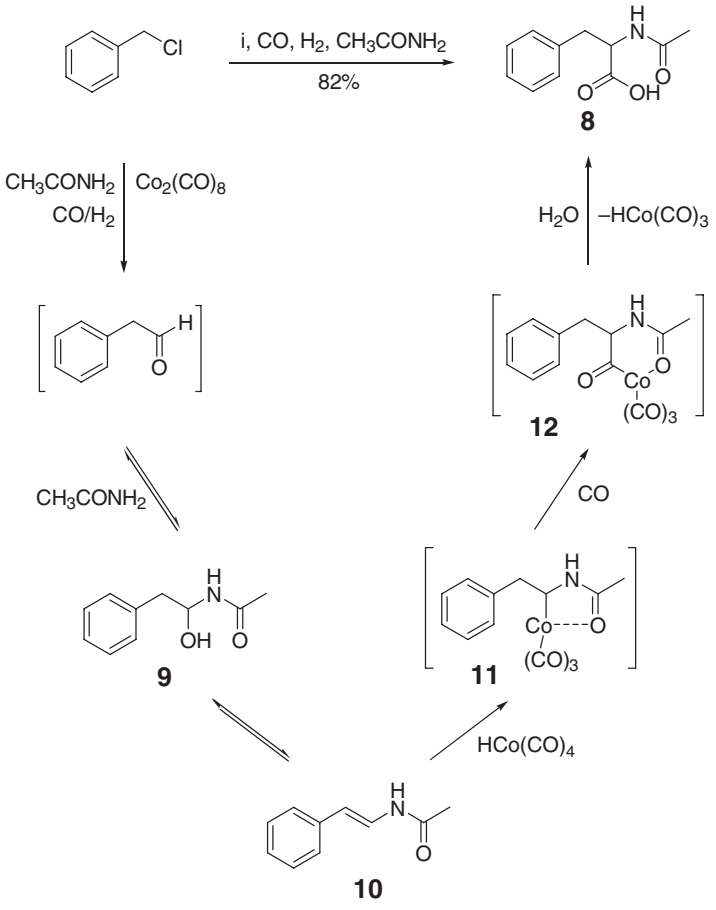
i, $Pd(PPh_3)_2Br_2$ (0.25 mol%), H_2SO_4 (1.5 mol%),
LiBr (35 mol%), CO (59.2 atm), 100 °C, 12 h

A detailed study on the reaction parameters has shown[12] that the reaction temperature and the pressure of CO as well as the amount of LiBr and sulfuric acid are critical for the reaction. High pressures (80–120 atm) of CO guarantee the efficient insertion of CO in the presence of triphenylphosphine. Thus, CO and triphenylphosphine (PPh_3) are competing ligands for Pd metal, and PPh_3 serves as the stabilizer for Pd(0) catalyst species although the excess use of it inhibits the reaction.[12]

The first platinum-catalyzed amidocarbonylation of aldehydes was reported in 2003.[14] Although the efficiency of palladium catalysts is unequaled with those of cobalt, rhodium, iridium, and ruthenium catalysts for amidocarbonylation,[24] the occurrence of fast racemization during the reaction shuts down a hope for asymmetric amidocarbonylation using chiral ligands. In contrast, a platinum catalyst, K_2PtCl_4/(*R*)-MOP, does not cause the racemization of optically active *N*-acetyl-α-amino acid under the reaction conditions in a controlled experiment.[14] For example, (*S*)-*N*-acetylphenylalanine was recovered in 99% yield and 96% ee in the presence of K_2PtCl_4/(*R*)-MOP catalyst, while total racemization (0% ee) of the amino acid (89% recovery yield) took place when $PdBr_2(PPh_3)_2$/LiBr/H_2SO_4 was used as a catalyst.[14] Accordingly, the first asymmetric amidocarbonylation for the synthesis of *N*-acyl-α-amino acids may be achieved in the near future using chiral platinum catalysts although, to date, no asymmetric induction has been observed in the Pt-catalyzed amidocarbonylation of aldehydes using a chiral ligand.[14]

Although the standard amidocarbonylation reaction involves an aldehyde and an amide, benzyl chloride can be used as the reactant. The amidocarbonylation of benzyl chloride was first reported by Wakamatsu *et al*. in 1976 using $Co_2(CO)_8$ as catalyst precursor.[25] This process was revisited by de Vries *et al*. in 1996 and *N*-acetylphenylalanine **8** was obtained in 82% yield under the optimized conditions (Scheme 2).[11] Since the Co-catalyzed amidocarbonylation is carried out in the presence of CO and H_2, formylation of benzyl chloride takes place first to form phenylacetaldehyde *in situ*. In this particular case, as Scheme 2 illustrates, *N*-acetylenamine **10** is formed as intermediate, followed by the chelation-controlled $HCo(CO)_4$ addition to give alkyl-Co intermediate **11**. Insertion of CO to the carbon–Co bond of **11**, forming acyl-Co complex **12**, followed by hydrolysis affords **8** and regenerates active Co catalyst species.

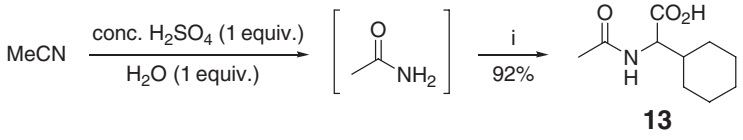
Primary amides can also be generated *in situ* from nitriles. Thus, one-pot synthesis of *N*-acyl-α-amino acids by Pd-catalyzed amidocarbonylation of alkyl- and arylnitriles has been developed.[23] For example, acetonitrile was hydrolyzed to acetamide first and subjected to the reaction with cyclohexanecarbaldehyde in the same reaction vessel to give *N*-acetyl-2-cyclohexylglycine **13** in 92% yield (Equation (2)).[23] This process is



i, $Co_2(CO)_8$ (12.5 mol%), CO/H_2 (271.4 atm, 1 : 1), CH_3CONH_2 (2 equiv.), $NaHCO_3$ (0.75 equiv.), Bu^iCOMe(1 M), 100 °C, 1.5 h

Scheme 2

particularly relevant to the Pd-catalyzed amidocarbonylation, which is carried out under strongly acidic conditions (pH = 2).

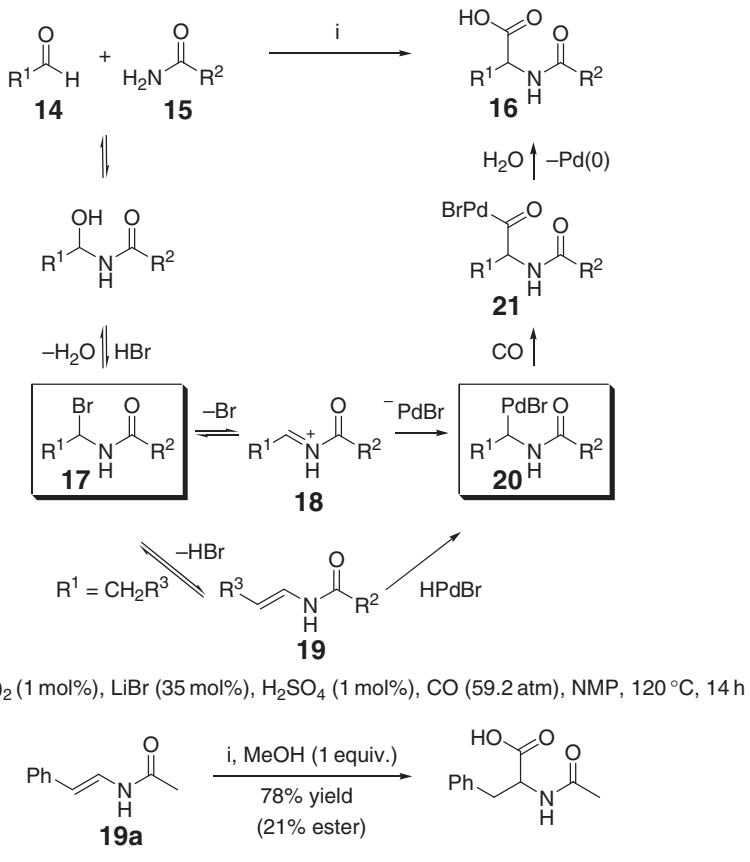


(2)

i, Cy-CHO (1 equiv.), $PdBr_2/2PPh_3$ (0.25 mol%), LiBr (35 mol%), CO (59.2 atm), 120 °C,12 h

11.15.2.2 Amidocarbonylation of Enamides

Although a proposed mechanism of the Pd-catalyzed amidocarbonylation of aldehydes is illustrated in Scheme 1 (*vide supra*), there are other possibilities and further studies have been performed.[18,22,26] For example, as Scheme 3 illustrates, the formation of α-bromoamide **17** (including **2** in Scheme 1) has been proposed as a key intermediate, which undergoes oxidative addition to Pd(0), forming alkyl-Pd complex **20** and then acyl-Pd complex **21**.[22,26] However, alternatively, α-bromoamide **17** can form iminium salt **18** or enamide **19** as the next intermediate. In order to investigate these possibilities, enamide **19a** was synthesized and subjected to the



Scheme 3

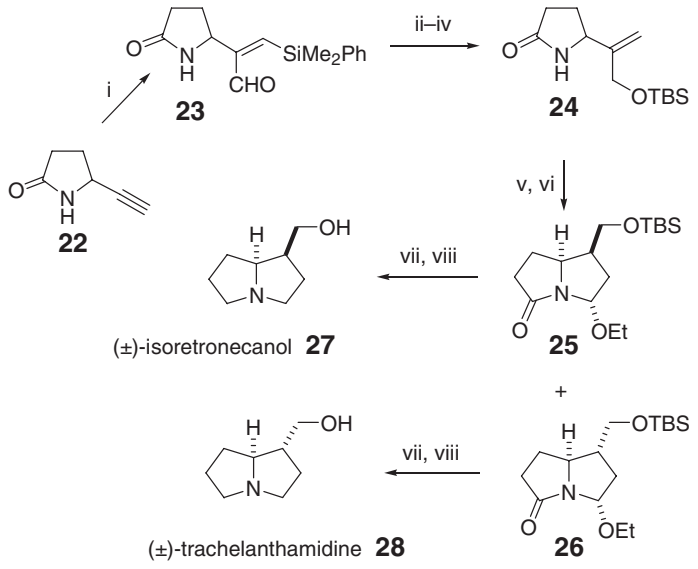
Pd-catalyzed amidocarbonylation conditions. Then, it was found that *N*-acylphenylalanine was indeed formed in 78% yield (including 21% as its methyl ester). Accordingly, enamide **19** is likely to be an intermediate of this reaction. When an aryl aldehyde is used, the corresponding enamide cannot be formed and an *N*-acylimine or an *N*-acyliminium ion **18** should be the intermediate instead. These intermediates can readily form the key intermediate alkyl-Pd complex **20** as well (Scheme 3).[18]

11.15.3 Cyclohydrocarbonylation Reactions

Cyclohydrocarbonylation is an intramolecular cascade process, consisting of the hydroformylation of a functionalized alkene to form an aldehyde intermediate, followed by the addition of a nucleophile in the same molecule to the aldehyde, leading to the formation of the corresponding cyclization product(s) (see 00158). As a variant, the cyclohydrocarbonylation also includes an intramolecular cascade process involving the hydrocarbonylation of a functional alkene, generating an acyl-metal intermediate, which undergoes intramolecular nucleophilic substitution to give the corresponding cyclic carbonyl compounds. Amide, amine, and hydroxyl groups as well as carbon nucleophiles are representative functional groups in the alkene substrates in these processes. The cyclohydrocarbonylation reaction has been incorporated to more sophisticated cascade processes, forming bicyclic and polycyclic compounds in a one-pot process. This section describes the applications of cyclohydrocarbonylation reactions in organic synthesis.

11.15.3.1 Cyclohydrocarbonylation of Alkenes

A combination of intermolecular silylformylation and cyclohydrocarbonylation provides an efficient route to pyrrolizidine alkaloids.[27,28] The regio- and diastereoselective Rh-catalyzed silylformylation of 5-ethynyl-2-pyrrolidinone **22** afforded (*Z*)-**23** in an excellent yield. Subsequent reduction and protodesilylation, followed by protection of the



i, $HSiMe_2Ph$, CO (20 atm), $Rh(acac)(CO)_2$, RT, 98%; ii, $NaBH_4$, 0 °C, 100%; iii, TsH, MeCN (2% H_2O), 75%; iv, TBS–Cl, imidazole, 98%; v, CO, H_2, $HRh(CO)(PPh_3)_3$, $HC(OEt)_3$, 72% (*syn* : *anti* = 2 : 1); vi, SiO_2 column; vii, Bu^n_4NF, RT, 96%; viii, $LiAlH_4$, 65–70%

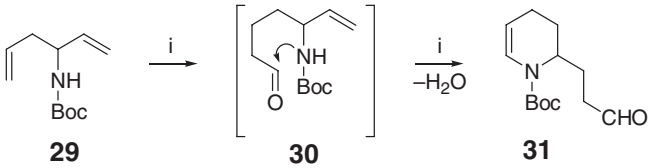
Scheme 4

resulting hydroxyl group as *tert*-butyldimethylsilyl (TBS) ether gave **24**. Cyclohydrocarbonylation of **24** catalyzed by rhodium carbonyl tris(triphenylphosphine) complex ($HRh(CO)(PPh_3)_3$) afforded a diastereoisomeric mixture (*syn* : *anti* = 2 : 1) of bicyclic products **25** and **26**, which were readily separable by flash chromatography. Removal of the silyl-protecting group and reduction of both the amidal and amido groups yielded (±)-isoretronecanol **27** and (±)-trachelanthamidine **28**, respectively (Scheme 4).[27,28]

The combination of rhodium dicarbonyl acetylacetonate complex ($Rh(acac)(CO)_2$) and a diphosphite ligand, (2,2′-bis[(biphenyl-2,2′-dioxy)phosphinoxy]-3,3′-di-*tert*-butyl-5,5′-dimethoxy-1,1′-biphenyl (BIPHEPHOS),[29] is an excellent catalyst system for the linear-selective hydroformylation of a wide range of alkenes.[28–32] This catalyst system has been successfully applied to the cyclohydrocarbonylation reactions of alkenamides and alkenylamines, which are employed as key steps for the syntheses of piperidine,[33–35] indolizidine, and pyrrolizidine alkaloids.[31]

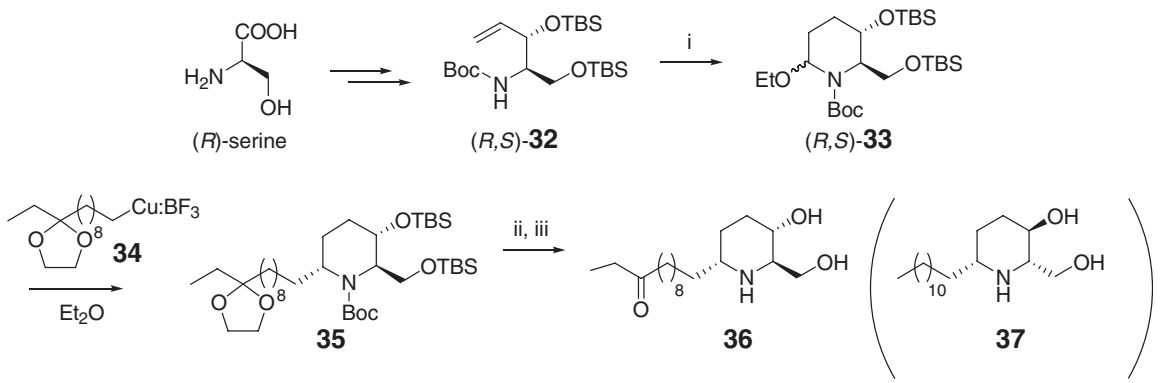
Cyclohydrocarbonylation of unsymmetrical amidodiene **29** catalyzed by Rh–BIPHEPHOS complex yielded dehydropiperidine aldehyde **31** as the sole product (Scheme 5).[34] The fact that no pyrroline was formed indicates that this reaction was extremely chemo- and regioselective so that the hydroformylation took place at the homoallylic olefin moiety exclusively, yielding the linear aldehyde intermediate **30**.

A short total synthesis of (+)-prosopinine **36** from (*R*)-serine was achieved via cyclohydrocarbonylation catalyzed by Rh–BIPHEPHOS complex for the construction of the key piperidine ring (2*R*,3*S*)-**33** (Scheme 6).[36] Compound **33** was converted to (+)-prosopinine **36** via the nucleophilic displacement of the ethoxy group with organocopper reagent **34** forming **35**, followed by deprotection. A similar procedure has been used for the total synthesis of (−)-deoxoprosophylline **37**.



i, $Rh(acac)(CO)_2$, BIPHEPHOS, CO, H_2 (1 : 1, 4 atm), THF, 65 °C, 24 h

Scheme 5



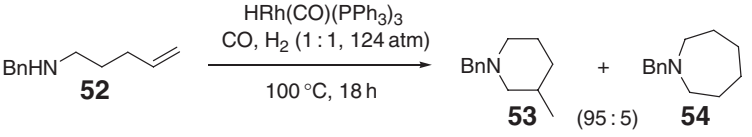
i, $Rh(acac)(CO)_2$ (1 mol%), BIPHEPHOS (2 mol%), CO, H_2 (1 : 1, 4 atm), 92%; ii, Bu^n_4NF, THF; iii, TFA, CH_2Cl_2

Scheme 6

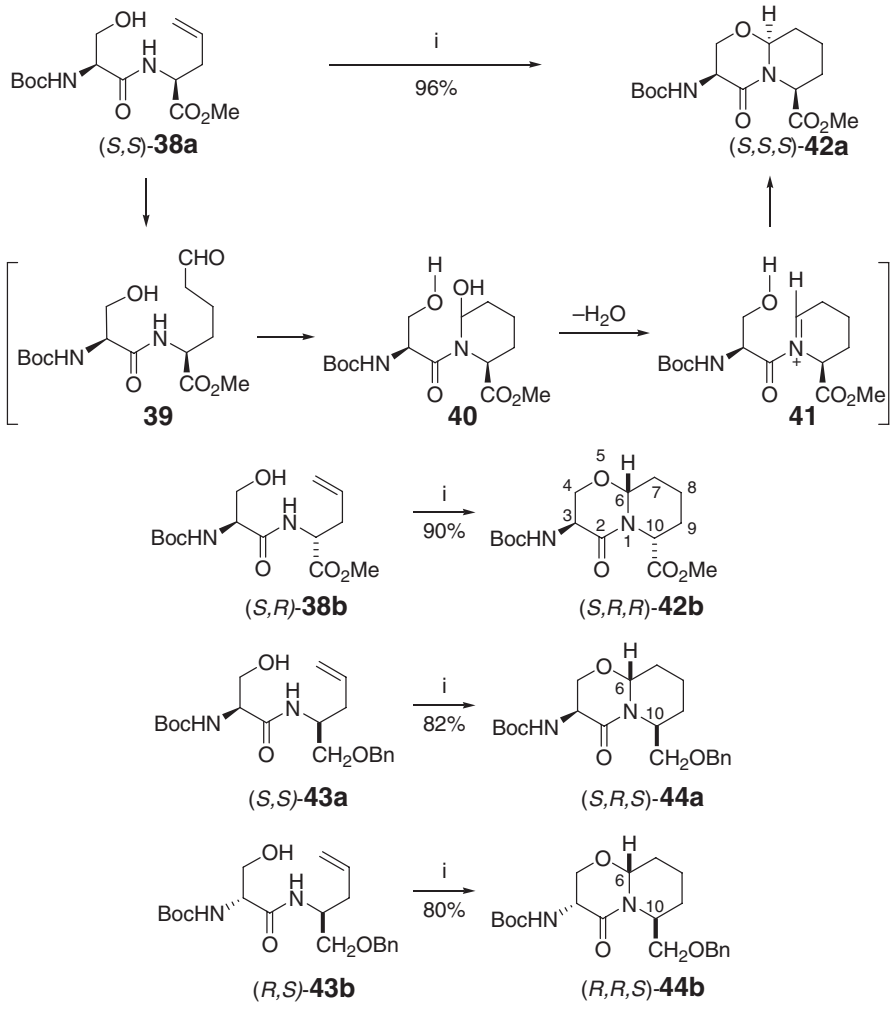
The Rh–BIPHEPHOS-catalyzed cyclohydrocarbonylation has also been successfully applied to the rapid synthesis of a variety of 1-azabicyclo[X.Y.0]alkane amino acids, which serve as conformationally restricted dipeptide surrogates for enzyme inhibitors and receptor antagonists, directly from dehydrodipeptide substrates (Scheme 7).[37,38] Reaction of (*S,S*)-*N*-*t*-Boc-serinylallylglycinate (*S,S*)-**38a** under the standard cyclohydrocarbonylation conditions gave 5-oxo-1-azabicyclo[4.4.0]decanecarboxylate (*S,S,S*)-**42a** in an excellent yield. This reaction included an extremely selective hydroformylation to form linear aldehyde **39**, followed by the formation of hemiamidal **40**. Subsequent generation of acyliminium ion **41** and intramolecular nucleophilic addition of the hydroxyl group of the serine moiety yields (*S,S,S*)-**42a** with excellent diastereoselectivity at C6 (Scheme 7). The reaction of the other diastereoisomer, (*S,R*)-**38b**, gave (*S,R,R*)-**42b** as the single product in 90% yield. Thus, the C10 position appears to be the stereogenic center in these reactions. The stereochemistry at the C6 position, however, is also dependent on the nature of the C10 substituent. For example, the reaction of (*S,S*)-**43a**, bearing a benzyloxymethyl (CH_2OBn) group in place of a methylester (CO_2Me) group at C10, afforded (*S,R,S*)-**44a**, in which the absolute configuration at C6 was *R*. In the same manner, the reaction of (*R,S*)-**43b** gave (*R,R,S*)-**44b**, that is, the absolute configuration at C6 was *R* as well. The results confirmed that the C10 position is the stereogenic center in this process, but also indicated that the stereoelectronic nature of the C10 substituent governs the diastereoface selection in the cyclization step.[39]

In a similar manner, the reaction of (*S,S*)-**45** bearing a β-aminoalanine residue in place of the serine residue proceeded efficiently in the presence of *p*-toluenesulfonic acid (PTSA) to give (*S,S,S*)-**46** as the single product in 95% yield (Scheme 8).[37,38] It should be noted that no 1-azabicyclo[4.3.0] product was formed in spite of the fact that either *t*-BOC-amino group in the β-aminoalanine residue could have reacted with the acyliminium intermediate. In the case of a dipeptide substrate bearing a cysteine residue, an *S*-trityl derivative (*S,S*)-**47** was used. When the thiol group is protected, spontaneous cyclization cannot take place. Thus, the reaction of (*S,S*)-**47** was carried out in MeOH to trap the resulting aldehyde moiety by converting it *in situ* to the corresponding acetal (*S,S*)-**48**. The subsequent deprotection and cyclization with a catalytic amount of TFA afforded (*S,S,S*)-**49** in 77% isolated yield over two steps in one pot. The reaction is readily applicable for the construction of 1-azabicyclo[5.4.0] system. Thus, the reaction of (*S,S*)-**50** under the standard conditions affords (*S,S,S*)-**51** in 87% yield.[39] The stereocontrol at the C6 position is governed by the C10 ester group in accordance with the general mechanism proposed for this cascade process (Scheme 8).

Cyclohydrocarbonylation of 5-benzylaminopentene **52** catalyzed by $HRh(CO)(PPh_3)_3$ led to the regioselective formation of piperidine **53** and a small amount of azepane **54** (Equation (3)).[40] The regioselectivity-determining step in this reaction is the hydroformylation of the olefin moiety of **52**, which strongly favors the formation of the corresponding branched aldehyde. This regioselectivity is opposite to that for the reaction of usual alkenes. This indicates the presence of a strong amine-directed chelation control,[32,41] which is very similar to the amide-directed chelation control mentioned in the preceding section. The branched aldehyde, thus formed, underwent intramolecular reductive amination to give **53**.



(3)



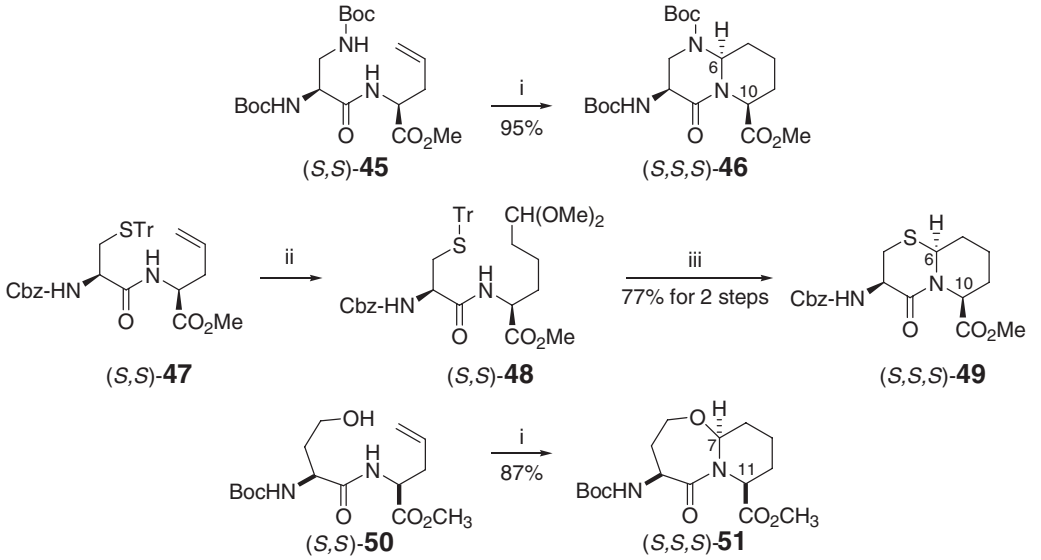
i, $Rh(acac)(CO)_2$, (2 mol%); BIPHEPHOS (4 mol%), CO, H_2 (1 : 1, 4 atm), PTSA (10 mol%), toluene, 65 °C, 20 h

Scheme 7

A quinazoline alkaloid skeleton has been synthesized by means of the Rh-catalyzed cyclohydrocarbonylation of diaminoalkenes.[42,43] The reaction of 2-(*N*-allylaminomethyl)aniline **55** gave quinazoline **59** in excellent yield through the highly linear-selective hydroformylation of **55** to aldehyde **56**, followed by the sequential formations of hemiaminal **57** and iminium ion **58** as intermediates and then the subsequent intramolecular amine addition (Scheme 9).[42] In the same manner, the reaction of *N*-allyl-2-aminomethylaniline **60** afforded **61** in 96% yield.[43]

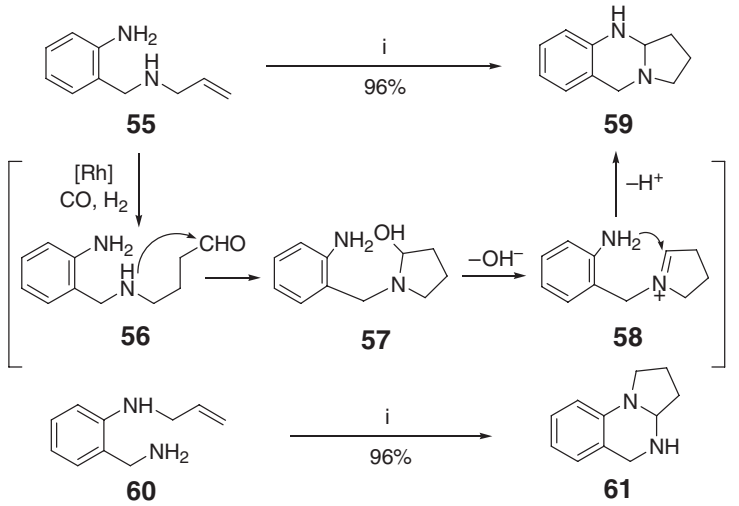
The same type of cascade cyclization has been applied to the one-step synthesis of fused azabicyclic compounds with medium to large-membered rings (Scheme 10).[44]

The Rh–XANTPHOS-catalyzed reactions (XANTPHOS = 4,5-bis(disphenylphosphino)-9,9-dimethylxanthene) of dimethyl 2-allylmalonate **64**, 2-allylacetoacetate **66**, 2-(3-butenoyl)propanoate **68**, and 2-(4-pentenoyl)propanoate **70** with "syngas" in the presence of chlorodicyclohexylborane (Cy_2BCl) and triethylamine gave the corresponding cycloalkanols **65**, **67**, **69**, and **71**, respectively, in fairly good to high yields (Scheme 10).[45] These cycloalkanols possess a quaternary carbon center next to the hydroxyl group in a molecule, and would serve as useful polyfunctionalized synthetic intermediates in organic synthesis. The observed diastereoselectivity in these reactions can be accommodated by

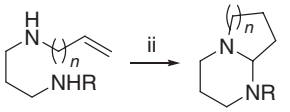


i, $Rh(acac)(CO)_2$ (2 mol%), BIPHEPHOS (4 mol%), CO, H_2 (1 : 1, 4 atm), PTSA (10 mol%), toluene, 65 °C, 20 h
ii, $Rh(acac)(CO)_2$ (2 mol%), BIPHEPHOS (4 mol%), CO, H_2 (1 : 1, 4 atm), MeOH, 65 °C, 20 h
iii, TFA (cat.), CH_2Cl_2

Scheme 8



i, $Rh_2(OAc)_4$, 4 PPh_3, CO, H_2 (1 : 1, 27 atm), EtOAc, 80 °C, 20 h

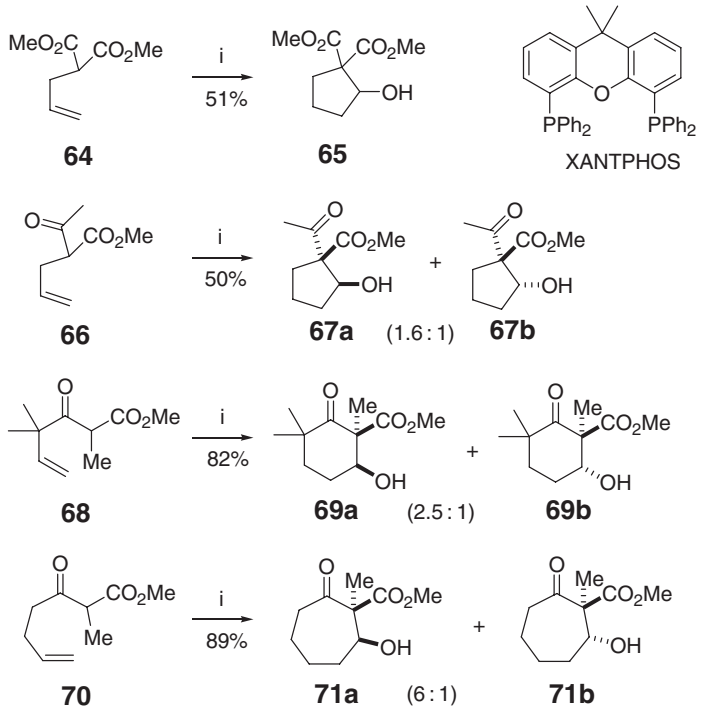


62 63

n	*R*	H_2 : CO	*Yield* (%)
9	H	1 : 1	80
6	Bn	1 : 5	95
4	Bn	1 : 5	95

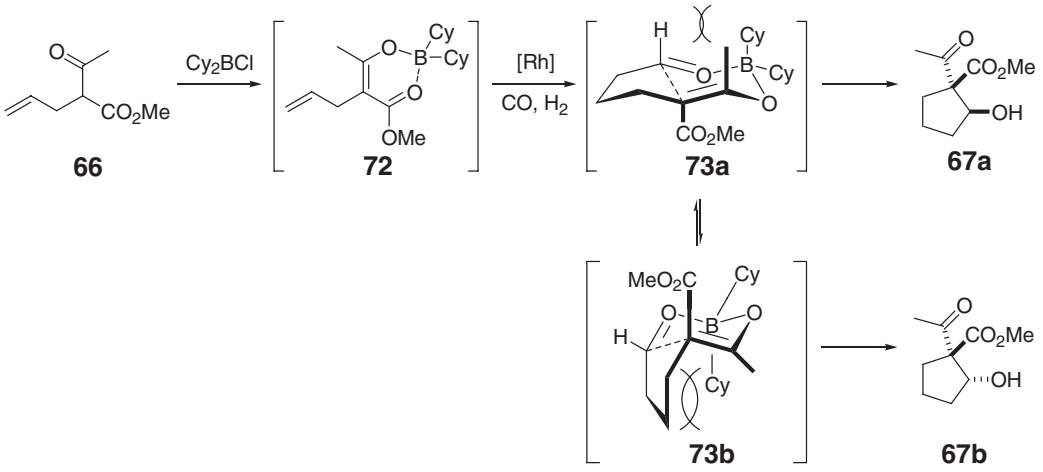
ii, $Rh_2(OAc)_4$ (0.5 mol%), BIPHEPHOS (2 mol%), CO, H_2 (27 atm), benzene, 80 °C, 20 h

Scheme 9



i, $Rh(acac)(CO)_2$ (0.9 mol%), XANTPHOS (1.8 mol%), $CO : H_2$ (1 : 1, 60 atm), Cy_2BCl (1.05 equiv.), Et_3N, CH_2Cl_2, 80 °C

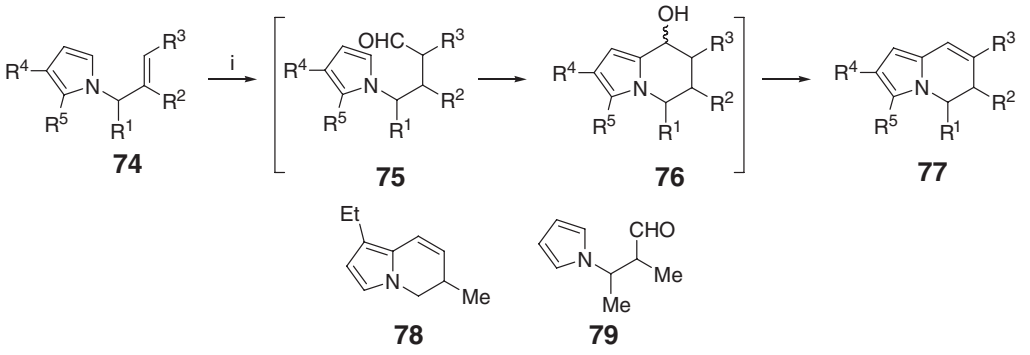
Scheme 10



Scheme 11 Reproduced from Keränen, M.D.; Eilbracht, P. *Org. Biomol. Chem.* **2004**, *2*, 1688–1690, with permission from The Royal Society of Chemistry.

taking into account the relative extent of 1,3-diaxial interactions in the bicyclic transition states involving a chair structure, for example, **73a** and **73b**, for the preferential formation of **67a** (Scheme 11).[45]

Cyclohydrocarbonylation of 1-allylpyrroles **74a–d** catalyzed by $Rh_4(CO)_{12}$ gave the corresponding 5,6-dihydroindolizines **77a–d** in good yield and excellent regioselectivity (Scheme 12).[46] This reaction proceeded through a cascade hydroformylation–cyclization–dehydration sequence (Scheme 12). Exclusive introduction of a formyl group



i, $Rh_4(CO)_{12}$ (0.25 mol%), CO : H_2 (1 : 1,100 atm), 100 °C, toluene (0.4 M)

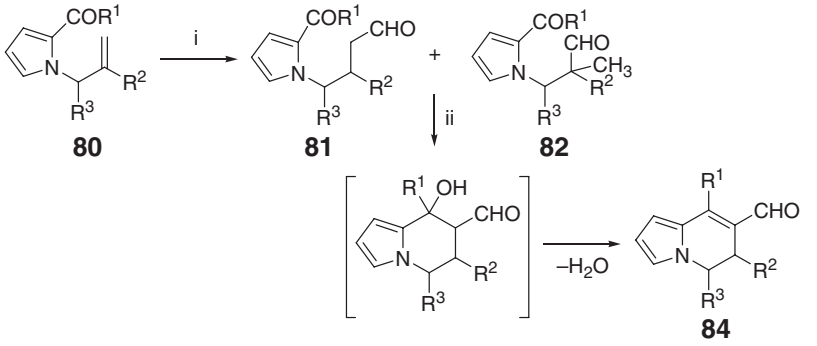
Substrate	R^1	R^2	R^3	R^4	R^5	*Product*	*Yield* (%)[a]
74a	H	Me	H	H	H	**77a**	75
74b	H	H	Ph	H	H	**77b**	80
74c	H	Me	H	H	Et	**77c**	72
74d	H	Me	H	Et	H	**77d**, **78** (90 : 10)	75
74e	Me	H	H	H	H	**77e**, **79** (59 : 41)	62

[a]Isolated yield.

Scheme 12

at the terminal position of a *gem*-disubstituted olefin or at the carbon α to a phenyl group is typical for Rh-catalyzed hydroformylation reactions. However, in the reaction of **74e**, which had unsubstituted terminal vinyl group (i.e., $R^2 = R^3 = H$), a mixture of linear and branched aldehydes was formed, which were converted to **77e** and **79**, respectively, in 59 : 41 ratio.[46]

In a similar manner, the cyclohydrocarbonylation of *N*-1-allyl-2-formylpyrrole **80a–c** afforded 7-formyl-5,6-dihydroindolizine **84a–c** in good yield through one-pot cascade hydroformylation–aldol condensation process (Scheme 13).[47]



i, $Rh_4(CO)_{12}$ (0.25 mol%), CO : H_2 (1 : 1, 100 atm), 100 °C, toluene (0.4 M), 0.5–2 h
ii, 100 °C under N_2 for 70 h (R^1 = H) or EtONa/EtOH, 5 min (R^1 = Me)

Substrate	R^1	R^2	R^3	*Product*	*Yield* (%)[a]
80a	H	H	Me	**84a**	60
80b	H	Me	H	**84b**	75
80c	Me	Me	H	**84c**	75

[a]Isolated yield.

Scheme 13

11.15.3.2 Cyclohydrocarbonylation of Dienes

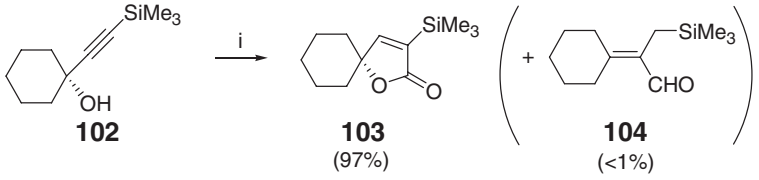
The cascade hydroformylation–allylboration–hydroformylation of (*E*)-aminoallylborate **85** catalyzed by $Rh(acac)(CO)_2$–BIPHEPHOS afforded oxazabicyclic lactol **87** via linear aldehyde **86** in 83% yield (Scheme 14).[48] The regioselective hydroformylation of γ-amidoallylboronate **88** gave linear aldehyde **89** which was in equilibrium with lactol **90**. Removal of the benzyloxycarbonyl (Cbz) group by hydrogenolysis initiated another cascade process, that is, amination–hydrogenation, affording indolizidine **91** in 60% overall yield.[48–50]

Reaction of 3,3-disubstituted-1,4-pentadiene **92** with a primary amine under cyclohydrocarbonylation conditions yielded cyclopenta[*b*]pyrrole **96** as the predominant product accompanied by a small amount of cyclopentanone **95** (Scheme 15).[51] This unique reaction is proposed to proceed through a cascade hydrocarbonylation–carbonylation process. The first hydrocarbonylation of **92** and the subsequent carbocyclization formed cyclopentanoylmethyl-Rh complex **93**. If **93** immediately reacts with molecular hydrogen, 2-methylcyclopentanone **95** is formed. However, if CO insertion takes place faster than the hydrogenolysis, cyclopentanoylacetyl-Rh complex **94** is generated, which undergoes the "Paal–Knorr" condensation with a primary amine to yield cyclopenta[*b*]pyrrole **96**.[52]

11.15.3.3 Cyclohydrocarbonylation of Alkynes

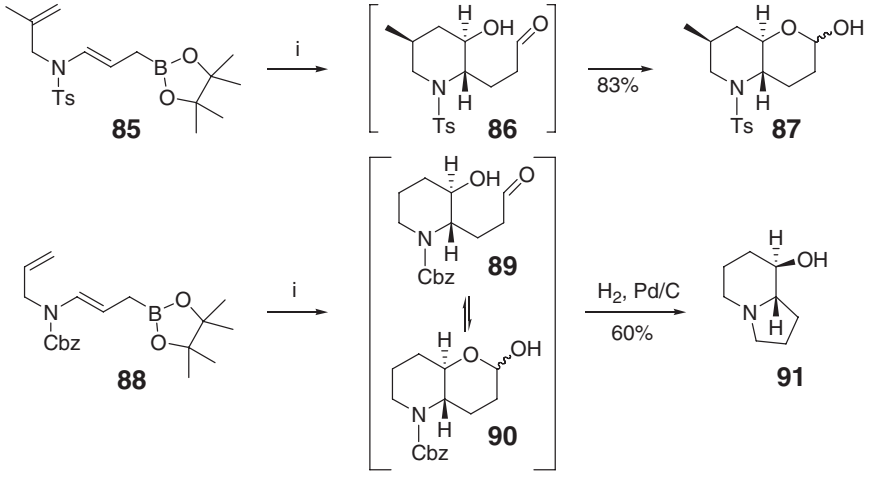
Hydroformylation of phenylacetylene **97** in the presence of *n*-hexylamine **98** catalyzed by (1,5-cyclooctadienyl)-rhodium tetraphenylboronate, $[Rh(1,5\text{-}COD)]^+[(\eta^6\text{-}C_6H_5BPh_3)]^-$, gave the corresponding 2-pyrrolidone **101** (Scheme 16). However, the reaction suffered from competing side-reactions such as hydrogenation of allylamine intermediate **100**.[53]

Cyclohydrocarbonylation of 3-TMS-propargyl alcohols cleanly gives the corresponding 2(5*H*)-furanones. For instance, the reaction of **102** catalyzed by $Rh_4(CO)_{12}$ yielded spirobicyclic furanone **103** almost exclusively in 97% yield (Equation (4)).[54]



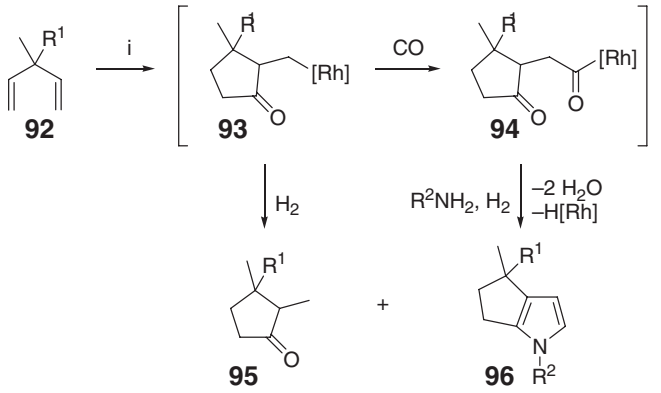
(4)

i, $Rh_4(CO)_{12}$, CO : H_2 (1 : 1, 20 atm), benzene, 90 °C, 3 h



i, $Rh(acac)(CO)_2$, BIPHEPHOS, CO : H_2 (1 : 1, 5 atm), 60 °C

Scheme 14

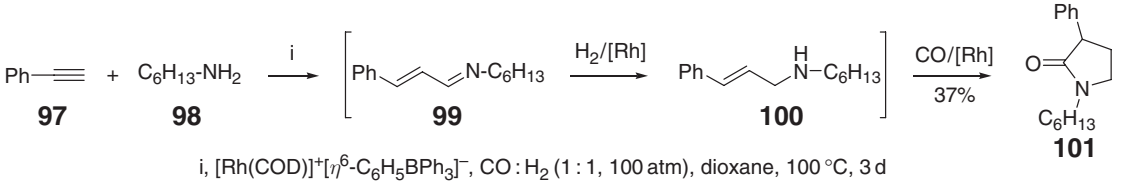


i, $[Rh(cod)Cl]_2$ (0.5 mol%), CO : H_2 (100 atm), dioxane (0.48–0.59 M), 120 °C, 40–70 h

R^1	R^2	CO : H_2 (atm)	*Time* (h)	*Yield* (%)[a]	
				96	**95**
Me	Bu^n	50 : 50	70	54 (17)	<2
Me	Pr^i	50 : 50	70	38 (21)	8
Me	Bn	50 : 50	70	54 (30)	7
Me	(*R*)-MeCHPh	50 : 50	40	47 (26)	
Me	4-MeO-C_6H_4	50 : 50	70	31 (17)	17
$CH(OH)CH_3$	Bn	85 : 15	40	(40)	
CH_2CH_2OH	Bn	85 : 15	70	(20)	

[a]GC yield. The value in parentheses is isolated yield.

Scheme 15

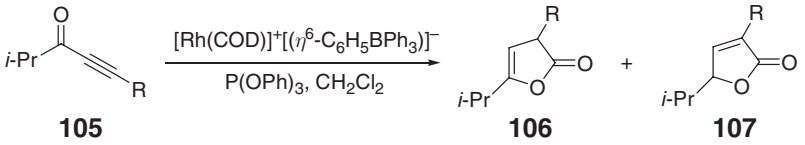


i, $[Rh(COD)]^+[\eta^6\text{-}C_6H_5BPh_3]^-$, CO : H_2 (1 : 1, 100 atm), dioxane, 100 °C, 3 d

Scheme 16

Furanones **106** or **107** have also been synthesized through cyclohydrocarbonylation of ynones **105** catalyzed by $[Rh(1,5\text{-COD})]^+[(\eta^6\text{-}C_6H_5BPh_3)]^-$–$P(OPh)_3$.[55] The reaction required a total pressure of 20–40 atm with an increased CO : H_2 ratio (up to 11 : 1) to prevent undesirable reductions. The nature of the substituent of the alkyne moiety has a significant influence on the regioselectivity of the reaction. For example, the reaction of **105a**, **105c**, and **105d** afforded the corresponding **106a**, **106c**, and **106d**, while the reaction of **105b** gave **107** in high yields (Equation (5)).[55]

A proposed mechanism for this transformation is illustrated in Scheme 17. Complexation of **105** to [Rh]–H species forms the intermediate **108**. The acetylene moiety of **108** undergoes a stereoselective intramolecular insertion into the [Rh]–H bond to give **109**. Two pathways are possible for the generation of key intermediate **114** from **109**, that is, (i) through CO insertion to **110**, followed by rearrangement to zwitterionic ketene **111** and the subsequent cyclization to **114** or (ii) through isomerization to **112** followed by CO insertion to **113** and subsequent cyclization to **114**. Then, intermediate **114** gives furanonyl-[Rh] complexes **115** and **116**, which afford **106** and **107**, respectively, through oxidative addition of molecular hydrogen to the [Rh] moiety followed by reductive elimination.[55]

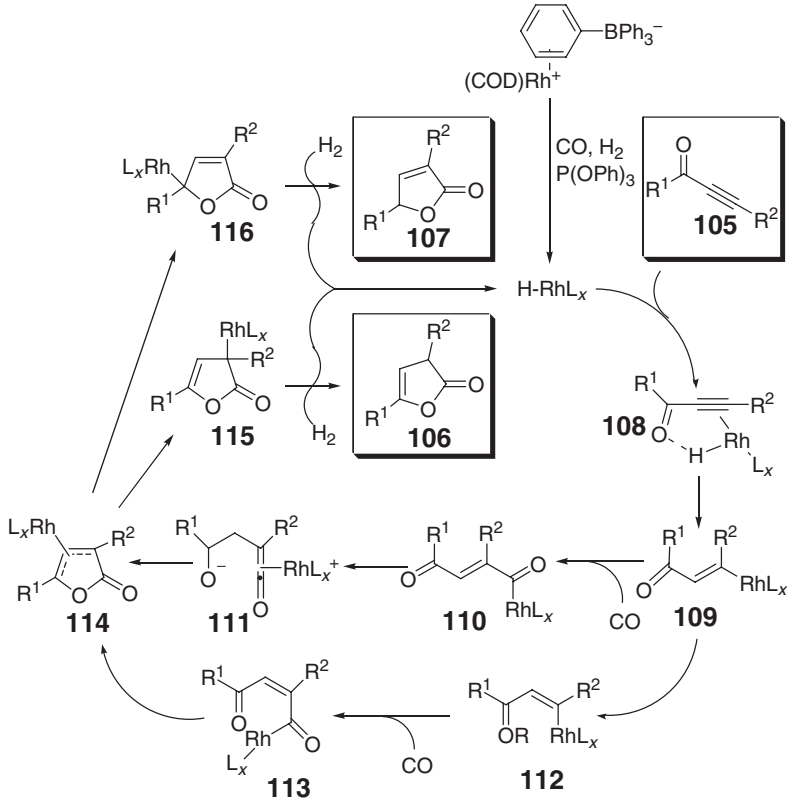


Substrate	R	CO (atm)	H_2 (atm)	Temp. (°C)	Time (h)	Yield (%)[a] 106	107
105a	Bu^n	38.5	3.5	90	36	88	
105b	Ph	38.5	3.5	120	24		88
105c	$C(CH_3)=CH_2$	17.5	3.5	70	24	71	
105d	CH_2OMe	17.5	3.5	70	24	92[b]	

[a]Isolated yield.
[b]R = Me in the product.

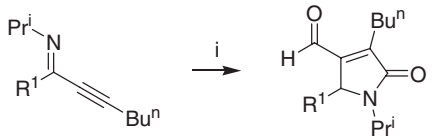
(5)

A similar cyclohydrocarbonylation of alkynylimines **117a–e** catalyzed by $[Rh(1,5\text{-COD})]^+[(\eta^6\text{-}C_6H_5BPh_3)]^-$–$P(OPh)_3$ afforded the corresponding 4-formylpyrrolinones **118a–e** through a cascade carbonylation–hydroformylation process (Equation (6)).[56] The proper composition of "syngas" ($CO:H_2 = 11:1$, 42 atm) was essential to avoid the formation of pyrrolinones as well as polymeric side-products. When **117f–i**, bearing a phenyl group conjugated to the imine moiety, was used as the substrate, a double bond migration from the $\Delta^{3,4}$ position to the $\Delta^{4,5}$ position took place to yield **118f–i** in which the double bond was conjugated to the phenyl group at C5 as shown in Equation (7). Relatively



Scheme 17

bulky substituents at the acetylene moiety of **117**, for example, isopropyl (**117g**) and cyclohexylmethyl (**117h**), were tolerated in this reaction, but the introduction of *tert*-butyl group to this position (**117i**) shut down the reaction.



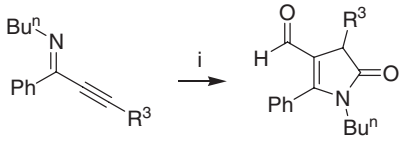
117a–e **118a–e**

i, $[Rh(COD)]^+[(\eta^6\text{-}C_6H_5BPh_3)]^-$ (2 mol%), $P(OPh)_3$ (8 mol%), $CO:H_2$ (11 : 1, 42 atm), CH_2Cl_2 (0.15 M), 90 °C

Substrate	R^1	*Time* (h)	*Yield* (%)[b]
117a	C_6H_5	24	80
117b	4-MeC_6H_4	24	81
117c	4-$MeOC_6H_4$	24	78
117d	4-ClC_6H_4	36	72
117e	β-Naphthyl	36	75

(6)[a]

[a]Adapted with permission from Van den Hoven, B. G.; Alper, H. *J. Am. Chem. Soc.* **2001**, *123*, 10214–10220. © 2001 American Chemical Society.
[b]Isolated yield.



117f–i **118f–i**

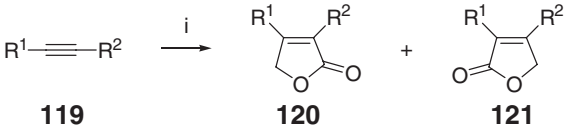
i, $[Rh(COD)]^+[(\eta^6\text{-}C_6H_5BPh_3)]^-$ (2 mol%), $P(OPh)_3$ (8 mol%), $CO:H_2$ (11 : 1, 42 atm), CH_2Cl_2 (0.15 M), 90 °C

Substrate	R^3	*Time* (h)	*Yield* (%)[b]
117f	Bu^n	24	80
117g	Pr^i	24	75
117h	CH_2–Cy	24	79
117i	Bu^t	24	No reaction

(7)[a]

[a]Adapted with permission from Van den Hoven, B. G.; Alper, H. *J. Am. Chem. Soc.* **2001**, *123*, 10214–10220. © 2001 American Chemical Society.
[b]Isolated yield.

The application of immobilized heterobimetallic cobalt–rhodium in nanoparticles has also been reported.[57] In the presence of water, CO, and amine, internal acetylenes **119** were converted to 3,4-disubstituted furan-2(5H)-ones **120** and **121** in high yields, in which an amine was necessary for the formation of furanone and a higher CO pressure was required for good yield (Equation (8)).[57] It is important to notice that the catalyst has been easily recovered without loss of activity or formation of hydrogenated side-products. The reaction proceeded in good yield for the symmetric substrates (entries 1 and 2) while it always gave two regioisomers for asymmetric alkyne substrates (entries 3–8). The isomer ratio was dependent on the steric and electronic nature of the substituents.



119 **120** **121**

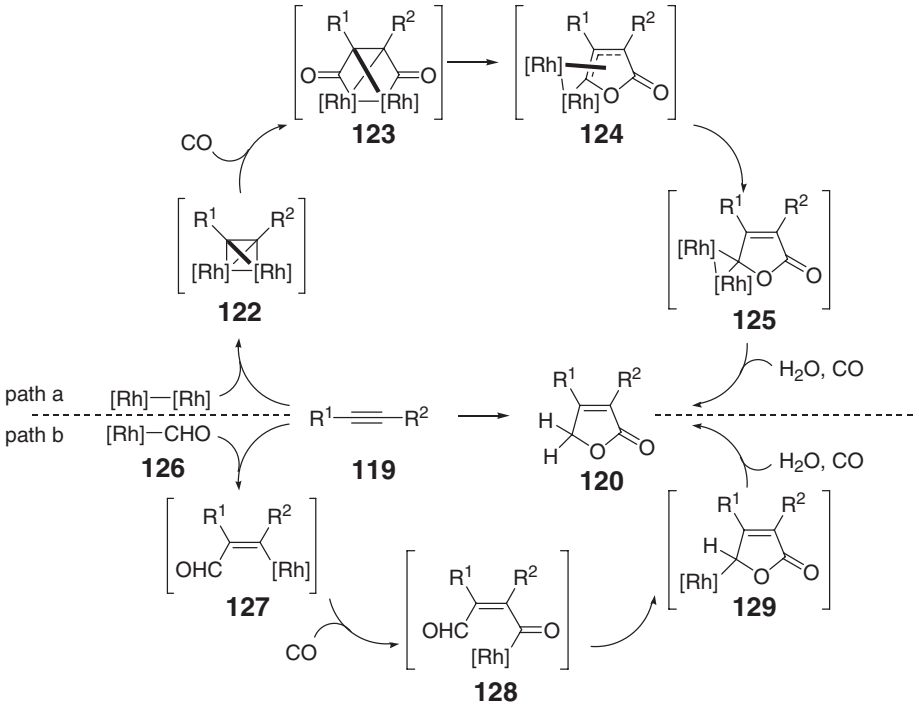
i, Co_2Rh_2 (7.6 mol%), CO(30 atm), THF (0.49 M, 10 ml), H_2O (1 ml), Et_3N (2 ml), 100 °C, 18 h

		Substituents		*Yield* (%)[b]	
Entry	*Substrate*	R^1	R^2	**120**	**121**
1	**119a**	Ph	Ph	87	
2	**119b**	Et	Et	89	
3	**119c**	H	Ph	40	53
4	**119d**	Me	Ph	61	31
5	**119e**	Et	Ph	72	18
6	**119f**	CO_2Et	Ph	23	14
7	**119g**	CO_2Et	Me	30	54
8	**119h**	CO_2Et	H	17	68

(8)[a]

[a]Reproduced from Park, K. H.; Kim, S.Y.; Chung, Y. K. *Org. Biomol. Chem.* **2005**, *3*, 395–398. Reproduced by permission of The Royal Society of Chemistry.
[b]Isolated yield.

It was found that only deuterated furanone was obtained if water had been replaced with deuterated water (D_2O).[58] This observation corroborated the fact that water was the hydrogen source in this reaction. Two possible mechanisms were proposed. The first one is described as follows (Scheme 18, path a): acetylene **119** can react with bimetallic species to afford μ,η^2-acetylene complex **122**, which reacts further with CO to give μ,η^1-furanone



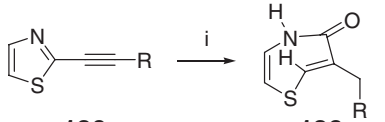
123 **124** **125** **122** **126** **119** **120** **127** **128** **129**

Scheme 18

complex **125** via intermediate **124**. The complex **125** is reduced by H_2O and CO under water–gas shift conditions to afford the furanone **120**. Another possible mechanism (Scheme 18, path b) involves a formyl-metal complex **126** as the intermediate. Formylrhodation of the alkyne to **127**, followed by CO insertion, affords the acyl complex **128**, which cyclizes to σ-furanoyl complex **129**. Further reduction of the complex by water yields the furanone **120**.

11.15.3.4 Ring Expansion via Cyclohydrocarbonylation

2-Alkynylthiazoles **130** undergo unique cyclohydrocarbonylation, involving ring expansion, catalyzed by [Rh(1,5-COD)]$^+$[(η^6-$C_6H_5BPh_3$)]$^-$ to give 2-(*Z*)-6-(*E*)-4*H*-[1,4]thiazepin-5-ones **136** (Equation (9)).[59]



130 **136**

i, [Rh(COD)]$^+$[(η^6-$C_6H_5BPh_3$)]$^-$, $P(OPh)_3$, $CO:H_2$ (1 : 1, 21 atm), CH_2Cl_2, 110 °C

R	*Time* (h)	*Yield* (%)[a]
Bu^n	24	86
Ph	18	90
$C(CH_3)=CH_2$	24	72
CH_2OMe	24	74

[a]Isolated yield.

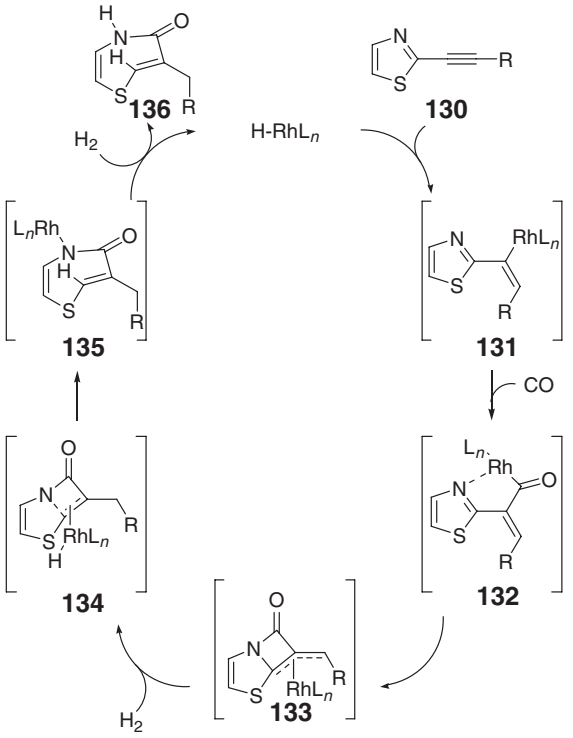
(9)

A possible mechanism for this unique transformation is shown in Scheme 19.[59] The insertion of the alkyne moiety of **130** into the [Rh]–H bond of the active catalyst species [Rh]–H gives **131** regioselectively. The regioselectivity is attributed to heteroatom–[Rh] interactions. The CO insertion to intermediate **131** leads to the formation of acyl-[Rh] intermediate **132** in which the nitrogen atom coordinates to [Rh]. A combination of reductive elimination and [Rh] shift gives π-allyl-[Rh] complex with a penem skeleton **133**. Oxidative addition of molecular hydrogen, followed by H shift affords π-olefin-[Rh] intermediate **134**. Ring opening of **134** via formal σ-bond metathesis between [Rh]–H and N–C bond yields N–[Rh]–thiazepinone complex **135**. Subsequent oxidative addition of molecular hydrogen to **135**, followed by reductive elimination, gives thiazepinone **136** and regenerates the active catalyst species [Rh]–H.

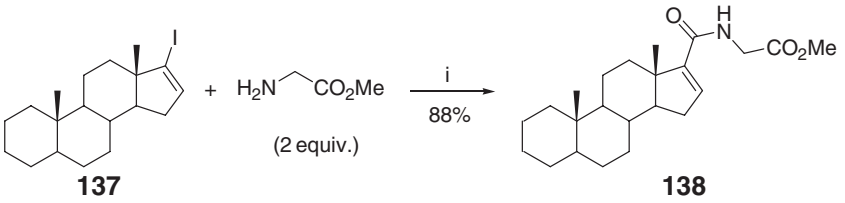
11.15.4 Aminocarbonylation Reactions

11.15.4.1 Aminocarbonylation of Alkenyl and (Hetero)Aryl Halides

Aminocarbonylation provides an efficient method for the synthesis of carboxamides from readily available alkenyl halides. This reaction finds many applications in organic synthesis, especially for the introduction of amides with a variety of *N*-substituents. For example, steroidal alkenyl iodide **137** was transformed to the corresponding amide derivative **138** in 88% yield through aminocarbonylation (Equation (10)).[60–62] In this reaction, the palladium catalyst was recovered by using an ionic liquid, 1-butyl-3-methylimidazolium salt **139**, as reaction media, and reused five times with only a minor loss of activity.[62]



Scheme 19



(10)

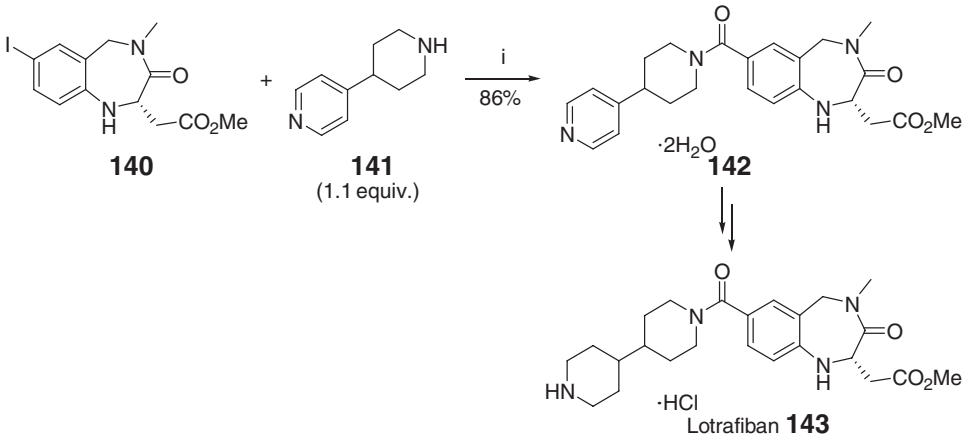
i, Pd(OAc)$_2$ (5 mol%), 4-(diphenylphosphino)benzoic acid (10 mol%), Et$_3$N (5 equiv.),

CO (1 atm), 100 °C, 8 h, Bu^n-N⁺(Me)=CH-N [BF$_4$]$^-$ (20 equiv.)

139

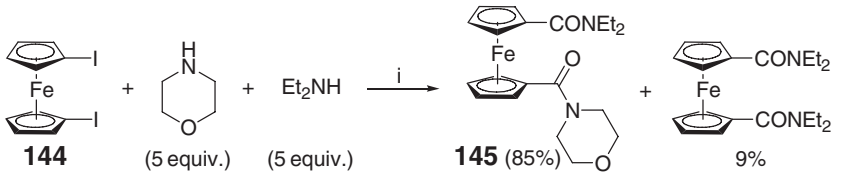
The aminocarbonylation of aryl or heteroaryl halides also provides direct access to the corresponding (hetero)arenecarboxamides. Since the palladium catalyst systems used for the aminocarbonylation process tolerate a wide range of functional groups, this reaction serves as a versatile method in organic synthesis. Thus, aminocarbonylation of heteroaryl halides,[63–66] or triflates,[67] with secondary amines has been applied for the synthesis of rather complex molecules of medicinal interest.[68–70] For example, the synthesis of Lotrafiban **143**, a potent nonpeptidic glycoprotein IIb/IIIa antagonist, was performed in large scale (several 100 kg scale) (Scheme 20),[68–70] wherein the key step of this synthesis was the aminocarbonylation of the aryl iodide **140** with 4,4′-pyridylpiperidine **141** to produce amide **142**. This process was operated in a standard pilot plant to give **143** in 86% yield.[68]

Aminocarbonylation has also been applied to the synthesis of unsymmetrical ferrocene-1,1′-bis-carboxamides.[71,72] Ferrocene-based chiral ligands are very useful in asymmetric catalysis, and enantiomerically pure ferrocenyl ligands can be obtained by optical resolution of unsymmetrically substituted ferrocenes. However, the synthesis of such unsymmetrical ferrocenes is not an easy task.[73] The use of aminocarbonylation gave a solution to this challenge. For example, the Pd-catalyzed reaction of symmetrical ferrocenyl diiodide **144** with two different amines, morpholine and diethylamine (5 equiv. each) under 39.5 atm of CO, gave the desired unsymmetrically disubstituted ferrocenebiscarboxamide **145** in 85% yield (Equation (11)).[71]



i, $PdCl_2(PPh_3)_2$ (2 mol%), anisole (26.5 equiv.), dicyclohexylamine (2.5 equiv.), CO (1 atm), 100 °C, 2.5 h

Scheme 20



(11)

i, $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), Et_3N (7 equiv.), toluene, CO (39.5 atm); 100 °C; 8 h

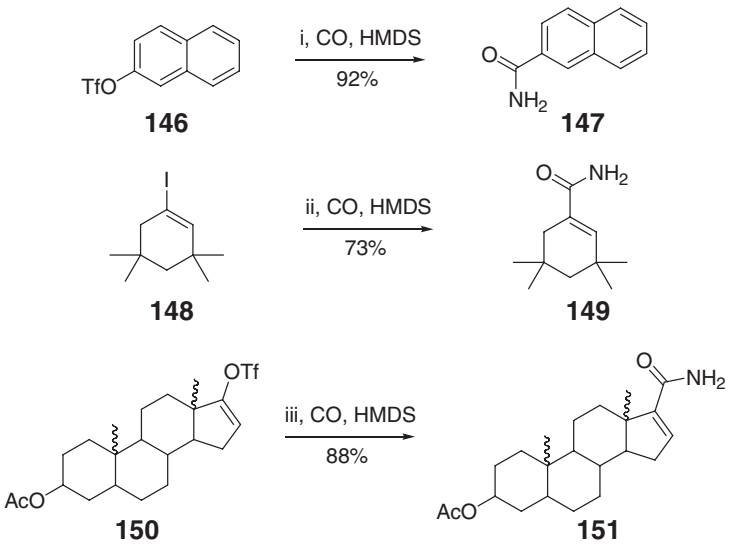
The synthesis of aromatic primary amides through aminocarbonylation of aryl halides with ammonia is not well documented due to the technical difficulty in using gaseous ammonia. To resolve this problem, methods using ammonia equivalents such as hexamethyldisilazane (HMDS),[74] formamides,[75,76] and a titanium–nitrogen complex[77] have been developed.

HMDS is known as an ammonia substitute in the preparation of primary amides via ammonolysis since 1985.[78] With the use of excess HMDS, the Pd-catalyzed aminocarbonylation of various aryl and vinyl iodides and triflates (e.g., **146**, **148**, and **150**) has been successfully performed to give the corresponding vinyl and aryl amides (e.g., **147**, **149**, and **151**, respectively) in good to excellent yields (Scheme 21).[74]

Another solution is the use of formamide as the ammonia substitute.[75,79] Thus, the Pd-catalyzed aminocarbonylation of (hetero)aryl halides with formamide as ammonia substitute as well as solvent under CO afforded the corresponding primary amides in moderate to excellent yields (Scheme 22).[75]

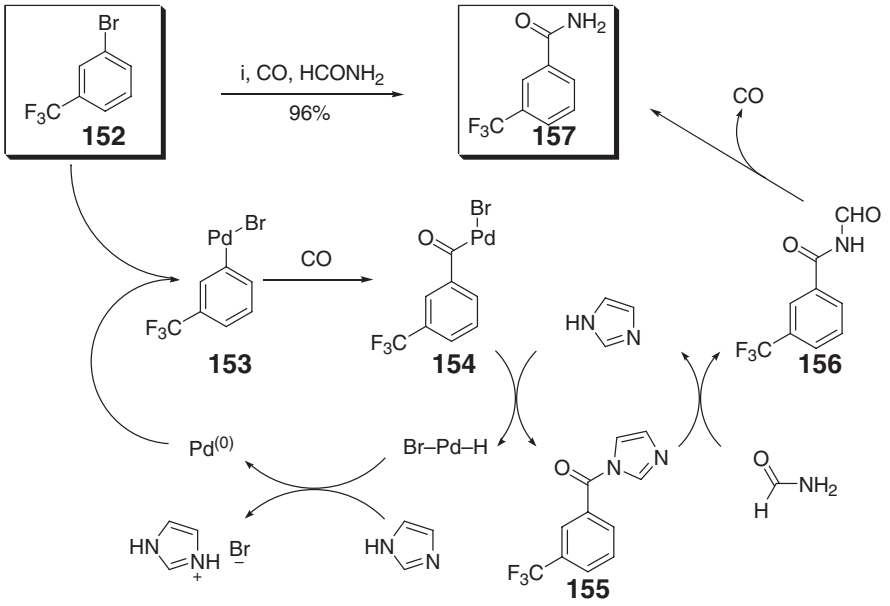
Since formamide is a weak nucleophile, the use of imidazole or 4-dimethylaminopyridine (DMAP) is necessary for acyl transfer to formamide via an activated amide (imidazolide) or acylpyridinium ion. As Scheme 22 illustrates,[79] the reaction starts with the oxidative addition of aryl bromide **152** to Pd(0) species, followed by CO insertion to form acyl-Pd complex **154**. Imidazole receives the aroyl group to form imidazolide **155** and liberates HPdBr species. Then, imidazolide **155** reacts with formamide to form imide **156**. Finally, decarbonylation of imide **156** gives amide **157**. In fact, the formations of imidazolide intermediate **155** and imide **156** as well as the subsequent slow transformation of imide **156** to amide **157** by releasing CO were observed. This mechanism can accommodate the CO pressure variations observed during the first few hours of aminocarbonylation. When the reaction temperature (120 °C) was reached, a fast drop of pressure occurred. This corresponds to the formation of the intermediary imide **156**.[79] Then, the increase of pressure after 3–4 h of reaction was observed. This phenomenon corresponds to the release of CO from imide **156** to form amide **157**.[79]

In connection with the aminocarbonylation processes described above, an apparent CO-free aminocarbonylation reaction of aryl and alkenyl iodides was reported using *N*,*N*-dimethylformamide (DMF) as the ammonia substitute in the presence of phosphorus oxychloride ($POCl_3$) (Scheme 23).[76] This reaction is so far restricted to DMF at present.



i, $PdCl_2$ (3 mol%), PPh_3 (6 mol%), HMDS (4 equiv.), CO (1 atm), DMF, 80 °C, 2.5 h; ii, $PdCl_2$ (5 mol%), PPh_3 (6 mol%), HMDS (4 equiv.), CO (1 atm), DMPU, 100 °C, 4 h; iii, $PdCl_2$ (5 mol%), PPh_3 (6 mol%), HMDS (4 equiv.), CO (1 atm), DMPU, 80 °C, 5 h

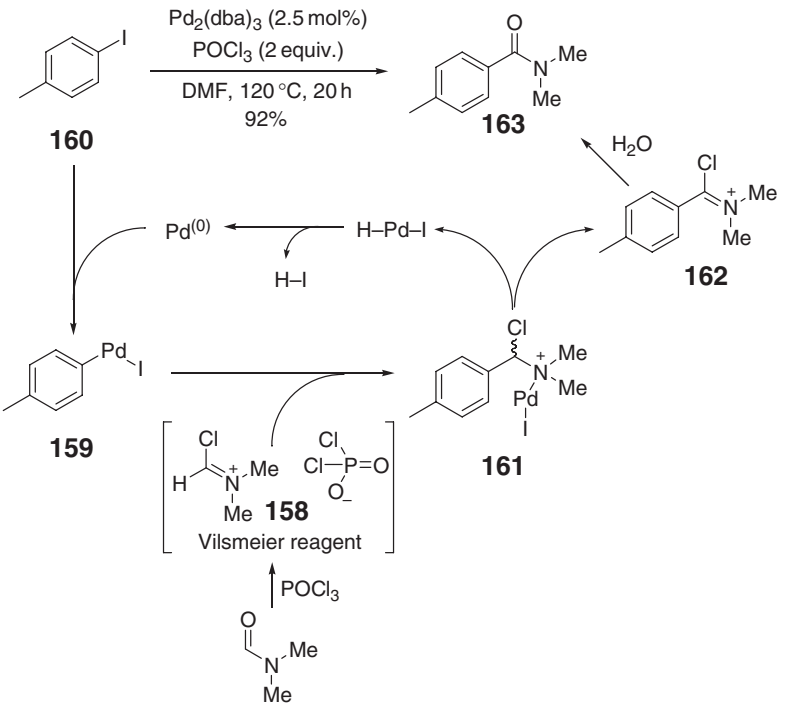
Scheme 21



i, $Pd(OAc)_2$ (1 mol%), PPh_3 (4 mol%), imidazole (1.05 equiv.), CO (4.9 atm), formamide, 120 °C, 18 h

Scheme 22

As Scheme 23 illustrates,[76] DMF reacts with $POCl_3$ to form Vilsmeier reagent **158**.[80] Aryl-Pd–I species **159**, generated by the oxidative addition of iodotoluene **160** to Pd(0) species, reacts with the reagent **158** to yield chloroiminium ion **162** via an adduct **161** through a hetero-Heck-type reaction mechanism, and liberates H–Pd–I species. Finally, the hydrolysis of chloroiminium ion **162** gives amide **163**.



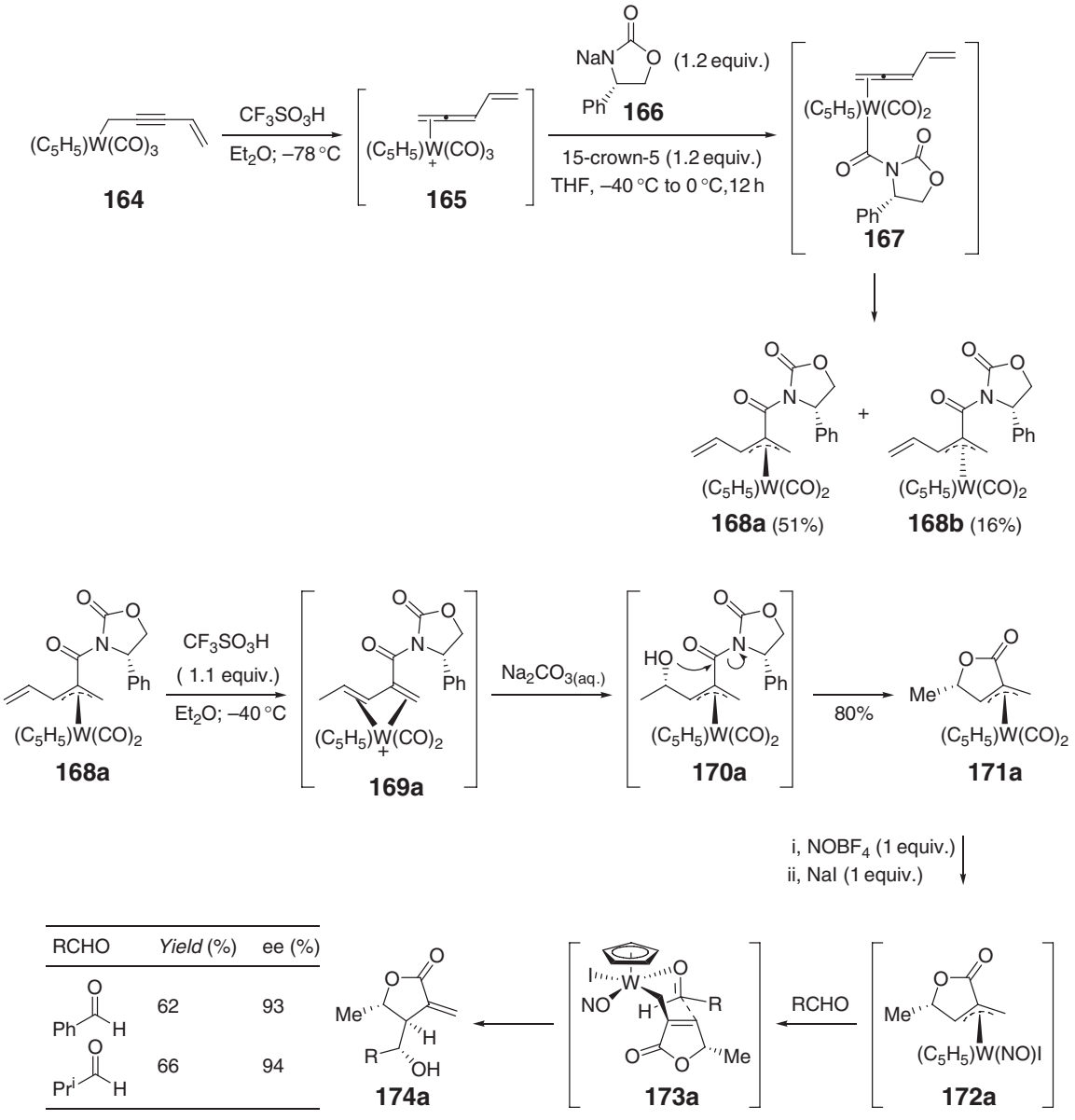
Scheme 23

11.15.4.2 Aminocarbonylation of Alkynes

The aminocarbonylation of alkynes has been less explored as compared to that of alkenyl and (hetero)aryl halides. Nevertheless, several noteworthy applications of this reaction have been reported, including the syntheses of 2-ynamides,[81] chiral 2-carbamoyl-π-allylic tungsten complexes,[82] angular triquinanes,[83] 2-(carbamoylmethylene)tetrahydrofurans,[84] allenyl amides,[85] and others.[86,87]

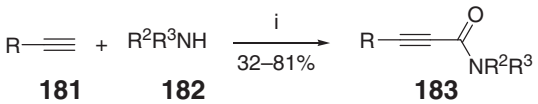
The diastereoselective aminocarbonylation of vinylallene–tungsten complex **165** with the sodium salt of enantiomerically pure oxazolidinone **166** was carried out to give readily separable diastereomeric 2-amido-π-allylic tungsten complexes **168a** (51%) and **168b** (16%) (Scheme 24).[82] Vinylallene–W complex **165** was formed *in situ* by the protonation of vinylpropargyl–W complex **164** with trifluoromethanesulfonic acid (CF_3SO_3H). The treatment of enantiomerically pure **168a** with CF_3SO_3H, followed by aqueous Na_2CO_3, gave γ-lactone-π-allyl-W complex **171a** in 80% yield via intermediates **169a** and **170a**. Then, π-allyl-W complex **171a** was reacted with nitrosyl tetrafluoroborate ($NOBF_4$) and NaI successively to form π-allyl-W(NO) complex **172a** *in situ*. Finally, the highly diastereoselective allylic alkylation of **172a** with an aldehyde afforded the corresponding α-methylene-γ-butyrolactone **174a** with 93–94% ee in good yield.[82] Thus, three chiral centers were created with excellent enantioselectivity through this asymmetric synthesis. In the same manner, the other diastereoisomer **168b** was converted to the corresponding α-methylene-γ-butyrolactone **174b**, the enantiomer of **174a**.[82]

Aminocarbonylation has been combined with the Pauson–Khand reaction[88] to construct fused tricyclic alkaloid skeletons (see 00154). The tandem aminocarbonylation/Pauson–Khand reaction of haloalkynes with a chiral allylic amine promoted by $Co_2(CO)_8$ gave angular triquinanes as exemplified in Scheme 25.[83] Thus, the reaction of 1-chloro-2-phenylethyne **175** with $Co_2(CO)_8$ at 0 °C gave alkyne–dicobalt complex **176**, which was converted to enoyl–dicobalt complex **177** upon warming to 25 °C. The reaction of enoyl–dicobalt complex **177** with cyclopentenylmethyl(1-phenylethyl)amine **179** yielded Pauson–Khand reaction product, angular triquinane **180**, via *N*-allylic aminocarbonylated alkyne–dicobalt complex **178** (Scheme 25).[83]



Scheme 24

The oxidative aminocarbonylation of terminal alkynes **181** with diethylamine or morpholine led to the formation of 2-alkynamides **183** in moderate to high yields (Equation (12)).[81]

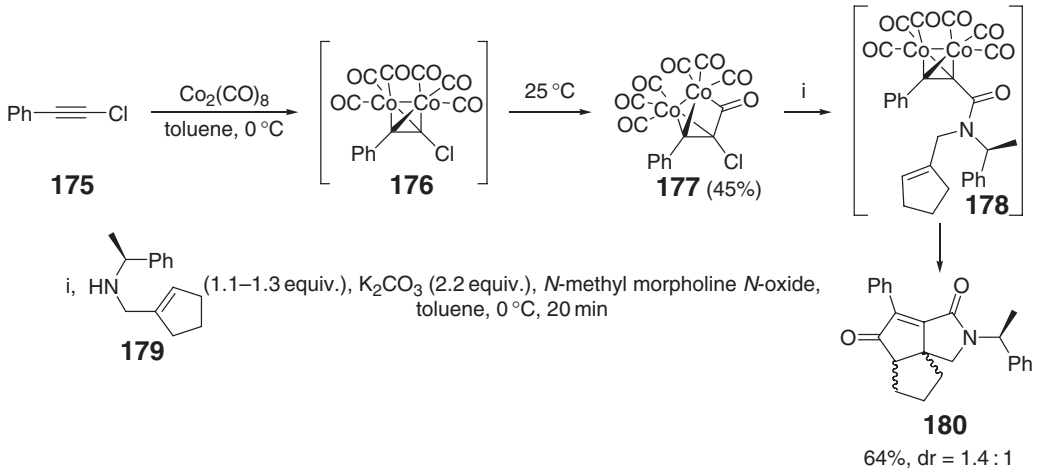


(12)

R = alkyl, aryl

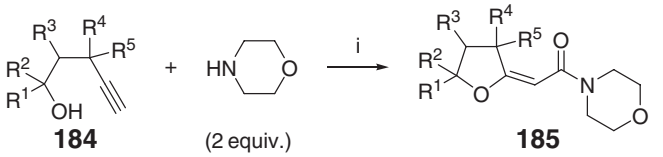
R^2R^3NH = Et_2NH, morpholine

i, PdI_2 (0.2 mol%), KI (2 mol%), CO : air = 4 : 1 (20 atm), 1,4-dioxane (0.5 M), 100 °C; 24 h



Scheme 25

The oxidative aminocarbonylation of 4-pentyn-1-ols **184** with morpholine catalyzed by PdI_2/KI under CO : air (20 atm, 4 : 1) gave 2-(carbamoylmethylene)tetrahydrofurans **185** in one step (Equation (13)).[84] A proposed mechanism of this unique process is illustrated in Scheme 26.[84] As Scheme 26 shows, oxygen is required to regenerate the active Pd(II) catalyst species in this process and related reactions.[81,84,89] The reaction starts from the formation of alkynyl-Pd-I complex **186**, followed by CO insertion to generate alkynoyl-Pd(II) intermediate **187**. Nucleophilic substitution of alkynoyl-Pd(II) complex **187** with morpholine and stereoselective intramolecular conjugate addition of the hydroxyl moiety to the triple bond gives carbamoylmethylene tetrahydrofurans **185** and liberates Pd(0) species and HI. The active catalytic species PdI_2 is regenerated by the reaction of Pd(0) and I_2, which is formed by air oxidation of HI.[81,89]

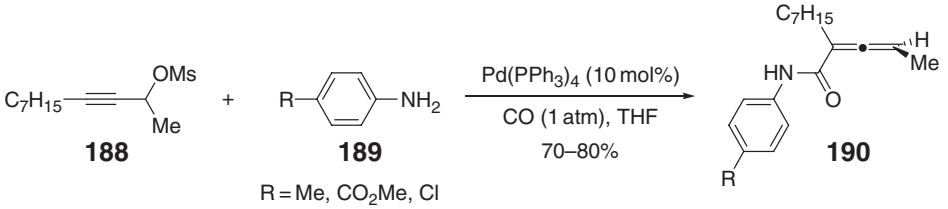


R^1	R^2	R^3	R^4	R^5	*Yield* (%)
H	H	H	H	H	65
Me	H	H	H	H	75
Me	Me	H	H	H	70
H	H	CH_2OH	Me	Me	79

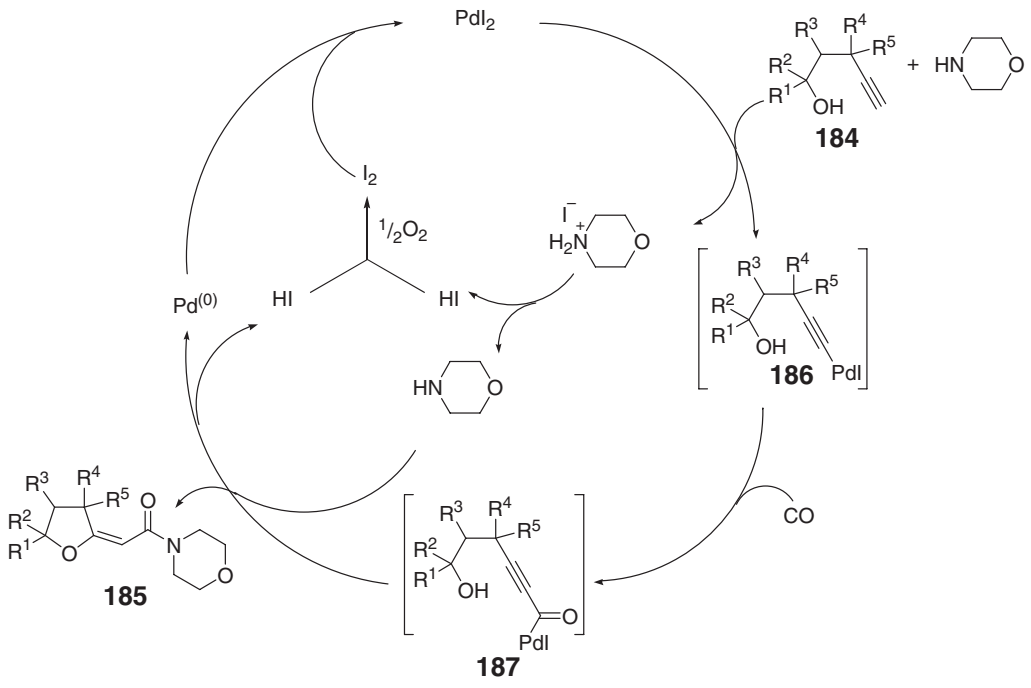
i, PdI_2 (1 mol%), KI (10 mol%), CO : air = 4 : 1 (20 atm), DME (1 M),100 °C; 15 h

(13)

Allenyl amides **190** were synthesized in good to high yields through aminocarbonylation of propargylic mesylate **188** with arylamines **189**, catalyzed by $Pd(PPh_3)_4$ under ambient pressure of CO (Equation (14)).[85]



(14)



Scheme 26

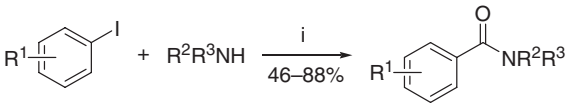
11.15.4.3 Aminocarbonylation Reactions without Using Gaseous Carbon Monoxide

Since the early 2000s, different sources of CO have been explored and applied to carbonylation reactions for laboratory organic synthesis.[90–93] For example, the use a stoichiometric amount of metal–carbonyl complexes,[94] thermolysis of formic acid at high temperature,[93] and the use of aldehydes[21] via decarbonylation have been investigated. For the use of metal–carbonyl complexes and formaldehyde as carbonyl source, it has been shown that microwave irradiation greatly accelerates the process.[90–92,95,96]

The aminocarbonylation of aryl iodides **191** with various amines **192**, including α-amino esters, catalyzed by palladium diacetate ($Pd(OAc)_2$) in the presence of $Mo(CO)_6$ (1 equiv.) and DBU (3 equiv.) completed in 15 min with microwave irradiation to give the corresponding amides **193** in 46–88% yields (Scheme 27).[95] Also, the Pd-catalyzed aminocarbonylation of polystyrene–resin-bound iodobenzenesulfonamide **194** with benzylamine was carried out in the presence of $Mo(CO)_6$ (5 equiv.) and DBU (30 equiv.) in THF with microwave irradiation for 30 min to give the corresponding amide **195** after cleavage from the resin (Scheme 27).[95]

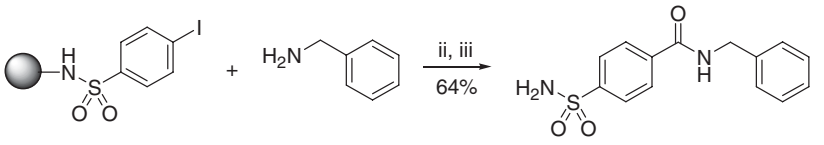
An example of the use of DMF as CO source in the Pd-catalyzed aminocarbonylation with microwave irradiation is shown in Scheme 28.[91] Thus, *o*-bromotoluene was reacted with benzylamine (4 equiv.) in the presence of Pd–dppf catalyst, imidazole, $KOBu^t$, and DMF (17 equiv.) with microwave irradiation for 20 min to give amide **196** in 94% yield (Scheme 28).[91] A proposed mechanism (Scheme 28) has a close similarity to that of the aminocarbonylation of aryl bromide with formamide (see Scheme 22). However, in this process, a large excess (4 equiv.) of benzylamine was used to suppress a possible reaction involving dimethylamine generated *in situ* from DMF under reaction conditions.

As mentioned earlier, the synthesis of primary amides is rather challenging due to technical difficulty in handling gaseous ammonia. Thus, the use of ammonia substitutes such as HMDS and formamide has been studied (see Schemes 21 and 22). With the use of microwave irradiation, however, it has been shown that it is possible to generate both CO and ammonia at the same time for the synthesis of primary amides from aryl bromides.[92] This protocol is very useful for laboratory organic syntheses, especially combinatorial syntheses. As Scheme 29 illustrates, the Pd-catalyzed aminocarbonylation of aryl bromides **200** with formamide (33.5 equiv.) in the presence of $KOBu^t$ (1.5 equiv.) and imidazole (1 equiv.) with microwave irradiation for 400 s (6.7 min) gave the corresponding benzamides

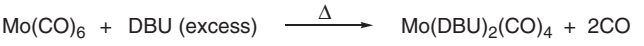


R^1 = H, 4-MeO, 2-Me, 4-CF_3
R^2 = H
R^3 = alkyl, (hetero)aryl, H-Val-OH, H-Gly-OH(OBu^t)
R^2-R^3 = $-(CH_2)_5-$

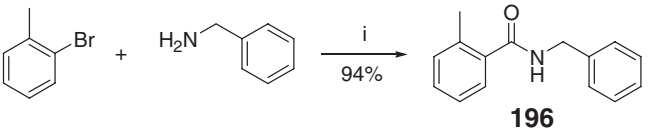
i, Ar–I (1.0 equiv.), amine (3.0 equiv.), $Mo(CO)_6$ (1.0 equiv.), DBU (3.0 equiv.), and $Pd(OAc)_2$ (10 mol%), THF, microwave irradiation (100 °C), 15 min



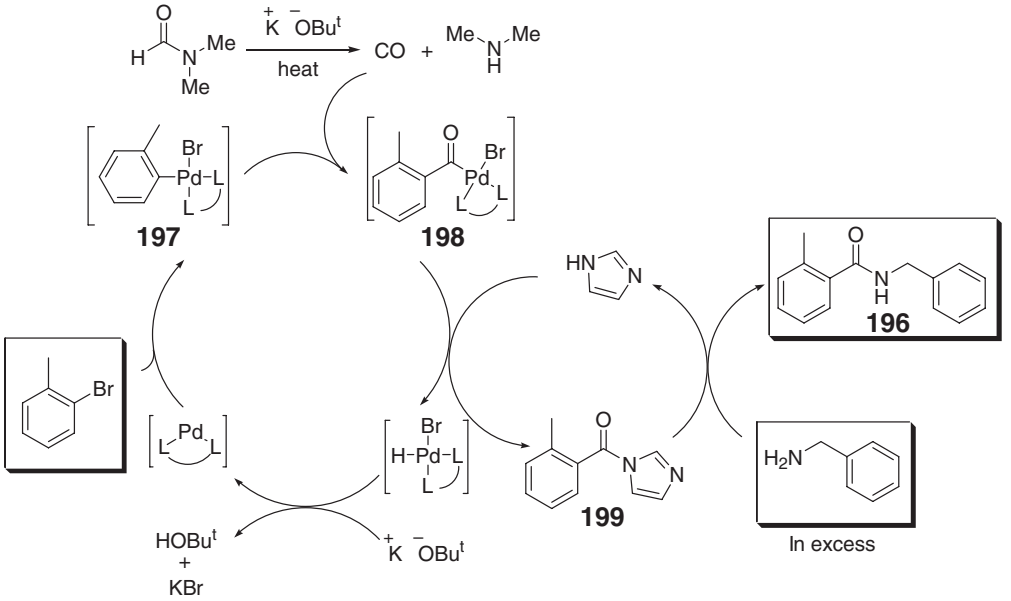
ii, $Pd(OAc)_2$ (0.5 equiv.), $Mo(CO)_6$ (5 equiv.), DBU (30 equiv.), THF, 30 min, microwave irradiation (100 °C); iii, 20% TFA : CH_2Cl_2, 15 min



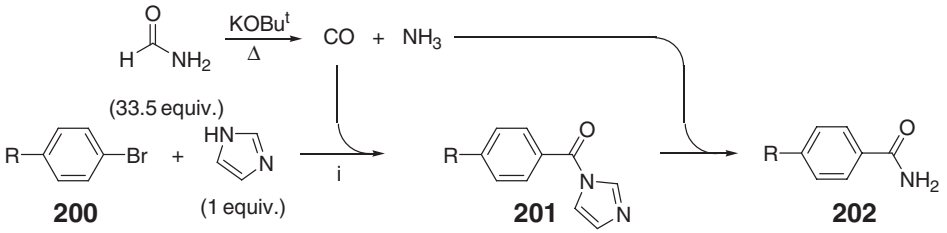
Scheme 27



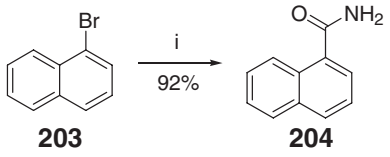
i, $Pd(OAc)_2$ (0.05 equiv.), dppf (0.05 equiv.), imidazole (1 equiv.), $KOBu^t$ (1.5 equiv.), DMF(17 equiv.), microwave irradiation (190 °C), 20 min



Scheme 28 Reprinted with permission from Wan, Y.; Alterman, M.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2002**, *67*, 6232–6235. © 2002 American Chemical Society.



R	*Yield* (%)
CN	52
OMe	74
Me	81
H	83
CF_3	84



i, $Pd(OAc)_2$ (5 mol%), dppf (5 mol%), KOBu^t (1.5 equiv.), microwave irradiation (180 °C), 400 s

Scheme 29 Reprinted with permission from Wan, Y.; Alterman, M.; Larhed, M.; Hallberg, A. *J. Comb. Chem.* **2003**, *5*, 82–84. © 2003 American Chemical Society.

202 in moderate to high yields. In the same manner, the reaction with 1-bromonaphthalene afforded naphthalene-1-carboxamide **204** in 92% yield.[92]

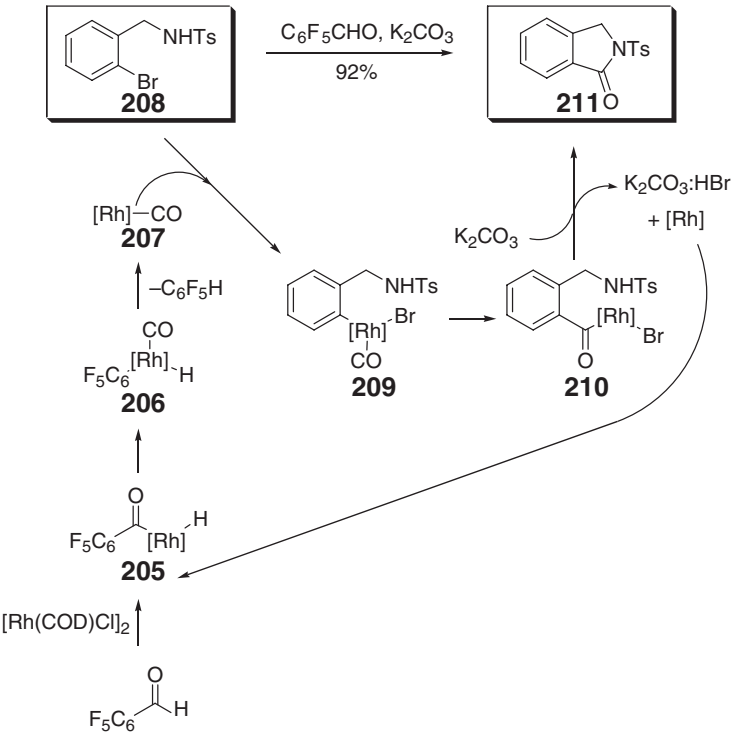
Other examples of carbonylation performed with microwave irradiation are discussed in Section 11.15.6.7.

11.15.4.4 Intramolecular Aminocarbonylation Reactions

The Rh-catalyzed intramolecular aminocarbonylation of 2-tosylaminoalkyl-1-bromobenzenes, using pentafluorobenzaldehyde or cinnamaldehyde as CO source, was carried out to give the corresponding five-to-seven-membered ring benzolactams in high yields.[21] As Scheme 30 illustrates, pentafluorobenzaldehyde reacts with $[Rh(COD)Cl]_2$ to undergo decarbonylation, forming, for example, Rh(I)–CO species **207**. The oxidative addition of aryl bromide **208** forms aryl-Rh(III) complex, followed by migratory CO insertion to yield aroyl-Rh(III) complex **210**. Then, intramolecular aminolysis of aroyl-Rh bond takes place to give benzolactam **211** and generates H–[Rh^{III}]–Br species, which is reduced by K_2CO_3 to regenerate the active [Rh^I] catalyst species.

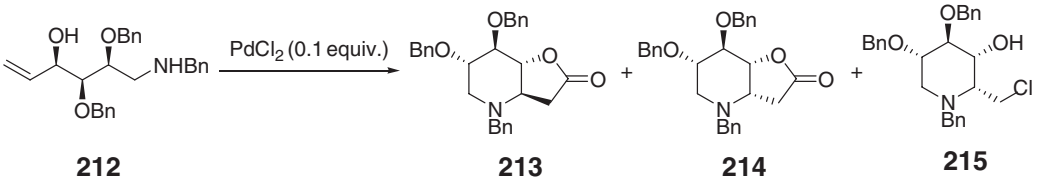
Although the intramolecular aminocarbonylation described above is an extension of the standard amide-forming reaction, a different type of intramolecular aminocarbonylation has been studied, wherein the amine moiety adds across the olefin moiety activated by a Pd catalyst to generate β-aminoalkyl-Pd species, followed by CO insertion and alcoholysis, forming a lactone or an ester.[97–99]

The Pd-catalyzed intramolecular aminocarbonylation of trihydroxy-6-amino-1-hexene derivative **212** under ambient pressure of CO gave key precursors to 1-deoxynojirimycin and 1-deoxy-*l*-idonojirimycin, **213** and **214**, in moderate to fairly good yields (Equation (15)).[97,98] The diastereoselectivity of this reaction depends on the reaction conditions and the use of THF as solvent and running the reaction at room temperature favors the formation of **213**, which is the key precursor to 1-deoxynojirimycin, while the reaction in acetic acid at 50 °C affords **214**, the key precursor to 1-deoxy-*l*-idonojirimycin.



Conditions $[Rh(COD)Cl]_2$ (2.5 mol%), dppp (5 mol%), C_6F_5CHO (2 equiv.), K_2CO_3 (2 equiv.), xylenes, 130 °C, 10 h

Scheme 30



212 **213** **214** **215**

Conditions	*Yield* (%) (**213** + **214**)	**213** : **214** (% de)	*Yield* (%) **215**
A	46	1 : 4.8 (65)	9
B	32	1 : 5.6 (70)	
C	66	3.7 : 1 (58)	

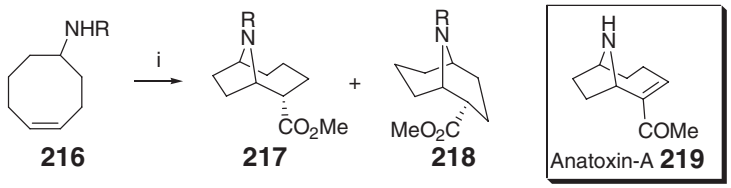
(15)[a]

conditions **A**: CO (1 atm), $CuCl_2$ (3 equiv.), AcONa (3 equiv.), AcOH, 50 °C, 4–7 h
conditions **B**: CO (1 atm), *p*-benzoquinone (1 equiv.), LiCl (2 equiv.), AcONa (2 equiv.), AcOH, 50 °C, 47 h
conditions **C**: CO (1 atm), *p*-benzoquinone (1 equiv.), LiCl (2 equiv.), AcONa (2 equiv.), THF, RT, 17 h

[a]Reproduced from Szolcsányi, P.; Gracza, T.; Koman, M.; Prónayová, N.; Liptaj, T. Pd(II)-catalysed aminocarbonylation as a key step in the total synthesis of C-6 homologues of 1-deoxynojirimycin and 1-deoxy-*l*-idonojirimycin. *Tetrahedron: Asymmetry* **2000**, 11, 2579–2597, with permission from Elsevier.

The Pd-catalyzed intramolecular aminocarbonylation has also been applied to the formal total synthesis of Anatoxin-A **219**, an acetylcholine mimic (Equation (16)).[99] Thus, the reaction of 5-(methoxycarbonylamino)-cyclooctene **216a** in the presence of a catalytic amount of $PdCl_2$ and cupric chloride ($CuCl_2$) (3 equiv.) in methanol under ambient pressure of CO gave the desired azabicyclo[4.2.1]nonane **217** as the predominant product. The regioselectivity of this reaction is highly dependent on the nature of the *N*-substituent. Thus, the

reaction of 5-(benzylamino)cyclooctene **216b** under the same conditions afforded azabicyclo[3.3.1]nonane **218** with 97% product selectivity.



i, $PdCl_2$ (0.1 equiv.), $CuCl_2$(3 equiv.), CO (1 atm); MeOH, RT; 1–2 day(s) (16)[a]

216	*R*	*Yield* (%)	217 : 218
a	CO_2Me	61	72 : 28
b	Bn	47	3 : 97

[a]Reproduced from Oh, C.-Y.; Kim, K.-S.; Ham, W.-H. A formal total synthesis of (+)-anatoxin-A by an intramolecular Pd-catalyzed aminocarbonylation reaction. *Tetrahedron Lett.* **1998**, *39*, 2133–2136, with permission from Elsevier.

11.15.5 Ring Expansion Via Carbonylation Reactions

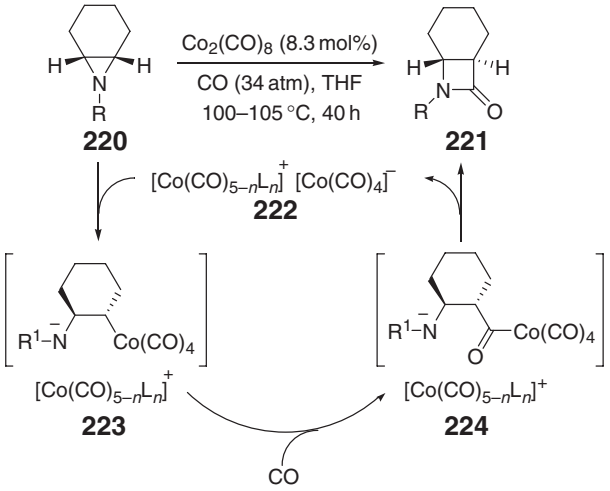
11.15.5.1 Ring Expansion of Aziridines

Carbonylative ring-expansion reactions catalyzed by transition metal complexes provide efficient methods for the synthesis of heterocyclic compounds, especially nitrogen heterocycles.[100–106]

Since Alper and co-workers reported the first Rh-catalyzed carbonylative ring expansion of aziridines, yielding β-lactams in 1989,[100] this ring-expansion reaction catalyzed by Rh or Co complexes and its mechanism have been extensively studied.[101,102,105,107]

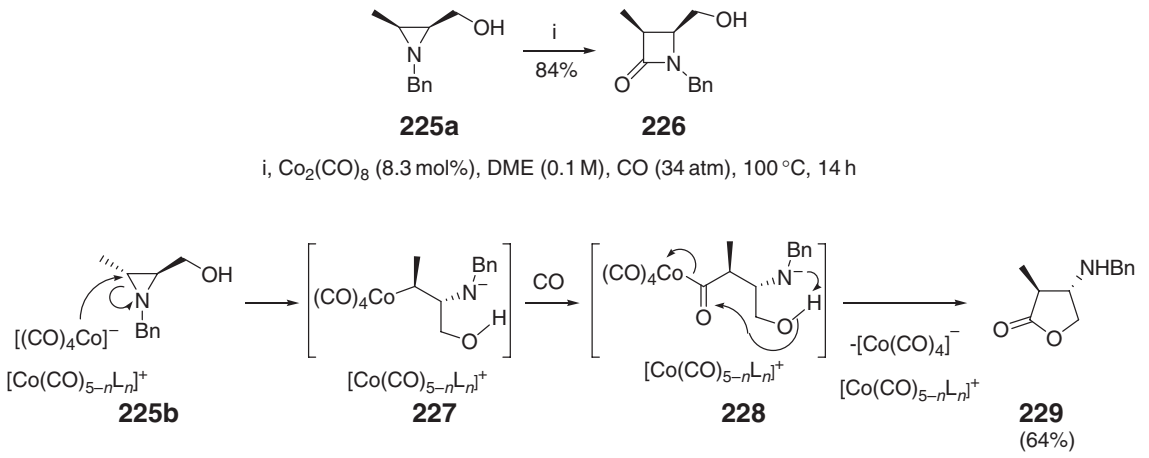
Scheme 31 illustrates, as an example, the $Co_2(CO)_8$-catalyzed carbonylative ring expansion of bicyclic aziridine **220**, forming the corresponding highly strained *trans*-bicyclic β-lactam **221**, and a proposed reaction pathway.[107] In this reaction, it is believed that tetracarbonylcobaltate, $Co(CO)_4^-$, generated from $Co_2(CO)_8$ is the active catalyst

R	*Yield* (%)
Cyclohexyl	69
1-Adamantyl	80



$$Co_2(CO)_8 + nL \rightleftharpoons [Co(CO)_{5-n}L_n]^+[Co(CO)_4]^- + (n-1)\,CO$$
(L = THF) **222**

Scheme 31

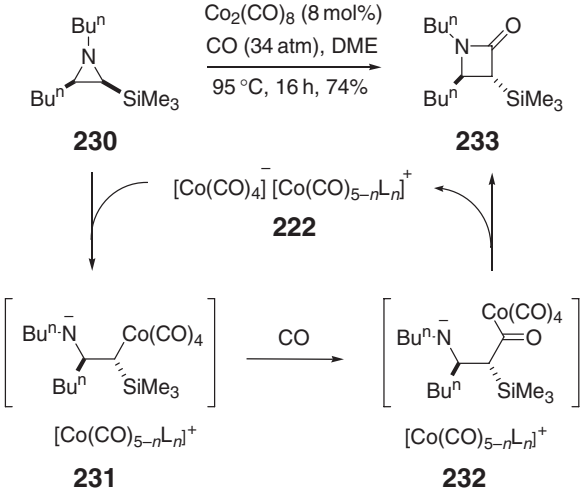


Scheme 32 Reproduced from Davoli, P.; Forni, A.; Moretti, I.; Prati, F.; Torre, G. On the effect of ring substituents in the carbonylation of aziridines. *Tetrahedron* **2001**, *57*, 1801–1812, with permission from Elsevier.

species. The nucleophilic ring opening of aziridine **220** by $Co(CO)_4^-$ with an inversion of configuration gives β-aminoalkyl–Co complex **223**, which is subsequently converted to acyl–Co complex **224**. The ring closure of **224** through intramolecular nucleophilic acyl substitution affords β-lactam **221** and regenerates $Co(CO)_4^-$.

The carbonylative ring expansion of *cis*-2-hydroxymethyl-1-benzylaziridine **225a** catalyzed by $Co_2(CO)_8$ under CO (34 atm) gave the corresponding *cis*-3-methyl-4-hydroxymethylazetidin-2-one **226** in 84% yield. However, the Co-catalyzed reaction of *trans*-2-hydroxymethyl-1-benzylaziridine **225b** gave lactone **229** exclusively in 64% yield (Scheme 32).[108] Thus, it has been shown that γ-lactone formation may take place selectively, depending on the stereochemistry of the aziridine used, when the β-lactam ring formation has a competing lactonization process. The result can be accommodated by taking into account the likely reaction pathway in the favorable conformation of the key intermediate **228** derived from *trans*-aziridine **225b**, wherein the selective intramolecular nucleophilic acyl substitution occurs with the oxygen nucleophile. The highly regioselective ring-opening of aziridine **225** with $Co(CO)_4^-$ is also noteworthy in this reaction.

The Co-catalyzed reaction of 2-TMS-3-butylaziridine **230** gave *trans*-3-TMS-4-butyl-β-lactam **233** exclusively in 74% yield (Scheme 33).[106] The result clearly indicates that the nucleophilic attack of $Co(CO)_4^-$ takes place exclusively at the C2 position, that is, α to the silicon moiety, with inversion of configuration in this reaction, which also demonstrates the directing effect of the silicon moiety. Thus, the reaction is believed to proceed through intermediates **231** and **232**.[106]

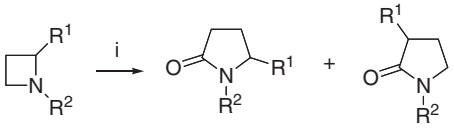


Scheme 33 Reprinted with permission from Aggarwal, V.K.; Alonso, E.; Ferrara, M.; Spey, S.E. *J. Org. Chem.* **2002**, *67*, 2335–2344. © 2002 American Chemical Society.

Dendritic rhodium catalyst systems on a resin have been developed for the carbonylative ring expansion of aziridines.[109,110] This catalyst system exhibited same high activity as the homogenous counterpart, that is, $[Rh(CO)_2Cl]_2$, and reused for several times without loss of activity.[109]

11.15.5.2 Ring Expansion of Azetidines

In a manner similar to the reactions of aziridines, the Co-catalyzed carbonylative ring expansion of azetidines **234** proceeds under mild conditions to give the corresponding pyrrolidinones in high yields (Equation (17)).[102] The regioselectivity of the formation of pyrrolidinone **235** or **236** is controlled by the stereoelectronic nature of the substituent at the 2-position of azetidines. Thus, the reactions of 2-alkylazetidines **234a** and **234b** gave 5-alkylpyrrolidin-2-ones **235a** and **235b** in 83% and 91% yields, respectively, while the reaction of 2-phenylazetidine **234c** afforded 3-phenylpyrrolidin-2-one **236** in 90% yield (Equation (17)).[102]



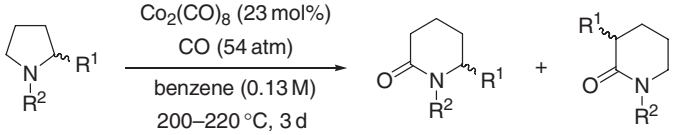
234 **235** **236**

i, $Co_2(CO)_8$ (5 mol%), CO (3.4 atm), benzene (0.35 M), 85–90 °C, 24 h (17)

Substrate	R^1	R^2	**235** (%)	**236** (%)
234a	Me	Bu^t	83	
234b	CH_2OMe	Bu^t	91	
234c	Ph	Me	Trace	90

11.15.5.3 Ring Expansion of Pyrrolidines

The carbonylative ring-expansion reaction of pyrrolidines is promoted by $Co_2(CO)_8$ catalyst. However, this reaction is more challenging than those of aziridines and azetidines, requiring drastic conditions to offset the lack of ring-strain energy. For example, the Co-catalyzed reaction of pyrrolidine **237** was carried out using 23 mol% of $Co_2(CO)_8$ at 200–220 °C and 54 atm of CO for 3 days to give 6-substituted piperidinone **238** and/or 3-substituted piperidinone **239** in moderate to fairly good yield (Equation (18)).[102] The regioselectivity of this reaction is highly dependent on the stereoelectronic nature of the substituent at the 2-position of pyrrolidine **237** in the same manner as that observed for aziridines and azetidines.

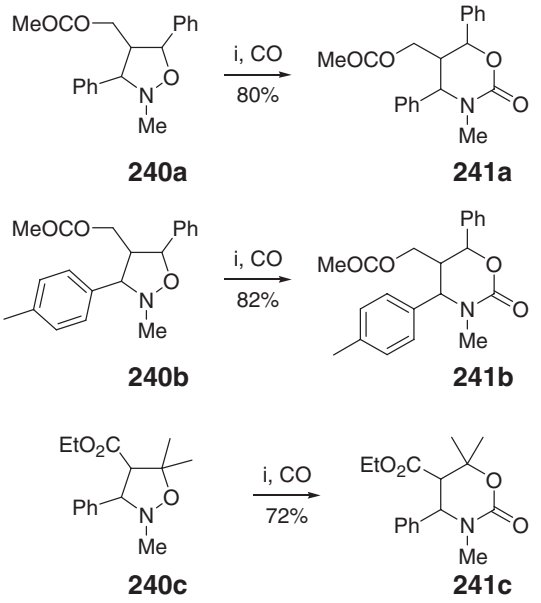


237 **238** **239**

		Yield (%)	
R^1	R^2	**238**	**239**
Ph	Me		56
Bn	Me	24	15
CH_2OMe	CH_2CO_2Et	49	
CH_2OMe	CH_2COBu^t	61	

(18)

The Co-catalyzed carbonylative ring-expansion reaction has also been applied to other five-membered ring heterocycles such as oxazolidines,[111] oxazines,[112] oxazolines,[113,114] and thiazolidines.[115]

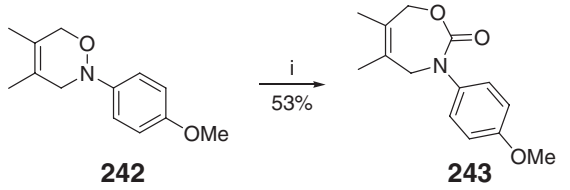


i, $[Rh(COD)Cl]_2$ (1 mol%), CO (65 atm), benzene (0.5 M), 150–170 °C, 24 h

Scheme 34

The Rh-catalyzed reaction of isoxazolidine **240** at 150–170 °C and 65 atm of CO gave tetrahydro-1,3-oxazin-2-one **241** in good yields, wherein the insertion of CO took place selectively into the N–O bond of isoxazolidine (Scheme 34).

The carbonylative ring-expansion reaction via CO insertion into the N–O bond has been applied to the six-membered ring system, that is, oxazines, but using $Co_2(CO)_8$ as the catalyst.[112] For example, the Co-catalyzed reaction of oxazine **242** at 120 °C and 68 atm of CO gave oxazepinone **243** in 53% yield (Equation (19)).[112]



(19)

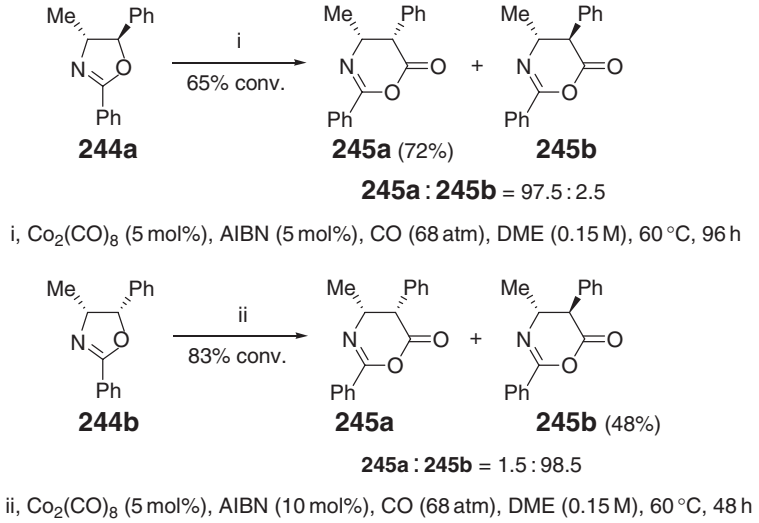
i, $Co_2(CO)_8$ (50 mol%), CO (68 atm), benzene (0.2 M),120 °C, 24 h

The $Co_2(CO)_8$-catalyzed ring-expansion reaction of enantiopure *trans*- and *cis*-4-methyl-5-phenyl-1,3-oxazolines, **244a** and **244b**, was carried out using AIBN (5–10 mol%) as a radical activator to give the corresponding oxazinones, **245a** or **245b**, with high diastereoselectivity (Scheme 35).[113,114] The CO insertion took place specifically into the benzylic C(5)–O bond of oxazoline with inversion of configuration with slight epimerization.

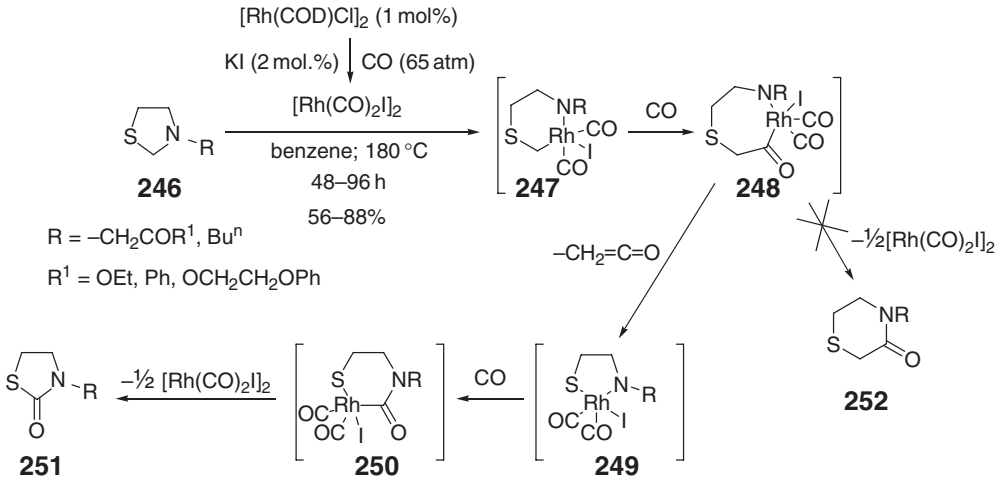
The Rh-catalyzed ring-expansion reaction of thiazolidine **246** in the presence of a catalytic amount of KI (2 mol%) at 180 °C and 65 atm of CO gave thiazolidinone **251** in 56–88% yields.[115] Formation of thiomorpholinone **252** was not observed at all. Thus, a proposed mechanism of this reaction involves the elimination of a ketene molecule from a key intermediate **248** to form rhodathiazolidine complex **249**, which undergoes migratory CO insertion, followed by reductive elimination to yield thiazolidinone **251** (Scheme 36).[115]

11.15.5.4 Ring Expansion via Rearrangement of Nitrogen Heterocycles

The reaction of 2-vinylazetidines **253** catalyzed by $Co_2(CO)_8$ under the same conditions as those for azetidines **234** (see Equation (17)) gave the corresponding azepinones **259** in moderate to excellent yields (Scheme 37).[102,116] A proposed mechanism includes the C–N cleavage of the allylic amine moiety of **255** to give cyclic π-allyl-Co-amine complex **256**, which rearranges to form seven-membered ring azametallacycle **257**. The migratory CO insertion of



Scheme 35

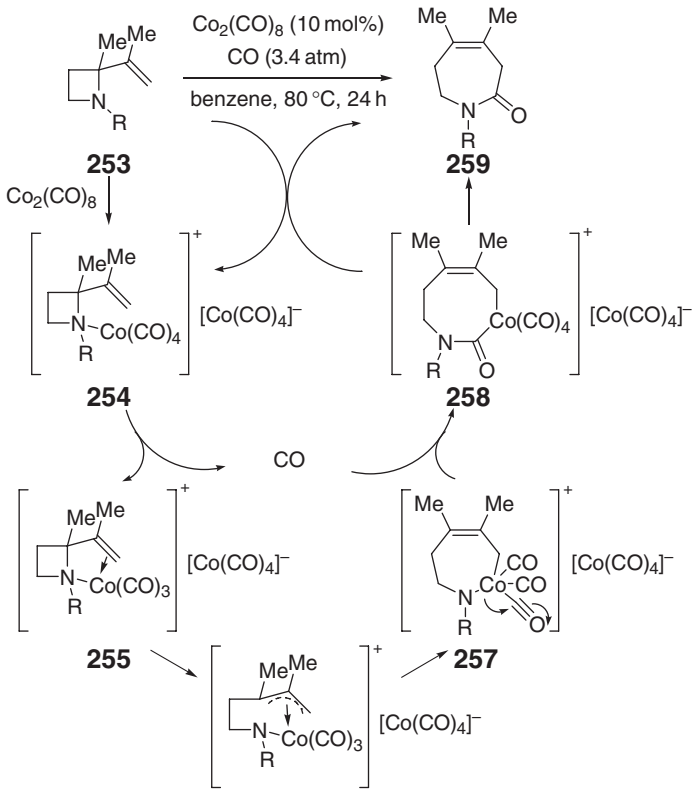


Scheme 36 Reprinted with permission from Khumtaveeporn, K.; Alper, H. *J. Am. Chem.* Soc. **1994**, *116*, 5662–5666. © 1994 American Chemical Society.

257 yields eight-membered ring metallalactam **258**, followed by reductive elimination to give azepinone **259** and regenerate the active catalyst species, which reacts with **253** to form a key intermediate **254**.[102]

The Pd-catalyzed reaction of 5-vinyl-1,3-oxazolidin-2-ones **260** at 65–70 °C and 65 atm of CO in ethanol gave *δ*-lactams **263** in fairly good to high yields (Scheme 38).[117] As Scheme 38 illustrates, this "decarboxylative" carbonylation reaction is likely to involve (i) the cleavage of the allylic C–O bond of **260** to form *π*-allyl-Pd complex *syn*-**261**, (ii) isomerization to *anti*-**261**, (iii) decarboxylation forming *π*-allyl-Pd-amine complex **262**, and (iv) CO insertion to **262** followed by aminolysis to yield *δ*-lactam **263**.

The Co-catalyzed reaction of azepane **264** ($n = 3$) at 220 °C and 54 atm of CO gave the normal ring-expansion product **265** ($n = 3$) in 42% yield (Scheme 39). However, when $Ru_3(CO)_{12}$ was used as co-catalyst of $Co_2(CO)_8$ under the same conditions, azepanone **266** ($n = 3$) was obtained as the sole product in 72% yield (Scheme 39).[102,118] The attempted reaction only with $Ru_3(CO)_{12}$ as catalyst under the same conditions resulted in the recovery of the substrate **264** ($n = 3$).[118] Thus, this unique rearrangement requires both Co and Ru catalysts. A proposed mechanism for the formation of **266** is illustrated in Scheme 40, which proposes that the origin of the lactam oxygen is the carbonyl oxygen of the *N*-pivaloylmethyl group of pyrrolidine **264**.[118]



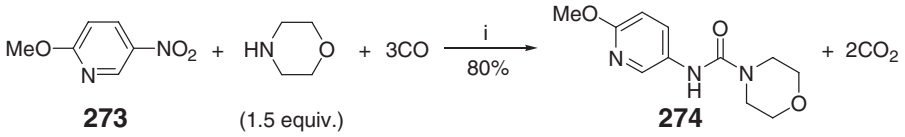
R	*T* (°C)	*Yield* (%)
H	80	52
$(CH_2)_2COMe$	50	54
$(CH_2)_2CO_2Me$	50	60
$(CH_2)_2CO_2Me$	80	93
$(CH_2)_2CN$	80	86

Scheme 37

11.15.6 Other Carbonylation Reactions

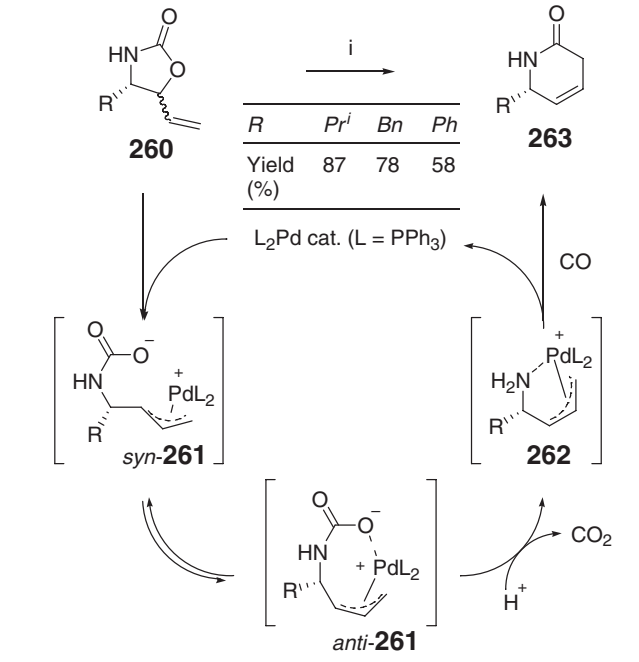
11.15.6.1 Reductive Carbonylation Reactions

The reductive aminocarbonylation of nitrobenzenes and nitropyridines is catalyzed by SeCO, generated *in situ* from SeO_2 and CO, to form the corresponding isocyanates, which are trapped by amines to afford symmetrical and unsymmetrical ureas (see 00158).[119–124] For example, the reaction of nitropyridine **273** with morpholine in the presence of SeO_2 (5 mol%) and triethylamine (1 equiv.) in refluxing toluene under 30 atm of CO gave unsymmetrical pyridyl urea **274** in 80% yield (Equation (20)).[124]

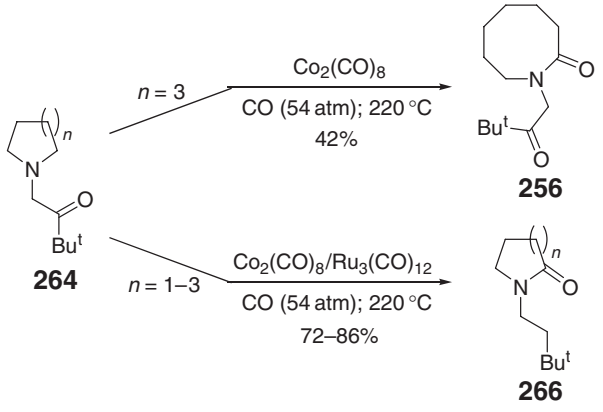


(20)

i, SeO_2 (5 mol%), Et_3N (1 equiv.), CO (30 atm), toluene (1 M), 140–150 °C, 4 h



Scheme 38



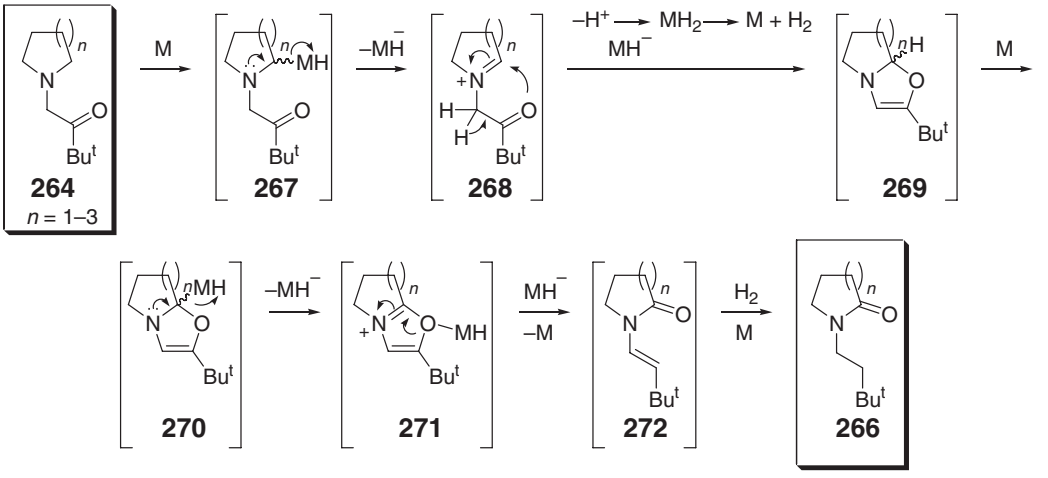
Scheme 39

In this reaction, the initially introduced SeO_2, insoluble in organic solvent, is converted to soluble SeCO by CO (30 atm) under reflux in toluene, which is the active catalyst for the reductive carbonylation of nitrobenzene or nitropyridine. The metallic selenium (insoluble) is also converted to SeO under CO pressure. After completion of the reaction, soluble selenium catalyst solution was readily recovered by simple filtration and reused. The recovered catalyst solution was used for five cycles without loss of activity.[124]

It has been shown that this reaction is also promoted by $RhA(CO)_2$ (A = anthranilato).[125] This finding led to the development of a reusable polymer-anchored Rh-catalyst for this process.[126,127]

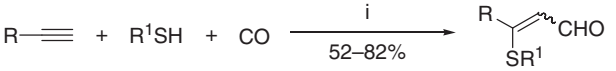
11.15.6.2 Thiocarbonylation Reactions

Besides alkoxy-, amino-, and amidocarbonylation reactions, a carbonylation process using a thiol as nucleophile, that is, "thiocarbonylation," has been extensively studied.[128–143] It has been shown that the thiocarbonylation takes place with 1-alkynes,[133,134,144] propargyl alcohols,[136] allenes,[131] 1,3-dienes,[129,130] propargylic mesylates,[128] and bicyclopropylidene[135].



Scheme 40 Reprinted with permission from De Wang, M.; Alper, H. *J. Am. Chem. Soc.* **1992**, *114*, 7018–7024. © 1992 American Chemical Society.

The reaction of 1-alkynes **275** gives thioformylation products **277** (Equation (21)),[144] while that of propargyl alcohols **278** afforded thiofuranones **280** (Equation (22)).[136] The reaction of allenes **281** gives alkenylthiolate **282** (Equation (23)),[131] while dithiocarbonylation took place to yield **284** in the reaction of propargylic mesylates **283** (Equation (24)).[128]



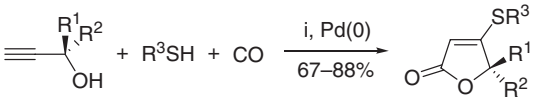
275 **276** **277**

R, R^1 = Ph, alkyl

E : *Z* = 86 : 14–1 : 99

(21)

i, $RhH(CO)(PPh_3)_3$ (3 mol%), CO (30 atm), CH_3CN (1 M), 5 h



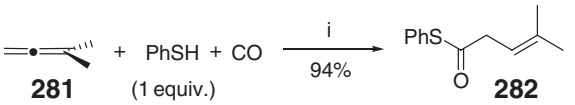
278 **279** **280**

R^1, R^2 = alkyl

R^3 = Ph, *n*-octyl, furanyl

(22)

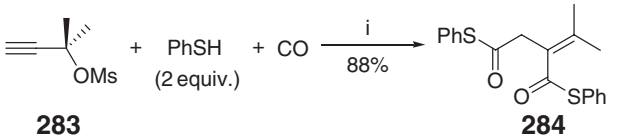
i, $Pd(PPh_3)_4$ (3 mol%), CO (27.2 atm), DME, 100 °C, 48 h



281 (1 equiv.) **282**

(23)

i, $Pd(OAc)_2$ (3 mol%), PPh_3 (12 mol%), CO (27.2 atm), THF (0.3 M), 100 °C, 48 h

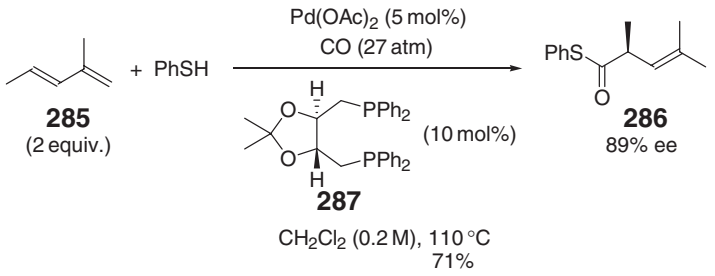


283 **284**

(24)

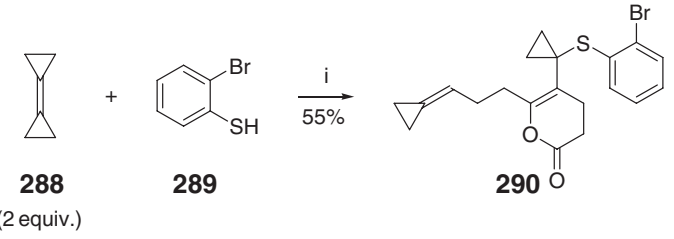
i, $Pd(PPh_3)_4$(3 mol%), CO (27.2 atm), THF (0.2 M), 90 °C, 48 h

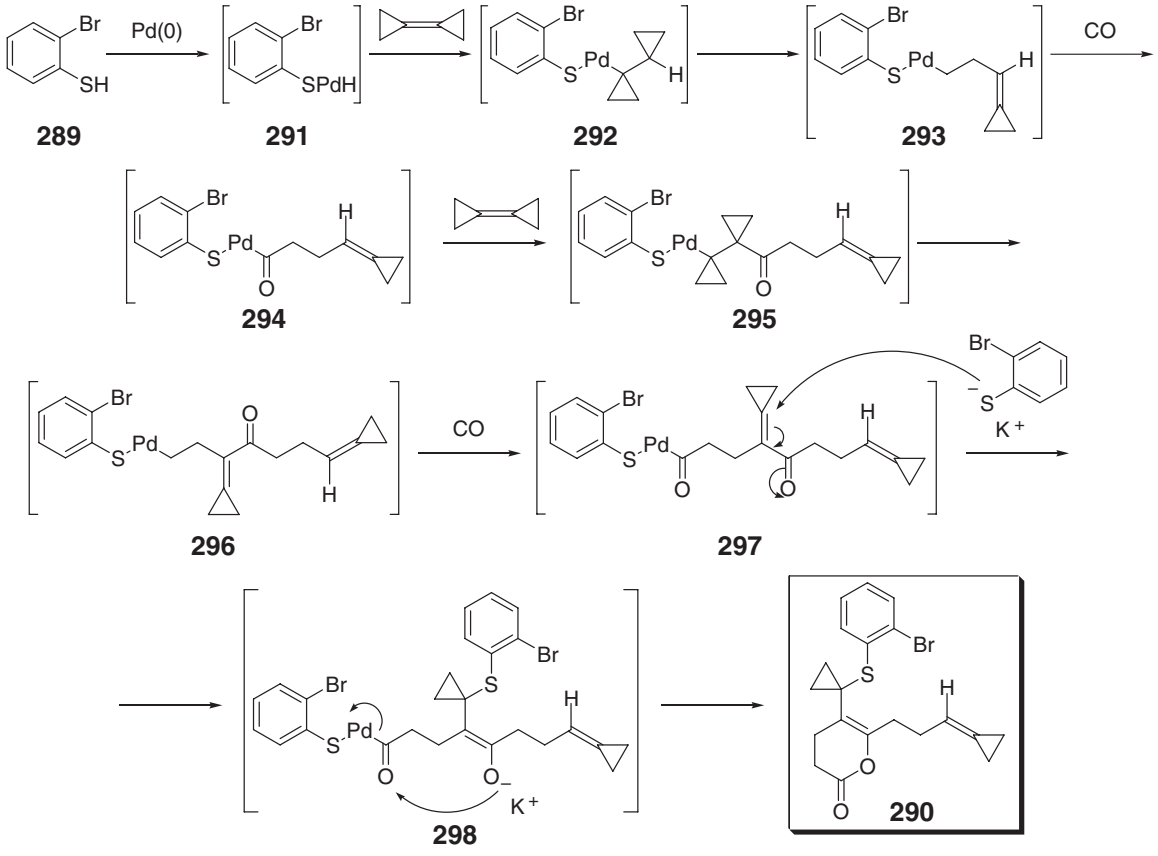
The highly regio- and enantioselective thiocarbonylation of 1,3-diene **285** with benzenethiol was carried out using $Pd(OAc)_2$ (5 mol%) with (*R*,*R*)-DIOP **287** (10 mol%) as chiral catalyst at 110 °C and 27 atm of CO to give alkenylthioate **286** with 89% ee in 71% yield (Equation (25)).[129]



(25)

A unique five-component cascade thiocarbonylation reaction (two molecules of bicyclopropylidene **288**, one molecule of bromothiophenol **289**, and two molecules of CO) was successfully carried out to give the lactone **290** in 55% yield in one step (Scheme 41).[135] A proposed mechanism for this cascade process is illustrated in Scheme 41.



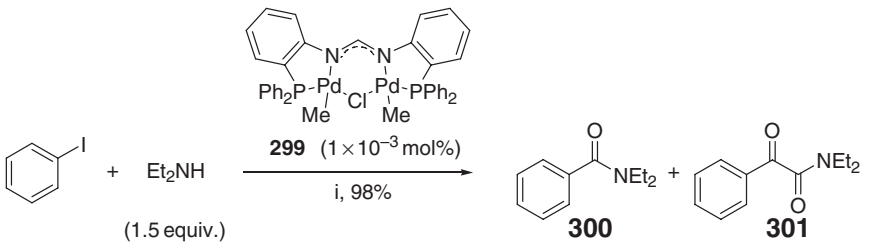


Scheme 41

This process is fully exploiting the high strain energy of bicyclopropylidene **288** and cyclopropylidene intermediate **297** as well as stability of arylthio-Pd bond to facilitate the CO insertion to carbon–Pd(SAr) bond.

11.15.6.3 Double Carbonylation Reactions

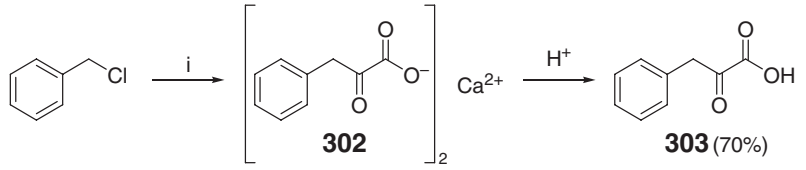
An efficient dinuclear Pd catalyst **299** was developed for the double carbonylation of iodobenzene with diethylamine,[145–148] which substantially improved the process yield (98%) and product selectivity of *N*,*N*-diethylphenylglyoxamide **301** (96%) (Equation (26)).[149]



(26)

i, CO (20 atm), K_3PO_4 (1 equiv.), 1,4-dioxane (1.7×10^{-5} M), 100 °C, 48 h

The $CoCl_2$-catalyzed double carbonylation of benzyl chloride was carried out in the presence of potassium pyridine-2-carboxylate and calcium hydroxide (3.75 equiv.) under 28 atm of CO to give phenylpyruvic acid in 70% yield (Equation (27)).[150]



(27)

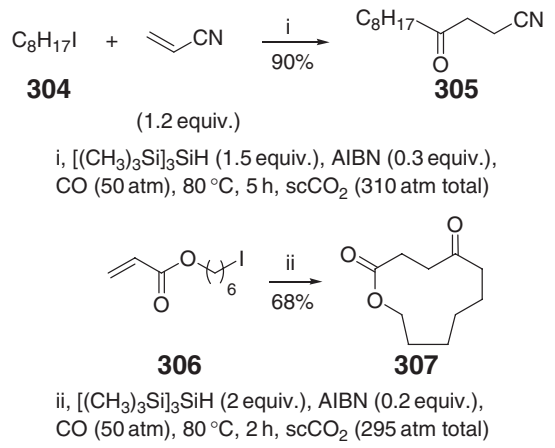
i, $Ca(OH)_2$ (3.75 equiv.), $CoCl_2$, CO (27.6 atm), potassium pyridine-2-carboxylate, H_2O, 1,4-dioxane, 80 °C

11.15.6.4 Carbonylation Reactions in Supercritical CO_2

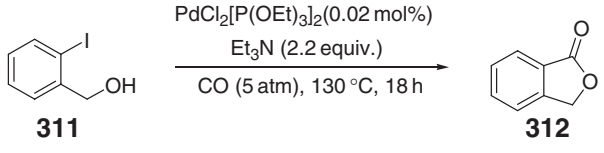
Supercritical carbon dioxide ($scCO_2$) is currently considered as an environmentally benign medium, and has been applied to free-radical reactions as well as various homogeneous catalytic reactions.[151,152] It has been shown that $scCO_2$ prevents side-reactions such as radical chain transfer and possesses a high miscibility with reactant gases.[151,152] For these reasons, $scCO_2$ has been adapted for carbonylation reactions as advantageous medium.[153–158]

The free-radical carbonylation of iodoalkanes in $scCO_2$ initiated by AIBN (0.2–0.3 equiv.) with $(TMS)_3SiH$ (1.5 equiv.) was studied for both intermolecular reactions and intramolecular reactions (Scheme 42).[153] For example, the carbonylative addition of 1-iodooctane **304** to acrylonitrile was carried out at 80 °C and 50 atm of CO in $scCO_2$ under a total pressure of 310 atm to give 4-oxododecanenitrile **305** in 90% yield. Also, the intramolecular carbonylation of 6-iodohexyl acrylate **306** under similar conditions afforded 11-membered macrolide **307** in 68% yield.[153]

The lactonization of *o*-iodobenzyl alcohol **311** was performed in the presence of $PdCl_2[(P(OEt)_3]_2$ (0.02 mol%) and triethylamine (2.2 equiv.) at 130 °C and 5 atm of CO in $scCO_2$ (200 atm) to give phthalide **312** quantitatively (Equation (28)).[154,156] In this reaction, the turnover number (TON) in $scCO_2$ reached 5000 after 18 h, which was considerably better than that in toluene (3800).[156] Moreover, the reaction in $scCO_2$ reached 4700 TON after 6 h as compared to only 1100 TON for that in toluene.



Scheme 42



(28)

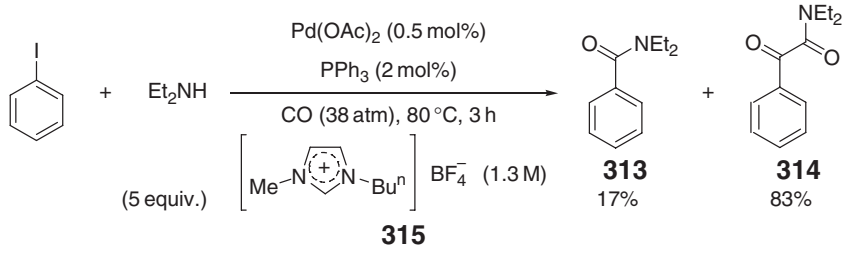
Solvent	*TON (product mol/catalyst mol)*
$scCO_2$ (200 atm)	5000
toluene (0.01 M)	3800

11.15.6.5 Carbonylation Reactions in Ionic Liquids

Ionic liquids serve as very useful reaction media, which can facilitate easy separation of product(s) and a catalyst after the reaction. These substitutes of organic solvents as reaction media have already been successfully applied to a variety of transition metal-catalyzed organic reactions such as Heck reaction, Suzuki cross-coupling, hydroformylation, and alkoxycarbonylation.[159–162]

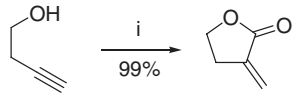
Ionic liquids have been used for the selenium- or palladium-catalyzed carbonylation of primary amines to form carbamates or ureas.[163–166] After completion of the carbonylation, addition of water induced the precipitation of desired products, which were isolated by filtration and separated from the ionic liquid, containing the catalytic species. Then, the catalyst could be reused after removal of residual methanol and water by distillation. Although the conversion of the reaction slightly decreased after the second run, the catalytic activity was considerably improved (from 70% to 99 %) by the addition of a small amount of the fresh catalyst.[166]

The double carbonylation of iodobenzene with diethylamine catalyzed by $Pd(OAc)_2$–PPh_3 was carried out in 1-butyl-3-methylimidazolium tetrafluoroborate **315** as reaction medium at 80 °C and 38 atm of CO to give phenylglyoxamide **314** as the predominant product (83%) accompanied by benzamide **313** (17%) (Equation (29)).[167] The use of ionic liquids showed the same reactivity and product selectivity as those using diethylamine as solvent for this reaction, while separation of products and recycling of the catalyst was easier.[167]



(29)

The synthesis of α-methylene-γ-lactone **317** through carbonylation of but-3-yn-1-ol **316** catalyzed by Pd(II)–PPh_2(2-Py) has been carried out in 1-butyl-3-methylimidazolium tetrafluoroborate **315** as reaction medium in high yield with excellent product selectivity (Equation (30)).[168] Although the ionic liquid containing the catalytic species was recovered, a significant decrease in yield occurred with the recycled catalyst, which appears to be attributed to the decomposition of the catalyst during the isolation procedure.[168]



316 **317**

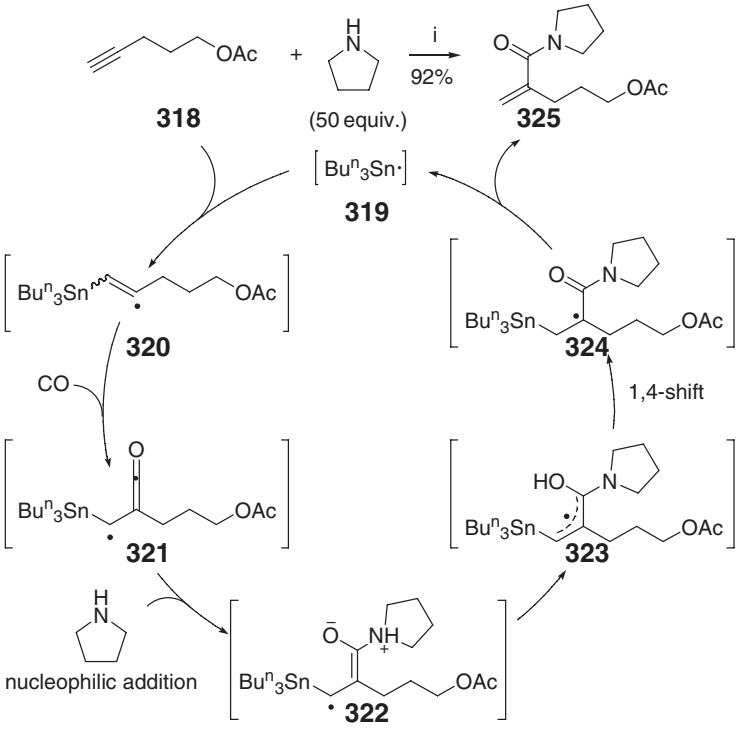
i, $Pd(OAc)_2$ (0.1 mol%), 2-$PyPPh_2$ (1 mol%), *p*-TSA (1 mol%), BMI-BF_4 (or BMI-PF_6)(3.3 M), CO (25 atm), 60 °C, 2 h (30)

BMI-BF_4 (or BMI-PF_6) =  BF_4^- (or PF_6^-)

315

11.15.6.6 Radical Carbonylation Reactions

Radical carbonylation reaction serves as a powerful tool for the synthesis of a range of carbonyl compounds. Radical carbonylation has been successfully applied to the synthesis of functionalized ketones from alkyl, aryl, and alkenyl halides.[169–171] The radical aminocarbonylation reaction of alkynes and azaenynes provided efficient routes to 2-substituted acrylamides, lactams, and pyrrolidinones.[172–175] For example, the aminocarbonylation of 4-pentyn-1-yl acetate **318** initiated by tributyltin hydride (Bu^n_3SnH) (30 mol%) with AIBN (20 mol%) gave acrylamide **325** in 92% yield (Scheme 43).[172] A proposed mechanism starts from the addition of tributyltin radical **319** to alkyne



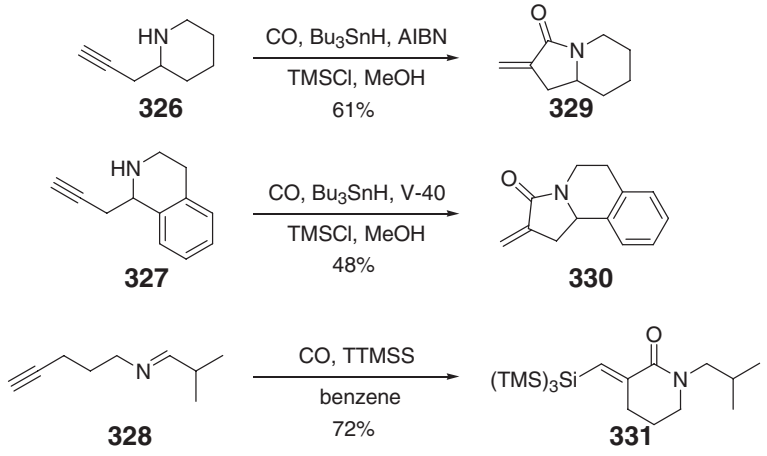
i, Bu^n_3SnH (30 mol%), AIBN (20 mol%), CO (85 atm), benzene (0.05 M), 90 °C, 4 h

Scheme 43 Reproduced from Uenoyama, Y.; Fukuyama, T.; Nobuta, O.; Matsubara, H.; Ryu, I. *Angew. Chem., Int. Ed.* **44**, 1075–1078, with permission from Wiley-VCH.

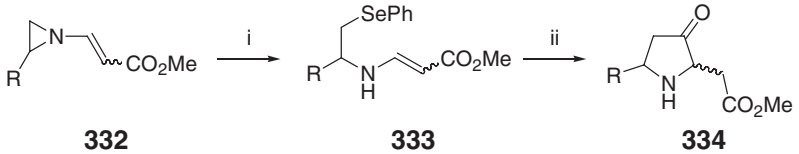
318 to generate vinyl radical **320**, which is carbonylated to form α-ketenyl radical **321**. Pyrrolidine adds to the ketene carbonyl moiety of radical **321** to form hydroxyl-π-allylic radical **323** via hydroxyl-σ-allylic radical **322**. Then, a 1,4-H shift occurs to form α-keto radical **324**, which undergoes β-elimination to give acrylamide **325** and regenerate tributyltin radical **319**.

As Scheme 44 exemplifies, the radical intramolecular aminocarbonylation of alkynes **326** and **327** and an azaenyne **328** afforded the corresponding α-methylene lactams (**329**, **330** and **331**, respectively) in moderate to good yields.[173,174]

Radical carbonylation has also been applied to the ring expansion of vinylepoxides and vinylaziridines to form tetrahydrofuranones and pyrrolidinones, respectively.[176,177] For example, the radical carbonylation of 3-(1-alkyl-2-phenylselenylethyl)aminoacrylates **333** initiated by $(TMS)_3SiH$ (1.7 equiv.) with AIBN (0.3 equiv.) at 80 °C and 80 atm of CO gave the corresponding pyrrolidin-3-ones **334** in fairly good to high yields (Scheme 45).[177] Phenylselenylethylaminoacrylates **333** were prepared in high yields through regioselective ring opening of aziridines **332** with benzeneselenolate, prepared *in situ* by reduction of diphenylselenide with $NaBH_4$.



Scheme 44



332 **333** **334**

R	*Yield* (%)	*E* : *Z*	*Yield* (%)	*cis* : *trans*
Bn	84	4 : 5	79	4 : 1
$PhOCH_2$	73	2 : 1	85	3 : 1
C_6H_{13}	85	1 : 4	65	3 : 1
Bu^t	83	1 : >25	71	12 : 1

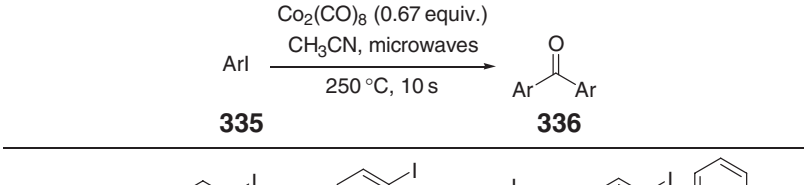
i, $NaBH_4$ (0.66 equiv.), Se_2Ph_2 (0.6 equiv.), EtOH, 7 h, RT; ii, AIBN (0.3 equiv.), $(TMS)_3SiH$ (1.7 equiv.), CO (80 atm), benzene, 80 °C, 12 h

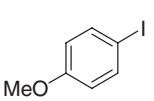
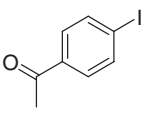
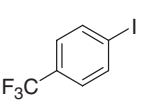
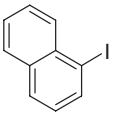
Scheme 45

11.15.6.7 Carbonylation Reactions with Microwave Irradiation

Carbonylation reactions with microwave irradiation have been investigated in connection with solid-state combinatorial chemistry.[90,94,95,178–183] Since reactions requiring gaseous reagents cannot use microwave irradiation, metal carbonyl complexes, such as $Mo(CO)_6$, $Cr(CO)_6$, $W(CO)_6$, and $Co_2(CO)_8$ have been employed as source of carbon monoxide.[94,178,184,185] Examples of aminocarbonylation performed with microwave irradiation are presented in Section 11.15.4.3 (*vide supra*).

Moreover, reaction time was reduced from hours to minutes or even seconds. Indeed, the carbonylation of aryl halides **335** was completed in 10 s to give symmetrical diaryl ketones **336** in excellent yields (Equation (31)).[179] The process optimization to reduce the amount of catalyst disclosed the fact that this carbonylation reaction followed a radical pathway, initiated by the homolytic cleavage of $Co_2(CO)_8$ into $\cdot Co(CO)_4$. It also appeared that the amount of the Co catalyst had a direct correlation with the internal temperature reached during the reaction.[179] These findings are critical for the development of extremely fast synthesis using carbonylations.



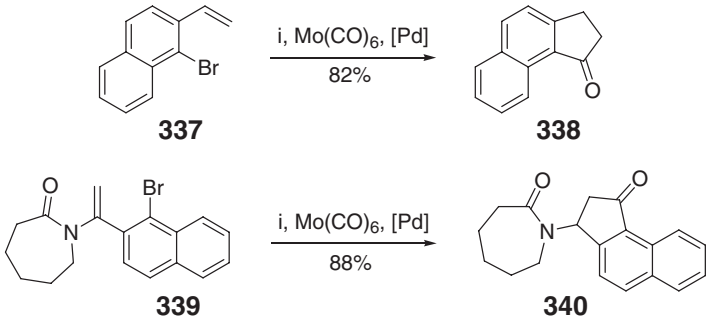
ArI					
Yield (%)	57	91	96	97	97

(31)

[a]Reprinted with permission from Enquist, P.-A.; Nilsson, P.; Larhed, M. *Org. Lett.* **2003**, *5*, 4875–4878. © 2003 American Chemical Society.

Microwave irradiation was also successfully used to synthesize 26 different acyl sulfonamides through carbonylation of sulfonamides with (hetero)aryl halides in only 15 min, using $Pd(OAc)_2$ as catalyst and $Mo(CO)_6$ as source of CO.[183]

The Pd-catalyzed carbonylation of *o*-vinylaryl bromides using $Mo(CO)_6$ as CO source with microwave irradiation gave indanone **338** and 3-acylaminoindanone **340**, which are key intermediates for the synthesis of inhibitors of human immunodeficiency virus type 1 (HIV-1) protease and Plasmepsin I and II (Scheme 46).[186] These polycyclic compounds were obtained in less than 30 min in high yields. The results clearly indicate the power and advantage of this protocol, especially for the combinatorial parallel synthesis of a library of compounds.



i, $Pd(OAc)_2$ (5 mol%), $(Bu^t)_3PHBF_4$ (10 mol%), $Mo(CO)_6$ (0.5 equiv.), $(Bu^n)_4NCl$ (1 equiv.), pyridine (2 equiv.), dioxane, 150–160 °C, microwave irradiation, 20–30 min

Scheme 46

11.15.7 Conclusion

In this chapter, the recent advances in amidocarbonylations, cyclohydrocarbonylations, aminocarbonylations, cascade carbonylative cyclizations, carbonylative ring-expansion reactions, thiocarbonylations, and related reactions are reviewed and the scope and mechanisms of these reactions are discussed. It is clear that these carbonylation reactions play important roles in synthetic organic chemistry as well as organometallic chemistry. Some of the reactions have already been used in industrial processes and many others have high potential to become commercial processes in the future. The use of microwave irradiation and substitutes of carbon monoxide has made carbonylation processes suitable for combinatorial chemistry and laboratory syntheses without using carbon monoxide gas. The use of non-conventional reaction media such as $scCO_2$ and ionic liquids makes product separation and catalyst recovery/reuse easier. Thus, these processes can be operated in an environmentally friendly manner. Judging from the innovative developments in various carbonylations in the last decade, it is easy to anticipate that newer and creative advances will be made in the next decade in carbonylation reactions and processes.

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11.16 Polymerization of Acetylenes

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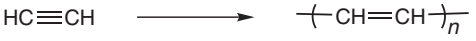
11.16.1 Introduction

Acetylene and its derivatives can be polymerized by chain growth in the presence of suitable transition metal catalysts to give high molecular weight (MW) polymers (Equations (1)–(4)). The monomers include acetylene, mono- and disubstituted acetylenes, and α,ω-diynes. The polymers possess carbon–carbon alternating double bonds along the main chain and exhibit unique properties (e.g., metallic conductivity) that are not expected with vinyl polymers.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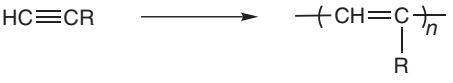
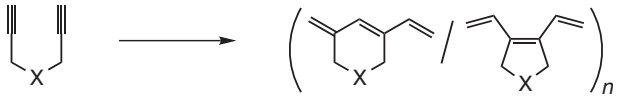

(2)


(3)



(4)

In 1958, Natta and co-workers polymerized acetylene for the first time by using a Ti-based catalyst. This polymerization proceeds by the insertion mechanism like the polymerization of olefins. Because of the lack of processability and stability, early studies on polyacetylenes were motivated by only theoretical and spectroscopic interests. Thereafter, the discovery of the metallic conductivity of doped polyacetylene in 1977 stimulated research into the chemistry of polyacetylene, and now polyacetylene is recognized as one of the most important conjugated polymers. Many publications are now available about the chemistry and physics of polyacetylene itself.[1–5]

Incorporation of various side groups onto polyacetylene has been attempted to improve its processability and to endow it with unique properties and functions. Early attempts led to the conclusion that only sterically unhindered monosubstituted acetylenes can be polymerized with the Ziegler-type catalysts. Traditional ionic and radical initiators also turned out to lack the ability to provide high MW polymers from substituted acetylenes. The first successful polymerization of substituted acetylene was achieved in 1974; it was found that group 6 transition metals are quite active for the polymerization of phenylacetylene to provide a polymer with MW over 10^4. After this finding, there has been much effort to develop highly active catalysts, to tune the polymer properties, and also to precisely control the polymer structure. These energetic studies have produced a wide variety of polymers from acetylene derivatives including mono- and disubstituted acetylenes, and α,ω-diynes (Table 1). The carbon–carbon alternating double bonds in the main chain of these polymers provide an opportunity to obtain unique properties such as conductivity, non-linear optical properties, magnetic properties, gas permeability, photo- and electroluminescent properties, and so on, which are not accessible from the corresponding vinyl polymers.

Typical transition metal catalysts used for the polymerization of acetylenes are shown in Table 2. It is clear that metals of various groups in the periodic table are useful. The kind of monomers polymerizable with a particular catalyst is rather restricted, and hence it is important to recognize the characteristics of each catalyst. Two kinds of reaction mechanisms participate depending on the polymerization catalysts (Scheme 1). One is the metathesis mechanism where the active species are metal carbenes, namely species having a metal–carbon double bond, and the other is the insertion mechanism in which the active species are alkenylmetals, namely species having a metal–sp^2 carbon single bond. These mechanisms can be distinguished from each other based on the catalysts used but are rather difficult to distinguish on the basis of resulting polymer structure.

Table 1 Examples of polymerizable acetylene and its derivatives

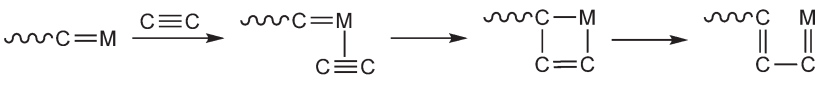
	Unsubstituted	*Monosubstituted*	*Disubstituted*	*α,ω-Diyne*
Hydrocarbon	HC≡CH	HC≡C-*t*-Bu HC≡C–	MeC≡C-*n*-C_5H_{11} MeC≡C– –C≡C–*t*-Bu	 Ph Ph
Heteroatom-containing acetylene		Me HC≡CCO$_2$– *i*-Pr HC≡CCH$_2$NHC-*s*-Bu* O Me$_3$Si HC≡C– F$_3$C HC≡C–	ClC≡C-*n*-C_6H_3 ClC≡C– MeC≡CSiMe$_3$ –C≡C–SiMe$_3$	 EtO$_2$C CO$_2$Et Si Ph Ph

Table 2 Catalysts for the polymerization of acetylenes and reaction mechanism[a]

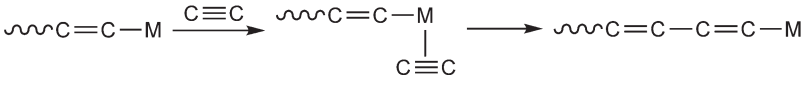
Group	4	5	6	8–10
Catalyst (monomer[a])	$Ti(O\text{-}n\text{-}Bu)_4$–$Et_3Al$ ($HC{\equiv}CH$)	$NbCl_5$, $TaCl_5$ ($RC{\equiv}CR^1$)	$MoCl_5$-n-Bu_4Sn, WCl_6–Ph_4Sn ($HC{\equiv}CR$, $RC{\equiv}CR^1$)	$Fe(acac)_3$–Et_3Al ($HC{\equiv}CR$)
		$TaCl_5$-n-Bu_4Sn ($PhC{\equiv}CC_6H_4$-p-X)	$M(CO)_6$–CCl_4–$h\nu$ (M = Mo, W) ($HC{\equiv}CR$, $ClC{\equiv}CR$)	$[(nbd)RhCl]_2$($HC{\equiv}CPh$, $HC{\equiv}CCO_2R$)
			$(RO)_2Mo(=NAr)=CH$-t-Bu ($(HC{\equiv}CCH_2)_2C(CO_2Et)_2$)	$(nbd)Rh^+BPh_4^-$ ($HC{\equiv}CCH_2NHCOR$)
Mechanism	Insertion	Metathesis	Metathesis	Insertion

[a]$HC{\equiv}CR$ and $RC{\equiv}CR^1$ denote mono- and disubstituted acetylenes, respectively.

Metal carbene (metathesis) mechanism



Metal alkenyl (insertion) mechanism



Scheme 1 Propagation mechanisms and propagating species (M: metal).

This chapter surveys the polymerization of substituted acetylenes focusing on the research during this decade. Monomers and polymers, polymerization catalysts, controlled polymerizations, and functional polyacetylenes are discussed. Readers are encouraged to access other reviews and monographs on the polymerization of substituted acetylenes,[2,6–15] and α,ω-diynes.[16,17]

11.16.2 Monomers and Polymers

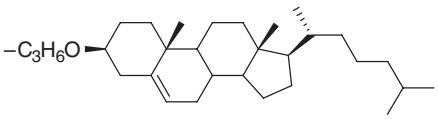
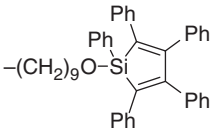
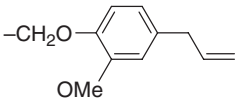
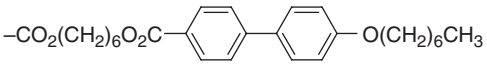
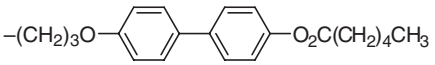
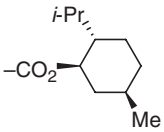
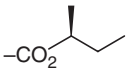
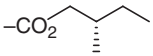
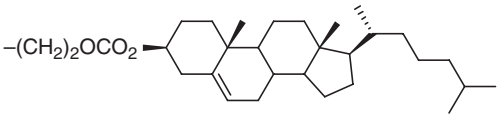
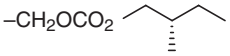
11.16.2.1 Polymerization of Acetylene

Polymerization of acetylene was first achieved by Natta and his co-workers using a Ti-based catalyst.[18] At present, polyacetylene membrane can be directly obtained by the polymerization using $Ti(O\text{-}n\text{-}Bu)_4$–$Et_3Al$. This is called the Shirakawa method, which features high catalyst concentrations.[19,20] Typical polymerization conditions are: $[Ti(O\text{-}n\text{-}Bu)_4] = 0.25\,M$, $[Et_3Al] = 1.0\,M$, in toluene, $-78\,^{\circ}C$, the pressure of acetylene 500–600 mmHg. A tremendous amount of research about the so-called synthetic metals has been carried out since the discovery of the metallic conductivity of doped polyacetylene in 1977.[21] Naarmann has reported a method of preparing a highly conducting polyacetylene, in which the catalyst solution is aged in silicone oil at a temperature as high as $120\,^{\circ}C$.[22] Akagi *et al.* have synthesized helical polymers in the field of chiral nematic liquid crystal systems which were prepared by adding chiral dopants to phenylcycloheyl-based binary nematic liquid crystals. They observed very clear twisted fibrils of polyacetylene by SEM.[23,24] The Ru carbene complex having pyridine instead of tricyclohexylphosphine in the Grubbs second generation complex was found to polymerize acetylene to give mostly *trans*-polyacetylene whose conductivity was $10^2\,S\,cm^{-1}$ after doping.[25]

11.16.2.2 Polymerization of Monosubstituted Acetylenes

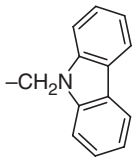
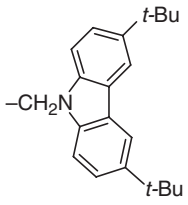
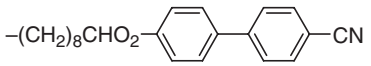
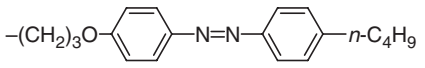
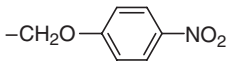
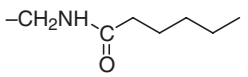
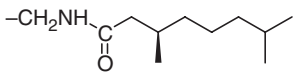
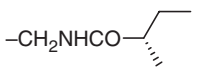
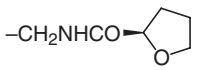
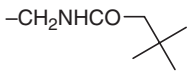
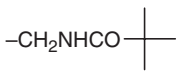
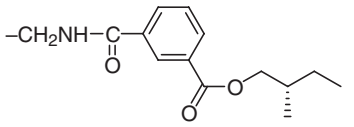
Typical examples of the polymerization of monosubstituted acetylenes are shown in Table 3. Transition metal catalysts that involve Mo, W, and Rh are particularly effective. Whereas Mo and W catalysts are sensitive to polar groups in the monomer, Rh catalysts are tolerant to such groups. Another point is that Mo and W catalysts are effective to various sterically crowded monomers, while Rh catalysts are useful to rather restricted kinds of monomers including

Table 3 Polymerization of monosubstituted acetylenes

Monomer	*Catalyst*	$M_n(\times 10^{-3})$	*References*
(a) *Monosubstituted aliphatic acetylenes [HC≡CR]*			
R = –1-Cyclohexenyl	$[(nbd)RhCl]_2$–Et_3N	24	26
	$\{Mo[OC(Me)(CF_3)_2]_2$ $=N(2,6\text{-}Me_2C_6H_3)$ $=CHCMe_2Ph\}$	40	27
	WCl_6–Ph_4Sn	34 (M_w)	28
	$[(nbd)RhCl]_2$	31	29
$-CO_2$-(−)-menthyl	$[(nbd)RhCl]_2$	250	30
	$MoOCl_4$-*n*-Bu_4Sn	18	30
$-CH_2O_2CCH_3$	$Pd(PPh)_3(C\equiv$ $CC_6H_4C\equiv CH)_2$	15 (M_w)	31
	$[(nbd)RhCl]_2$	354 (M_w)	32
	WCl_6	11	33
	$[(nbd)RhCl]_2$	110	34
	$[(nbd)RhCl]_2$	21	35
	$[(nbd)RhCl]_2$	80	35
	$(nbd)Rh^+BPh_4^-$	28	36
	$[(nbd)RhCl]_2$	19	37
$-CH_2OH$	$Pd(PPh)_3(C\equiv$ $CC_6H_4C\equiv CH)_2$	33 (M_w)	31
$-CH_2OH$	$Pd(PPh_3)_2(C\equiv CCH_2OH)_2$	53	38
$-CH_2OH$	$[(cod)RhCl]_2$	6	39
$-(CH_2)_{10}OH$	$(nbd)Rh^+BPh_4^-$	32	40
$-CH_2N(CH_3)_2$	$Pd(PPh_3)_2[C\equiv$ $CCH_2N(CH_3)_2]_2$	15	38
$-CH_2$-*N*-indolyl	$[(nbd)RhCl]_2$–Et_3N	71	41

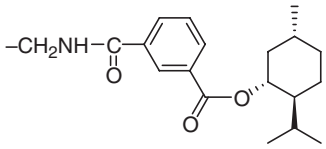
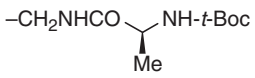
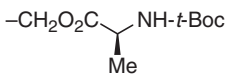
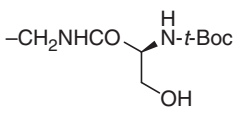
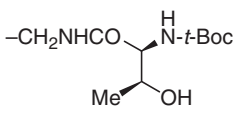
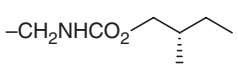
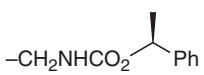
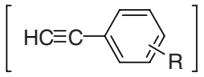
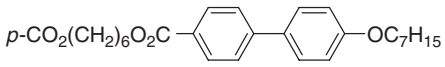
(*Continued*)

Table 3 (Continued)

Monomer	*Catalyst*	$M_n(\times 10^{-3})$	*References*
	$MoCl_5$	Insoluble	42
	$MoCl_5$–Ph_4Sn	148	43
	WCl_6–Ph_4Sn	14	44
–CN	$(Ph_3P)_2NiCl_2$	9	45
	$[(nbd)RhCl]_2$–Et_3N $Fe(acac)_3$–Et_3Al	96 121	46 46
	$MoCl_5$–$EtAlCl_2$	480	47
–CONH-*n*-Bu	$(PhCN)_2PdCl_2$	1	48
	$(nbd)Rh^+BPh_4^-$	18	49
	$(nbd)Rh^+BPh_4^-$	25	49
	$(nbd)Rh^+BPh_4^-$	19	50
	$(nbd)Rh^+BPh_4^-$	6	50
	$(nbd)Rh^+BPh_4^-$	4	51
	$(nbd)Rh^+BPh_4^-$	3	51
$–CH_2NHCOCMe_2Ph$	$(nbd)Rh^+BPh_4^-$	6	52
$–CH_2NHCOCPh_3$	$(nbd)Rh^+BPh_4^-$	3	52
	$(nbd)Rh^+BPh_4^-$	100	53

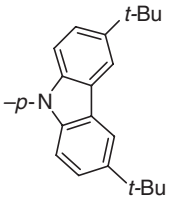
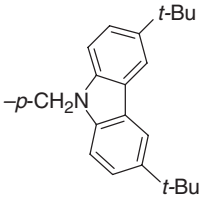
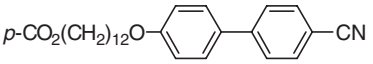
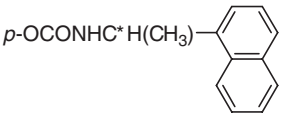
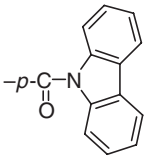
(*Continued*)

Table 3 (Continued)

Monomer	*Catalyst*	$M_n(\times 10^{-3})$	*References*
	$(nbd)Rh^+BPh_4^-$	98	53
	$(nbd)Rh^+BPh_4^-$	16	54
	$(nbd)Rh^+BPh_4^-$	224	54
	$(nbd)Rh^+BPh_4^-$	9	55
	$(nbd)Rh^+BPh_4^-$	10	55
	$[(nbd)RhCl]_2$	52	37
	$[(nbd)RhCl]_2$	30	56
$-CH_2NHSO_2Et$	$(nbd)Rh^+BPh_4^-$	6	57
$-CH_2NHSO_2CH_2Ph$	$(nbd)Rh^+BPh_4^-$	6	57
$-CH_2NHSO_2Ph$	$(nbd)Rh^+BPh_4^-$	3	57
$-CH_2CH(CO_2C_2H_5)PO(OC_2H_5)_2$	WCl_6–$EtAlCl_2$	9	58
$-CH_2{}^+PPh_3BPh_4^-$	$MoCl_5$–Ph_4Sn	12	59
(b) *Ring-substituted phenylacetylenes*			
			
R = –*p*-Adamantyl	$[(nbd)RhCl]_2$–Et_3N	>1000	60
–*o*,*o*-$(CH_3)_2$-*p*-*t*-Bu	$W(CO)_6$–CCl_4-$h\nu$	2600 (M_w)	61
–*p*-(-≡-Si-*i*-Pr_3)	$[(cod)Rh(\mu\text{-}OMe)]_2$	24	62,63
–*p*-Si*MePh-1-Np	$[(nbd)RhCl]_2$	2500 (M_w)	64
–*p*-Si*MePh-*t*-Bu	$[(nbd)RhCl]_2$	2100 (M_w)	65
–*p*-I	$WOCl_4$	19	66
–*p*-OCH_3	$[(nbd)RhCl]_2$	1160	67
–*p*-CO_2CH_3	$(nbd)Rh^+BPh_4^-$	218	68
	$[(nbd)RhCl]_2$–Et_3N	122	69
–*p*-CO_2H	Heat	n.d.	70
–*p*-$CH_2NHC^*H(CH_3)C^*H(OH)Ph$	$[(nbd)RhCl]_2$	48	71
–*p*-N(*n*-$C_4H_9)_2$	$[(nbd)RhCl]_2$–Et_3N	>1000	72
–*p*-N(*i*-$C_3H_7)_2$	$[(nbd)RhCl]_2$–Et_3N		73
–*p*-CH_2N(*i*-$C_3H_7)_2$	$[(nbd)RhCl]_2$	n.d.(M_w)	73
–*p*-*N*-Carbazolyl	WCl_6-*n*-Bu_4Sn	104	43

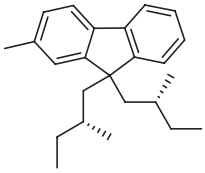
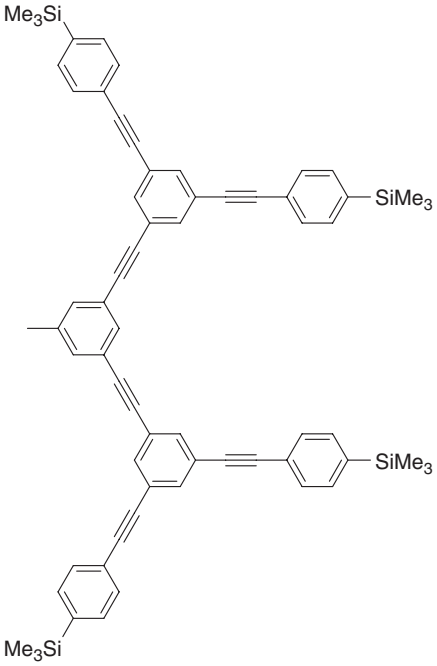
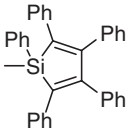
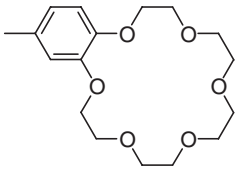
(*Continued*)

Table 3 (Continued)

Monomer	*Catalyst*	$M_n(\times 10^{-3})$	*References*
	$[(nbd)RhCl]_2$	212	43
	$[(nbd)RhCl]_2$	115	74
–*m*-CH=NPh	$[(nbd)RhCl]_2$–Et_3N	588	75
	$[(nbd)RhCl]_2$–Et_3N	158	76
–*m*-N=NPh	$[(nbd)RhCl]_2$–Et_3N	110	
–*p*-N=NPh	$[(cod)RhCl]_2$	20	
–*p*-N=NPh-*p*-Me	{Mo[OC(Me)$(CF_3)_2]_2$ =N(2,6-*i*-$Pr_2C_6H_3$) =CHCMe_2Ph}	9	
–*p*-NO_2	$[(cod)RhCl]_2$	16	
–*p*-NO_2	$[(nbd)RhCl]_2$	2	
–*p*-OCONHC*H(CH_3)Ph	$[(nbd)RhCl]_2$	320	
	$[(nbd)RhCl]_2$–Et_3N	51	
–*p*-CONHCH(*i*-C_4H_9)CO_2Me	$[(nbd)RhCl]_2$	1240 (M_w)	83
–*p*-CONHCH(*i*-C_3H_7)CO_2Me	$[(nbd)RhCl]_2$	370 (M_w)	84
	$[(nbd)RhCl]_2$	240	85
–*o*-Fc	{Mo[OC(Me)$(CF_3)_2]_2$ =N(2,6-$Me_2C_6H_3$) =CHCMe_2Ph}	16	86
–*p*-CH=CHFc	{Mo[OC(Me)$(CF_3)_2]_2$ =N(2,6-$Me_2C_6H_3$) =CHCMe_2Ph}	19	86
–*p*-N=NFc	{Mo[OC(Me)$(CF_3)_2]_2$ =N(2,6-$Me_2C_6H_3$) =CHCMe_2Ph}	11	86
–*p*-C≡CC_6H_4-*p*-C≡CFc	{Mo[OC(Me)$(CF_3)_2]_2$ =N(2,6-$Me_2C_6H_3$) =CHCMe_2Ph}	18	87
	$WOCl_4$–Me_4Sn		88

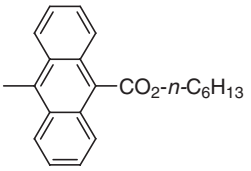
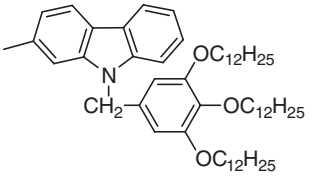
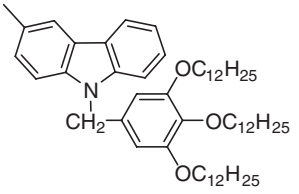
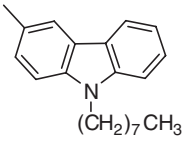
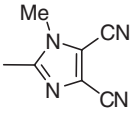
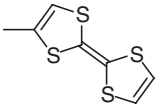
(*Continued*)

Table 3 (Continued)

Monomer	*Catalyst*	$M_n(\times 10^{-3})$	*References*
(c) *Other monosubsutituted arylacetylenes [HC≡CAr]*			
Ar = 1-Naphthyl	WCl_6–Ph_3Bi	46	89
1-Anthryl	WCl_6–Ph_4Sn	37	90
2-Anthryl	WCl_6–Ph_4Sn	9	90
9-Anthryl	WCl_6	Insoluble	89
2-Phenanthryl	WCl_6–Ph_3Bi	10	90
3-Phenanthryl	WCl_6–Ph_3Bi	24	90
1-Pyrenyl	WCl_6–Ph_3Bi	6	91
	$[(nbd)RhCl]_2$	100	92
	$[(nbd)RhCl]_2$–Et_3N	340	93
	$NbCl_5$–Ph_4Sn	69 (M_w)	28
	$[(nbd)RhCl]_2$–Et_3N	26	94

(*Continued*)

Table 3 (Continued)

Monomer	*Catalyst*	$M_n(\times 10^{-3})$	*References*
	WCl_6	171	9596
N-carbazolyl	WCl_6-*n*-Bu_4Sn	13	97
	$Rh(C{\equiv}CPh)(nbd)(PPh_3)_2$	1150	98
	$Rh(C{\equiv}CPh)(nbd)(PPh_3)_2$	800	98
	$[(nbd)RhCl]_2$	160	99
	$[(nbd)RhCl]_2$	3	101
	$[(nbd)RhCl]_2$–Et_3N	12	101
Ferrocenyl $[(\eta^6\text{-}C_5H_4)Fe(\eta^6\text{-}C_5H_5)]$	$Mo[OC(Me)(CF_3)_2]_2$ ═$N(2,6\text{-}Me_2C_6H_3)$ ═$CHCMe_2Ph$	16	102
Ruthenocenyl $[(\eta^6\text{-}C_5H_4)Ru(\eta^6\text{-}C_5H_5)]$	$Mo[OC(Me)(CF_3)_2]_2$ ═$N(2,6\text{-}Me_2C_6H_3)$ ═$CHCMe_2Ph$	16	102

phenylacetylenes, alkyl propiolates, and *N*-propargyl amides. In some cases, Fe and Pd complexes are also useful. It is noted that not only sterically unhindered monomers but also very crowded ones afford high MW polymers with W and Mo catalysts. Typical monosubstituted acetylene monomers such as aliphatic acetylenes, ring-substituted phenylacetylenes, and other arylacetylenes are discussed below.

(i) Aliphatic acetylenes. Aliphatic terminal acetylenes with *prim*- and *sec*-alkyl groups provide orange to yellow, high MW polymers, when polymerized with iron alkanoate-organoaluminum catalysts. On the other hand, *tert*-alkylacetylenes, which are sterically very crowded, can be polymerized by Mo and W catalysts, and the MW of the polymers reaches several hundred thousand.

Examples of the polymerizations of heteroatom-containing acetylenes have been increasing. The heteroatoms include Si, halogens, O, S, and N. Especially, Si and F endow the polymers with unique properties and functions, and

they are unlikely to deactivate polymerization catalysts. Hence, the synthesis of Si- and F-containing polyacetylenes has been examined particularly extensively. For instance, (trimethylsilyl)acetylene is polymerizable with W catalysts, but the product polymer is partly insoluble in any solvent. (Perfluoroalkyl)acetylenes yield white polymers soluble only in fluorine-containing solvents.

Recently, many monomers containing ether, ester, amide, carbamate, sulfamide groups have successfully been polymerized by using Rh catalysts, mostly $[(nbd)RhCl]_2$ and $(nbd)Rh^+BPh_4^-$. While Rh catalysts can polymerize monomers having an OH group, a COOH group is known to terminate the Rh-catalyzed polymerization. Late transition metals such as Ru, Rh, and Pd are not oxophilic and accordingly they will be useful as catalysts for the polymerization of highly polar monomers. If highly active Ru and Pd catalysts are developed, they will be very useful.

(ii) Phenylacetylene and its ring-substituted derivatives. The typical catalysts for the polymerization of phenylacetylene include W, Rh, and Fe catalysts. W catalysts produce an auburn polymer having *trans*-rich structure; WCl_6–Ph_4Sn is highly active, while $W(CO)_6$–CCl_4–$h\nu$ is useful to achieve high MW ($M_n \sim 1 \times 10^5$). The polymerization by Rh catalysts proceeds in alcohols and amines to form a yellow polymer. A feature of Rh catalysts is high tolerance to polar groups, and hence they are useful to various phenylacetylenes with functional groups. Another feature of Rh catalysts is that they give poly(phenylacetylene) whose MW reaches up to around one million. When $Fe(acac)_3$–Et_3Al is used, the poly(phenylacetylene) formed is insoluble in any solvent and has *cis*-cisoidal structure.

An interesting trend has been observed so far in the polymerization of *ortho*-substituted phenylacetylenes by W and Mo catalysts: phenylacetylene itself does not produce a very high MW polymer with W and Mo catalysts ($MW < 10^5$). On the other hand, phenylacetylenes having bulky CF_3 and Me_3Si groups at *ortho*-position provide, in high yields, polymers whose MW is as high as about one million. Thus, the steric effect of the *ortho*-substituents greatly affects the polymerizability and the polymer MW of phenylacetylenes, while the electronic effect hardly influences them. For a similar steric reason, (*p*-*t*-butyl-*o*,*o*-dimethylphenyl)acetylene, an *ortho*-dimethyl substituted phenylacetylene also polymerizes into high MW polymer with W and Mo catalysts.

Unlike W and Mo catalysts, Rh catalysts are not suited to *ortho*-substituted phenylacetylenes because Rh catalysts are rather sensitive to the steric effect. Instead, Rh catalysts are suitable to various phenylacetylenes having polar groups (e.g., ether, ester, amine, carbazole, imine, nitrile, azobenzene, nitro groups) at *para*-position, resulting in the formation of high MW poly(phenylacetylenes). Many such examples are found in Table 3.

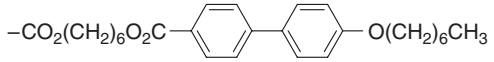
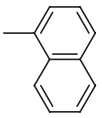
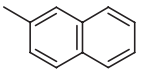
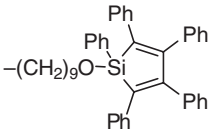
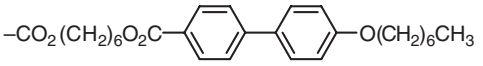
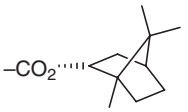
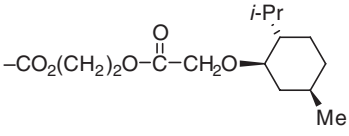
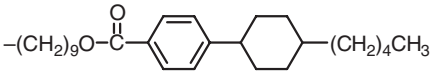
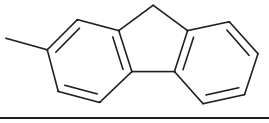
(iii) Other arylacetylenes. Various polymers have been prepared from monosubstituted acetylenes having condensed aromatic rings instead of phenyl group. Such condensed aromatic rings include naphthyl, anthryl phenanthryl, fluorenyl, pyrenyl, and so on. These monomers polymerize with W, Mo, and Rh catalysts, where the polymer yield usually decreases in the order of W, Mo, and Rh. The *cis*-content of the polymers increases in the order of $W < Mo < Rh$, and the polymer solubility decreases in this order. Both 1- and 2-naphthylacetylenes polymerize in high yields with W catalysts. 9-Anthrylacetylene polymerizes with W catalysts into a polymer insoluble in any solvents. However, if a long *n*-hexoxycarbonyl group is introduced at the 10-position, the formed polymer becomes soluble. This polymer has dark purple color. Sterically less hindered 1- and 2-anthrylacetylens give solvent-soluble polymers. These polymers having condensed aromatic rings are generally colored deeply (dark brown to dark purple), and show third-order non-linear optical properties.

The examples of polyacetylenes whose main chain is directly bonded to heteroaromatic rings (e.g., silole, carbazole, imidazole, tetrathiafulvalene, ferrocene) are increasing in number. Such polymers are usually obtained by one of catalysts (W, Mo, and Rh). The formed polymers are expected to display interesting (opto)electronic properties such as electrochromism, cyclic voltammetry, electroluminescence, and so on.

11.16.2.3 Polymerization of Disubstituted Acetylenes

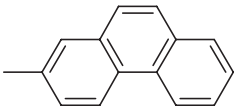
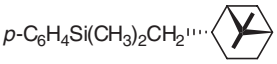
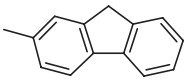
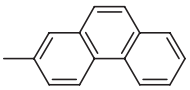
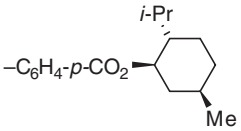
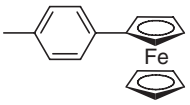
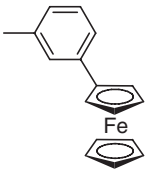
In general, disubstituted acetylenes are sterically more crowded than their monosubstituted counterparts and, consequently, their effective polymerization catalysts are restricted virtually to group 5 and 6 transition metal catalysts; Rh catalysts are not effective at all. Among disubstituted acetylenes, those with less steric hindrance polymerize with Mo and W catalysts and tend to give cyclotrimers with Nb and Ta catalysts. On the other hand, sterically crowded disubstituted acetylenes do not polymerize with Mo or W catalysts, but do polymerize with Nb and Ta catalysts. The polymers from disubstituted acetylenes having two identical groups or two groups of similar sizes are generally insoluble in any solvent. Most polymers from disubstituted acetylenes are colorless, though some aromatic polymers are colored yellow. Table 4 lists typical examples of the polymerization of disubstituted acetylenes.

Table 4 Polymerization of disubstituted acetylenes

Monomer		*Catalyst*	$M_w(\times 10^{-3})$	*References*
(a) *Aliphatic acetylenes* $[R^1C{\equiv}CR^2]$				
$R^1 = CH_3$	$R^2 = -Si(CH_3)_2CH_3$ 	$TaCl_5$–Ph_3Bi	80 (M_n)	103
CH_3	$-Ge(CH_3)_3$	$TaCl_5$	1400	104
CH_3		$MoCl_5$–Ph_4Sn	11	32
–SPh	$-n-C_{12}H_{25}$	$MoCl_5$–Ph_4Sn	25	105
(b) *Monoarylacetylenes* $[R^1C{\equiv}CR^2]$				
$R^1 = Me$	$R^2 =$ 	$NbCl_5$–Et_3SiH	350	106
Me	$-C_6H_4$-*p*-adamantyl	$TaCl_5$-*n*-Bu_4Sn	1000	107
Cl	$-C_6H_4$-*p*-adamantyl	$MoCl_5$-*n*-Bu_4Sn	110 (M_n)	107
Cl		$MoCl_5$–Et_3SiH	270	108
Ph		WCl_6–Ph_4Sn	33	28
Ph		$MoCl_5$–Ph_4Sn	239	32
Ph		WCl_6–Ph_4Sn	13	109
Ph		$MoCl_5$–Ph_4Sn	61	110
Ph		WCl_6–Ph_4Sn	62 (M_n)	111
-S-*n*-Bu	Ph	WCl_6–Ph_3SiH	10	105
(c) *Diarylacetylenes* $[R^1C{\equiv}CR^2]$				
$R^1 = Ph$	$R^2 = Ph$	Desilylation	Insoluble	112
Ph	$-C_6H_4$-*p*-adamantyl	$TaCl_5$-*n*-Bu_4Sn	2200	107
2-Np	Ph	Desilylation	Insoluble	113
Ph		Desilylation	Insoluble	114

(*Continued*)

Table 4 (Continued)

Monomer		*Catalyst*	$M_w(\times 10^{-3})$	*References*
Ph		Desilylation	Insoluble	114
Ph	$-C_6H_4$-*p*-$SiMe_3$	$TaCl_5$-*n*-Bu_4Sn	1500	112
Ph	$-C_6H_4$-*p*-$SiPh_3$	$TaCl_5$-*n*-Bu_4Sn	1900	115
Ph		$TaCl_5$-*n*-Bu_4Sn	>100	116
Ph	$-C_6H_4$-*m*-$Ge(CH_3)_3$	$TaCl_5$-9-BBN	1000	117
2-Np	$-C_6H_4$-*p*-$SiMe_3$	$TaCl_5$-*n*-Bu_4Sn	3400 340	113
$-C_6H_4$-*p*-$SiMe_3$		$TaCl_5$-*n*-Bu_4Sn		114
$-C_6H_4$-*p*-$SiMe_3$		$TaCl_5$-*n*-Bu_4Sn	70	114
Ph	$-C_6H_4$-*p*-$OSiMe_2$-*t*-Bu	$TaCl_5$-*n*-Bu_4Sn	4000	118
Ph		WCl_6–Ph_4Sn	30	109
Ph	$-C_6H_4$-*p*-OH	Desilylation	Insoluble	118
Ph	$-C_6H_4$-*p*-*N*-Carbazolyl	$TaCl_5$-*n*-Bu_4Sn	190	119
Ph		$TaCl_5$-*n*-Bu_4Sn	Insoluble	121
Ph		$TaCl_5$-*n*-Bu_4Sn	530	121

(i) Aliphatic and monoaromatic acetylenes. 2-Alkynes (e.g., 2-octyne), which are sterically not very crowded, polymerize with Mo catalysts to give polymers with MW over one million. For these monomers, W and Nb catalysts are less active, and Ta catalysts yield only cyclotrimers. Symmetrical dialkylacetylenes (e.g., 4-octyne) are slightly more crowded, and consequently Nb, Ta, and W catalysts exhibit high activity, while Mo catalysts are not active. Since 1-phenyl-1-alkynes (e.g., 1-phenyl-1-propyne) involve even larger steric effects, Nb and Ta catalysts produce polymers having MW of $1 \times 10^5 - 1 \times 10^6$. In contrast, W catalysts yield only oligomers of MW lower than 1×10^4, and Mo catalysts are inactive.

Regarding heteroatom-containing acetylenes, 1-trimethylsilyl-1-propyne (TMSP), sterically highly crowded Si-containing acetylene polymerizes with Nb and Ta catalysts, but does not with Mo or W catalysts. The MW of the polymer obtained with $TaCl_5$–Ph_3Bi reaches four million, which is among the highest for all the substituted polyacetylenes. 1-(Trimethylgermyl)-1-propyne polymerizes in a similar way to TMSP.

Mo catalysts are uniquely effective in the polymerization of S-containing disubstituted acetylenes. Though there is a possibility that S and O in the monomer deactivate group 5 and 6 transition metal catalysts, the basicity of S is weakened by the conjugation with the triple bond, resulting in the lower coordinating ability to the propagating

species. Cl-containing monomers afford high MW polymers. For instance, the polymerization of 1-chloro-2-phenylacetylene and 1-chloro-2-β-naphthylacetylene is catalyzed by $MoCl_5$-*n*-Bu_4Sn to give polymers whose MW exceeds 10^5. It appears that the electron-withdrawing chlorine atom plays some role in the inertness of these monomers to Nb, Ta, and W catalysts.

(ii) Diphenylacetylenes and analogs. Diphenylacetylene (DPA) itself forms a polymer in the presence of $TaCl_5$-*n*-Bu_4Sn. The polymer possesses a very high thermal stability, but is insoluble in any solvent. Regarding polymer solubility, there is a tendency that polyacetylenes having two identical alkyl groups in the repeat unit are insoluble in any solvent, whereas polyacetylenes having methyl and a long alkyl group are soluble in various solvents. By analogy, one can hypothesize that *para*- or *meta*-substituted DPAs provide soluble polymers.

In fact, soluble, high MW polymers have been obtained from many DPAs with various substituents. For instance, 1-phenyl-2-[(*p*-trimethylsilyl)phenyl]acetylene polymerizes with $TaCl_5$co-catalyst in high yield. The polymer thus obtained is totally soluble in toluene and $CHCl_3$, and its MW is as high as about two million. In contrast, $TaCl_5$ alone and $NbCl_5$ co-catalyst are ineffective to this monomer unlike TMSP. The DPAs with *m*-Me_3Si, *m*-Me_3Ge, *p*-*t*-Bu, and *p*-*n*-Bu groups polymerize similarly, leading to totally soluble, high MW polymers. Polymers which have a *p*-(trimethylsilyl)phenyl and one of β-naphthyl, 2-fluorenyl, and 2-phenanthryl groups in place of one phenyl group have also been prepared; they are also solvent-soluble. Membranes of the trimethylsilyl-containing poly(DPA) and its analogs undergo desilylation reaction to give poly(diarylacetylene) membranes. They are interesting polymers as separation membrane materials because of their high thermal stability and insolubility.

Since only Ta and Nb catalysts, which are not tolerant to polar groups, are available for the polymerization of disubstituted acetylenes, it is generally difficult to synthesize disubstituted acetylene polymers having such a highly polar substituent as a hydroxy group. Recently, synthesis of poly[1-phenyl-2-(*p*-hydroxyphenyl)acetylene] has been achieved by the polymerization of 1-phenyl-2-(*p*-siloxyphenyl)acetylene and the subsequent acid-catalyzed deprotection reaction.

11.16.3 Polymerization Catalysts

As shown above, a number of transition metal catalysts for polymerization of acetylenic compounds have been reported, especially for substituted acetylenes. Here, typical catalysts are described first; the other catalysts not mentioned in detail, but summarized in Table 8, are shown after the typical ones.

11.16.3.1 Mo and W Catalysts

Group 6 transition metal derivatives composed of Mo and W have been widely used as catalysts for the polymerization of substituted acetylene monomers.[2,7,10,12–15] These catalysts can be divided into the following three categories: (i) metal halide-based catalysts, (ii) metal carbonyl-based catalysts, and (iii) metal carbene catalysts.

11.16.3.1.1 Metal halide-based catalysts

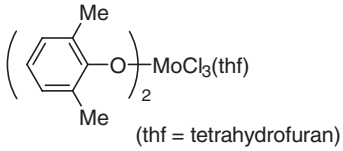
Metal halides, $MoCl_5$ and WCl_6, are one of the most convenient catalysts in group 6 transition metal catalysts, which can give high MW polymers from various monosubstituted acetylenes, in particular, monomers bearing bulky substituents (Table 5). When less bulky monomers such as 1-alkyne and phenylacetylene are applied, $MoCl_5$ and WCl_6 give the polymer in relatively low yield with unsatisfactory MW ($M_n < 1 \times 10^5$) due to unavoidable cyclotrimerization. The monomers sterically crowded on its carbon–carbon triple bond like *tert*-butylacetylene and *ortho*-substituted phenylacetylenes selectively polymerize with $MoCl_5$ and WCl_6 to give high MW polymers. The addition of appropriate organometallic co-catalysts such as *n*-Bu_4Sn, Ph_4Sn, Et_3SiH, Ph_3Sb, and Ph_3Bi into the catalytic systems enhances catalytic activity and allows the fast polymerization even in the case of sterically less bulky monomers such as 2-octyne, 1-chloro-1-octyne, and disubstituted acetylenes.

WCl_4 catalyzes the polymerization of *tert*-butylacetylene and phenylacetylene to give high MW polymers with M_w over 1×10^5.[121] In the presence of oxygen-containing compounds such as methyl acetate, acetylacetone, acetophenone, and 1,4-dioxane, the catalyst activity increases significantly, and thus allows these monomers to give the polymers under moderate conditions in higher yields.

Table 5 Examples of group 5 and 6 metal halide catalysts and organometallic co-catalysts

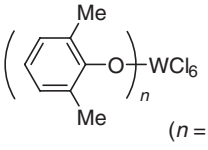
Metal chloride

$MoCl_5$ $MoOCl_4$ $CpMoCl_4$ Cp_2MoCl_2



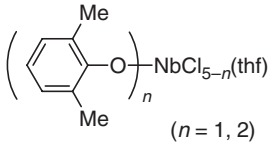
(thf = tetrahydrofuran)

WCl_6 WCl_4 $WOCl_4$ $WOCl_3(OAr)$



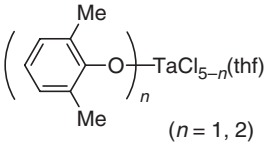
(n = 1–4)

$NbCl_5$



(n = 1, 2)

$TaCl_5$



(n = 1, 2)

Organometallic co-catalysts

n-Bu_4Sn, *n*-Bu_3SnCl, Ph_4Sn Et_3Al, Et_2AlCl, $EtAlCl_2$ Et_3SiH, Ph_3SiH *n*-BuLi, Et_2Zn, EtMgBr Ph_3Sb, Ph_3Bi

$WOCl_4$ is combined with Ph_4Sn (ratio $WOCl_4 : Ph_4Sn = 1 : 2$) in 1,4-dioxane/benzene to afford poly(phenylacetylene) efficiently, whose M_w reaches 1.1×10^6 ([η] 1.23 dL g^{-1}) and whose *cis*-content is 73%.[122] High polymer yields can be achieved even in the case of a high monomer/catalyst ratio, 1260. The viscosity index, a, of poly(phenylacetylene) formed by this catalyst was determined to be 0.61, indicating a sufficiently flexible chain.

Bulky aryloxy groups replace the chlorine ligand(s) of WCl_6 to improve the application range of acetylenic monomers. The catalyst systems, $WCl_n(dmp)_{6-n}$/alkylating reagents (dmp = 2,6-dimethylphenoxo, $n = 1 - 4$), show high activity in the polymerization of *tert*-butylacetylene leading to very high MW ($M_n > 2 \times 10^6$) and narrow molecular weight distribution (MWD) ($M_w/M_n \cong 1.2$).[123] Increasing the number of aryloxo ligands on hexavalent W species, even less bulky 1-alkynes such as 1-butyne, gave high MW polymer with $M_n = 9.4 \times 10^4$ and $M_w/M_n = 3.5$. $WCl_5(OAr)$ and $WOCl_3(OAr)$, where Ar is a phenyl ligand with *o-tert*-butyl or *o*-chloro substituents, and have proved to be single-component catalysts for the polymerization of phenylacetylene at room temperature; the M_n reaches about 1×10^5.[124]

Metallocene and half-metallocene complexes also work as catalysts for polymerization of substituted acetylenes; for example, a metallocene catalyst, Cp_2MoCl_2 (Cp: cyclopentadienyl), in conjunction with $EtAlCl_2$ (1 : 3 mole ratio) polymerizes phenylacetylene into a polymer having M_n ca. 4×10^3.[125] A half-metallocene-based ternary catalyst system, $CpMoCl_4$–EtMgBr–EtOH (1 : 2 : 2), polymerizes *o*-CF_3-phenylacetylene in a living fashion to give a polymer whose M_w/M_n is 1.06; a feature of $CpMoCl_4$ compared to $MoOCl_4$ is high stability against air and moisture.[126]

11.16.3.1.2 Metal carbonyl-based catalysts

Mo and W hexacarbonyls, $Mo(CO)_6$ and $W(CO)_6$, alone do not induce polymerization of acetylenic compounds. However, UV irradiation toward these catalysts in the presence of halogenated compounds can form active species for polymerization of various substituted acetylenes. Carbon tetrachloride, CCl_4, when used as the solvent for the polymerization, plays a very important role for the formation of active species, and thus cannot be replaced by toluene that is often used for metal chloride-based catalysts.[2,13–15] Although these metal carbonyl-type catalysts are less active compared to the metal halide-based counterparts, they can provide high MW polymers. It is a great advantage that the metal carbonyl catalysts are very stable under air and thus handling is much easier.

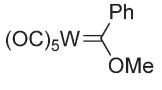
In the metal carbonyl catalysts, the use of a catalytic amount of Ph_2CCl_2 enables the omission of CCl_4. For example, the polymerization of phenylacetylene with $W(CO)_6$ in the presence of Ph_2CCl_2 in toluene upon photoirradiation proceeds homogeneously to give a polymer with M_n of ca. 2×10^4.[127,128] High MW polymers ($M_w > 10^5$) are attainable from sterically bulky aromatic and aliphatic acetylenes. It is also effective to use a catalytic amount of Lewis acids instead of CCl_4 in the $M(CO)_6$-based catalysts (M = W, Mo).[129]

An alternative metal carbonyl catalyst, (mes)$Mo(CO)_3$ (mes = mesitylene), polymerizes substituted acetylenes in CCl_4 without photoirradiation.[130] It is argued that ligating mesitylene is readily released by heating, and that the same active species as in photoirradiation system would be formed. The acetonitrile complexes $M(CO)_3(CH_3CN)_3$ (M = W, Mo) polymerize various mono- and disubstituted acetylenes at room temperature.[131,132] The arene and diene complexes, (mes)$W(CO)_3$ and (nbd)$Mo(CO)_3$ (nbd = 2,5-norbornadiene), are tolerant to polar groups such as ester, ether, and nitrile in monomers. The halogenated complexes, $MI_2(CO)_3(CH_3CN)_2$ (M = Mo, W), are able to catalyze polymerization of phenylacetylene in toluene (see Table 8). Another type of metal carbonyl catalysts, $MCl_2(CO)_3(AsPh_3)$ (M = Mo, W), that induces the ring-opening polymerization of norbornene and its derivatives, has been shown to polymerize *tert*-butylacetylene and *ortho*-substituted phenylacetylenes without photoirradiation or the use of CCl_4.[133] The reaction of *tert*-butylacetylene in the presence of seven-coordinate W(II) and Mo(II) compounds [$MCl(M'Cl_3)(CO)_3(NCR)_2$] (M = Mo, W; M′ = Sn, Ge; R=Me, Et) leads to the formation of high MW polymer ($M_n > 10^5$).[134,199,200,220]

11.16.3.1.3 Metal carbene catalysts

Well-defined carbene catalysts show excellent activity for polymerization, and are isolable and thus suggest that the polymerization mechanism is of the metathesis type. The first example of isolated single-component carbene catalysts is Fischer **1** and Casey carbenes **2**, which polymerize phenylacetylene, *tert*-butylacetylene, and cyclooctyne in low yields.[135] The bulk polymerization of phenylacetylene with **1** gives the polymer with M_w 17,000 in 49% yield. In the case of *tert*-butylacetylene, **1** produced the corresponding polymer with high MW, M_n = 260,000, in 28% yield. Photoirradiation and/or addition of Lewis acids promotes the generation of active species. Casey carbene **2** is a less stable catalyst and thus more active compared to Fischer carbene. Rudler carbene **3** readily releases the intramolecularly coordinated double bond upon the approach of an acetylenic monomer, and is more active than the Fischer and Casey carbenes. Polymerization of 1-methoxy-1-ethynylcyclohexane and co-polymerization of norbornene with *tert*-butylacetylene catalyzed by **3** have been reported.[136,136a]

Mo and W alkylidene complexes **4**, the so-called Schrock carbenes, have explosively evolved the polymerization chemistry of substituted acetylenes. Although the preparation of these catalysts is relatively difficult because of their low stability, in other words, high reactivity, they elegantly act as living polymerization catalysts for substituted acetylenes such as *ortho*-substituted phenylacetylenes[137,138] and α,ω-diynes.[139–141] The details of the living polymerization are described below.



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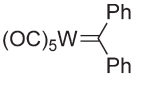

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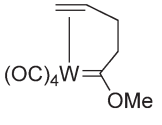

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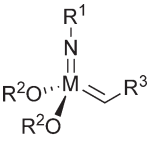

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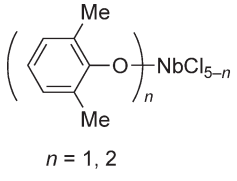
11.16.3.2 Nb and Ta Catalysts

Nb and Ta catalysts are very effective for the polymerization of the acetylenic compounds bearing bulky substituents. In case of sterically small substituted acetylenes, the side-reactions such as cyclo- and linear oligomerization are unavoidable. For example, cyclotrimerization of linear 1-alkynes and phenylacetylene readily occurs in the presence of $NbCl_5$ and $TaCl_5$. Bulky substituents can evade the cyclooligomerization to give the polymer successfully. Crowded disubstituted acetylenes such as internal octynes, 1-phenyl-1-propyne, TMSP, and DPAs are suitable for the polymerization by group 5 catalysts.[2,12,13] The simplest and most convenient catalysts are $TaCl_5$ and $NbCl_5$ in this class (Table 5), which can polymerize TMSP quantitatively without any co-additives in toluene at 80 °C to give a

high MW polymer ($M_w = 10^5 - 10^6$). The formed polymer is soluble in many common solvents such as toluene and chloroform.[10] A 1 : 1 mixture of $TaCl_5$ and Ph_3Bi works as a more active catalyst toward TMSP to produce a polymer whose M_w reaches 4×10^6, which is the highest MW among those of the substituted polyacetylenes ever known. The polymerization of TMSP by $NbCl_5$ in cyclohexane affords a polymer with narrow MW distribution ($M_w/M_n \sim 1.2$) irrespective of conversion. The M_n increases in direct proportion to conversion, indicating the presence of a long-lived propagating species. Poly(TMSP) exhibits extremely high gas permeability and hence its gas permeation behavior has been intensively studied (see Section 11.16.4.3).

DPAs are unable to polymerize with $NbCl_5$ and $TaCl_5$ alone. However, 1 : 1 mixtures of $TaCl_5$ and suitable co-catalysts such as *n*-Bu_4Sn, Ph_4Sn, and Et_3SiH afford poly(DPA)s in good to high yield. Poly(DPA)s are thermally very stable (up to ca. 500 °C on thermogravimetric analysis (TGA)). Although simple poly(DPA) is insoluble in any solvents, totally soluble polymers can be obtained with $TaCl_5$-*n*-Bu_4Sn catalyst when the substituents such as *p*-Me_3Si, *p*-*t*-Bu, *p*-*n*-Bu, *p*-PhO, and *p*-*N*-carbazolyl groups are introduced into aromatic rings on the side-chain.[142,143] These polymers have high MWs, approximately 1×10^6.

In addition to group 6 transition metal catalysts, bulky aryloxo ligands can replace the chlorine ligand(s) of $NbCl_5$ to form $Nb(dmp)_nCl_{n-5}$(solvent) (**5**: $n = 1$–2), which exert unique ability with co-catalysts such as EtMgBr or Et_3Al to polymerize terminal acetylenes such as *tert*-butylacetylene and phenylacetylene.[123] Such an exceptional ability of the co-catalyst system **5** originates from the presence of bulky aryloxo groups that have the same effect as bulkiness of the monomer. Ta carbene **6** induces living polymerization of 2-butyne (see Section 11.16.4.3).[144]



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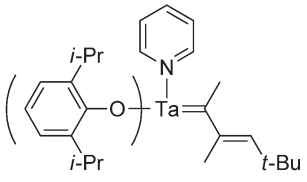
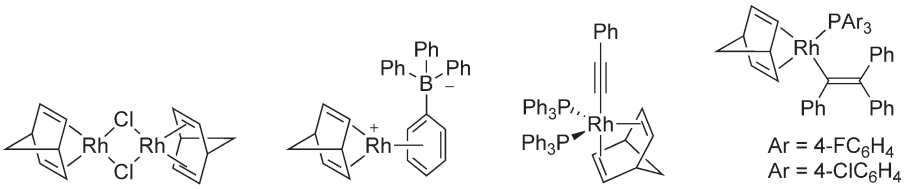


6

11.16.3.3 Rh Catalysts

Rh complexes are examples of the most effective catalysts for the polymerization of monosubstituted acetylenes, whose mechanism is proposed as insertion type. Since Rh catalysts and their active species for polymerization have tolerance toward polar functional groups, they can widely be applied to the polymerization of both non-polar and polar monomers such as phenylacetylenes, propiolic acid esters, *N*-propargyl amides, and other acetylenic compounds involving amino, hydroxy, azo, radical groups (see Table 3). It should be noted that, in the case of phenylacetylene as monomer, Rh catalysts generally achieve quantitative yield of the polymer and almost perfect stereoregularity of the polymer main chain (*cis*-transoidal). Some of Rh catalysts can achieve living polymerization of certain acetylenic monomers. The only one defect of Rh catalysts is that they are usually inapplicable to the polymerization of disubstituted acetylenes. Only one exception has been reported which is described below.

Chloride-bridging dinuclear Rh complexes, $[(nbd)RhCl]_2$ **7**, $[(cod)RhCl]_2$ (cod = 1,5-cyclooctadiene),[11] and zwitter ionic Rh complexes, $(nbd)Rh^+BPh_4^-$ **8**,[68] have been frequently employed for the polymerization of phenylacetylenes. Catalyst **7** is usually more active than $[(cod)RhCl]_2$ because of the strongly coordinating nbd ligand which stabilizes the active species. Catalyst **7** is very stable under air and moisture, which facilitates the experimental procedure. The most widely applied catalyst is a binary catalyst, **7**–Et_3N,[11,145,146] which gives excellent yields of stereoregular poly(phenylacetylene) with high MW ($M_n > 10^5$). The role of Et_3N is suggested to expedite the formation of Rh single site species, $[(nbd)RhCl(Et_3N)]$, via the cleavage of bridging Rh–Cl bonds and the coordination of triethylamine, that could easily shift to the true active species.[145] Combinations of **7** with suitable organometallics such as *n*-BuLi and Et_3Al greatly accelerate the polymerization of phenylacetylene.[147] Living polymerization of phenylacetylenes is feasible by using a well-characterized Rh complex, (nbd) $(PhC{\equiv}C{-})Rh(PPh_3)_2$ **9**, in conjunction with 4-(dimethylamino)pyridine.[148–151] An extension of this system is a multicomponent catalyst, $[(nbd)RhOMe]_2$–PPh_3-4-(*N*,*N*-dimethylamino)pyridine.[152] A ternary Rh catalyst system, $[(nbd)RhCl]_2$–$LiCPh{=}CPh_2$–PPh_3,[153,154] induces the living polymerization of phenylacetylenes. In the latter case, the initiating species is a vinylrhodium **10**, which was isolated and well characterized by X-ray analysis.[155] The details for the living polymerization are described in Section 11.16.4.1.

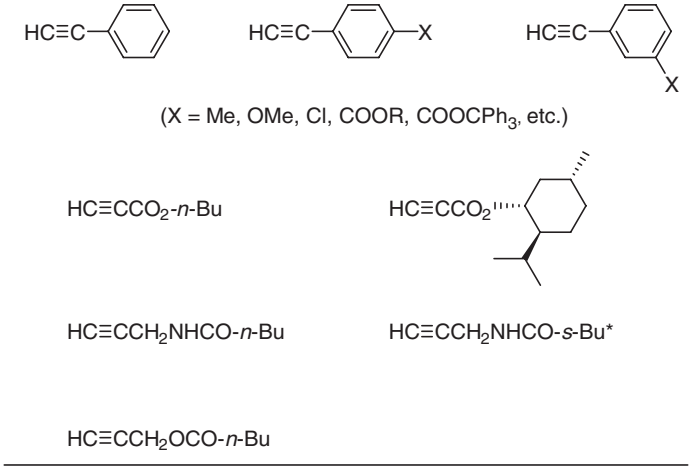


7 **8** **9** **10**

The Rh-catalyzed polymerization proceeds in various solvents such as benzene, tetrahydrofuran (THF), ethanol, and triethylamine.[11,144] Among the solvents, ethanol and triethylamine are favorable for phenylacetylenes from the viewpoint of both polymerization rate and polymer MW. Polymerization of phenylacetylenes is feasible even in aqueous media by using water-soluble catalysts. For example, $(cod)Rh^{+}(mid)_2PF_6^{-}$ (mid = *N*-methylimidazole) provides *cis*-transoidal poly(phenylacetylene) (*cis* content 98%) in high yield (98%).[156] $(cod)Rh(O_3SC_6H_4\text{-}p\text{-}CH_3)(H_2O)$ and $(nbd)Rh(O_3SC_6H_4\text{-}p\text{-}CH_3)(H_2O)$ also work as water-soluble catalysts. Polymerization of phenylacetylene in compressed (liquid or supercritical) CO_2 has been studied using a rhodium catalyst, [(nbd)Rh(acac)].[157] Higher polymerization rate is obtained in CO_2 than in conventional organic solvents such as THF and hexane. Recently, ionic liquids have been examined as media for Rh-catalyzed polymerization of phenylacetylene.[158]

In an initial period of the researches on Rh-catalyzed polymerization of substituted acetylenes, a range of monomers was limited to phenylacetylene and its *para*- and *meta*-substitute derivatives.[11,159] However, various monomers have recently been examined (Tables 3 and 6). For instance, alkyl propiolates polymerize in moderate yields with Rh catalysts.[160] Relatively high yields of poly[(−)-menthyl propiolate] with high MWs are accessible when the polymerization is conducted in alcohols or acetonitrile at high monomer and catalyst concentrations.[30] A characteristic feature of the poly(alkyl propiolates) is their almost perfect *cis*-stereoregularity and eventually they exist in a well-ordered helical conformation (see below for details for the synthesis of helical polyacetylenes).[34,35] Although carboxylic acids are known to serve as terminators, sodium *p*-ethynylphenylcarboxylate and propiolate polymerize in the presence of various cationic Rh complexes.[161,162] It was found that *N*-propargyl alkylamides polymerize with Rh complex **8** to produce helical polymers. The helicity of these polymers is induced not by steric effect but by hydrogen bonding (see below for details).[49,163] In general, Rh catalysts are not very effective for sterically crowded monosubstituted acetylenes such as *tert*-butylacetylene and *ortho*-substituted phenylacetylenes. Although disubstituted acetylenes cannot generally be polymerized with Rh catalysts, only one exception has been found as for cyclooctyne as a monomer, whose very large ring strain (~38 kJ mol^{-1}) enables very rapid polymerization with $[(nbd)RhCl]_2$, giving an insoluble polymer in good yield.[164]

Table 6 Examples of the monomers polymerizable with Rh catalysts



11.16.3.4 Other Group 8–10 Metal Catalysts

Compared to early transition metals, the number of group 8–10 transition metal catalysts for the polymerization of substituted acetylenes has been relatively small except for Rh. However, unique aspects of these late transition metal catalysts have been revealed which cannot be seen in early transition metals and conventional Rh catalysts.

Among group 8 transition metal catalysts, iron-based Ziegler-type catalysts such as $Fe(acac)_3$–$Et_3Al(1:3)$ (acac = acetylacetonate) have been well known from the early stage of the catalyst investigation, which are readily prepared *in situ* to polymerize sterically unhindered terminal acetylenes such as *n*-alkyl-, *sec*-alkyl-, and phenylacetylenes.[10,12] The formed poly(phenylacetylene) has red color and *cis*-cisoidal structure, and is insoluble and crystalline.

Recently, well-defined Ru carbene catalysts, which are well known as very active catalysts for olefin metathesis reactions, have been elucidated to polymerize unsubstituted and substituted acetylenes such as α,ω-diynes, propiolic acid esters, and DPAs. Not only Grubbs first and second generation catalysts, but also a 3-bromopyridine Ru carbene complex, $[(3\text{-bromopyridine})_2RuCl_2(IMesH_2)=CHPh]$ ($IMesH_2$ = 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene), polymerizes unsubstituted acetylene.[25] By modifying Grubbs–Hoveyda Ru carbene catalyst, $[RuCl_2(IMesH_2)(=CH\text{-}2\text{-}(2\text{-PrO})\text{-}C_6H_4)]$, in electronic nature and steric placement of the ligand, living cyclopolymerization of an α,ω-diyne was achieved.[165,166] It is noteworthy that Grubbs–Hoveyda Ru carbene can also polymerize monosubstituted and DPAs, even in the presence of polar functional groups such as ester, amide, and carbonate in a DPA monomer.[167] It has been difficult to achieve the polymerization by using early transition metal catalysts including group 5 and 6 metals, and Rh catalysts.

Group 10 transition metal catalysts including Ni and Pd are known as a new class of catalysts for the polymerization of substituted acetylenes, but the reports treating these catalysts are still not many. Some of the reports in an early stage displayed that the group 10 catalysts rather induce cyclic and linear oligomerizations of acetylene monomers. Thus, only fragmental information is available in some of the papers.

The polymerization of *N*,*N*-dimethylpropargylamine and ethynylpropargylsilane with $Ni(NCS)_2PPh_3$[168] and $[Pd(C{\equiv}CR)_2(PPh_3)_2]$ (R=$SiMe_3$, CH_2OH, CH_2NMe_2),[169] respectively, provides insoluble metal-coordinated conjugated polymers. The 2-, 3-, and 4-nitrophenyl propargyl ethers polymerize with $PdCl_2$ in DMF giving soluble brown polymers, which show broad MWD with peak tops at 4×10^3 and 1×10^5.[170] $[Pd(C{\equiv}CC_6H_4C{\equiv}CH)_2(PPh_3)_2]$ is a more active catalyst for the polymerization of polar substituted acetylenes such as propargyl alcohol and propargyl esters. The corresponding polymers formed in moderate to good yields (66–81%) and had relatively high MW ($M_w > 1.5\times10^4$).[31] An Ni analogue, $[Ni(C{\equiv}CC_6H_4C{\equiv}CH)_2(PPh_3)_2]$, gives the polymers in much lower yield (less than 20%). In both cases, the formed poly(propargyl alcohol) and poly(propargyl ester)s are completely soluble in polar and non-polar organic solvents. 3-Diethylaminophenyl propargyl ether affords a low MW ($M_n \sim 4\times10^3$) soluble polymer. Poly(cyanoacetylene) has been prepared from the corresponding monomer using a variety of Pd and Ni catalysts such as $(Ph_3P)_2PdCl_2$ and $(Ph_3P)_2NiCl_2$.[34] The formed polymers have M_w of around 1×10^4, and always contain catalyst metals according to elemental analysis. A catalyst system, $Ni(cod)_2$–$CF_3COO(allyl)$, polymerizes phenylacetylene to give a polymer of M_n 12,000 in good yield.[171] Cyclopentadienylnickel complexes produce a mixture of polymers ($M_n \sim 3\times10^3$), linear and cyclic oligomers.[172]

11.16.4 Controlled Polymerizations

It is quite important to control the structure and MW of polymers precisely with regard to their specific properties and functions. Transition metal catalysts can achieve these objectives by designing metal catalysts, modifying ligands, and investigating appropriate conditions and co-catalysts. As for π-conjugated polymers, the reported examples are quite limited, and it can be said that substituted polyacetylenes are typical ones except for a few examples. Thus, synthesis of tailor-made conjugated macromolecules such as end-functionalized polymers, block co-polymers, star-shaped polymers is achievable by the polymerization of substituted acetylenes. Among diverse transition metal catalysts shown above, a limited number of the catalysts can achieve living polymerization, and are classified into the following three groups: (i) metal halide-based catalysts, (ii) metal carbenes, and (iii) Rh complexes. Table 7 shows typical examples of the living polymerization of substituted acetylenes. (The structures (catalysts) in appearing in column 2 of Table 7 are given at the end of this paragraph.) The structure of monomers undergoing living polymerization significantly depends on the type of catalyst. Thus, appropriate catalysts must be selected in order to synthesize well-defined polymers from the individual monomers.

Table 7 Living polymerization of substituted acetylenes

Monomer	*Catalyst*	M_w/M_n	*References*
ClC≡C-*n*-C_6H_{13}	**11**	1.13	173,174
HC≡CC_6H_4-*o*-CF_3	**11**	1.06	175
HC≡CC_6H_4-*o*-$SiMe_3$	**11**	1.07	176
HC≡CC_6H_4-*o*-$GeMe_3$	**11**	1.08	177
HC≡CC_6F_4-*p*-Bu	**11**	1.16	179
HC≡C-*t*-Bu[a]	**11**	1.12	183
MeC≡CMe	**6**	1.03	144
$(HC{\equiv}CCH_2)_2C(CO_2Et)_2$	**4a**	~1.20	139–141
HC≡CC_6H_4-*o*-$SiMe_3$	**4g′**	1.05	137
HC≡CPh[b]	**9**	1.15	148–151
HC≡CPh[b]	**12**	1.11	152
HC≡CPh[b]	**13**	1.14	153,154
HC≡CPh[b]	**10**	1.05	155

[a]Stereoregular (*cis* 97%) and living polymer is formed.
[b]Stereoregular (all-*cis*) and living polymers are formed.

$MoOCl_4$–*n*-Bu_4Sn–EtOH (1 : 1 : 1)

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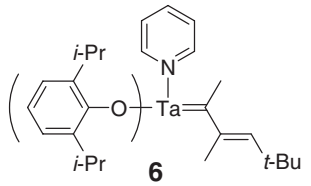

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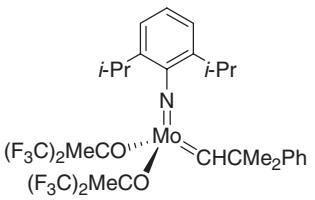
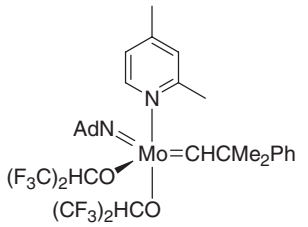
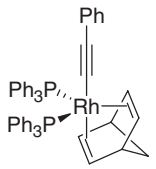


4a



4g′



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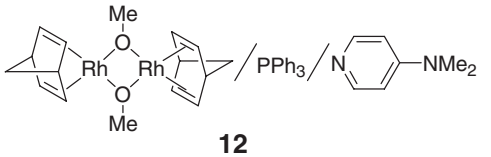

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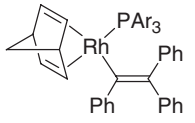


(Ar = 4-FC_6H_4, 4-ClC_6H_4)

10

11.16.4.1 Living Polymerization

11.16.4.1.1 Living polymerization by metal halide-based metathesis catalysts

In this category, the most convenient living catalysts are group 6 transition metal chloride or oxychloride, generally expressed as MO_nCl_m–co-catalyst–ROH (M = Mo or W, $n = 0$ or 1, $m = 5$ or 4).[12,142] While quantitative initiation efficiency is not achievable, these catalysts have advantage in accessibility. As the first example of living polymerization of acetylene monomers, $MoCl_5$-*n*-Bu_4Sn–EtOH was reported in case of 1-chloro-1-octyne as a monomer.[173] The formed poly(1-chloro-1-octyne) has narrow MWD ($M_w/M_n < 1.2$), and the living nature was confirmed by the linear dependence of MW on monomer conversion, and by the successful initiation of the polymerization of second-charged monomers with the living prepolymer.

A molybdenum oxychloride-based catalyst system, $MoOCl_4$-*n*-Bu_4Sn–EtOH, is more active than $MoCl_5$ ones.[174] In the polymerization of 1-chloro-1-octyne by the oxychloride-based catalyst, propagation rate is improved to be faster and MWD of the formed polymer is smaller. This ternary catalyst also induces living polymerization of *ortho*-substituted phenylacetylenes bearing bulky groups such as CF_3, $SiMe_3$, $GeMe_3$, and so on.[175–177] The bulky *ortho*-substituents are essential to achieve excellent living polymerization. Actually in case of using (*o*-methylphenyl)-acetylene, a sterically smaller monomer, the living nature is slightly low.[178] This would be because *ortho*-substituents preclude chain transfer and termination. It is noteworthy that a phenylacetylene derivative, (4-*n*-Bu-2,3,5,6-tetrafluorophenyl)acetylene, which has two medium-size *ortho*-substituents, also yields a polymer with low polydispersity.[179] $MoOCl_4$-*n*-Bu_4Sn–EtOH catalyst also induces the polymerization of the following disubstituted acetylenes in a living fashion: internal alkynes (e.g., 2-nonyne, 3-nonyne),[180] 1-chloro-2-phenylacetylene,[181] and diethyl di-2-butynyl malonate [$(EtO_2C)_2C(CH_2C{\equiv}CMe)_2$].[182] Stereospecific living polymerization of *tert*-butylacetylene is possible with $MoOCl_4$-*n*-Bu_4Sn–EtOH, which gives a polymer with a narrow MWD.[183] The *cis*-content reaches 97% at low temperature (−30 °C) and it decreases when the polymerization is conducted with $MoOCl_4$ or $MoOCl_4$-*n*-Bu_4Sn. A detailed NMR study on the stereoregularity of poly(*tert*-butylacetylene) showed that the *cis*-content depends on the rate of Lewis–acid-catalyzed isomerization from the *cis*- to the *trans*-form.[184]

A variety of co-catalysts such as Et_3Al,[185,186] Et_2Zn,[187] and *n*-BuLi[188,189] can be used instead of *n*-Bu_4Sn. It is of interest that the addition of the third component, the protic additive, affects the initiation efficiency and block co-polymerization behavior except for *n*-BuLi case. Initiation efficiency decreases in the order of *n*-$Bu_4Sn > Et_3Al > Et_2Zn >$ *n*-BuLi. Consequently, extremely high MW polymers ($>10^5$) with very narrow MWD (<1.03) are attainable by using $MoOCl_4$-*n*-BuLi.[188] Tungsten-based multicomponent catalysts, $WOCl_4$-*n*-Bu_4Sn-*t*-BuOH, $WOCl_4$-*n*-BuLi, and $WOCl_4$–EtMgBr have been proved to achieve the controlled polymerizations of *o*-CF_3-phenylacetylene, *o*-Me_3Si-phenylacetylene, (4-*n*-Bu-2,3,5,6-tetrafluorophenyl)acetylene, 3-decyne, and 5-dodecyne.[190,191]

With a half-metallocene ternary catalyst, $CpMoCl_4$–co-catalysts–EtOH, *ortho*-substituted phenylacetylenes polymerize in a living fashion, where the co-catalysts are EtMgBr, Et_3Al, and *n*-BuLi. $CpMoCl_4$ is stable to air and moisture more than $MoOCl_4$ owing to the steric and electronic effect of the Cp ligand, while the activity of $CpMoCl_4$-based catalysts is slightly lower and the initiation efficiency is still low (up to 13.1%).

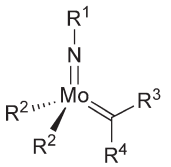
11.16.4.1.2 Living polymerization by single-component metal carbene catalysts

Considering the metathesis mechanism (Scheme 1) in the polymerization of acetylene compounds, an ideal initiator composed of transition metals has a carbene ligand, which promisingly achieves precisely controlled polymerization.

A Ta vinylalkylidene complex **6**, confirmed by a single crystal X-ray analysis, was revealed to polymerize 2-butyne in a manner of living polymerization.[143] The initiation efficiency is quantitative, and the living end can be end-capped with aromatic aldehydes. As polymers from symmetric acetylenes are generally insoluble, soluble poly(2-butyne) is accessible if the degree of polymerization is suppressed below 200. The NMR analysis of living oligomers of 2-butyne clearly indicates that both *cis*- and *trans*-structures exist in the main chain.

A number of Mo carbene catalysts, bearing various modified ligands, have been reported and proven to elegantly induce living polymerization of acetylene monomers. The first example is the cyclopolymerization of 1,6-heptadiynes catalyzed by Mo carbenes **4a–4c**.[139,140] Mo carbenes ligated by bulky imido and alkoxy groups are quite effective. In this catalyst system, the initiation efficiency of catalysts and polymerization behavior can be improved by detailed modification of the ligands as well as polymerization conditions. Consequently, a disubstituted alkylidene complex **4d** gives a relatively narrow MWD of 1.17. This would be because the initiation rate is accelerated by the modification to be close to the propagation rate. The ability of these Mo carbenes to tolerate polar functional groups permits living polymerization of functionalized monomers containing ester, sulfonic ester, and siloxy groups. End-capping of the polymers is readily accomplished using aromatic aldehydes including *p-N,N*-dimethylaminobenzaldehyde and

p-cyanobenzaldehyde. Cyclopolymerization of 1,6-heptadiynes with **4a–4d** offers polymers having both five- and six-membered cyclic structures. In contrast, **4e** and **4f**, which have bulky carboxylate ligands, produce polymers bearing only six-membered rings.[141]



4

4a: $R^1 = C_6H_3$-2,6-*i*-Pr_2; $R^2 = OCMe(CF_3)_2$; $R^3 = CMe_2Ph$; $R^4 = H$

4b: $R^1 = C_6H_3$-2,6-*i*-Pr_2; $R^2 = OC(CF_3)_3$; $R^3 = CMe_2Ph$; $R^4 = H$

4c: R^1 = 1-Adm; $R^2 = OCMe(CF_3)_2$; $R^3 = CMe_2Ph$; $R^4 = H$

4d: $R^1 = C_6H_3$-2,6-*i*-Pr_2; $R^2 = OCMe(CF_3)_2$; $R^3 = Ph$; $R^4 = Me$

4e: $R^1 = C_6H_4$-2-*t*-Bu; $R^2 = O_2CCPh_3$; $R^3 = CMe_3$; $R^4 = H$

4f: $R^1 = C_6H_4$-2-*t*-Bu; $R^2 = O_2CCPh_3$; $R^3 = CMe_2Ph$; $R^4 = H$

4g: R^1 = 1-Adm; $R^2 = OCH(CF_3)_2$; $R^3 = CMe_2Ph$; $R^4 = H$

4h: R^1 = 1-Adm; $R^2 = OCH(CF_3)_2$; $R^3 = Ph$; $R^4 = Me$

4i: R^1 = 1-Adm; $R^2 = OCH(CF_3)_2$; $R^3 = R^4 = Ph$

4j: $R^1 = C_6H_3$-2,6-Me; $R^2 = OCMe(CF_3)_2$; $R^3 = CMe_2Ph$; $R^4 = H$

Phenylacetylenes bearing substituted groups on their phenyl ring have been adopted in the Mo carbene-initiated polymerization. Well-defined polymers are readily obtained with Mo carbenes **4g–4i**.[137,138] Isolation of **4g–4i** cannot be accomplished without the addition of an appropriate base because of their instability. In addition to metal halide-induced living polymerizations, bulky ring substituents at the *ortho*-position of monomers are required for controlled polymerization. The most characteristic point of these polymerization systems is that all the steps including initiation and propagation can be readily monitored by an NMR technique. Eventually it was found that the alkylidene groups of **4** selectively undergo α-addition onto *o*-Me_3Si-phenylacetylene, whereas the selectivity of α-addition decreases with the decrease in the bulkiness of *ortho*-substituents.

Metal-containing monomers, ferrocenylacetylene and ruthenocenylacetylene, have been subjected to living polymerization with Mo carbene **4j** that has bulky alkoxy ligands.[102] Living polymers are inaccessible with **4g–4i** that suit *ortho*-substituted phenylacetylenes. Due to the poor solubility of these polymers, the degree of polymerization must be restricted below ca. 40 in order to produce the soluble polymers. Similar metallocene-containing monomers, HC≡CC_6H_4-*o*-Fc (Fc = ferrocenyl), HC≡CC_6H_4-*p*-CH=CHFc, HC≡CC_6H_4-*p*-N=NFc, and HC≡CC_6H_4-*p*-C≡CC_6H_4-*p*-C≡CFc, polymerize in a living manner in the presence of **4j**.[86,87]

11.16.4.2 Stereospecific Living Polymerization by Rh Catalysts

Among a number of transition metal catalysts for polymerization of acetylenes, Rh catalysts can be classified as the most excellent ones in both stereospecificity and living nature. Rh-catalyzed living polymerization was first accomplished in 1994.[147] A well-characterized catalyst **9** in conjunction with 4-(*N*,*N*-dimethylamino)pyridine (DMAP) demonstrated its excellent ability to offer quantitative yield of poly(phenylacetylenes) with narrow MWD. The single crystal X-ray analysis of **9** confirmed the presence of phenylethynyl ligand coordinating through σ-bond between Rh metal center and terminal ethynyl carbon atom. It is considered that in the initiation step of polymerization, the monomer molecule inserts into this σ-bond, and then Rh–H species would be formed via the elimination of 1,4-diphenyl-1,3-butadiene, which is actually detected in experiments.[150] The presence of DMAP is essential to control the polymerization. In the absence of DMAP, the polydispersity index of the formed polymer increases to 1.3, and the gel permeation chromatography profile gives a small new peak whose MW is twice as that of the major product. High stability of the propagation centers allows the isolation of poly(phenylacetylene) having active propagation sites that can sequentially polymerize different monomers to give precisely controlled block co-polymers.

A striking feature of the stereoregular polyacetylenes is their simple NMR spectral patterns, which facilitates elucidation of the polymerization mechanism as well as the polymer structure. A co-polymer of phenylacetylene with partly ^{13}C-labeled phenylacetylene (Ph^{13}C≡^{13}CH) shows two doublet carbon signals with $J_{13C–13C}$ of 72 Hz, indicating the presence of ^{13}C=^{13}C bond in the polymer backbone.[150] This is a clear indication of the insertion mechanism instead of the metathesis pathway.

A further developed system, [(nbd)RhOMe]$_2$–Ph_3P–DMAP, has enabled the enhancement of the initiation efficiency to 70% from 35%.[151] The polymerization with [(nbd)Rh(OMe)]$_2$–Ph_3P–DMAP is three to four times

faster than that with **9**. The isolation of $[(nbd)RhOMe]_2$ is unnecessary; a simple mixture of commercially available $[(nbd)RhCl]_2$, Ph_3P, NaOMe, and DMAP induces the living polymerization of phenylacetylene without broadening the polydispersity.

A next-generation isolable catalyst is a rhodium vinyl complex **10**, which is also fully characterized by X-ray analysis.[154] Catalyst **10** gives the living polymers derived from phenylacetylene and its *para*-substituted analogs. Living polymerization is also possible even in the presence of water. The *in situ* formation of **10** by combination of $[(nbd)RhCl]_2$ **7**, LiCPh=CPh_2, and Ph_3P also induces living polymerization in quantitative initiation efficiency.[152] A feature of this polymerization system is the ability to introduce functional groups at the initiation terminal. For example, living poly(phenylacetylene) bearing a terminal hydroxy group is readily obtained by using a three-component catalyst, $[(nbd)RhCl]_2$, LiCPh=C(Ph) (C_6H_4-*p*-$OSiMe_2t$-Bu), and Ph_3P, followed by the desilylation of the formed polymer. Polymerization of β-propiolactone with the terminal phenoxide anion of this polymer gives a new block co-polymer of phenylacetylene with β-propiolactone (Table 8).[192]

Table 8 Various transition metal catalysts for polymerization of typical acetylenic monomers[a]

Catalyst	*Monomer*[b]	*References*
Mo catalyst		
$MoCl_5$–HC≡CCH_2OH	PA (58%, $M_w = 7200$)	193
$Mo(CO)_6$–PhOH	PA (quant., $M_n = 40700$)	194,195
$Mo(CO)_6$–protic co-catalysts	PA, *t*-BuC≡CH, 1,7-octadiynyl (all quant)	196
$M(CO)_6$ (activated by refluxing in solvent) [M = Mo, W, Cr]	PA (high yield, MW = 6000–17,000)	197
$Cp_2Mo_2(CO)_6$–PhOH, 3-chlorophenol, or iodine	PA, internal alkyne, 1-alkyne	198
$Mo(CO)_4$(nbd)	PA, monosubstitued acetylenes ClC≡C-*n*-Hex (quant, $M_w = 238,000$)	131
$Mo(CO)_3(CH_3CN)_3$	PA, monosubstitued acetylenes, ClC≡CPh, ClC≡C-*n*-Hex (99%, $M_w = 855,000$)	131
$MoI_2(CO)_3(CH_3CN)_2$	PA (low yield <15%)	131
$[MoCl(SnCl_3)(CO)_3(CH_3CN)_2]$	PA (quant, MW = 5000–6000)	199
$[MoCl(GeCl_3)(CO)_3(CH_3CN)_2]$	PA (conv. = 45%, MW < 10000)	200
$Mo(NO)_2(O_2CPh)_2$–Lewis acid ($TiCl_4$, $SnCl_4$, $EtAlCl_2$)	PA (80%, $M_w = 1000$, MWD = 1.15)	201
$Mo_2(O_2CCH_3)_4$–Lewis acid ($TiCl_4$, $SnCl_4$, $GeCl_4$, $EtAlCl_2$)	PA, *t*-BuC≡CH (quant, living manner in $GeCl_4$)	202
cis-$[Mo(NO)_2Cl_2(MeCN)_2]Cl$–$EtAlCl_2$	PA, 3-hexene, *t*-BuC≡CH (MWD = 1.10)	203
cis-$[Mo(NO)_2Cl_3(i\text{-PrOH})]\cdot 3i\text{-PrOH}$–$EtAlCl_2$	PA, 2-hexyne, *t*-BuC≡CH	203
$[Mo_2Cl_6(tht)_3]$ (includes isomers C_{2y} and C_s)	Acetylene, 2-butyne, 3-butyne, propargyl chloride, *t*-BuC≡CH (61%, $M_w = 110,000$)	204
$Mo(NMe_2)_2(NHMe_2)$(dpma)	3-Hexyne (no details)	205
$M_2(Ot\text{-Bu})_6$ (M = Mo, W)	Acetylene	206
$Mo(Ph_2PCH_2CH_2PPh_2)(C_7H_7)$	*t*-BuC≡CH ($M_w = 63,000$)	207
$MoBr_3$–acidic or organometallic co-catalysts	*t*-BuC≡CH (quant, $M_n = 210,000$)	208
$Mo(OEt)_5$ (with/without $EtAlCl_2$ or Et_3Al)	Propargyl alcohol and its derivatives	209,210
W catalyst		
WBr_5	*t*-BuC≡CH (quant, $M_n = 33,000$)	208
$Na_4[W_2Cl_8]$	PA (92%)	211
$[W(CO)_3(CH_3CN)_3] - [Cp_2Fe]PF_6$	PA (40–45%, MW = 25,000)	212
$W(CO)_6$–PhC≡CH (co-catalyst)–$h\nu$	PA and internal alkyne	213
$(CO)_5W$=C(Ph)OMe	PA, 1-hexyne (no details)	214
trans-$[(CO)_4BrW$≡CPh]	Acetylene, PA, 1-alkynes, internal alkynes	215
$[(t\text{-BuO})_3W$≡C-*t*-Bu]	PA (conv. = 100%, $M_w = 20,000$), C_5H_{11}C≡CH (conv. = 100%, $M_w = 25,000$)	216
Cl_3(dme)W≡C-*t*-Bu	PA (69%, 32,000), *t*-BuC≡CH (82%, 300,000)	217
WCl_5(*o*-4-*t*-Bu-C_6H_4)	PA (66%, $M_w = 150,000$)	124
WCl_5(*o*-2,6-$Cl_2C_6H_3$)	PA (89%, $M_w = 47,000$), TMSA (15%), 1-hexyne (37%, $M_w = 12,000$), *t*-BuC≡CH (34%)	124
WCl_5(*o*-2,6-di-*t*-Bu-C_6H_3)	PA (78%, $M_w = 230,000$)	124
$WOCl_3$(*o*-2,6-di-*t*-Bu-C_6H_3)	PA (58%, $M_w = 35,000$)	124
$WOCl_3$(*o*-2,6-$Cl_2C_6H_3$)	PA (85%, $M_w = 67,000$)	124

(*Continued*)

Table 8 (Continued)

Catalyst	*Monomer*[b]	*References*
$[NEt_4][W(CO)_5Cl]–ZrCl_4$	PA (no details)	218
$[W(CO)_4(piperidine)_2]–ZrCl_4$	PA (no details)	218
$[W(CO)_4(bipy)]–ZrCl_4$	PA (no details)	218
$[W(CO)_4(dppe)]–ZrCl_4$	PA (no details)	218
$[WCl_2(CO)_3(PPh_3)_2]–ZrCl_4$	PA (no details)	218
$[(CO)_4W(\mu\text{-}Cl)_3W(SnCl_3)(CO)_3]$	PA (MW = 8,300), *t*-BuC≡CH	219
$[(CO)_4W(\mu\text{-}Cl)_3W(GeCl_3)(CO)_3]$	PA (no details)	220
$[WCl(GeCl_3)(CO)_3(CH_3CN)_2]$	PA (no details)	220
$[WX_2(CO)_3(CH_3CN)L]$ (X = Cl, L = CH_3CN; X = I, L = CH_3CN, PPh_3, or $AsPh_3$)	PA (36–43%)	221
$[WBr_2(CO)(CH_3CN)(\eta^2\text{-}HC{\equiv}CPh)_2]$	PA (25%)	221
$[WCl(SnCl_3)(CO)_3(EtCN)_2]$	*t*-BuC≡CH (50%, M_n = 23,000)	222
$Q[W_2H(CO)_{10}]$ (Q = Et_4N, Ph_4P)	Co-polymer of PA, PhC≡CMe, etc.	223
$[(CO)_5W]_2[\mu\text{-}CH(C_6H_4\text{-}p\text{-}R)]$ (R=H, Me, OMe)	2-butyne, *t*-BuC≡CH (no details)	224
$(CO)_9W_2[\mu\text{-}CH(C_6H_4\text{-}p\text{-}R)]$ (R=H, Me, OMe)	2-butyne, *t*-BuC≡CH (no details)	224
$[W_3(\mu^3\text{-}O)(\mu\text{-}OH)_2(\mu\text{-}Cl)_2(O)(\eta^2\text{-}PhC{\equiv}CPh)_5]$	PA (MW = 8300), *t*-BuC≡CH	219
$[W_2Cl_6(tht)_3]$ (includes isomers C_{2v} and C_s)	Acetylene, 2-butyne, 3-butyne, prpoargyl chloride, *t*-BuC≡CH (60%, M_w = 56,000)	204
Rh catalyst		
$Rh_2(PF_3)_8$	PA, *t*-BuC≡CH	225
[Rh(LL)chel]X (LL = cod, nbd; chel = bipy, etc.; X = PF_6, ClO_4, BPh_4)	PA (up to 96%, high *cis*-content)	226–228
$[Rh(cod)_2]BF_4$	PA derivatives (>85%)	160
[(*NN′N*)Rh(cod)]	PA (24%)	229
$[Rh(cod)Cl_2]L$ (L = tmeda, teda)	PA (up to 91%, high *cis*-content)	226
$[(cod)RhCl(H_2NCH_2CH_2CH_2NH_2)]Cl$	PA (>95%, MW = 6600), PA derivatives	230
$(cod)RhCl(Ph_2PC_6H_4\text{-}m\text{-}SO_3Na)$	PA	230
trans-$[Rh(CO)(Ph_2PC_6H_4\text{-}3\text{-}CO_2H)(\mu\text{-}NCMe{=}CHCMe{=}N)]_2$	PA	230
$(Ph_2PC_6H_4\text{-}1\text{-}COO)Rh(CO)(NHMe{=}CHCMe{=}N)$	PA	230
$(Ph_2PC_6H_4\text{-}2\text{-}COO)Rh(CO)(indazole)$	PA	230
trans-$[Rh(CO)(Ph_2PC_6H_4\text{-}2\text{-}CHO)(\mu\text{-}NCMe{=}CHCMe{=}N)]_2$	PA	230
$[Rh(cod)(SC_6X_5)_2]$ (X = H, F)	PA (X = F; 50%, MW ~ 35,000)	231
$Rh(cod)(SC_6F_5)(PPh_3)$	PA (41%)	231
$[Rh(diene)L_2]PF_6$ (diene = cod, nbd; L = dbn, dbu)	PA (42–53%, M_w = 200,000–1,750,000)	232
RhCl(diene)L (diene = cod, nbd)	PA (~80%, M_w = ~1,400,000)	232
$[Rh(cod)Cl]_2(pda)$	PA (39%, M_w = 7,300)	156
Rh(cod)(mid)Cl	PA (75%, M_w = 12,500)	156
Rh(cod)(L)Cl (L = NH_3, *t*-$BuNH_2$, piperidine)	PA (57–72%, M_w = 6,500–23,000)	156
Rh(cod)(bbpmt)	PA (64%, M_w = 11000)	156
$RhCl(CO)(TPPTS)_2$	PA	233
$[RhCl(cod)]_2(\mu^2\text{-}PCHP)$	PA (no details)	234
$RhH(PCP)(\mu\text{-}Cl)_2Rh(cod)$	PA (no details)	234
$RhCl(PCP)(\mu^2\text{-}Cl)_2Rh(cod)$	PA (no details)	234
$[RhF(cod)(PPh_3)]$	PA (preliminary experiment)	235
$[Rh(CF_3)(cod)(PPh_3)]$	PA (preliminary experiment)	235
$[(cod)Rh\{CH_3CO^-{=}CHCOO(CH_2)_2OCO(CH_3){=}CH_2\}]$	PA (>82%, M_w = 11,000–16,000), PA derivatives	236
RhTp(cod) and its analogs	PA (quant), PA derivatives	237,238
RhBp(cod)	PA (100%, M_w = 66,000, MWD = 1.7)	237,238
$[(cod)Rh(LL)]ClO_4$ (LL = dppf, FcNP, FcNN)	PA (up to 94%, M_w = 145,000)	239
Ni catalyst		
$NiCl_2–NaBH_4$	Acetylene, 1-alkyne, propargyl alcohol, etc.	240
$Ni(C_3H_5)_2$	PA	241,242
$NiI(C_3H_5)$	PA	241
$Ni(\eta^3\text{-}CH_3CH{=}CHCH_2)_2$	PA	241
$NiX(\eta^3\text{-}CH_3CH{=}CHCH_2)$	PA (no details)	243
$Ni(CO)_4$	Propiolic acid ester (oligomerization)	244

(*Continued*)

Table 8 (Continued)

Catalyst	*Monomer*[b]	*References*
Cp_2Ni	PA (29–50%, MW = 1600, in bulk polymn), PA derivatives	245,246
Cp_2Ni–LiR (R=Me, Ph, C≡CPh)	DPA (74%), PA (58%, M_w = 1100)	247,243
$Ni(cod)_2$–$CF_3CO_2CH_2CH{=}CH_2$	PA (65%, M_w = 12,000), PA derivatives	172
$[CpNi]_2(PhC{\equiv}CH)$	PA (53%)	234
$[CpNi(CO)]_2$	PA (40%)	234
CpNi(NO)	PA (23%)	234
$CpNi(GeBr_3)(CO)$	PA (26%)	234
$CpNi[P(n\text{-}Bu)_3]I$	PA (56%)	234
$CpNi[L]Cl$ (L = $P(OMe)_3$, PPh_3)	PA (38, 52%, respectively)	234
$Ni(CH_3CN)_6(BF_4)_2$–Et_2AlCl	PA (65%, M_n = 5000)	248
(1-R-indenyl)$Ni(PPh_3)(OTf)$ (R=Et, *i*-Pr, Bz)	PA (5%, M_n = 4400)	249
(1-R,2-R^1-indenyl)$Ni(PPh_3)$(thienyl) (R, R^1 = H, alkyl, Ph)	PA (M_w = 50,000–75,000)	250
$[(\eta^3{:}\eta^1$-indenyl$(CH_2)_2NMe_2)Ni(PR_3)]X$ – MAO (R=Ph, Me, Cy)	PA (M_w = 34,500–57,700)	251
(1-Me-indenyl)$Ni(PR_3)(C{\equiv}CPh)$–MAO (R=Ph, Cy)	PA (59% and 32%, respectively)	252
(1-Me-indenyl)$Ni(PR_3)Cl$ – MAO (R=Ph, Cy)	PA (30% and 35%, respectively), 1- or 3-hexyne (M_w < 2,400)	218
Pd catalyst		
$[Pd(CH_3CN)_4](BF_4)_2$	PA (30%, M_n = 9,000), propiolic acid ester (90%, M_n = 3,000)	253,254
[(dppf)$Pd(CH_3)(CH_3CN)$]OTf	PA (81–100%, M_n = 7,275–12,000)	255
[(dippf)$Pd(CH_3)$ (CH_3CN)]OTf	PA (94%, M_n = 3,900)	255
[(dppf)$Pd(CH_3CN)_2](OTf)_2$	PA (90%, M_n = 18,800)	255
[(dippf)$Pd(CH_3CN)_2](OTf)_2$	PA (49%, M_n = 4,300)	255
[Pd(*NN′O*)Cl]	PA (totally 55%, M_w = 1300 ~ 1400 (main peak))	256
$[Pd(\eta^1,\eta^2\text{-}5\text{-}OMe\text{-}C_8H_{12})(N,O)]BF_4$	PA (<9%)	257
$PdCl_2$	propargyl alcohol, propiolic acid, propiolic acid ester (~90%)	258–262
$(PPh_3)_2PdCl_2$	propiolic acid ester (~80%), propargyl alcohol	262,263
$[Pd(C{\equiv}CCH_2OH)_2(PPh_3)_2]$	propargyl alcohol (90%)	39,264,265
Pt catalyst		
cis- and *trans*-$PtCl_2(PPh_3)_2$	PA (MW <2,000)	266
trans-$PtHCl(PPh_3)_2$	PA (MW <2,000)	266
$Pt(PPh_3)_2$	PA (MW <2,000)	266
$(PPh_3)_2Pt(\eta^2\text{-}HC{\equiv}CPh)$	PA (MW <2,000)	266
cis-$Pt(C{\equiv}CPh)_2(PPh_3)_2$	PA (MW = 6,400)	266
trans-$Pt(C{\equiv}CPh)_2(PPh_3)_2$	PA (MW = 7,200)	266
$[Pt(CO)_4][Sb_2F_{11}]$ in CO atom.	PA (M_w = 3,000–4,300)	267
cis- and *trans*-$PtCl_2(PPh_3)_2$	PA (MW <2,000)	266
trans-$PtHCl(PPh_3)_2$	PA (MW <2,000)	266
$Pt(PPh_3)_2$	PA (MW <2,000)	266
$(PPh_3)_2$ $Pt(\eta^2\text{-}HC{\equiv}CPh)$	PA (MW <2,000)	266
$[Pt(CO)_4][Sb_2F_{11}]$ in CO atom.	PA (M_w = 3,000–4,300)	267
Other transition metal catalyst		
$RuTp(L)(L^1)Cl$ (L, L^1 = P, N, O donors)	PA (98%, M_n = 7,000, PDI = 1.48)	268
$Et_2NCO_2RuH(CO)(PCy_3)_2$	PA (low yield ~15–20%)	269
$(PhC{\equiv}C)_2Ru(CO)(PCy_3)_2$	PA (low yield ~15–20%)	269
$[(Cp^*)RuCl2]_2$	propiolic acid (74%, M_n = 4,000), propargy alcohol (65%, insoluble), etc.	270
$Re(CO)_5Cl$	PA, terminal acetylene	271,272
$Re(CO)_5Br$	PA, terminal acetylene	271,272
$(Mesitylene)Cr(CO)_3$	PA (MW = 12,000)	273–275
$[Cp^*Cr(\mu\text{-}Cl)Me]_2$	2-butyne (no details)	276
$Fe(naph)_3$–$AlEt_3$	PA	277
$Fe(EtCO_2)_3$–$AlEt_3$	PA	277
$Fe(acac)_3$–$AlEt_3$	PA	277

(*Continued*)

Table 8 (Continued)

Catalyst	*Monomer*[b]	*References*
$Fe(dmg)_2 \cdot 2(NC_5H_5)$–$AlEt_3$	PA	277
$Fe(CH_3CH_2CO_2)_3$–$AlEt_3$	PA	278
[Fe(propionate)$_3$]–$AlEt_3$	PA, 1-hexene	279
Fe(naph)–Al(*i*-Bu)$_3$	1-Butyne,1-hexyne,1-dodecyne	280
$Fe(RCO_2)_3$–$AlEt_3$	Internal alkyne	281
$Fe(prp)_3$–$AlEt_3$	Internal alkyne	282,283
$Fe(chc)_3$–$AlEt_3$	Internal alkyne	282,283
Fe(acac)–Al(*i*-Bu)$_3$	4-Methyl-4-hexyne	284
$Fe(sal)_3$–$AlEt_3$	PA	285
$Co(oxin)_2$–$AlEt_3$	PA	285
$Co(sal)_2$–$AlEt_3$	PA	285
$Ni(saldxm)_2$–$AlEt_3$	PA	285
$VO(sal)_2$–$AlEt_3$	PA	285
$VO(saldim)_2$–$AlEt_3$	PA	285
$V(acac)_3$–$AlEt_3$	PA	286
$Ti(edbp)Cl_2$–$AlEt_3$	PA (conv. = 96%, selectivity = 98%, M_n = 2,200)	287
$Ti(OBu)_4$–$AlEt_3$	PA	286
$TiCl_3$ (or $TiCl_4$)–$AlEt_nCl_{3-n}$	Internal alkyne, mainly cyclic trimerization	288
$TiCl_3$–$AlEt_3$	PA good yield	289
Sc naphthenate–AlR_3 (R=Et, *i*-Bu)	1-hexane, etc.	290
$Nd(P_{204})_3$–Fe(acac)–Al(*i*-Bu)$_3$	PA (conv. = 47%, M_w = 870,000)	291
$Nd(naph)_3$–$AlEt_3$	PA	277

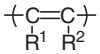
[a]Abbreviations: PA = phenylacetylene, dpma = di-*N,N*-(pyrrolyl-a-methyl)-*N*-methylamine, tht = tetrahydrothiophene, bipy = 2,2′-bipyridyl, *NN′N* = *N*-benzyl-*N*-(2-pyridylmethyl)-*N*-(2-pyrrolatomethyl)amine, tmeda = *N,N,N′,N′*-tetramethylethylendiamine, teda = triethylendiamine, dbn = 1,5-diazabicyclo[4.3.0]non-5-en, dbu = 1,8-diazabicyclo[5.4.0]undec-7-en, pda = *o*-phenylenediamine, Cp = cyclopentadienyl, mid = *N*-methylimidazole, bbpmt = bis(4-*t*-Bu)-2-pyridylethylthiolate, TPPTS = $P(C_6H_4$-*m*-$SO_3Na)_3$, PCHP = 1,3-$(Ph_2PCH_2)_2C_6H_4$, Tp = hydridotris(pyrazolyl)borate, Bp = bis(pyrazolyl)borate, dppf = 1,1′-bis(diphenylphosphino)ferrocene, FcNP = 1-diphenylphosphino-2-(*N,N*-dimethylamino)methylferrocene, FcNN = 1,6-diferrocenyl-2,5-diazahexane, *NN′O* = 2-acetylpiridine or 2-formylpyridine benzoylhydrazones, *N,O* = 2,6-(*i*-Pr)$_2$(C_6H_3)N=C(Ph)-C(Ph)=O or 2-benzoylpyridine, dippf = 1,1′-bis(diisopropylphosphino)ferrocene, Cy = cyclohexyl, Cp* = pentamethylcyclopentadienyl, naph = paphthenate, acac = acetylacetonate, dmg = dimethylglyoxime, oxin = 8-hydroxyquinoline, sal = salicylaldehyde, saldxm = salicylaldoxime, saldim = salicylaldehydeimine, edbpH2 = 2,2′-ethylidenebis(4,6-di-tert-butylphenol).
[b]The values in parentheses are yield of polymer, conversion, average molecular weight of polymer, and the other properties.

11.16.4.3 Gas-permeable Polyacetylenes

Substituted polyacetylenes has been most intensively examined as gas-permeable materials aiming at practical application.[292–296] These studies are motivated by the extremely high gas permeability of poly(TMSP),[10,297] which is the most permeable material among the polymers available. Its oxygen permeability (P_{O2} = 4,000–9,000 barrers) is about 10 times larger than that of poly(dimethylsiloxane). In addition to its high permeability, the ability of poly(TMSP) to give a free-standing film and its gas permeation mechanism different from that of poly(dimethylsiloxane) have attracted much attention of membrane scientists.

Examples of highly gas-permeable substituted polyacetylenes are shown in Table 9. The P_{O2} values and oxygen/nitrogen selectivities (P_{O2}/P_{N2}) (25 °C) of about 100 substituted polyacetylenes have been measured so far.[10] Among those substituted polyacetylenes, many of the polymers with large P_{O2} values contain spherical substituents, such as *t*-Bu, Me_3Si, and Me_3Ge groups. On the other hand, a majority of the less-permeable polyacetylenes possess long *n*-alkyl groups. When the phenyl group is a main substituent, the gas permeability of the resulting polyacetylenes is usually considerably lower. For comparison, P_{O2} values (P_{O2}/P_{N2}) of commercially available oxygen-permeable polymer membranes at 25 °C are as follows[293,294,310]: poly(dimethylsiloxane) 600 barrers (2.0); poly(4-methyl-1-pentene) 32 barrers; natural rubber 23 barrers (2.3); poly(oxy-2,6-dimethylphenylene) 15 barrers (5). Thus, compared to these commercial polymers, substituted polyacetylenes are very permeable to oxygen. The unusually high gas permeability of polyacetylenes is attributed to the high free volume and unusual free volume distribution, which presumably derives from their low cohesive energy structure, stiff main chain, and spherical substituents.

Table 9 Oxygen permeability coefficients (P_{O2}) and P_{O2}/P_{N2} of gas permeable substituted polyacetylenes



R^1	R^2	P_{O2} *barrer*[a]	P_{O2}/P_{N2}	*References*
Me	$SiMe_3$	4×10^3–9×10^3	1.8	10
Me	$SiEt_3$	860	2.0	298,299
Me	$SiMe_2Et$	500	2.2	299,300,301
Me	$SiMe_2$-*i*-C_3H_7	460	2.7	299,300
Me	$GeMe_3$	7,800		104
Me	*i*-C_3H_7	2,700	2.0	302
Ph	C_6H_4-*p*-$SiMe_3$	1,100–1,550	2.1	303,304
Ph	Ph	910	2.2	305
Ph	C_6H_4-*m*-$SiMe_3$	1,200	2.0	306,307
Ph	C_6H_4-*m*-$GeMe_3$	1,100	2.0	117
Ph	C_6H_4-*p*-*t*-C_4H_9	1,100	2.2	306
β-Naphthyl	C_6H_4-*p*-$SiMe_3$	3,500	1.8	113
β-Naphthyl	Ph	4,300	1.6	113
C_6H_4-*p*-F	C_6H_4-*p*-$SiMe_3$	2,900	1.5	307
C_6H_4-*p*-F	Ph	3,000	1.4	307
C_6H_3-*m*,*p*-F_2	C_6H_4-*p*-$SiMe_3$	3,600	1.5	307
C_6H_3-*m*,*p*-F_2	Ph	3,800	1.3	307
Ph	C_6H_4-*p*-$OSiMe_2$-*t*-Bu	160	3.2	118
Ph	C_6H_4-*p*-OH	8.0	3.3	118
H	C_6H_2-2,4,5-$(CF_3)_3$	780	2.1	308
H	C_6H_3-2,5-$(CF_3)_3$	450	2.3	308
H	C_6H_3-*o*,*p*-$(SiMe_3)_2$	470	2.7	309

[a]1 barrer = 1×10^{-10} cm^3 (STP).cm/(cm^2.s.cmHg).

High gas permeability is also observed in poly(DPAs) with spherical ring substituents.[143,306,304,117] They are thermally very stable ($T_0 > 400\,°C$) and possess film-forming ability. The ease in modifying ring substituents provides an opportunity to tune the permeability as well as the solubility and second-order conformation. The permeability of poly(DPAs) significantly depends on the shape of ring substituents. Generally, those with bulky ring substituents such as *t*-Bu, Me_3Si, and Me_3Ge groups exhibit very large P_{O2} values up to 1,000–1,500 barrers, which is about a quarter of that of poly(TMSP) and approximately twice as large as that of poly(dimethylsiloxane). Poly(phenylacetylenes) tend to show lower permeability than do poly(DPAs).

While poly(DPA) is insoluble in any solvent, its derivatives with bulky ring substituents are usually soluble in common solvents such as toluene and chloroform and give membranes by solution casting. A poly(DPA) membrane has been prepared by the desilylation of a poly[1-phenyl-2-*p*-(trimethylsilyl)phenylacetylene] membrane catalyzed by trifluoroacetic acid.[112] The prepared polymer membrane shows high thermal stability, insolubility in any solvents, and high gas permeability (e.g., an oxygen permeability of 910 barrers at 25 °C).[305] The high gas permeability of poly(DPA) seems to be due to the generation of molecular-scale voids. In a similar way, poly(DPA)s having various silyl groups, such as Me_2*i*-PrSi, Et_3Si, and Me_2*n*-$C_8H_{17}Si$ groups, are soluble in common solvents, from whose membranes poly(DPA) membranes can be obtained by desilylation. These oxygen permeability coefficients (120–3,300 barrers) are quite different from each other irrespective of the same polymer structure. When bulkier silyl groups are removed, the oxygen permeability increases to larger extents.

Poly[1-aryl-2-*p*-(trimethylsilyl)phenylacetylene]s [aryl = naphthyl, fluorenyl, phenanthryl] are soluble in common solvents, and afford free-standing membranes.[113,114] These Si-containing polymer membranes are desilylated to give the membranes of poly[1-aryl-2-phenylacetylene]s. Both of the starting and desilylated polymers show very high thermal stability and high gas permeability. For instance, the T_0 and P_{O2} values of poly(1-β-naphthyl-2-phenylacetylene) are 470 °C and 4,300 barrers, respectively.[113] Poly(DPAs) with silyl groups and fluorine atoms are highly gas permeable.[311] The fractional free volume (FFV) of poly[1-(4-fluoro)phenyl-2-*p*-(trimethylsilyl)phenylacetylene] is 0.28 and of poly[1-phenyl-2-*p*-(trimethylsilyl)phenylacetylene][311] is 0.26 (appreciably large)). The oxygen permeability coefficient of poly[1-(4-fluoro)phenyl-2-*p*-(trimethylsilyl)phenylacetylene] is as high as 2900 barrers, which is

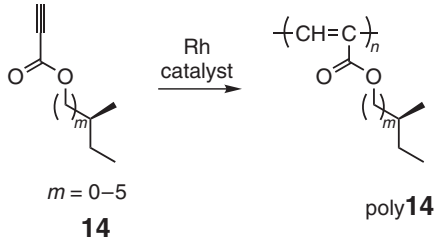
about twice that of poly[1-phenyl-2-*p*-(trimethylsilyl)phenylacetylene]. The incorporation of fluorine atoms into poly[1-phenyl-2-*p*-(trimethylsilyl)phenylacetylene] generally enhances gas permeability.

Disubstituted acetylenes with hydroxy groups cannot be polymerized because Ta and Nb catalysts are deactivated by polar groups such as hydroxy groups. 1-Phenyl-2-*p*-(*t*-butyldimethylsiloxy)phenylacetylene, however, polymerizes to give a high molecular weight polymer.[118] This polymer is soluble in common organic solvents and provides a free-standing membrane. Desilylation of a membrane of poly[1-phenyl-2-*p*-(*t*-butyldimethylsiloxy)phenylacetylene] yields a poly(DPA) having free hydroxy groups. This is the first example of a highly polar group carrying poly(DPA). Poly(1-phenyl-2-*p*-hydroxyphenylacetylene) is insoluble in non-polar solvents such as toluene and chloroform unlike the starting polymer. The PCO_2/PCH_4 and PCO_2/PN_2 permselectivity ratios of poly(1-phenyl-2-*p*-hydroxyphenylacetylene) membrane are as large as ca. 46, while keeping relatively high PCO_2 of 110 barrers.

11.16.4.4 Helical Polyacetylenes

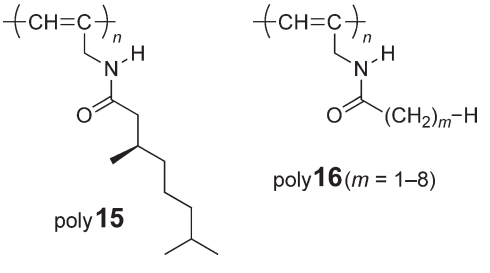
Helix is the most common higher-order structure of synthetic polymers such as peptides, polymethacrylates, polychloral, polyisocyanides, polyisocyanates, and polysilanes. Polyacetylenes bearing appropriate substituents also form a helix. Substituted helical polyacetylenes are promising candidates for enantioselective permeable materials, polarization-sensitive electro-optical materials, asymmetric electrodes, and hence their synthesis is currently under intensive research. This section overviews the synthesis and properties of helical polyacetylenes recently reported.

Propiolates **14** having various chiral alkyl substituents undergo polymerization with $[(nbd)RhCl]_2$ to give highly *cis*-stereoregular polymers [poly**14**] (Equation (5)).[35] The polymers display large specific rotations and intense CD signals, indicating that they exist in a helical conformation with predominantly one-handed screw sense. The Mark–Houwink–Sakurada plots of the stereoregular *cis*-transoidal poly(propiolates) clearly indicate the stiff main chain; namely, the slope of the plot of poly(hexyl propiolate) is 1.2, which is comparable to that of poly(hexyl isocyanate)].[34] The stiffness of poly(propiolates) originates from the helical conformation with a large helical domain size.

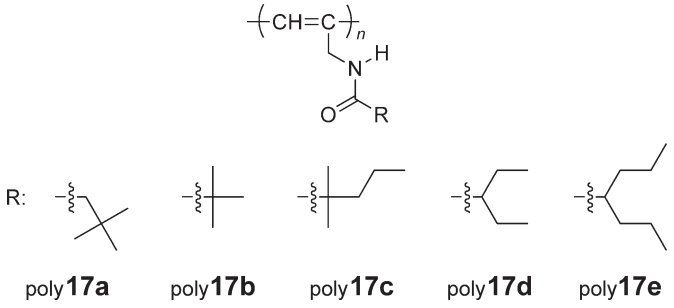


(5)

Chiral *N*-propargylamide **15** polymerizes with an Rh catalyst to give a *cis*-stereoregular polymer with a moderate MW.[49] Poly**15** shows a large specific rotation and an intense CD signal in the absorption region of the main-chain chromophore, indicating that it takes a helical conformation. The amide I absorption in the liquid-state IR spectrum of poly**15** appears at 1636 cm^{-1} irrespective of its concentration, which is low compared to that of the monomer. These data lead to a conclusion that intramolecular hydrogen bonds are constructed between the pendant amide groups in poly**15**. The chain length of poly(*N*-propargylamides) largely affects the helical properties. Poly**16** with $m = 5$ and 6 exhibit the highest helix contents among the polymers having pendant groups with different lengths ($m = 1$–8).[312,312a] The bulkiness of pendant groups is also important to induce a helical structure in poly(*N*-propargylamides).[51]



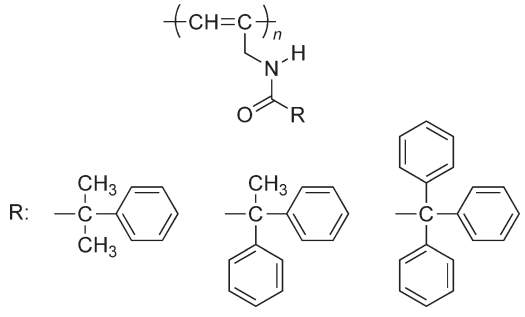
Poly**17a**–poly**17e** form a helix in chloroform, which is stable even at 60 °C. Poly(**16** ($m = 4$) $_{0.63}$-*co*-**17a**$_{0.37}$) and poly(**16** ($m = 4$) $_{0.40}$-*co*-**17b**$_{0.60}$) show the highest helix content among the series of homopolymers and co-polymers. The co-polymerization of monomers **17a** and **17b** with **16** ($m = 4$) decreases the steric repulsion between the bulky side chains, resulting in stable helix formation.



poly**17a** poly**17b** poly**17c** poly**17d** poly**17e**

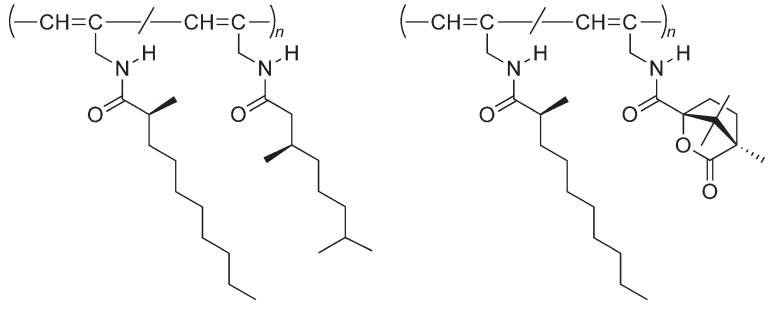
Only poly**18a** forms a helix at 60 °C among poly**18a**, poly**18b**, and poly**18c** having one, two, and three phenyl groups at the position α to the carbonyl group.[52] Conformational analysis of the polymers has revealed that the bulky substituents of poly**18b** and poly**18c** hamper the formation of hydrogen bonding between the amide groups, resulting in unfavorable helix formation.

These achiral poly(*N*-propargylamides) form helices with an equivalent amount of right- and left-handed screw senses. Addition of chiral alcohols induces predominantly one-handed screw sense in poly**17a** and poly**17d**.[313] ^{1}H NMR spectroscopic analysis has revealed that the amide side chains interact with optically active alcohols by hydrogen bonding. Terpenes also induce a one-handed helix. In this case, hydrophobic interaction plays an important role for helix induction.



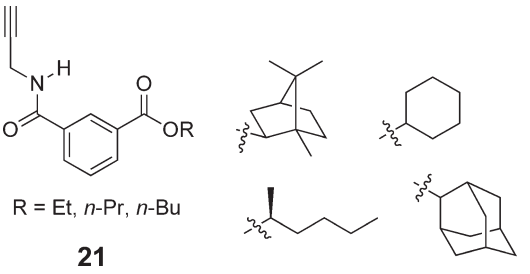
poly**18a** poly**18b** poly**18c**

Poly(**19**-*co*-**15**) and poly(**19**-*co*-**20**) undergo helix–helix transition upon temperature change.[314] All the co-polymers exhibit no optical activity at certain temperatures, which depends on the co-polymer composition. The helical structure of poly(**19**-*co*-**15**) carrying long alkyl chains is much affected compared to poly(**19**-*co*-**20**). The thermodynamic parameters of helix transition also depend on solvent.



poly**19**-*co*-**15** poly**19**-*co*-**20**

The helical sense of co-polymers of *N*-propargylbenzamides **21** can be tuned by varying the content of either chiral bulky monomer and achiral non-bulky monomer or chiral non-bulky monomer and achiral bulky monomer.[315] The smaller the pendant group of the achiral monomer is, the more easily the preferential helical sense changes with the co-polymer composition. The free energy differences between the plus and minus helical states as well as the excess free energy of the helix reversal of those chiral–achiral random co-polymers are estimated by applying the modified Ising model.

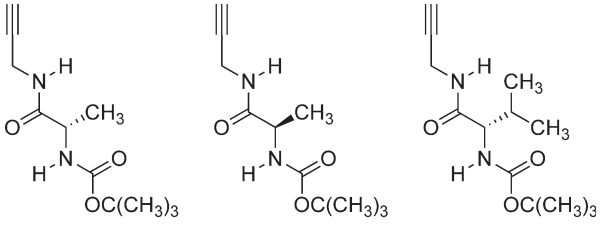


21

The secondary structure of poly(*N*-alkynylamides) is influenced by the position of the chiral center and amide group.[316] The position of the chiral center mainly affects the helical pitch, which becomes short when the chiral center is positioned away from the main chain. The stability of the helical structure is also influenced by the position of the amide group. Based on molecular orbital study, it is concluded that poly(*N*-propargylamides) with right-handed helical structure display a plus Cotton effect around 390 nm. This is also confirmed by the exciton chirality method using porphyrin as a chromophore.[317]

Amino acids are widely used as cheap and highly pure chiral source in organic synthesis. Amino acids feature a wide variety of functional groups including amino, carboxy, hydroxy, and mercapto groups, which can be converted into other groups. Peptide, a synthetic macromolecule of amino acids, is studied as a model compound of protein, and the higher-order structure and catalytic activity are extensively investigated. Amino acid-derived polymers are synthesized not only by the polymerization of amino acid *N*-carboxyanhydrides, but also by radical, cationic, and anionic coordination, polycondensation, and polyaddition. Varieties of amino acid-based polymers are designed using amino acid as a chiral source of *N*-propargylamides.

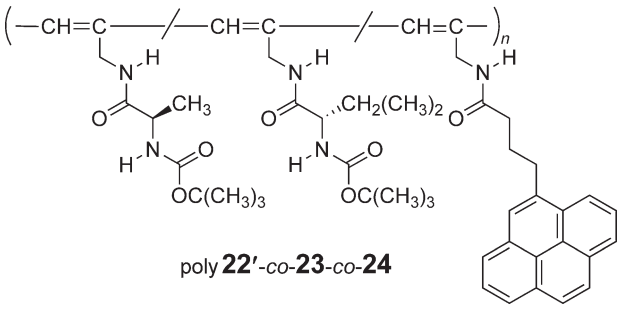
L-Alanine derived *N*-propargylamide **22** undergoes polymerization with (nbd)$Rh^{+}BPh_4^{-}$ to give a helical polymer carrying alanine moieties.[54] The co-polymers of **22** and the enantiomer **22′**, and achiral *N*-propargylamides show non-linear relationships between the co-polymer composition and specific rotation, CD spectra, and UV–VIS spectra, the so-called "majority rule" and "sergeants and soldiers rule."[318] The co-polymer obtained from D-alanine-derived *N*-propargylamide **22′** and L-valine-derived monomer **23** undergoes helix–helix transition upon temperature change.[319] This phenomenon results from chiral competition between the structurally different enantiomeric amino acid-derived units. The helix-forming abilities of the two units differ according to temperature.



22 **22′** **23**

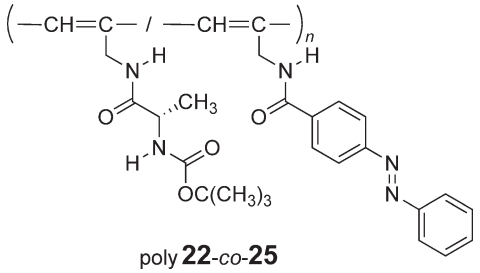
The co-polymerization of D-alanine-derived *N*-propargylamide **22′**, L-valine-derived **23**, and pyrene-based monomer **24** gives helical poly(**22′**-*co*-**23**-*co*-**24**) carrying pyrene.[320] The secondary structure of the co-polymer is tunable by the composition of the optically active amino acid units and solvent, which makes it possible to control the direction of the pyrene groups in the side chain. The interaction between the pyrene groups is small when the co-polymer takes a helical structure. The pyrene groups are regularly positioned in the polymer side chain. The co-polymer emits weak

fluorescence, because the population of excimer is small. On the other hand, the pyrene groups get close when the co-polymer takes a random structure. In this case, the co-polymer emits strong fluorescence based on excimer.



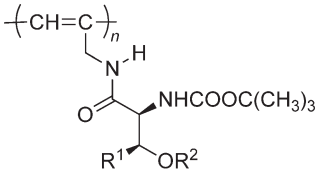
poly **22′**-*co*-**23**-*co*-**24**

Alanine-derived optically active *N*-propargylamide **22** and azobenzene-containing monomer **25** afford a co-polymer forming a helix.[321] The azobenzene moiety isomerizes from *trans*-form to *cis*-form upon UV light irradiation, accompanying transition from helix to random coil. Then upon irradiation of visible light, the *cis*-azobenezene moiety re-isomerizes into *trans*, while the polymer main chain keeps a random structure. This is presumably due to large steric repulsion around the azobenzene moiety to disturb recovery of a helical structure.



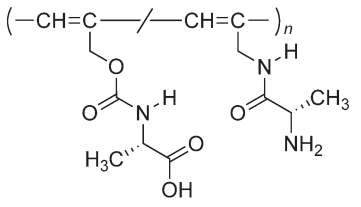
poly **22**-*co*-**25**

Monomers **26** and **27** derived from serine and threonine having hydroxy groups, and *O*-silylated ones **26′** and **27′** give polymers showing large specific rotations, and apparent CD signals based on the helical polyacetylene main chain.[55] The CD signals of poly**26** and poly**27** appear at 270–350 nm, while those of poly**26′** and poly**27′** do around 400 nm. Consequently, it is considered that these polymers take predominantly one-handed helical conformations with different tightness. Participation of hydroxy group greatly affects the helical structure.



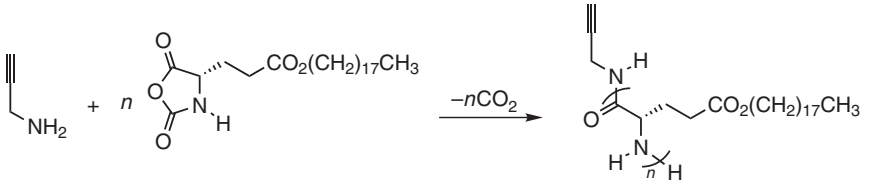
poly **26**: R^1 = H; R^2 = H
poly **27**: R^1 = Me; R^2 = H
poly **26′**: R^1 = H; R^2 = $SiEt_3$
poly **27′**: R^1 = Me; R^2 = $SiEt_3$

Poly(**28**-*co*-**29**) carrying carboxy and amino groups exhibits CD signals larger than the homopolymers.[322] The polymer mixture obtained by the polymerization of **28** in the presence of poly**29**, and the counterpart obtained by the polymerization of **29** in the presence of poly**28** exhibits specific rotations larger than expected from the content and the values of the homopolymers. The template polymers affect the conformation of the formed polymers.



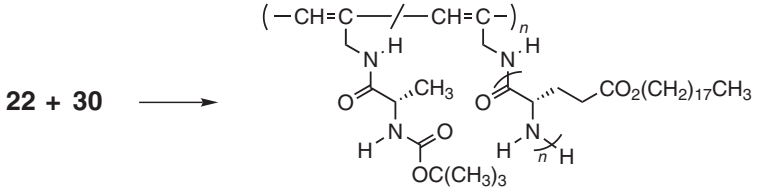
poly **28**-*co*-**29**

γ-Stearyl-L-glutamate-*N*-carboxyanhydride undergoes polymerization with propargylamine as an initiator to give peptide macromonomer **30** having *N*-propargylamide structure at the initiating end.[323] Structure **30** exhibits Cotton effect at 208 and 220 nm, indicating that the peptide moiety takes α-helix (Equation (6)). A graft co-polymer, poly(**22**-*co*-**30**), forms a tobacco mosaic virus-shaped structure consisting of helical main chain and helical side chain (Equation (7)).



(6)

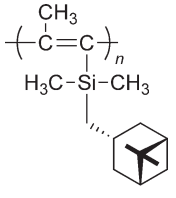
30



(7)

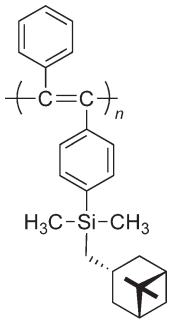
poly**22**-*co*-**30**

The first example of chiral disubstituted polyacetylene is a poly(TMSP)-based one, [poly**31**], synthesized in good yields using $TaCl_5$–Ph_3Bi.[103] The main chain of poly**31** is not well ordered, judging from the small specific rotation and CD signal. This is probably due to the less controlled geometrical structure (*cis* and *trans*) and low regioselectivity (head-to-tail and head-to-head) of the polymer.



poly **31**

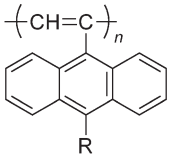
Poly(DPA) having a dimethyl-(−)-pinanylsilyl group [poly**32**] exhibits a very large specific rotation ($[\alpha]_D > 2000°$), and complicated but very intense CD signals.[116] The desilylation of a poly**32** membrane provides a poly(DPA) membrane, which exhibits a large specific rotation ($[\alpha]_D + 5590°$) and intense CD signals in the 350–450 nm region, indicating that the main chain retains the helical conformation with a large excess helix sense irrespective of the absence of chiral pendant groups.[112]



poly**32**

11.16.4.5 Photoelectronically Functional Polyacetylenes

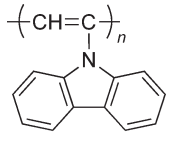
Luminescence is one of the most important functions of conjugated polymers, and energetic studies have been carried out on the photo- and electroluminescence of substituted polyacetylenes. Although the homopolymer of 9-ethynylacetylene **33** obtained with W catalyst is insoluble,[89] the polymer from **34** is a soluble dark purple polymer having an absorption maximum at 580 nm. Poly**34** exhibits the largest third-order non-linear optical susceptibility among the polymers from monosubstituted acetylenes.[95] Poly(anthrylacetylenes) bearing oligooxyethylene units **35** exhibit blue emission (emission maximum 470 nm) upon photoexcitation at 380 nm.[324] They show a fairly large ionic conductivity (4.1×10^{-5} S cm^{-1}) at 80 °C upon doping with $Li(CF_3SO_2)_2NLi$.



poly**33**: R = H
poly**34**: R = CO_2-*n*-Hex
poly**35**: R = $CO_2(CH_2CH_2O)_mCH_3$ (*m* = 2, 4)

Polymers from terminal acetylenes strongly emit luminescence upon photoexcitation.[325] Higher photoluminescent efficiency is observed for polyacetylenes having biphenyl moieties, which emit strong deep blue light at 380 nm. This unexpected strong emission seems to originate from ordering of the pendant mesogens that enhance the main-chain conjugation of the polymers.

N-Carbazolylacetylene **36** also polymerizes with W catalysts, giving poly**36** with high degree of main-chain conjugation and a large third-order susceptibility.[97] Carbazole-containing W-based polyacetylenes exhibit UV–VIS absorption apparently at a longer wavelength than the Mo- or Rh-based counterparts do. They show photoconductivity and electroluminescence.[43,74,85]



poly**36**

DPAs and 1-phenyl-1-alkynes show intense photo- and electroluminescences. A systematic investigation on the luminescence of poly(DPAs) has revealed that these polymers exhibit photoluminescence around 530 nm and electroluminescence around 550 nm. In a similar way, poly(1-phenyl-1-alkynes) photochemically and electrochemically emit strong lights with spectral maxima located around 455 and 470 nm, respectively. Green and blue emissions are observed from the electroluminescent devices using poly(DPAs) and poly(1-phenyl-1-alkynes) as the emission layers, respectively.[326,326a–326c]

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11.17
Polymerization of Epoxides

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11.17.1 Introduction

Epoxides are classified as a member of ethers, having partially positive charged carbons and a Lewis-basic oxygen atom in a three-membered ring system. Because such "inherent polarity" coupled with ring strain makes epoxides susceptible to various reactions with a large number of reagents (nucleophiles, electrophiles, acids, and bases) to elaborate new useful functional groups, epoxides have been considered to be versatile starting materials in organic synthesis.[1,2] Along with the development of the petrochemical industry where ethylene oxide (EO) and propylene oxide (PO) are produced on a large scale, polyethers and oligoethers by ring-opening polymerization of these epoxides have become one of the most important products in the synthetic chemical industry. Indeed, PO is now produced in over 5 million tons per year, and almost two-thirds of the amount of this monomer is converted into the polyether.

The ring-opening polymerization of epoxides is one of the oldest examples of the polymer formation. The first success in synthesizing oligo(ethylene oxide) was reported by Wurtz in 1863,[3] and Staudinger *et al.* intensively developed the polymerization of EO in the very early stage in polymer chemistry. Polymerization of PO was first reported by Levene and Walti in 1927.[4] Since these precedents, many research efforts have focused on the polymerization of a variety of epoxides. In addition, co-polymerizations of epoxides with co-monomers, especially with carbon dioxide, have also been investigated. In the context of early studies on the epoxide polymerization, recent research has been directed to the development of well-defined catalyst systems, which show high activity and controlled molecular weight, molecular weight distribution (MWD), regioregularity, and stereoregularity, since such factors have significant influence on polymer properties.

In the following sections, we describe the recent development of catalyst systems for epoxide polymerization, focusing on homopolymerization, (alternating) co-polymerization with CO or CO_2 reported from 1993 to 2004. Although aluminum and zinc are not classified as transition metals, polymerization catalyst systems using those metals will be discussed since they greatly contribute to the field of epoxide polymerization.

11.17.2 Regio- and Stereoregularities

Polymerization using epoxides as monomers includes the ring opening of epoxides via C–O bond cleavage. Thus, a mode of C–O bond cleavage (S_N2 or S_N1) and selectivity, that is, which C–O bond is cleaved, coupled with the symmetry of epoxides (symmetrical or unsymmetrical), cause regio- and stereochemical issues to be controlled in the epoxide polymerization.

Regioregularity. In the homopolymerization of unsymmetrical epoxides, there are three possible regioisomers of two repetitive constitutional units. Those in the homopolymerization of terminal epoxides are illustrated in Figure 1. The similar regioisomers of two adjacent constitutional units are possible in the alternating co-polymer with CO or CO_2. In general, polymerization via anionic mechanism tends to give the head-to-tail polymer because the nucleophilic growing species preferably attack the less-substituted carbon via S_N2 mechanism for steric reason. On the other hand, in the polymerization via cationic or coordination anionic mechanism, the positively charged oxygen weakens the C–O bond to enhance positive charge at the epoxide carbon, shifting the reaction mechanism to a "borderline S_N2." Thus, the reaction course can be controlled by subtle change of substrate, catalyst structure, and reaction conditions to give regioregular or regioirregular polymer.

Stereoregularity. Representative stereoregularities of the two adjacent constitutional units in the homopolymer and co-polymers of terminal epoxides and symmetrical *cis*-epoxides are listed in Figure 1. A diad is described as *meso* (*m*) if the absolute configurations of the two adjacent constitutional units are the same, and *racemo* (*r*) if they are the

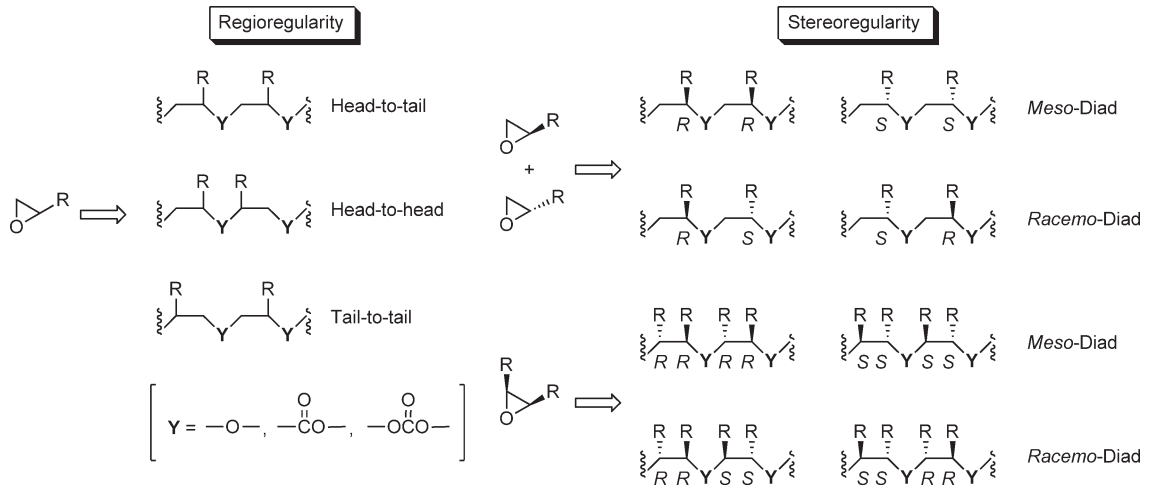
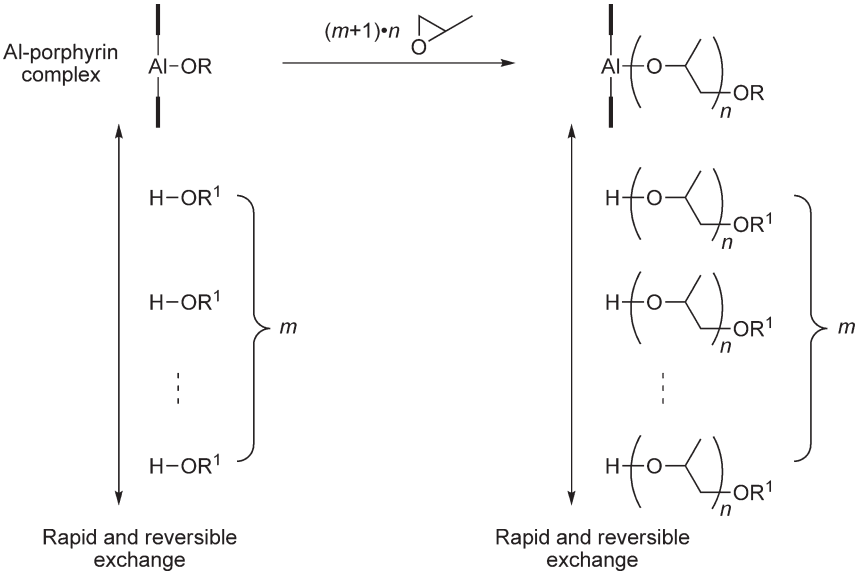


Figure 1 Regio- and stereoregularities in homopolymer of epoxide and alternating co-polymer of epoxide with CO or CO_2.

opposite. The tacticity of these polymers concerns the arrangement of the diads: isotactic and syndiotactic polymers mainly include consecutive *meso* (···*mmmmm*···) and *racemo* (···*rrrrr*···) diads, respectively.

11.17.3 Homopolymerization of Epoxides

As mentioned in Section 11.9.1, poly(propylene oxide) (PPO) and poly(ethylene oxide) (PEO) are produced in industrial scales, and are widely used as surfactants, plasticizers, adhesives, coatings, and raw materials for the manufacture of urethane elastomers and foams. Homopolymer of epichlorohydrin (ECH) is also produced as a rubber industrially. Thus, the catalyst systems for the epoxide homopolymerization have been of importance in the synthetic polymer chemistry and investigated intensely. Epoxides can be polymerized by both cationic and anionic mechanisms.[5] The typical catalysts for the cationic polymerization are BF_3, $AlCl_3$, and $SnCl_4$. A protic compound such as water is often required as a co-catalyst, interacting with Lewis acid to release protons. The most widely used PO anionic polymerization initiators are alkali metal alkoxides and hydroxides. However, the early developed cationic and anionic polymerization systems generally give the polymers with low molecular weight, broad MWD, or low regio- and/or stereoregularities because of the inherent side-reactions in these polymerization mechanisms (*vide infra*). For the well-controlled polymerization, the catalysts for coordination anionic polymerization have been developed by focusing on less basic species.[6] Zinc or aluminum complexes derived from mixtures of organozinc or organoaluminum with (poly)hydric compounds can give high molecular weight polyethers with high regioregularity. In addition, the chiral family of these complexes controlled the stereoregularity in the main chain.[7–11] In spite of these advantages, most of the coordination anionic polymerization systems in the early stage were not favorable for the synthesis of the polymer with a controlled molecular weight, since these initiators tend to form aggregates and the resulting different sites may have different reactivities. One of the most successful examples for the controlled polymerization of epoxides has been aluminum–porphyrin system reported by Inoue *et al.*[12–14] The polymerization of PO proceeded in a living manner to yield highly regioregular polyethers with narrow MWDs. These authors also developed the immortal polymerization of epoxides where polymers with narrow MWDs were obtained with the number of polymer chains exceeding the number of initial aluminum–porphyrin complexes (Scheme 1).[15,16] The key in the immortal polymerization is a reversible chain transfer, which is much more rapid than the chain propagation. In the presence of an alcohol (R^1OH) as a chain-transfer reagent, an aluminum–porphyrin complex with a growing species reacts with R^1OH reversibly, so that the polymerization takes place from all the molecules of aluminum–porphyrin complex and R^1OH.



Scheme 1 Concept of immortal polymerization of epoxides.

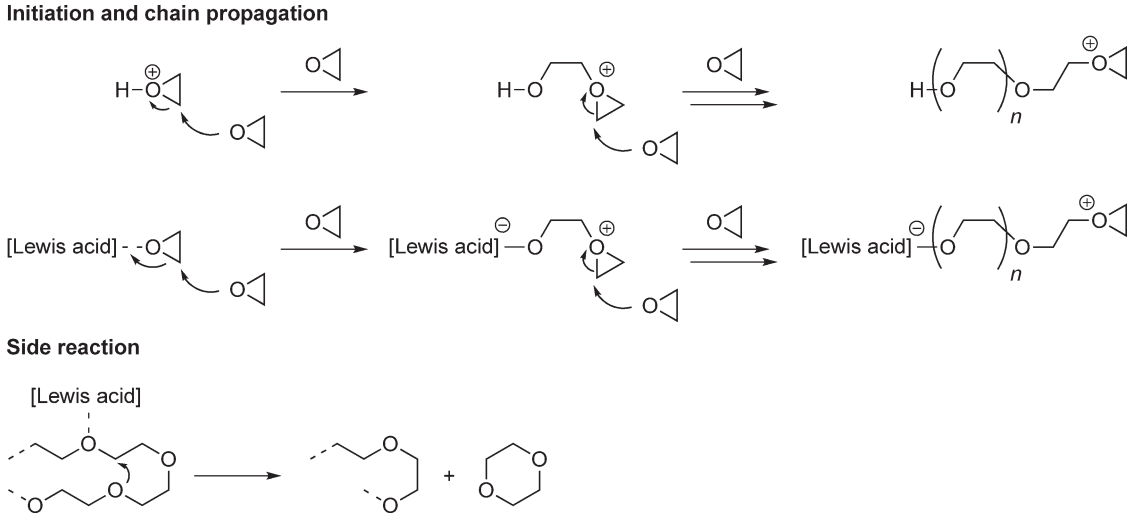
11.17.3.1 Mechanistic Aspects

11.17.3.1.1 Cationic polymerization

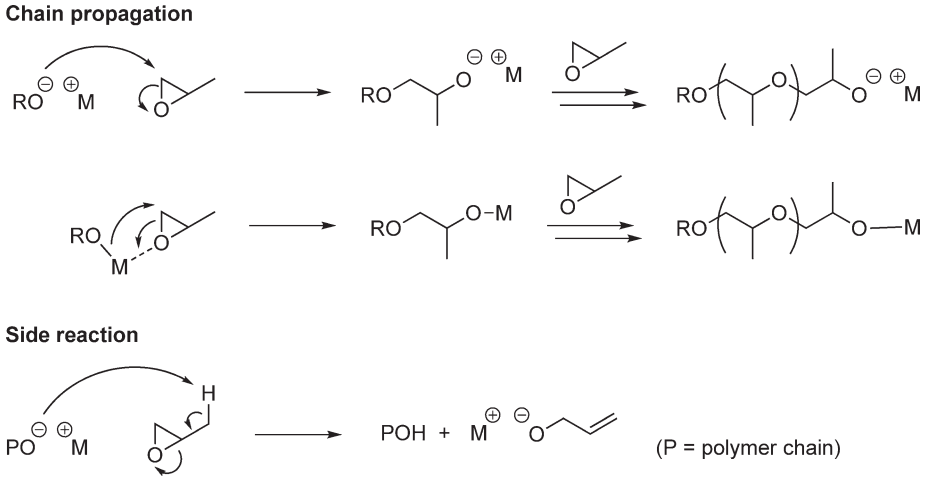
In the proton-induced cationic polymerization, the initiation reaction is ring opening of a protonated epoxide by the reaction with a free epoxide to form a tertiary oxonium ion (Scheme 2). In the case of Lewis acid-induced cationic polymerization, ring opening of the activated epoxide is the initiation reaction to give a tertiary oxonium ion. After the initiation, the activated epoxide carbon at the chain end reacts with a free epoxide to propagate a polymer chain. However, the actual reaction is more complicated because of side-reactions. The representative is a formation of 1,4-dioxane derivatives, which is derived by intramolecular nucleophilic attack of an ether oxygen in the main chain at the methylene carbon next to oxonium ion. In general, the regioselectivity in cationic polymerization of terminal epoxides is not so high owing to the fact that the ring opening takes place equally at both methylene–oxygen and methine–oxygen bonds. Accordingly, it is difficult for the cationic polymerization to control the polymer properties (regioregularity, tacticity, molecular weight, etc.).

11.17.3.1.2 Anionic polymerization

For the (coordination) anionic polymerization, metal alkoxides are often employed as initiators. In this system, the ring opening of epoxide takes place by a nucleophilic attack of an alkoxide on the (activated) epoxide carbon to generate another metal alkoxide which behaves as the propagating species (Scheme 3). The nature of metal–alkoxide



Scheme 2 Polymerization of epoxide in a cationic mechanism and a possible side reaction.



Scheme 3 Polymerization of epoxide in an anionic mechanism and a possible side reaction.

bond in the initiator and the propagating chain end varies widely from highly ionic to almost covalent. When highly basic alkali metal alkoxides, typical anionic polymerization initiators, are used for the PO polymerization, a proton abstraction from methyl group of PO can take place because of the high basicity of the initiating and propagating species (Scheme 3). This chain-transfer reaction results in the significant formation of oligomers with a terminal allyl group as an initiating group. Use of larger counterions such as rubidium and cesium or use of crown ether additives is slightly effective for reducing the chain transfer to give PPO with higher molecular weights, although details remain yet to be clarified. Less basic metal alkoxides, such as zinc and aluminum alkoxides, are also effective for the production of high molecular weight polymer.

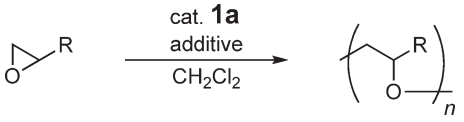
When a terminal alkene epoxide is used as a monomer, the ring opening generally occurs at a less hindered methylene–oxygen bond without configurational change at the original stereogenic center. Accordingly, the regioregularity of the resulting polymer tends to be highly controlled, and coordination anionic polymerization system provides with possible tools to control the stereoregularity.

11.17.3.2 Aluminum–Porphyrin/Lewis Acid Catalyst System

As mentioned above, aluminum–porphyrin complexes can polymerize terminal epoxides in a living fashion, affording the corresponding polymers of controlled molecular weights with a narrow MWD. However, long reaction time is necessary for high conversion of substrate. In order to overcome this drawback, Inoue *et al.* further improved their system and achieved in 1994 the high-speed living polymerization of epoxides using an aluminum–porphyrin complex in combination with a bulky organoaluminum Lewis acid such as **2**.[17] When aluminum complex **1a** was used as an initiator ([PO]/[**1a**] = 200), the polymerization proceeded rather slowly to attain 20% conversion in 7 h [turnover number (TON) = 40 mol (mol of Zn)$^{-1}$, turnover frequency (TOF) = 5.7 mol (mol of Zn)$^{-1}$ h^{-1}], giving a polymer with an M_n of 3,300 g mol^{-1} and an M_w/M_n of 1.05 (Table 1). In contrast, methylaluminum bis(2,4,6-tri-*tert*-butylphenolate) (**2a**, [PO]/[**2a**] = 400), when added to the reaction mixture, induces rapid polymerization to attain 86% conversion within only 3 min [TON = 172 mol (mol of Zn)$^{-1}$, TOF = 3 440 mol (mol of Zn)$^{-1}$ h^{-1})]. The resulting polymer has an M_n of 11 900 g mol^{-1}, very close to the expected value of 9 900 g mol^{-1} from the conversion and the monomer-to-**1a** ratio, and a relatively narrow polydispersity index (PDI) of 1.21. Based on ^{13}C NMR spectroscopic analysis, the produced polymer is shown to consist exclusively of head-to-tail linkage and to be rich in *m*-diad (73%) and *mm*-triad (59%) sequences. The use of bulky Lewis acid **2a** is a key for the high-speed living polymerization of epoxide, where the aluminum–porphyrin complex **1a** and Lewis acid **2a** are both so large that the chain-end alkoxide on the aluminum–porphyrin complex cannot react with the Lewis acid **2a**, while an epoxide monomer is able to coordinate to the Lewis acid to be activated for nucleophilic attack (Figure 2). The resulting chain-end alkoxide gets released from **2a** and captured by **1a** to repeat the propagation step.

Aluminum–porphyrin complex **1b** with an alkoxide ligand also demonstrates the same reactivity as **1a** in the presence of only 0.1 mol.% of **2a**.[17] The polymerization rate with **1b**/**2a** catalyst system is dependent on the concentration of **2a**: in the range from 0.025 to 2.5 mol.%, the increase of **2a** results in more rapid polymerization. On the other hand, molecular weight and the number of polymer chains are independent of the molar ratio of **2a** to

Table 1 Polymerization of terminal epoxides catalyzed by aluminum–porphyrin complexes



Epoxide	*[Epoxide]/[**1a**]/[**2a**]/[^{i}PrOH]*	*TON* (mol(mol of **1a**)$^{-1}$)	*TOF* (mol(mol of **1a**)$^{-1}$ h^{-1})	M_n(g mol^{-1})	M_w/M_n
PO	200/1/0/0	40	5.7	3300	1.05
PO	200/1/0.5/0	172	3440	11 900	1.21
PO	1000/1/0/49	840	2.2	1100	1.08
PO	1000/1/1/49	860	573	900	1.10
ECH	1000/1/1/49	660	27.5	1100	1.09

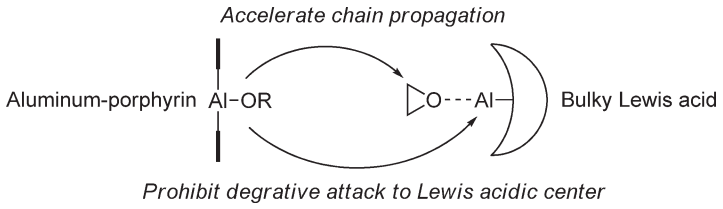
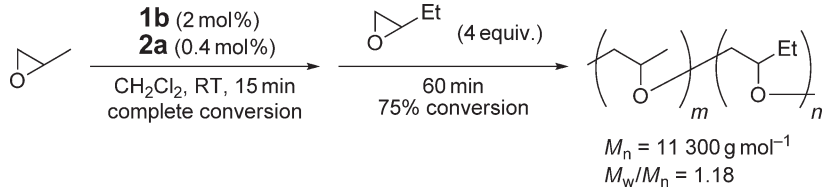
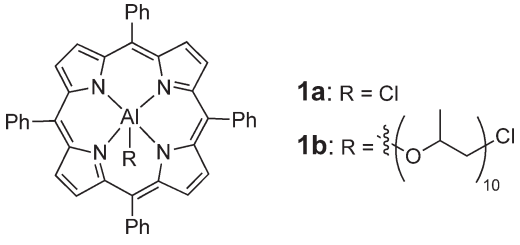


Figure 2 Schematic diagram of the concept of the high-speed living polymerization.



Scheme 4 Synthesis of block co-polymer of PO and 1,2-butene oxide.

PO. In addition, the produced polymer does not include a phenolate terminal group which should be derived from **2a**. These facts indicate that **2a** does not initiate but accelerates the polymerization through coordination to PO. The living nature of the PO polymerization by using **1b**/**2a** system is advantageous for the production of a block co-polymer: the polymerization of PO followed by addition of 1,2-butene oxide to the polymerization mixture gives diblock co-polymer with a narrow MWD (Scheme 4).

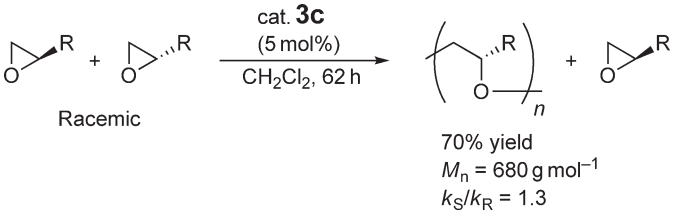


Immortal polymerization of epoxides with **1a** and an alcohol is also accelerated by co-use of bulky Lewis acid **2a**.[18] The polymerization of PO with **1a**/2-propanol system ([PO]/[**1a**]/[2-propanol] = 1000/1/49) in the presence of **2a** ([PO]/[**2a**] = 1000/1) proceeds rapidly to achieve 86% conversion in 1.5 h, while the polymerization in the absence of **2a** requires 380 h to reach 84% conversion (Table 1). The polyether produced in the presence of **2a** has an M_n of 900 g mol^{-1} and an M_w/M_n of 1.10, which indicates that almost all of **1a** and 2-propanol participate in the initiation of the polymerization. Other protic chain-transfer reagents, such as methanol, benzyl alcohol, and 4-*tert*-butylphenol, are also applicable to the high-speed immortal polymerization to give similar results as 2-propanol. As a substrate, ECH is also employable. Polymerization of ECH ([ECH]/[**1a**]/[2-propanol]/[**2a**] = 1000/1/49/1) gives a polymer with an M_n of 1100 g mol^{-1}, close to the value estimated from the conversion and [PO]/([**1a**] + [2-propanol]) ratio, and a narrow M_w/M_n of 1.10, while the conversion is lower than the case of PO.

Use of bulky Lewis acid **2a** is essential to ideal immortal polymerization. When **2b** or Al(O^{i}Pr)$_3$ is used instead of **2a**, the polymerization is less accelerated than in the case of **2a**, and the ligand exchange on **2b** and Al(O^{i}Pr)$_3$ is detected, in contrast to **2a**. In immortal polymerization, chain transfer should occur much more rapidly than propagation to achieve the uniformity of the resulting polymer molecular weight. Thus, the successful high-speed immortal polymerization demonstrates that addition of a bulky Lewis acid accelerates not only propagation reaction but also the chain-transfer reaction, which was indeed indicated by NMR studies on the alcoholate–alcohol ligand exchange reaction at the axial position of the aluminum–porphyrin complex.

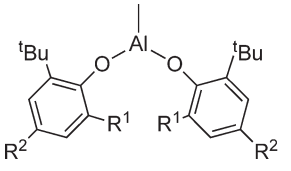
11.17.3.3 Aluminum–Tetradentate Ligand Catalyst System

In relation to aluminum–porphyrin complexes mentioned above, aluminum complexes with an O–N–N–O or N–N–N–N tetradentate ligand have been investigated. Spassky *et al.* reported that aluminum–Schiff base complexes **3** oligomerized terminal epoxides such as PO and methoxymethyloxirane, while long reaction time was required for high conversion of substrates in spite of high catalyst loading and relatively high reaction temperature of 80 °C.[19] Enantiomer-differentiating polymerization is achieved by using chiral aluminum complex **3c**. When PO is used as a substrate, (*S*)-enantiomer is preferably incorporated in the oligomer chain with the selectivity of $r_S = k_S/k_R = 1.3$, which is somewhat lower than that observed by using chiral zinc complex (Equation (1)).[20]

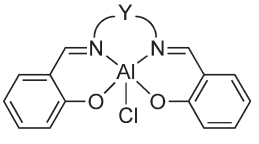


(1)

Catalytic activity of the aluminum–Schiff base system is dramatically enhanced by adding a bulky Lewis acid (Table 2). Inoue *et al.* reported that a combination of **3** with **2c** led to over 1000 times acceleration in the polymerization of PO at room temperature compared with the polymerization in the absence of **2c**.[17] The resulting polymers have narrow MWDs, molecular weights close to those estimated, assuming that every molecule of **3** forms one polymer chain. The same accelerating effect of **2c** is also demonstrated in the polymerization of PO by using aluminum–phthalocyanine and aluminum–tetraazaannulene complexes, **4** and **5**, which exhibit very low catalytic activities without **2c**.



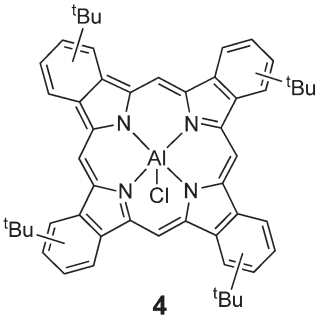
2a: $R^1 = R^2 = {}^t$Bu
2b: R^1 = H; R^2 = OMe
2c: $R^1 = {}^t$Bu; R^2 = Me



3a: Y = -CH2CH2CH2-

3b: Y =

3c: Y =



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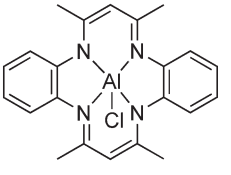

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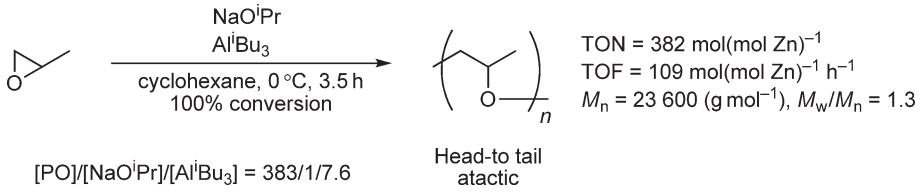
Table 2 Polymerization of PO catalyzed by aluminum complex in the absence or in the presence of **2c**

Al	*In the absence of* **2c**		*In the presence of* **2c**				
	t (days)	conv. (%)	*t*	conv. (%)	M_n (g mol^{-1})	M_w/M_n	*meso diad* (%)
3b	7	5.1	70 min	43	4200	1.18	57
4	3	<1	3 d	51	1800	1.14	*
5	4	29.9	1.5 min	74	5800	1.40	48

*Not described in the literature.
[epoxide]/[Al]/[**2c**] = 200/1/1.

11.17.3.4 Aluminate/Lewis Acid Catalyst System

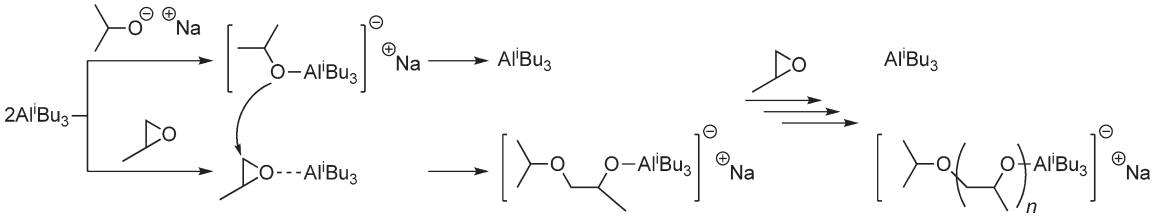
Recently, Lewis acid-accelerated high-speed polymerization of epoxides has been achieved with aluminate complexes. Deffieux *et al.* investigated the polymerization of PO by using a mixture of NaO^iPr and Al^iBu_3.[21] When an excess amount of Al^iBu_3 to NaO^iPr is added ([PO]/[NaO^iPr]/[Al^iBu_3] = 382/1/7.6), polymerization proceeds rapidly to give the polyether [100% conversion, TON = 382 mol (mol of NaO^iPr)$^{-1}$, TOF = 109 mol (mol of NaO^iPr)$^{-1}$ h^{-1}] with a relatively narrow MWD (PDI = 1.3) and an M_n of 23 600 g mol^{-1} close to the theoretical molecular weight calculated assuming the formation of one polymer chain per one molecule of NaO^iPr (Equation (2)). Based on the ^{13}C NMR analysis, regioregularity of the produced PPO is shown to be mainly with head-to-tail sequence, while stereoregularity is fully atactic.



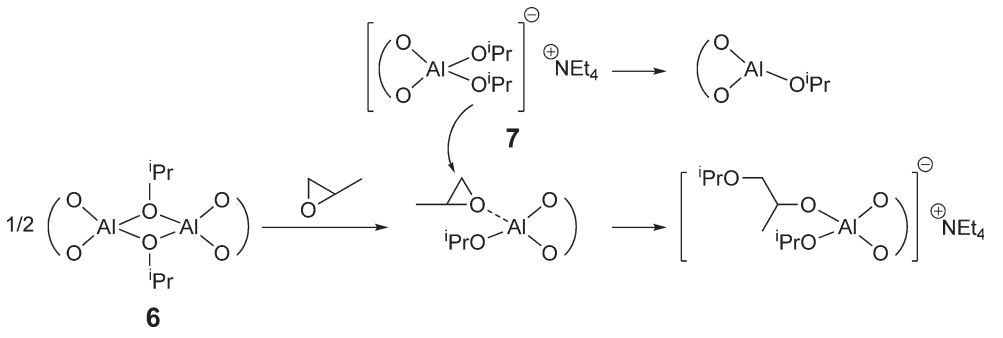
(2)

The amount of Al^iBu_3 critically influences the polymerization behavior: when the molar ratio [Al^iBu_3]/[NaO^iPr] is less or equal to 1, polymerization does not proceed. This suggests that all molecules of Al^iBu_3 are involved in the formation of an aluminate complex, which cannot activate and polymerize PO (Scheme 5). In contrast, in the presence of excess amount of Al^iBu_3, free Al^iBu_3 molecules can activate PO. The activated PO may be attacked by a nucleophile (propagating chain-end) on the aluminate complex, regenerating free Al^iBu_3 and aluminate complex (Scheme 5). Similarly to the aluminum–porphyrin/Lewis acid system discussed above, the increase of the amount of Al^iBu_3 resulted in the more rapid polymerization, while the molecular weight, that is, the number of polymer chains, was independent. Activation of PO was confirmed by ^1H NMR of a mixture of PO and Al^iBu_3, where a strong downfield chemical shift ($> +0.7$ ppm) of methylene and methine protons of PO indicated the strong deficiency of electron density on these carbons through a coordination to the aluminum center. On the other hand, the chemical shift of methyl protons shifted much less ($\sim +0.2$ ppm), indicating less activation through the complexation. This was one of the reasons why the polymerization proceeded in a living fashion without a significant chain-transfer reaction via the proton abstraction from the methyl group in spite of the use of alkali metal alkoxide. Reduction of basicity of the alkoxide in the aluminate complex also contributed to the decrease in the chain-transfer reaction.

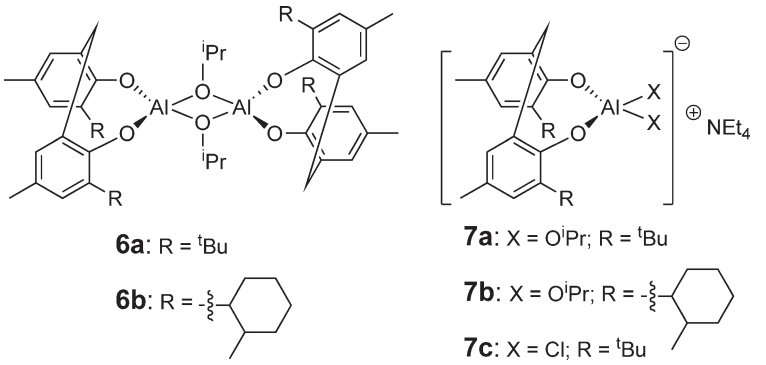
Okuda *et al.* also developed a polymerization system that involves use of a mixture of neutral aluminum complex and aluminate complex.[22] A combination of neutral and anionic aluminum complexes, **6** and **7**, realizes the high polymerization activity for PO, while the use of only **6** or **7** results in much slower or no polymerization, respectively. The best result is attained by using **6b** and **7b** to afford PPO in 77% conversion [TON = 154 mol (mol of Al)$^{-1}$, TOF = 51 mol (mol of Al)$^{-1}$ h^{-1}]. The produced polymer consists of exclusive head-to-tail bonding and is atactic with an M_n of 3580 g mol^{-1} and an M_w/M_n of 1.22. As shown in Scheme 6, the proposed reaction mechanism is related to that in Scheme 5. Dimeric neutral complex **6** reacts with PO to a labile adduct. The activated PO is attacked by a nucleophile, isopropoxide on aluminate complex **7**. The reaction is initiated by all of the isopropoxide ligands. Thus, an equimolar mixture of **6** and **7** ideally gives four polymer chains. According to the activation mechanism of PO, the higher catalytic activity with **6b** and **7b** is attributed to the bulky 1-methylcyclohexyl substituent on bisphenolate ligand, which causes a significant shift of monomer–dimer equilibrium in favor of the Lewis-acidic monomeric species.



Scheme 5 Proposed reaction mechanism catalyzed by NaO^iPr/Al^iBu_3 system.

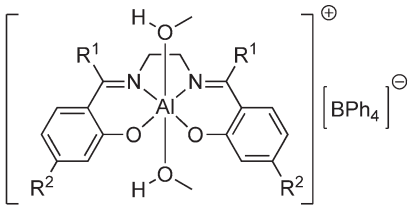


Scheme 6 Proposed reaction mechanism catalyzed by **6/7** system.

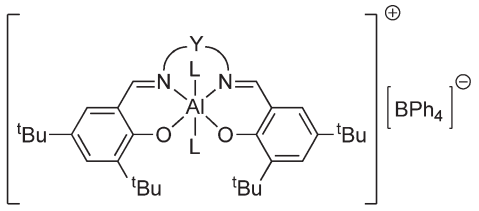


11.17.3.5 Cationic Aluminum Catalyst System

Cationic aluminum complex is one of the series of aluminum-based polymerization catalysts for epoxides. They are naturally electron deficient, advantageous for the effective activation of epoxides through coordination. On the other hand, the electron deficiency leads to the cationic propagation mechanism, generally resulting in the production of low molecular weight polyether. The first fully characterized cationic aluminum complex is reported by Atwood *et al.* They synthesized a series of cationic aluminum complexes **8** with a salen-type tetradentate Schiff base ligand and two methanol ligands.[23,24] These complexes are active for the polymerization of PO, and the resultant materials are oligomeric PPOs with an M_n of 750–1000. In contrast, cationic aluminum complexes **9** with THF ligands give high molecular weight polyether with narrow MWDs [**9a**: $M_n \approx 400\,000\ g\,mol^{-1}$, $M_w/M_n = 1.32$; **9b**: $M_n \approx 180\,000\ g\,mol^{-1}$, $M_w/M_n = 1.16$]. Cationic aluminum complexes **10**, **11**, and **12** are also synthesized and applied to the PO polymerization, resulting in the production of oligomeric materials with M_n of $<3000\ g\,mol^{-1}$ and PDIs of <1.6.[25–27] Recently, Dagorne *et al.* have developed a series of cationic aluminum complexes **13**, each of which consists of two regioisomers, with aminophenolate ligands.[28] These complexes have high catalytic activities for the PO polymerization at room temperature in toluene ([PO]/[**13**] = 200) to attain 50–60% conversion in 15 min, affording polyethers with M_n values of $<3100\ g\,mol^{-1}$ and M_w/M_n values of ≈1.6. In addition, the reaction with **13a** at 0 °C results in higher conversion of 70% to give the higher molecular weight polymer [$M_n = 9020\ g\,mol^{-1}$ and $M_w/M_n = 1.73$]. Regio- and stereoregularities are not discussed in the literature. Reed *et al.* successfully synthesized aluminum ion of Et_2Al^+ **14** with an icosahedral carborane counteranion.[29] This aluminum cation is employed for the polymerization of cyclohexene oxide (CHO) at room temperature to give poly(cyclohexene oxide) (PCHO) with an $M_n = 7600\ g\,mol^{-1}$ and an $M_w/M_n = 1.5$ in quantitative yield.

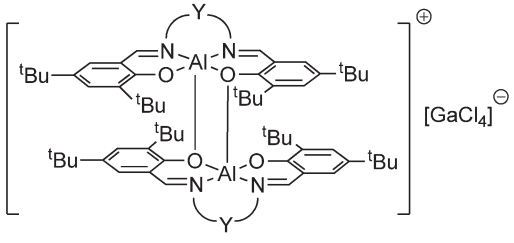


8a: $R^1 = R^2 = H$
8b: $R^1 = H$, $R^2 = Cl$
8c: $R^1 = Me$, $R^2 = H$



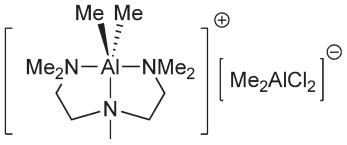
9a: Y = -CH2CH2-
9b: Y = -CH2CH2CH2-

L = thf



10a: Y = -CH2CH2CH2-

10b: Y =



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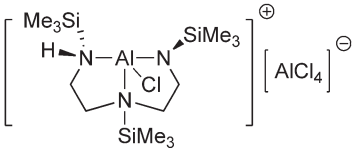

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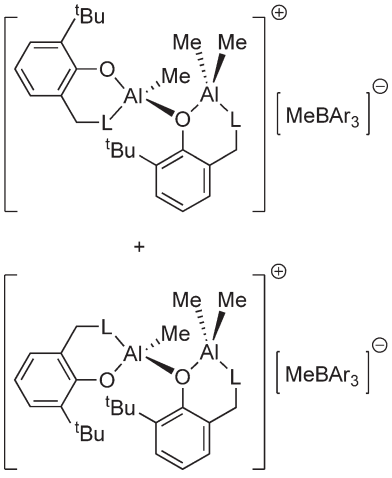
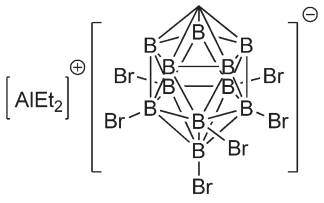


13a: L = NMe_2

13b: L = -N⟨ ⟩

13c: L = -N⟨ ⟩



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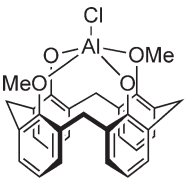
11.17.3.6 Other Aluminum-based Catalyst Systems

In the course of the investigation of epoxide polymerization catalysts, using a mixture of organometallic reagents and (poly)hydric compounds, Kuran *et al.* synthesized aluminum–calix[4]arene complex **15**.[30] The complex exhibits PO polymerization activities, though very low. The produced PPO contains only head-to-tail linkages, and molecular weights are in the range of 780–4770 g mol^{-1}. The same complex is also found to oligomerize CHO. Aluminum–carboxylate complexes **16** are also used for the CHO polymerization.[31] Tacticity of PCHOs produced by these aluminum complexes is generally atactic.



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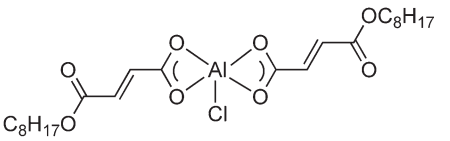

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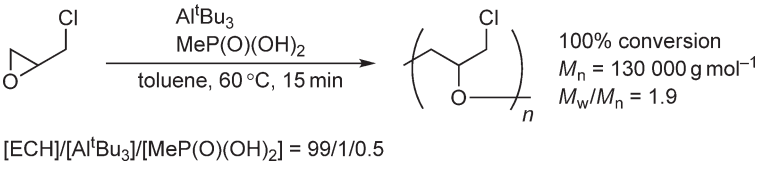
In 2000, Mason and Perkins reported a unique aluminum-based epoxide polymerization system.[32] When an aluminum complex prepared from a 2 : 1 mixture of Al^tBu_3 and methylphosphonic acid is used, ECH polymerizes rapidly at room temperature to give high molecular weight poly-ECH [$M_n = 130\,000\,g\,mol^{-1}$, $M_w/M_n = 1.9$; Equation (3)]. Polymerization of PO also proceeds rapidly to give the low molecular weight PPO [$M_n = 4050\,g\,mol^{-1}$, $M_w/M_n = 1.2$]. Since the molecular weight of polymer indicates that less than 10% of aluminum sites are active for producing the polymer, an oligomeric aluminum complex is supposed to be an active species although the characterization is not fully achieved. In this system, exclusion of a coordinated compound such as THF is essential for the high catalytic activities. Thus, aluminum complex prepared by the reaction of Al^tBu_3 and methylphosphonic acid in the presence of THF exhibits much less catalytic activity.



(3)

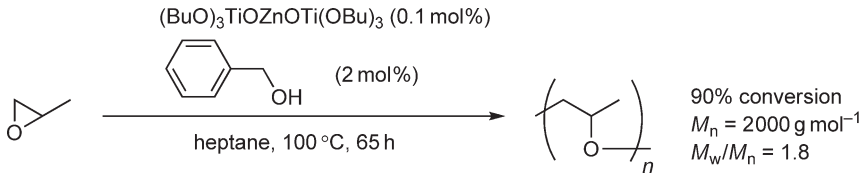
11.17.3.7 Zinc-based Catalyst System

As mentioned above, zinc complexes, particularly those derived from a mixture of diethylzinc and a (poly)hydric compound, have also been investigated as catalysts for the homopolymerization of epoxides, in relation to the co-polymerization of epoxides with CO_2. Kuran *et al.* developed the PO and CHO polymerization catalyst systems, using a mixture of $ZnEt_2$ with 4-*tert*-butylcatechol and/or phenol, or 1-phenoxy–2-propanol and a mixture of $ZnEt_2$ and pyrogallol. Here, multi-centered zinc complexes are supposed to catalyze the polymerization.[33] In general, the catalytic activity and initiating efficiency are very low. The obtained PPO has two fractions: higher and lower molecular ones; both are assigned to isotactic and atactic PPO, respectively. Well-defined discrete diphenoxyzinc complexes have also been demonstrated by Darensbourg *et al.* to be active for the homopolymerizaion of epoxide.[34] These complexes are investigated mainly as the catalysts for the co-polymerization with CO_2, as will be discussed later.

One of the most promising systems for the homopolymerization of epoxides is a multiple metal cyanide catalyst system, $Zn_3[Co(CN)_6]_2$, which was first reported in the 1960s.[35] This system was significantly studied during the following decade and shown to give narrow molecular weight polyethers in a wide range of molecular weight. However, the detailed reaction mechanism remained to be clarified, though few papers besides some patents were reported.[36] Recently, Wang *et al.* have developed a new multiple metal cyanide system for the polymerization of PO.[37] A mixture of $Zn_3[Co(CN)_6]_2$ and a protic compound, such as alcohol, carboxylic acid, and water, results in the formation of PPO with relatively narrow MWDs and head-to-tail linkages. The molecular weight of the produced polymer is generally dependent on a [PO]/[protic compound] ratio, while it is independent on a [PO]/[$Zn_3[Co(CN)_6]_2$] ratio. Thus, this system is much like the immortal polymerization described above (Scheme 1). Slow addition of PO is necessary for achieving a narrow MWD. In contrast, one-step PO addition gives rise to broad MWD, which is understood in the following way: high concentration of PO causes an increase in rate of propagation reaction {$P_nCH_2CH(CH_3)OH{\cdot}Zn_3[Co(CN)_6]_2 + PO \rightarrow P_{n+1}CH_2CH(CH_3)OH{\cdot}Zn_3[Co(CN)_6]_2$, P = polymer chain} prior to the rate of reversible exchange between the growing species and alcohol molecules {$P_nCH_2CH(CH_3)OH{\cdot}Zn_3[Co(CN)_6]_2 + P_mCH_2CH(CH_3)OH \leftrightarrow P_mCH_2CH(CH_3)OH{\cdot}Zn_3[Co(CN)_6]_2 + P_nCH_2CH(CH_3)OH$}.

A catalyst system with a zinc complex that also induces the chain-transfer reaction has been developed by Jérôme *et al.*[38] When the polymerization of PO is conducted by using a mixture of zinc/aluminum bimetallic complex $(BuO)_2AlOZnOAl(OBu)_2$ and phenoxyethanol ([PO]/[Zn]/[phenoxyethanol] = 1000/1/20), the conversion reaches 97% to give PPO that contains low and high molecular weight fractions. An additive of lithium chloride or

zinc/titanium bimetallic complex $(BuO)_3TiOZnOTi(OBu)_3$ exhibits a detrimental effect on the high molecular weight fraction, giving the polyether with a relatively narrow MWD (Equation (4)).



(4)

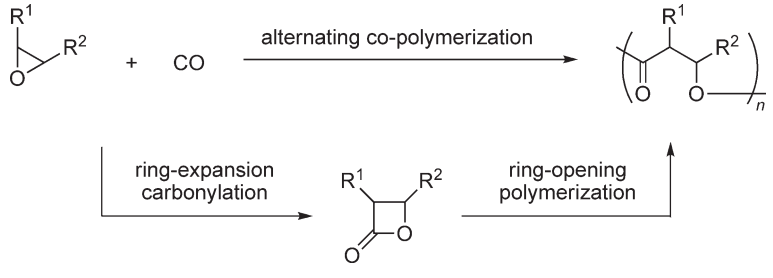
11.17.4 Alternating Co-polymerization of Epoxides with Carbon Monoxide

Alternating co-polymerization of epoxides with CO gives poly(3-hydroxyalkanoate)s. These polyesters have received considerable attention as engineering plastics or biomedical materials because of their biodegradable and biocompatible nature. One of the synthetic approaches to the polyesters is ring-opening polymerization of β-lactones,[39–42] which can also be effectively produced by ring-expansion carbonylation of epoxides (Scheme 7).[43–48] Meanwhile, "direct" alternating co-polymerization of epoxides with CO should be a more efficient route to produce them (Scheme 7).

11.17.4.1 Catalyst System for the Alternating Co-polymerization

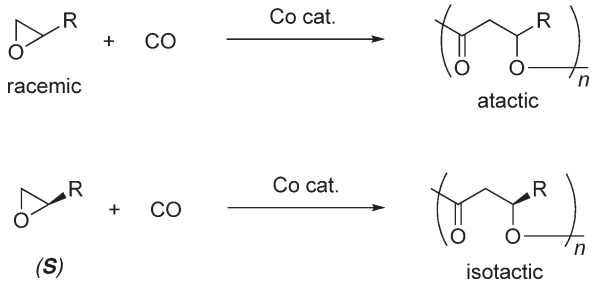
The first successful example of a co-polymerization was reported by Furukawa *et al.* in 1965.[49] Using a mixture of $AlEt_3$, H_2O, and $Co(acac)_3$, EO or PO co-polymerizes with CO to produce the corresponding polyesters. Although no advances were made in the following three decades, some cobalt complexes have recently been developed as active catalysts for the alternating co-polymerization of epoxides with CO. Rieger *et al.*[50,51] and Osakada *et al.*[52] independently studied a co-polymerization, using $Co_2(CO)_8$/3-hydroxypyridine catalyst system, which was originally discovered by Drent and Kragtwijk as a catalyst for ring-expansion carbonylation of epoxides.[43] When EO is co-polymerized with CO (Co: 0.64 mol.%), an almost completely alternating co-polymer with an M_n of 7,400 g mol^{-1} and an M_w/M_n of 1.6 is produced in 39% yield [TON = 61 mol (mol of Co)$^{-1}$; Table 3]. Co-polymerization of PO with CO gives the corresponding alternating co-polymer with high regioregularity. Racemic PO gives atactic polyester, whereas enantiomerically pure (*S*)-PO affords isotactic polyester with retention of configuration, indicating ring opening at the less-hindered epoxide carbon. A mixture of $Co_2(CO)_8$, $Ru_3(CO)_{12}$, and an amine additive is also revealed to be active for the co-polymerization of PO with CO.[52] Generally, molecular weight of the obtained co-polymer is lower [$M_n < 4000$ g mol^{-1}] than that estimated from a monomer-to-catalyst ratio and conversion of the monomer. One possible termination reaction is hydrolysis of a growing chain end, an acyl–cobalt complex, induced by a trace amount of water contaminated in the reaction system or produced by dehydration from the polymer chain end (*vide infra*).[51] Thus, addition of a dehydrating reagent such as dimethoxypropane slightly enhances the molecular weight.

As an active initiator for a co-polymerization, acyl–cobalt complexes also work well. As demonstrated by Alper and Lee, an equimolar mixture of $Co_2(CO)_8$, benzyl bromide (BnBr), and dihydro–1,10-phenanthroline **17**, possibly generating $BnCOCo(CO)_4$ under the reaction conditions, co-polymerized PO or 1,2-butene oxide with CO, and the



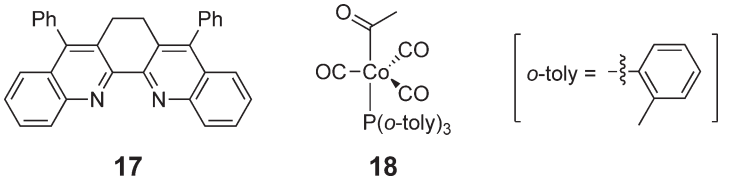
Scheme 7 Synthesis of poly(3-hydroxyalkanoate)s from epoxide and CO.

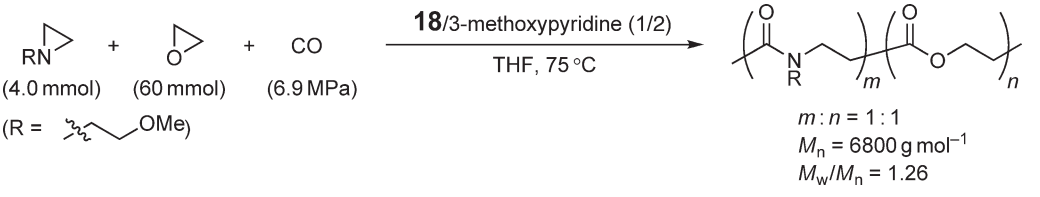
Table 3 Alternating co-polymerization of terminal epoxides with CO



Epoxide	*CO* (MPa)	*Catalyst system* (molar ratio)	*Co* (mol.%)	*Solvent*	*Yield* (%)	M_n (g mol^{-1})	M_w/M_n
EO	6.0	$Co_2(CO)_8$/3-hydroxypyridine (1/2)	0.64	Diglyme	39	7,400	1.6
EO	6.9	**18**/3-methoxypyridine (1/2)	0.33	THF	35	8,400	1.18
rac-PO	6.0	$Co_2(CO)_8$/3-hydroxypyridine (1/2)	2.2	Diglyme	73	3,800	2.0
(*S*)-PO	6.0	$Co_2(CO)_8$/3-hydroxypyridine (1/2)	2.2	Diglyme	57	4,200	1.3
rac-PO	6.2	$Co_2(CO)_8$/BnBr/**17** (1/1/1)	0.70	Benzene	55	19,400	1.63
1,2-butene oxide	6.2	$Co_2(CO)_8$/BnBr/**17** (1/1/1)	0.90	Benzene	61	16,700	1.28
(*S*)-PO	6.9	**18**/3-methoxypyridine (1/2)	0.47	DME	33	4,300	1.17

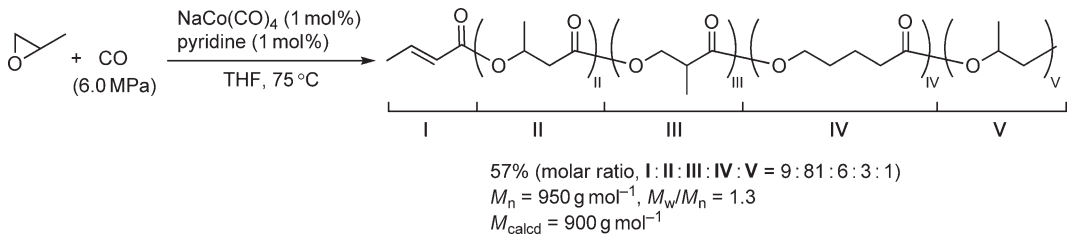
corresponding atactic polyesters are given with high regioregularities and high molecular weights.[53] A mixture of isolated acyl–cobalt complex **18** and pyridine derivatives is also applicable to the co-polymerization, as reported by Jia and Liu, although the high molecular weight co-polymer is not obtained because of base-assisted chain scission (*vide infra*).[54] Terpolymerization of EO, *N*-butylaziridine, and CO to produce the polyamide–polyester diblock polymer was also reported (Equation (5)).





(5)

Nozaki *et al.* demonstrated a successful example of selective synthesis of oligoesters bearing a crotonate terminal group through the alternating co-polymerization of PO with CO using $NaCo(CO)_4$ in the presence of an organic base (Equation (6)).[55] The relatively basic condition appears to lead to the dehydration from the polymer chain end and the chain scission to give oligoesters bearing a crotonate terminal group.

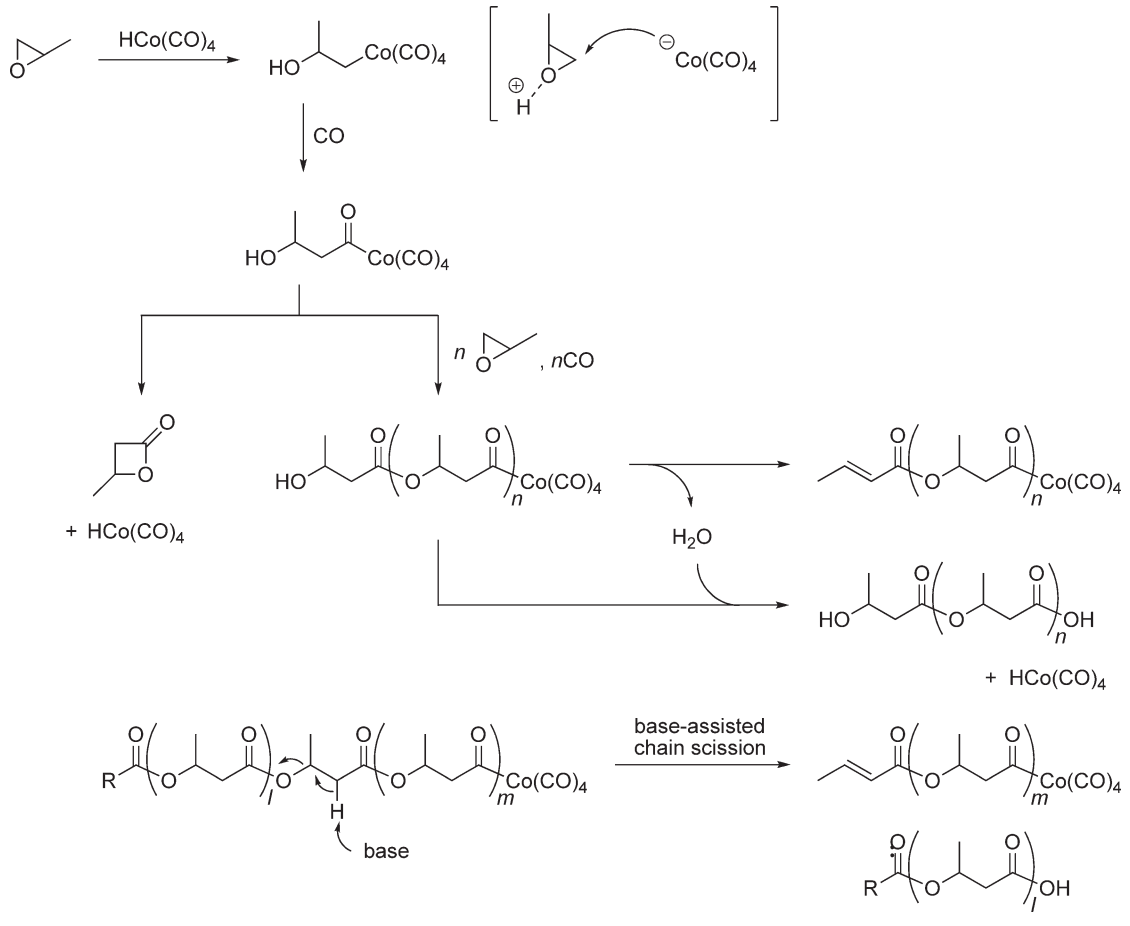


(6)

57% (molar ratio, **I** : **II** : **III** : **IV** : **V** = 9 : 81 : 6 : 3 : 1)
M_n = 950 g mol^{-1}, M_w/M_n = 1.3
M_{calcd} = 900 g mol^{-1}

11.17.4.2 Mechanistic Aspects

As mentioned above, the reaction of epoxides with CO can give the corresponding β-lactones. Thus, there are two possible routes to polyester formation: direct polymerization of epoxides with CO or ring-opening polymerization of β-lactone; these are the ring-expanding carbonylation products. In the catalyst systems described above, the direct polymerization of epoxides with CO is found to actually proceed to give the corresponding polyesters, on the basis of the fact that β-butyrolactone does not react under the reaction conditions. Some mechanisms for the polymerization mechanism have been proposed, and it has generally been accepted that the ring opening of epoxides proceeds by a nucleophilic attack of tetracarbonylcobaltate anion $[Co(CO)_4]^-$, although the detailed reaction mechanism has not yet been elucidated (Scheme 8).[56] In the $Co_2(CO)_8$/3-hydroxypyridine catalyst system, $HCo(CO)_4$ should work as an initiator. Ring opening of activated epoxides by the nucleophilic attack of tetracarbonyl cobaltate anion and the



Scheme 8 Reaction sequence in co-polymerization of PO with CO.

subsequent CO insertion gives the acyl–cobalt complex (Scheme 8). This species gives the co-polymers that have terminal hydroxy group, which may undergo dehydration to release a water molecule. Water behaves as a chain-transfer reagent by hydrolysis of acylcobalt to regenerate $HCo(CO)_4$. In contrast, acyl–cobalt complex initiators do not give the co-polymer containing a terminal hydroxyl group as reported by Alper and Lee and Jia and Liu. Thus, these initiators potentially produce high molecular weight co-polymers. Under the basic conditions, a random chain scission is proposed to take place to give the polyester with a crotonate end group, leading to a broad MWD (Scheme 8).

11.17.5 Alternating Co-polymerization of Epoxides with Carbon Dioxide

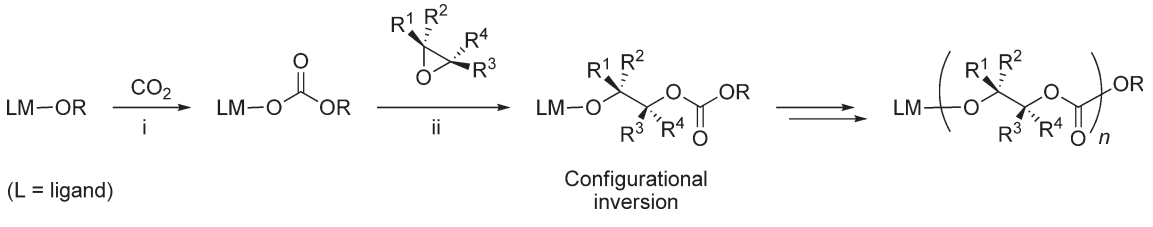
Epoxides can co-polymerize with CO_2 to give aliphatic polycarbonates. The co-polymerization is one of the most promising methods to utilize CO_2 as a C1 feedstock. The product polycarbonates have many potential applications because of their unique properties. For example, poly(propylene carbonate) (PPC) decomposes completely at 300 °C in any environment to leave a very small amount of ash. This feature makes it applicable to pore former for mesoporous carbon composites. Poly(cyclohexene carbonate) (PCC) has glass-transition temperature (T_g) of 115 °C, higher than 35–40 °C of PPC, endowing the materials with properties very similar to polystyrene.[57]

The co-polymerization of epoxide and CO_2 was first reported by Inoue, Koinuma, and Tsuruta in 1969, using Et_2Zn–H_2O catalyst system.[58] This discovery stimulated worldwide research in the subsequent two decades for exploration of more efficient catalyst systems for co-polymerization.[59–61] In general, the active catalysts consist of alkylmetal reagents (e.g., diethylzinc, triethylaluminum) and polyhydric compounds (e.g., resorcinols, pyrogallol, dicarboxylic acids). A combination of zinc hydroxide and dicarboxylic acids was also reported as a more highly active catalyst system. However, most of these catalysts are heterogeneous, and have low reproducibility and inability to achieve sufficiently high catalytic turnovers. Although the active species in the catalyst systems remain unknown, several mechanistic studies were carried out to indicate the multi-nuclei form for the co-polymerization. It was only during the last decade that well-defined and highly active catalyst systems were developed.[62,63] The mechanism is also detailed.

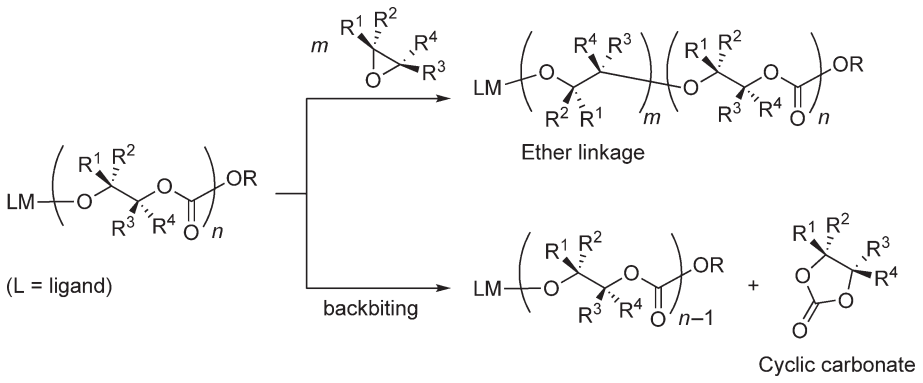
11.17.5.1 Mechanistic Aspects

The alternating co-polymerization of epoxides with CO_2 is accepted to proceed through a coordination anionic mechanism. The propagation process involves the following two steps (Scheme 9): (i) the insertion of CO_2 into metal–alkoxide bond and (ii) the insertion of epoxides into the resulting metal–carbonate bond. Thus, most metal initiators have (an) initiation group(s) such as alkoxide, carboxylate, and halide; all can attack CO_2 or epoxides nucleophilically. In most cases, the insertion of epoxides occurs via nucleophilic backside attack of a carbonate chain end, resulting in an inversion of the epoxide stereogenic center.

The alternating co-polymerization of epoxides with CO_2 is not free from two side-reaction paths (Scheme 10). One is a continuous insertion of epoxides to give a co-polymer with an ether linkage. The other is the production of cyclic carbonates, which are thermodynamically more stable than polycarbonates. Cyclic carbonate is typically formed through backbiting of metal–alkoxide growing species. These two undesirable paths are controlled by tuning the catalyst systems or reaction conditions (epoxide concentration, CO_2 pressure, reaction temperature).



Scheme 9 Proposed mechanism in the alternating co-polymerization of epoxides with CO_2.



Scheme 10 Side-reaction during the alternating co-polymerization of epoxides with CO_2.

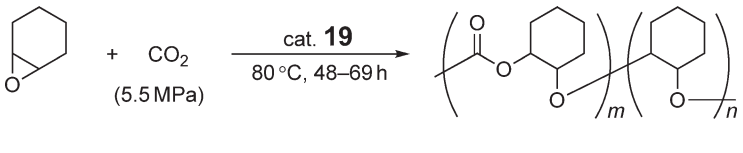
11.17.5.2 Zinc Catalyst System

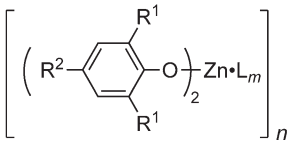
11.17.5.2.1 Diphenoxyzinc complex

Most of the prototype catalysts for the alternating co-polymerization are heterogeneous zinc complexes, which are usually prepared *in situ* and used without isolation. These complexes have the disadvantage of further tuning to achieve high reproducibility, high catalytic activity, and high selectivity. A leading work for the development of well-defined zinc catalysts was reported by Darensbourg and Holtcamp in 1995.[64] Bis(2,6-diphenylphenoxy)zinc complex **19a**, isolated as a diethyl ether adduct, co-polymerized CHO and CO_2 (5.5 MPa) at 80 °C to give the high molecular weight co-polymer [$M_n = 38\,000$ g mol^{-1}, $M_w/M_n = 4.5$, 91% carbonate linkage] with a TON of 173 mol (mol of Zn)$^{-1}$, and a TOF of 2.5 mol (mol of Zn)$^{-1}$ h^{-1} (Table 4). Based on ^{13}C NMR analysis, stereochemistry of the resulting co-polymer is shown to be atactic.

Substituents at 2,6-positions of a phenoxide ligand significantly influence the catalytic activity and carbonate/ether selectivity.[34,65,66] Complex **19b** with *ortho*-dimethyl substituents on the phenoxide ligand shows catalytic activity 2.4 times higher than complex **19a** to give the co-polymer with >90% carbonate linkage, indicating that the steric bulk is not essential for the high catalytic activity. Complex **19c** with *tert*-butyl substituents also exhibits high catalytic activity, yet gives the co-polymer with only 50% carbonate linkage. In contrast to complexes **19a–19c**, bis(2,6-dihalophenoxy)zinc complexes give almost completely alternating co-polymers (>99% carbonate linkage). The order of catalytic activity as a function of halogen substituents at 2,6-positions on the phenoxy ligand is F > Cl > Br. This trend reflects electron density on the zinc center: the more electron-withdrawing nature of F makes the zinc center more electron deficient, thereby rendering higher binding ability to epoxide. Addition of a phosphine ligand to the diphenoxyzinc complex is also effective for the production of the co-polymer with high carbonate linkage content. Thus, the tricyclohexylphosphine adduct of **19c**

Table 4 Alternating co-polymerization of CHO with CO_2 by using diphenoxyzinc complexes





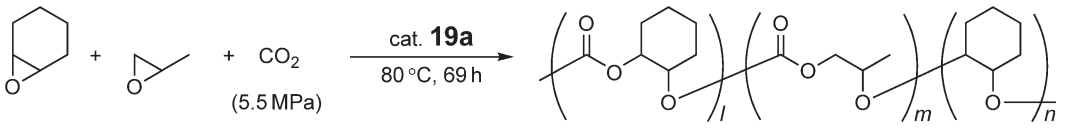
19a: R^1 = Ph; R^2 = H; L = Et_2O; m = 2; n = 1
19b: R^1 = R^2 = Me; m = 0; n = polymeric
19c: R^1 = ^{t}Bu; R^2 = H; L = THF; m = 2; n = 1
19d: R^1 = F; R^2 = H; L = THF; m = 1; n = 2
19e: R^1 = ^{t}Bu; R^2 = H; L = PCy_3; m = n = 1

Catalyst	*TON* (mol(mol of Zn)$^{-1}$)	*TOF* (mol(mol of Zn)$^{-1}$ h^{-1})	M_n (g mol^{-1})	M_w/M_n	*Carbonate linkage* (%)
19a	173	2.5	38 000	4.5	91
19d	363	7.6	42 000	6.0	>99
19e	380	6.1	*	*	92

*Not described in the literature.

produces the co-polymer containing 92% carbonate linkage without loss of a catalytic activity, while **19c** in the absence of a phosphine ligand gives the co-polymer with high ether linkage content as mentioned above.

The diphenoxyzinc derivatives generally catalyze the terpolymerization of CHO, PO, and CO_2 (Equation (7)).[64] In the presence of complex **19a**, the reaction of CHO, PO, and CO_2 (CHO/PO = 1/0.86) gives terpolymer [$M_n = 18\,000\ g\ mol^{-1}$ and $M_w/M_n = 11.9$] with little amount of propylene carbonate (PC) production. The resulting terpolymer is a random mixture of cyclohexene carbonate linkage (67%), propylene carbonate linkage (23%), and ether linkage (10%). In some cases, PC is formed via backbiting mechanism, leading to a decrease in catalytic activity because PC coordinates more strongly to zinc center than epoxides. Under the reaction conditions where diphenoxyzinc derivatives actively catalyze the terpolymerization, the reaction of PO with CO_2 leads predominantly to the production of PC.



(CHO/PO/**19a** = 100/86/0.19)

(7)

$l : m : n = 67 : 23 : 10$
$M_n = 18\,000\ g\ mol^{-1}$, $M_w/M_n = 11.9$
TON = 193 mol(mol of Zn)$^{-1}$
TOF = 2.8 mol(mol of Zn)$^{-1}$ h^{-1}

11.17.5.2.2 Zinc–β-diiminate (zinc–BDI) complex

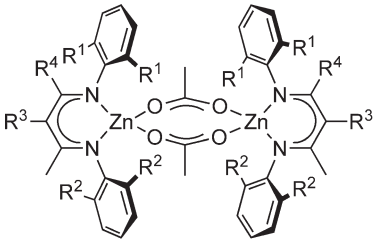
Coates *et al.* have developed a series of single-site zinc–BDI complexes **20** and **21** for the co-polymerization of epoxide with CO_2.[67,68] Design concept of the zinc complexes is a combination of (i) monoanionic chelating BDI ligand, which serves as a permanent ligand and (ii) an initiating group such as alkoxide and carboxylate, which mimics the putative propagating species of the polymer chain. One of the significant advantages of the BDI ligand is that the electronic and steric effects of ligand on the catalytic performance can be readily probed by systematic ligand variation.

In general, zinc–BDI catalysts show high catalytic activity under low pressure (0.69 MPa) and relatively low temperature (50 °C) and give almost completely alternating co-polymer with narrow MWD (Table 5). For instance, complex **20a** with isopropyl groups at 2,6-positions on the *N*-aryl rings promoted the co-polymerization of CHO with CO_2, giving the polycarbonate [$M_n = 15\,800\ g\ mol^{-1}$ and $M_w/M_n = 1.11$, carbonate linkage = 95%] with a high TOF of 360 mol (mol of Zn)$^{-1}$ h^{-1}. Subtle modification of *ortho*-substituents on the *N*-aryl rings brings a drastic change on catalytic activity. Sterically less-hindered ethyl group enhances the catalytic activity (complex **20b**), while much less hindered methyl group (complex **20c**) or larger *n*-propyl group (complex **20d**) results in no polymerization. Electronic feature also influences the catalytic activity: complex **21** with an electron-withdrawing cyano group on the β-diiminate framework promotes the co-polymerization, giving the highest catalytic activity [TOF = 2290 mol (mol of Zn)$^{-1}$ h^{-1}].

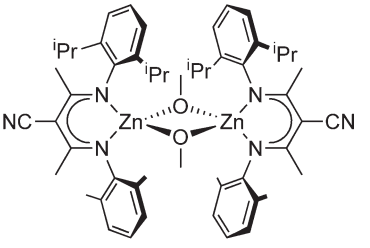
Table 5 Alternating co-polymerization of CHO with CO_2 catalyzed by zinc–BDI complexes

Catalyst	*TON* (mol(mol of Zn)$^{-1}$)	*TOF* (mol(mol of Zn)$^{-1}$ h^{-1})	M_n (g mol^{-1})	M_w/M_n	*Carbonate linkage* (%)
20a	180	360	15,800	1.11	95
20b	216	431	17,300	1.15	97
21	382	2,290	22,900	1.09	90

Reaction condition: [CHO]/[**20**] = 1,000/1, CO_2 (0.69 MPa), in neat CHO at 50 °C.



20a: $R^1 = R^2 = {}^iPr$; $R^3 = H$; $R^4 = Me$
20b: $R^1 = R^2 = Et$; $R^3 = H$; $R^4 = Me$
20c: $R^1 = R^2 = Me$; $R^3 = H$; $R^4 = Me$
20d: $R^1 = R^2 = Pr$; $R^3 = H$; $R^4 = Me$
20e: $R^1 = Et$; $R^2 = {}^iPr$; $R^3 = CN$; $R^4 = Me$
20f: $R^1 = {}^iPr$; $R^2 = Et$; $R^3 = H$; $R^4 = CF_3$



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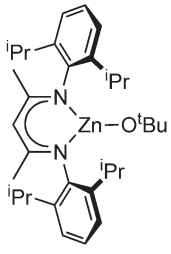
The zinc–BDI derivatives are also developed by other research groups for the co-polymerization of cyclohexene oxide with CO_2. Chisholm *et al.* isolated the monomeric zinc–BDI complex **22** with bulky alkoxide ligand, which should work as an initiating group for the co-polymerization.[69] The zinc–BDI complex **23** bearing ethylsulfinate ligands was synthesized by Rieger *et al.*[70] These two complexes are comparable to **20a** in catalytic activity. Zhang *et al.* investigated the oligomeric zinc–BDI catalyst **24**, which produced the highly alternating co-polymer.[71,72] Although the *N*-aryl group does not have 2,6-substituents, oligomeric structure should provide the steric hindrance, resulting in a moderate catalytic activity [TON = 275 mol (mol of Zn)$^{-1}$, TOF = 12 mol (mol of Zn)$^{-1}$ h^{-1})], lower than that of a simple zinc–BDI system. Immobilization of the zinc–BDI complex was developed by Jones and Yu.[73] The zinc–BDI complex **25** with trimethoxysilyl terminal group is supported on a well-defined hexagonal mesoporous silica material, SBA-15, with an average mesopore size of 105 Å and a surface area of 830 m^2 g^{-1}, and on a controlled-pore glass material, CPG-246, with a larger average pore size of 246 Å and a lower surface area of ~80 m^2 g^{-1}. The resultant silica-immobilized zinc–BDI catalysts co-polymerize CHO and CO_2 with lower catalytic activities and lower carbonate linkage contents compared to **20a**. This is partially due to the poor diffusion of CO_2 into the pores of the supported catalyst. A monomeric zinc species is supposed to promote the co-polymerization because the immobilization should significantly inhibit dimer formation.



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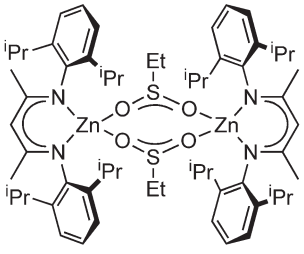

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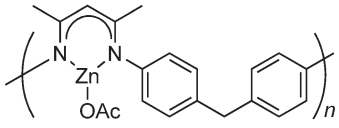

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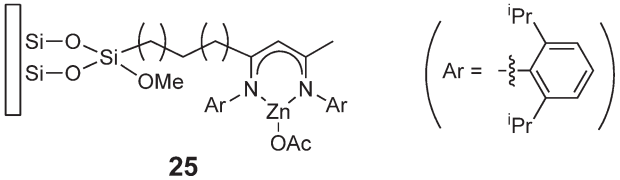
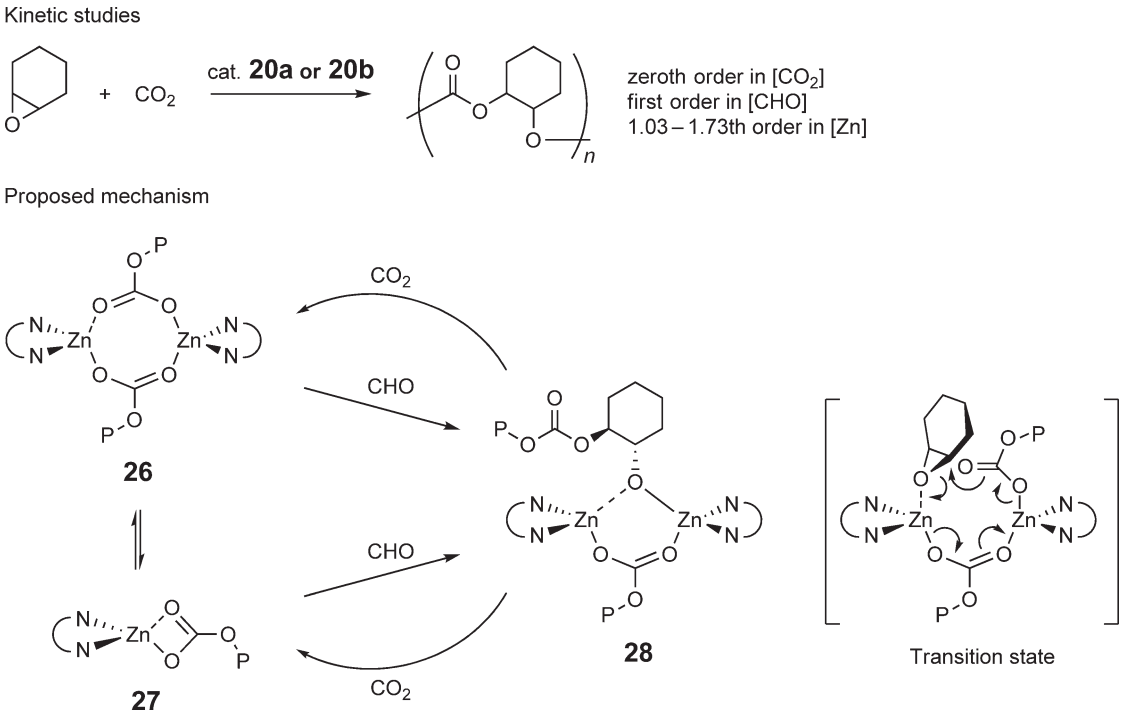


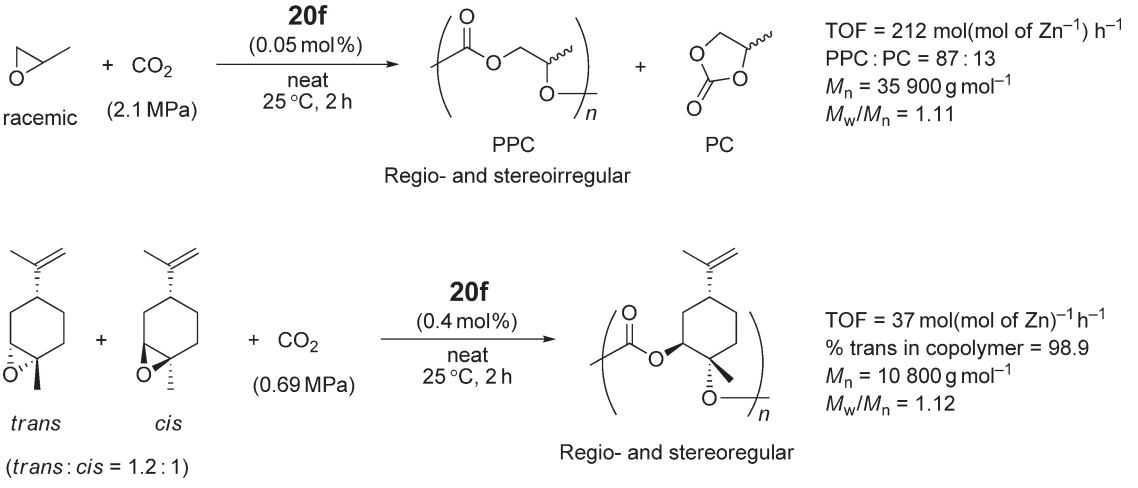
25

Enchainment mechanism is proposed to be based on the kinetic studies on the co-polymerization initiated by zinc–BDI complexes **20** (Scheme 11).[74] The rate of polycarbonate formation by using zinc–BDI is determined by *in situ* infrared monitoring of the emerging carbonyl stretch at approximately 1750 cm^{-1}. Reaction order in CO_2 monomer and CHO monomer is found to be zeroth and first order, respectively. With complex **20a**, orders in total zinc concentration at 30 and 50 °C are disclosed to be 1.37 ± 0.04 and 1.73 ± 0.06, respectively. The order in total zinc concentration apparently approaches two, and is most reasonably explained by a bimetallic transition state for epoxide ring opening and a predominantly monomeric ground state. The dynamic solution studies show that complex **20a** is in both dimer and monomer forms from −20 to 80 °C, and that the monomer form concentration increases along with temperature rise. Thus, if a bimetallic mechanism is operating, a higher percentage of monomeric ground state at higher temperature would increase the order in total zinc concentration. In contrast to the case of complex **20a**, the kinetic studies on the co-polymerization at 50 °C by using complex **20b** revealed that an order in total zinc concentration was 1.02 ± 0.03. According to the fact that complex **20b** existed as a dimer form in solution even at an elevated temperature of 100 °C, the order of 1.02 ± 0.03 minimized the possibility of monometallic transition state where the tight dimer form of **20b** should cause an order in total zinc concentration of 0.5. Based on these kinetic studies, a cooperative bimetallic enchainment mechanism is proposed, as described in Scheme 11. Both **26** and **27** participate in the ground state, and the ratio of **26** to **27** changes, depending on reaction temperature and steric and electronic factors of BDI ligand to alter the order in total zinc concentration. These monomeric and dimeric zinc–carbonate species both access a bimetallic transition state in the rate-determining step of the co-polymerization: one zinc species activates the epoxide and the other zinc species delivers the carbonate-propagating species. The ring opening of epoxide in a concerted fashion gives dizinc species **28** with alkoxide and carbonate chain end, followed by CO_2 insertion to regenerate zinc–carbonate species **26** and **27**.



Scheme 11 Kinetic studies on and proposed mechanism of the co-polymerization of CHO with CO_2 catalyzed by zinc–BDI complexes.

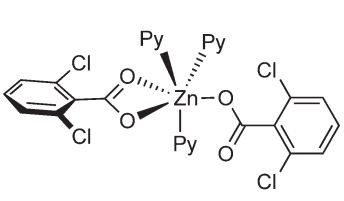
The zinc–BDI catalyst is active for the co-polymerization of PO with CO_2 (Scheme 12).[75] Complexes **20e** and **20f** with an electron-withdrawing group (CN or CF_3) and different *N*-aryl groups (2,6-diethyphenyl and 2,6-diisopropylphenyl groups) demonstrate the highest catalytic activity to give the completely alternating co-polymer (carbonate linkage >99%). The reaction gives cyclic PC as a byproduct, where the selectivity for the co-polymer is affected by subtle change of reaction temperature and CO_2 pressure. The resulting co-polymers are regio- and stereoirregular and exhibit narrow MWDs. Coates *et al.* also investigated the co-polymerization of limonene oxide with CO_2 (Scheme 12).[76] When the commercially available limonene oxide (*trans* : *cis* = 1.2 : 1) is used as a substrate, zinc–BDI complex **20f** selectively co-polymerizes *trans*-isomer to produce the co-polymer with high regio- and stereoregularities.



Scheme 12 Alternating co-polymerization of PO with CO_2 and limonene oxide with CO_2 catalyzed by zinc–BDI complex.

11.17.5.2.3 Other zinc complexes

A variety of well-defined zinc complexes has been investigated for the co-polymerization of epoxides with CO_2. For example, Darensbourg *et al.* synthesized zinc complexes **29–31** with benzoate, salicylaldiminate, and cyclopentadienyl ligands, respectively.[77–79] The complexes **29** and **30** exhibit almost the same catalytic activities as a series of bisphenoxyzinc complexes to give the completely alternating co-polymer, whereas complex **31** produces the co-polymer with <20% ether linkage in a lower catalytic activity [TOF = 1.2 mol (mol of Zn)$^{-1}$ h^{-1}]. Recently, Nozaki *et al.* demonstrated that chiral zinc complex **32** with amino alcoholate ligands catalyzed the co-polymerization of CHO with CO_2 to give optically active PCC (*vide infra*).[80,81] Zinc–pyridine alkoxide complex **33** is also found to catalyze the co-polymerization of CHO with CO_2 by Kim *et al.*[82] The catalytic activity is relatively high [TOF = 153 mol (mol of Zn)$^{-1}$ h^{-1}]. However, the resulting co-polymer possesses only 63% carbonate linkage content.



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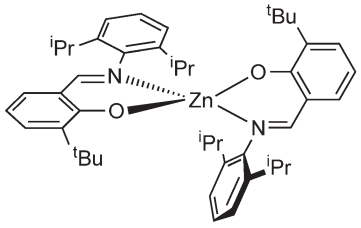

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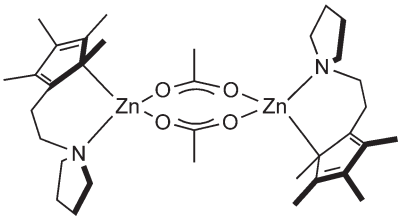

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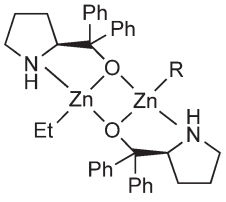
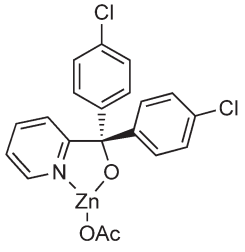


32a: R = Et
32b: R = OEt



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Heterogeneous zinc catalysts have also been investigated after the development of the pioneering catalyst systems based on a mixture of zinc sources and polyhydric compounds. Representatives are zinc glutarate systems, which now operate on an industrial scale for the production of PO/CO_2 co-polymer in China. As reported by Ree *et al.* in 1999, zinc glutarate co-polymerizes PO with CO_2 with a TOF of 3.4 mol (mol of Zn)$^{-1}$ h^{-1} to give high molecular weight co-polymer [M_n = 210 000 g mol^{-1}] with a relatively narrow PDI of 1.3.[83–85]

11.17.5.3 Cobalt Catalyst System

The cobalt catalyst for the co-polymerization of epoxides with CO_2 was first reported in 1979 by Soga *et al.*[86] Cobalt acetate co-polymerizes PO with CO_2 to give the almost completely alternating co-polymer, yet with a quite low catalytic activity. For the next quarter of a century, cobalt-based catalyst for the co-polymerization was not developed.

Recently, Coates *et al.* investigated cobalt–salen complex for the co-polymerization of PO with CO_2.[87] Under the conditions of high CO_2 pressure (5.5 MPa) and the optimal reaction temperature (25 °C), the enantiopure cobalt–salen complexes **34a–34c** catalyze the co-polymerization of *rac*-PO with CO_2 to selectively give the co-polymer without cyclic byproducts in measurable quantities (Table 6). The produced polycarbonates are highly alternating with >95% carbonate linkages, MWDs being narrow. Regarding the regioselectivity of PO enchainment, complex **34c** is highly selective with 80% head-to-tail linkage, while complexes **34a**, **34b**, and zinc complex **20f**, described above, have regioselectivities of 70%, 75%, and 60%, respectively.

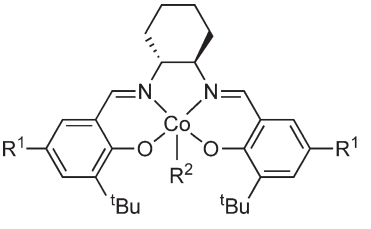
Addition of a quaternary ammonium salt to a cobalt–salen catalyst drastically enhances the catalytic performance for the co-polymerization of PO with CO_2. Lu and Wang investigated the binary catalyst system that consisted of a cobalt–salen complex and a tetrabutylammonium salt (Table 6).[88] This binary catalyst system is able to promote

Table 6 Alternating co-polymerization of terminal epoxides with CO_2 catalyzed by cobalt–salen complexes

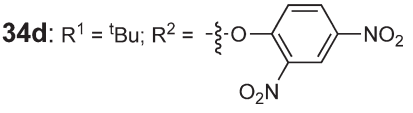
Epoxide	*Catalyst*	*CO_2* (MPa)	*Co* (mol.%)	*T* (°C)	*TON* (mol(mol of Co)$^{-1}$)	*TOF* (mol(mol of Co)$^{-1}$ h^{-1})	*M_n* (g mol^{-1})	*M_w/M_n*	*Carbonate linkage* (%)	*Head-to-tail linkage* (%)
rac-PO	**34a**	5.5	0.2	25	243	81	15 300	1.22	95	70
rac-PO	**34b**	5.5	0.2	25	198	66	9000	1.31	96	75
rac-PO	**34c**	5.5	0.2	25	177	59	8100	1.57	99	80
(*S*)-PO	**34c**	5.5	0.2	25	213	71	6900	1.58	>99	93
rac-PO	**34d**/Bu_4NCl (1 : 1)	2.0	0.05	25	771	257	30 400	1.36	>99	>95
rac-1,2-Butene oxide	**34d**/Bu_4NCl (1 : 1)	2.0	0.05	25	366	61	11 600	1.26	>99	*
rac-1,2-Hexene oxide	**34d**/Bu_4NCl (1 : 1)	2.0	0.05	40	384	48	7300	1.11	>99	*

*Not described in the literature.

co-polymerization and shows high selectivity for PPC over PC under low CO_2 pressure (0.20–2.0 MPa). The axial group in the cobalt complex and a counteranion of ammonium salt are essential for the high selectivity. Thus, a combination of cobalt–salen complex **34d** with dinitrophenoxy axial group and tetrabutylammonium chloride produces the completely alternating co-polymer with a high selectivity for PPC (>99%), while a mixture of **34a** and tetrabutylammonium bromide predominantly gives PC. Furthermore, the co-polymers obtained with the binary catalyst system, in general, have an unprecedented head-to-tail content of >95%. Other terminal epoxides, such as 1,2-butene oxide and 1,2-hexene oxide, are also co-polymerized to give the corresponding polycarbonate with >99% carbonate linkage.

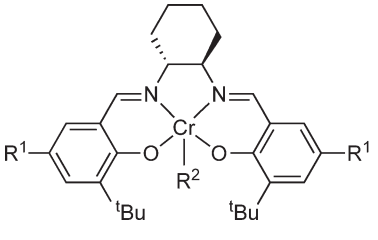


34a: R^1 = Br; R^2 = OAc
34b: R^1 = H; R^2 = OAc
34c: R^1 = ^{t}Bu; R^2 = OAc

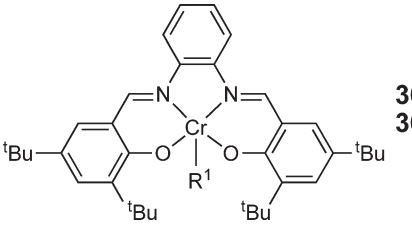


11.17.5.4 Chromium Catalyst System

Chromium complexes have been found to promote the co-polymerization of epoxides with CO_2.[86] Recently, Darensbourg *et al.* have demonstrated that the chromium–salen complexes, remarkably more stable to the air and moisture than zinc-based co-polymerization catalysts, are effective catalysts for the co-polymerization of CHO with CO_2.[89–92] Under the condition of 5.9 MPa CO_2 pressure at 80 °C, complex **35a** transforms CHO to the completely alternating co-polymer with a TON of 250 mol (mol of Zn)$^{-1}$ and a TOF of 10 mol (mol of Zn)$^{-1}$ h^{-1}, along with a small amount of cyclic carbonate production (Table 7).



35a: R^1 = ^{t}Bu; R^2 = Cl
35b: R^1 = OMe; R^2 = N_3



36a: R^1 = Cl
36b: R^1 = N_3

Table 7 Alternating co-polymerization of epoxide with CO_2 catalyzed by chromium–salen complexes

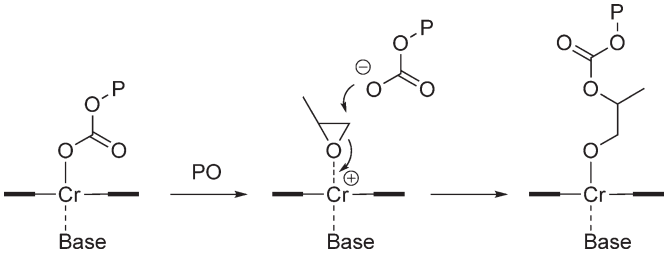
Epoxide	*Catalyst*	*CO_2* (MPa)	*Cr* (mol.%)	*T* (°C)	*TON* (mol(mol of Cr)$^{-1}$)	*TOF* (mol(mol of Cr)$^{-1}$ h^{-1})	M_n (g mol^{-1})	M_w/M_n	*Carbonate linkage* (%)	*Polymer/cyclic*
CHO	**35a**	5.9	0.04	80	250	10	8900	1.2	> 99	*
CHO	**35b**/$PPNN_3$ (1 : 1)	3.5	0.04	*	*	1150	50 000	1.1	> 99	*
rac-PO	**36a**/DMAP (1 : .5)	1.3	0.067	75	177	154	15 800	1.89	91	82/18
rac-PO	**36b**/PPNCl (1 : 1)	3.4	0.03	60	768	192	*	*	99	93/7

*Not described in the literature.

The catalytic activity is enhanced by addition of a neutral Lewis base (*N*-Me–imidazole and tricyclohexylphosphine) or anionic additive (chloride and azide with PPN^+ (bis(triphenylphosphoranylidene)ammonium) as a non-interactive countercation), which should bind to the vacant axial site of chromium–salen complex. The catalytic activity increases in the order of azide > chloride > tricyclohexylphosphine > *N*-Me–imidazole. Substituents on the salen ligand and the axial ligand on the chromium center also influence the catalytic activity. In general, bulky groups on the ethylenediimine backbone oriented perpendicular to the salen plane reduce the catalyst activity, whereas such groups oriented parallel to the salen plane do not retard the co-polymer formation. Additionally, chromium–salen complexes with 3-*tert*-butyl–5-methoxysalicylidene unit and/or azide as an axial ligand give better results. Accordingly, under identical conditions, complex **35b** demonstrates the activity of TOF = 1150 mol (mol of Cr)$^{-1}$ h^{-1} to produce the co-polymer with > 99% carbonate linkage, $M_n = 50\,000\,g\,mol^{-1}$, and $M_w/M_n = 1.1$. None of the single enantiomers of chromium–salen complexes **35a** and **35b**, applied to the co-polymerization, induces asymmetric desymmetrization of CHO.

The chromium–salen complexes are active for the co-polymerization of terminal epoxides with CO_2 (Table 7). Rieger *et al*. developed the chromium–salen catalyst for the co-polymerization of PO with CO_2.[93] The catalyst system composed of complex **36a** and DMAP (0.5–1.0 equiv. to **36a**) shows high catalytic activity to give mainly PPC, with a significant formation of cyclic carbonate [TOF = 154 mol (mol of Cr)$^{-1}$ h^{-1}) for PPC, TOF = 34 mol (mol of Cr)$^{-1}$ h^{-1}) for PC]. The relatively high selectivity for the production of co-polymer over cyclic carbonate is due to the phenylene backbone. Indeed, use of complex **35a** leads to the predominant production of cyclic carbonate. Subsequent investigation by Darensbourg *et al*. demonstrates that a combination of complex **36b** with azide as the axial ligand and $PPNN_3$ or PPNCl (1 equiv. to **36b**) affords higher catalytic activity, minimizing the production of cyclic byproduct ($PPNN_3$: PPC/PC = 84/16, PPNCl : PPC/PC = 93/7) in spite of relatively high polymerization temperature. The resulting co-polymer has a completely alternating sequence, yet regioirregular structure.

Mechanistic studies on the co-polymerization using a mixture of chromium–salen complex and a neutral base or an anionic additive have been investigated by *in situ* infrared monitoring. The propagating step is found to be a first order in chromium concentration. Although the detailed mode in the ring-opening process is not clear at the current time, the consensus on the role of a neutral or anionic base is that the chromium–carbonate chain-end bond is forced to be labile for the attack to the epoxide. One of the most plausible mechanisms is proposed by Rieger *et al*.: the dissociated carbonate chain end attacks the epoxide, which coordinates to and is activated by a cationic chromium center (Scheme 13). In addition, a neutral base or an anionic additive is supposed to often behave as an initiator.

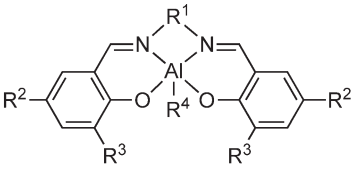


Scheme 13 Proposed mechanisms in the co-polymerization of CHO with CO_2 catalyzed by chromium–salen complexes.

11.17.5.5 Aluminum Catalyst System

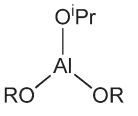
Potential activity of aluminum as a catalyst for the co-polymerization of epoxides with CO_2 has been known for a few decades. A mixture of triethylaluminum with water or a Lewis base, such as 2,2′-bipyridyl or triphenylphosphine, shows the catalytic activity.[94] Inoue *et al.* reported the first single-site catalyst for the co-polymerization by using aluminum–porphyrin complexes **1a**.[95] These catalysts give polycarbonates in a living manner with low MWDs. The catalytic performance is significantly enhanced by addition of an ammonium or phosphonium salt to give the co-polymer with high carbonate linkage contents. The aluminum–porphyrin catalyst system is one of the most successful examples in the aluminum-based catalyst systems and should be the roots of the recent advances in the chromium- or cobalt-based catalyst systems.

In 1998, Kuran *et al.* reported aluminum–calix[4]arene catalyst **15** for the co-polymerization of PO or CHO with CO_2.[30] The catalytic activity was low and gave the co-polymer with high ether linkage content. Inoue and Sugimoto investigated a combination of aluminum–salen complex **37a** and quaternary ammonium salt (Et_4NOAc) as a catalyst system for the co-polymerization of CHO with CO_2.[62] The co-polymer obtained has a highly alternating sequence (94% carbonate linkage content) with an M_n and an M_w/M_n of 10 000 g mol^{-1} and 1.5, respectively. Darensbourg *et al.* independently developed a **37b**/Bu_4NN_3 catalyst system, giving completely alternating co-polymer of CHO with CO_2 with TOF of 35 mol (mol of Zn)$^{-1}$ h^{-1}).[96] Beckman *et al.* demonstrated the catalytic activities of aluminum–carboxylate complex **16**[31] and aluminum–alkoxide complexes **38**,[97,98] showing the composition of the PO/CO_2 co-polymers varied between a homopolymer to a completely alternating co-polymer. They also showed that the co-polymer with relatively low carbonate linkage content exhibited lower miscibility pressure than poly(perfluoroether)s with the same number of repeating units.

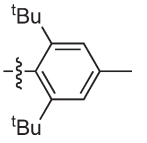


37a: R^1 =  ; $R^2 = R^3 = H$; $R^4 = Me$

37b: R^1 =  ; $R^2 = NO_2$; $R^3 = {}^tBu$; $R^4 = Me$

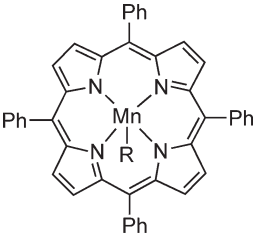


38a: R = 

38b: R = 

11.17.5.6 Manganese Catalyst System

Recently, Sugimoto *et al.* demonstrated that manganese–porphyrin complex **39** co-polymerized CHO with CO_2.[99] Even under 0.10 MPa of CO_2, the co-polymerization proceeds to give a co-polymer with high carbonate linkage content of 95%.



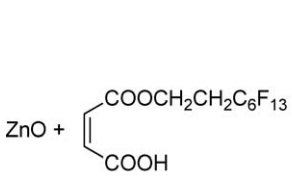
R = OAc

39

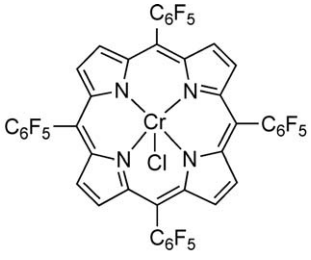
11.17.5.7 Co-polymerization in Supercritical Carbon Dioxide

Supercritical fluids show unique physicochemical properties, such as density, diffusivity, solubility, and viscosity; all can be easily controlled by changing temperature and pressure. Thus, these fluids are attractive as a useful solvent for chemical reactions and the following purification. Particularly, supercritical CO_2($scCO_2$) has the advantages of relatively low critical temperature and pressure (critical temperature (T_c) = 304.2 K, critical pressure (P_c) = 7.28 MPa), non-flammability, and inexpensiveness.

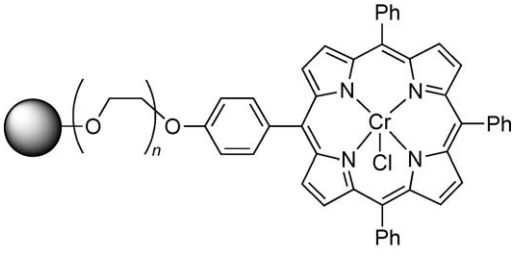
Co-polymerization of epoxides in $scCO_2$ was reported by Darensbourg *et al.*, who used heterogeneous zinc glutarate prepared from zinc oxide and glutaric acid as a catalyst.[100] Under 8.3 MPa CO_2 at 85 °C, co-polymerization of PO gives PPC with high carbonate linkage content. A CO_2-soluble zinc catalyst **40** prepared from zinc oxide and perfluorinated maleic acid monoester was developed by Beckman *et al.* for the co-polymerization of CHO with CO_2.[101,102] The reaction produces the alternating co-polymer containing a small content of polyether linkage. The high molecular weight co-polymers are generally obtained, but with broad MWDs. The chromium porphyrin catalyst **41** with four pentafluorophenyl substituents is also investigated by Holmes *et al.* as a CO_2-soluble catalyst for the co-polymerization.[103] The complex **41**/DMAP system shows high catalytic activity to co-polymerize CHO and CO_2, affording the co-polymer with PDIs of <1.4 and molecular weights of <10 000 g mol^{-1} lower than those estimated from the co-polymer yields and the monomer/catalyst ratios. Holmes *et al.* also investigated co-polymerization under $scCO_2$ by using a polymer-supported chromium porphyrin catalyst system **42**.[104] The immobilized chromium catalyst can successfully be recycled, although a decrease in molecular weight and yield is observed. This may be due to minor leaching of the metal from porphyrin ligand, as indicated by mild coloration of the produced co-polymer. In spite of the slight coloration, the immobilized chromium catalyst appears to prevent the polymer products from becoming intensely green colored as observed when complex **41** is used. Common to the co-polymerization system in $scCO_2$, co-polymer production is significantly affected by CO_2 pressure, which changed a phase behavior.



40



41

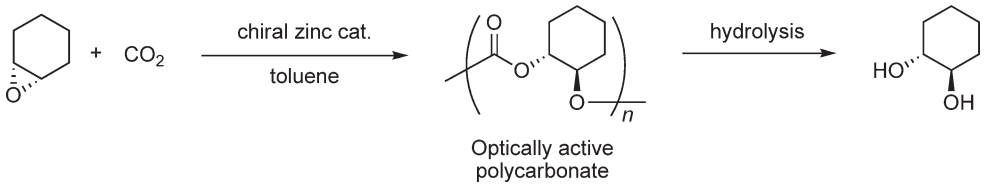


42

11.17.5.8 Asymmetric Co-polymerization of Epoxides with CO_2

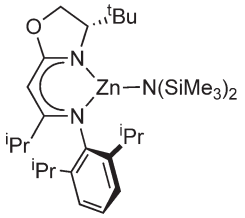
The first asymmetric alternating co-polymerization of *meso*-epoxide and CO_2 was successfully achieved with CHO and chiral zinc complexes by Nozaki *et al.*[80,81] Homochiral dimeric zinc complex **32a**, prepared from diethylzinc and (*S*)-diphenyl(pyrrolidin-2-yl)methanol, catalyzes the co-polymerization of CHO and CO_2 to produce completely alternating, optically active polycarbonate (Table 8). Enantioselectivity of the diol unit in the co-polymer is estimated to be 49% based on ee of the *trans*-cyclohexane–1,2-diol unit, which is isolated after alkaline hydrolysis of the resulting co-polymer. Chain-end assignment by MALDI-TOF mass spectrometry of the obtained co-polymer reveals that the co-polymer (co-polymer **I**) has an amino alcoholate moiety at a chain end, and that the reaction is initiated by CO_2 insertion into the Zn–amino alkoxide bond. Treatment of complex **32a** with 0.2–1.0 molar equiv. of ethanol enhances the catalytic performance, resulting in higher yields, lower MWD, and higher enantioselectivity up to 80% ee. In contrast, use of 2.0 molar equiv. of ethanol reduces the catalytic activity drastically. The ethanol effect is remarkable, as evidenced by MALDI-TOF mass spectrometry. When ethanol is added to the reaction mixture, the co-polymerization gives co-polymer **II**, which is shown to include an ethoxy end group. These results show that dizinc complex **32b** with an ethoxy group on one zinc center and an ethyl group on the other zinc center should be an effective initiator to start the co-polymerization through CO_2 insertion into the Zn–OEt bond. Accordingly, a bimetallic mechanism is proposed for the enchainment steps. The ^{13}C NMR spectroscopic studies on the resulting optically active polycarbonate and the model oligomers revealed that ^{13}C NMR signals in the carbonyl region split, reflecting the tetrad stereoseqences, and the signals for isotactic diads appeared in a lower field (153.7 ppm) than those for syndiotactic diads (153.3–153.1 ppm).[105] In spite of high stereoregularity, the optically active co-polymer has a T_g almost the same as the atactic one.

Table 8 Asymmetric alternating co-polymerization of CHO with CO_2 catalyzed by chiral zinc complexes



Catalyst	*CO_2* (MPa)	*Zn* (mol.%)	*T* (°C)	*TON* (mol (mol of Zn)$^{-1}$)	*TOF* (mol(mol of Zn)$^{-1}$ h^{-1})	M_n (g mol^{-1})	M_w/M_n	*ee of diol* (%)
32a	3.0	5.0	40	11	0.6	11 800	15.7	49
32a/EtOH (1 : 0.2)	3.0	5.0	40	19	1.0	12 300	7.18	64
32a/EtOH (1 : 0.8)	3.0	5.0	40	18	1.0	6300	1.43	75
32a/EtOH (1 : 0.8)	3.0	1.7	40	53	1.2	16 100	1.19	70
32a/EtOH (1 : 1)	3.0	5.0	40	14	0.7	4500	1.82	76
43	0.69	1.0	20	100	4.2	14 700	1.35	72

Chiral zinc complex **43** with imine–oxazoline ligand also co-polymerizes CHO and CO_2 in an asymmetric manner.[106] This zinc complex exhibited higher catalytic activity [TOF = 4.2 mol (mol of Zn)$^{-1}$ h^{-1}] and slightly lower enantioselectivity (72% ee of the diol unit) than a mixture of **32a** and ethanol, giving a co-polymer with > 99% carbonate linkage, an $M_n = 14{,}700$ g mol^{-1}, and an $M_w/M_n = 1.35$. The same complex is also applicable to asymmetric co-polymerization of cyclopentene oxide with CO_2.



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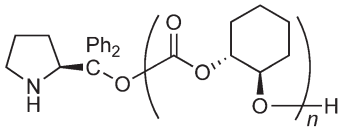
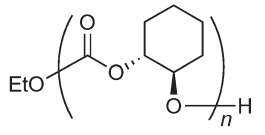
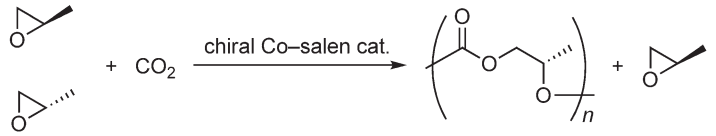


Co-polymer I



Co-polymer II

Enantiomer-differentiating co-polymerization of terminal epoxides is achieved by chiral chromium and cobalt complexes. Jacobsen *et al.* reported the co-polymerization of 1-hexene oxide with CO_2 by using complex **35a**.[107] The reaction proceeds with kinetic resolution: at 90% conversion, the unreacted epoxide is found to be enriched in the (*R*)-enantiomer of 90% ee. Detailed information about the resultant polymer, however, is not described. As discussed in the previous section, chiral cobalt–salen complex **34c** co-polymerizes PO and CO_2 (Table 3).[87] When **34c** with *trans*-(1*R*,2*R*)-diaminocyclohexane backbone is applied to the co-polymerization, (*S*)-PO is consumed preferentially over (*R*)-enantiomer with a k_{rel} of 2.8 to give optically active PPC (Equation (8)). In a similar manner, a binary catalyst system, **34d**/Bu_4NCl, preferentially consumes (*S*)-PO over (*R*)-PO with $k_{rel} = 2.8$–3.5.[88]



(8)

In this chapter, polymerization of epoxides and co-polymerization of epoxides with CO or CO_2, which give polyethers, polyesters, and polycarbonates, respectively, are reviewed. During the last decade, significant advances

in catalyst systems for these polymerizations have been achieved. In particular, the development of homogeneous and well-defined metal complex catalysts is of importance because a tailored design and a fine tuning of metal complex catalysts is easier than the case of heterogeneous ones. Indeed, some of the well-defined homogeneous catalyst systems have succeeded in much higher polymerization rate and the control of molecular weights and/or regio- and stereoregularities to some extent.

Needless to say, the potential utility of the polymer depends on its repeating unit, end group, molecular weight, and regio- and stereoregularities. Thus, based on the recent significant advances, future study would be directed to the development of new catalyst system, which expands the scope of epoxide monomer and further improves productivity, molecular weight control, and regio- and stereoselectivities. In addition, a new combination of epoxides and other co-monomers should lead to the production of unique co-polymers. As a result, the field of polymerization of epoxides should constitute a more important part of macromolecular chemistry.

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11.18
Ring-opening Metathesis Polymerization (ROMP)

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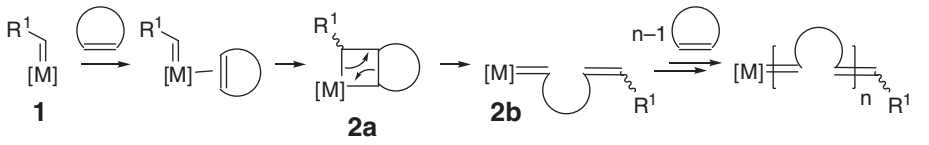
11.18.1 Introduction

Since its discovery more than 50 years ago, olefin metathesis has evolved from its origins in binary and ternary mixtures of the Ziegler–Natta type into a research area dominated by well-defined molecular catalysts. Surveys of developments up to 1993 were presented in COMC (1982) and COMC (1995).[1,2] Major advances in ROMP over the last 10 years include the development of modular, stereoselective group 6 initiators, and easily handled, functional-group tolerant ruthenium initiators. The capacity to tailor polymer functionality, chain length, and microstructure has expanded applications in materials science, to the point where ROMP now constitutes one of the most powerful methods available for the molecular-level design of macromolecular materials. In addition to an excellent and comprehensive text on olefin metathesis,[3] a three-volume handbook[4] has recently appeared, of which the third volume focuses specifically on applications of metathesis in polymer synthesis.

A simplified model of the Chauvin mechanism for olefin metathesis, showing only productive, irreversible metathesis polymerization, is represented in Equation (1). This model applies most stringently to ROMP of strained (typically bicyclic) olefins under non-equilibrium conditions, in which chain transfer and backbiting reactions are minimized. The initiator, a metal alkylidene complex **1**, reacts with incoming cycloolefin to generate a metallacyclobutane intermediate **2a**. Ring-opening yields the first insertion product, **2b**, after which chain growth is propagated by further reaction with monomer. The majority of the well-defined catalysts reported since 1993 are alkylidene complexes. Few new, stable metallacyclobutane complexes have been reported. In the important Ru systems, computational[5,5a] and experimental[5b,5c] evidence suggest that metallacyclobutane species commonly function as relatively high-energy intermediates on the reaction coordinate.



(1)

11.18.2 ROMP Initiators

At the beginning of the 1990s, metathesis chemistry was dominated by ROMP, and virtually all new examples of metal alkylidene complexes were evaluated for activity in ROMP of cyclooctene (COE), cyclooctadiene (COD), or norbornene (NBE) monomers. The tremendous growth in applications of olefin metathesis in organic chemistry has caused ring-closing metathesis (RCM) to displace ROMP as the "benchmark" reaction in which the most active new catalysts are assayed. In the discussion below, new alkylidene complexes are described irrespective of whether they have been tested in ROMP, or more demanding metathesis reactions. Of particular importance in ROMP applications are tunable activity (which enables matching of the reactivity of monomer and initiator), and initiator efficiency; that is, the extent to which the turnover number (TON) observed for a given precatalyst reflects the activity of the ensemble of catalyst molecules, versus that of a smaller proportion of "initiated" species. High efficiency is critical for the construction of well-defined polymer materials, as low rates of initiation, relative to propagation, result in high molecular weights and broad polydispersity index (PDI) values. While specification of these parameters can be less stringent for structural materials, controlled polymerization remains important for specification of polymer properties and ease of processing. The efficiency of catalyst utilization can also affect the economic viability of industrial processes, particularly for construction of commodity materials.

The following sections highlight the synthesis and applications of well-defined metal alkylidenes, though an emerging focus on assembly of such initiators *in situ*, with the attendant advantages of economy and potential ease of tuning, should be acknowledged. In keeping with the definition proposed by Schrock,[6] we reserve the term "well defined" to describe alkylidene complexes that—barring changes in the alkylidene and/or loss of a donor ligand—are essentially identical to the propagating species. Classical initiators, multi-component systems consisting of a high oxidation state metal salt and a co-catalyst, typically give poorly defined propagating species, and will not be discussed. However, such systems offer inexpensive, easily accessible routes to ROMP polymers, and continue to dominate the industrial applications of ROMP technologies.[7,8] Comprehensive surveys of such catalyst systems have appeared.[3,9] In some instances the co-catalyst may be non-innocent: $AlCl_2Et$ and methylaluminoxane, for example, are used as co-catalysts with a number of Ti, Mo, and W initiators, but can themselves effect ROMP of NBE (albeit with low efficiency),[3,10] and $MgCl_2$ has also been reported to be ROMP-active.[11] Despite these examples, metathesis by non-transition metals is rare. The majority of effective initiators are derived from transition metals of groups 4–9. Of these, most important are those well-defined alkylidene complexes of Mo, W, and Ru which effect controlled ROMP of both strained and unstrained cycloolefins. Discussion is confined to molecular species, examples of which are shown in Figure 1. For advances in the development and applications of supported metathesis catalysts, readers are referred to recent reviews.[12,12a,13] ROMP activity is often benchmarked in polymerization of NBE. Where available, these data are collected in Table 1. Other monomers discussed are represented in Figure 2; water-soluble monomers are shown separately in Figure 5. Monomers are distinguished from transition metal complexes by use of the prefix "M" in their numbering scheme. A note concerning oxidation states: the alkylidene functionality is treated as a dianionic donor to group 4–7 metals, but as a neutral donor to later transition metals, including ruthenium.

11.18.2.1 Initiators Based on Transition Metals Other than Mo, W, and Ru

Stable titanacyclobutane complexes played an important role in the development of well-defined olefin metathesis catalysts.[1,2] Group 4 alkylidene species, long presumed to participate in ROMP of NBE by classical initiator systems such as Cp_2TiCl_2–MeMgI[14] and MCl_4–MeLi (M = Ti, Zr),[15] are often higher in energy than the titanacyclobutanes. A number of well-defined Ti alkylidene complexes have now been prepared by α-hydrogen abstraction in sterically crowded environments,[16–21] although their ROMP activity does not compare with that of the titanacyclobutane systems. Their formation and reactivity have been reviewed.[22,23] A DFT study of olefin metathesis by Cp_2TiRR' species showed metallacyclobutane geometries and barriers for olefin exchange in general agreement with the experimental data.[24] No strong evidence was found for a local minimum corresponding to a Ti–alkylidene–olefin species. Well-defined alkylidene complexes of tantalum, though more common,[6,23] exhibit a tendency to homologation that can inhibit polymerization.[3] Pincer complex **3** effects ROMP of NBE at 70 °C (see Table 1), probably via dissociation of the dimethylamino group; Ta(V) species **4** also slowly polymerizes NBE.[25,26] Benzylidene complex **5**, prepared by thermally-induced α-hydrogen elimination from a bis(benzyl) precursor, exhibits low activity for ROMP of NBE at 65 °C,[27] though this species and its η^2-butadiene analog exhibit high, tunable selectivity for *cis*- or *trans*-olefin linkages in the poly-NBE products (>92% *trans* and >97% *cis*, respectively).[28] Thermolysis of the related dialkylniobium species $Cp^*NbMe_2(\eta^4\text{-}C_4H_6)$ afforded a nascent methylidene species, which on trapping with NBE gave metallacyclobutane **6**.[29] Niobium alkylidene complexes are rare,[30,31] and their ROMP application are little explored. Initiator **6** effected slow ROMP of NBE at 65 °C, with ca. 10 turnovers in 30 h.[29]

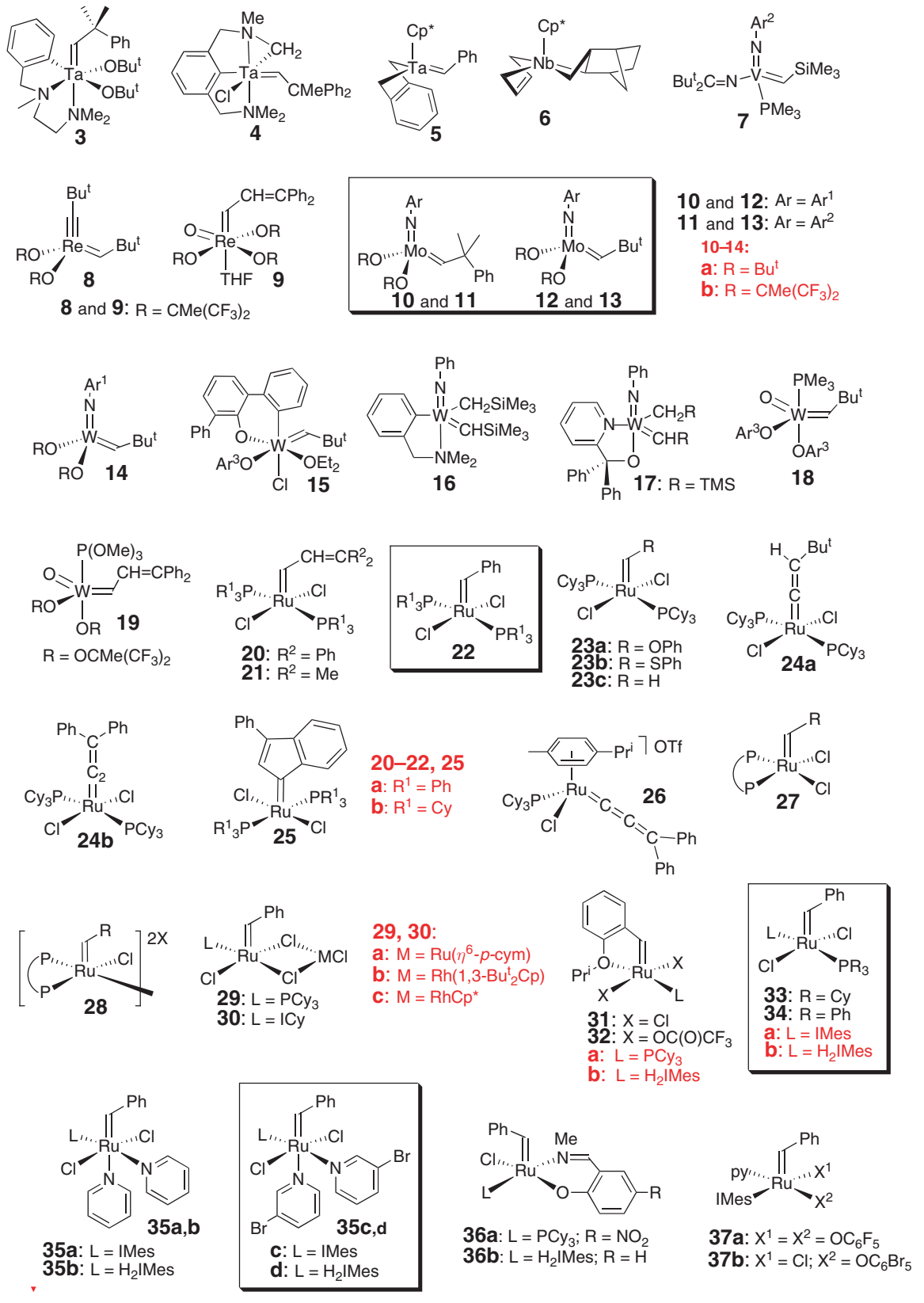


Figure 1 Summary of well-defined initiators discussed. Aryl groups are abbreviated as $Ar^1 = 2,6\text{-}Pr^i_2C_6H_3$; $Ar^2 = 2,6\text{-}Me_2C_6H_3$; $Ar^3 = 2,6\text{-}Ph_2C_6H_3$.

Table 1 Performance of well-defined initiators in ROMP of NBE

Init.	[*M*] : [*C*]	*Conditions*	*Solvent*	*Yield (%)*	*PDI*	*Alkene geometry*	*References*
3	250	70 °C, 1 h	C_7H_8	Quant	1.3	88% *trans*	25
5	100	65 °C, 30 h	C_7H_8	8	2.1	90% *trans*	27
6	100	65 °C, 30 h	C_7H_8	12	4.8	91% *cis*	29
7	2,120	80 °C, 2 h	C_6H_6	98	1.6	-	32
12a	200	25 °C, 15 min	C_7H_8	Quant	1.04	55% *trans*	44
14a	200	25 °C, 10 min	C_7H_8	Quant	1.03	-	45
15	500	25 °C, <1 min	-	Quant	-	70% *cis*	46
16	200	RT, 10 min	C_6H_6	Quant	-	90% *cis*	47
17	250	70 °C, 30 min	C_6H_6	Quant	-	12% *trans*	48
20a	70	RT, 3 h	1 : 8 CD_2Cl_2 : C_6D_6	-	1.25	90% *trans*	49
20b	142	RT, <1 min	1 : 4 CD_2Cl_2 : C_6D_6	Quant	2.65	86% *trans*	50
22a	100	RT, 1 h	CH_2Cl_2	95–99	1.04	90% *trans*	51
22b	100	RT, seconds	CH_2Cl_2	Quant	2–2.5	-	51
23b	100	RT, seconds	CH_2Cl_2	Quant	1.8	-	52
24a	100	RT, 10 min	CH_2Cl_2	Quant	2.03	90% *trans*	52
26	1,000	RT, 5 min	C_6H_5Cl	90	1.8	75% *trans*	53
35b	100	−20 °C, 30 min	CH_2Cl_2	87	1.1	-	54
36a	800	70 °C, 4 h	C_6H_5Cl	Quant	1.5	75% *trans*	55
36b	2,000	70 °C, 4 h	C_7H_8	Quant	1.31	77% *trans*	56

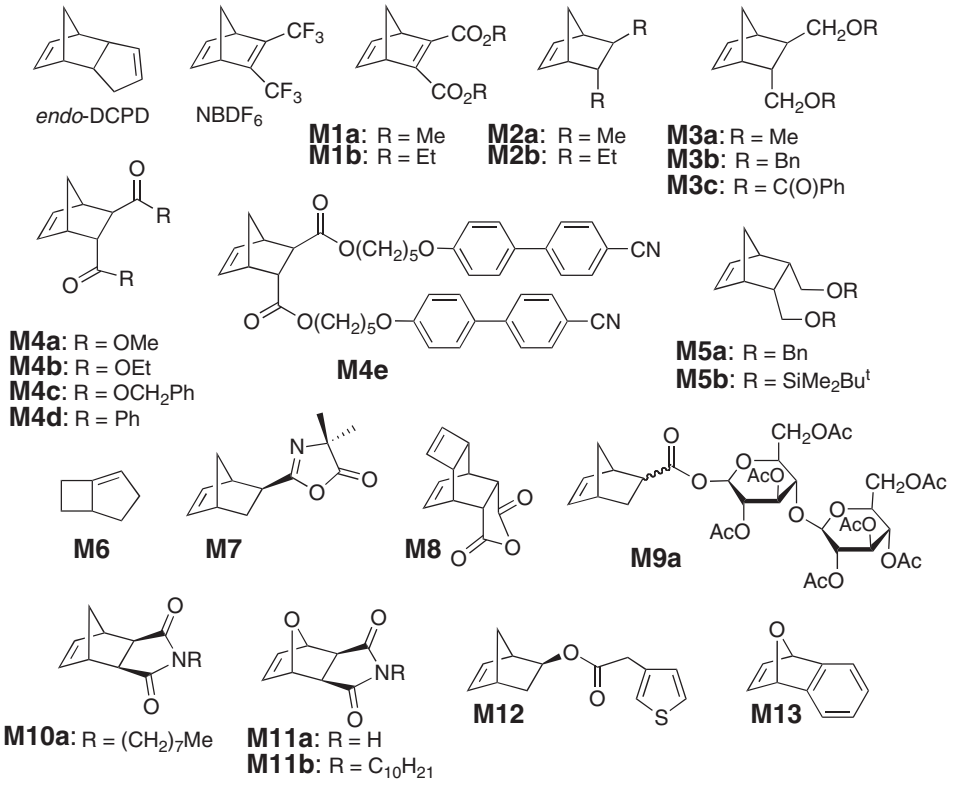


Figure 2 Summary of monomers discussed. (For water-soluble monomers, see Figure 5).

Vanadium precursors tend to promote addition polymerization of olefins on activation with aluminum co-catalysts.[3] Nomura and coworkers recently reported the first example of catalytic olefin metathesis by a vanadium alkylidene complex.[32] The well-defined, thermally stable V(v) alkylidene complex **7** effected ROMP of NBE at 80 °C. Certain alkylvanadium complexes, including $V(CH_2Ph)_2(=NAr^2)(OAr^1)$[33] ($Ar^1 = 2,6\text{-}Pr^i{}_2C_6H_3$; $Ar^2 = 2,6\text{-}Me_2C_6H_3$) and

$CpV(CH_2Bu^t)_2(PMe_3)$,[34] effect slow ROMP of NBE at room temperature, presumably via α-abstraction. Despite the key role of supported rhenium complexes in metathesis chemistry, well-defined Re–alkylidene complexes show lower activity than the related Mo or W initiators. For both the mixed alkylidene–alkylidyne complex **8** and oxo-alkylidene **9**, reactivity toward internal olefins is low.[35,36] The emergence of important Ru systems has lent stimulus to studies directed at expanding the range of effective late transition metals. Several ROMP-active osmium complexes have been reported. Representative systems include $OsCl_2$(*p*-cymene)(PR_3) (R = Cy, Pr^i), which requires activation by UV irradiation;[37] $Cp^*_2Os_2Br_4$, which requires activation by MAO;[38] and $OsHCl(CO)(PPr^i_3)_2$, which effects ROMP of strained cycloolefins without additives or photolysis, but for which, as in the other systems, the nature of the active species is unknown.[39] The alkylidene complex $Os(CH_2Bu^t)_2(=CHBu^t)_2$ has been isolated, but its metathesis activity was not examined.[40] More recently, half-sandwich complexes of the type (η^6-Mes)Os-Cl$(PPh_3)(=CPh_2)]PF_6$[40a] and [(η^6-*p*-cymene)OsCl(IMes)(=CHPh)]OTf have been prepared.[40b] The latter effected ROMP of cyclooctene at 60 °C; free *p*-cymene was detected by GC-MS analysis. Development of iron alkylidene complexes is of considerable interest. Several coordinatively saturated cyclopentadienyl examples have been reported,[41,41a] but attempts to prepare complexes of the type $FeCl_2(PR_3)_2(=CHPh)$ using $PhCHN_2$ as the source of alkylidene resulted only in insertion of the diazoalkane into the iron-phosphorus bond.[42] Well-defined initiators with good metathesis activity are still sought. Polymerization of NBE by diimine complexes of iron, cobalt, nickel, and palladium gives predominantly the vinyl polymer; though some ROMP also occurs,[43] variations that increase polymerization activity reduce the extent of ROMP.

11.18.2.2 Group 6 Initiators

The most important of the well-defined group 6 initiators are the pseudo-tetrahedral, d^0 Schrock catalysts, in which the bulk of the imido, alkoxide, and alkylidene ligands inhibit bimolecular decomposition. Some key examples (**10–14**) are shown in Figure 1: comprehensive tabulations appear in recent reviews.[6,23,57] The synthesis, selectivity, and ROMP performance of these species was described in COMC (1995).[2] The well-established correlation between metathesis activity and the electron deficiency of the alkoxy groups was recently examined in a kinetic study of ROMP of NBE, which suggested that monomer binding is rate determining for **10a**, but not for initiator **10b**, the electron-deficiency of which favors reaction with olefin.[58] The Mo systems are preferred over their tungsten analogs for their improved control over reactivity, greater functional-group tolerance, and lower sensitivity to impurities. The modular nature of these initiators enables controlled ROMP of a range of monomers, as discussed in Section 11.18.3. Despite their high sensitivity toward oxygen and water, a wide range of (non-protic) functionalities is tolerated, including esters, acetals, nitriles, thioethers, and ethers. Secondary amides, maleimides, and some sterically protected alcohols are also tolerated, though other alcohols, primary amines, and carboxylic acids are not.[6,6c,57] Aldehydes are rapidly deoxygenated in a Wittig-like reaction to give ROMP-inactive Mo=O species, providing an efficient, convenient means of quenching reaction once ROMP is complete.

While **10** and **11** remain the most widely used Schrock catalysts, the range of such initiators has been expanded by reaction of the bis(triflate) precursor $Mo(OTf)_2(=NAr)(=CHR)(DME)$ ($Ar = Ar^1$, Ar^2) with chiral aryloxide salts,[6,23,57] including binaphtholate,[59,59a–d] octahydrobinaphtholate,[60,60a] biphenolate,[59,59a,b,61,61a–c] and other diolate[62] derivatives. Analogous arylamido complexes proved metathesis-inactive.[57] Alternative imido ligands bear 2,6-diethylaryl,[61a] 2,6-diethylaryl,[61a] or 2,6-dichloroaryl,[60,60a] 2-alkylaryl,[61a] and adamantyl[61c,63a] substituents. Complexes **10a** and **10b**, and the triflate precursor, are commercially available (Strem). A convenient and reportedly high-yield alternative route to the fluoroalkoxide derivatives involves protonolysis of the basic *tert*-butylimido ligand in $Mo(=NAr)(=NBu^t)(CH_2R)_2$ (R = Me, Ph) with pentafluorophenol.[64] The ROMP-active species was also generated by addition of phenol *in situ*, for polymerization of dicyclopentadiene (DCPD) in a reaction injection molding (RIM) process. Alkoxide exchange on the initiators themselves has been effected *in situ*,[65] including on living polymers.[65a] Addition of $HOCMe(CF_3)_2$ following ROMP of $NBDF_6$ by **12a** effected exchange of the *tert*-butoxide ligand on the metal endgroup.[65a] Further polymerization afforded stereoblock co-polymers containing *cis*- and *trans*-segments, owing to the higher *cis*-selectivity of the fluoroalkoxide initiator. The four-coordinate Mo initiators exist as a mixture of interconverting rotamers, in which the alkylidene substituent lies *syn* or *anti* to the imido ligand.[2,63,66,66a] Because the *anti* rotamer yields *cis*-olefin linkages, where the *syn* rotamer yields *trans*-linkages, the rate of interconversion is a key factor in determining selectivity. The higher reactivity of the *anti* isomer—in some cases orders of magnitude higher than that of the *syn* rotamer—offsets its lower abundance. A reduction in the rate of rotamer interconversion with increasing electron-deficiency of the alkoxide ligand enables formation of *cis*-poly($NBDF_6$) in ROMP via **10b**, where **10a** yields high-*trans* polymer. The *syn*/*anti* conversion rates, and hence *cis*/*trans* olefin geometry, can also be manipulated by carrying out ROMP at different temperatures.[66]

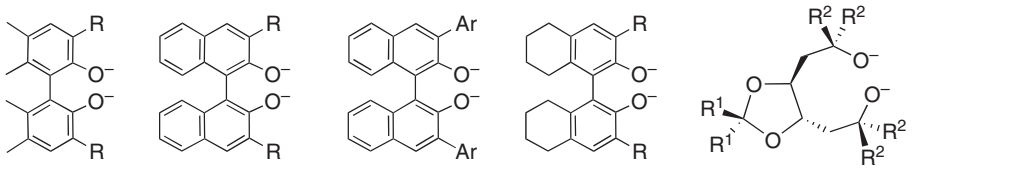
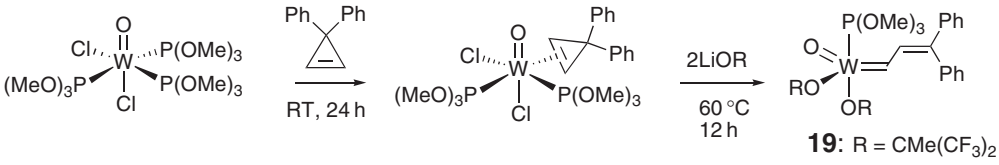


Figure 3 Examples of chiral diolate ligands employed within Schrock-class initiators.

Reports from the Schrock group demonstrated striking control over polymer microstructure by use of chiral versions of **10–13**, incorporating aryloxides such as those of Figure 3.[59] COMC (1995) discussed the advantages of enantiomorphic site control in promoting consistent stereoselection during propagation.[2] Stereoselective ROMP via achiral initiators relies on chain-end control: that is, the chirality of the β carbon atom in the first insertion product determines which diastereotopic face of the [M]=C bond is approached by the incoming monomer. Both the aryloxide and the imido substituents play a part in stereodifferentiation, highlighting the importance of a modular catalyst structure. Very high selectivity for *cis*, isotactic polymers was found in ROMP of a series of norbornadiene (NBD) and NBE monomers of type **M1–M4**, as well as enantiomerically pure NBEs.[59,66] Detailed tabulations of these results, including monomers, initiators, and polymer microstructure (tacticity and olefin geometry), have appeared,[57,67] as well as overviews of the use of NMR methods to assign tacticity and stereochemistry in these and related systems.[68,69] Dielectric analyses of poly($NBDF_6$) have also been correlated with tacticity.[70,70a] Bimodal molecular weight distributions occasionally observed on use of racemic initiators to polymerize enantiomerically pure monomer were attributed to a difference in the rate of chain growth from the enantiomeric metal centers.[59a] Consistent with this interpretation was the observation of unimodal distributions on use of the enantiomerically pure initiator.[59b] The chiral complexes have been used most extensively as catalysts in asymmetric olefin metathesis directed at organic synthesis, particularly asymmetric RCM (including enantioselective desymmetrization and kinetic resolution of racemic dienes), tandem asymmetric ring-opening/CM, and tandem asymmetric ring-closing/CM reactions (CM = cross-metathesis).[57,71] Lower reactivity was found for related tungsten catalysts, W(BIPHEN)(=CHCMe$_2$Ph)(=NAr) (Ar = Ar^1, Ar^2), an observation attributed to the greater stability of the tungstacyclobutane moiety.[72] Other chiral tungsten complexes, including W(R_2BINO)(OBu^t)$_2$(=CHPh) (prepared by reaction of the alkylidyne precursor W(≡CR^3)(OBu^t)$_3$ (R^3 = Ph, Bu^t) with the free binaphthols R_2BINO (R = Me, Ph, Br)), exhibit modest stereoselectivity in ROMP of NBE,[73] although the proportion of *cis*-polymer increased with the steric demand of the binaphtholate substituent. These initiators require activation by $GaBr_3$, conditions under which alkoxide exchange is probable.

Related W(=CR$_2$)(OCH$_2$Bu^t)$_2$Cl$_2$·GaCl$_3$ initiators effect rapid polymerization of COE at room temperature, but addition polymerization competes with ROMP.[74] Tungsten neopentylidene complex **15** effects rapid, selective ROMP of a range of monomers, including NBE and CPE, at −45 °C: its impressive performance, noted previously,[2] has been reviewed.[75] Five-coordinate imido-alkylidene complexes containing monoanionic *C,N*- or *O,N*-chelating ligands can exhibit temperature-dependent activity.[47,48] ROMP via **16** proceeds at ambient temperatures.[47] Complexes such as **17** are unreactive for polymerization of NBE at ambient temperatures; at 70 °C, 250 equiv. of NBE are polymerized within 1 min.[48] "Latent" ROMP initiators can offer advantages in polymer processing in RIM applications, as discussed in more detail below. Tungsten and molybdenum oxo– and imido–alkylidene complexes containing a trispyrazolylborate (Tp) ligand have been prepared: six-coordinate complexes such as M(OR)(NAr)(Tp)(=CHCMe$_2$Ph) (M = Mo, W; R = Me, Tf) offer reasonable stability toward air, heat, and moisture, but good ROMP activity is achieved only on addition of $AlCl_3$.[76,76a] Oxo–alkylidene complexes such as **18** are of particular interest for their potential relevance to the active species in olefin metathesis by classical tungsten catalysts. Despite the potential for deactivation of such species via formation of oxo-bridged dimers,[6] **18** exhibited high activity in ROMP of norbornadiene monomers $NBDF_6$ and **M1a** to yield highly *cis*, tactic (>95%) polymers; the implied lability of the PMe_3 group was confirmed by NMR studies.[77]

Stepwise conversion of an olefin into an alkylidene has been reported in [calixarene]W(olefin) complexes. Where the olefin was ethylene or propylene, deprotonation afforded an anionic alkylidyne species, which on protonation



Scheme 1

yielded the alkylidene complex.[78,78a] Formation of alkylidene complexes by protonation of alkylidynes is a long-standing synthetic strategy. In some cases, this has been shown to involve a 1,2-hydrogen shift within a hydrido-alkylidyne complex (though the shift also commonly occurs in the opposite sense, favoring the alkylidyne complex). Evidence for a 1,2-hydrogen migration from the metal to the alkylidyne carbon was found in the transformation of $WH(CO)[P(OMe)_3]_3(\equiv CMes)$ into $W(CO)[P(OMe)_3]_3(L)(=CHMes)$ ($L = CO$, $P(OMe)_3$, PMe_3).[78b] A DFT analysis of the $WH(CO)(PH_3)_3(\equiv CR)W(CO)(PH_3)_3(=CHR)$ interconversion suggested that reaction is promoted by π-acceptors that compete with the alkylidyne or alkylidene ligand for back-donation, but impeded by π-donors.[79] In comparison, the 1,2-hydrogen shift in an isoelectronic osmium alkylidyne complex did not appear to proceed via a single, unimolecular reaction step. A DFT study of $OsHCl_2(PR_3)_2(\equiv CR)$ and $OsCl_2(PR_3)_2(=CHR)$[80] suggested that although the energies of the two isomers are similar, the energy for hydride migration is excessive. Nucleophilic assistance by an incoming π-acid CO ligand lowered the activation energy for the hydride to alkylidyne migration, enabling conversion of $OsHCl_2(PPr^i_3)_2(\equiv CEt)$ to $OsCl_2(CO)(PPr^i_3)_2(=CHEt)$.[80a] Caulton has commented on the preference of Os (versus Ru; vide infra) for saturation and higher oxidation state.[80b] The coordinative saturation of these complexes can be expected to limit metathesis activity.

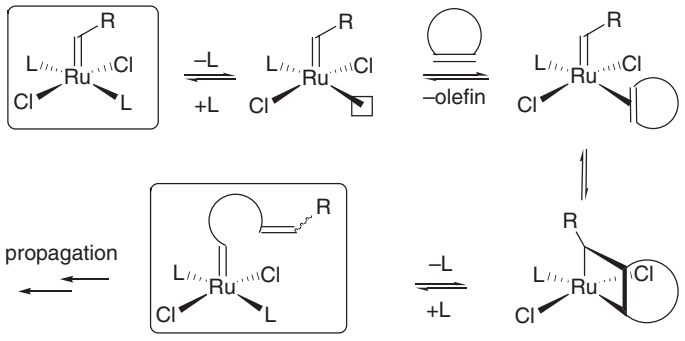
Alkylidene-transfer reactions offer a well-established alternative to α-abstraction methodologies for the construction of metal alkylidene complexes.[2,6] In tungsten chemistry, phosphorane reagents[81] and 3,3-disubstituted cyclopropenes[82,82a] have been used as sources of the alkylidene ligand. The latter approach was subsequently employed in the ruthenium chemistry. Tungsten alkylidene complexes were formed via thermal rearrangement of an initially formed η^2-cyclopropene adduct (Scheme 1).[82,82a] Oxo–alkylidene product **19** was active for ROMP of NBE at room temperature: these complexes undergo loss of phosphine more readily than the corresponding imido complex, for which a Lewis acid additive was required to generate the phosphine-free, metathesis-active species. The dichloro precursors also undergo the thermal rearrangement, but are unstable with respect to elimination of the alkylidene.[82b] The formal product of carbene coupling, $Ph_2C{=}CHCH{=}CHCH{=}CPh_2$, was observed. In related Ru-vinylalkylidene systems, bimolecular decomposition likewise results in formation of the triene, accompanied by trichloro-bridged diruthenium species of low ROMP activity.[83,83a]

Tungsten alkyl complexes such as $W(=NPh)(OCMe(CF_3)_2)_2(CH_2SiMe_3)_2$ and $W(=NPh)Cl(CH_2SiMe_3)_3$ effect photoinduced ROMP of NBE and DCPD, respectively,[84] presumably by an α-elimination process.

11.18.2.3 Group 8 Initiators

The growing dominance of Ru initiators is due to their ease of handling. Much less oxophilic than the group 6 or early transition metal systems, they are less susceptible to decomposition by air and water, and can therefore be deployed under less stringently controlled reaction conditions. Precatalysts can exhibit reasonable stability toward oxygen in the solid state, though the active species generated on ligand loss is oxygen-sensitive. Trialkylphosphine derivatives not uncommonly show improved metathesis activity in air. The beneficial effect can be traced to oxidation of the released phosphine to the weaker-binding phosphine oxide, the rate of metathesis by the 14-electron intermediate (Scheme 2) exceeding the rate of metal oxidation by some margin. As in the group 6 chemistry, the [2 + 2]-cycloaddition step is sensitive to the steric and electronic properties of both the ligands and the incoming olefin.[85] To date, catalyst design in the Ru systems has focused on amplifying activity to the level of the molybdenum systems: issues of selectivity are only beginning to be addressed.

The majority of Ru metathesis initiators are square-pyramidal complexes of the type $RuCl_2L^1L^2(=CHR)$, the prototypical example being the "Grubbs catalyst" **22b**. Because the high *trans*-influence alkylidene ligand exhibits a strong apical site preference, productive metathesis requires placement of incoming olefin in the basal plane, and complexes containing four non-labile ligands in the basal sites exhibit low metathesis activity. While the required basal vacancy can be generated by abstraction of chloride (see later), activation by loss of a neutral ligand is more common. In



Scheme 2 Aspects of the initiation step in ROMP promoted by Grubbs-class Ru initiators. Observable species are shown in frames.

consequence, synthetic convenience (which benefits from strong ligand binding) and initiation efficiency are typically at odds. Metathesis activity is maximized where one neutral ancillary donor is a strongly σ-donating alkylphosphine or *N*-heterocyclic carbene (NHC) ligand, and the other a weakly donating "placeholder" ligand that readily dissociates. Evidence for the dissociative mechanism was recently summarized.[86] Key data include kinetics studies,[87,88] tandem ESI-MS observations,[5b] computational studies,[5,89] and interception of an intermediate in which a phosphine ligand of $RuCl_2(PCy_3)_2(=CHPh)$ is replaced by an olefin subtended by the alkylidene group.[90]

Routes to the important class of well-defined ruthenium initiators of the Grubbs type (**20b–22b**) are summarized in Figure 4; for details, see Table 2. COMC (1995) described the first example of this family, vinylalkylidene **20a**, prepared by reaction of $RuCl_2(PPh_3)_3$ with 2,2-diphenylcyclopropene. Subsequent treatment with PCy_3 yields **20b** (path (a)). (The corresponding complex **21a** was later prepared by reaction of $RuHCl(PPh_3)_3$ with propargyl chloride; see below). Initiator **20a** effected controlled ROMP of **M4b**[91] and bicyclo[3.2.0]heptene **M6**,[92] but ROMP of less reactive monomers, such as COE, required use of the more electron-rich PCy_3 derivative **20b**.[50] The effect of the phosphine group on metathesis activity, studied most extensively in parallel RCM experiments, follows the trend

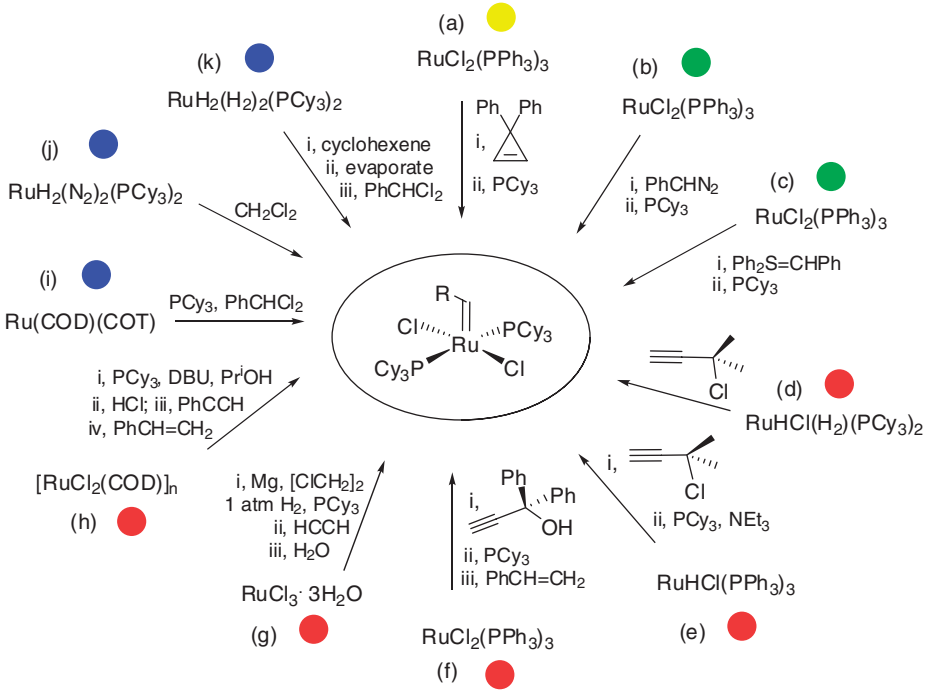


Figure 4 Routes to the Grubbs catalyst **22b** and related alkylidene species. Routes based on ring opening (yellow dot), alkylidene transfer (green), alkyne reagents (red), chloroalkanes (blue) are shown in the figure.

Table 2 Details for synthetic routes summarized in Figure 4

Path	*Prod.*	*Reaction*	*Yield (%)*	*References*
(a)	**20b**	(i) $RuCl_2(PPh_3)_3$ + 3,3-diphenylcyclopropene; CH_2Cl_2-C_6H_6, 53 °C, 11 h (ii) $2PCy_3$	99	49
(b)	**22b**	(i) $RuCl_2(PPh_3)_3 + PhCHN_2$; CH_2Cl_2, −78 °C, 5 min (ii) $2PCy_3$; RT, 30 min	85–90	51
(c)	**22b**	(i) $[Ph_2SCH_2Ph]BF_4 + KN(SiMe_3)_2$; THF, −30 °C (ii) $RuCl_2(PPh_3)_3$; CH_2Cl_2, −30 °C, 30 min (iii) $2PCy_3$; CH_2Cl_2, RT, 2 h	96	95
(d)	**21b**[a]	$RuHCl(H_2)(PCy_3)_2$ + 3-chloro-3-methyl-1-butyne; CH_2Cl_2, −30 °C, 15 min	95	96
(e)	**21b**[b]	(i) $RuHCl(PPh_3)_3$ + 3-chloro-3-methyl-1-butyne; CH_2Cl_2, RT, 30 min (ii) $2PCy_3$; RT, 10 min	88	83a
(f)	**22b**	(i) $RuCl_2(PPh_3)_3$ + 1.3 equiv. 1,1-diphenyl-2-propyn-1-ol; THF, Δ, 3h (ii) $2.1PCy_3$; RT, overnight (iii) $60H_2C{=}CHPh$ (added in 3 batches); Δ, 3 h	80	98
(g)	**23d** (R = Me)	(i) $RuCl_3 + 4PCy_3$, Mg/$ClCH_2CH_2Cl$, 1 atm H_2; THF, 65 °C, 2 h, then 85 °C, 2 h (ii) HC≡CH; −40 °C, 5 min (iii) $4H_2O$; warm to RT	75	104
(h)	**22b**	(i) $[RuCl_2(COD)]_n + 2PCy_3$, 2DBU, Pr^iOH; Δ 3h (ii) $HCl{\cdot}Et_2O$; −20 °C, 25 min (iii) 2HC≡CPh;[d] −20 °C, 2 h (iv) $4PhCH{=}CH_2$; RT, 1 h	–[c]	99
(i)	**22b**	$Ru(COD)(COT) + 2PCy_3 + PhCHCl_2$; toluene, RT, 2 days	50	101
(j)	**23c**[c]	$RuH_2(N_2)_2(PCy_3)_2 + 4CH_2Cl_2$; pentane, RT, 20 min	70	102
(k)	**22b**	(i) $RuH_2(H_2)_2(PCy_3)_2$ + 10 cyclohexene; pentane, RT, 1 h (ii) remove volatiles (iii) $3PhCHCl_2$; pentane, 45 min	61	101

[a]Use of vinyl chloride gave several products.
[b]Use of NEt_3 as a co-reagent to scavenge traces of HCl inhibits formation of a Ru-vinylalkylidyne byproduct.
[c]75% yield reported for PPr^i_3 analog.
[d]A later variant uses 1-hexyne.[109]
[e]Use of $PhCHCl_2$ as the chloroalkane afforded ca. 65% **23b**, with $RuH_2Cl_2(PCy_3)_2$ and $RuHCl(H_2)(PCy_3)_2$ as co-products. Reaction via $RuH_2(H_2)_2(PCy_3)_2$ increased the proportion of the latter.

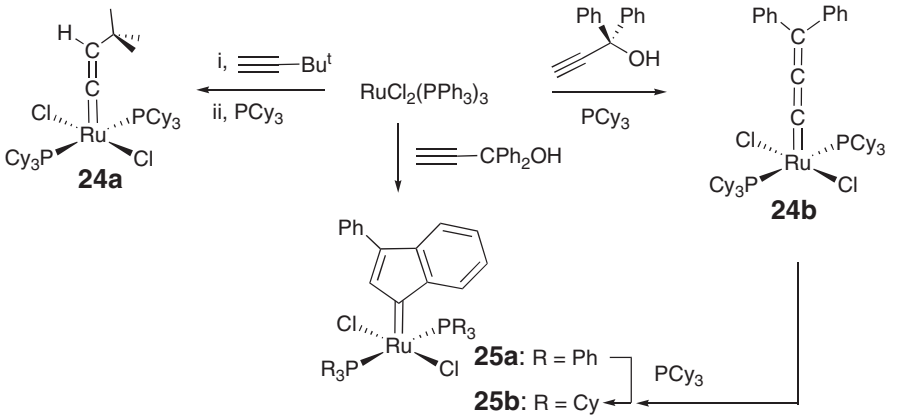
$PPh_3 << PPr^i_2Ph < PCy_2Ph < PPr^i_3 < PCy_3$.[87] As the utility of **20** is undermined by the instability and synthetic inconvenience of the 2,2-diphenylcyclopropene reagent, the development of routes based on diazoalkanes as alkylidene-transfer agents proved to be a major advance (Figure 4, path (b)).[51] The breakthrough catalyst **22b** was obtained by treating $RuCl_2(PPh_3)_3$ with $PhCHN_2$ to give $RuCl_2(PPh_3)_2(=CHPh)$ (**22a**), and subsequent phosphine exchange with PCy_3.[51] The phosphine exchange is best carried out as a one-pot procedure without workup, in order to minimize formation of the dimer $RuCl(PPh_3)_2(\mu\text{-}Cl)_3Ru(PPh_3)_2(=CHR)$.[83a] Other donor ligands can likewise be introduced by *in situ* modification of the intermediate **22a**, but **22b**, owing to its commercial availability, is itself the most commonly used precursor to new Ru alkylidenes (despite the rather low lability of the PCy_3 groups, which impedes exchange).[93] Replacement of PCy_3 by $PCy_2(CH_2SiMe_3)$ resulted in much faster initiation, though slower propagation, in ROMP of NBE imides.[93] Of interest for reasons of economy, despite somewhat attenuated activity, are $P(Cyp)_3$ derivatives (Cyp = cyclopentyl).[51] An analog based on the relatively inexpensive phosphabicyclononane ("phoban") ligand effected near-quantitative ROMP of COD (12,500 equiv.) within 10 minutes at 50 °C, as compared to 20% conversion for **22b** under identical conditions.[94] The high reactivity of the phoban catalyst may arise from the effect of the phosphine ligand on the orientation of the alkylidene ligand. Complexes of several water-soluble phosphines have also been prepared for aqueous ROMP (see below).

Phenyldiazomethane remains the dominant source of the benzylidene ligand, despite its toxicity and instability, and stoichiometric limitations arising from its low synthetic purity, facile decomposition, and consumption by free PPh_3 (which is evolved from, and frequently contaminates, the $RuCl_2(PPh_3)_3$ precursor). $Ph_2S{=}CHPh$ provides an alternative source, as shown in path (c).[95] A number of routes based on 1-alkyne reagents have been developed: vinylalkylidene derivatives of type **21** are readily accessible on reaction of 3-chloro-3-methyl-1-butyne ("propargyl chloride") with $RuHCl(H_2)(PCy_3)_2$

(path (d)),[96] or the more conveniently accessible $RuHCl(PPh_3)_3$ (path (e)).[83a,97] Werner and co-workers[104] demonstrated that hydridovinylidene species of the type $RuHCl(PR_3)_2(=C=CHPh)$ (R = Cy, Pr^i) are formed during reaction of $RuHCl(PR_3)_2(H_2)$ with phenylacetylene, and that these yield alkylidene derivatives on addition of a source of HCl (vide infra). This chemistry underlies the transformations of paths (g) and (h). In paths (f) and (h), the benzylidene functionality is installed by CM of styrene with the indenylidene[98] or benzylalkylidene[99] complexes generated *in situ*. CM of $RuCl_2(PCy_3)_2(=CHR)$ with sterically accessible terminal olefins was earlier shown to yield the alkylidene, rather than the methylidene, as the kinetic product.[51,100] The low reactivity of the Ru-cumulenylidene moiety may limit yields of **22b**, owing to erosion of this kinetic preference at the elevated temperatures typically required for reaction, or thermal decomposition of the benzylidene product. Chloroalkyl reagents can furnish an alternative source of alkylidene (and chloride) ligands in reactions with Ru–hydrides. Examples include reaction of Ru(COD)(COT) with $CHXCl_2$ (X = H, Ph, CO_2Me),[101] and of $RuH_2(N_2)_2(PCy_3)_2$ (or, less effectively, $RuH_2(H_2)_2(PCy_3)_2$) with CH_2Cl_2[102] (paths (i) and (j), respectively). A clever variant on the latter approach makes use of cyclohexene as a stabilizing ligand and hydrogen acceptor (path k).[101] A drawback to several of these routes is the low reactivity and short lifetime[103] of the Ru–methylidene product. In addition, some of the ruthenium precursors are themselves non-trivial to prepare, and routes based on $RuXCl(PPh_3)_3$ (X = H, Cl) or $RuCl_3$ offer greatest practical convenience to date.

Within a family of benzylidene complexes of type **22b** (Ar = *p*-C_6H_4X; X = H, NMe_2, OMe, Me, F, Cl, NO_2), the phenyl derivative initiated fastest in a CM assay.[51] These electronic effects proved minor in ROMP of NBE via **22a**: for all of the PPh_3 complexes, the rate constant for initiation exceeded that of propagation. An advantage to the vinylalkylidene ligand can be inferred from the early finding that this ligand is less readily displaced than benzylidene,[105] though it also confers lower metathesis activity. Complex **22b** was originally suggested to initiate 1,000 times faster than **20b** in CM experiments with 1-hexene,[51] although vinylalkylidene **21b** later proved about 80% as active as **22b** in ROMP of COD.[106] A composite trend in activity for [Ru]=CHR ($H << CHCH=CMe_2 < Ph < Et$) emerges from studies of derivatives of **22**[51,100] and the later-developed, progressively more reactive (vida infra) NHC complexes **33** and **35**.[88,107] The extremes are represented by methylidene (which initiates very slowly) and alkylidene: the latter complexes are much more reactive than their benzylidene analogs, though by the same token less well adapted to synthetic purposes.[107] Both steric and electronic features are thought to play a role in the influence of the alkylidene moiety on reactivity. While complexes of Fischer carbenes, of which $Ru(O_2CCF_3)_2(PPh_3)_2(=CHER)$ (ER = SCH_2Ph, OEt) represent early examples,[108] have long been regarded as metathesis-inactive, this is not the case for more reactive Ru initiators. Competing ROMP was observed on use of $RuCl_2(PCy_3)_2(=CHEPh)$ (E = O (**23a**), S (**23b**), Se) for the ring-opening cross-metathesis of NBE with $H_2C=CHEPh$ at room temperature.[52a] The trend in ROMP reactivity was E = O > S > Se. In the absence of the acyclic olefin, **23b** effected ROMP of NBE within seconds at ambient temperatures (Table 1).[52] High activity was likewise reported for the PPr^i analog in ROMP of DCPD,[109] and in ROMP of COD proceeded via analogs of **33** containing the =CHER moiety, where ER = OEt, SEt, or *N*-carbazole.[110] The corresponding derivatives of **22b** effected ROMP of COD at 65 °C. The reactivity of the ethoxyalkylidene species has implications for the efficacy of ethyl vinyl ether as a quenching agent used to terminate metathesis via highly active Ru catalysts particularly **32** (Section 11.18.3). The Fischer carbene complexes are accessible in quantitative yields by CM of **22b** or related species with $H_2C=CHER$,[52,109,110] or by reaction of Ru(*p*-cymene)(COD) with PCy_3 and Cl_2CHSPh.[111]

The challenges associated with introduction of the alkylidene ligand have heightened interest in "*in situ*" catalyst systems, such as that generated by addition of commercially available N_2CHTMS to $[RuCl_2(p\text{-cymene})]_2$ in the presence of PCy_3[112] or an NHC precursor.[113] These systems initiate ROMP of NBEs and cyclooctenes at 60 °C: an alkylidene species was observed (NMR) for the PCy_3 complex. Complicating the *in situ* use of diazoalkanes, especially in excess, is their tendency to promote extrusion of the benzylidene ligand.[114] Considerable attention has focused on readily accessible cumulenylidene and indenylidene species formed by reaction of Ru precursors with 1-alkynes, although the synthetic convenience of these routes is offset by reduced initiation efficiency in ROMP. Use of 2-alkyl or 2-arylacetylenes yields vinylidene derivatives, the catalytic applications of which were recently reviewed.[115,116] Highest metathesis activity was found for derivatives of type **24a** (Scheme 3),[52,117] which effected ROMP of NBE at 25 °C (Table 1).[52] High molecular weights and PDI values indicate slow initiation, relative to propagation: transformation of the cumulenylidene ligand into an alkylidene in the first catalytic cycle contributes to the faster rate of propagation. Lower activity was found for the pincer complex $[Ru(NN'N)(PPh_3)(=C=CHPh][BF_4]_2$ (NN′N = 2,6-bis[(dimethylamino)methyl]pyridine). The latter initiator did not polumerize NBE at room temperature, though ROMP proceeded efficiently at 80 °C in dichloroethane.[118] Of interest, the poly(NBE) product displayed a relatively low PDI value of 1.2 (vs. 2.03 for ROMP via **24a** at RT). Use



Scheme 3 Routes to five-coordinate cumulenylidene and indenylidene derivatives.

of vinyl ethers as chain-transfer agents (CTAs) with **24a** improved control over molecular weights[52,119] (though see later). Use of halide-bearing CTAs enabled subsequent atom-transfer radical polymerization (ATRP). Replacement of one PCy_3 ligand by IMes decreased metathesis activity,[120,121] probably because the reduced lability of phosphine *trans* to NHC (*vide infra*) compounds the lower reactivity of the cumulenylidene ligand. ROMP of COE and other low-strain monomers is effected at 80 °C, albeit with low initiation efficiencies. In agreement with earlier work on the PPh_3 systems, activity was a function of the vinylidene substituent, decreasing in the order TMS > Bu^t > Ph. Schiff base complexes showed lower activity.[121] Addition of HBF_4 to $RuHCl(=C=CH_2)L_n$ ($L_n = \eta^1,\eta^6$-$Bu^t{}_2P(CH_2)_2Ph$, η^1,η^6-$Bu^t{}_2PCH_2OCH_2Ph$) enabled ROMP of COE at ambient temperatures, with quantitative ROMP of 1250 equivalents of monomer in <10 min.[122] The activity of these systems exceeds that of **22b**, possibly because phosphine dissociation is faster for the cations ($[RuHCl(\eta^1\text{-}L)_2(OEt_2)(\equiv CMe)]^+$), which are formed *in situ*, and observed spectroscopically at −78 °C. The alkylidene tautomer is presumably responsible for metathesis.[122a] The hydridoalkylidyne-alkylidene equilibrium was discussed in section 11.18.2.2.

Depending on the other ligands present, propargyl alcohols may function as a source of allenylidene or indenylidene ligands.[123,127] Reaction of $RuCl_2(PPh_3)_3$ with PCy_3 and 1,1-diphenyl-2-propyn-1-ol yields allenylidene **24b**; in the absence of PCy_3, phenylindenylidene **25a** is formed (Scheme 3). An earlier report [126] identified the latter product as the spectroscopically very smaller[127a] $RuCl_2(PPh_3)_2(=C=C=CPh_2)$. Complex **24b** shows low metathesis activity,[123] as does an allenylidene complex containing a chelating $PCy_2(CH_2CH_2OMe)$ ligand.[124] Ligand exchange of **25a** with PCy_3 affords **25b** (which on CM with styrene gives access to **22b**, see Figure 4).[98,125] Mixed PCy_3–NHC derivatives are accessible,[98,125b] but the reduced lability of the phosphine ligand in these complexes is compounded by the lower reactivity of the cumulenylidene ligand, versus alkylidene. Both the indenylidene[98] and the allenylidene[125b] complexes show very low activity even for RCM of diethyl diallylmalonate. Commercially available **25b** shows RCM activity comparable to **22b**,[127] but its ROMP applications have not been explored.

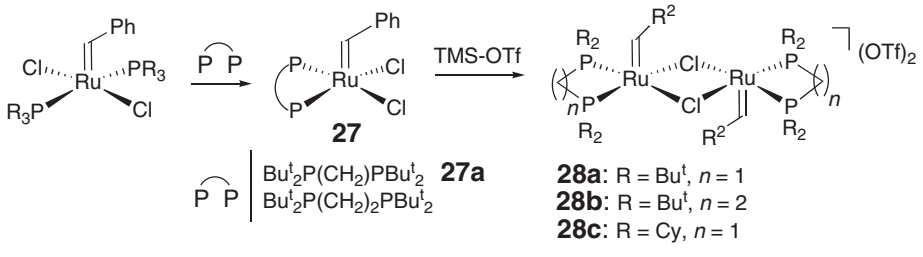
Extensive studies by the Dixneuf group, in particular, have demonstrated the high metathesis activity of readily accessible piano-stool complexes such as **26** (Equation (2)), as described in recent reviews.[123] The *p*-cymene derivatives are preferred for the relative lability of the arene donor. Loss of the η^6-arene ligand generates a very reactive, coordinatively unsaturated species. A diarylallenylidene derivative with a triflate counter-ion proved most effective.[53,123] In closely related systems, the presence of electron-donating substituents (e.g., *p*-methoxy) on the aryl rings increased polymer yields while decreasing PDI values.[128] The order of activity for different phosphine derivatives ($PCy_3 > PPr^i{}_3 >> PPh_3$)[129] agrees with that found for **22b**. Surprisingly, replacement of phosphine by an NHC ligand reduces activity, possibly because conversion into a more reactive indenylidene intermediate is disfavored.[123] The PCy_3 complex requires a photochemical or thermal trigger for efficient initiation in ROMP of low-strain monomers such as COE, but ROMP of NBE occurs spontaneously at room temperature.[53] The reaction has been shown to involve transformation of the allenylidene group into the corresponding phenylindenylidene moiety: in the presence of a proton source, an alkenylcarbyne intermediate has been implicated.[130,131] Addition of strong acid (HBF_4, CF_3SO_3H) to **26** enables ROMP of COE and cyclopentene at ambient temperatures or below.[130] Turnover frequencies of nearly 700 h^{-1} were reached in ROMP of CPE at 0 °C in the presence of 5 equiv. HOTf, though catalyst lifetimes were limited. Chelation of the η^6-arene ligand via a pendant phosphine ligand was explored in the hope of improving stability of these

initiators, but metathesis (RCM) activity was significantly reduced.[132] Incorporation of a chelating σ,π-bound NHC donor gave products of low stability.[133] Low metathesis activity was found for analogs of **26** containing an IMes ligand.[125,125a]

$$[RuCl_2(p\text{-cymene})]_2 \xrightarrow[\text{ii, } HCCCPh_2(OH)\ AgOTf]{\text{i, } PCy_3} \mathbf{26} \qquad (2)$$

Most successful of the diphosphine derivatives (e.g. **27, 28**) are the cationic, edge-bridged dimers of type **28** developed by the Hofmann group, and described in a recent review.[134] Routes to the neutral diphosphine complexes commonly utilize **22b** as precursor (Scheme 4),[134–136] its commercial availability, and consequent synthetic convenience, counterbalancing its slower rate of phosphine exchange, relative to **22a** or **21a**.[83a,97,137] Vinylalkylidene complexes of type **27** could not be isolated for diphosphines that lead to a seven-membered chelate ring (PP = BINAP or $R_2P(CH_2)_4PR_2$; R = Cy, Ph), but such initiators generated *in situ* by the propargyl chloride route effected ROMP of NBE at room temperature to yield low-polydispersity polymer (PDI <1.06;[114] cf. 2.75 for neutral **27a**). Neither halide loss nor phosphine dechelation was apparently required, possibly because of the energetic accessibility of an isomer in which the alkylidene ligand occupies the basal plane. Dinuclear, phosphine-bridged species of the type $[RuCl_2(=CHPh)]_2(\mu\text{-PP})_2$ were obtained on reaction of **22b** with $Cy_2P(CH_2)_nPCy_2$ ($n = 5, 8$).[137] In these complexes, as for the four- and five-membered chelates of type **27**, the absence of a labile ligand in the basal plane (or, apparently, a low-energy isomerization pathway) limits metathesis activity. Abstraction of chloride (Scheme 4) dramatically increases the ROMP activity of $RuCl_2(PP)(=CHR)$ (PP = dtbpm, dtbpe). The edge-bridged, dicationic dimer **28**[134,138] gives ready access to the mononuclear species in solution.[134] Maximum RCM activity was associated with a smaller chelate angle ($n = 1$) and limited steric demand ($Cy > Bu^t$) within the diphosphine ligand, though a decrease in ROMP activity for the dcpm ($Cy_2PCH_2PCy_2$) system was related to backbiting of the polymer chain.[138] A similar trend was found for $RuCl_2[\kappa^2\text{-}PhCH_2N(CH_2PR_2)_2](=CHAr)$ (R = Cy, Bu^t; Ar = *o*-OPr^i–C_6H_4), which form six-membered chelate rings.[139,140] Metallodendrimers bearing these entities promoted ROMP of NBE (affording star-shaped polymers) more rapidly than the mono-Ru species: both presumably undergo decoordination of one phosphine arm. Abstraction of chloride affords a dimer analogous to **28**, but does not increase ROMP activity, probably because of stable chelation.

The lability of the dative chloride bond within edge-bridged dimers such as **28–30** confers high ROMP activity and high initiation efficiency.[141,142] Complex **29b** was 80 times more reactive than **22b** in ROMP of COD at room temperature.[141] Reactivity varies with the nature of the second metal species, a reflection of the ease with which the dimeric structure gives access to the mononuclear (14-electron) Ru–alkylidene. Of particular interest, given the dominance of mesitylene-functionalized NHC ligands in olefin metathesis chemistry, are findings from the Herrmann group which demonstrated that Rh^{III}–Ru^{II} dimer **30c**, bearing an ICy ligand,[142] is one of the most active ruthenium initiators so far developed. Initiator **30c** effected ROMP of 4000 equivalents of 5-norbornene-2-acetate within one minute at 25 °C, while **30a** enables living ROMP of **M1a**.[142,142a] In contrast, $RuCl_2(IPr)_2(=CHPh)$, though active for ROMP of COD and COE at 25 °C,[143,143a] gives polymers with broad PDIs, owing to the slow rate of loss of the second NHC ligand. Similar behavior is found for the "second-generation" Grubbs catalysts $RuCl_2(NHC)(PCy_3)(=CHPh)$ **33**,[144,145] the discovery of which has been reviewed.[67,146–147] The exceptional activity of Ru initiators of type **33b** has been the subject of much discussion. While their strong electron-donor properties are clearly important, Straub makes a persuasive argument for the relevance of the influence of the NHC ligand on the relative orientation of the alkylidene and alkene ligands.[5a] Only the conformer in which these ligands are parallel and coplanar (as in **2a**, Equation (1)) is



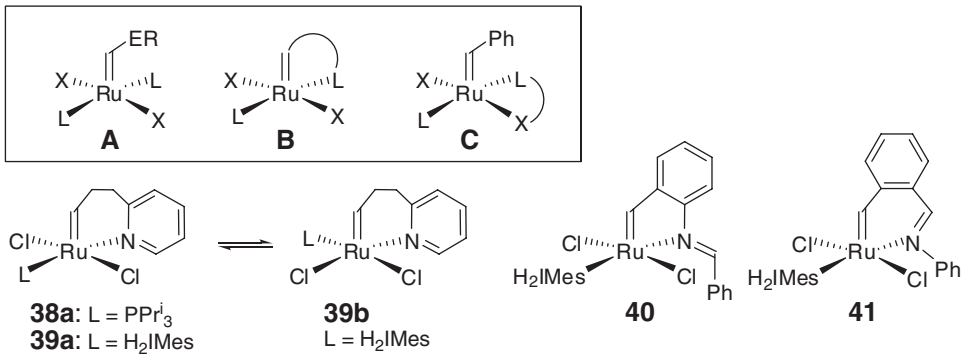
Scheme 4 Selected Ru alkylidenes containing chelating diphosphines.

geometrically and electronically predisposed for immediate rearrangement into the ruthenacyclobutane. A DFT analysis indicated that alkylidene rotation to give the active conformer was disfavored for the first-generation, but not the second-generation, complexes. Electronic and steric stabilization of the "active conformation" of the alkylidene moiety in the latter may thus account for their high metathesis activity.[67,146,147] (However, several alternative *N*-heterocyclic carbenes, including four- and six-membered heterocyclic rings,[148–150] and triazol-5-ylidene[106] donors, showed lower activity.)

While **33** has had an enormous impact on RCM and CM chemistry, its utility for controlled ROMP is diminished by its poor initiation efficiency and fast propagation.[151] Loss of PCy_3 from **33b**, for example, is ca. 100 times slower than from **22b**,[88,152] resulting in polymers with very high molecular weights and PDI values.[93,151,153] The extreme unreactivity of the second-generation methylidene derivatives[88,100] should also be noted in context of their relevance to potential applications in tandem RCM–ROMP or CM–ROMP processes. Even for the benzylidene derivative, however, initiation efficiency is problematic, a very small proportion of the added complex conferring the observed activity.[151,153] A similarly low percentage of initation was reported for the "Hoveyda" catalysts[154,155] **31a** and **31b**.[151,154–157] The initiation efficiency of these complexes is attenuated by the high thermodynamic stability of the five-membered chelate ring, which disfavors dissociation of the ether donor. Control over molecular weights and polydispersities is further limited by the rapid rates of propagation associated with removal of the ether donor from the coordination sphere. In ROMP of COE at 22 °C, **31a** underwent initiation ca. 30 times slower than **22b**, but propagated nearly four times faster.[154] While these factors have limited deployment of **31** in many ROMP applications, derivatives in which metathesis activity is amplified by steric or electronic destabilization of the chelate[158–161] offer promise for controlled ROMP. Such applications have not yet been explored. Analogs in which the chelating ether group is replaced by an ester or aldehyde donor, forming a six-membered chelate ring, also display low initiation efficiency.[162,162a]

The activity and homogeneity of initiation are significantly improved by replacing the PCy_3 ligand in **33** by a more labile donor. Initiators **29b**,[142] **34b**,[88] and **35b**, **d**,[163,161c] containing a dative bond from chloride, PPh_3, or a pyridine ligand, are all active for ROMP of COD at ambient temperatures. Complex **34b**, for example, initiated >50 times faster than **33b**,[88] effecting ROMP of COD within seconds of adding monomer, while a $P(p\text{-}CF_3\text{-}C_6H_4)_3$ analog was ca. 350 times faster.[152] In contrast with **33b**, the arylphosphine derivatives undergo complete initiation during polymerization. The pyridine[163,164] and, in particular, the bromopyridine[54,88,156,163] complexes, are even more effective. Initiator **35d** exhibited high activity toward challenging (see later) *endo*-disubstituted NBEs, while retaining excellent control over chain lengths.[54] PDI values of ca. 1.05 were found in ROMP of **M5a**: the linear relationship between molecular weight and [M]:[I] ratio suggests a living polymerization. ABC triblock co-polymers were accessible on ROMP of **M4b**, **M4c** and nitrile monomer **M4e** (though the order of addition is critical; see Section 11.06.03.02).[157] Given the high reactivity of this initiator, it is unsurprising that ROMP of NBE itself is not living at room temperature, though chain transfer could be controlled at −20 °C, decreasing PDI values from 1.65 to as low as 1.08.[54] The py derivatives are accessible in quantitative yield by treating **33** with the appropriate pyridine.[163] The PPh_3 derivatives were prepared by reaction of **35** with PPh_3,[152] or by treating **21a**[166] or **22a**[145] with the free NHC ligand. A further development comes from the recent discovery of phosphonium alkylidenes of the type $[RuCl_2(H_2IMes)(=CHPCy_3)][B(C_6F_5)_4]$.[164] As structural mimics for the four-coordinate transition state in the Grubbs systems, these species initiate rapidly and efficiently. They are characterized by very high RCM reactivity, though lifetimes are short, presumably owing to decomposition of the unprotected Ru-methylidene intermediate. Of considerable interest is their potential in ROMP, given the longer lifetimes characteristic[103] of Ru-alkylidene species.

The effect of the anionic donor on reactivity has not been systematically explored in the ruthenium systems. RCM activity in the series $RuX_2(PR_3)_2(=CHCH=CPh_2)$ followed the trend I < Br < Cl,[87] while ROMP of COD via **33b** and its dibromo and diiodo analogs showed the trend I > Br > Cl.[88] Notably, however, the iodo complex is only 1.4 times faster than **33b** in ROMP, despite initiating 250 times faster. The propagating species formed on phosphine loss is significantly less active for metathesis than is the case for **33b**, consistent with the earlier findings.[87,100] While this raises intriguing questions about the electronic effects in Ru-promoted olefin metathesis, the steric and electronic contributions cannot be deconvoluted in these systems. In related studies involving comparison of **20a** with its bis(trifluoroacetate) derivative, the latter proved consistently more reactive toward functionalized olefins.[108] However, a study of a series of six fluoroacetate derivatives of **22b** showed no correlation between the pK_a of the parent acid and metathesis activity.[167] Interpretation is complicated by the ligating ability of the carboxylate carbonyl. The Buchmeiser group has intensively explored the applications of a range of initiators,[13,168–170] including **32**,[169] for construction of ROMP-based monoliths and silica surfaces. Of particular interest is the potential of such assemblies for "flow-through" metathesis. Derivatives of **22b** in which a chloride and a phosphine ligand are replaced by chelating iminopyrrolato[171] or tris-pyrazolylborate[172] ligands showed limited ROMP activity. This is



Scheme 5

unsurprising, given the low lability of the remaining PCy_3 ligand, and the absence of a strong donor ligand in the 14-electron intermediate formed on loss of PCy_3. Schiff base initiators likewise exhibited low activity at room temperature, and ROMP (or RCM) was carried out at 70 °C.[55,173] On the basis of the correlation observed between metathesis activity and the electron-deficiency of the *O*-aryl group, activation of **36a**[55] was proposed to involve decoordination of the nitrogen donor, rather than phosphine. A remarkable increase in activity was found for an indenylidene derivative related to **36b**, which enabled ROMP of COE at room temperature (10,000 equiv., 15 min).[174] These species also enable ATRP chemistry (see below). Complexes **37**, containing monodentate aryloxide ligands, are of limited utility in ROMP applications, owing to their high rates of propagation, vs. initiation.[175] Initiation efficiency is limited by the low lability of the pyridine ligand, and may thus be improved by incorporation of less electron-deficient aryloxide ligands.

"Latent" initiators are of interest in industrial ROMP applications, as they extend the period over which monomer-catalyst resins can be handled before polymerization (Section 11.18.5). Design criteria for well-defined, latent ruthenium systems have been discussed.[176] The most desirable characteristics are proposed to be exhibited by systems of class **A** and **B** (Scheme 5), in which initiation is suppressed by modification of the alkylidene ligand.[176] Systems of class **C**, containing a pendant donor that can come into play throughout the ROMP process, may exhibit better control over PDIs (see above), at the price of propagation rates. The slow initiation but potentially rapid propagation possible with **A** and **B** offers extended handling periods and rapid curing, though challenges arise in integrating this behavior with high initation efficiency, and control over the reaction exotherm, materials properties, and rate and extent of cross-linking. These issues are discussed further in Section 11.18.5. Their limitations in terms of controlled ROMP were discussed above in context of the Hoveyda complexes **31**, prototypical class **B** systems. In studies examining the potential of Fischer carbenes as latent class **A** initiators, $RuCl_2(PPr^i_3)_2(=CHSPh)$, proved unexpectedly reactive (see earlier), and complete gelation of 5 g of neat DCPD monomer was observed within ca. 10 min at 60 °C.[109] In comparison, gel times of >40 min were recorded for the class **B** complex **38a**, in which the alkylidene ligand chelates the metal via a pendant 2-pyridylethane functionality. The Materia group, seeking olefin metathesis catalysts that initiate slowly while maintaining the activity of the Ru-NHC systems, examined the behavior of the corresponding H_2IMes complex **39** in ROMP of DCPD at 30 °C. Initiation was slow relative to **33b** or **31b**, with a striking difference in activity depending on initiator geometry: isomer **39a**, in which the py and NHC ligands are mutually *trans*, reached its exotherm in 3 min in bulk ROMP of DCPD ([M] : [I] = 30,000 : 1), versus 25 min for **39b**.[177] This remarkable difference in behavior may offer possibilities for tuning initiation rates via isomerization. Use of methyl-substituted pyridyl rings had minimal impact on ROMP performance. Related benzylidene–imine derivatives **40** and **41** exhibit non-zero activity for ROMP of **M4b** at room temperature, but high reaction rates at 110 °C in neat monomer.[176] Initation efficiencies, as inferred from molecular weight data, ranged from 4% to 6%. η^2-Pyridinyl alcoholate ligands also demonstrated thermal activation for solution ROMP of NBE and COE at 60 °C, albeit at lower catalyst loadings (NBE, 100 equiv.; COE, 500 equiv.).[178] A hazard associated with thermal initiation lies in the potential to accelerate catalyst decomposition. This is a particular concern when using electron-rich Ru complexes in CH_2Cl_2 or $CHCl_3$ solvent. Chlorination of such species under these conditions is facile (and readily overlooked, as the paramagnetic Ru(III) products are not detected by NMR analysis). ROMP of **M7** via

38a (or **23b**) was found to plateau at ca. 65% conversion in refluxing chloroform;[179] similar, less drastic behavior was found in ROMP of **M4b**.[161]

11.18.3 ROMP Polymers

11.18.3.1 Monomer Architecture and Functionality

A survey of monomer classes, comprehensive up to 1997, has appeared;[3] a subset of the more commonly used examples is shown in Figure 2. The NBE derivatives have seen most widespread use (see Section 11.18.5). Functionalized poly(NBE) scaffolds are very widely deployed, owing to the ease with which the monomers (or their precursors) can be prepared by Diels–Alder[3] or S_NAr[180,181] methods, and to the relative stability of the polymers (vs. functionalized poly(COE), for example) to backbiting and inter-chain metathesis. As with the Schrock systems, the Grubbs-class initiators polymerize a wide range of monomers (Table 3); their generally greater tolerance for oxygen-donor and some protic functionalities, and trace impurities, including air and water, has opened up new opportunities. Issues of functional group tolerance are discussed in more detail below. ROMP of monocyclic, substituted cycloolefins is of great interest, especially where coupled with hydrogenation (Section 11.18.4), this providing a "back-door" route to functionalized polyolefins unattainable by Ziegler–Natta or metallocene catalysis. Low-strain monomers such as cyclopentene (CPE), cycloheptene (CHE), or cyclooctene, are more challenging to polymerize than strained cycloolefins, as the lower reaction enthalpy for ring opening reduces the driving force for polymerization. The barrier for the reverse reaction is also reduced. This is particularly problematic for CPE and CHE monomers functionalized at the 4- and 5-positions, respectively, for which the Thorpe–Ingold effect promotes RCM. Methods for computational evaluation of the ring strain (hence polymerizability) of functionalized cycloolefins have been proposed.[182,183] Low ring strain imposes higher demands in terms of initiator activity. Given the accessibility of the olefinic units in the polymer backbone, however, this compounds the difficulty of controlling secondary metathesis, even for comparatively "well-behaved" initiators such as **10a**[3,184] or **22b**.[185] ROMP of any cycloolefin can, in principle, generate an equilibrium mixture of linear ROMP polymers, monomer, and cyclooligomers formed by backbiting.[3,186] The position of equilibrium is sensitive to the ring size, and the nature and location

Table 3 Functional group tolerance of well-defined Mo and Ru initiators

Entry	*Monomer*	*Functionality*	*Init.*	*Conditions*[a] ([*M*] : [*I*])	*Mn* × 10^3 (*PDI*)	*Yield* (%)	*References*
1	**M4e**	CN	**10b**	CH_2Cl_2 (50)	41.3 (1.2)	87	191
			22b	CH_2Cl_2 (50)	Fails	0	191
			33a	CH_2Cl (100)	42.4 (2.4)	78	191
2	**M4a**	CO_2R	**12a**	C_7H_8 (100)	1.04	100	192
	M4b		**22b**	C_7H_8 (300)	83 (1.08)	98	151
			33b	C_7H_8 (300)	688 (2.4)	93	151
3	**M3a**	CH_2OR	**10a**	C_7H_8 (100)	18 (1.05)	98	59a
	M3b		**22b**	CH_2Cl_2 (300)	64 (1.4)	84	156
			31a	CH_2Cl_2 (300)	65.7 (1.3)	85	156
			35d	CH_2Cl_2 (300)	64.4 (1.04)	85	156
4	**M3c**	$CH_2OC(O)R$	**22b**	CH_2Cl_2 (300)	433 (2.1)	96	156
			31a	CH_2Cl_2 (300)	720 (2.2)	91	156
			35d	CH_2Cl_2 (300)	120 (1.2)	87	156
5	**M4d**	C(O)R	**22b**	CH_2Cl_2 (300)[b]	72 (1.05)	89	156
			31a	CH_2Cl_2 (300)[b]	74 (1.09)	89	156
			35d	CH_2Cl_2 (300)	62 (1.04)	95	156
6	**M9a**	CO_2R	**10a**	C_7H_8 (20)	13.6 (1.1)	90	193
			22b	C_7H_8 (20)	4.2 (1.2)	[c]	193
			33b	C_7H_8 (20)	26.9 (1.3)	[c]	193
7	**M11a**	NH	**22b**	THF (20)	4.22 (1.05)	80	194
8	**M12**	SR_2	**22b**	CH_2Cl_2 (74)	14.4 (1.4)	88	195

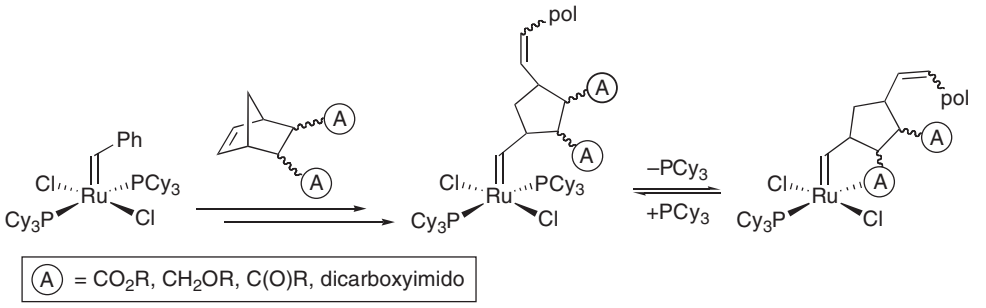
[a]Reactions at room temperature, unless otherwise stated.
[b]ROMP at 40 °C.
[c]ROMP does not proceed to completion.
[d]R indicates bulky substituent.

of substituents. These ring-chain equilibria are also strongly concentration dependent, as Jacobson–Stockmayer theory predicts.[187,187a] As formation of cyclooligomers is favored with increasing dilution,[186–188] low-strain cycloolefins are commonly polymerized in neat monomer. For ROMP of large cycloolefins at high concentrations or in neat monomer, the loss in translational entropy associated with polymerization declines, and can ultimately be outweighed by the positive entropic contribution associated with the conformational mobility of the polymer chain. In an elegant demonstration of these effects, the Hodge group reported entropically driven ROMP of 21–84 membered macrocycles using **38b** as initiator.[189] Coupled RCM–ROMP approaches open a new range of possibilities, subject to limitations on chain-length control imposed by the low reactivity of [Ru]=CH_2 species (see above). ROMP of macrocyclic, functionalized crown ethers synthesized by Li^+-templated RCM, for example, afforded polyethers with pendant amino acid groups[190] (though better specification of chain lengths and architectures was obtained with oligopeptide-functionalized NBEs).[190a,190b]

Initiator **20b** effects ROMP of 5-functionalized COE monomers bearing alcohol, ketone, ester, and bromine functionalities, though attempted ROMP of epoxy- and cyano-substituted cyclooctenes failed.[196] Controlled ROMP of COD by **22b** was achieved by use of an equivalent of PPh_3 to attenuate propagation rates; PDIs decreased from 1.25 to 1.04 for ROMP in neat monomer.[197] Well-controlled ROMP of CPE has been achieved with **10a**.[184] PDIs below 1.1 can be obtained at room temperature in toluene by using PMe_3 to temper propagation rates, and limiting conversions to 40%.[198] Yields of ca. 80% were reported in ROMP of neat CPE and CHE by **22b** and **33b**, with PDIs on the order of 1.5.[182] Polymer yields decrease at lower concentrations, as expected from the concentration dependence of the ring-chain equilibrium. ROMP of symmetrically substituted five- or seven-membered cycloolefins gives polymers with a perfectly regioregular distribution of functionality, providing that secondary metathesis can be prevented. Nearly 90% yield was reported for ROMP of neat 4-cycloheptenone using **35d**, though the molecular weight was approximately double that expected, possibly reflecting the low solubility of the initiator. Low yields (24%) in ROMP of 3-cyclopentenone may be due to chelation of the ketone functionality in the propagating species, as ROMP of 4-CPE monomers bearing acetate or $SiBu^t$ groups proceeded in 65–75% yield using **35d**, **22b**, or **33b**.[182]

Strained monocyclic systems have been extensively investigated. Living ROMP of cyclobutenes, enabling synthesis of functionalized polybutadienes and their block co-polymers, was achieved via **14a** (again in the presence of PMe_3)[199] or by use of **10c** ($R = CMe_2CF_3$).[200] Complete head-to-tail regiospecificity (as also observed for ROMP of 3,3-dipropylcyclobutene by **10a**)[201] was attributed to steric "steering" by the 3-methyl group of the incoming cyclobutene.[200] In the presence of $PPhMe_2$, low-PDI polymer was obtained, which on hydrogenation afforded the perfectly alternating polyolefin. Living ROMP of 3,4-disubstituted cyclobutenes bearing protected alcohol and carboxylic acid groups (benzyl ether, benzyl ester functionalities) by **10a** enabled synthesis of homopolymers or block co-polymers, which were converted into the acid- and alcohol-functionalized polymers by post-polymerization workup.[202] 3-Functionalized cyclobutenes bearing ether, ester, alcohol, secondary or tertiary amine, amide, and, most notably, carboxylic acid substituents, were polymerized by **20b** and **22b** without protecting groups.[203] Living ROMP was achieved, providing that excessively stable chelation of oxygen or nitrogen donors to the metal could be minimized. Substrates that enabled formation of seven-membered chelate rings in the propagating species slowed propagation to the point that initiator decomposition occurred over the timescale of ROMP. Where the chelate ring size or the bulk of the donor group enabled operation of a fast, dynamic equilibrium between free and chelated species, low PDI values (1.07–1.13) and living ROMP were observed.[203] A comparative study involving ROMP via the cyclobutene unit in **M8** and related monomers by **10a** and **22b** highlighted the importance of controlled polymerization of this highly strained monomer. Well-controlled, living ROMP was attainable only with the Ru initiator, owing to its lower reactivity.[204] Underlining the importance of matching the reactivity of a given monomer to a given initiator, a recent study indicated that **10a** was superior to **22b** or **33b** for efficient, controlled ROMP of NBEs bearing acetyl-protected maltose or glucose groups (**M9**, the maltose monomer, is shown in Figure 2). The reactivity followed the trend **10a** > **33b** > **22b**, but good control over molecular weights and narrow PDI values (<1.2) were found only with **10a** and **22b**.[193] Finally, nitrile donors remain somewhat problematic for the ruthenium initiators (Table 3, entry 1). While ROMP of **4e** by Mo initiator **10b** affords low-PDI polymer with high yields, polymerization failed for **22b**, and polydispersities were rather high (2.4) for **33a.**

The greater rigidity and steric congestion of polymers obtained by ROMP of functionalized bicyclic substrates reduce the tendency toward backbiting and inter-chain metathesis, relative to monocyclic monomers, but *endo*-difunctionalization can be problematic for both Mo[2] and Ru[205] initiators. In mixtures of *exo*- and *endo*-DCPD, the slow reaction of the *endo* isomer was shown to be due to steric interactions between incoming monomer and the penultimate repeat unit of the growing chain, as well as coordination of the endocyclic double bond.[205] *Endo,exo* mixtures of 5-monosubstituted norbornenes, or *exo,endo*-5,6-disubstituted NBEs (e.g., **M2**, **M3**), do not impede ROMP to the same extent. Such substrates can normally be polymerized.[206] However, some rate inhibition by



Scheme 6 Oxygen-chelated propagating species observed during **22b**-initiated ROMP.[208]

chelation of an *endo*-substituent within the propagating species, first noted with **20**,[91] appears to be a common feature for the Ru initiators,[207] although the high reactivity of **35d** enabled rapid, controlled, and living ROMP even of *endo*,*endo*-disubstituted **M5a**.[54] In *exo*,*endo*-disubstituted NBEs, coordination of oxygen donors from *endo*-carbonyl or -ether substituents, forming a six-membered chelate ring, was proposed to account for the order of reactivity: ester (carbonyl) ~ ether > ketone (Table 3, Entries 2–5).[156,208] In a detailed NMR study, an equilibrium between the chelated and PCy_3-bound species was observed for **22b** (Scheme 6).[151] Again, labile chelation improved control over polymer molecular weights and PDI values, though reaction times increased. Most striking was the unexpectedly low polydispersity found even on use of the slow-initiating **31a** to polymerize **M4d** (Table 3, entry 5). The nature of the group used to tether substituents to the NBE ring is evidently of key importance in determining reaction rates, molecular weights, and PDI values.[156] Steric factors are also critical, however, even for otherwise reactive 2-substituted-5-NBEs.Entry 6 illustrates the challenge presented by a bulky maltose-substituted NBE, for which only **10a** gives high yields. In ROMP via **20b**, the bulk of the protecting group had a dramatic impact. Replacing the acetate protecting group on a glucose substituent with a bulky (but more easily removed) triethylsilyl ether, for example, increased reaction times from 5 min to 2–3 days.[209]

Succinimide-derivatized NBEs such as **M10** and **M11** have been extensively used, owing to the diversity of monomers accessible by nucleophilic substitution of the NH site in the parent compound (e.g., **M11a**). Of considerable interest is the ease and control with which **M11a** itself undergoes ROMP by **22b** (entry 7) to afford a well-defined, readily functionalizable polymer platform (see also Section 11.18.4).[194] The mild reaction conditions, and the accessibility of living polymers of **M11a** and **M11b**, indicate that poisoning does not interfere. A somewhat high PDI value for ROMP of thiophene monomer **M12** (entry 8) may be due to poisoning and/or chelation.[195] More unequivocal is the ROMP behavior of norbornadiene monomers bearing an alkoxy group in the 7-position, which again led to a chelated propagating species in ROMP via **22b**.[210] This is more deleterious than the effects noted above, co-regeneration of the initiator implying inter- or intra-chain metathesis. Coordination of the ether oxygen in the propagating species may facilitate backbiting, as ROMP of 7-alkyl norbornadienes showed no such behavior. In contrast, the presence of the oxygen atom in 7-oxabenzonorbornadiene **M13** has a positive effect, this monomer exhibiting ca. 20 times the ROMP reactivity of the corresponding benzonorbornadiene on treatment with **22b**.[211] Similar results were earlier noted with catalysts of type **10a**, despite the oxophilic nature of the metal.[3]

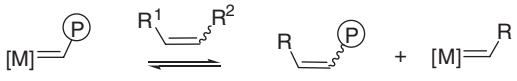
11.18.3.2 Controlling Molecular Weights

Initiator efficiency, and the accessibility of chain-transfer and termination processes, are key factors in determining polymer chain lengths. Slow rates of initiation relative to propagation result in polymers with high, poorly controlled molecular weights, while highly reactive initiators can promote backbiting or inter-chain metathesis, particularly for low-strain monomers, as noted above. Where the reactivity of the monomer and initiator is well matched, living ROMP enables construction of polymers with precisely specified chain lengths and end groups, and complex block architectures are accessible by sequential addition of monomers. Long established with the Schrock initiators,[2] living ROMP is now possible with the important Ru initiators **22b** and **35**, depending on the monomer and reaction conditions. An overview of systems for which living ROMP has been achieved recently appeared.[212]

Aiding controlled ROMP via the Schrock initiators is their modular nature (which facilitates matching of initiator and monomer reactivity); their high initiation efficiency; the capacity to modulate activity by appropriate choice of solvent;[213] and the ease with which ROMP can be quenched by addition of aldehydes, preventing secondary metathesis processes. In these and other early or mid-transition metal systems, however, chain termination can result from side-reactions with impurities or polar functional groups, while the presence of trace air or water leads to double molecular weight[2] or high molecular weight polymer. The ruthenium systems are less susceptible to unwanted termination (though their sensitivity to alcohol solvents[214,215] (see below) and oxygen should be recognized), but highly active versions are likewise susceptible to secondary metathesis.[51] As with any other initiators reactive enough to effect CM of internal olefins, polymerization must be quenched before the reaction can come to equilibrium, if control over chain lengths and microstructure is to be maintained. The robustness of the Ru complexes can make this challenging: the conventional reliance on ethyl vinyl ether as a quenching agent for Ru ROMP must be reexamined in light of the metathesis activity of Fischer carbenes,[52,110] as well as the potential for formation of hydride products that may promote undesired reaction pathways.[108,110]

In both group 6 and group 8 systems, addition of a Lewis base can temper excessive propagation rates. The lability of this additive is critical to establishing a fast, dynamic equilibrium between the dormant (additive-bound) and active species. In the group 6 chemistry, THF or amine donors are customarily used,[2] where PPh_3 is more suitable for the Ru systems;[197] indeed, secondary amines (as well as nitriles, thiols, and pyridines) can severely retard or arrest ROMP via the latter.[206] As chloride-bridged dimers appear to be implicated in deactivation of the Grubbs-class catalysts,[83,83a] additives that can disrupt chloride bridging are of interest. Small amounts of phenol, 2-propanol, or acetone (300 equiv.) have been found to accelerate ROMP via **33b**.[206] A beneficial effect of phenol on the activity and lifetime of **22b** and **33a** has been linked to reduced rates of phosphine rebinding,[216] and hydrogen-bonding interactions between the chloride ligand and phenol.[216,217] Deliberate promotion of (heterobimetallic) chloride bridging has been used to manipulate polymer microstructure.[218] Thus, addition of $MoCl_5$ during co-polymerization of NBE–CPE by **22b** in CH_2Cl_2 yielded almost perfectly alternating co-polymers, possibly because formation of chloride-bridged, heterometallic species prevents access of the more reactive NBE monomer to poly(NBE), but not the sterically less demanding poly(CPE) segment. The effect is disrupted in ether solvents. With **33b**, $MoCl_5$ acted as a poison for all propagating steps, irrespective of the nature of the incoming monomer, and reaction rates were very slow. While the foregoing suggests that use of donor solvents such as THF may be advantageous for metathesis via chlororuthenium initiators (and a correlation between metathesis activity and dielectric constant of the solvent has been proposed),[88] no consistent trend has emerged. The heightened demands on solubility in ROMP, versus small-molecule catalysis, mean that the choice of solvent may in any case be imposed by the monomer (and initiator) employed.

An alternative solution to low initiation efficiency involves carrying out ROMP in the presence of olefins as chain-transfer agents (CTAs), which react with the metal-terminated polymer by CM (Equation (3)). This approach is widely used to prepare telechelic polymers (see below).[219] As transfer constants (k_{tr}) are typically small relative to propagation,[3] high CTA concentrations are required if a significant reduction in molecular weights is desired. Use of CTAs to control molecular weights in living ROMP can result in a bimodal molecular weight distribution, if $k_i \sim k_p >> k_{tr}$ (where k_i and k_p are the rate constants of initiation and propagation, respectively).[220] Even use of a large excess of CTA does not confer control over molecular weights for living polymerizations, unless k_{tr} is an order of magnitude larger than k_p. While use of 1-alkenes as CTAs maximizes transfer constants, this may be undesirable in the ruthenium chemistry, owing to the low metathesis activity[88,100] and instability[103] of Ru–methylidene species.



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Although solution polymerizations are typically employed, ROMP can also be carried out by bulk, emulsion, and suspension polymerization, and in a number of reaction media.[221,222] Reaction efficiencies, molecular weights, and PDI values for ROMP of NBE and COE in supercritical CO_2 using **10b**, **22b**, and **33a** were generally similar to those found in organic solvents.[223,224] In a study of ROMP of NBE by **22b**, **33b**, and allenylidene **26** in ionic liquids, **26** proved most active, possibly because its cationic nature improves solvation. It was reused up to six times without detrimental effects on polymer yield or PDI, though an increase in molecular weight on recycling suggests some loss in initiator concentration.[225] Greater attention has focused on aqueous ROMP, which—apart from the attractions of

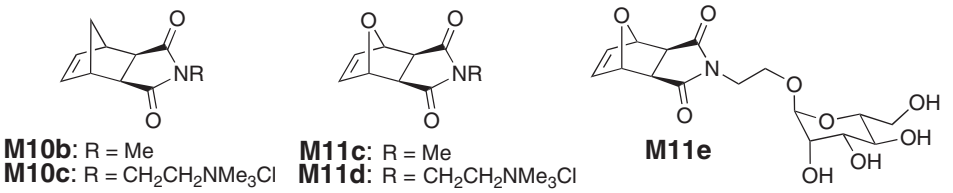


Figure 5 Representative water-soluble monomers explored in ROMP.

an inexpensive and non-toxic reaction medium—offers the opportunity for polymerization of hydrophilic monomers. Potential hazards, including hydrolysis of ester or anhydride functionalities[226,227] and retro-Diels–Alder reactions of oxanorbornene monomers,[3] have been noted in systems using classical catalysts. Indeed, stability seems likely to emerge as a key issue for deployment of functionalized ROMP materials in aqueous environments. Weck and co-workers recently reported on the hydrolytic susceptibility of a range of tether groups by which pendant functionalities are bound to poly(NBE) backbones.[228] In studies using functionalized NBEs as probe systems, monomers containing ester linkages (see, e.g., **M1**, **M4**) were not stable under a wide range of temperature and pH values.

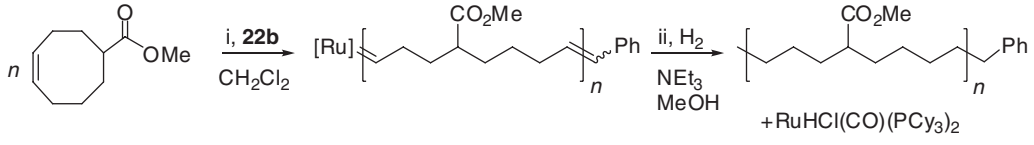
The advent of well-defined, relatively robust ruthenium initiators has opened up new possibilities in water-soluble metathesis. While **22b** and **33b** are decomposed by alcohol solvents, particularly at elevated temperatures,[214,215] alcohols may be more aggressive media than water, owing to the accessibility of β-elimination pathways. Ionization of the Ru–Cl bond in water (or methanol) is indicated by the observation of proton exchange between D_2O and CD_3OD solvents and the benzylidene functionality of **22b** and water-soluble analogs.[229] This may facilitate the halide-exchange reactions noted with bromide surfactants (use of which led to broadened PDIs and low yields), but does not appear to impede polymerization of reactive monomers. Several ROMP-active, water-soluble Ru initiators have been prepared by replacing the PCy_3 groups of **22b** and **24b**, respectively, with the cationic phosphine ligands [PCy_2R]Cl (R = $CH_2CH_2NMe_3$, 4-(*N*,*N*-dimethylpiperidinium))[230,230a] or the anionic phosphine [PPh_2R]Na (R = *o*-OS-$(O)_2C_6H_4$),[231] or by modifying **33b** with a PEG-functionalized NHC ligand (PEG = polyethylene glycol).[232] The water-soluble initiators promoted ROMP of strained cycloolefins (Figure 5) in water. Decomposition over the timescale of polymerization for monomers **M10c** and **M11d** (possibly resulting from reaction with hydroxide ion) was circumvented by adding up to 1 equiv. of DCl. Quantitative, living ROMP was then achieved within 15 min at 45 °C, with PDI values of ca. 1.2.[230] Homopolymers and block co-polymers were accessible. The beneficial effect of acid was attributed to quenching of hydroxide, and to acceleration of metathesis by sequestration of free PCy_3, thus permitting polymerization to outcompete deactivation. A number of other studies have focused on emulsion ROMP of hydrophilic and hydrophobic monomers, employing **22b** or **33b** dissolved in small amounts of a chlorinated solvent, in conjunction with various surfactants. These advances were recently reviewed.[233] Of particular note is the application of these methods to ROMP of unprotected, carbohydrate-functionalized monomers such as **M11e**.[234,235] Work from the Kiessling group has highlighted the potential of ROMP routes to neoglycopolymers and other biologically relevant materials.[234–236,236a] An overview of the convergence between synthetic and biological polymers has also recently appeared.[237]

11.18.4 Hybrid and Modified ROMP Polymers

The ease of constructing well-defined ROMP polymers has led to much interest in using these materials as platforms that can be modified at the olefinic sites, the endgroups, or the pendant groups. Functionalities installed on the end groups or built into pendant groups have been used to graft ROMP polymers to other entities, including surfaces (the so-called "grafting to" approach). As a corollary, appropriately functionalized surfaces or materials can be used as substrates on which growth of ROMP polymers can be triggered ("grafting from"), providing that a suitable functionality can be demasked or installed; this constitutes a special case of endgroup modification. As particular aspects within each of these areas of polymer modification have been highlighted in recent, specialized reviews,[67,170,212,219,235,237–246,293,298,301,302] advances will be summarized in brief.

11.18.4.1 Modification of Backbone C=C Bonds

Hydrogenation of ROMP polymers increases their thermal stability by eliminating the potential for oxidative or thermal degradation of the olefinic sites. Reduction with diimide (generated *in situ* from *p*-toluenesulfonylhydrazide) was reportedly more successful than use of $Pd/BaSO_4$ under H_2 at high pressure.[247] However, forcing conditions are required, during which polymer degradation (including functionalization) can occur.[248] Homogeneous hydrogenation is therefore widely employed. Tandem catalysis routes to the saturated polymers are possible with the ruthenium catalysts.[238,239] "Assisted" tandem catalysis, in which a change in mechanism is triggered once an initial transformation is complete,[239] has been extensively used to carry out one-pot ROMP–hydrogenation sequences (typically on COE–**22b** systems) since the first report in 1997.[249] The reaction involves post-ROMP hydrogenolysis of the Ru–alkylidene bond by treatment with hydrogen and base.[250] The ruthenium endgroup is thus removed from the polymer as a well-defined ruthenium hydride species. Hydrogenation rates are maximized by use of alcohol co-solvent (in part due to transformation of the Ru species into a more reactive RuHCl(CO) species). This enables reduction of polyoctenes at 1 atm and 60 °C (Equation (4)).[251] Recent reviews provide an overview of examples of this methodology,[238,239] including an elegant double tandem ROMP–ATRP–hydrogenation sequence.[252] The Nguyen group recently reported use of this approach for reduction of polymers derived from *exo*-5-(benzyloxy)NBE and *exo*-5-[(4-*tert*-butyl)benzyloxy]–NBE, for which diimide reduction, as well as H_2-hydrogenation via the Crabtree catalyst, proved ineffective.[253] The increased steric bulk and relatively long chain lengths (700–800 repeat units) necessitated use of more forcing conditions and long reaction times. (This report was also the first example of the application of ROMP to the construction of gradient co-polymers, in which the monomer composition changes continuously along the backbone). Functionalization of the olefinic units by bromination and bromoalkoxylation was also effected.[253]



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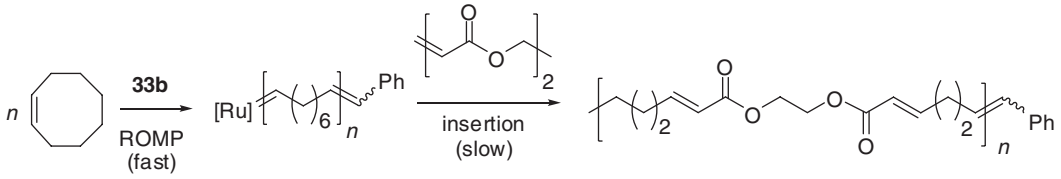
In a further recent advance, the high activity of **33a** was exploited to prepare highly alternating AB co-polymers via ring-opening insertion metathesis polymerization (ROIMP). Treatment of 1 : 1 mixtures of ethylene diacrylate and cyclooctene monomers with **33b** permitted sequential steps of ROMP and insertion (Equation (5)).[254] Backbiting of flexible rings was also deliberately exploited by Grubbs and co-workers to devise a route to cyclic polyolefins. ROMP of COE was carried out using a Class **B** initiator in which an NHC ligand was tethered to the alkylidene.[254a] Backbiting eliminated the unsaturated poly(octene) rings, following which hydrogenation generated the cyclic polyolefins.



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The accessibility of the backbone olefins in poly(octene) likewise facilitates CM, as noted above. While in many cases an undesired side-reaction, this susceptibility has been exploited to develop methods for depolymerization of polybutenes by CM with ethylene.[188] The area was recently reviewed.[240]

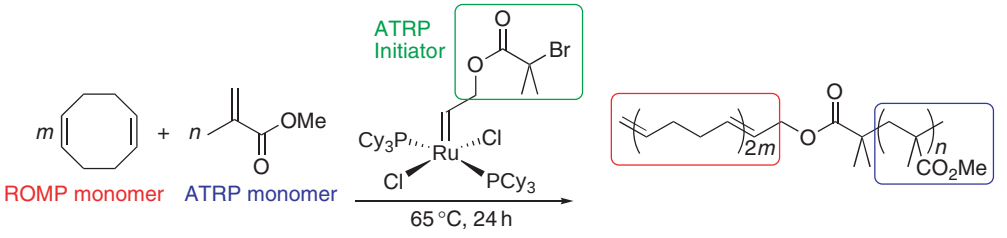
11.18.4.2 Modification of Endgroups

Endgroup functionalities, typically introduced via aldehyde-"capping" agents or chain-transfer agents, have long been exploited for construction of polymers with interesting topologies, such as star polymers,[255] as well as telechelic polymers.[2] This approach was recently adapted to the assembly of amphiphilic multiblock co-polymers by coupling an end-functionalized ROMP co-polymer with poly(ethylene glycol) (PEG). Termination of a ROMP block co-polymer (prepared via **10a**) with an aldehyde or silyl-protected alcohol functionality, followed by deprotection and potassium hydride-mediated attachment of PEG, gave low-PDI materials.[255a] Star-shaped (tri-arm) amphiphilic

co-polymers were accessible by use of an appropriate trialdehyde. While the Ru catalysts do not undergo the analogous Wittig-like reaction with aldehydes, treatment of living, amino acid-functionalized poly(NBE)s prepared via **22b** with molecular oxygen was reported to effect a highly selective chain-end functionalization.[256] CM with olefinic CTAs is more commonly used to install desired endgroups, although the need for high concentrations of the chain-transfer agent in order to maximize the efficiency of CM was noted above. Routes to telechelic materials, which serve as building blocks for a variety of complex macromolecules, were recently summarized.[219] Hydroxy-terminated polymers, which have found much use in polyurethane synthesis, are of particular interest. Attempts to gain access to hydroxy-telechelic polybutadienes by ROMP of COD using a silylether-functionalized olefin as a CTA led to decomposition of the tungsten initiator, whereas a functionality approaching 2.0 could be realized using initiator **10b**.[257] Unprotected chain-transfer agents, such as 1,4-diacetoxy-2-butene, have been used in conjunction with **22b** and **24b**.[258] Use of allylic alcohols in conjunction with **22b** resulted in the unexpected formation of aldehyde-terminated polymers, possibly owing to decomposition of the Ru complex to an isomerization-active hydride species. Rapid decomposition of **22b** in the presence of allylic alcohols at room temperature was previously described.[258a] While the higher reactivity of **33b** increased the efficiency of the CM reaction, eliminating this problem,[259] the isomerization activity of Ru–NHC species[260] may be problematic under forcing conditions. Use of more reactive, vinylic CTAs is thus advantageous where semi-telechelic polymers are targeted. ROMP of NBE by **24a** in the presence of vinyl ethers as CTAs has been used to prepare monofunctional macroinitiators for subsequent use in ATRP (see below).[119]

The CTA approach is limited by the ability of the ROMP initiator to mediate chain transfer,[52] and the tendency of highly reactive catalysts to promote excessive chain transfer.[219] In an alternative approach, functionalized initiators have been used to install a desired endgroup. $RuCl_2(=CHCH_2OAc)(PCy_3)_2$ was used to effect living ROMP of a functionalized NBE to generate an acetoxy-terminated polymer.[261] Subsequent reaction with 1,4-diacetoxy-2-butene as CTA, followed by hydrolysis, gave the hydroxy-terminated telechelic polymer. More recently, vinylidene species such as **24a**[52] were used to effect ROMP of NBE in the presence of vinyl sulfide. The Fischer carbene **23b** is generated *in situ*: subsequent ROMP generates a semi-telechelic polymer, which on CM with the vinyl sulfide affords a thiophenoxide-functionalized telechelic polymer.[52] Similar behavior was shown for isolated **23b**.[110]

Telechelic ROMP polymers have been extensively used to couple ROMP with other polymerization methodologies, giving access to polymers with novel structures and properties. Routes to such materials have been extensively investigated.[219,243] Block co-polymers of this class are typically prepared by carrying out first ROMP, and then the second polymerization process, of which Zeigler–Natta polymerization, group-transfer polymerization (GTP), and ATRP have been most explored. In an early example, block co-polymers of ring-opened NBE and ethylene were prepared by sequential ROMP and Ziegler–Natta polymerization of NBE and ethylene using well-defined titanocene catalysts.[262] The switch in mechanism was effected by adding an alcohol, followed by $AlEtCl_2$ and ethylene, to a living, titanacyclobutane-terminated poly-NBE.[262] A switch from vinyl to ROMP polymerization has also been effected by addition of phenylacetylene.[263] A related approach was used to construct alternating and multiblock co-polymers of ethylene and cyclopentene via a living bis(phenoxyimine)titanium catalyst.[264] Coupled ROMP–ATRP sequences have also been much explored. Use of the Schrock initiator **10a** for ROMP of NBE, followed by quenching and transformation of the aldehyde endgroup into a halide derivative, generated a macroinitiator for ATRP.[265] Diblock co-polymers were prepared by subsequent polymerization of acrylate monomers in the presence of a copper bromide catalyst. Ruthenium initiators have also been used, as noted above. The Schiff base complexes of type **36**, and an indenylidene analog, initiate both ROMP and ATRP with exceptionally high efficiency,[174] though coupled processes have not yet been explored. Ru initiators containing a halide-functionalized alkylidene moeity (Scheme 7), have been used to effect sequential ROMP and ATRP of COD and methyl methacrylate, respectively (as well as a subsequent hydrogenation step; see above).[252]



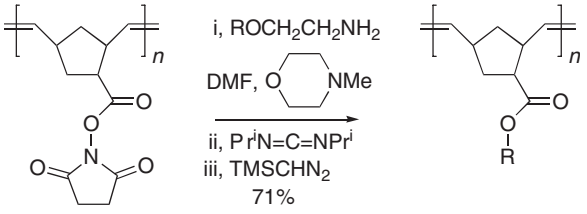
Scheme 7

Use of CTAs expands the range of functionalities that can be introduced, and hence the range of polymerization techniques that can be coupled with ROMP. The Ozawa group has used heterodifunctional CTAs to introduce initiation sites for two different types of polymerization process. 1-Arylthio-1-propen-3-ols bearing bromo, amino, and 4-(chloromethyl)benzamido substituents give heterotelechelic poly-NBEs, which serve as macroinitiators for anionic ring-opening polymerization (AROP) of caprolactone and ATRP of styrene.[119,119a] AB- and ABC-type block co-polymers were synthesized via sequential processes of ROMP, ATRP, and AROP. Living ROMP polymers have also been terminated with anionically polymerized macromolecular aldehydes.[266] Alternatively, NBE substituents can be tethered to the reactive endgroup(s) of a polymer chain prepared by cationic or anionic polymerization; subsequent ROMP can be induced by addition of a suitable initiator and further monomer. For example, anionic polymerization of ethylene oxide, followed by termination with vinylbenzyl chloride, afforded polyethylene oxide (PEO) macromonomers with a terminal vinyl group. CM afforded a ruthenium-terminated macroinitiator that effected ROMP of NBE derivatives.[267]

The latter approach can be recognized as a variant on the "grafting from" approach heavily used for modification of surfaces. Construction of polymer brushes by this means was recently reviewed.[241] The versatility of this methodology is suggested by the range of substrates explored: among many other examples, polymers have been grown from nanoparticles,[268–270] liposomes,[271] and, following chemical treatment[241a,241b] or electrografting,[272] from metal surfaces. In an alternative to electrografting, contact metathesis polymerization (in which a well-defined ROMP initiator is used to polymerize a highly reactive monomer such as DCPD as a sandwich between a metal substrate and a plastic or rubber layer), offers potentially broad applications in materials technologies.[242] Self-assembly of appropriately end-functionalized telechelic homopolymers offers the opportunity for construction of complex, versatile architectures while simplifying synthetic procedures. In a recent example, polyoctenes were reacted with CTAs to install terminal hydrogen-bonding or "pincer" ligand motifs for metal coordination. Self-assembly with their complementary homopolymers or metal species afforded block co-polymer architectures.[273]

11.18.4.3 Modification of Pendant Groups

Functionalization of pendant groups in ROMP polymers is of considerable interest, given the potential for installation of diverse functional groups on a single, well-defined polymer platform. A strategy based on nucleophilic substitution of pendant succinimide groups (Equation (6)) was used to prepare a range of neoglycopolymers in a single step following polymerization, circumventing the need for time-consuming synthesis of the carbohydrate-functionalized NBE.[274,275] The NH–succinimide polymers derived from **M11a** are also hold considerable potential in this regard (as well as for the possibility of self-assembly via hydrogen-bonding interactions with, e.g., nucleic acids).[194] Steric constraints may limit these approaches to oligomeric species, if complete substitution is essential. Reaction of a terminal succinimide block with a nucleophilic fluorophore and base has also been used to install a fluorescent tag onto norbornyl oligopeptide polymers that serve as inhibitors of *in vitro* fertilization in mouse models.[276] Where rigorous control over the number of tags is an issue, a pre-installed endgroup may be required. In other approaches, Sharpless 1,3-dipolar cycloadditions (so-called "click reactions") were used to functionalize poly(oxa–NBE)s bearing acetylenic and azido moieties.[277] Incorporation of molecular recognition elements into ROMP polymers is attracting increasing attention. Of particular interest are DNA–ROMP polymer conjugates; such composites have been prepared by tethering DNA strands to poly(NBE) chains bearing rigid, hydroxy-functionalized linker groups,[278] while NBE-based block co-polymers containing oligonucleotide and ferrocenyl side chains have been applied to the electrochemical detection of DNA.[279] ROMP polymers bearing a luminescent Ru–bipy functionality were recently developed as fluorescent tags for biological compounds.[280] Amphiphilic polymers were prepared that carry a terminal biotin unit: these undergo self-assembly into star micelles in water, with the Ru–bipy elements in the core of the micelle, and biotin as a molecular recognition element on the periphery. Addition of the protein streptavidin effected cross-linking into extended networks.



(6)

Graft polymers have been prepared via ROMP–ATRP methods by carrying out a random ROMP co-polymerization to incorporate a proportion of a monomer bearing a halide group suitable for initiating subsequent ATRP.[281] Addition of the acrylate monomer was carried out as above, once ROMP was complete. A wide range of materials has been prepared by this approach.[243] Organic–inorganic nanocomposites have also been prepared from poly(NBE) scaffolds bearing suitable donor groups, including cyclopentadienyl, amide, phosphine, ether, and carboxylate ligands. Considerable effort has focused on fabrication of composites containing metal nanoparticles or semiconductor quantum dots with chemically tailorable shell properties. Synthesis of diblock co-polymers by living ROMP, typically via **10a** or **22b**, is followed by addition of prefabricated nanoparticle or their organometallic precursors.[67] Uniform dispersion of nanoclusters is promoted by the affinity of the metal for the donor groups distributed throughout a given domain type. In the absence of such donors, or on use of homopolymer blends, macrophase separation occurs.[270,282] Microphase separation during evaporation produces films containing one metal-rich domain. A subsequent decomposition step (thermal or chemical) is required for the polymer-bound metal precursors; this triggers aggregation of nanoclusters within microphase-separated domains, albeit with limited (±20%) control over particle size. Monomers functionalized with organometallic precursors can be treated similarly.[67,283–285] Spherical, cylindrical, or lamellar morphologies were achieved by altering the ratio of the two blocks. A summary of the systems studied, comprehensive up to 2002, has appeared.[67] Applications of these materials are potentially broad. Gold nanoparticles exhibit particular versatility. Such materials been incorporated into conducting matrices potentially relevant to device applications, and into hybrid materials that offer promise as probes in chemical and biochemical detection strategies.[268,269] Much work has focused on the use of ROMP-nanocluster and other ROMP-based composites in device applications.[67] A recent advance is the development of an organic field-effect transistor, in which surface-initiated ROMP was used to assemble a polymer dielectric layer with highly uniform, controllable layer thicknesses with covalent attachment to the surface. Such control, which is difficult to achieve using conventional processing methods, is critical to the proper functioning of organic materials as dielectric components.[286]

Modification of pendant groups through self-assembly, several examples of which were noted above, further expands the range of potential applications of ROMP materials. Liquid crystalline ROMP polymers have been extensively investigated.[244,245] Interesting morphologies can be realized by this approach, including tubular architectures produced by self-assembly of tapered side-groups into helical arrays.[287] Several reports have demonstrated that amphiphilic block co-polymers (prepared via **22b**) can assemble into nanoparticles of controlled size.[285,288,289] Such micellar aggregates are being explored for applications in drug delivery. ROMP polymers prepared from NBEs bearing hydrophilic (PEG) and hydrophobic (indomethacin, doxorubicin) groups, for example, permit partial release of the drug in acidic environments at physiological temperatures.[289,290] Colloidal poly-NBE particles with surface-active groups, prepared by ROMP of a norbornenyl-functionalized PEG macromonomer, have likewise been shown to release active molecules in response to pH changes.[288a] The capacity of such polymers to interact with (and potentially disrupt) phospholipid membranes is clearly a key issue, in which polymer size, hydrophobicity, and ionic nature all appear to come into play.[291] Polymers prepared via ROMP methodologies have now been functionalized with a range of biologically relevant entities, including penicillin, nucleosides, carbohydrates, and peptides.[235,237,246] One of the most important aspects of pendant group functionalization, however, lies in the application of ROMP materials in organic synthesis.[246,292,293] ROMP polymers, particularly swelled ROMPgels,[246] provide versatile supports for immobilized scavengers, reagents, and catalysts.[13,246,292,293] ROMP polymers bearing acid chloride, phosphonate, carbodiimide, phosphonyl chloride, and phosphine groups have been used as platforms in phase-switching, sequestration, capture–release, and soluble support applications.

11.18.5 Applications

To date, structural and optical applications remain the core focus of industrial ROMP methodologies. Industrially important ROMP polymers are produced from cyclopentene, cyclooctene (Vestenemer), NBE (Norsorex), and DCPD (Metton, Telene, Pentam).[7,8] Hydrogenated ROMP polymers are of interest as high-performance, completely amorphous polymers for the optically clear plastics market.[8,294] A focus of particular interest for the production of large molded objects is ROMP of DCPD via RIM and resin-transfer molding. Several NBE-based monomers have been investigated as alternatives to DCPD, which despite the advantages of rapid reaction and desirable product properties (high toughness, low water absorption, low density), suffers from stench and the difficulty in controlling cross-linking. ROMP of 5-(3-cyclohexen-1-yl)-2-NBE gives a very lightly cross-linked polymer with a lower exotherm, and greater control in the molding process.[295] ROMP of mono- and difunctional imido–NBE monomers bearing different *N*-alkyl side chains likewise offered better control over the rates of ROMP and cross-linking

reactions.[296] Potential advantages of such monomers lie in the wide range of materials properties, and their ease of access from cheap feedstocks.

Given the price sensitivity of the commodity markets, classical, heterogeneous initiator systems based on Mo, W, or Ru salts and various co-catalysts continue to dominate the area. Well-defined initiators must offer new advantages to offset their higher cost. The functional-group tolerance and ease of handling of well-defined ruthenium catalysts constitutes such an advantage. While the reactivity of the first-generation ruthenium initiator **22b** was insufficient for industrial materials applications, the much higher activity of the NHC derivatives offers potential, providing that the induction period for cross-linking (as well as other issues associated with the exothermicity of the reaction) can be regulated.[8] Extremely fast initiation is problematic in RIM processes, as the material can set before mixing is complete. Uncontrolled cross-linking reduces processability and control over mechanical properties, and while cure times can be extended slightly by use of additives (for example, increasing the amount of antioxidant used with Ru–phosphine initiators), excessive initiation rates must be avoided. Very poor initiation efficiencies are also undesirable, particularly where followed by exceedingly rapid propagation. Rapid increases in viscosity can result in diffusion-controlled polymerization, leading to higher proportions of residual monomer and low molecular weight polymers in the product. RIM-based DCPD materials can be very sensitive to the latter: small proportions of low molecular weight species can drastically reduce T_g values, and adversely affect mechanical properties.[3] "Latent" initiators with a sharp turn-on threshold (see earlier) hold promise in this regard, especially if high initiator efficiency can ultimately be achieved. An as-yet unrealized goal in this area is an initiator that remains latent until switched on by, for example, thermal or photochemical treatment. Among other possibilities, this would permit packaging of monomer and initiator together. However, the high reactivity of the monomers of interest makes this challenging: while many transition metal salts or complexes are poor ROMP initiators, their activity is non-zero, and systems offering a perfectly binary combination of zero and high activity have not yet been found.

Future industrial prospects are suggested by the exceptionally diverse range of applications in which ROMP polymers have now been deployed.[8,67] The impact of ROMPgel reagents was alluded to above.[246,292,293] These and "flow-through" or otherwise supported metathesis catalysts[12,13] offer major opportunities for advances in organic synthesis. The applications of ROMP to synthesis of surface-functionalized monoliths and supports have significantly expanded opportunities in these areas.[170,297] Biomedical applications are emerging as an area with enormous potential, as indicated above: particularly notable are advances in ROMP-based neoglycopolymers as platforms for multivalent drugs[8,235,298] and diverse ROMP polymers as vehicles for drug delivery,[289,299] DNA detection,[279] and probes for specific protein interactions.[276,300] Interest in electronics and photonics applications, dating back to the discovery of the Durham "Feast" route to polyacetylene, has continued to expand.[301] Myles and Branda have reviewed developments in ROMP methodologies for the fabrication of photochromic homopolymers suitable for optical storage devices with non-destructive erasable memory.[302] ROMP-based routes to electro- or photoluminescent and non-linear optical materials were reviewed in 2000:[67] leading references to subsequent advances are provided.[303–307] Advances in development of ROMP-based liquid crystalline materials have also been considerable.[244,245] Both the range and the depth of interest indicated by this large number of specialized reports augurs well for the development of ROMP technologies over the coming years. Fundamental to the remarkable advances of the last two decades have been the advances in mechanistic understanding that have guided the iterative process of initiator design. These achievements, most recently recognized with the 2005 Nobel prize, awarded to Chauvin, Schrock, and Grubbs, have made the molecular-level design of ROMP-based, macromolecular materials a reality, the full potential of which is likely to be realized over the coming decade.

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11.19
Cross-coupling Polymerization

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11.19.1 Introduction

Cross-coupling polycondensation has been employed as a method for the synthesis of a wide range of polymeric materials.[1–3] In particular, it has been of great interest to synthesize π-conjugated polymers that may be applicable to electrically conductive materials, photoluminescence, and electroluminescence for light-emitting diodes (LEDs).[4–7] Properties, such as liquid crystallinity and non-linear optics, have also been of major concern.[8,9] Extensive progress of transition metal-catalyzed coupling reactions made synthesis of such advanced materials an extremely useful methodology.

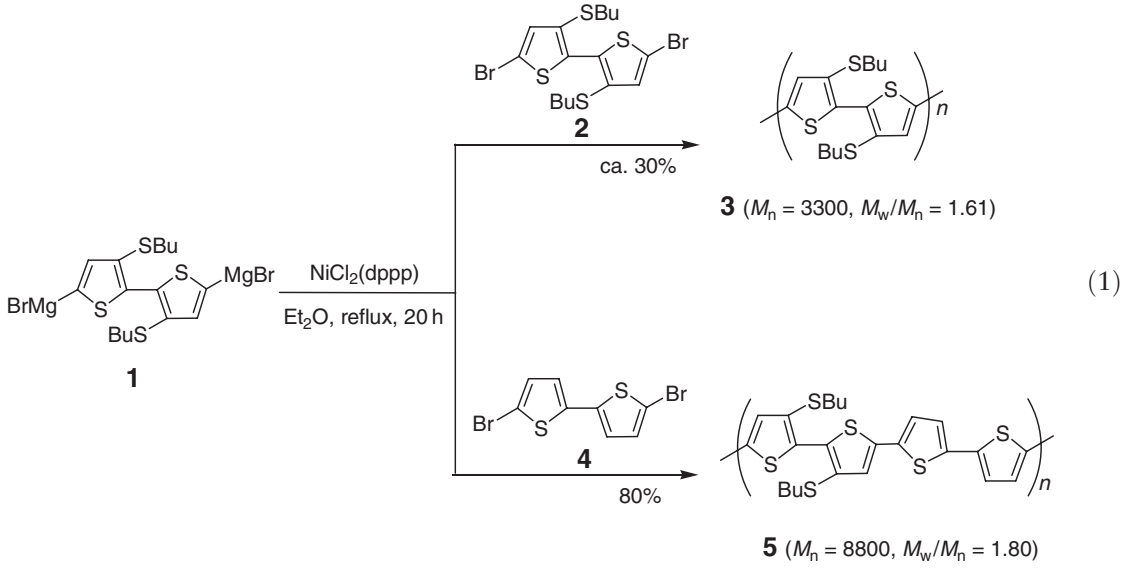
This chapter summarized cross-coupling polymerization reactions focusing on the bond formation of metallic reagents bearing sp^2- (Section 11.19.2), *sp*- (Section 11.19.3), and sp^3- (Section 11.19.4) carbons with a variety of organic electrophiles through multiple condensation reactions. Reactions at carbon–hydrogen bonds (Sections 11.19.3 and 11.19.4) instead of metallic reagents are also described. In addition, cross-coupling polymerization to form carbon–heteroatom bond is reviewed in Section 11.19.4.

11.19.2 Cross-coupling Polymerization with Organometallic Reagents of sp^2-Hybridized Carbons

11.19.2.1 The Reaction with Grignard and Organozinc Reagents (Kumada–Tamao and Negishi Coupling)

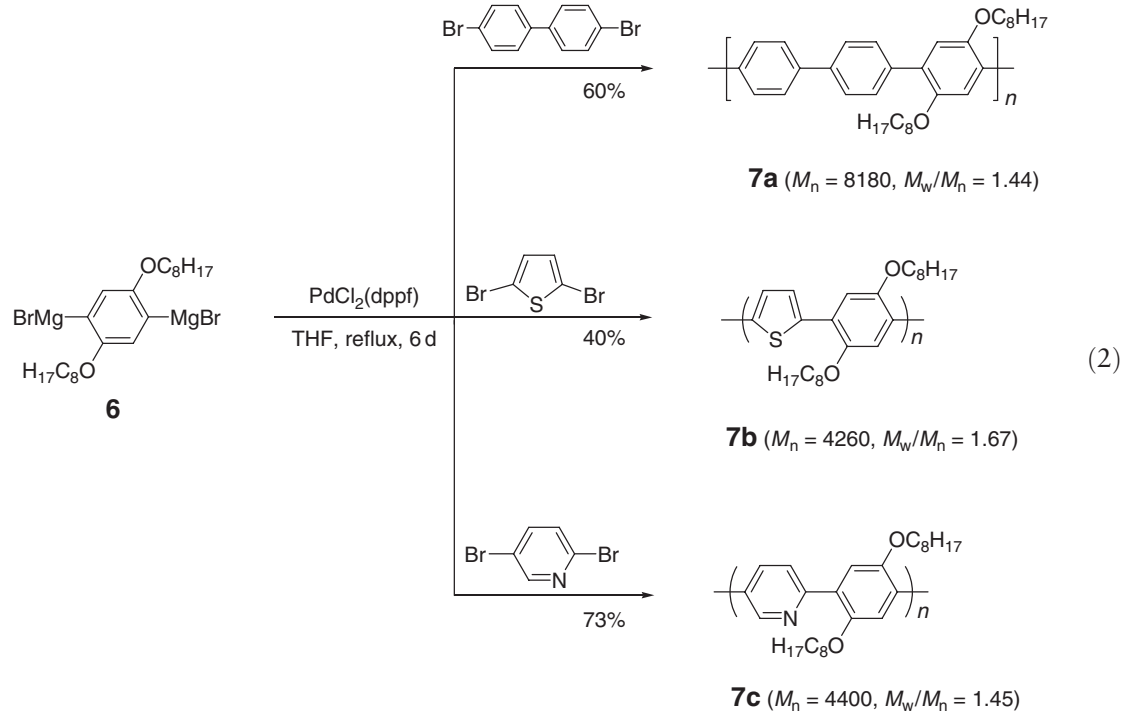
Grignard reagents are widely used to form a carbon–carbon bond with a wide range of organic molecules. The transition metal-catalyzed cross-coupling reaction between Grignard reagents and organic halides has been employed in organic synthesis. Thereby, the reaction of a bifunctional Grignard reagent with a dihalogenated counterpart leads to polymers via polycondensation. Ng[10] reported nickel-catalyzed polycondensation of a Grignard reagent **1** with dibromobithiophene **2** bearing the same substituents as **1** to isolate the corresponding polythiophene **3**. On the other hand, the cross-coupling with dibromobithiophene **4**, which lacks the same substituents, gives alternate polymer **5** as shown in Equation (1). Butylsulfanyl groups at 3- and 3′-positions in bithiophenes **1** and **3** allows the resulting polymers to be soluble in organic

solvents. Homopolymer **3** was obtained in ca. 30% yield to show the molecular weight of 3300 (M_n) and molecular weight distribution of 1.61 (M_w/M_n). On the other hand, yield of co-polymerization product **5** is found to be superior (80%) with higher M_n (8800; $M_w/M_n = 1.80$) when unsubstituted dibromobithiophene **4** is employed as a coupling partner.



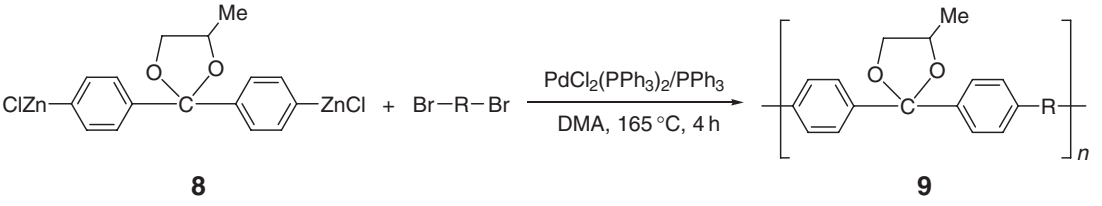
(1)

A palladium complex is also shown to undergo the cross-coupling polymerization by Naso[11,12] with 1,4-dimagnesiobenzene reagent **6** to afford polyarylenes **7a–c** (Equation (2)). Model reaction of **6** with bromobenzene shows that use of 1.5 mol% of $PdCl_2$(dppf) in refluxing THF affords a bis-coupled product in an excellent yield. The reaction with $Pd_2(dba)_3/AsPh_3$ (1.5 mol% of Pd, L/Pd = 4) is also found to proceed efficiently. Polymerization of several bifunctional electrophiles affords the corresponding copolymers in 40–73% yields with M_n of ca. 4000–8000 ($M_w/M_n = 1.44$–1.67). Molecular weights and molecular weight distributions are estimated by MALDI-TOF mass spectra in addition to usual size-exclusion chromatography (SEC) analysis.

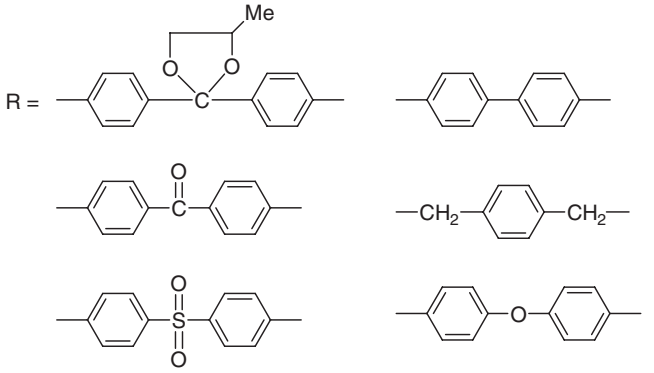


(2)

Bifunctional organozinc reagents are also employed in a similar polycondensation reaction. As demonstrated by Bochmann,[13] polymerization reaction of bisorganozinc reagent **8** with several dibromoarenes affords the corresponding polymer **9** (Equation (3)). The bifunctional zinc reagent **8** is readily prepared by metal exchange of the corresponding dilithium reagent, which was prepared by treatment of the corresponding dibromide with 2 molar equiv. of butyllithium, followed by transmetallation with $ZnCl_2$ in diethyl ether. The polymerization was carried out at 165 °C for 4 h in DMA in the presence of the palladium catalyst, catalyst/monomer ratio being 1/100–1/5,000, to afford the polymer bearing M_n of 1000–6000. Various aromatic halides bearing acetals, ketones, sulfones, and ethers are shown to be available as a coupling partner.

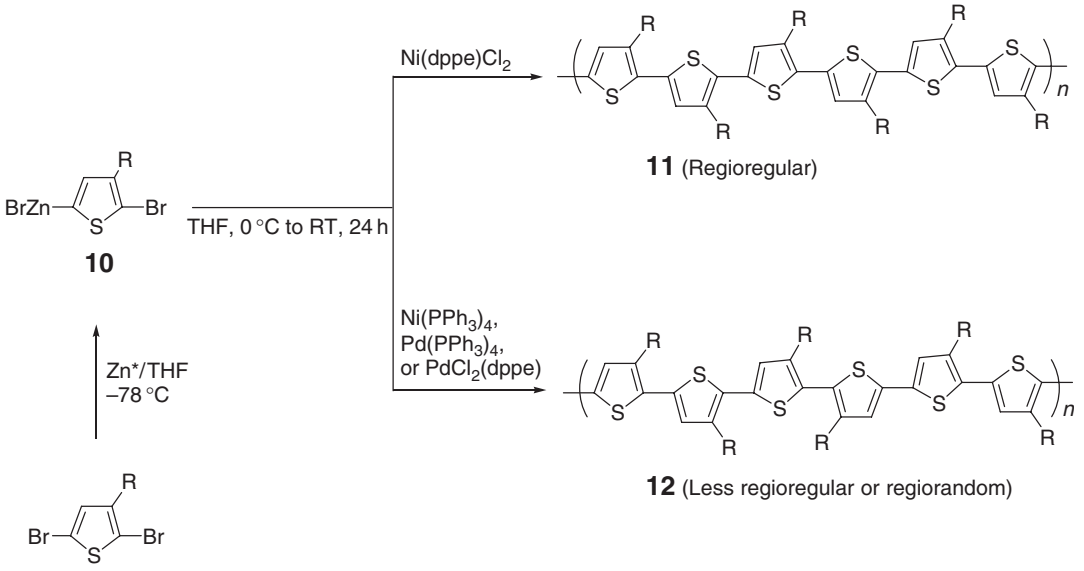


8 **9**



(3)

The cross-coupling polymerization with an organozinc reagent was successfully applied by Rieke[14] and McCullough[7] for synthesis of oligothiophenes with well-defined head and tail structures. A key for the regiocontrolled polymerization is *in situ* formation of zinc reagent with Rieke zinc (Zn^*)[15] by treatment of dibromothiophene bearing both carbon–zinc and carbon–bromine bonds **10**. Polymerization reaction with $Ni(dppe)Cl_2$ affords poly(alkylthiophene) (**11**, HT–HT–HT–HT) high regioregularity, whereas use of palladium catalyst $Pd(PPh_3)_4$ results in formation of **12** (HT–HT–HH–TT) with lower selectivity[14] (Equation (4)).

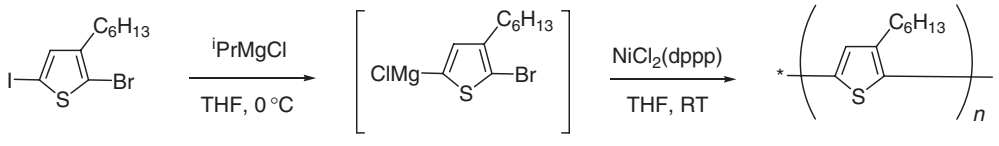


(4)

The regioselective formation of organozinc species **10** is successfully achieved when the reaction with Zn^* is carried out at −78 °C to room temperature over 4 h. Treatment of *in situ* formed **10** with an $Ni(dppe)Cl_2$ catalyst

induces regioregular polymerization to afford **11**. The degree of regioregularity in polymerization depends on both catalyst metal (Ni vs. Pd) and ligand (dppe vs. PPh_3). Switching the ligand from dppe to PPh_3 (with $Ni(PPh_3)_4$ as a catalyst) led to decrease in the regioregularity, namely, HT/HH = 65 : 35. Polymerization in the presence of $PdCl_2$(dppe) also resulted in low regioregularity (HT/HH = 70 : 30). A totally regiorandom polymer is produced by use of $Pd(PPh_3)_4$ catalyst. These results suggest that a smaller ionic radius along with higher steric demand of the ligand is the key for the control of regioregularity.

Although polythiophenes synthesized by the method of Equation (4) show a regioregular structure, molecular weight distribution is not controlled successfully. Yokozawa[16] reported synthesis of highly regioregular polythiophene **11** with lower molecular weight distribution using thienyl magnesium reagent **13**, which was prepared from 3-alkyl-2-bromo-5-iodothiophene **14** with isopropylmagnesium chloride. Molecular weight of the polymer was found to increase in proportion to the conversion of the monomer **13**, and the M_w/M_n ratios were 1.30–1.39 throughout the polymerization (Equation (5)). It was also shown that the molecular weight of the polymer increased as a function of the feed ratio of **13**/Ni catalyst indicating a step-growth polymerization mechanism.



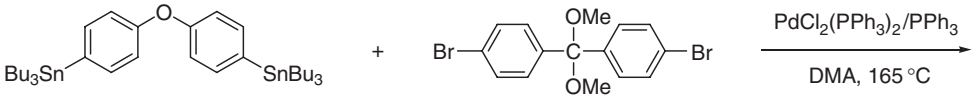
14 **13** **11** (R = $^nC_6H_{13}$)

M_n = ca. 20 000
M_w/M_n = ca. 1.3

(5)

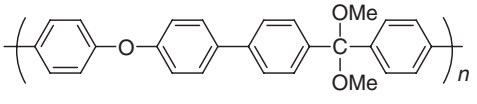
11.19.2.2 Reaction with Organotin Reagents (Migita–Kosugi–Stille Coupling)

Organotin reagents are also employed as a monomer of cross-coupling polymerization in addition to the magnesium and zinc reagents. The polymerization with tin reagents has advantage in simplicity, because these reagents are stable and isolate generally under aerobic atmosphere at an ambient temperature. Although the monomer composed of magnesium or zinc reagents must be prepared *in situ*, organotin reagents can be generally prepared separately, and subjected to the polymerization by accurately measuring the amount of pure components. Cross-coupling polymerization similar to Equation (3) with the tributylstannyl derivative **15** and diaryl bromide **16** takes place under the conditions similar to the case of zinc reagents. Polymerization was successfully carried out at 165 °C in DMA in the presence of a palladium catalyst to afford polymer **17** of M_n = 18 800 (Equation (6)).[13]



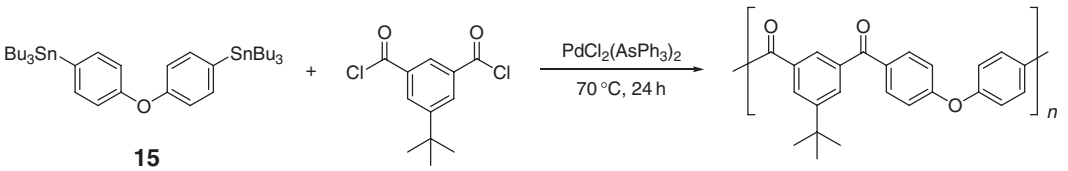
15 **16**

(6)



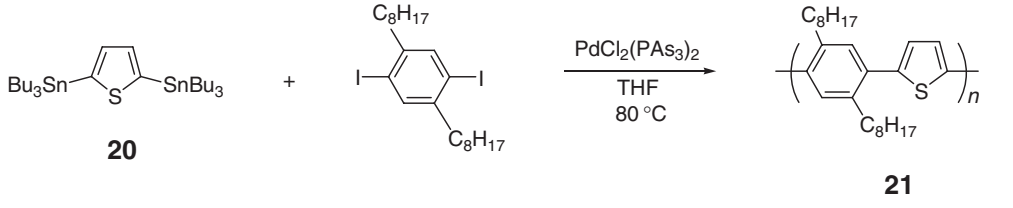
17

Moore also showed the cross-coupling polymerization of bifunctional organotin reagent **15** with a bifunctional acid chloride **18**. The reaction leads to polyketone **19** bearing a *t*-butyl group that allows it to improve solubility of the resulting polymer. The reaction proceeds at 65 °C in the presence of 1 mol% of palladium catalyst containing $AsPh_3$ as a ligand and gives **19** in 90% yields with degree of polymerization (DP) of 148. The polymerization was shown to proceed with several tin reagents and acid chlorides affording polyketones in up to 90% yield with DPs ranging from 50 to 150.[17]

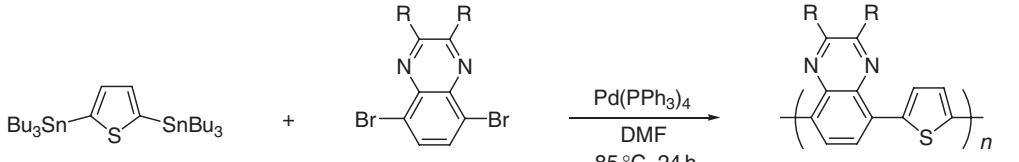


15 18 19 (7)

A variety of bisstannyl aromatic and heteroaromatic compounds were similarly subjected to the polymerization in the presence of a palladium catalyst with bifunctional aromatic halides, as shown in Equations (8)–(16). Bis(tributylstannyl)thiophene **20** couples with several dihaloarenes to give to poly(arylene–thienylene)s.[18,19] Reaction conditions are well studied to effect polymerization efficiently and to give polymers of high molecular weight in high yield. It is found that any solvents that keep the macromolecules and any palladium(0) species in solution are applicable. In general, a combination of an electron-rich distannyl monomer and an electron-deficient dihalide or ditriflate monomer is suitable to obtain polymers with relatively high molecular weights. Accordingly, polar aprotic solvents such as dioxane, THF, and DMF are mostly employed for the polymerization reaction. The effective ligand for the palladium-catalyzed polymerization is $AsPh_3$. The reaction goes to completion quickly to give high molecular weight polymer. The polymerization with tri-2-furyl phosphine is slightly slower than the one with $AsPh_3$. However, decomposition of the palladium catalyst to result in the formation of palladium black is not observed. On the other hand, the polymerization using triphenylphosphine is much slower. When $(o\text{-tol})_3P$ or $P(OPh)_3$ is used, the catalyst appears to be unstable and decomposes before polymers of high molecular weights are formed. The most favorable ratio of the palladium metal to ligand (Pd/L) falls in between 2 and 4.[18]



20 21 (8)



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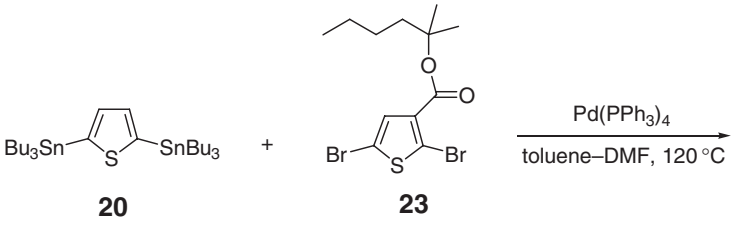

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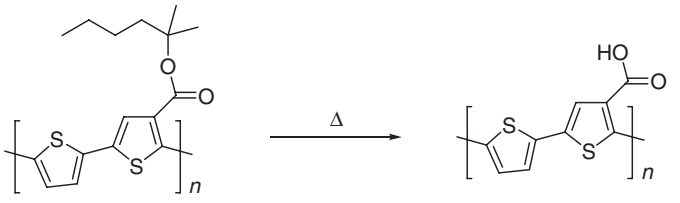
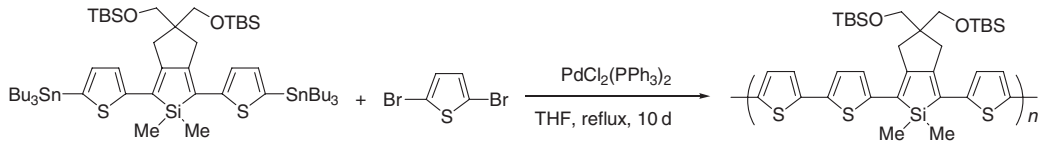
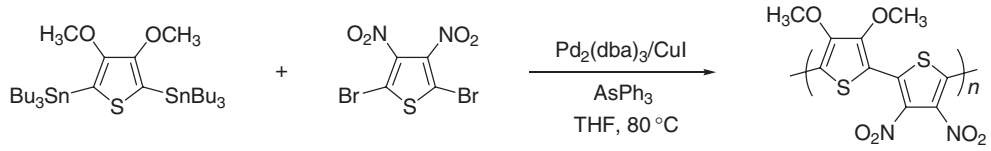


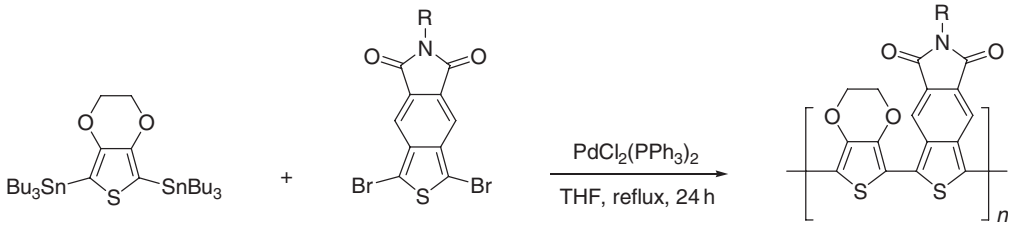
24: Soluble **25**: Insoluble



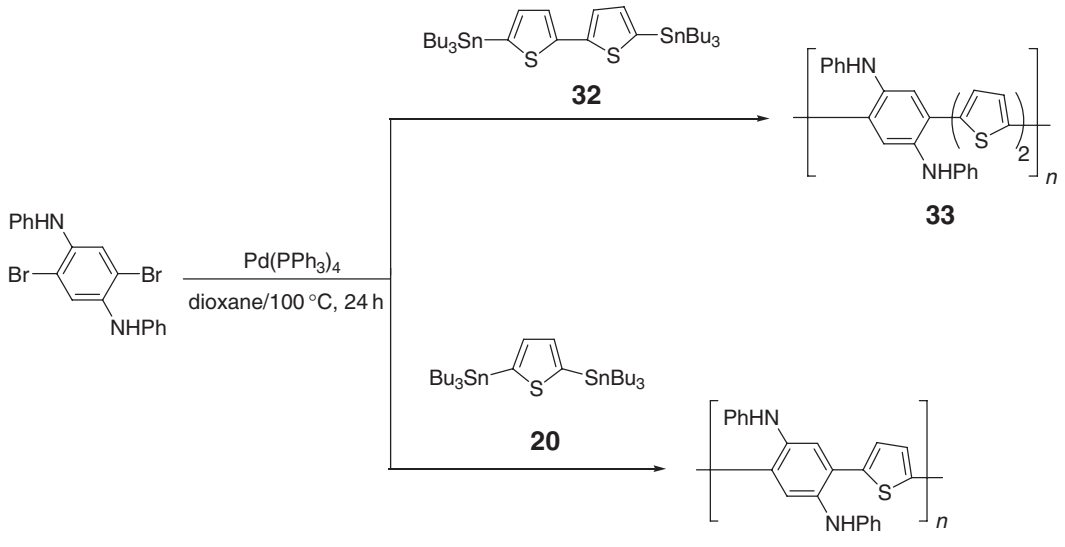
26 **27** (11)



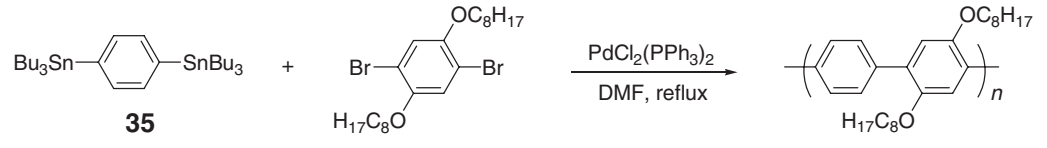
28 **29** (12)



30 **31** (13)



(14)



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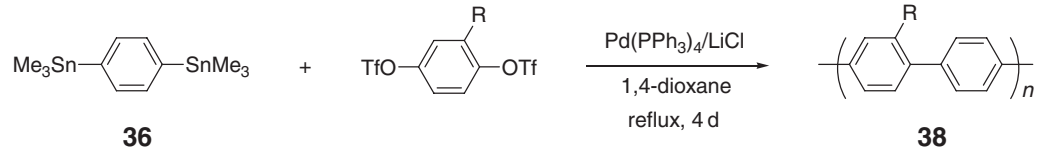
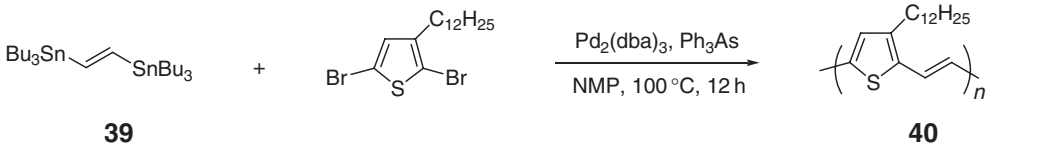


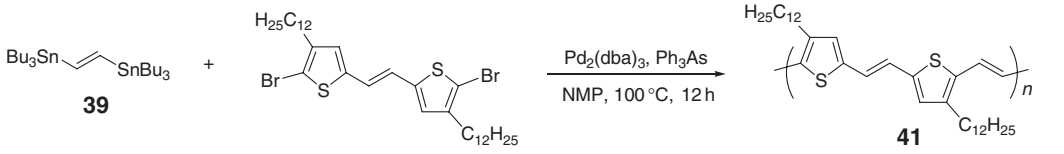
(16)

Following examples are worth mentioning, particularly in view of application to advanced materials. Frechet showed polycondensation of **20** with alkoxycarbonyl-substituted dibromothiophene **23** to form solution-processible polythiophene **24**, which showed M_n of 16 600 and M_w/M_n of 2.2. The obtained polymer **24** was converted into the insoluble carboxylic acid **25** upon thermal deprotection of the ester group. The method is applied to the preparation of a thin film of **24** on a TiO_2 layer. The device is used as a polythiphene–titania hybrid solar cell, where interaction between the carboxylic acid moiety of **25** and TiO_2 is a key for success.[20] Bifunctional organostannanes **26**, **28**, **30**, and **32**, all bearing a thiophene core, are also subjected to the cross-coupling polymerization in a similar manner.[21–24] Spectroscopic characteristics and electrochemical behaviors of polymers **27**, **29**, and **31** are studied. The reaction of bis(trialkylstannyl)benzene **35** and **36** with dihaloarenes also proceeds successfully to afford the corresponding poly(arylene)s **37** and **38**, respectively.[25,26]

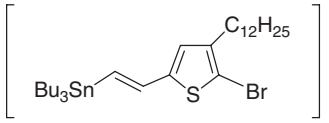
(*E*)-1,2-bis(tributylstannyl)ethene **39** also undergoes the cross-coupling smoothly with several arylene dihalides to afford poly(arylene–vinylene)s (PAVs). The reaction with 2,5-dibromothiophene and 1,2-bis(5-bromothienyl)ethene gives poly(thienylene–ethylene)s **40** and **41** (Equations (17) and (18)). The resulting polymer **40** shows regioregularity greater than 90%. The selectivity is ascribed to higher reactivity of the C(5)–Br bond in the dibromothiophene toward palladium to form intermediate **A**, which underwent further cross-coupling polymerization leading to regioregular polymer **40**. On the other hand, the reaction of the thienylene–vinylene–thienylene dibromide affords completely regioregular polymer **41**.



39 **40** (17)



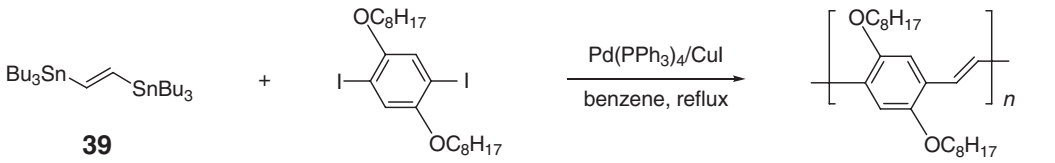
39 **41** (18)



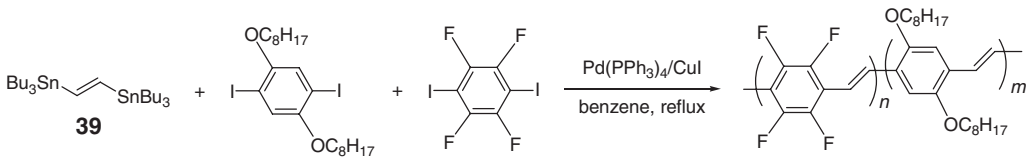
A

The cross-coupling polymerization with dihaloarenes leads to poly(phenylene–vinylene)s (PPVs), which are widely employed as conductive and electroluminescent polymers.[27]

Since unsubstituted PPV of a moderate molecular weight is hardly soluble in organic solvent, substituents of longer alkyl or alkoxy chains are generally introduced into 1,4-dihalobenzenes to improve the solubility. In view of the LED properties, it is effective to introduce an electron-withdrawing group such as a fluoro or cyano group in addition to an electron-donating alkoxy group (OR). Naso[28] prepared a co-polymer of poly[(tetrafluorophenylene)vinylene][(dialkoxyphenylene)vinylene] **43** and compared the performance with poly[(dialkoxyphenylene)vinylene–phenylene(vinylene)] **42**. The reaction of 1,4-diiodotetrafluorobenzene and 1,4-diiodo-2,5-bis(octyloxy)benzene with **39** in the presence of $Pd(PPh_3)_4$ and CuI afforded **43**, which contained 63% of tetrafluorophenylene moiety.[29,30] The high non-linear optical susceptibility coefficient of the co-polymer than that of homopolymer PDOPV **42** demonstrates the advantage of the presence of the electron-deficient phenylene moiety (Equations (19) and (20)).

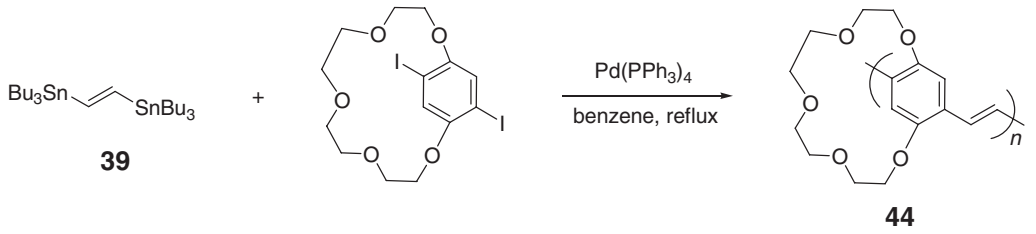


39 **42** (PDOPV) (19)

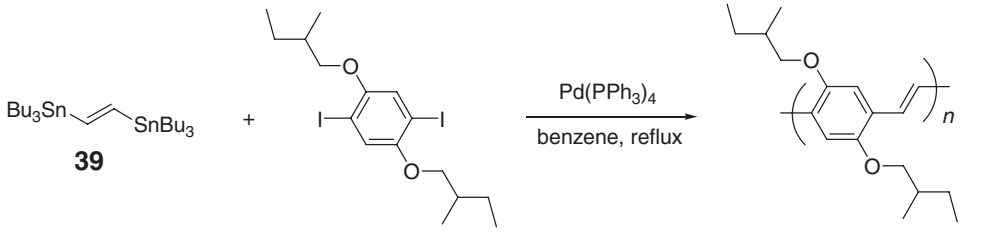


43 co(TFPV-DOPV) (20)

Synthesis of several bridged macrocylic poly(*p*-phenylene–vinylene)s **44** is also reported by Naso.[31] The presence of such a ring structure improves the emission properties of the synthesized polymer more than that of non-bridged and branched polymer **45** (Equations (21) and (22)).



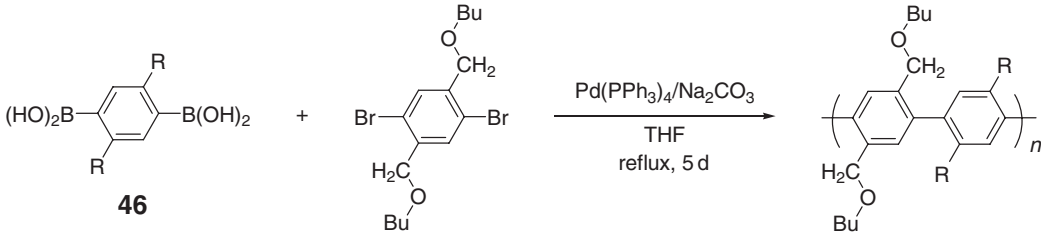
44 (21)



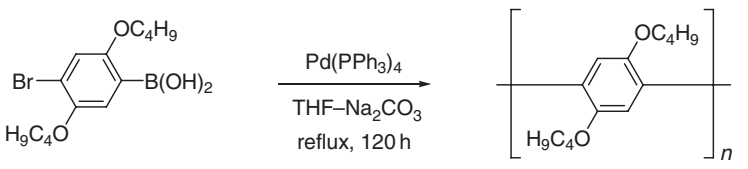
45 (22)

11.19.2.3 Reaction with Organoboron Reagents (Suzuki–Miyaura Coupling)

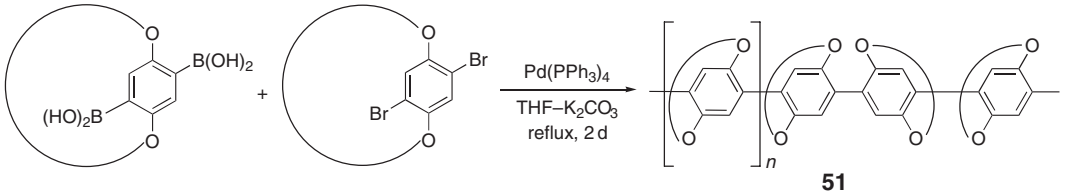
Bifunctional organoboron reagents[32] are the most frequently employed monomers for the cross-coupling polymerization compared with other organometallic reagents, as shown in the previous sections. A palladium complex is generally employed as the catalyst for the polymerization reaction to afford poly(aryrene)s and PAVs showing light-emitting characteristics and several other physical properties based on the extended π-conjugation.[33] Examples of the polymerization reaction are shown in Equations (23)–(35).[24,25,34–45] The employed palladium catalysts are $Pd(PPh_3)_4$, $Pd(dba)_2/L_n$, and $PdCl_2L_2$ ($L = 2PR_3$ or bidentate phosphines) in most cases. Bifunctional boronic acids or boronate esters are usually employed as the boron coupling partner. As an activator, Na_2CO_3, K_2CO_3, or $NaHCO_3$ is used in an aqueous solution. Consequently, the polymerization reaction is carried out generally in mixed organic solvents such as THF, dioxane, or DME with water. The reaction requires high temperatures and longer reaction periods. Thus, refluxing conditions for a period of days are necessary to obtain polymers of reasonable molecular weights.



47 (23)

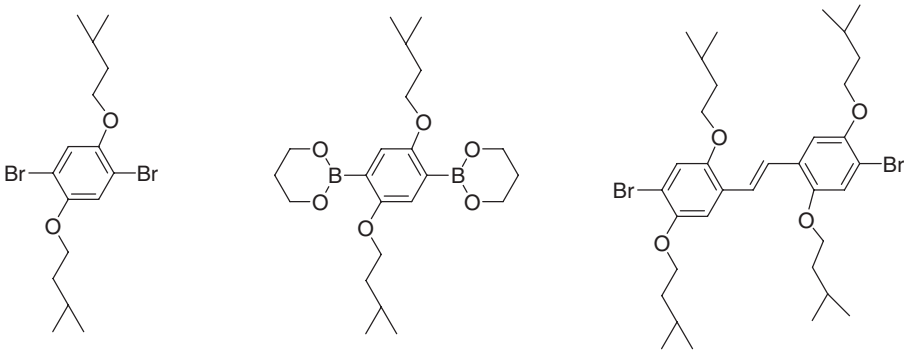


48 **49** (24)



50 **51** (25)

(= $(CH_2)_{10}$



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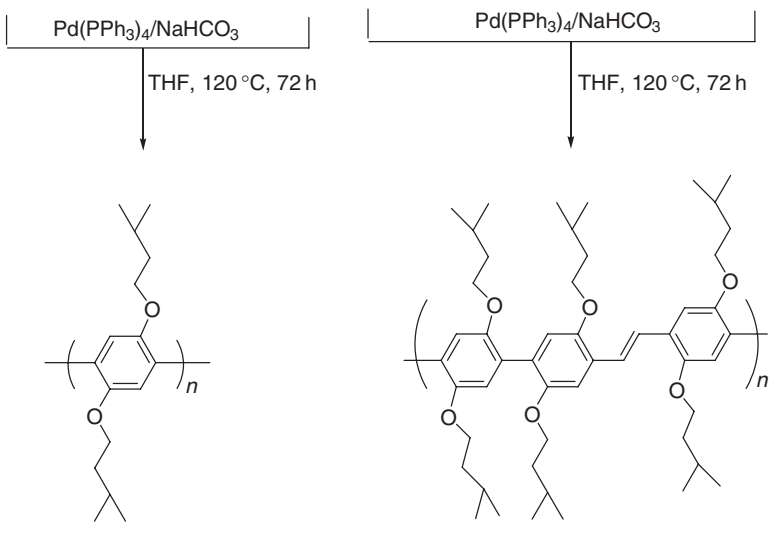
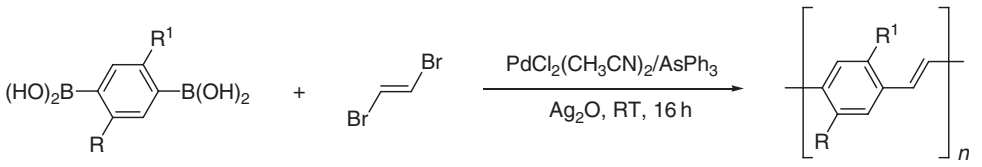


PPP **53** P3V **54** (26)

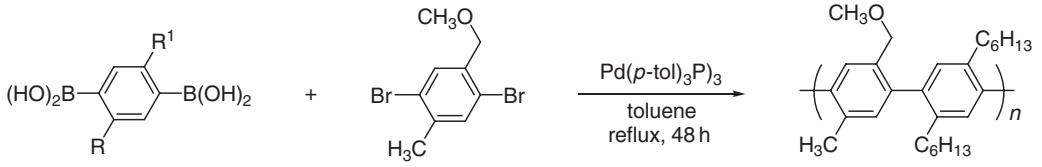


46

R, R^1 = 2-ethylhexyloxy
R, R^1 = methoxy
R = Ph, R^1 = H

55

(27)

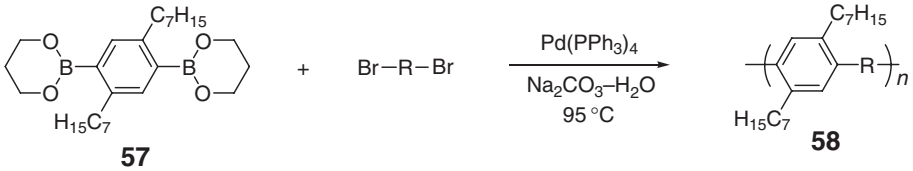


46

($R = R^1 = {}^nC_6H_{13}$)

56

(28)



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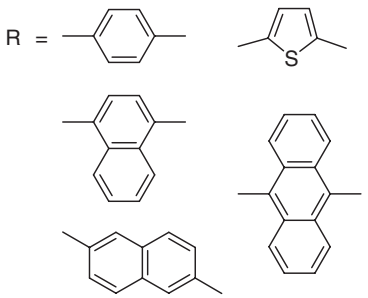
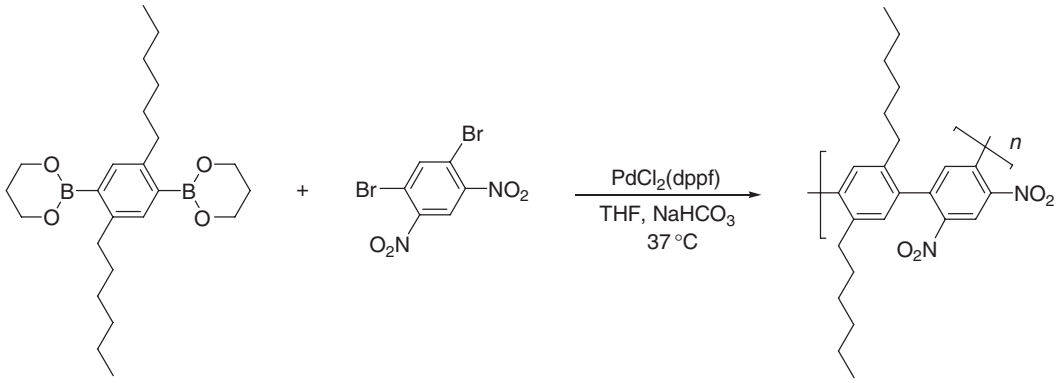
58



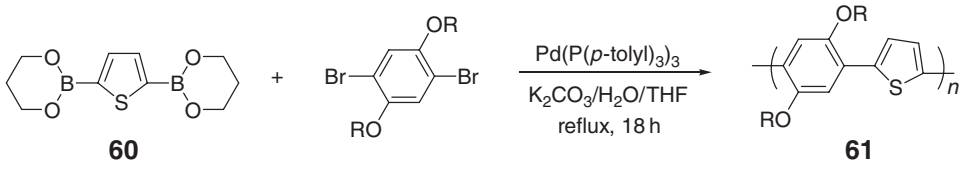
(29)



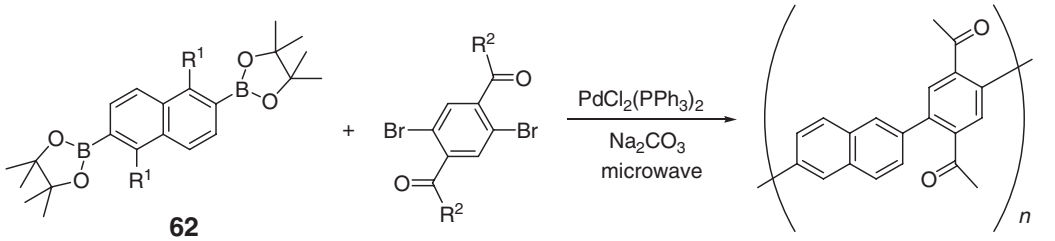
58

59

(30)



60 61 (31)



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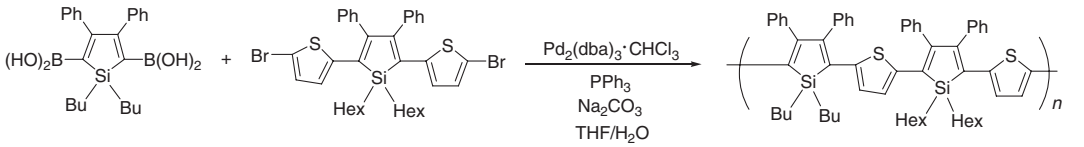
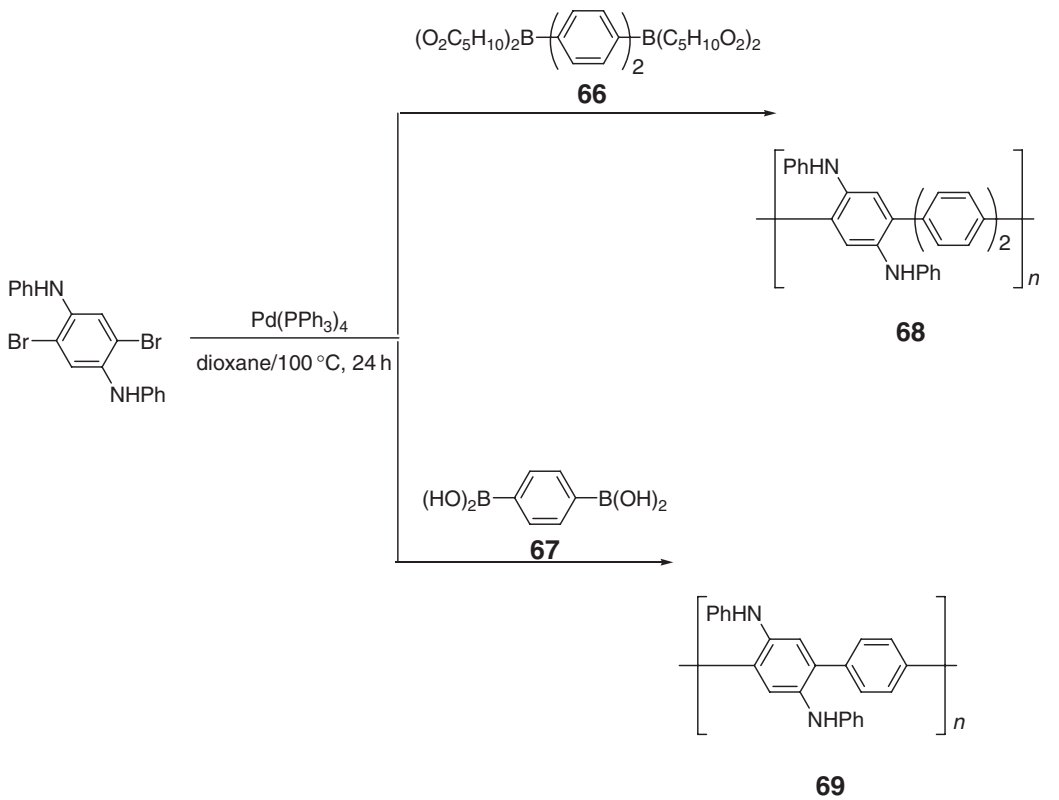
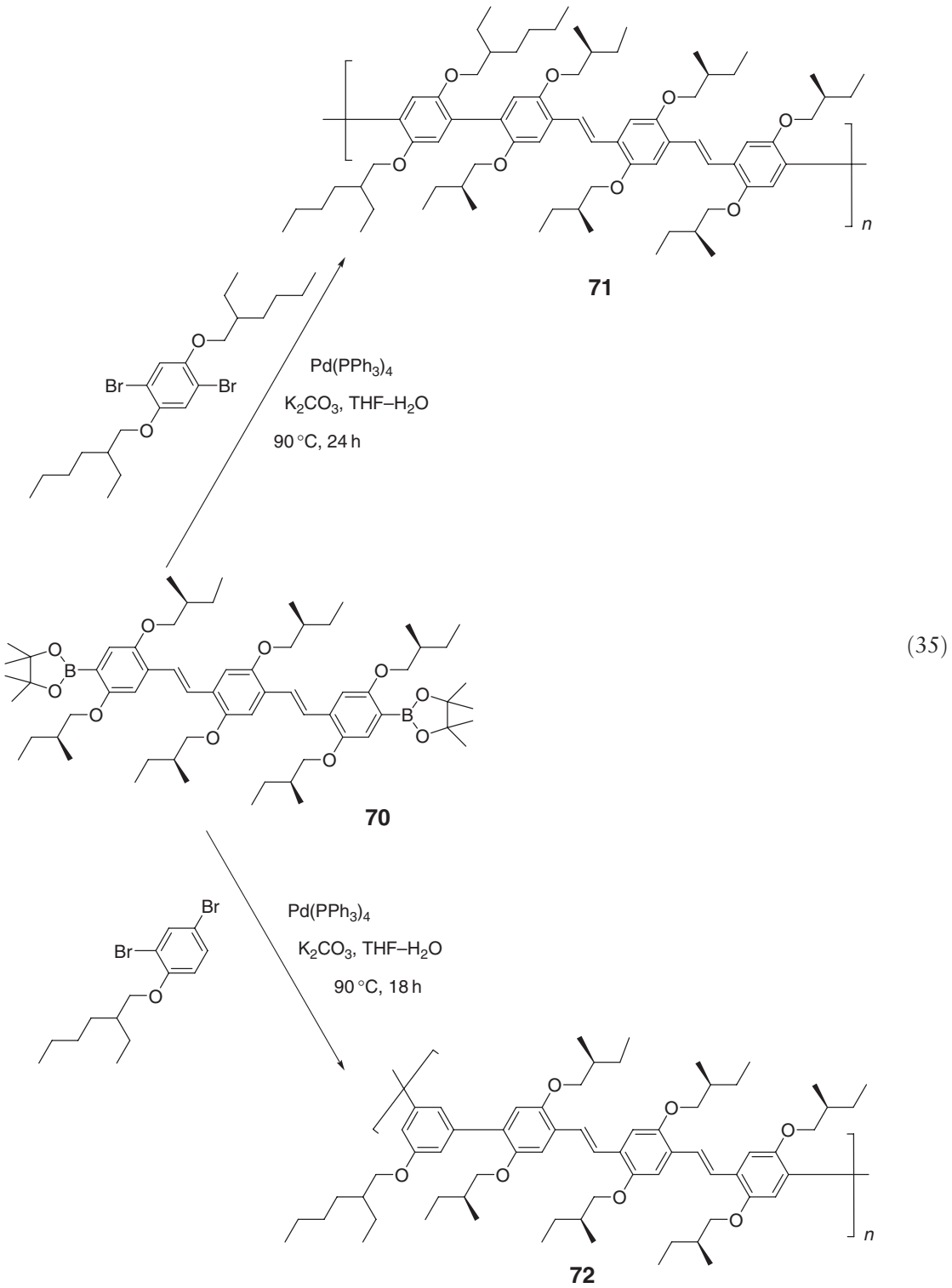


64 65 (33)



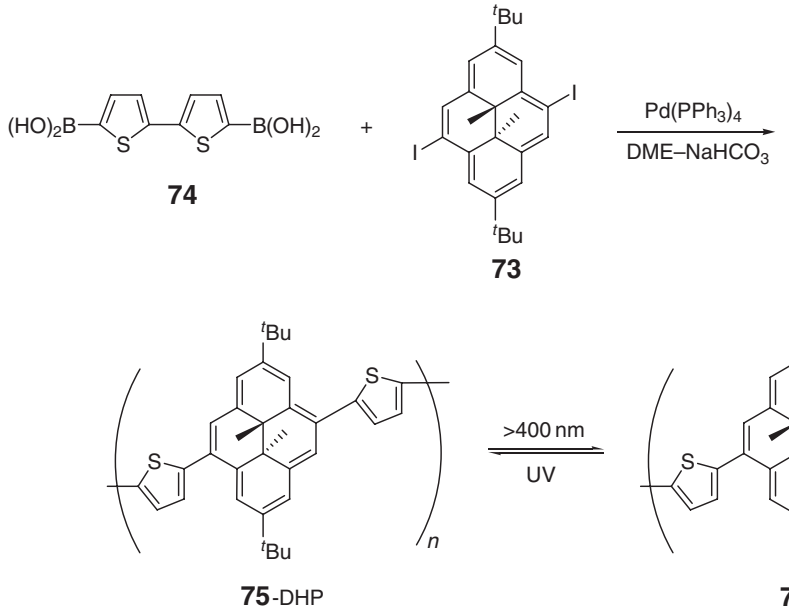
66 67 68 69 (34)



(35)

Photochromic moieties are readily introduced to the polymer main chain and side chains by the cross-coupling polymerization. Marcella employed diiododimethyldihydropyrene (**73**: DHP) as a coupling polymerization monomer, which was reacted with bithiophene bis-boronic acid **74** to form fully conjugated polymer **75**-DHP, which induced switching to cross-conjugated **75**-CPD (cyclophanediene) by the irradiation of visible light (>400 nm), while **75**-CPD was converted back to

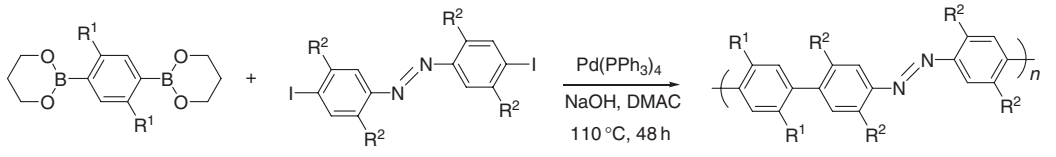
75-DHP by UV irradiation[46] (Equation (36)). Although the average degree of polymerization of **75** is not high ($n \sim 5$), monomer **73** has a large π-conjugated system, and thus the average polymer chain possesses ca. 80 contiguous sp^2-carbons along its backbone. Photochromic interconversion is confirmed by spectroscopic measurement of **75**-CPD and **75**-DHP.



(36)

75-DHP **75**-CPD

On the other hand, Masuda has synthesized polymers **76** containing an azobenzene moiety, which causes *cis–trans*-isomerization[47] (Equation (37)). The polymerization was carried out with $Pd(PPh_3)_4$ or $PdCl_2$(dppf) as a catalyst and NaOH as an activating agent of the bifunctional boron reagent in a mixed-solvent system of DMAC and water under heating to reflux to afford the corresponding polymer in excellent yields. Average molecular weight of the polymer reached 1500–9700. Although the isolated polymer **76** ($R^1 = R^2 = H$) was completely insoluble in most solvents, **76** (R^1 and/or $R^2 = {}^nC_6H_{13}$) was shown to be soluble in common organic solvents such as chloroform, toluene, and THF. UV–VIS spectrum of **76** reveals that λ_{max} of **76** red-shifts as compared with the corresponding monomer due to the generation of long π-conjugation in the main chain. The results suggest that the azobenzene unit behaves as a conjugative building unit in the main chain of **76**. *Cis–trans*-isomerization of polymer **76** is indeed examined and it has been shown that the *cis–trans*-interconversion actually takes place.



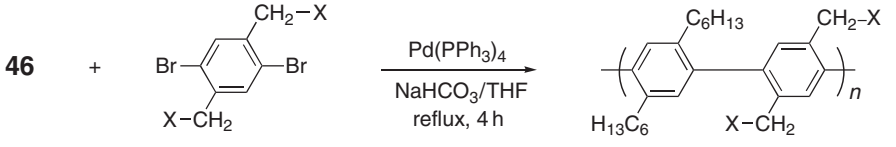
(37)

R^1 = H, ${}^nC_6H_{13}$

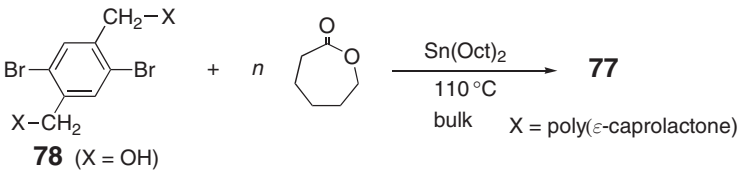
R^2 = H, ${}^nC_6H_{13}$

76

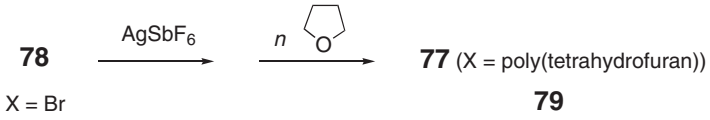
Yagci prepared poly(*p*-phenylene) graft co-polymers using **77** {X = poly(ε-caprolactone)} as a dibromoarene moiety, which was separately prepared by anionic ring-opening polymerization of ε-caprolactone with *p*-xylylenediol **78** as an initiator in the presence of tin(II) reagent[48] (Equations (38a) and (38b)). A monomer **79** for graft co-polymers bearing a poly(tetrahydrofuran) was also synthesized via cationic ring-opening polymerization by treatment of **78** (X = Br) with $AgSbF_6$ followed by the addition of THF[49] (Equation (38c)). The dibromide **79** also was co-polymerized with **46** to give the corresponding graft polymers.



(38a)

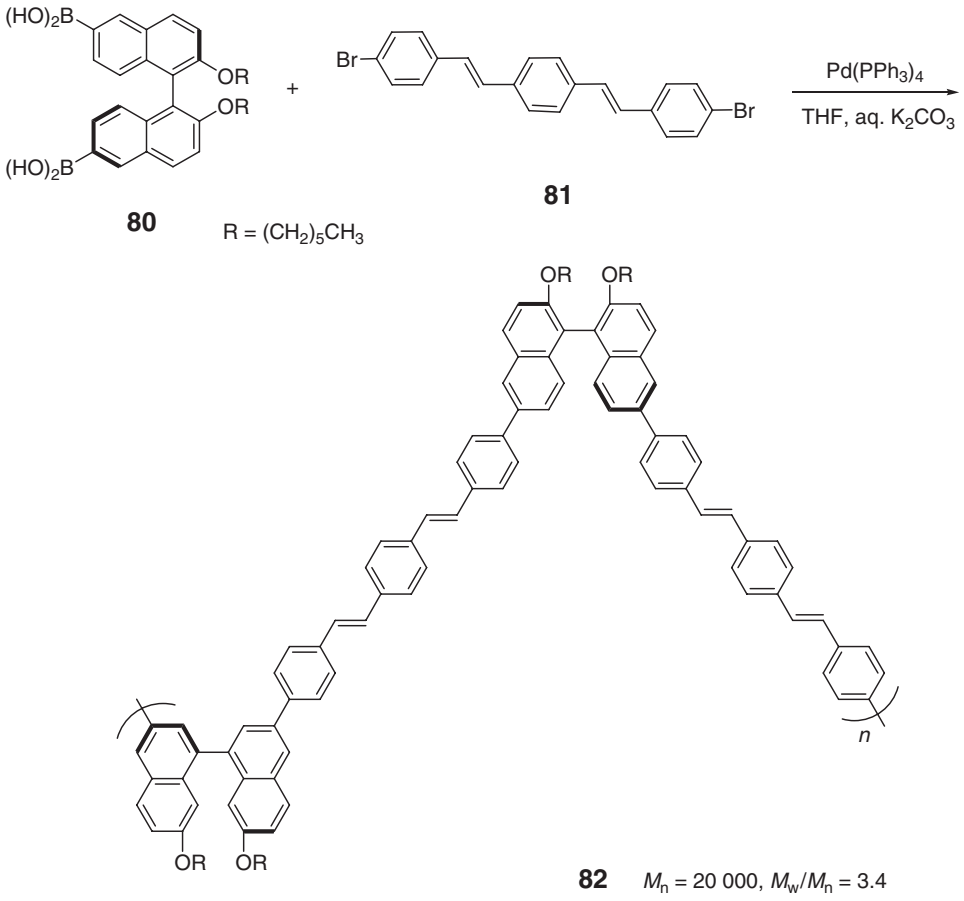


(38b)



(38c)

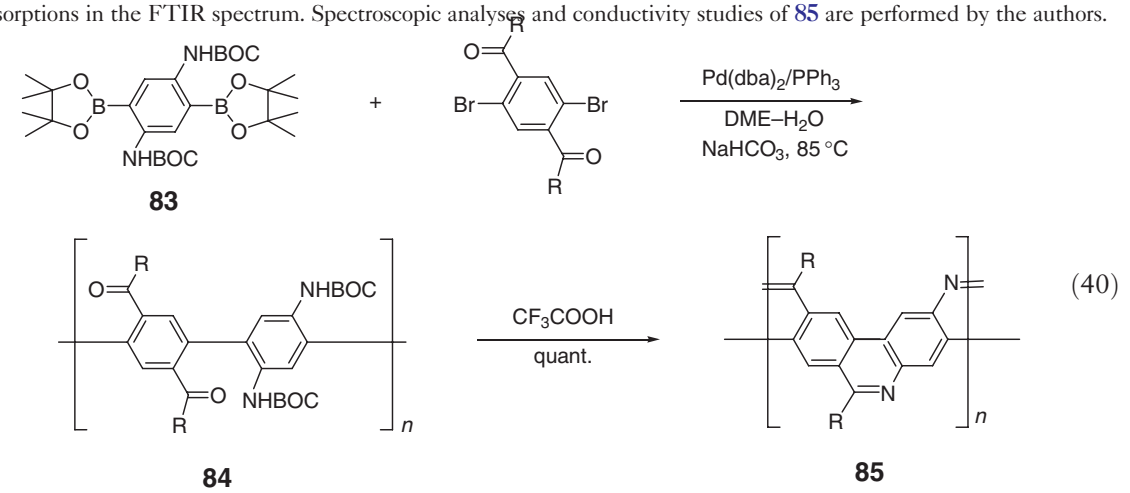
Pu[50] reported the synthesis of axially chiral-conjugated polymer **82** bearing a chiral binaphthyl moiety in the main chain by the cross-coupling polymerization of chiral bifunctional boronic acid **80** with dibromide **81** (Equation (39)). The polymer is soluble in common organic solvents, such as THF, benzene, toluene, pyridine, chlorobenzene, dichloromethane, chloroform, and 1,2-dichloroethane. The polymer composed of racemic **80** was also synthesized, and the difference of characteristics was examined. Optically active polymer **82** was shown to enhance fluorescence quantum yield up to $\Phi = 0.8$ compared with the racemic **82** ($\Phi = 0.5$). Morphologies of the optically active and racemic polymers were also compared with a systematic atomic-force microscopy (AFM).



(39)

Further intramolecular reaction of the poly(phenylene)-type polymer leads to more condensed polymers. Tour synthesized polymer **84** bearing a carbonyl moiety and a protected amino group in the phenylene rings by the reaction of boronate **83** and a dibromobenzene monomer. The polymerization takes place in the presence of a palladium catalyst in DME–H_2O at 85 °C to give **84** that showed $M_n = 9850$–$28\,400$ ($M_w/M_n = 1.85$–3.70) in 63–97% yields. The resulting polymer **84** is treated with CF_3COOH to afford azaphenanthrene–diyl-type polymer **85** through formation of Schiff base in quantitative yields as shown in Equation (40).[51] The polymer **85** is also prepared from cast film of **84** by treatment of anhydrous HCl/

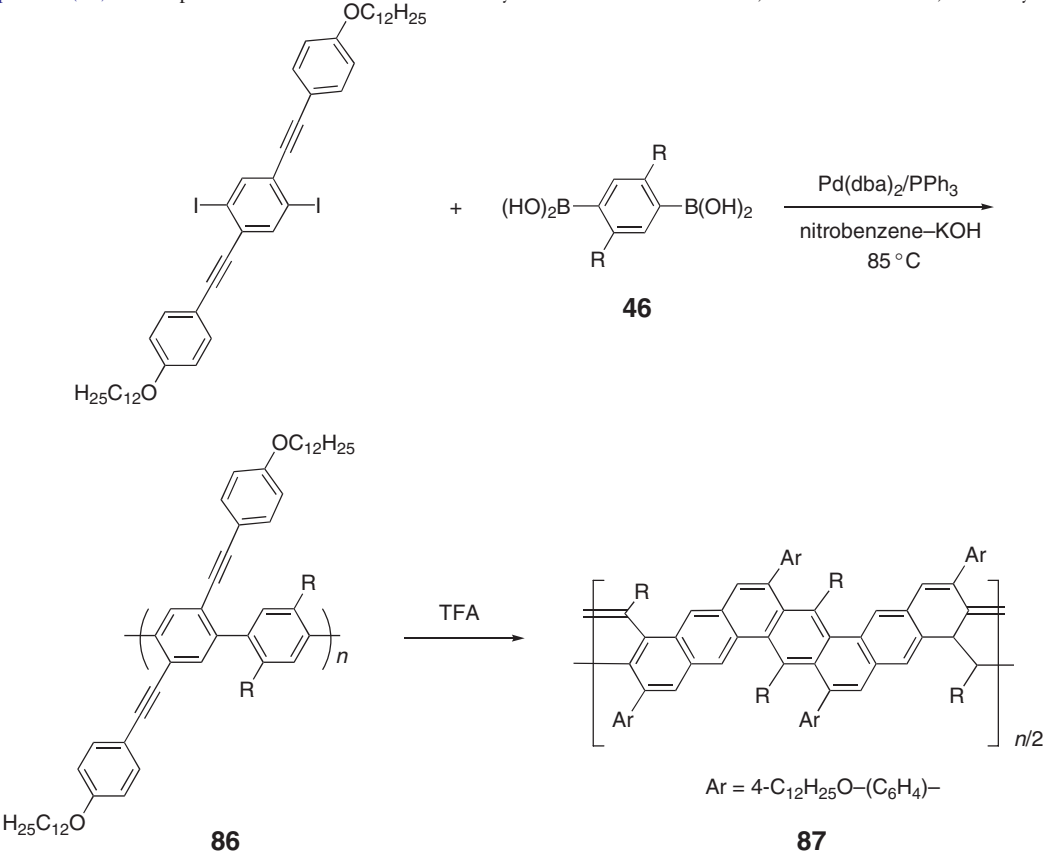
EtOAc followed by neutralization with Et_3N/NaOH. The film of **85** is shown to be devoid of ketone, carbamate, or amine absorptions in the FTIR spectrum. Spectroscopic analyses and conductivity studies of **85** are performed by the authors.



(40)

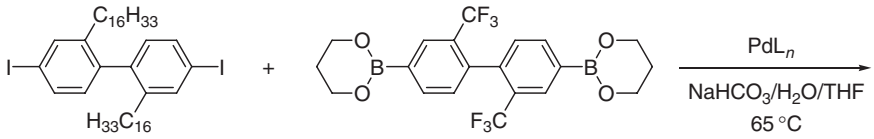
Yield: 63–97%
M_n = 9850–28 400 (M_w/M_n = 1.85–3.70)

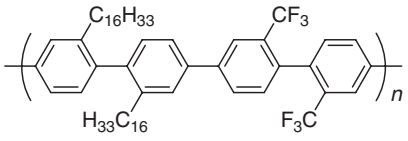
Swager also reported the synthesis of polymers containing fused polycarbocyclic aromatics by electrophile-induced cyclization. Cross-coupling polymerization of bifunctional boronic acid **46** was carried out with a diiodoarene bearing two acetylenic moieties to afford the corresponding polymer **86** in a quantitative yield. The catalyst loading is better reduced to 0.3 mol% in order to obtain high molecular weight polymer (M_n = 4500–55 000). It is also found that use of nitrobenzene/water as the solvent and KOH as the base is highly effective for high conversion during polymerization. Treatment of the polymer **86** with TFA induces multiple cyclization to afford polycondensed polymer **87** as shown in Equation (41).[52] IR spectrum of **87** shows that an acetylene stretch at 2214 cm^{-1}, observable for **86**, is totally absent.



(41)

Novak studied the mechanistic aspect of the cross-coupling polycondensation of biphenyl-4,4′-diyldiboronic acid reagent, and found that use of triphenylphosphine (TPP)-induced chain transfer between TPP via aryl exchange affords $Ph_nP(polyarylene)_{3-n}$ ($n = 0$–2). The chain-transfer side-reaction causes decrease in molecular weight and gives branched polymer containing a phosphorous atom in the main chain. On the other hand, use of tri(*o*-tolyl)phosphine (TOTP) in lieu of TPP affords linear and high molecular weight polymer.[53] (Equation (42)) Janssen also studied the mechanism of the polycondensation using MALDI-TOF mass spectrometry and confirmed the incorporation of phenyl group derived from TPP at the chain end.[54]





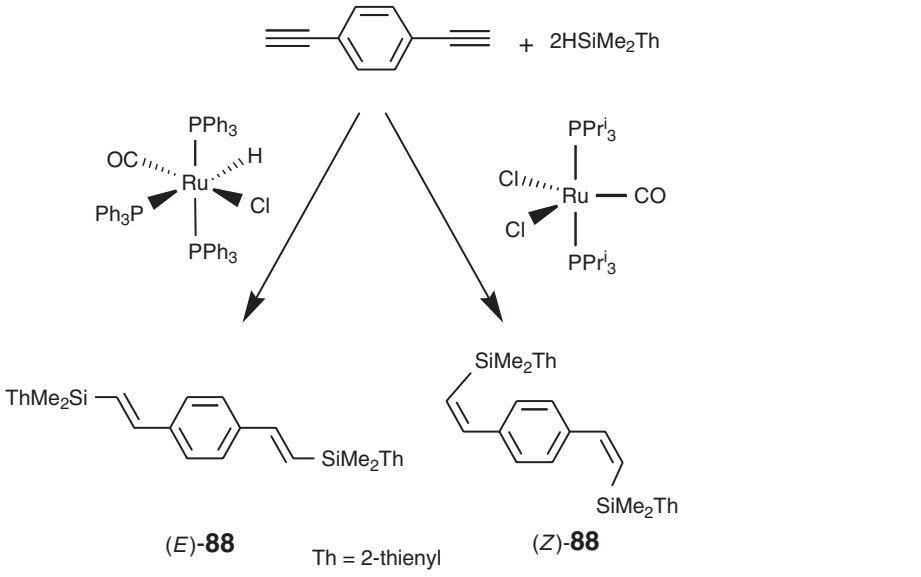
(42)

L_n = TPP: low molecular weight and branched
L_n = TOTP: high molecular weight and linear

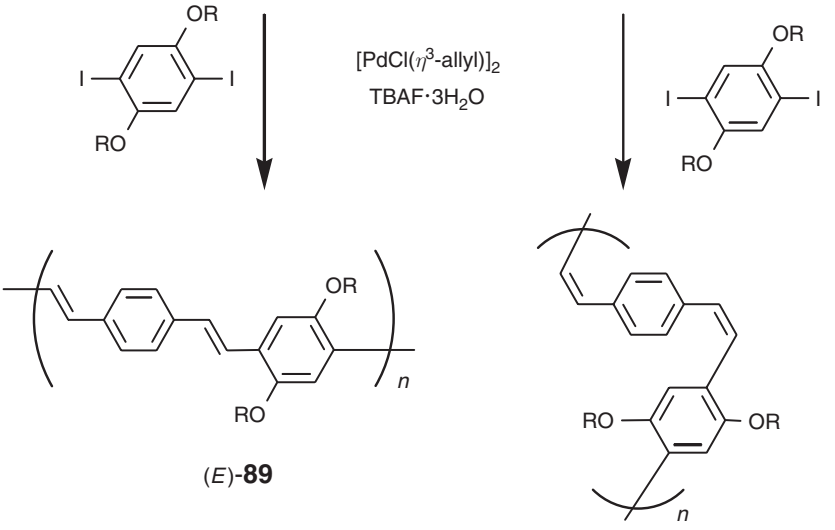
11.19.2.4 Reaction with Organosilicon Reagents (Hiyama Coupling)

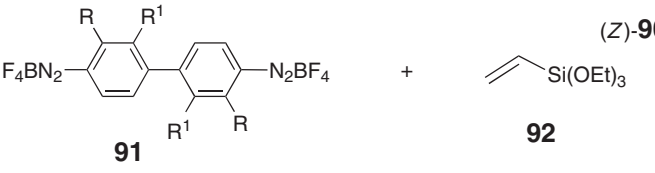
Although organosilicon compounds also serve as a reagent for the transition metal-catalyzed cross-coupling reactions (Hiyama coupling),[55] only a few examples have been employed for the polycondensation. Katayama and Ozawa employed bifunctional (*E*)- and (*Z*)-alkenylsilanes **88**, which were prepared by the ruthenium-catalyzed hydrosilylation of 1,4-diethynylbenzene, for the palladium-catalyzed cross-coupling polycondensation.[56] The polymerization with (*E*)-**88** using a palladium catalyst such as $[PsCl(\eta^3\text{-allyl})]_2$, $Pd(dba)_2$, and $Pd(OAc)_2$ affords poly(arelene–vinylene) **89** with retention of the stereochemistry ($E/Z = >99:<1$) and molecular weight (M_n) of **89** being 500–6300 ($M_w/M_n = 1.4$–2.3), whereas use of $Pd(PPh_3)_4$ results in no polymerization. The cross-coupling polymerization of (*Z*)-**88** is also effected under similar conditions. However, the molecular weight of resultant polymer **90** was slightly lower than that of the corresponding (*E*)-**89**. In addition, scramble of the olefinic stereochemistry is observed in the polycondensation with (*Z*)-**88** to give the corresponding (*Z*)-enriched polymer **90** ($Z/E = 45:55$–$34:66$) (Equation (43)).

Sengupta showed that the reaction of bis-arenediazonium salt **91** with vinyl(triethoxy)silane **92** afforded poly(phenylene–vinylene) **93**.[57] Although the reaction apparently proceeds through the Heck reaction mechanism, which is described in Section 11.19.4, a part of the step-growth reaction is indeed a transformation of the carbon–silicon bond of **92** to the carbon–carbon bond (Equation (44)).

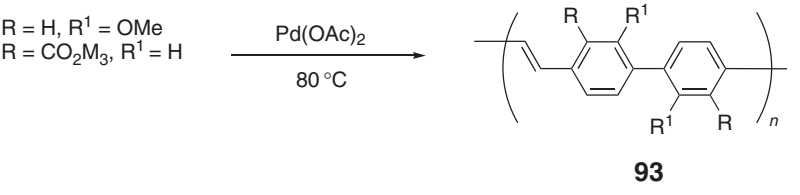


(43)





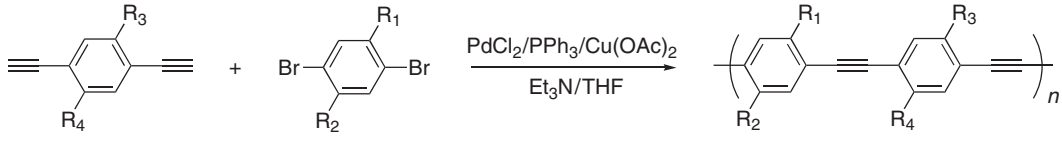
(44)



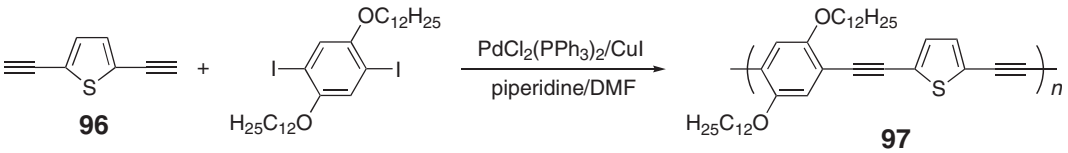
11.19.3 Cross-coupling Polymerization at *sp*-Hybridized Carbons

11.19.3.1 Polymerization by Sonogashira–Hagihara Coupling

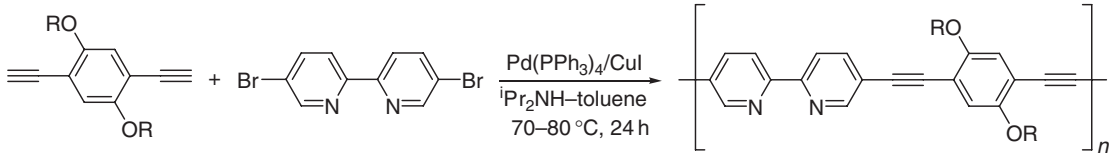
Sonogashira (or Sonogashira–Hagihara) coupling is a reaction that includes palladium/copper catalysts and terminal alkynes and organic halides as the partners. The reaction has been recognized as a highly practical method for introduction of an alkynyl moiety into organic molecules.[58] Hence, the Sonogashira coupling is very often employed also for the cross-coupling polymerization of bifunctional alkynes **94** with diaryl halides leading to poly(arylene–ethynylene)s (PAEs) **95**. A catalyst combination of $PdCl_2(PPh_3)_2$/CuI is generally employed as well as tertiary or secondary amines such as Et_3N, piperidine, or $^iPr_2NH$ as a solvent or co-solvent to effect the polymerization smoothly. A variety of bisalkynes and arylene or heteroarylene dihalides have been employed as the monomers.[59–71] Several examples are shown in Equations (45)–(52).



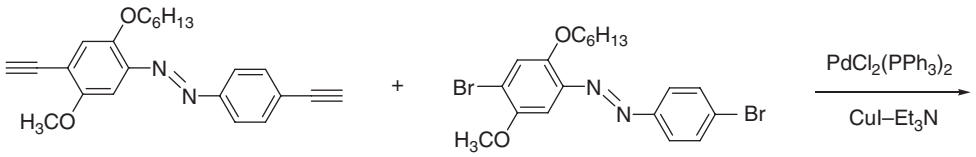
94 **95** (45)



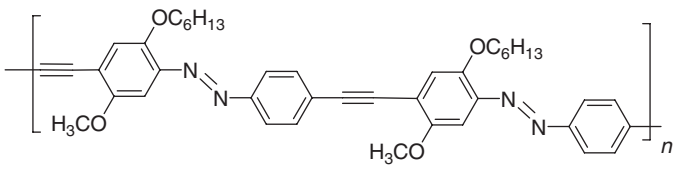
96 **97** (46)



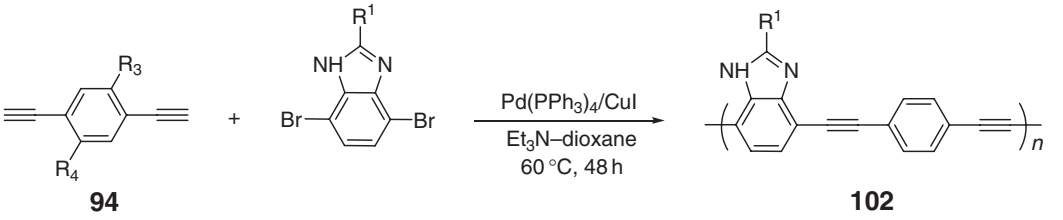
98 **99** (47)



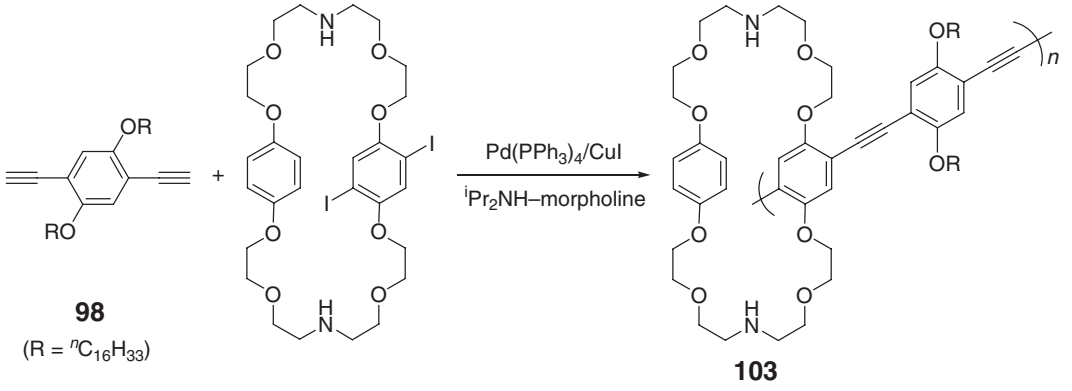
100 (48)



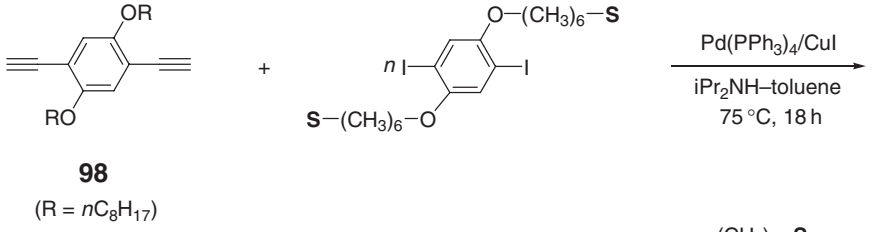
101

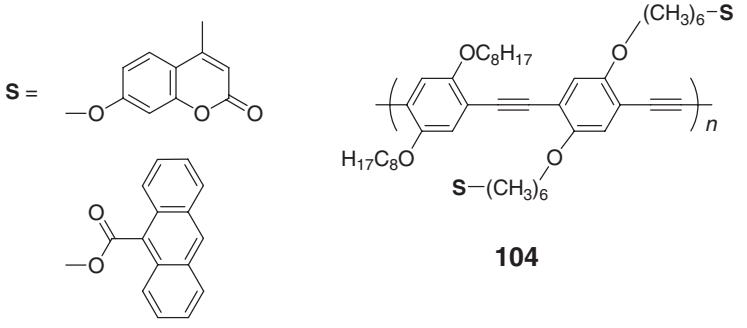


(49)

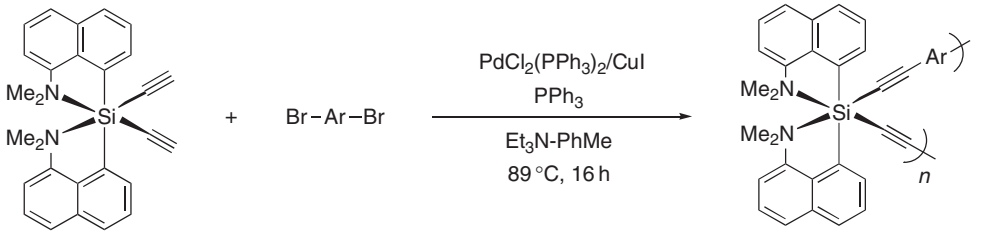


(50)



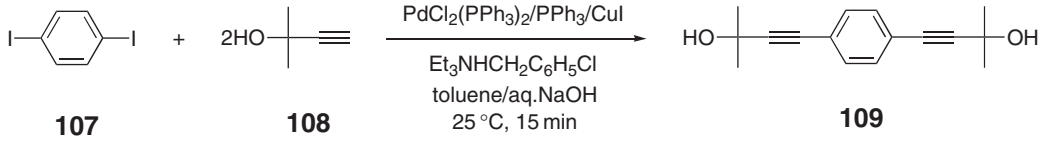


(51)

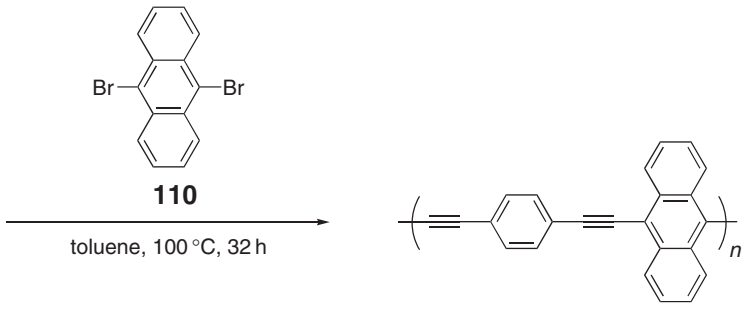


(52)

Heitz[72] has performed the cross-coupling polymerization using two-step one-pot process. The first step is the reaction of 1,4-diiodobenzene **107** with 2 equiv. of 2-methyl-3-butyn-2-ol **108** at room temperature in the presence of an aqueous base to give the protected bisalkyne **109**. Following polycondensation with another equivalent of dihaloarene **110** leads to the corresponding polymer **111** at 100 °C (Equation (53)). The overall yield of **111** was 50–90% and the average molecular weight (M_w) was 1400–48 200.



107 **108** **109**

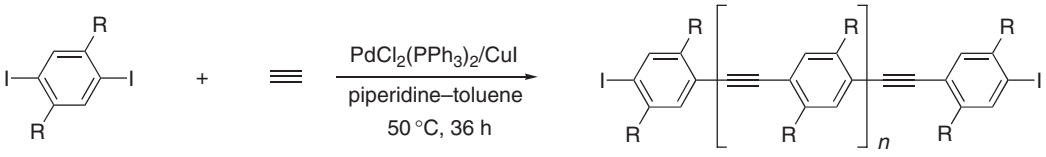


110 **111**

Overall yield: 50–90%
M_w = 1400–48 200

(53)

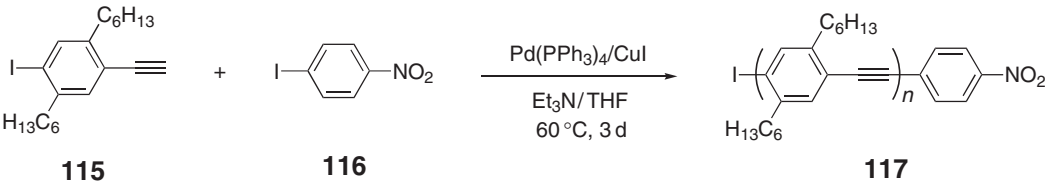
Bunz demonstrated a facile procedure for the preparation of high quality PAEs by a palladium-catalyzed cross-coupling reaction of acetylene gas with diiodoarenes. The polymerization proceeds at 50 °C, and poly(phenylene–ethynylene)s **114** were produced. Catalyst loadings of 0.1–0.2 mol% of palladium were best to achieve the complete conversion.[73]



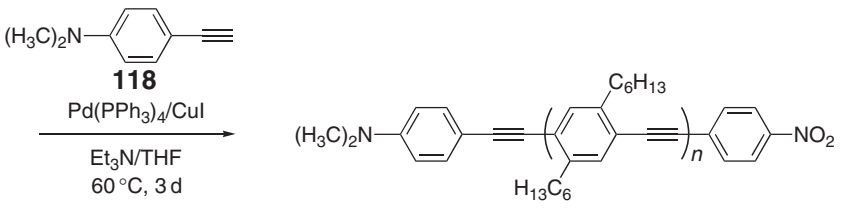
112 **113** **114**

(54)

Müllen has reported synthesis of α,ω-difunctionalized PAEs **119** using monomer **115** that bears terminal alkyne and aryl iodide moieties within the same molecule.[74] Monomer **115** polymerizes in the presence of Pd/Cu catalyst and 4-iodo-nitrobenzene **116** as an initiator to induce step-growth polymerization and gives the corresponding polymer **117** that possesses a nitroaryl group derived from **116** at one end and an iodoaryl moiety at the other end. End functionalization with an alkyne bearing an *N,N*-dimethylamino group **118** is successfully carried out, as shown in Equation (55). The resultant polymer thus possesses different end groups. The method is also applied to the synthesis of PAEs bearing a thiol group at the both ends. The polymer is applied to bridging the gap between two gold nanoelectrodes.



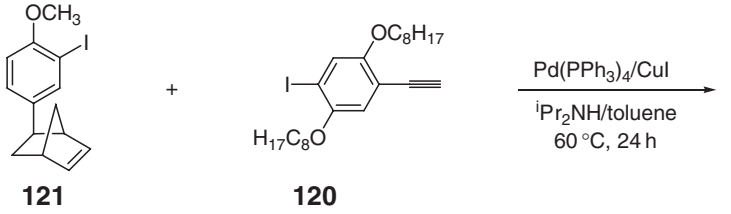
115 **116** **117**



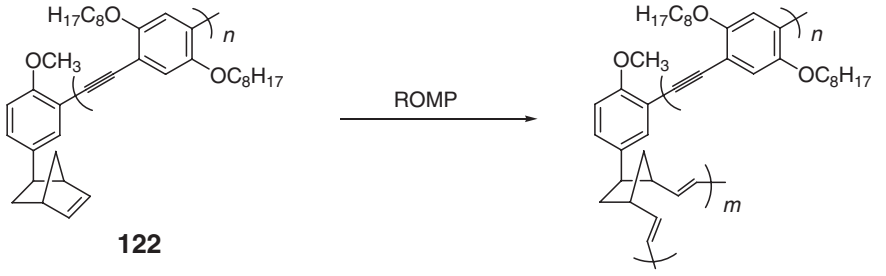
118 **119**

(55)

Block co-polymerization by the cross-coupling polycondensation is carried out with an initiator bearing a polymerizable functional group as demonstrated by Swager. He polymerized **120** in the presence of iodoarene **121** bearing a norbornene moiety. The reaction of **121** first occurs with Pd(0) to form an arylpalladium(II) species, which then undergoes step-growth polymerization with **120** to afford end-functionalized polymer **122** with M_n of 12 100 (PDI = 1.8). Subsequent ring-opening polymerization (ROMP) of **122** in the presence of a ruthenium catalyst affords block co-polymer[75] (Equation (56)). The method was available for the formation of PAE brushes, when ROMP of **122** was initiated by a ruthenium catalyst supported on oxidized silicon surfaces. The obtained PAE brushes were characterized by spectroscopic analyses and AFM analyses.



121 **120**

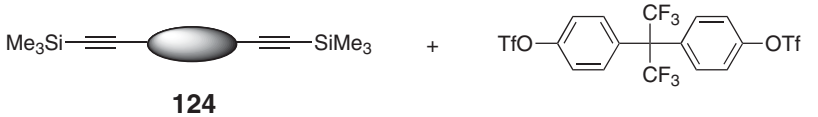


(56)

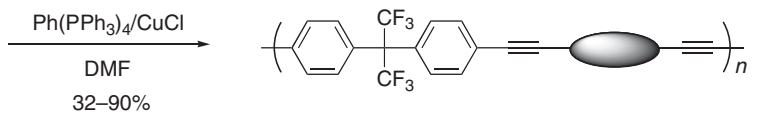
122 **123**

11.19.3.2 Polymerization with Alkynylmetal Reagents

Several alkynyl metallic reagents are available for similar transformations and used conveniently in lieu of terminal alkynes. Mori has shown that trimethylsilylalkynes react with aryl triflates in the presence of a catalytic amount of palladium(0) and copper(I) chloride in DMF without any further additive.[76,77] The reaction is successfully applied to the cross-coupling polymerization. The reaction of a monomer **124** bearing two trimethylsilylethynyl groups and two triflate groups in the presence of 5 mol% of $Pd(PPh_3)_4$ and 10 mol% of CuCl in DMF affords polymer **125** in moderate to excellent yields, as shown in Equation (57).[78] The obtained polymer shows M_n of 6000–12 000 (PDI = 1.2–1.4). UV–VIS absorption and fluorescence spectra of **125** are also measured. The key of the cross-coupling polymerization is the use of copper(I) chloride as the co-catalyst and bistriflate as an organic electrophile. The intermediate alkynyl copper species from trimethylsilylated alkyne is shown to be generated when chloride or triflate is employed as a counterion. However, no reaction takes place when CuI, a common co-catalyst for the coupling of terminal alkyne, is used. CuBr is also ineffective. On the other hand, the available organic electrophiles for the cross-coupling reaction are iodides, bromides, and triflates, while use of aryl chloride generally requires drastic conditions. Accordingly, only the combination of bistriflate and a catalyst system employing palladium and copper is effective.



124

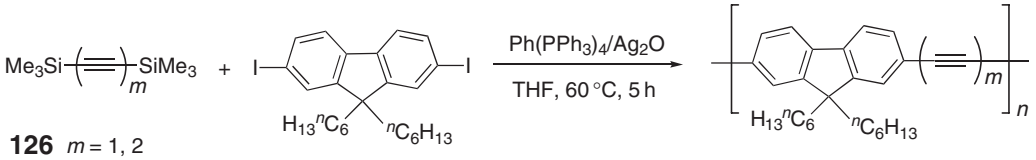


(57)

125

M_n = 6000–21 000
PDI = 1.2–1.4

The cross-coupling polymerization of bifunctional trimethylsilylalkynes with aryl iodides in the presence of silver(I) oxide as an activator is also shown by Mori[79] (Equation (58)). The reaction of bistrimethylsilylethyne ($m = 1$) or 1,4-bistrimethylsilylbutadiyne ($m = 2$) with diiodoarene derived from fluorene proceeds with 5 mol% of $Pd(PPh_3)_4$ in the presence of silver(I) oxide to give **127** in excellent yield after stirring at 60 °C in THF. The method is successfully applied to polymerization of PAEs, functionalized with acetylated glucopyranosyl units by Naso as shown in Equation (59).[80] Polymers **129** bearing several R groups of arylene moiety were obtained in excellent yields with M_n of 2600–19 500 and M_w/M_n of 1.4–6.4. Compared with conventional Sonogashira coupling conditions that are known to often produce compounds derived from oxidative homocoupling of the ethynyl derivative in a lower amount, the method gives the corresponding polymer **129** highly efficiently.

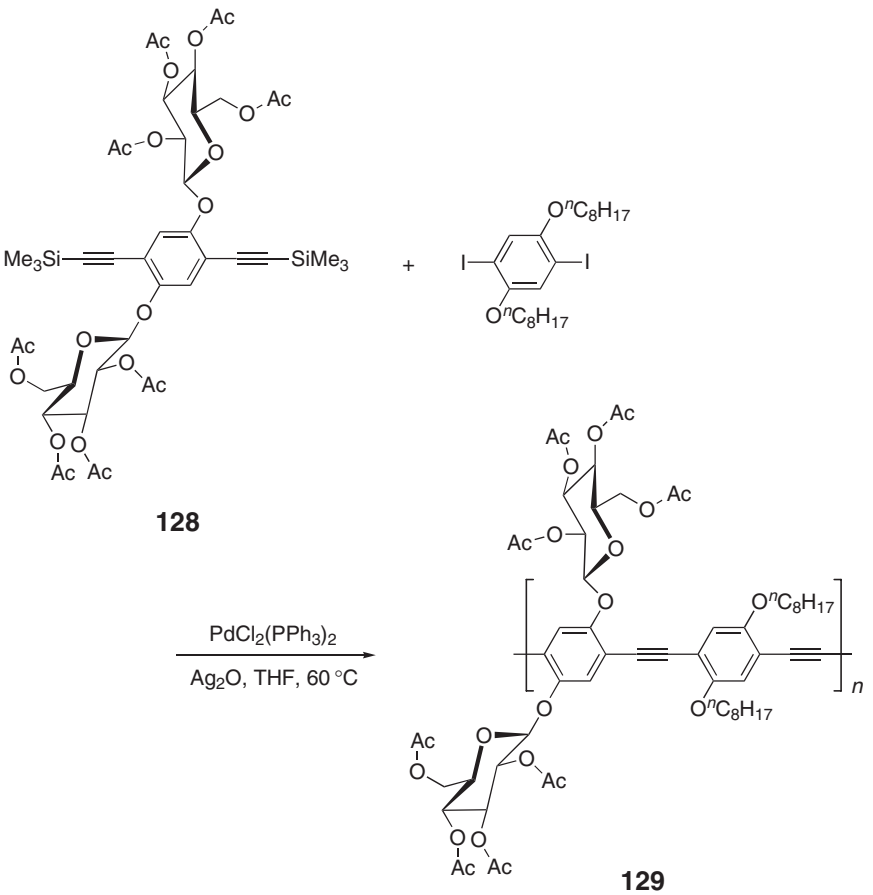


126 $m = 1, 2$

127

99%, M_w = 39 400, PDI = 2.9 (m = 1)
91%, M_w = 7800, PDI = 1.9 (m = 2)

(58)



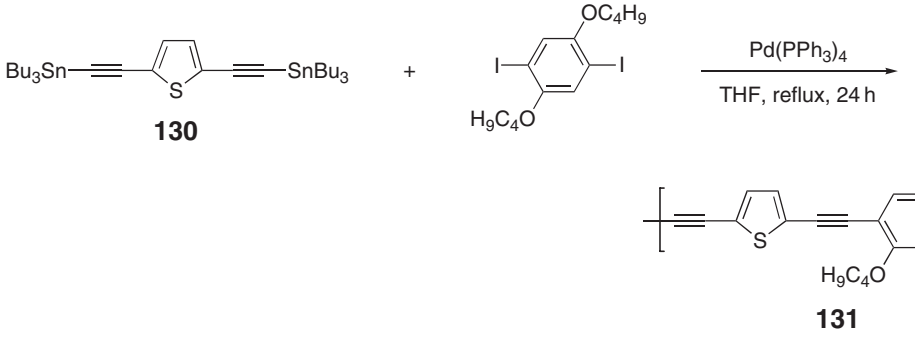
128

129

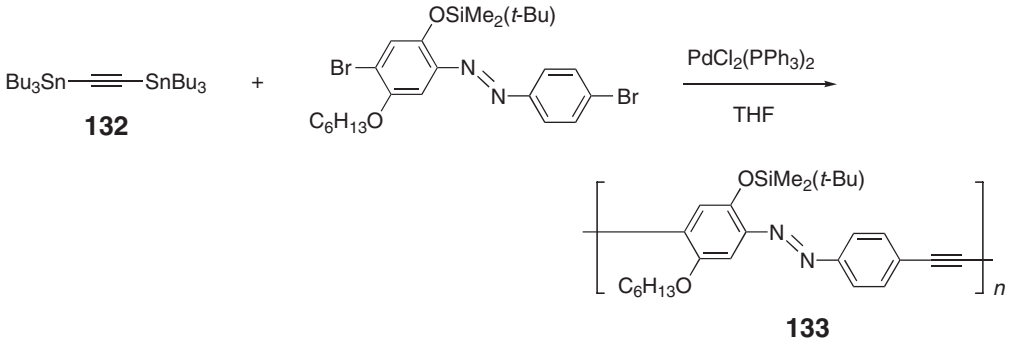
(59)

Polymerization with alkynyl tin reagents also proceeds smoothly as shown by Sterzo,[81] Wright,[62] and Tamao[44] (Equations (60)–(62)). The reaction takes place in the presence of a palladium catalyst, such as $Pd(PPh_3)_4$,

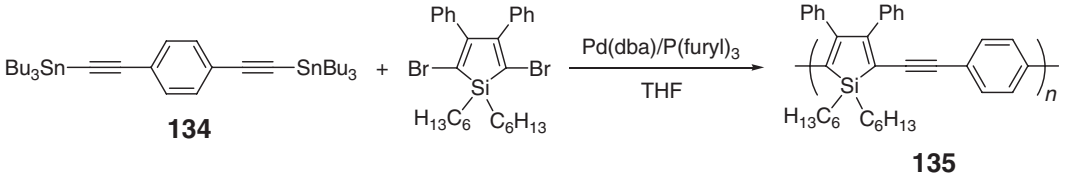
$PdCl_2(PPh_3)_2$, or $Pd(dba)_2/P(furyl)_3$. No further additive is necessary to activate the tin reagent and to induce the cross-coupling polymerization. In addition to the diiodoarenes with different substituents, dibromoazobenzenes and dibromosiloles (silacyclopentadiene) are also employed as the co-monomers.



(60)

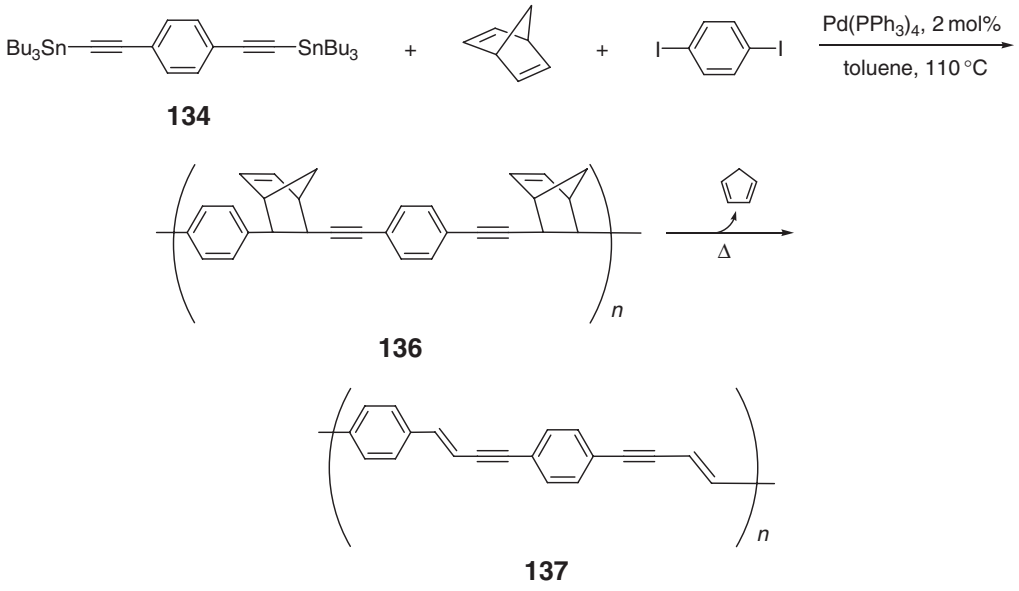


(61)



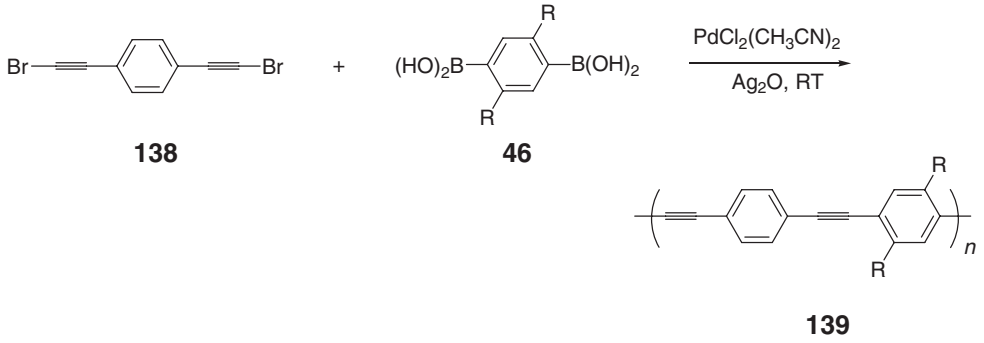
(62)

Tomita and Endo reported the palladium-catalyzed three-component coupling of bisalkynyl tin **134**, diiodoarene, and norbornadiene. The cross-coupling polymerization proceeds with insertion of norbornadiene with 2 mol% of $Pd(PPh_3)_4$ in toluene at 100 °C for 2 days to afford the first polymer **136** in 82% yield. The obtained polymer **136** shows M_n of 13 500 and M_w/M_n of 1.48 and is soluble in common organic solvents. Accordingly, the polymer forms a thin film when cast from chloroform. Upon heating the film at 165 °C, retro Diels–Alder reaction of **136** occurs to give poly(phenylene–ethenylene–ethynylene) **137**[82] (Equation (63)). The C═C stretching of norbornene moieties observed for **136** is not detected by IR analysis of **137**, and characteristic peaks of *cis*- and *trans*-alkenes are observed. During the thermal transformation process, the color gradually changes from colorless to yellow due to an increase in the average degree of conjugation along the polymer backbone. It is possible to monitor the color change by UV–VIS spectroscopy: as the reaction proceeds, the absorption spectrum of the polymer shifts toward red. Strong fluorescence is also observed with **137**.



(63)

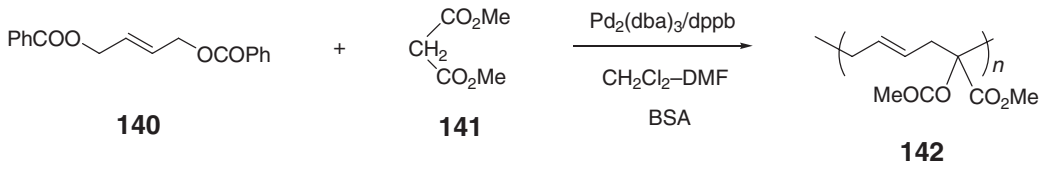
Alkynyl halides are possible monomers for the cross-coupling polymerization, in which boronic acids are used as the organometallic counterparts. For example, bifunctional boronic acid **46** is allowed to react with 1,4-di(bromoethynyl)benzene **138** to afford the corresponding PAE **139** as shown in Equation (64).[38] Polymerization proceeds at room temperature in toluene in the presence of silver(I) oxide as an activator of the boron reagent. The polymer **139** is obtained in 30–50% yield showing color of red-brown to deep red-brown and slight solubility in toluene (<0.1 wt.%). The molecular weight (M_n) of **139** was 1700–4300 (PDI = 1.3–3.6).



(64)

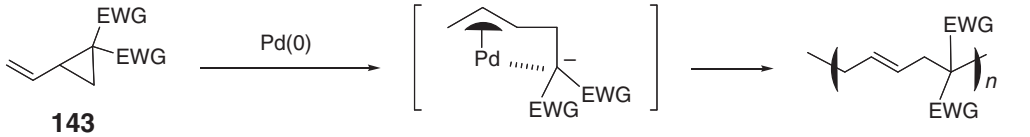
11.19.4 Cross-coupling Polymerization with Organometallic Reagents of sp^3-Hybridized Carbons

Examples of the transition metal-catalyzed cross-coupling polymerization through bond formation at sp^3-hybridized carbons are rarely reported compared with the number of successful examples of the reactions at *sp*- and sp^2-hybridized carbons. Nomura has focused on the use of Tsuji–Trost-type reaction[83] for polycondensation reaction, in which π-allylpalladium complex is a key intermediate to allow attack of the nucleophile. Allylic dielectrophile **140** was allowed to couple with a nucleophilic reagent such as malonate ester **141** to induce polycondensation reaction in the presence of a palladium catalyst, giving polymer **142**.[84,85] Use of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) as a base and dppb as a ligand for the palladium catalysis is essential for the successful polymerization. It is worth noting that the degree of polymerization does not depend on the ratio of electrophile **140** and nucleophile **141**[86,87] (Equation (65)), and allows high degree of polymerization, with results of $M_w > 10\,000$ (degree of polymerization > 100).



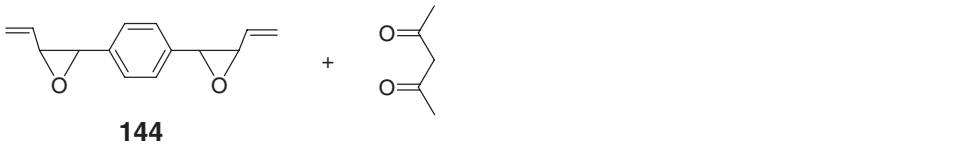
140 **141** **142** (65)

Suzuki has shown that vinylcyclopropane **143** behaves both as an electrophile and a nucleophile and thus undergoes palladium-catalyzed ring-opening polymerization as shown in Equation (66). Vinyl cyclopropane **143** first reacts with palladium(0) to induce ring opening of the cyclopropane ring and forms zwitterionic π-allylpalladium/molonate anion species. Repeated intermolecular attack of the malonate anionic moiety to the π-allylpalladium part through bond formation of an sp^3-carbon atom affords finally the polymer **142**.[88]

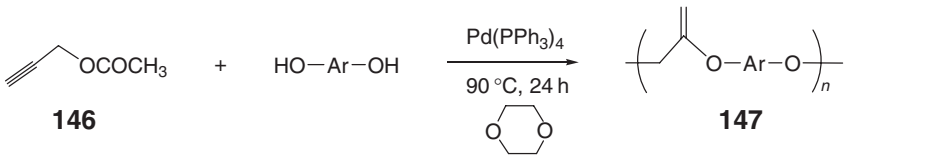


143 **142** (66)

The Tsuji–Trost-type reaction is applicable to bifunctional vinyl epoxide **144** and 1,3-diketone using a palladium catalyst as demonstrated by Koizumi, who obtained polymer **145**[89] (Equation (67)). The reaction proceeds at 0 °C to a reflux temperature of THF. The resulting polymer **145** is isolated in a quantitative yield. The molecular weight of **145** is ca. 3000 (PDI = 2.0–2.7) when 5 mol% of $Pd(PPh_3)_4$ is employed as a catalyst. Use of $Pd_2(dba)_3$ with several bidentate phosphines such as dppe, dppp, dppb, and dppf is also effective for the polymerization reaction. Propargyl carbonate **146** also reacts with bisphenols in the presence of a palladium catalyst to afford polyethers **147** via carbon–oxygen bond formation at sp^2- and sp^3-carbon atoms[90] (Equation (68)).

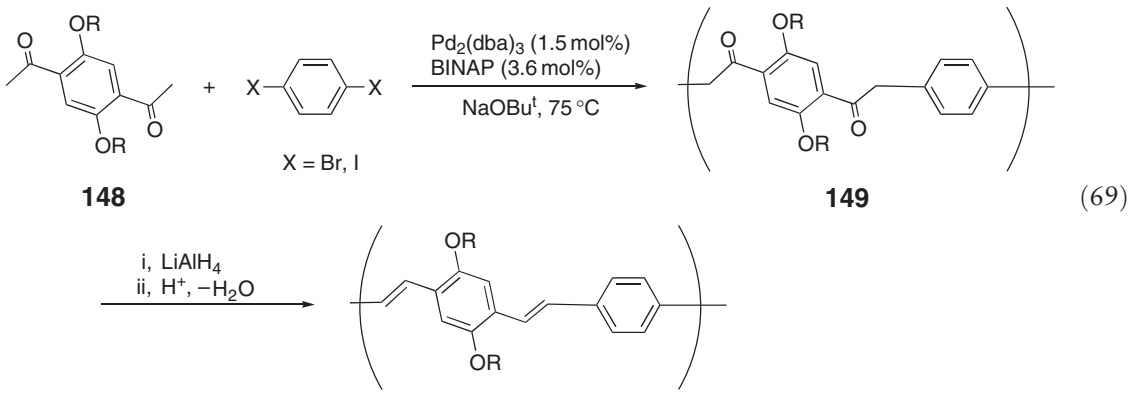


144 **145** (67)



146 **147** (68)

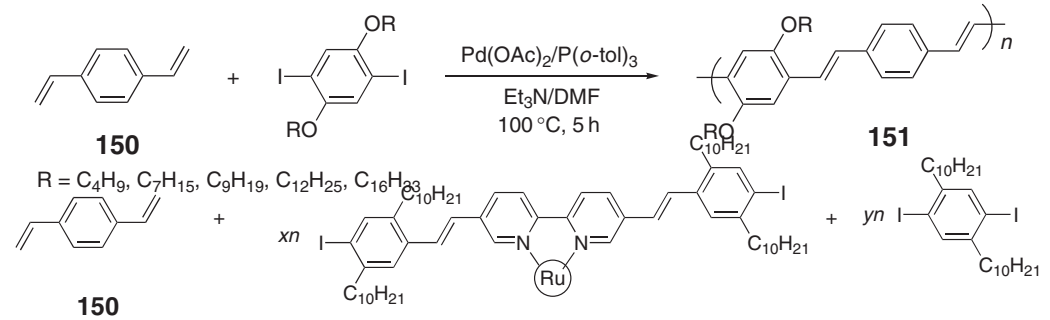
Palladium-catalyzed α-arylation of ketones[91] is performed with arylene dihalides and bifunctional aromatic ketones **148** to result in the bond formation at the sp^3-α-carbon of the ketone, leading to polyketone **149**. The reaction is carried out in the presence of Pd(0) and various phosphines. Several bidentate phosphines and bulky alkylphosphines such as dppf, BINAP, PCy_3, and P^tBu_3 are shown to be effective, while PPh_3 results in no reaction. Arylene dibromide and diiodide are applicable as the co-monomers. The polymerization reaction is carried out in THF in the presence of NaO^tBu at 75 °C under N_2, and polymers **149** are isolated in 60–80% yields (M_n = 7000–15 000). Polyketone **149** is further transformed to conjugated polymer PPV by reduction of the ketone moiety with $LiAlH_4$ followed by dehydration with an acid[92] (Equation (69)).



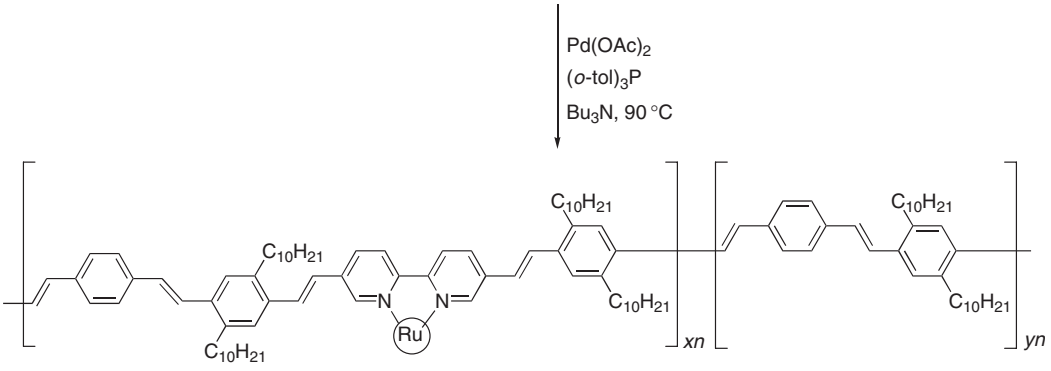
(69)

11.19.5 Miscellaneous Cross-coupling Polymerizations

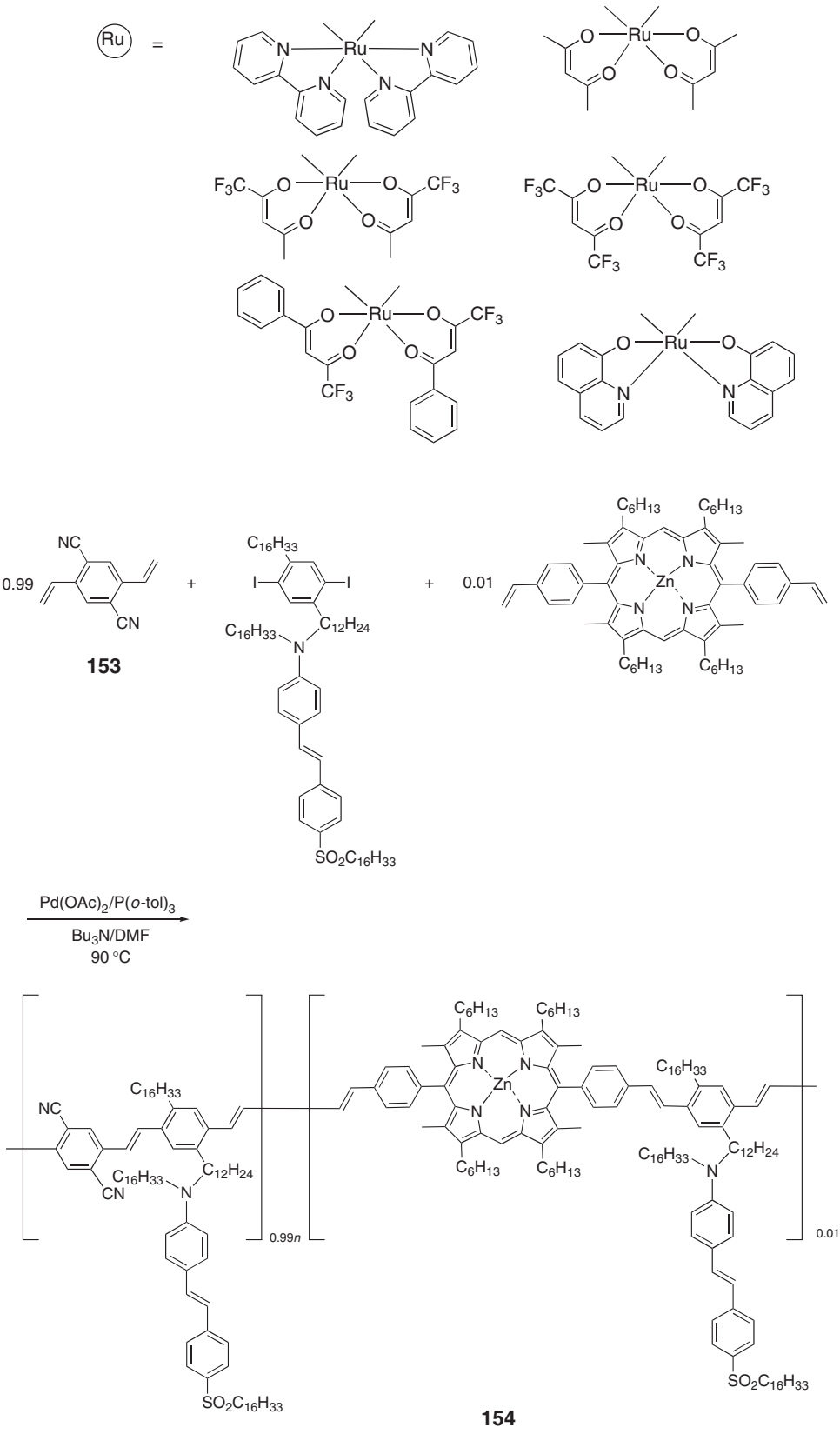
The Mizoroki–Heck reaction[93–95] is a powerful and straightforward tool for the preparation of PAVs. Thus, the reaction of arylene dihalides with an organic molecule bearing two independent olefinic moieties proceeds through addition–elimination of the arylene part toward the double bond in the presence of a palladium catalyst. Olefinic substrates most frequently employed are 1,4-divinylbenzene **150** and its derivatives. Yu synthesized a variety of PAVs including liquid crystalline polymers **151**,[96] conjugated polymers **152** containing a bipyridylruthenium complex part,[97] and polymers **154**[98] bearing a small amount of metalloporphyrins as illustrated in Equations (70)–(72). Polymerization was best carried out in DMF at 90–100 °C using P(*o*-tol)$_3$ for the palladium catalyst. The reaction proceeds quickly to give final polymers that precipitate from the solvent within a few hours. The results are in contrast to the cross-coupling reactions with boron and tin reagents, which need several days to complete the polycondensation. The obtained polymers **151** show M_n of ca. 8000–20 000 (PDI = 2.9–3.9). The reaction conditions are tolerable for the molecules bearing metal complexes such as ruthenium to afford **152**. The co-polymers involving various ranges of *x* and *y* values are obtained with proportional M_n and PDI values, and the content of the ruthenium complex is related to photoconductive properties. It is also shown that co-polymerization with bifunctional vinyl derivative bearing a zinc porphyrin moiety as a photosensitizer gives photorefractive polymers **154**.



(70)

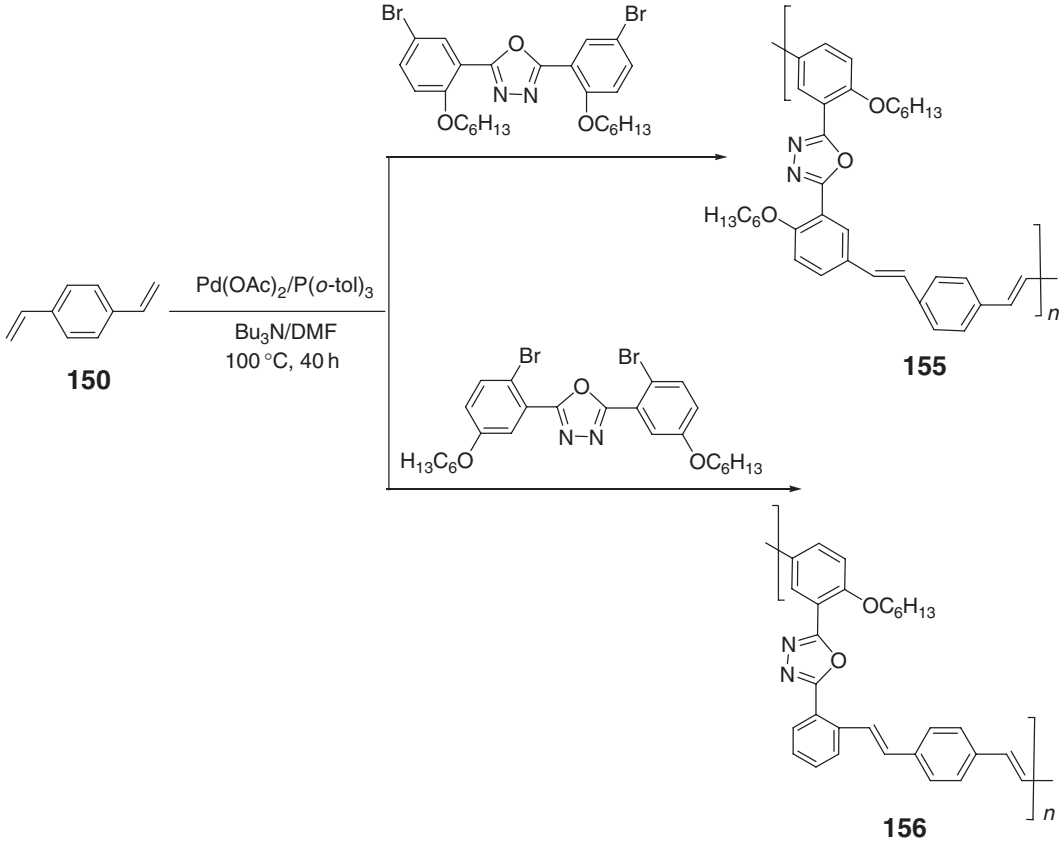


(71)

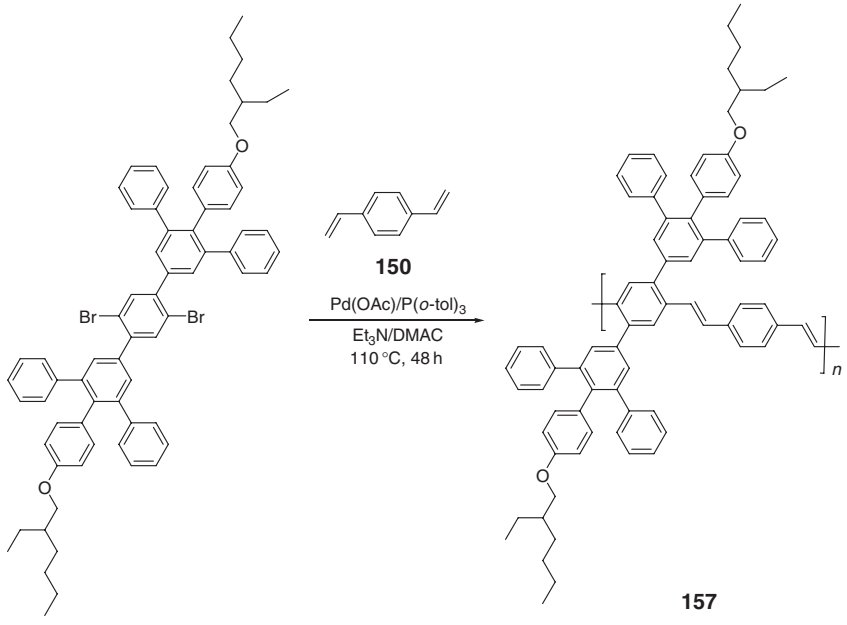


(72)

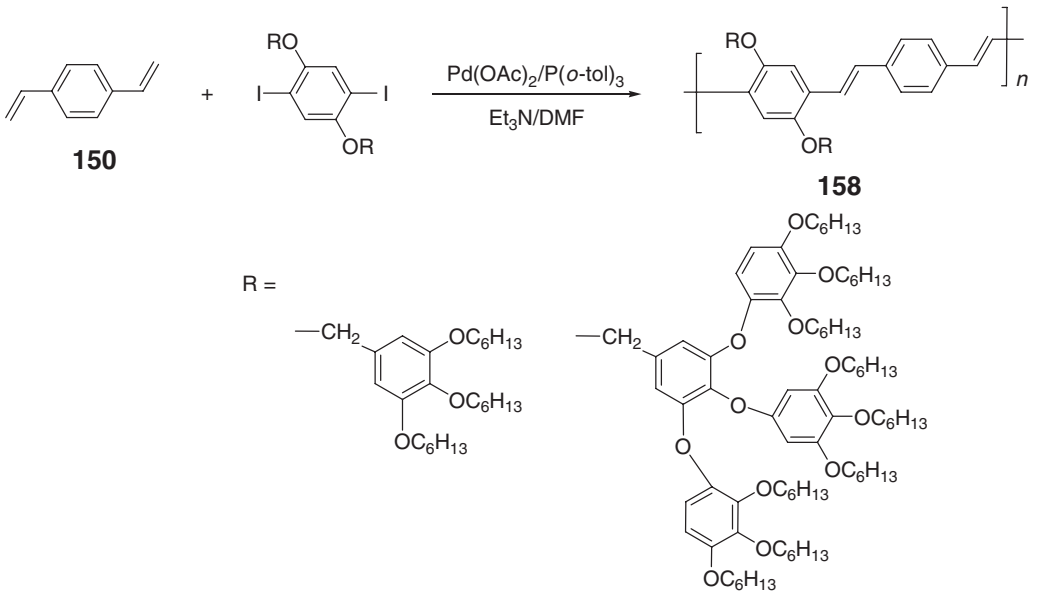
Synthesis of light-emitting PAVs **155–157** is also performed under similar conditions.[99,100] Polymers **158** bearing a dendric side chain are synthesized by Bao.[101] Dendric polymers bearing different generations are synthesized by the palladium-catalyzed polymerization with 1,4-divinylbenzene, and UV–VIS spectra in solution and film are compared. Several other functional polymers[52,102,103] are synthesized in a similar manner (Equations (73)–(76)).



(73)



(74)



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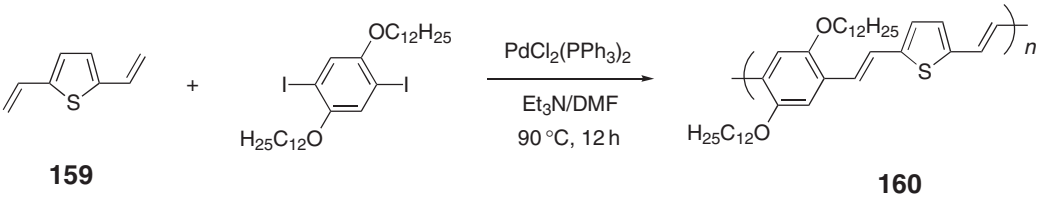
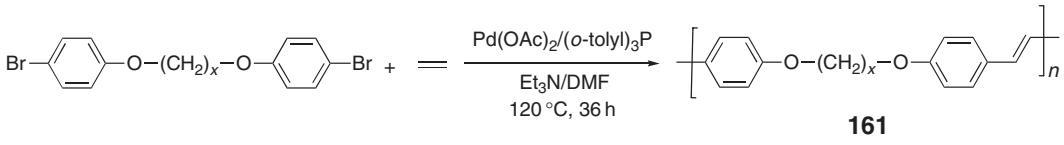


(76)

Ethylene is also employed as an olefinic component of the Mizoroki–Heck polymerization. Organic dihalides thus couple with ethylene in the presence of a palladium catalyst to afford PAV-type polymers **161** and **162**, as shown in Equations (77) and (78).[104 105]



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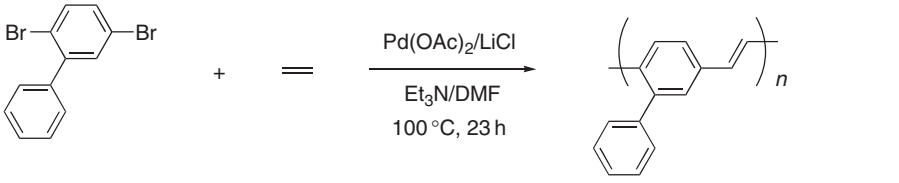
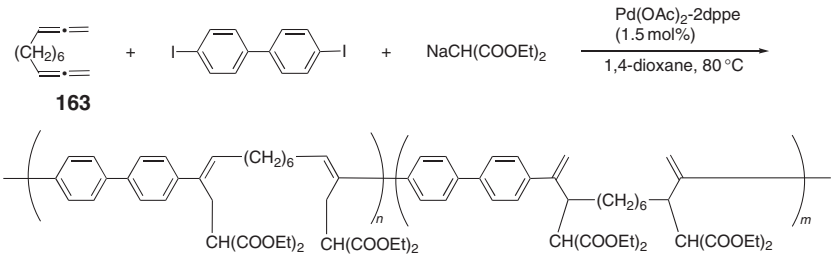


(78)

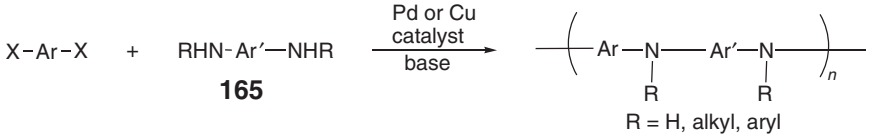
Tomita and Endo have shown that three-component coupling of bisallene **163**, aryl dihalide, and a malonate nucleophile takes place with a palladium catalyst. Arylpalladium species derived from the halide attacks the central carbon of allene to form a π-allylpalladium intermediate, which is then attacked by the malonate anion to form C–C bond. This sequence of C–C bond formation is repeated to afford the corresponding polymer **164**[106–109] (Equation (79)). Various arylene dihalides and heteroarylene dihalides are applicable to the reaction of bisallene **163**, and polymers **164** of various structures are available in good to excellent yields (M_n of 15 000–22 000 with PDI of ca. 2.0). Photoluminescent and electroluminescent properties of the polymer **164** are also studied.



163

164 (79)

Cross-coupling reaction of aryl halides with arylamines is a straightforward method for forming a carbon–nitrogen bond and is catalyzed by a palladium complex. This methodology was applied by Kanbara, Müllen, and several groups to polymer synthesis.[110–119] A variety of arylene dihalides are allowed to react with a bifunctional primary or secondary diamines **165** in the presence of a base to effect polycondensation, and a variety of the corresponding polydiarylamines **166** are prepared (Equation (80)). In general, NaO^{t}Bu (3 equiv. for monomer) is best employed as a base. When Pd(dba)$_2$–BINAP (2.5 mol%/7.5 mol%) is used, the reaction of arylene dibromides and diiodides proceeds in good to excellent yields to give polymers **166**. However, arylene dichlorides do not afford the polymer at all. On the other hand, use of a catalyst consisting of Ni(cod)$_2$ (10 mol%), dppf (30 mol%), and NaO^{t}Bu as a base induces the polymerization of arylene dichlorides under mild conditions. For example, polycondensation of 1,3-dichlorobenzene with bis(4-aminophenyl)methane at 60 °C in toluene for 24 h affords polymers of type **166** in 81% yield ($M_n = 72\,000$, PDI = 1.6). The polymerization with diarylamines is also shown to take place with palladium catalyst Pd(OAc)$_2$–dppf in the presence of NaO^{t}Bu to afford triarylamine-type polymers in good to excellent yields. Copper-mediated polycondensation is also possible and is shown to proceed in the presence of Cu/18-crown-6/K_2CO_3. The corresponding polymers are thus prepared at reflux temperature of *o*-dichlorobenzene for 5 days in 43–78% yields.

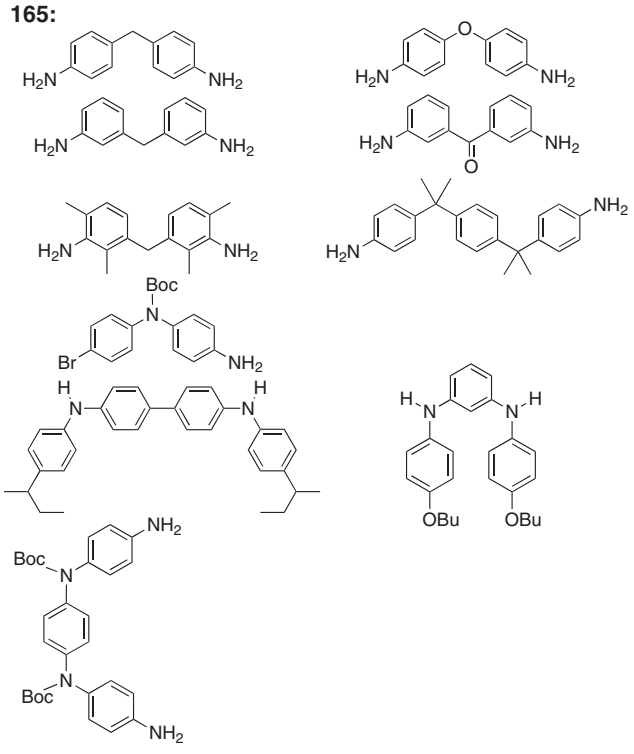


165

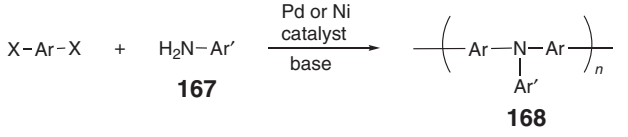
R = H, alkyl, aryl

166 (80)

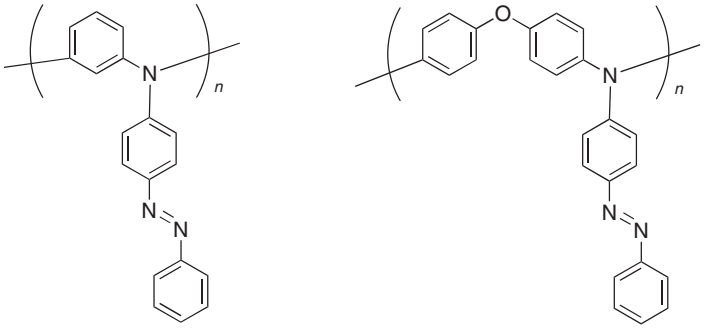
165:



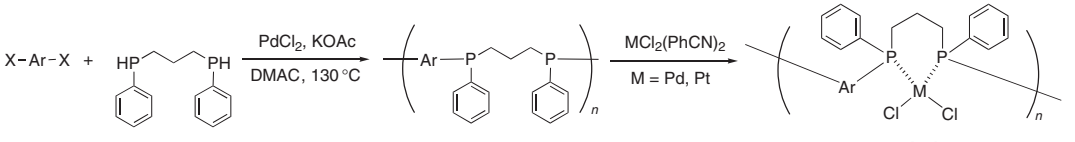
The palladium-catalyzed amination reaction with a monofunctional primary amine **167** effects *gem*-diarylation to afford the tertiary amine polymers **168**. Hence, polycondensation of **167** with bifunctional arylene dihalides leads to **168** (Equation (81)). Polycondensation of a primary amine bearing an azobenzene moiety with dibromides in the presence of $Pd_2(dba)_3$ (2.5 mol%)–$^tBu_3P$ (P/Pd = 3 : 1) and NaO^tBu at 100 °C for 24 h in toluene gives **168** in 81–93% yields, as reported by Kanbara.



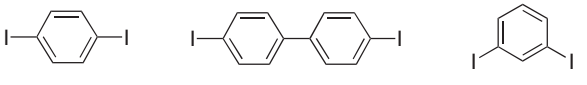
167 **168** (81)



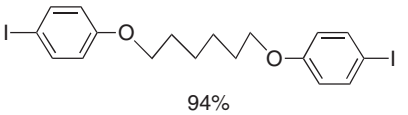
In a manner similar to amines, primary and secondary phosphines also undergo the polycondensation reaction with arylene dihalides.[120–124] Kanbara reported that cross-coupling polymerization of a bifunctional secondary phosphine, for example, (1,3-diphenylphosphino)propane **169**, with a variety of arylene diiodides and bromides leads to polymers **170**, containing phosphorous atoms in the main chain in moderate to excellent yields. The reaction with diiodoarenes is particularly carried out in the presence of $PdCl_2$ as a catalyst and a base such as KOAc or K_2CO_3 in DMAC at 100–130 °C for 24 h under nitrogen, and the polymers **170** were isolated in 40–80% yields. The reaction with diiodide proceeds in better yields, whereas the use of dibromide results in inferior yields. The obtained polymers are exposed to $MCl_2(PhCN)_2$ (M = Pd, Pt) to form metal-containing polymers **171**. (Equation (82))



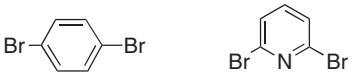
169 **170** **171**



82% 99% 78%

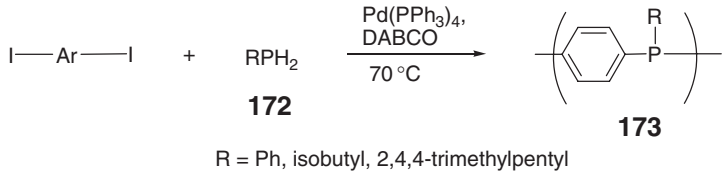


94%



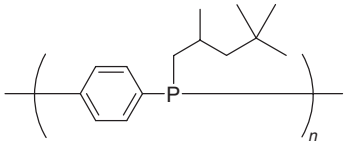
23% 54%

On the other hand, Lucht showed the cross-coupling polycondensation of primary phosphine **172** with arylene dihalide to give polymer **173**. (Equation (83)) The reaction takes place with a $Pd(PPh_3)_4$ catalyst in the presence of a tertiary amine base. In particular, the reaction of 1,4-diiodobenzene with isobutylphosphine proceeds at 70 °C in the presence of triethylamine to give the corresponding polymer **173a** (R = ^{i}Bu) in 83% yield (M_n = 1700, PDI = 1.3) **173b** (M_n = 5000, PDI = 1.6).

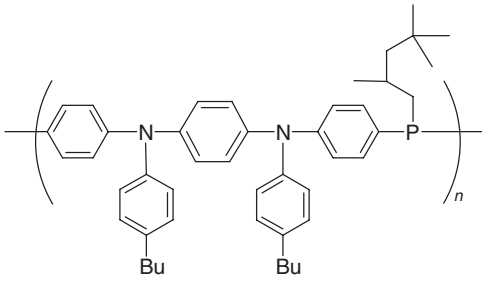


172 **173** (83)

R = Ph, isobutyl, 2,4,4-trimethylpentyl



173a (Ar = C_6H_4)

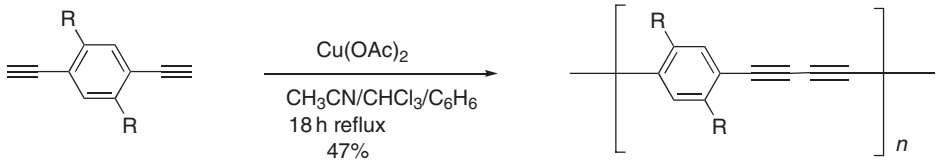


173b (Ar = C_6H_4–N–C_6H_4–N–C_6H_4; C_6H_4–Bu; C_6H_4–Bu)

Several phosphines, such as 2,4,4-trimethylpentylphosphine and phenylphosphine, give similarly the corresponding polymers. Several phosphorous-containing polyanilines are also prepared in a similar manner by the palladium-catalyzed polycondensation reaction.

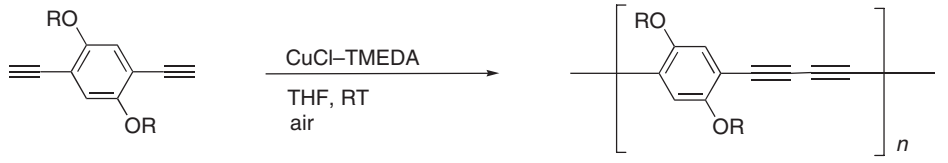
Some monomers are shown to undergo self-condensation reaction in the presence of a metal catalyst via homocoupling, although this type of reaction is, strictly saying, not classified as the cross-coupling polymerization. Bifunctional terminal alkynes are shown to homocouple in the presence of a palladium or copper catalyst, leading to polymers bearing a butadiynylene moiety. A substituted 1,4-diethynylbenzene **174** undergoes the homocoupling in the presence of excess $Cu(OAc)_2$ in $MeCN/CHCl_3$ under ambient atmosphere to afford poly(arylene–butadiynylene) **175** in 47% yield after refluxing the mixture for 18 h.[125] The obtained polymer shows M_n of 11 500 and PDI of 7. Kijima also showed homocoupling polycondensation of 1,4-diethynylbenzene derivatives bearing alkoxy substituents using a catalytic amount of CuCl and TMEDA under aerobic oxidation conditions. The reaction in THF at room temperature takes 2–3 days to afford the polymer **176** in 65–96% yields with M_n of 5000–9000 and PDI of 1.5–4.1.

On the other hand, Swager reported similar homocoupling polycondensation using a Pd/Cu catalyst in the presence of benzoquinone. The homocoupling polycondensation proceeds at 60 °C in 3 days in toluene and polymers **176** are isolated in excellent yields. Since the polymerization proceeds efficiently as compared with previous homocoupling reactions, the reaction allows in the preparation of the polymers **177** of extremely high molecular weight (M_n = 154 000, PDI = 5.2) by the co-polymerization with co-monomers containing a substituent of different chain length.[126]



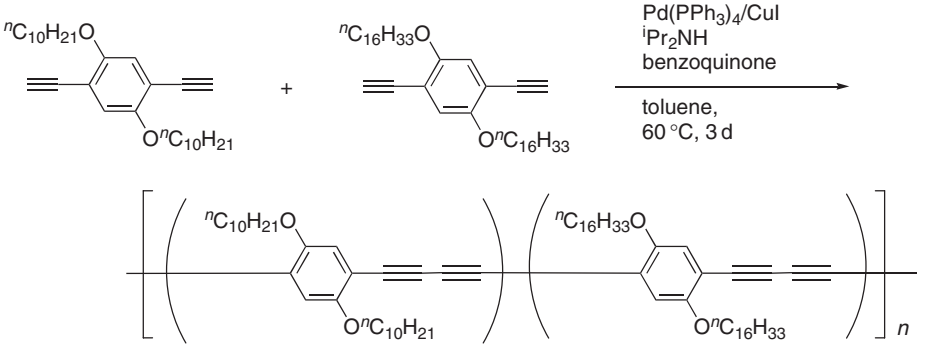
174
R = dodecyl

175
M_n = 11 500, PDI = 7



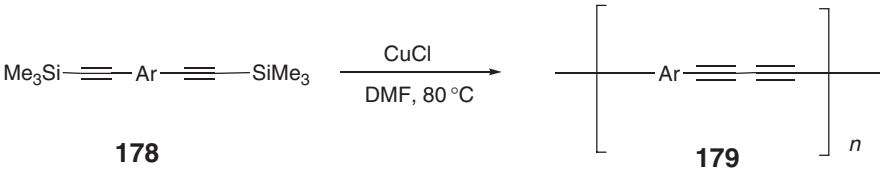
176 R = octyl, decyl, dodecyl
M_n = 5000–9100, PDI = 1.5–3.5

(84)



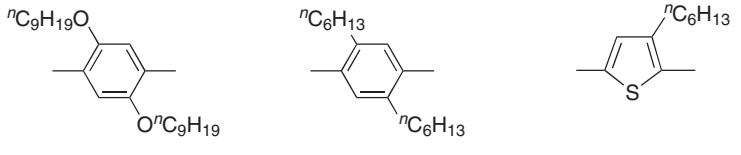
177 M_n = 154 000, PDI = 5.2

Homocoupling polycondensation of bifunctional trimethylsilylalkynes **178** is also feasible. The reaction proceeds in the presence of a stoichiometric amount of CuCl in DMF at 80 °C and affords several poly(arylene–butadiynylene)s **179** in moderate to good yields with M_n of 4000–9000 (PDI = 1.4–2.1).[127] (Equation (85))



178 **179**

Ar:



74%
M_n = 8900, PDI = 1.78

45%
M_n = 7900, PDI = 2.04

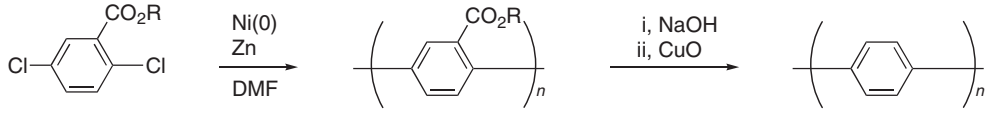
94%
M_n = 4000, PDI = 2.09

(85)

A variety of polyaryrens are prepared by nickel-catalyzed homocoupling polycondensation.[128–132] A 1,4-dichlorophenylene monomer **180** bearing an ester substituent undergoes homocoupling in the presence of an Ni(0) catalyst

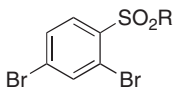
that is *in situ* prepared by $NiBr_2$–PPh_3 and Zn. The reaction proceeds at 45–80 °C in DMF and takes 24 h to afford the corresponding polymer **181** in 85% yield, the degree of polymerization being ca. 100 (PDI = 2.1). The obtained polymer is transformed to unsubstituted polyphenylene **182** by hydrolysis of the ester functional group followed by decarboxylation with CuO.

Low-valent palladium complex, for example, Pd(0), is readily prepared *in situ* by reaction of $PdCl_2(PPh_3)_2$/Zn. This is shown to induce the similar homocoupling polycondensation of metaphenylene **183** at 95 °C in DMF. Fluorinated alkyl esters **180** polymerize smoothly in supercritical CO_2; 1,4-dichlorophenylene **184** having a keto group also reductively polymerized similarly.

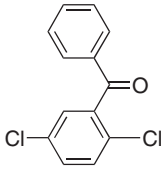


180 **181** (DP = 104, PDI = 2.1) **182**

R = CH_3, C_2H_5, $CH_2CF_2CF_3$, $(CH_2)_2(CF_2)_5CF_3$, etc.

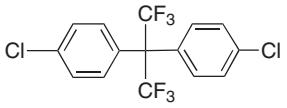


183

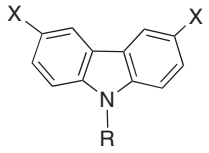


184

Other bifunctional aromatic dichlorides also undergo homocoupling polymerization in the presence of nickel or palladium catalysts under similar conditions. Polymerization of a fluorinated analog **185** of bisphenol A gives polymers with thermal stability, flame-retardant characteristics, and high glass-transition temperature.[133] Carbazole **186** and fluorene **187** monomers, both designed for conductive and light-emitting materials, respectively, also undergo the homocoupling polymerization by the catalysis of nickel and palladium.[134,135] Polymerization of bis(4-chlorophenyl)phenylphosphine oxide **188** leads to poly(arylene–phosphine oxide) with amorphous morphology and high molecular weight.[136]



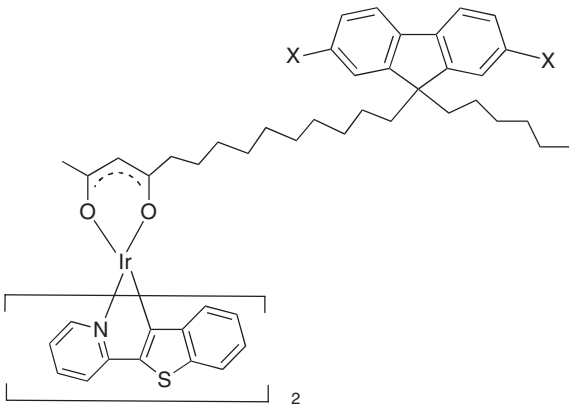
185



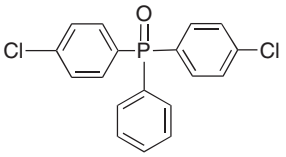
186

X = Br, I

R = 2-ethylhexyl, 2-hexyldecyl, dodecyl, hexadecyl

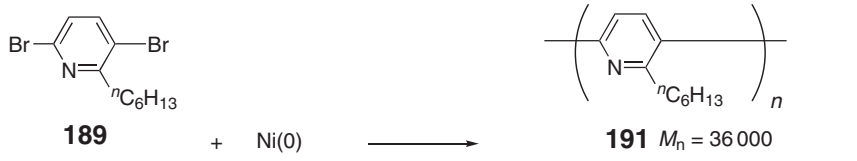


187



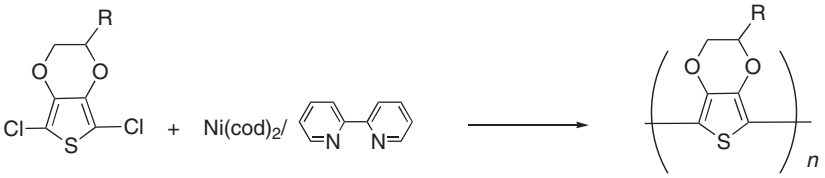
188

Dihalogenated heteroaromatic compounds are also applicable to the homocoupling polycondensation and actually do like carbocyclic analogs. Yamamoto extensively studied a wide range of five- and six-membered heteroaromatic compounds bearing oxygen, nitrogen, sulfur, and selenium atoms.[137,138] Dehalogenation–polycondensation of dibromopyridines **189** and dibromobipyridines **190** proceeds at 60 °C in excellent yields to afford π-conjugated polymers constituted of pyridine unit **191** and bipyridine unit **192**, respectively.[139] Molecular weight of both polymers **191** and **192** are 21 000–36 000. Pyridine derivatives bearing a hexyl group as a substituent give polymers of higher molecular weights. Dehalogenative polymerization of a thiophene derivative **193** also occurs similarly with a nickel complex.[140] Dehalogenative homocoupling of other heteroaromatic compounds also leads to the corresponding polymers **195–203** in a similar manner.[141–148]



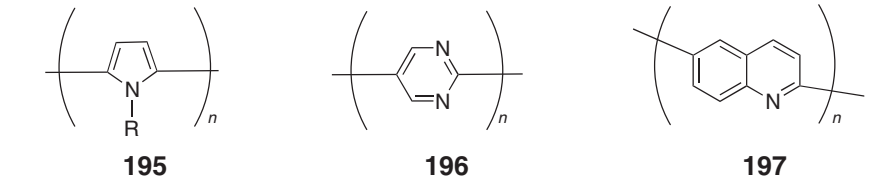
189 **191** M_n = 36 000

190 **192** M_n = 21 000

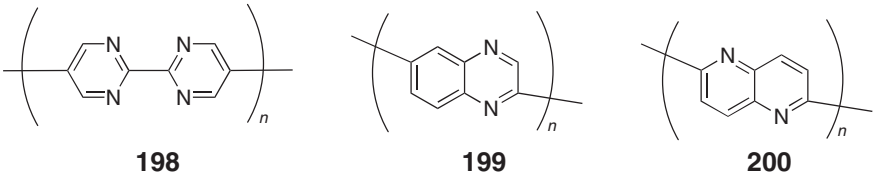


193 **194**

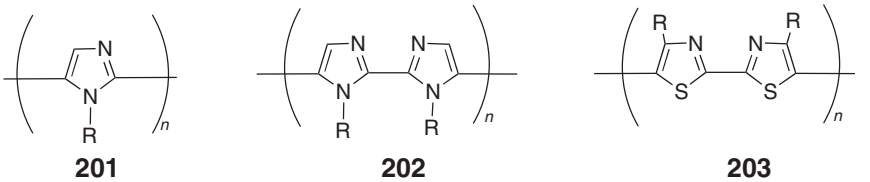
R	*Yield* (%)
H	82
nC_6H_{13}	90



195 **196** **197**



198 **199** **200**



201 **202** **203**

11.19.6 Summary

In summary, a variety of cross-coupling reactions, which have developed as synthetic organic reactions, are available for polymer synthesis with bifunctional metallic species and organic dihalides in the presence of a palladium or nickel catalyst. Most of the cross-coupling polymerizations afford π-conjugated polymers that are widely applicable to materials showing conductive, semi-conductive, photoluminescent, electroluminescent, and liquid crystalline characteristics. The cross-coupling methodology is highly effective for the synthesis of such materials, and an increasing number of polymers will be prepared by transition metal-catalyzed reactions in the future.

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11.20 Polymerization of Alkenes

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11.20.1 Introduction

Our literature search on alkene polymerization by transition metal catalysts yielded nearly 20,000 publications since 1993 even after the exclusion of the patents or patent applications, indicating a tremendous interest in this field. Three mutually interconnected trends were identified from the search.

The first trend shows that a great deal of research has been aimed at achieving a deeper understanding of the chemistry of group 4 metallocenes (Cp'_2MX_2) by taking advantage of their homogeneous and well-defined nature. This research has led to a rational interpretation of the relationship between catalyst/co-catalyst structures (static and dynamic) and polymerization characteristics for a wide range of monomers and polymerization reactions, and has thus increased opportunities for industrial applications.[1–4] Along with these fundamental studies, the group 4 metallocenes have expanded the scope of research into neighboring group 3 and 5 metallocenes and into other Cp-based ligands, that is, mono-Cp (which includes combination with a non-Cp ligand), linked Cp-amide or Cp-alkoxide ligands, etc.[5–8]

The second trend involves a re-evaluation of late transition metal catalysts, which have been industrially operational for C_8–C_{20} α-olefin synthesis since the early 1970s; this time, they are being studied as catalysts for high molecular weight polymers. The cationic α-diimine nickel or palladium catalysts developed by Brookhart and co-workers are able to polymerize ethylene and α-olefins into high molecular weight polymers that exhibit unique branched structures,[9] and these have brought late transition metals to the forefront of this field. Along these lines, highly active ethylene-polymerization catalysts based on metals from groups 8 and 9 (which have previously attracted little attention as polymerization catalysts) have now also been developed.[10,11]

The success of late metal catalysts, as well as those based on early transition metals with linked Cp–amide-based ligands,[7] invoked a renewed recognition of ancillary ligands, in that bis-Cp-based ligands or steric or electronic analogs of Cp ligands are not necessarily an essential qualification for high-performance catalysts. From this situation, a third trend has emerged: a thorough-going pursuit of early transition metal catalysts based on non-Cp ligands;[12,13] and this will obviously be included here.

This chapter does not intend to provide a complete collection of newly synthesized organometallic or coordination complexes for alkene polymerization, but rather aims to review a cross-section of transition metal catalysts from the viewpoint of polymers and polymerization reactions. We focus particularly on polymers that are difficult or virtually impossible to prepare using conventional catalysts. In this light, we narrow our attention to well-defined molecular catalysts, including a study of progress in the understanding of active species, reactive intermediates, and reaction mechanisms that are indispensable for the synthesis of such polymers.

11.20.2 Fundamental Understanding of Polymerization Mechanisms

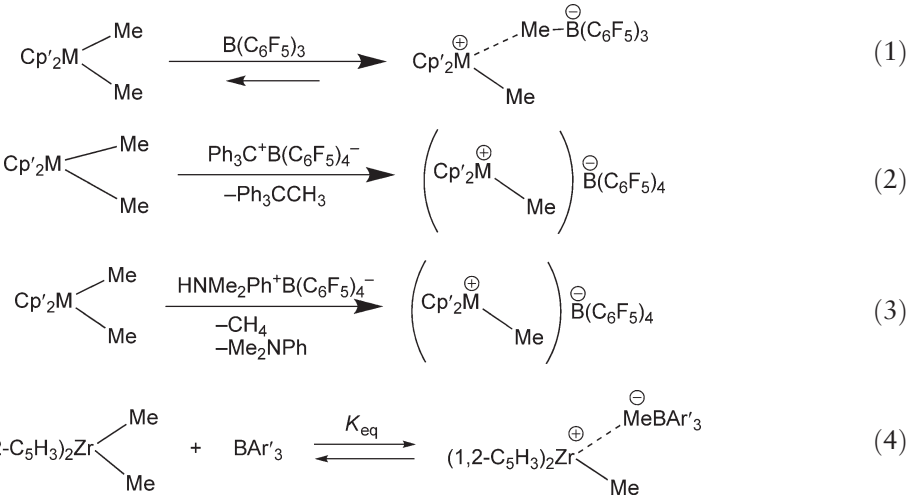
This section focuses on group 4 metallocenes, which have been the most widely and thoroughly investigated among the homogeneous alkene-polymerization catalysts. These will also serve as useful reference standards in the following discussions regarding non-metallocene catalysts.

11.20.2.1 Formation of Ion Pairs (Active Species)

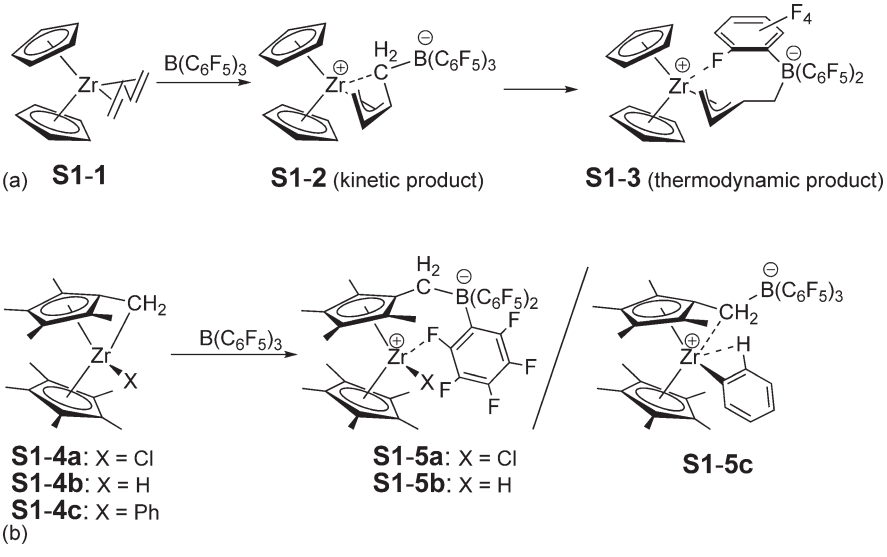
The discovery that highly active organometallic species for alkene polymerization can be generated *in situ* by treating neutral metallocene precursors with excess methylalumoxane (MAO) triggered off what has been referred to as the "metallocene revolution."[4,14] Instead of the rather "black-box" activation process with MAO, the well-defined stoichiometric activation of metallocene dialkyls (Cp'_2MR_2) with neutral or charged boron (sometimes aluminum or other metals) reagents, for example, $B(C_6F_5)_3$, $HNMe_2Ph^+B(C_6F_5)_4^-$, and $Ph_3C^+B(C_6F_5)_4^-$, were achieved later, providing compelling evidence that the active species are alkyl metal cations of the type Cp'_2M^+–R that are attended by weakly coordinating counteranions (Y^-) as a natural consequence.[1–4] This offered workable models for the active species and the intermediates in order to elucidate the reaction mechanism, as well as a number of practically important catalyst systems.

Activation takes place by heterolytic cleavage of M–R bonds via alkide (alkyl anion)/hydride abstraction or protonolysis (Equations (1–3)), or by one electron oxidation of M(III) to M(IV). When metallocene dihalide precursors (Cp'_2MX_2) have to be employed, alkylation of the precursors with R_3Al precedes alkide abstraction or protonolysis, which is probably also the case in the MAO activation of metallocene dihalides. Alkide abstraction by neutral boranes can be reversible, and the equilibrium lies far to the right when a strong Lewis acid is employed (Equation (4)). Thus, the equilibrium constant (K_{eq}) for $B(C_6F_5)_3$ is five orders of magnitude larger than that for $B(C_6F_5)_2(3,5\text{-}C_6H_3Me_2)$ in

the reaction with $(1,2\text{-}C_5H_3Me_2)_2ZrMe_2$, and the formation of ionic species is nearly quantitative for the former, while it is about 20% for the latter.[15]



The well-established chemistry of alkide abstraction by $B(C_6F_5)_3$ allows the facile synthesis of betaine-type complexes where the perfluoroarylborate counteranion is covalently attached to the metal cation via either a reactive alkyl group or an ancillary Cp ligand (Scheme 1).[16,17] For example, $B(C_6F_5)_3$ is added exclusively at a terminal CH_2 group on the diene ligand of (butadiene)metallocenes **S1-1** and related compounds, which results in formation of girdle-type betaine complexes: $Cp'_2M\{C_4H_6\text{–}B(C_6F_5)_3\}$ (Scheme 1(a)). Under kinetic control, (*Z*)-η^3-allyl-coordinated species **S1-2** are formed, which in most cases are isomerized into an (*E*)-η^3-allyl configuration **S1-3** under thermodynamic control. The zirconium metals in the former are chelated by the coordination of $CH_2B(C_6F_5)_3^-$, while those in the latter are stabilized by an M···F–C(aryl) interaction, for which the dissociation energy has been estimated to be ca. 8 kcal mol^{-1}.[16] Similarly, the so-called "tuck-in complexes," where a methyl group on a Cp′ ligand is intramolecularly metallated via C–H bond activation **S1-4**, generate a ring-type betaine complex upon treatment with $B(C_6F_5)_3$ (Scheme 1(b), **S1-5**).[17] These betaine complexes serve as active single-component alkene-polymerization catalysts. The incorporation of the borate as a bridging backbone in *ansa*-metallocenes or ring-tethered borates with different link lengths (no carbon or three carbons) requires different synthetic approaches.[17,18]



Scheme 1 Synthesis of betaine-type complexes.

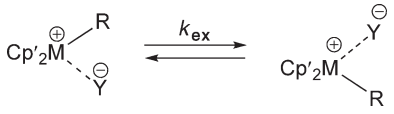
The second methyl group of the ion pair in $Cp'_2MMe(\mu\text{-}Me)B(C_6F_5)_3$ is not affected by an excess of $B(C_6F_5)_3$. Interestingly, 2 equiv. of $Al(C_6F_5)_3$ affords dicationic complexes with *ansa*-metallocenes or constrained-geometry catalysts, for example, $Me_2Si(Me_4C_5)(^tBuN)Ti\{\mu\text{-}MeAl(C_6F_5)_3\}_2$ and $Me_2Si(Ind)_2Zr\{\mu\text{-}MeAl(C_6F_5)_3\}_2$, which exhibit higher polymerization activity than the monocationic species derived from $B(C_6F_5)_3$ and $Al(C_6F_5)_3$.[19,20]

11.20.2.2 Nature of Ion Pairs

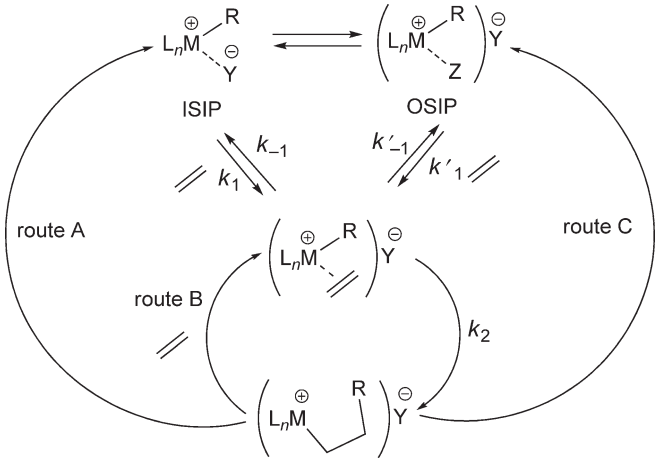
Although the cation–anion interaction of metallocenium ions is very weak, the counteranion is likely to remain in proximity with the metal cation to form a contact ion pair in low-permittivity solvents such as toluene (commonly used in polymerization reactions). If the metal cation allows the counteranion to penetrate into the first coordination sphere, it can form an inner-sphere ion pair (ISIP). When the counteranion is relegated to the second coordinating sphere, the ion pair becomes an outer-sphere ion pair (OSIP), which is more ionic in nature than ISIPs.[21] A schematic representation of the relationship between ISIPs and OSIPs is depicted in Scheme 2. This simple scheme shows us the principal elements that affect the cation–anion interactions (e.g., counteranion (Y^-), ancillary ligands (L_n), transition metal (M), and alkyl ligand (R)), and the subtle balance between these elements in the dynamic equilibria.

11.20.2.2.1 A latent vacant site in ISIPs and OSIPs

In typical examples of ISIPs such as $Cp'_2M\text{–}Me^+(\mu\text{-}Me)B(C_6F_5)_3^-$, the M···Me–B bridge intrudes into the first coordination sphere, in which case an elongated distance between M and the bridging Me and relatively normal Me–B and M–Me (terminal) bond lengths have been observed.[3,22] These findings indicate that the interaction is essentially electrostatic, and also has some coordinative character. In ion pairs of the type $[Cp'_2M\text{–}Me^+(\mu\text{-}F)Al(2\text{-}C_6F_5C_6F_4)_3^-]$, an even stronger M···F–Al interaction was found.[3,23] A latent vacant coordination site on the transition metal (M) for alkene binding and subsequent chain-migratory insertion of the alkene into a neighboring M–C bond is thus occupied by the counteranion in ISIPs. The strength of the ion pairing can be measured by the rate of the alkyl group side-exchange (k_{ex}), because the interaction must be at least weakened, if not completely dissociated, for the R group to move laterally from one side to the other (Equation (5)).[3,15,24] NMR studies of the alkyl exchange process have been extensively applied to many catalytic systems, and provide a quantitative measure of the cation–anion interactions.



(5)



Scheme 2 A conceptual model for propagation reactions mediated by ionic species.

Even though the counteranion is out of the first coordination sphere, the vacant site in OSIPs is not necessarily left unoccupied but rather stabilized inter- or intramolecularly by neutral nucleophiles or nucleophilic parts in the media (represented as *Z* in Scheme 2) to compensate for the electron deficiency and coordinative unsaturation (*vide infra*).

11.20.2.2.2 Counteranion (Y^-) and alternative stabilization (Z)

Since a positive correlation between the electrophilicity of the active sites and ethylene-polymerization activity can be expected and has actually been observed in a metallocene activated with homologous perfluoroarylboranes,[3,15] counteranions that are sterically and electronically less coordinative have been pursued in order to render the active species more electrophilic. To this end, many sterically encumbered activators incorporating extended conjugation systems based on perfluoroaryl groups have been developed, as shown in Figure 1.[3,25–44] It is rarely possible for most of the counteranions derived from these activators to enter the first coordination sphere of the metal cation to form

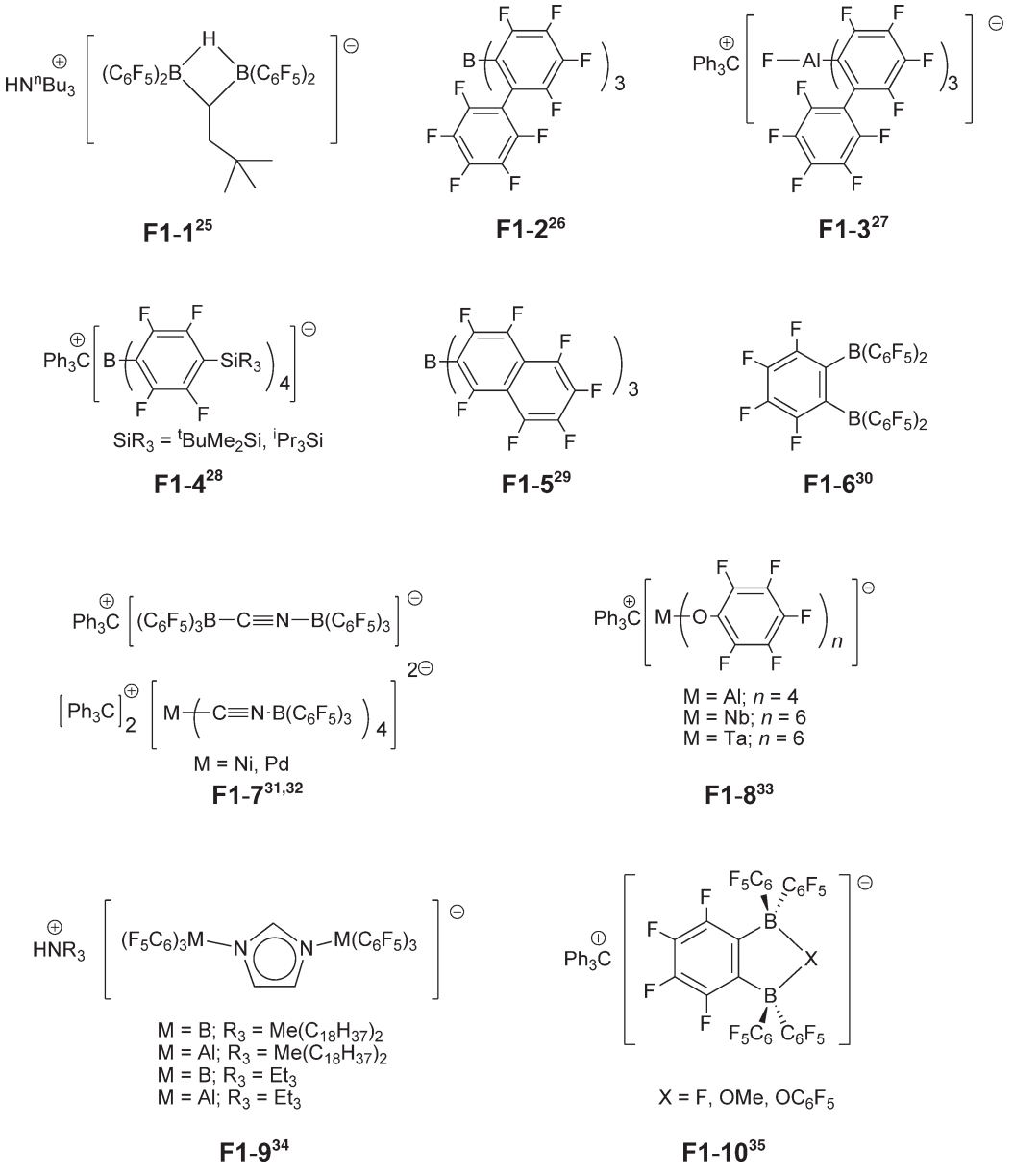


Figure 1 Co-catalysts for transition metal-catalyzed alkene polymerization.

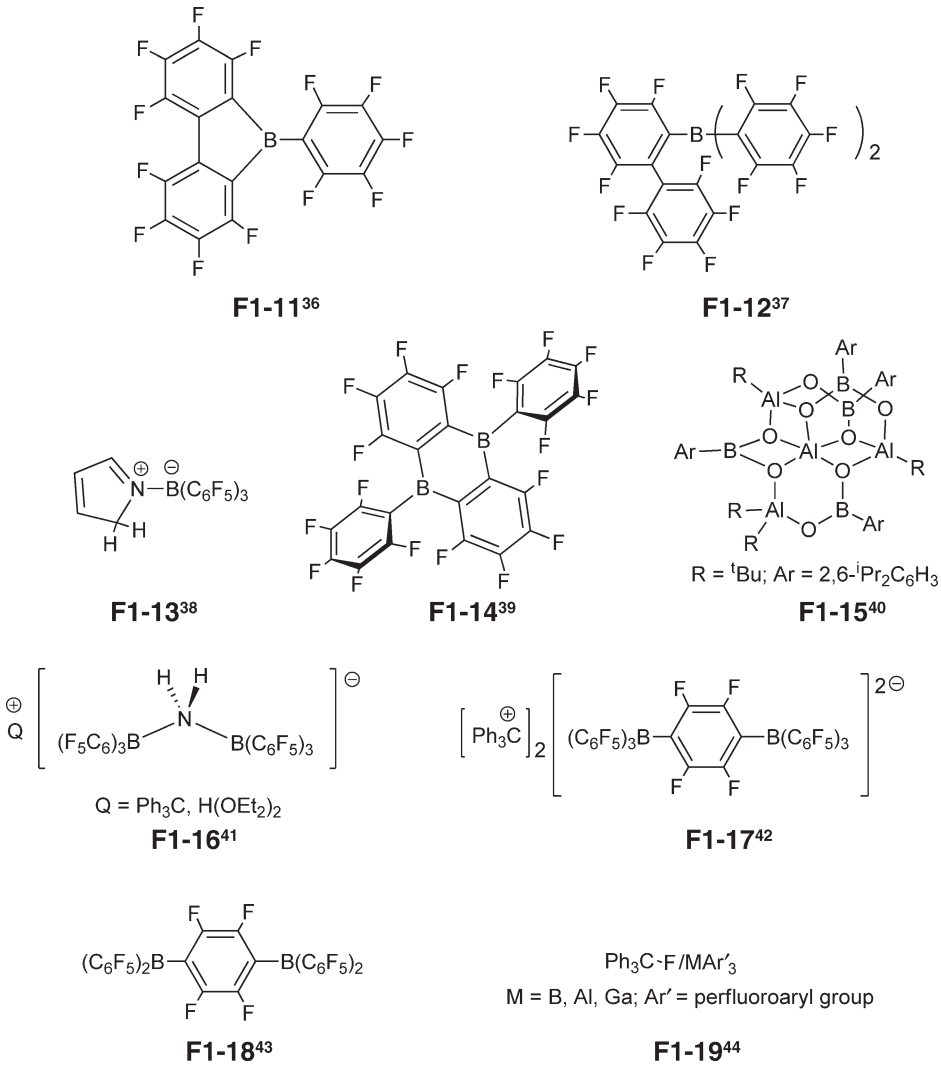


Figure 1 (*Continued*)

ISIPs, except for those cases where a dissociative transfer of the nucleophilic portion of the counteranion (e.g., $C_6F_5^-$, $OC_6F_5^-$, F^-) results in a neutral deactivated species.[3,45]

Alternative stabilizing forces (*Z*) include: (i) complexation with metal alkyls (or hydrides), forming hetero- and homodinuclear complexes such as $[Cp'_2M–(\mu\text{-}Me)_2AlMe_2]^+Y^-$ and $[(Cp'_2M–Me)_2(\mu\text{-}Me)]^+Y^-$ (Figure 2);[46–48] (ii) π-coordination of aromatic molecules, which is often observed for sterically open metal cations;[1,3] (iii) agostic interactions, M···H–C;[49] (iv) η^2- or higher η^n-coordination of benzyl groups;[1,3] (v) weak contact of the peripheral fluorine atoms of perfluoroarylborates;[1,3,16,47] and (vi) π-bonding with alkenes (Section 11.20.2.3). These interactions with Z can vary in strength from irreversible deactivation to the formation of dormant species that are only occasionally reactivated to an extent that provides only a minimum stabilizing effect for otherwise unstable cationic species.

Figure 2 Hetero- and homodinuclear complexes of metallocenes.

11.20.2.2.3 Ancillary ligand (L_n) and alkyl ligand (R)

Ancillary ligation also enhances cation–anion separation by estranging the counteranions by the introduction of bulky protecting substituents or by stabilizing the cation with more electron-donating ligands. In many alkene polymerizations, the insertion of the first alkene into an M–Me bond is much slower than the second or subsequent insertions,[50,51] because after the first monomer is inserted, R becomes sterically much more obstructive than Me, which precludes or retards the formation of ISIPs or dinuclear complexes to act as a possible dormant species (see above). This was actually confirmed by investigating a series of complexes that contained R groups of varying steric presence, for example, Me, CH_2CMe_3, CH_2SiMe_3, $CH(SiMe_3)_2$. Alkyl exchange was significantly facilitated in the same order, indicating more separated ion pairs for bulky R groups.[52] There is some argument over the dormancy of species with sterically crowding secondary alkyl R groups that are formed via the secondary insertion of α-olefins. This will be discussed in the next section.

It should be emphasized here that the ion pairing is sensitive to and relative to the steric and electronic characteristics of both the cation and anion components. This is the reason why structural matching must be attained for specific cations and anions to exercise their maximum performance.[3]

11.20.2.2.4 Solvent and concentration

Solvent polarity has a significant impact on the nature of ion pairing. The large acceleration of polymerization activity that is sometimes observed in halogenated solvents can be attributed to enhanced ion separation in more polar media, and to possible weak coordination of the solvent to the metal cation.[3,53]

Recently, the formation of ion quadruples or higher aggregates has been reported for many OSIPs, and it is suggested that such aggregation could significantly facilitate the above-mentioned alkyl exchange process.[54] This observation argues the validity of a theory that was developed on the basis of a discrete ion pair. Recent studies have established the view that the formation of aggregates is concentration dependent, and that substantial numbers of ion aggregates are present in OSIPs at concentrations that are relatively low (but still much higher than real polymerization conditions) above ca. 0.5 mM, whereas aggregates are not important for ISIPs, even at 10–20 mM.[55,56] Therefore, under typical polymerization conditions, the active species are likely to behave as discrete ions.

11.20.2.3 Alkene Coordination and Insertion

As intuitively deduced, coordinating Y^- and Z must be removed or displaced in order for alkenes to coordinate and form an alkene π-complex (Scheme 2). Since these intermediates, $Cp'_2MR(alkene)^+$, have never been observed in any detectable amounts for early transition metal-mediated polymerization, several chelate model systems have been devised (Figure 3).

Upon treatment with $B(C_6F_5)_3$, metallocene alkoxides of the type $Cp_2ZrMe(OCMe_2(CH_2)_nCH{=}CH_2)$ ($n = 1, 2, 3$) exhibited internal chelate coordination of the vinyl groups that competed with $MeB(C_6F_5)_3^-$ coordination, the relative strength of which depended on the length n of the methylene spacer (**F3-1**).[57] A similar system was assembled by using the neutral d^0-yttrium(III) complex, $(C_5Me_5)_2Y(CH_2CH_2C(R)_2CH{=}CH_2)$ (R = H, Me, **F3-2**), derived from the corresponding hydride and dienes.[58,59] Another intramolecular model was based on the aforementioned metallocene betaine systems.[16] $Cp'_2M(C_4H_6B(C_6F_5)_3)$ derived from Cp'_2M(butadiene) and $B(C_6F_5)_3$ allows the observation of mono-alkene insertion products **F3-3** at low temperature and enables the direct estimation of the energy profile of alkene association (k_1)/dissociation (k_{-1}) to a cationic metal and the insertion of the alkene into a metal–carbon bond (k_2) (see Scheme 2). A variety of betaine systems demonstrate a reaction profile whereby metal–alkene coordination pre-equilibrium precedes the insertion event by ca. 1–3 kcal mol^{-1} of energy difference. This indicates that dissociation of the alkene from the assumed alkene-coordinated intermediate is 3–80 times faster than the insertion of the alkene. The kinetic isotope effect (KIE) of C_1 to C_4 in 1-hexene was determined by Landis and co-workers with various counteranions. Irrespective of the counteranions that are used, KIE always exists at C_1 and C_2 ($KIE(C_2) \sim 1.02$; $KIE(C_1) \sim 1.01$), whereas no KIE is observed for C_3 and C_4, implying a pre-equilibrium state for monomer coordination and an irreversible chain-migratory insertion at C_2.[60] A dimethyl(allyl)silyl group attached to the Cp ring is also intramolecularly coordinated to the Zr cationic species **F3-8**.[61] Alkyl cationic zirconocenes where pendant alkenyl groups are tethered to metal were also prepared by research groups of Casey[62,63] and Bercaw[64](**F3-5** and **F3-7**). Recently, non-chelating alkene π-complexes were also developed by Jordan and Stoebenau (**F3-4** and **F3-6**).[65,66] Significant polarization of the vinyl groups was observed for all of the alkene π-complexes mentioned above, indicating the non-symmetric coordination of the alkene.

The displacement of $MeB(C_6F_5)_3^-$ from various zirconocene cations by weak bases (dibutyl ether, Me_2NPh, Me_2NCH_2Ph, etc.) was examined on the assumption that this process might mimic anion displacement by alkenes.

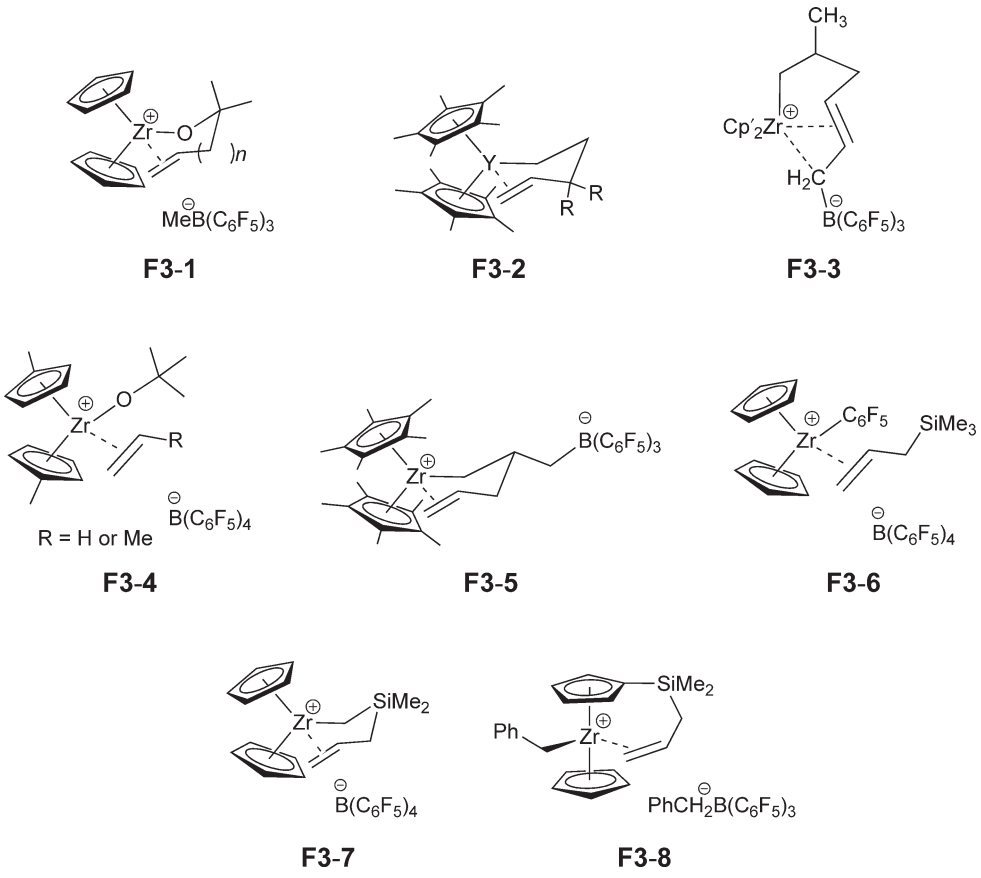
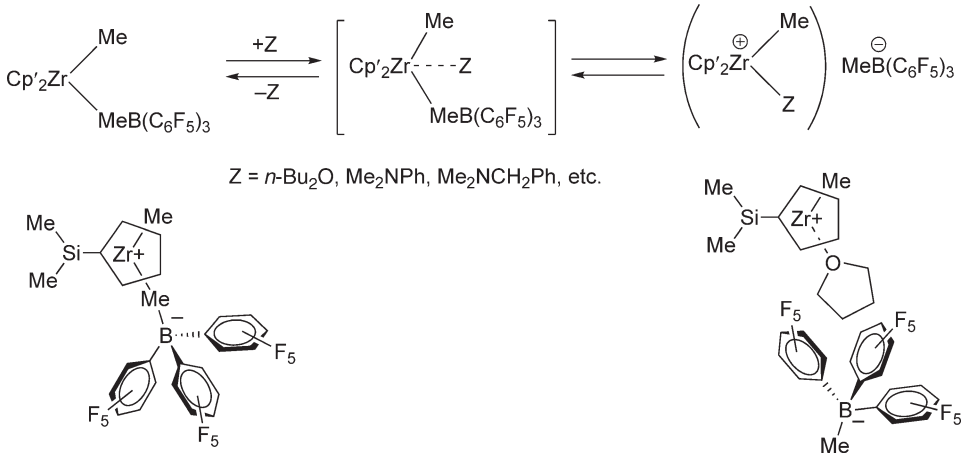


Figure 3 Examples of alkene π-complexes of metallocenes.

This reversible substitution was found to take place in an associative manner, probably via a five-coordinated intermediate and so the donor coordinates at a site that a counteranion has vacated (Scheme 3).[67] The solution structures of various ion pairs were investigated by NOE NMR experiments. An M···Me–B bridge structure similar to the solid-state structure was maintained for an ISIP in solution, while in the case of a base-coordinated OSIP, the counteranion was located on average at the side of the coordinated donor, opposite to the Zr–Me moiety and shifted slightly toward Me_2Si bridge, with the Me–B group pointed away from the zirconium cation, as illustrated in Scheme 3.[55]



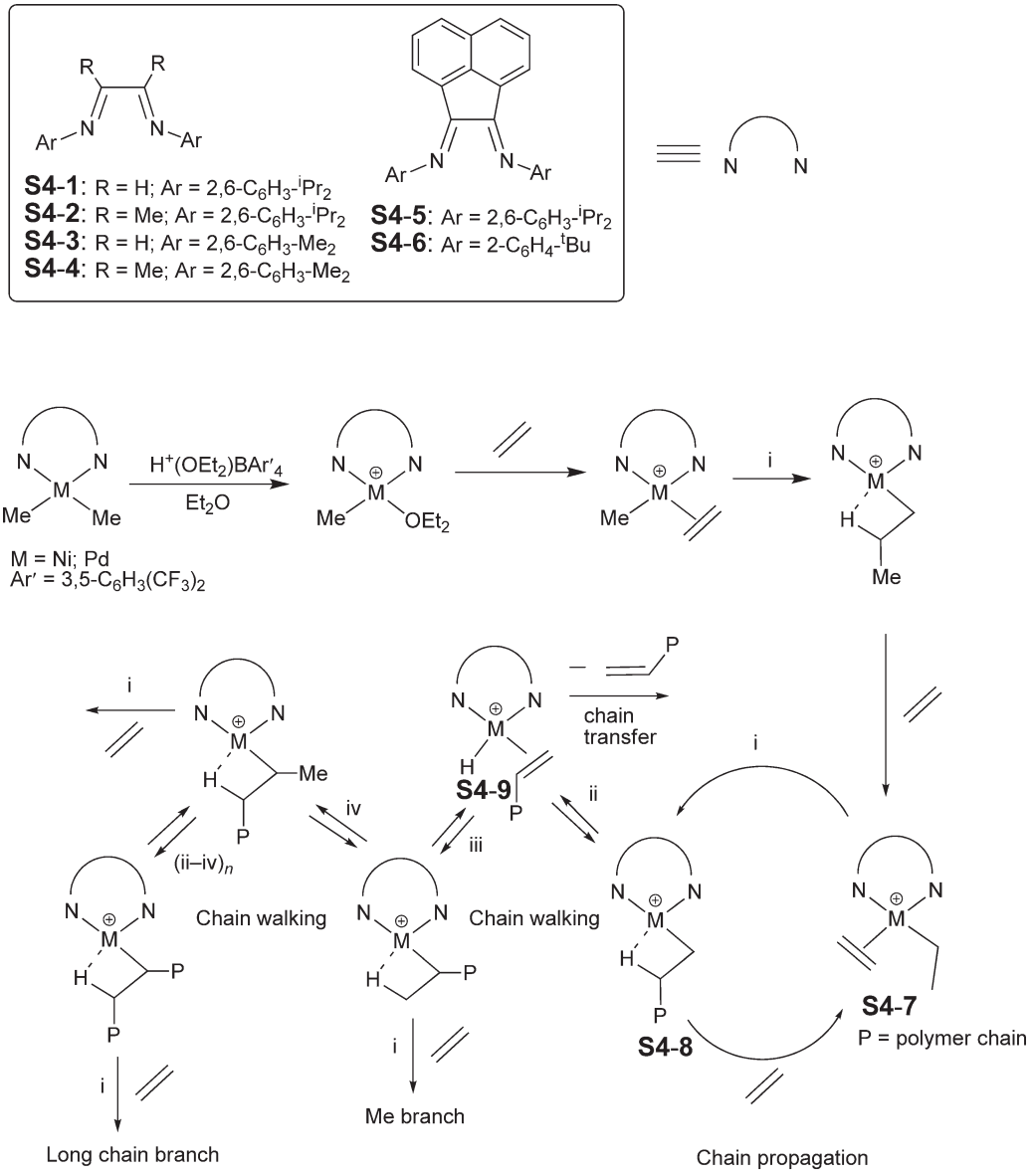
Scheme 3 A course of counteranion displacement with base.

The insertion of a coordinated alkene can be facilitated by α-agostic interaction,[68] evidenced by isotopic labeling experiments.[49] In the case of propylene polymerization with some *ansa*-metallocenes, the kinetic isotope effects at the α-position for the propagation reaction ($k_p(H)/k_p(D)$) were estimated at ~1.3.[69] Representative issues to be considered in propagation reactions are: (i) the reaction order in metal centers and in monomers, (ii) the nature of the dormant states, (iii) continuous versus intermittent propagation, and (iv) the participation of counteranions in (stereoselective) chain growth. The reaction orders with respect to the monomers are estimated sometimes to be ca. 1, which is in accord with the proposed propagation scheme, but are sometimes found to be >1.[70,76] This larger dependence on the monomer concentration is interpreted as being due to the distribution of active species equilibrated between catalytically active states and dormant states, rather than by the involvement of the second monomer in the transition state.[70] More than 90% of the active species have been estimated to be in dormant states by hydro-oligomerization,[71] microstructural analysis,[72] and by quenched-flow techniques.[73] With regard to the nature of the dormant states in propylene polymerization, many experiments suggest that sterically more demanding 2,1-mis-inserted secondary alkyl metal species exhibit lower reactivity to subsequent insertion than normal primary alkyl metal species.[74,75] However, other species discussed in Section 11.20.2.2.2 may also serve as a dormant species.[76] For example, *in situ* NMR observations of propylene propagation or quenched-flow kinetics and active site counting of 1-hexene polymerization exhibited no accumulation of such species.[77,78] The same group even proved that an α-branched secondary alkyl metal species of the type *rac*-(C_2H_4)(1-Ind)ZrCHCH$_3$CH$_2$CH$_3$(μ-Me)B$(C_6F_5)_3$ could exhibit higher reactivity toward ethylene, propylene, and hydrogen than the corresponding primary alkyl metal species.[79] Whether continuous or intermittent propagation prevails in a polymerization depends on the relative rate of monomer insertion to counteranion (Y^-) reassociation. In continuous propagation models, every insertion is interrupted by the reassociation of Y^- (route A in Scheme 2). In the case of the intermittent models, very rapid multiple insertions are only occasionally interrupted by Y^- coordination (routes B and A in Scheme 2). Brintzinger and co-workers suggested the intermittent model because the estimated rates of counteranion displacement by weak bases are very slow relative to the propagation rate,[67] while in the NMR experiments conducted by Landis and co-workers, 1-hexene polymerization with *rac*-$(C_2H_4)(1\text{-Ind})_2ZrR$ was strictly continuous.[79] Bochmann and co-workers found that propylene polymerization is more anion dependent than 1-hexene polymerization, which implies that monomer coordination is a rate-determining step for propylene, whereas chain-migratory insertion is more important for 1-hexene.[80] The kinetics of the propagation reaction are complicated by many factors, such as side-reactions that take place concurrently at the active site, the induction period, stereo-/regio-errors for α-olefin enchainments, the complex equilibria that are involved in these reactions, and by disturbances such as local mass and heat-diffusion limitation, and the results for particular metallocenes under particular conditions cannot be extended to a generalized condition as yet.

11.20.2.4 Polymerization Mechanisms of (α-Diimine)Ni and Pd Catalysts

In 1995, Brookhart and co-workers reported that group 10 catalysts bearing aryl-substituted α-diimine ligands could polymerize ethylene, α-olefins, cyclic olefins, and internal olefins into high molecular weight polymers with high activity.[9,81] Similar to group 4 metallocenes, catalyst precursors can be activated by appropriate cocatalysts (MAO, borates) to form cationic alkyl metal species. However, in contrast to group 4 metallocenes, low-temperature NMR experiments allowed the detection of an alkyl–ethylene complex as the resting state of the polymerization reaction (Scheme 4, **S4-7**).[82,83] Chain-migratory insertion of the coordinating ethylene into the M–C bond is the rate-determining step, resulting in zero-order chain growth in ethylene. After insertion, the metal alkyl intermediates are stabilized by β-agostic interactions **S4-8**, from which two reaction pathways are possible. If another ethylene molecule displaces the agostic interaction and is inserted, then linear polyethylene chain growth results, while if the agostic metal alkyl species undergo β-hydride elimination, olefin hydride intermediates **S4-9** are formed. Since β-hydride elimination is quite competitive with ethylene insertion in late transition metal catalysis, dissociation of the olefin typically leads to the formation of oligomers. In the case of α-diimine ligands, a key catalyst design to circumvent this situation involves the *ortho*-substitution of bulky aryl groups, which are located at positions axial to the square plane. These substituents effectively destabilize a hypothetical five-coordinate bis-olefin–hydride species, which can be an intermediate leading either to associative olefin displacement by ethylene monomers, or to direct chain transfer to ethylene monomers. Thus, the olefin of the olefin–hydride species will not dissociate easily, but rather reinsert into the metal hydride. Reinsertion with opposite regiochemistry results in a 1,2-shift of the metal along the alkyl backbone, which is again trapped as a β-agostic alkyl species. The β-agostic alkyl species can isomerize into another β-agostic alkyl species through rotation about the M–C bond if different β-carbon(s) are available. A repetitive sequence of β-H elimination/reinsertion/M–C bond rotation allows the metal to migrate back

and forth along the polymer chain (chain walking). The combination of these two mechanisms, chain migratory insertion and chain walking, leads to unique branched structures in the resulting polyethylene, which is discussed in the following section. In general, Ni catalysts exhibit higher activity than their Pd counterparts. Bulkier *ortho*-substituents on the aryl group lead to higher molecular weight polymers, in accord with the mechanism mentioned above, and also to higher polymerization activity due to an increase in the ground-state energy (the resting state) rather than a lowering of the energy of the transition state for migratory insertion. The less oxophilic character of late transition metals has offered an extraordinary opportunity for introducing polar monomers into non-polar polyolefin backbones by means of direct co-polymerization,[84] which will be discussed in Section 11.20.4.5.1.



Scheme 4 Initiation, propagation, chain-transfer, and chain-walking reactions in ethylene polymerization catalyzed with group 10 α-diimine catalysts.

11.20.3 Unprecedented Control Over Ethylene and α-Olefin Polymerization

11.20.3.1 Branched Structure

The introduction of branching into linear polymers has significant consequences for their polymer properties (toughness, strength, processability, etc.). Controlling the branch structures (length, frequency, topology, etc.) is thus important for obtaining polymers for particular applications. Polyethylene produced by radical polymerization under high pressure and high temperature contains many ethyl and butyl branches, as well as long chain branches (LCBs) that impart high melt strength and good processability (low density polyethylene: LDPE). Coordination catalysts generally afford linear polyethylene (high density PE: HDPE) and branches are introduced by co-polymerization with added α-olefins, typically C_4–C_8 (linear low density PE: LLDPE). These ethylene-based co-polymers were in fact the first arena where single-site metallocene catalysts could maximize their industrial potential against the traditional heterogeneous catalysts, because the single-site catalysts produce polymers that have narrow distributions of molecular weight and co-monomer composition. On the other hand, the conventional multi-site catalysts often give broad molecular weight distributions and a mixture of extensively branched shorter chains (sticky, reduced strength) and less-branched longer chains (crystalline, brittle). However, although a narrower molecular weight distribution contributes to the strength of the polymer, it is sometimes problematic from the viewpoint of processability. A new family of catalysts that have a linked Cp–amido ligand, for typical example, $Me_2Si(Me_4C_5)(^tBuN)MX_2$, has been developed by Bercaw (M = Sc),[85] Okuda (M = Ti),[86] and by Dow and Exxon (M = group 4 metal).[8] The structure of the Cp–amido complexes is best described by their sterically open nature, which allows higher co-monomer uptake in ethylene/α-olefin co-polymerization. Ethylene is typically one or two orders of magnitude more reactive relative to more sterically demanding α-olefins, which can be narrowed up to ca. 4 (vs. 1-octene) for the Cp–amido Ti complexes.[87] Moreover, by virtue of their open-ligand framework, a small but considerable level of LCB is incorporated, presumably through the reinsertion of *in situ*-generated vinyl-terminated macromers, which significantly improves the polymer processability despite the narrow molecular weight distribution of the polymers. Higher α-olefin incorporation often leads to reduction in polymer molecular weight because of an increased propensity for chain transfers via β-elimination, while this catalyst can even produce high molecular weight polymers at elevated temperature; as high as 160 °C for solution polymerization. These Cp–amido catalysts also exhibit the expanded scope of co-monomers such as cyclic olefins (Section 11.20.4.1), styrene and its derivatives (Section 11.20.4.2), isobutene, etc., due to their sterically open-ligand framework. All of these characteristics have made the Cp–amide-based catalysts one of the most important classes of catalysts for the production of ethylene-based co-polymers.

Alternative attempts have been made to prepare LLDPE by means of tandem catalysis, where one catalyst generates the co-monomer α-olefins and the other catalyst co-polymerizes them with ethylene to construct main chains from the same ethylene feed.[88] There are, however, long-standing challenges that still affect tandem polymerization. It is generally difficult to find appropriate reaction conditions for both catalysts to work at high efficiency, and moreover, to quantitatively incorporate the α-olefins into the co-polymer in order to obtain a narrow molecular weight distribution. The advent of metallocenes and Cp–amido complexes that possess an excellent aptitude for α-olefin uptake requires the development of matching oligomerization catalysts as partners for tandem catalysis. Recent progress in versatile, diverse, well-defined single-site catalysts has yielded just such oligomerization catalysts (Figure 4, see also Section 11.20.3.5). These catalysts, in conjunction with metallocenes or Cp–amido complexes, can produce LLDPE in which the branch number can be controlled to some extent by the molar ratio of each catalyst component.[89–91] The applicable catalyst molar ratio is often limited when MAO is employed as a co-catalyst, because the ratio of aluminum to transition metal must be kept within a certain range in order for each catalysts to show sufficient activity or to avoid catalyst decomposition. Well-defined single-component catalysts eliminate this problem, providing, in principle, a wider and more straightforward control over polymer properties.[92,93] Such catalysts have enabled even triple tandem catalysis, where a high-throughput screening method was implemented to find the optimized conditions.[88,93]

Another conceptually similar but possibly more efficient approach is the development of multinuclear catalysts. Conventional tandem catalysis is basically an intermolecular process that typically needs to work at very low catalyst/substrate concentrations, while if multiple catalytic sites are spatially situated in proximity, cooperative intramolecular processes might be envisioned. Marks and co-workers investigated nuclearity effects in a series of binuclear complexes and binuclear co-catalysts (**Zr_2** and **B_2**: Figure 5).[42] A significant increase in the number of branches (ethyl ≫ butyl > longer) and in co-monomer uptake (1-hexene, 1-pentane), and in polymer molecular weights were observed in the order of $\mathbf{Zr_2/B_2} > 2\mathbf{Zr_1/B_2} > \mathbf{Zr_2}/2\mathbf{B_1} > 2\mathbf{Zr_1}/2\mathbf{B_1}$ during ethylene (co)polymerizations. The time

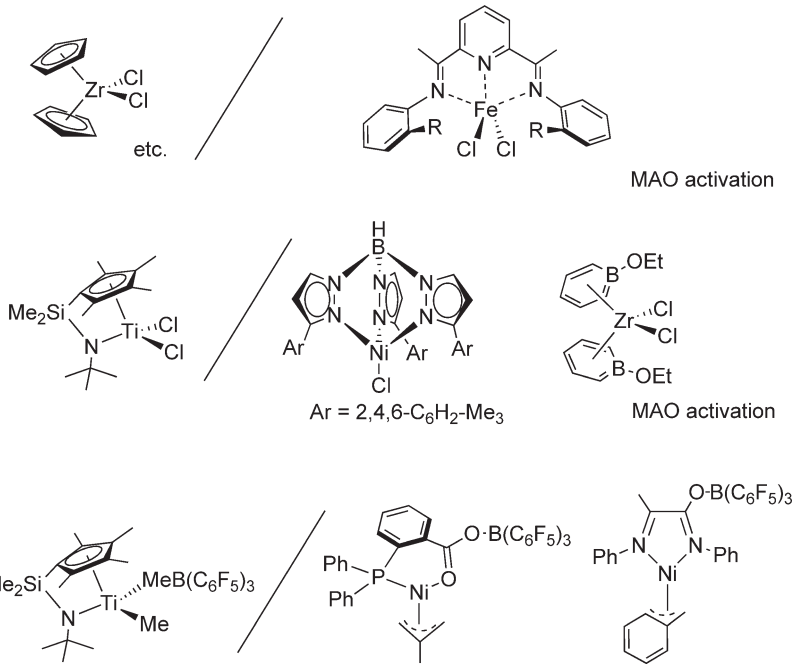


Figure 4 Tandem polymerization catalysts for the preparation of branched polyethylenes.

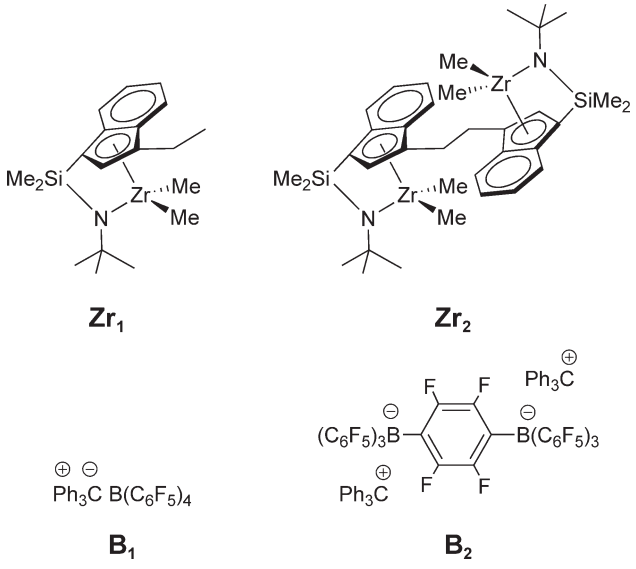
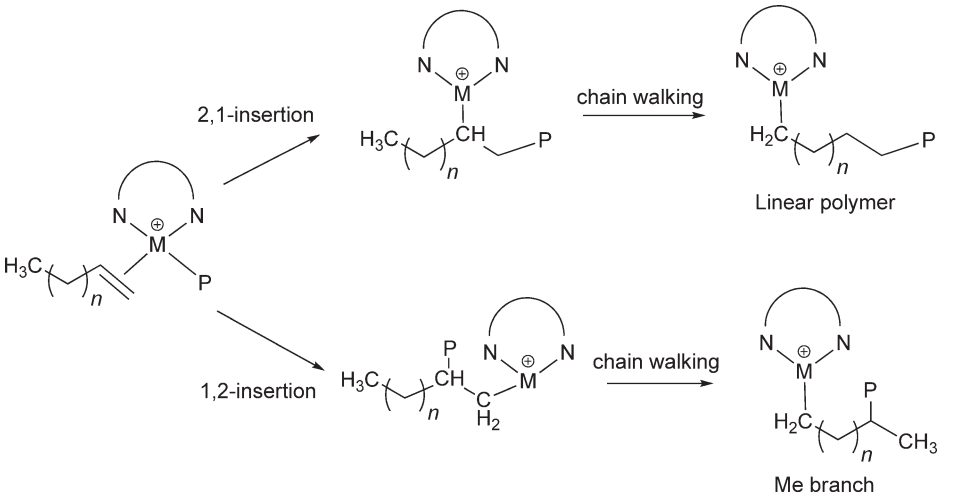


Figure 5 Mono- and binuclear catalysts and co-catalysts.

evolution of the ethyl-branch formation indicates very high branch numbers, even in the early stages of the reaction, which strongly suggests an intramolecular process. The authors proposed that a reaction pocket consisting of two metal centers binds the olefin substrates (presumably by agostic interactions) and thereby facilitates olefin insertion. The titanium version of this binuclear complex exhibits similar enhancement of co-monomer enchainment for 1-octene, styrene, and isobutene (a least reactive co-monomer), and, as a result of the inherent nature of the Ti complex, produces higher molecular weight polymers with higher polymerization activity than the Zr counterparts.[43] Heterobinuclear catalysts were also realized by covalent[94] and electrostatic[95] bonding strategies, demonstrating the effective formation of LCB relative to the mononuclear complexes.



Scheme 5 Polymerization of α-olefins with group 10 α-diimine catalysts.

A branched structure was also attained from a single monomer feed by the above-mentioned (α-diimine) group 10 complexes through a chain walking mechanism (Scheme 4).[9] Because chain walking is a unimolecular process and alkene coordination/insertion is a bimolecular process, the number of branches and/or the polymer topology is sensitive to both monomer concentration and polymerization temperature. As the monomer concentration (pressure) increases, fewer branches are formed for Ni complexes. The branch number with Pd complexes is independent of ethylene pressure, but the appearance of polymers is significantly affected, reflecting a different polymer topology. The higher polymerization temperature favors unimolecular chain walking, thus resulting in more branched structures. Pd complexes generally afford more extensively branched structures, even forming branches-on-branches (hyperbranches) due to their higher insertion barriers and lower 1,2-shift barriers relative to Ni complexes. The polymerization of α-olefins with this class of catalyst yields structures that are less branched than expected due to chain-straightening mechanisms, which stem from the rather slow (in the case of Ni) to the "hardly possible" (for Pd) α-olefin insertion into the secondary alkyl metal species. This allows the metal to walk along the polymer chain to locate a primary carbon (M–CH_2R) or, more preferably, to find a primary carbon adjacent to another primary carbon (M–CH_2CH_2R) before the next monomer insertion (Scheme 5). Thus, in the case of linear α-olefin polymerization, the metal tends to walk through to the end of a pendant side-chain, forming consecutive methylene groups in the main chain.

11.20.3.2 Stereoregular Polymerization

11.20.3.2.1 General considerations

The basic mechanisms for the stereoregular polymerization of α-olefins have been described in many previous reviews;[2,76,96] therefore, will only be briefly mentioned here. There are four possibilities, composed of 2×2 elements, for α-olefin insertion into the M–R bond, that is, primary (1,2-) or secondary (2,1-) insertion and identical (*meso*-dyad, *m*) or opposite (*racemo*-dyad, *r*) stereochemical configurations relative to that of the last-inserted monomer unit. Two general mechanisms can be distinguished from the microstructural analysis of polymers. Chain-end control has its chiral source at the asymmetric carbon of the last-inserted monomer unit of a growing polymer chain, causing *r*-defects for mis-insertions in isoselective propagation, while chirality elements under site control exist in the ligand/metal fragment of the catalyst. Therefore, consecutive isotactic sequences are disrupted by *rr*-defects under site control. In the case of site-controlled, 1,2-monomer enchainments, which are the case with heterogeneous Ziegler–Natta catalysts or most of the stereoselective metallocene catalysts, stereochemical information is relayed from the catalyst chirality to the confined C_α–C_β bond orientation of the growing polymer chain, possibly with the aid of α-agostic interaction,[49,69] and finally to incoming propylene as a non-bonded interaction between the Me group of the propylene and the C_α–C_β bond. In the rigid frameworks of C_2-, C_s-, and C_1-symmetric *ansa*-metallocenes, the X–M–X wedge (latent active site) becomes homotopic, enantiotopic, or diastereotopic, respectively (Figure 6). Homotopic active sites provide identical steric environments for both R–M–(olefin) and (olefin)–M–R intermediates, and thus

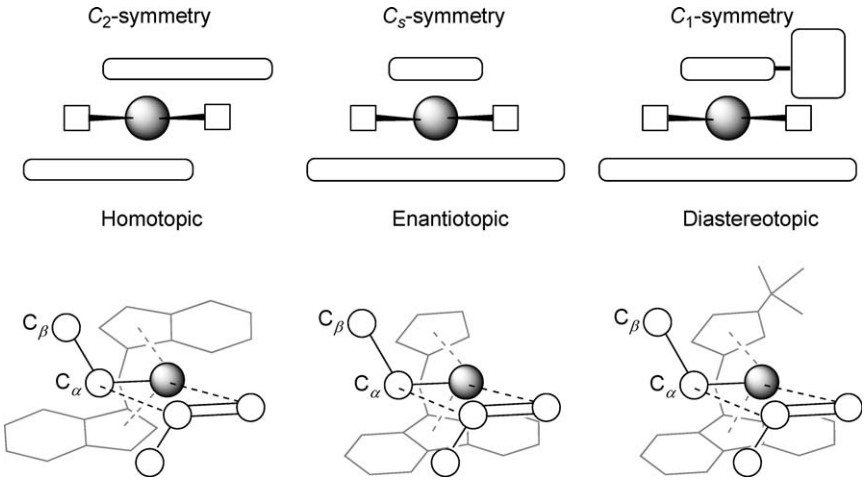


Figure 6 Relationship between catalyst symmetry and transition states of chain-migratory insertion of propylene monomer.

have a good chance of forming isotactic polymers. Likewise, in a framework of C_s symmetry, R–M–(olefin) and (olefin)–M–R are enantiomers of each other in which selectivity alternates between each side, potentially generating syndiotactic polymers.

With these principles in mind, and the technological progress of well-characterized single-site catalysts in hand, catalyst design at the molecular level for stereoregular polymerization has become a reality.

11.20.3.2.2 Isoselective metallocenes

Archetypal C_2-symmetric *ansa*-metallocenes such as *rac*-$(C_2H_4)(1\text{-Ind})_2ZrCl_2$ have improved their isoselectivity by ligand modification, basically aimed at attaining structural rigidity to avoid deformation from symmetry and to strengthen the particular polymer-chain orientation. To this end, the general motif of these highly isoselective complexes is that they change into structures having shorter Me_2Si-bridged Cp rings with relatively small substituents at the α-position and with very large substituents at the β-position *trans* to the α-substituents as illustrated in Figure 7(a).[97–101] This is most typically embodied by the highly isoselective *rac*-zirconocenes that have bis(2-alkyl- and 4-aryl-substituted indenyl) groups, which were developed by Spaleck and co-workers.[102] As demonstrated by Brintzinger and co-workers, the α-substituents also reduce regioerrors and β-H transfer to a coordinating monomer, and thus significantly increase polymer molecular weight.[103] When the two β-positions have similar steric environments, such as in the case of 3-Me-indenyl (Figure 7(b)), then isoselectivity is significantly reduced. However, a large ^{t}Bu group at the 3-position can sterically differentiate the two sites and can exhibit high isoselectivity, probably with the opposite enantioface selectivity to the original indenyl group (Figure 7(c)).[104]

Isoselective C_1-symmetric metallocenes are based on the concept that only one enantioselective site out of two diastereotopic sites is used for the polymerization. Typically, a large substituent blocks one of the sites and accelerates chain backskip without monomer insertion to the less crowded side where the growing polymer chain is confined in one orientation toward the sterically open quadrant (Figure 6). The C_1-symmetric isoselective metallocenes have several advantages over C_2-symmetric metallocenes, that is, there are no concerns about *meso*-isomers (either by isomerization or as a byproduct), isotacticity tends to be maintained at higher polymerization temperatures, and they are generally very regioselective. Typical examples of such catalyst precursors are listed in Figure 8 (complexes **F8-1**–**F8-4**).[98,105–108]

11.20.3.2.3 Syndioselective metallocenes

Site-controlled syndioselectivity of C_s-symmetric metallocenes is unprecedented and represents a major achievement of the rational molecular design of single-site catalysts. Recent highly syndioselective metallocenes are listed in Figure 8.[109–111] The flat fluorenyl ligand has been further spatially extended by substituents at the 2,6- and/or 3,7-positions **F8-5**. This expanded fluorenyl motif is able to turn the sterically open and generally non-stereoselective half-sandwich amido complex into highly syndiotactic catalysts **F8-7**. Non-fluorenyl-based catalysts have also proved to be syndioselective, as long as certain spatial requirements are fulfilled **F8-6**.

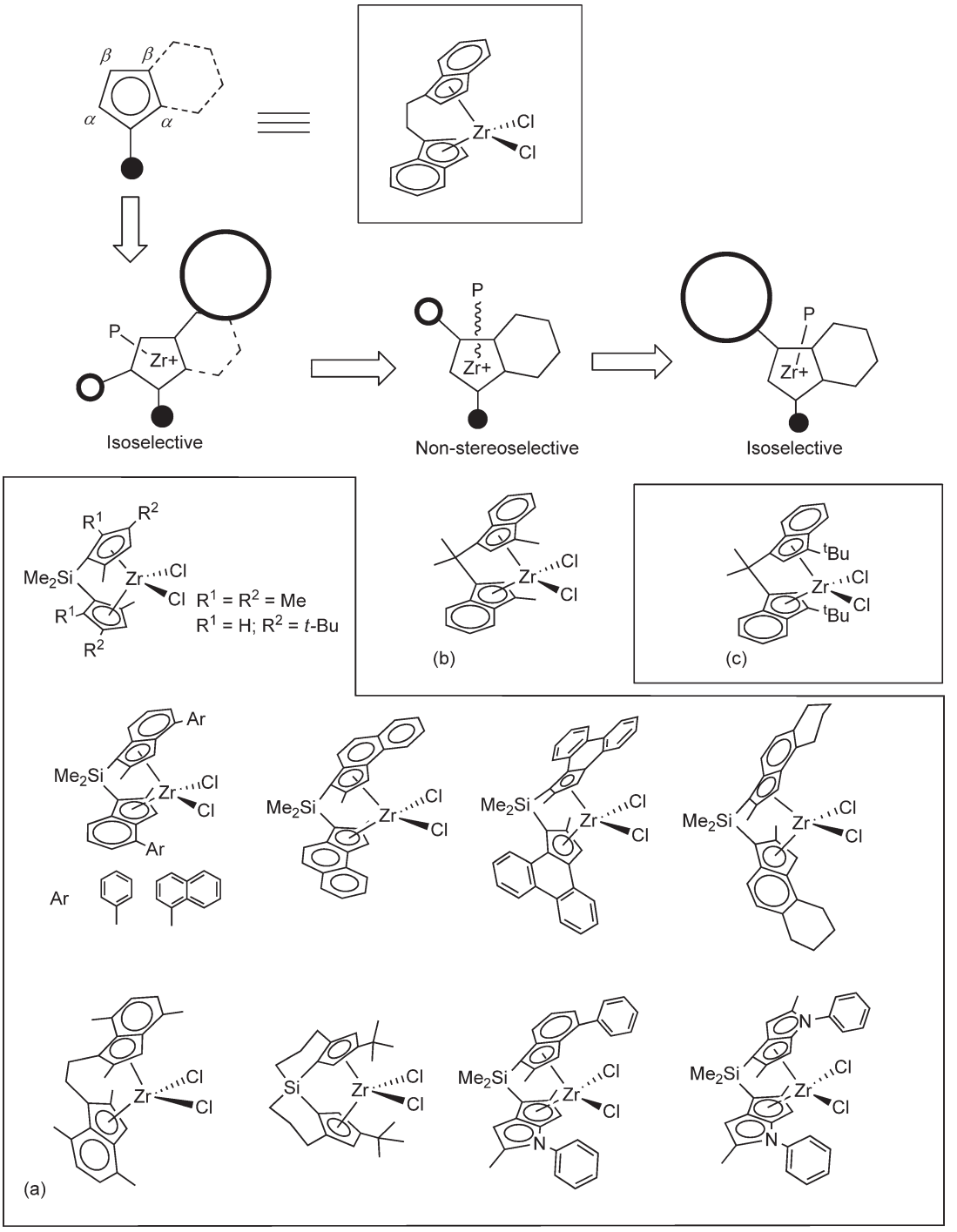


Figure 7 Isoselective metallocene complexes with C_2-symmetry.

11.20.3.2.4 Epimerization

Busico and co-workers have found that chain-end epimerization causes the deterioration of isoselectivity by racemizing the stereogenic center of the last-inserted monomer unit, and also that epimerization is the principal cause of stereoerrors, rather than the wrong enantiofacial selection at the insertion step.[112–114] Epimerization is a unimolecular reaction, whereas insertion is bimolecular; therefore, epimerization is more pronounced at low

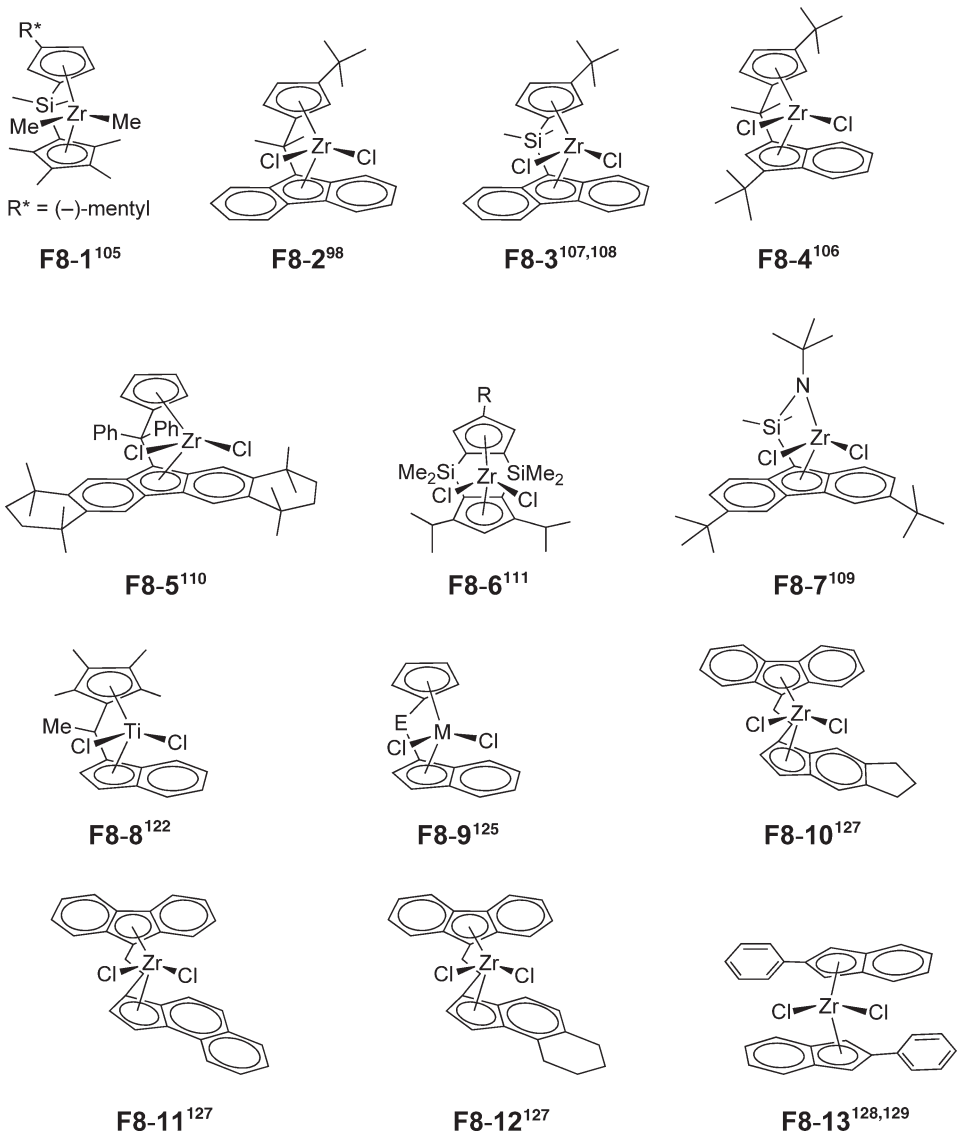


Figure 8 Metallocenes for iso-, syndio-, and stereoblock polypropylene synthesis.

monomer concentrations. Experiments using labeled propylene monomers clarify the mechanism, which goes through repetitive sequences of β-H elimination and reinsertion of the resulting olefin at the opposite carbon and/or the enantioface, without complete dissociation from the metal.[115,116] Additional evidence for this mechanism was obtained from direct observations of the epimerization process at low temperature[77] and from a living model catalyst.[117] The involvement of a zirconocene–allyldihydrogen intermediate appears to be rather unlikely from these results.[118]

For C_s-symmetric syndioselective metallocenes, simple chain backskip (alkyl group side-exchange) reverses enantiofacial selectivity to the incoming α-olefin (site epimerization) causing *m*-type stereodefects. As already described, the rate of backskip is quite sensitive to the nature of the ion pairing (see Section 11.20.2.2). An ISIP of the type $Me_2C(Cp)(Flu)ZrMe(\mu\text{-}F)Al(2\text{-}C_6F_5C_6F_4)_3$ effectively prevents this site epimerization from occurring in toluene, and, therefore, affords highly syndiotactic polypropylene compared to other, less coordinating, counteranions.[119] In a more polar solvent, for example, 1,3-dichlorobenzene, the cation–anion interaction is significantly weakened, and for all of the co-catalysts studied, the syndioselectivity was decreased to ca. 50% [*rrrr*], irrespective of the nature of the counteranion.

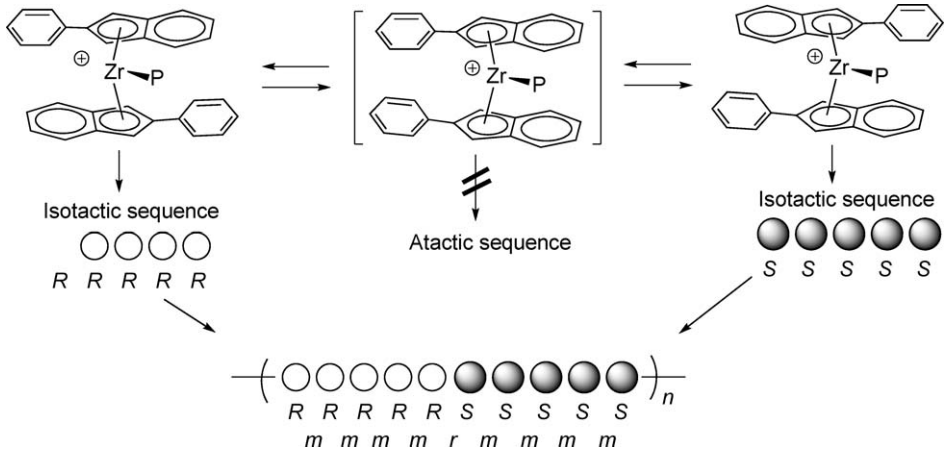
11.20.3.2.5 Stereoblock polymer

When two or more stable conformers of the catalytic species are separated by a relatively low-energy barrier, the species can interchange these conformers during polymerization, maybe on the timescale of the formation of a single polymer chain. Many examples of stereoblock polymers are believed to be generated in accordance with this principle, and two classes of such metallocene catalysts have been reported. The first is a class of bridged C_1-symmetric metallocenes that possess two different lateral coordinating sites (Figure 8, complexes **F8-8–F8-12**).[120–127] The formation of elastic polypropylenes by these catalysts was interpreted as occasional interconversion between the two diastereotopic sites: one coordinating site for the formation of isotactic sequences and the other for atactic sequences. The second, conceptually different class of catalyst is an unbridged bis(2-arylindenyl)zirconium dichloride (Figure 8, complex **F8-13**). This complex might interconvert between two fairly stable conformers similar to the *rac*- and *meso*-forms of typical bridged bis(indenyl)zirconium complexes by rotation of an indenyl ring (oscillating catalyst).[128,129] Upon activation with appropriate co-catalysts, the catalyst (assumed to be fluxional also) polymerizes propylene monomers into elastomeric to softened thermoplastic materials in which isotactic and atactic sequences are present. At first sight, the dynamic conformational change between the *rac*-like forms and the *meso*-like forms appeared to be responsible for the stereoblock structure (Scheme 6). The structures of the polypropylene depended heavily on the catalyst structures (ligand framework and metal) and the polymerization conditions such as temperature, monomer concentration (pressure), solvent polarity, and the counteranion derived from the co-catalyst. The relationship between these variables and the observed isotacticity was qualitatively consistent with the model, that is, the [*mmmm*]-content in the polymers increased under conditions where the ratio of the monomer insertion/conformational isomerization rates was supposed to be large. Based on high resolution NMR analysis of the polymers, it is suggested by Busico and co-workers that dynamic interconversion occurs between *rac*-like enantiomers rather than between the *rac*-like and *meso*-like forms, as initially assumed (Scheme 6).[130] The former interconversion would form isolated *r*-defects, as evidenced by the rather intense *mmmrmm* heptad sequence found in the polymer. When the rotation of an indenyl ring is comparable to monomer insertion, the isotactic sequence will often be disrupted by isolated *r*-defects, whereas relatively slow rotation of the indenyl ring would result in an appreciable length of isotactic stereosequences. The rate of ring rotation could be modulated by the nature of the ion pairing, which may account for the observed solvent and counteranion effect.

Another way of preparing stereoblock polymers is the use of binary catalyst systems, where the exchange of growing alkyl chains with different tacticity might be expected.[131–133] The alkyl chains are presumably carried by alkylaluminums and transferred between zirconocenes, and the products are a mixture of homopolymers from each catalyst and a stereoblock polymer containing both segments.

11.20.3.2.6 Stereoselective propylene polymerization with non-metallocene catalysts

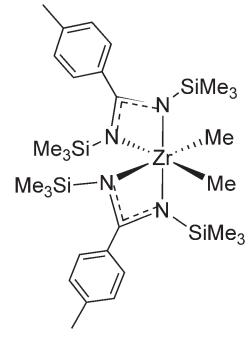
Non-metallocene catalysts have attracted much attention recently.[12,13] These catalysts generally contain oxygen and/or nitrogen (and sometimes sulfur and phosphorous) as ligating atoms, and those heteroatoms are often incorporated into a chelate ligand structure. These catalyst precursors often take an octahedral configuration, providing



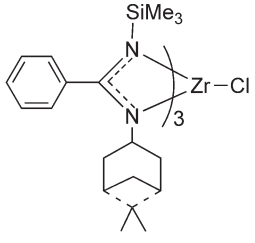
Scheme 6 Formation of stereoblock polypropylenes with an oscillating catalyst.

opportunities to see whether or not the symmetry rule for the tetrahedral metallocene still holds true for these configurationally and electronically very different complexes.

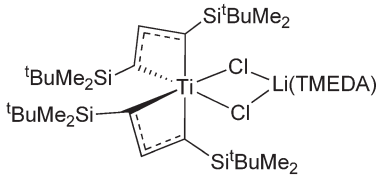
Bis(benzamidinate) zirconium catalysts (Figure 9, complexes **F9-1** and **F9-2**) can polymerize propylene monomers into highly isotactic polypropylene (MAO: up to 98% [*mmmm*], $T_m = 149\,^{\circ}C$) at 25 °C in CH_2Cl_2 under 9.2 atm of propylene monomer, as expected from the C_2-symmetric octahedral structure of the catalysts.[134,135] The polymerization reaction propagates via multiple 1,2-insertions, with occasional 2,1- and 1,3-insertions, and is terminated exclusively by β-methyl elimination. The observed isotacticity is sensitive to monomer concentration (pressure) because the concomitant unimolecular chain-end epimerization reaction is more pronounced than the bimolecular propagation reaction for low monomer concentrations, similar to the case of C_2-symmetric metallocenes. The elastic polypropylenes are produced using both this and related complexes **F9-3** and **F9-4**. The polymers consist of isotactic and atactic domains that seem to be covalently linked (no extractable atactic polymers).[135–137] Two mechanisms are proposed to be responsible for the formation of these stereoblock polymers. One is a chain-end epimerization that can be modulated by monomer pressure, and the other involves structural fluxionality of the active species (see also Section 11.20.3.2.5).



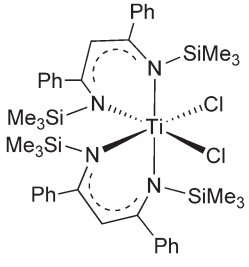
F9-1



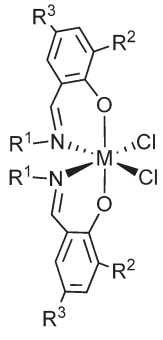
F9-2



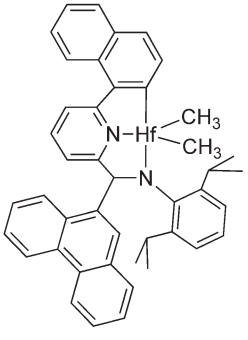
F9-3



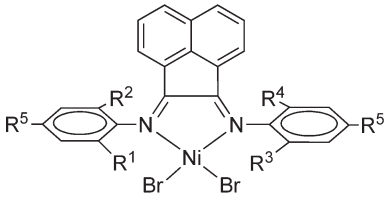
F9-4



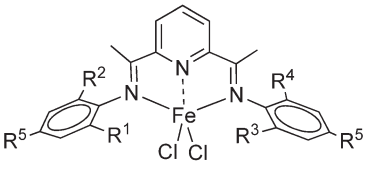
F9-5



F9-6



F9-7



F9-8

Figure 9 Non-metallocene complexes for stereoregular α-olefin polymerization.

Scientists at Mitsui recently discovered that bis(phenoxy–imine) Zr or Hf complexes **F9-5** polymerized propylene into isotactic polymers upon activation with $^{i}Bu_3Al/Ph_3CB(C_6F_5)_4$, where the imine functions were presumably reduced to amine by alkyaluminum.[138] Although these catalysts sometimes exhibit multiple-site character, isotacticity in *mmmm* pentad reaches 97%, and the melting temperature of the polymer is 165 °C after fractionation with boiling hexane when the complex has M = Hf, R^1 = cyclohexyl, R^2 = adamantyl, and $R^3 = CH_3$. Microstructural analyses of these isotactic polypropylenes suggested that the polymerization proceeds via a site-control mechanism involving the primary insertion of propylene monomers.

More recently, zirconium and hafnium complexes incorporating a C_1-symmetric pyridyl–amine ligand **F9-6** are discovered (by a high-throughput combinatorial methodology, see Section 11.20.5.2), which produces highly isotactic polypropylene at polymerization temperatures that are sufficiently elevated for a solution-polymerization process.[139] According to the literature, a subtle balancing of the combination of the ligand substituents is required in order to realize such high isotacticity, which seems to be difficult to attain without high-throughput screening. The Hf complexes give higher activity, higher molecular weight polypropylene, and possess higher isoselectivity than the Zr congeners under identical polymerization conditions. The isotactic polymerization proceeds through a site-control mechanism with successive 1,2-insertions. Theoretical studies demonstrate that each diastereotopic polymerization site exhibits opposite stereoselectivity, suggesting that only one of the two sites is used for the isotactic polymerization.[140]

There are no reports of highly stereoselective polymerization with late metal catalysts. The symmetry of the (α-diimine) Ni or Pd complexes can be modulated by bulky aryl substituents. At low polymerization temperature (−45 °C), C_{2v} and C_s Ni complexes **F9-7** furnish chain-end controlled syndiotactic polymers (61–75% [*rr*]; 1–8% [*mm*]), while the polymers formed by complexes with C_2-symmetry exhibit clearly intensified *mm* triad signals (25–34% [*rr*]; 23–41% [*mm*]), suggesting that the chain-end control and site-control mechanisms operate simultaneously.[141] Iron complexes with tridentate pyridine-bis(imine) ligands (**F9-8**) look similar to those for Ni diimine complexes, except for the fact that two metal-bound chlorine atoms (which are presumably transformed into a polymerization site upon activation) are located in the plane perpendicular to the FeN_3 plane, while they are in the NiN_2 plane for the square-planar Ni complexes. In iron complex-catalyzed polymerization, the propylene monomer is inserted in a highly regioregular 2,1-fashion, and yields exclusively 1-propenyl chain ends.[142,143] The polypropylene produced is prevailingly isotactic (up to 67% [*mmmm*] at −20 °C; 69% [*mm*] at 0 °C) irrespective of the catalyst symmetry, while the stereochemistry is dictated by chain-end control.

11.20.3.3 Living Polymerization of Ethylene and α-Olefins (Non-stereoselective)

Living polymerization is an excellent way of preparing chain-end functionalized polymers and various block co-polymers that are practically mono-dispersed in terms of molecular weight, although this has remained relatively unexplored in the field of Ziegler–Natta polymerization apart from a great deal of work on vanadium catalysts developed by Doi and co-workers[144] and on samarium catalysts by Yasuda and co-workers (see Section 11.20.4.5.4). There are many routes by which a growing chain can be terminated and which must be effectively blocked during the chain-growth reaction and even more preferably after monomer consumption, making the living chain end available for subsequent chemical modification or further chain growth of the next block segment. Quantitative evaluation of livingness is difficult and therefore cross-comparisons of each living catalyst are often not straightforward. Thus, this is consciously not attempted here except for those cases where directly comparable data are available.

11.20.3.3.1 Ethylene monomer

Mashima *et al.* synthesized a range of group 5 complexes, (η^5-C_5R_5)(η^4-diene)MX_2 (M = Nb, Ta; X = Cl, Me; R = Me, H), isoelectronic with group 4 metallocenes (Figure 10, complexes **F10-1–F10-5**). Upon activation with MAO, the complexes are capable of performing living ethylene polymerization. In comparisons of the metal center, the Nb complexes generally exhibit higher activity and lower polydispersity index (PDI = M_w/M_n) over a wider range of polymerization temperatures at 20 °C or below than the Ta congeners, while the Ta complexes require temperatures below −20 °C to achieve satisfactory living behavior.[145,146]

A cationic mono-Cp-based cobalt complex **F10-6** can initiate the living polymerization of ethylene, which has been successfully applied to the preparation of chain-end-functionalized polymers (see Section 11.20.4.5.4).[147]

Unique and versatile olefin polymerizations with group 4 bis(phenoxy–imine) complexes have been disclosed by scientists at Mitsui.[148,151] In a series of Ti complexes with fluorinated *N*-phenyl groups (Figure 10, complexes **F10-7–F10-14**), Mitani *et al.* observed a substantial difference in ethylene polymerizations between complexes having

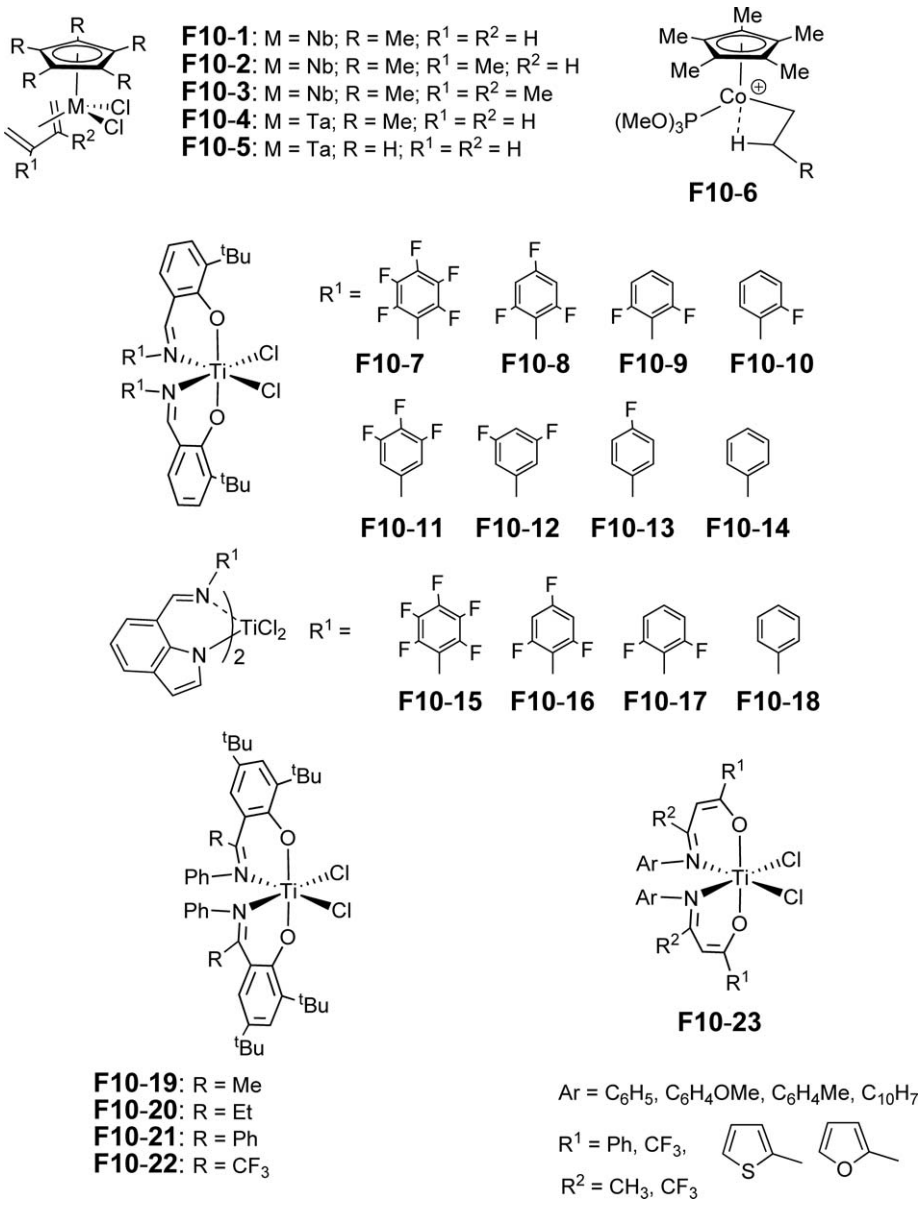


Figure 10 Living ethylene polymerization catalysts.

ortho-fluorinated phenyl groups on the imine nitrogens **F10-7–F10-10**, and those having fluorines at the *meta*- and/or *para*-positions **F10-11–F10-14**.[149] Under rather harsh polymerization conditions at 50 °C, **F10-7–F10-10** demonstrated living-polymerization characteristics (PDI = 1.05–1.25) but **F10-11–F10-14** behaved as non-living catalysts (PDI ~ 2). Non-living complexes that have *meta*-/*para*-F groups exhibit higher activity relative to their living counterparts that have the same number of fluorines. The perfluorophenyl complex ($R^1 = C_6F_5$, **F10-7**) exhibits surprising activity, as high as 40 kg mmol-Ti^{-1} h^{-1} atm^{-1} (50 °C), approaching that observed for prototypical zirconocene (Cp_2ZrCl_2/MAO) under the same conditions, and yet yields high molecular weight (up to 424 000) living polymers. The active species derived from the complex are stable for at least 1 h at room temperature, even without ethylene monomers. The bis(phenoxy-imine) Ti complexes in general tend to give higher molecular weight polymers than the Zr/Hf congeners[148] and some complexes without the aforementioned *ortho*-F groups certainly possess living character, though they are limited under specifically controlled conditions.[149] The observed *ortho*-F effects are substantial when compared under the same conditions, for which an attractive interaction is proposed between the *ortho*-F and a β-H

on the growing polymer chain based on DFT calculations. Living (syndioselective) propylene polymerization and the synthesis of various block co-polymers with these complexes will be discussed in Section 11.20.3.4.

Matsugi *et al.* reported that titanium complexes containing two indolide–imine chelate ligands with and without *ortho*-F at the *N*-phenyl groups, **F10-15–F10-18**, exhibited living ethylene-polymerization behavior at 25 °C or above.[150] Polymerization activity increases as the number of fluorines increases, such that ($C_6F_5 > 2,4,6\text{-}F_3$–$C_6H_2 > 2,6\text{-}F_2C_6H_3 > C_6H_5$), although the complex with perfluorophenyl groups, **F10-15**, is not living anymore. The complex bearing 2,4,6-F_3–C_6H_2 groups as *N*-aryl groups, **F10-16**, polymerizes ethylene at 25 °C in a living manner with high activity of 29 kg mmol-Ti^{-1} h^{-1} atm^{-1} to afford polyethylene with a narrow molecular weight distribution (PDI = 1.11; M_n = 47 000). The block co-polymer polyethylene-*b*-poly(ethylene-*co*-propylene) was successfully synthesized using this catalyst.

Coates and co-workers reported on bis(phenoxy-ketimine) Ti complexes,[151] which can also be catalysts for living ethylene polymerization at temperatures between 0 and 50 °C.[152] These complexes do not have fluorine atoms as the *N*-aryl groups **F10-19–F10-22** and exhibit rather low activities of 0.3–1.4 kg mmol-Ti^{-1} h^{-1} atm^{-1} with PDI ~ 1.1 and M_n = 21 000–60 000. Under the same conditions, bis(phenoxy-imine) Ti complexes without *ortho*-F as a control gave 3–4 kg mmol-Ti^{-1} h^{-1} atm^{-1} with PDI ~ 1.1 and M_n = 45 000–78 000. Another direct comparison among these catalysts was recently reported,[153] showing extraordinary living polymerizations with fluorinated bis(phenoxy-imine) Ti complexes and a rather limited living nature for non-fluorinated bis(phenoxy-imine) and bis(phenoxy-ketimine) Ti complexes in terms of activity and achievable molecular weight.

Related bis(β-enamino ketonato) titanium complexes with non-fluorinated *N*-aryl groups, **F10-23**, also afforded polyethylenes with relatively low PDI of 1.2–1.4 at 25 °C (1.3 kg mmol-Ti^{-1} h^{-1} atm^{-1}), where the molecular weight increases with polymerization time.[154]

11.20.3.3.2 α-Olefin monomers

At low temperatures below −50 °C, simple metallocenes, Cp_2MMe_2 (M = Zr, Hf), exhibit living polymerization characteristics for propylene and 1-hexene, albeit with low activity.[155,156] *In situ* observations of alkyl zirconocenes actually confirm the livingness, and serve as an excellent model for kinetic studies.[50] Shiono and co-workers demonstrated that a Cp–amido complex of the type $SiMe_2(Flu)(^tBuN)TiMe_2$ **F11-2** combined with MAO, from which $AlMe_3$ was removed under vacuum, could serve as a living propylene-polymerization catalyst at 0 °C to yield polypropylenes with relatively low PDI of 1.2–1.4 (Figure 11).[157]

Aryl Ni–α-diimine catalysts (with ligands **S4-5** and **S4-6** in Scheme 4) with MMAO (modified MAO) can polymerize propylene and 1-hexene in a living manner at −10 °C in toluene (M_n = 160 000; PDI = 1.13 for 1 atm propylene).[158] Combined with the chain-straightening mechanism mentioned previously (Scheme 5), diblock (A–B) and triblock (A–B–A) co-polymers were synthesized, where the semi-crystalline A block consisted of straightened 1-octadecene units, and the amorphous B block was formed by the co-polymerization of 1-octadecene and propylene. The molecular weights (M_n) of these block co-polymers are as high as 253 000, while their PDI values remain in the range 1.09–1.43. Aryl α-diimine Pd catalysts (with ligand **S4-2** in Scheme 4) catalyze ethylene living polymerization (in C_6H_5Cl, at 5 °C, 2.7 MPa ethylene) to afford high molecular weight (M_n up to 236 000), branched polyethylene with very low PDI (<1.10).[159] The versatility of the catalysts proved that the living polymerization of α-olefins (propylene, 1-hexene, 1-octadecene), block co-polymers of ethylene and α-olefins, and chain-end functionalization by means of functional chelate initiators and/or chain-end capping by alkyl acrylates are now accessible (see Section 11.20.4.5.4). Due to chain walking and straightening, unique topologies are obtained for the ethylene/1-octadecene block co-polymers, which can be altered by the order of monomer addition.

Scollard and McConville discovered that chelating titanium diamide complexes **F11-1** exhibited high activity toward 1-hexene polymerization.[160] Drawing on the observation that there were no unsaturated chain ends when activated with MAO, the authors reasoned that if chain transfer to alkylaluminums could be averted by the use of $B(C_6F_5)_3$ as a co-catalyst, then living polymerization might result, which was actually the case in the polymerization of C_6–C_{10} α-olefins (at 23 °C, in pentane, M_n up to 164 000, PDI < 1.10).[161] The polymerizations proceed in the primary (1,2-) non-stereoselective insertions of α-olefins. The enhanced polymerization activity in CH_2Cl_2 is consistent with a postulated cationic species that has formally 10 electrons. The electron deficiency seems to cause a decrease in activity in toluene due to the competitive coordination of toluene and the monomer to the metal. Shiono and co-workers obtained essentially the same results when MMAO, from which the trialkylaluminums were removed by evaporation, was used instead of $B(C_6F_5)_3$.[162] A related diamido zirconium complex **F11-3** is capable of polymerizing 1-hexene in a living manner in toluene at −10 °C with a PDI of as low as 1.18.[163]

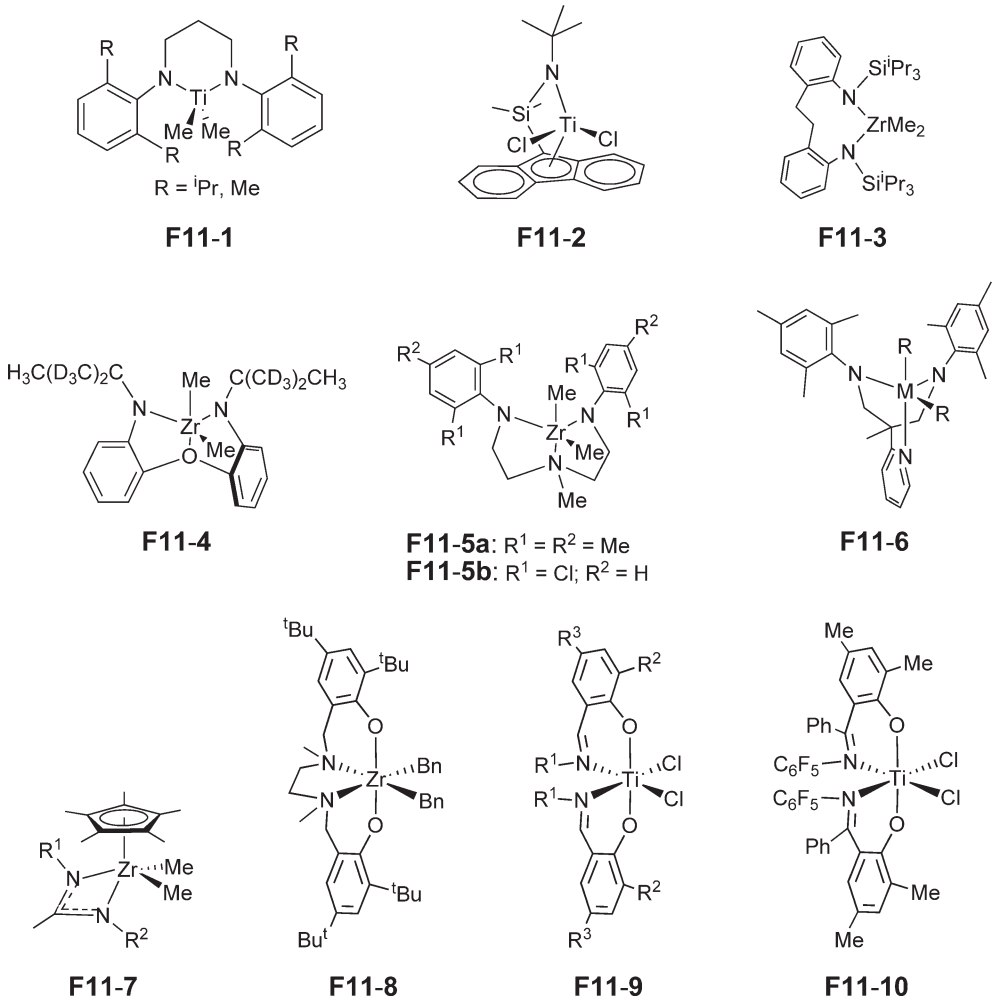


Figure 11 Living-polymerization catalysts for propylene and higher α-olefins.

Schrock and co-workers have investigated a series of complexes bearing tridentate diamido ligands of the type [*NON*]MX_2 or [*NNN*]MX_2. The activation of a complex of the type [(RN-*o*-$C_6H_4)_2O$]$ZrMe_2$ **F11-4** with $B(C_6F_5)_3$ (crystallographically characterized) and $[HNMe_2Ph][B(C_6F_5)_4]$ demonstrates the formation of cationic species to afford living atactic poly(1-hexene) when R is a bulky ^{t}Bu group (at 0 °C, in chlorobenzene, M_n at least 25 000, PDI < 1.10).[164] They proposed that the presence of ^{t}Bu groups on the equatorial amido nitrogens prevents the growing polymer chain from taking a conformation suitable for β-hydride elimination. In fact, the presence of sterically less demanding isopropyl and cyclohexyl as the R group make the complexes more vulnerable to β-hydride elimination, and so they afford oligomers of 1-hexene.[165] Complexes of the type $[(ArNCH_2CH_2)_2NMe]ZrMe_2$ show considerable activity for 1-hexene polymerization, but do not behave as well as the [NON] complexes as living polymerization catalysts when Ar is the 2,4,6-trimethylphenyl group **F11-5a**.[166] Subsequent studies revealed that intramolecular C–H bond activation of an *ortho*-Me group yielded a non-active cationic species, which eventually precipitated out as a dimeric dicationic complex.[167] Substitution of the methyl group with chlorines (Ar = 2,6-dichlorophenyl, **F11-5b**) was found to be a remedy for this problem. The chlorine-substituted complex exhibited well-behaved living characteristics for 1-hexene polymerization (at 0 °C in chlorobenzene, M_n up to 79 000, PDI < 1.05). Pyridyl diamido Zr or Hf complexes $[MeC(2\text{-}C_5H_4N)(CH_2N\text{-}2,4,6\text{-trimethylphenyl})_2]MR_2$ (M = Zr or Hf; R = Me or ^{i}Bu, **F11-6**) represent another successful implementation of [NNN]-tridentate ligands for 1-hexene living polymerization, in which a marked effect of the R group was observed.[168–170] When R is Me, methide (methyl anion) abstraction leads to a putative monocationic species, [*NNN*]M–Me^+. However, most of these cationic species are trapped by the neutral dimethyl complex to form an inactive monocationic dinuclear complex,

[*NNN*]M–(μ-Me)$_3$–M[*NNN*]$^+$, for which the equilibrium lies far toward the dimer at room temperature. The remaining mononuclear cationic species react with 1-hexene to form 2-methylheptyl (1,2-insertion, major) and 3-methylheptyl (2,1-insertion, minor). The former species is subject to further chain growth via primary monomer enchainments to yield atactic living 1-hexene, whereas the latter is inactive toward monomer insertion and is eventually deactivated with the concurrent formation of 2-heptenes. The introduction of isobutyl groups instead of methyl groups as R affords cationic species, [*NNN*]M–$CH_2CH(CH_2)_2^+$, as an initiating species, where dimer formation does not occur and preferential 1,2-monomer insertion circumvents the formation of 2,1-inserted dormant species.

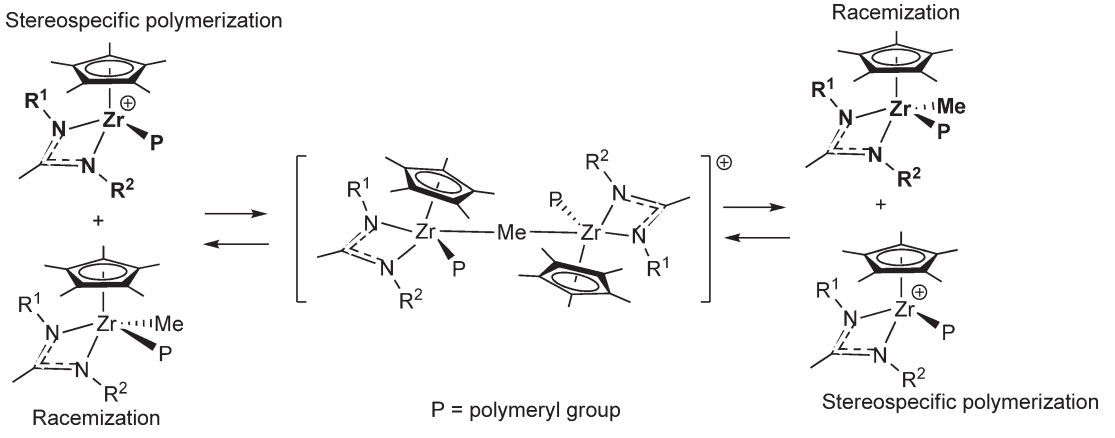
11.20.3.4 Stereoselective Living Polymerization of α-Olefins

The beauty of block co-polymers rests on multiple characteristics owing to constituent segments with physically and/or chemically contrasting properties (e.g., hard–soft, crystalline–amorphous, polar–non-polar, and hydrophilic–hydrophobic) and on the microphase separation that is thereby induced, which results in unique resin properties and functions. Therefore, the simultaneous pursuit of stereoselectivity and living nature is of great technological importance in order to obtain a highly crystalline hard segment.

Highly isotactic 1-hexene living polymerizations ([*mmmm*] > 95%) were achieved by Sita and co-workers by using a C_1-symmetric mono-Cp–zirconium amidinate complex (**F11-7**; R^1 = Et; R^2 = ^{t}Bu), (e.g., at −10 °C, in chlorobenzene, M_n = 49 000, PDI = 1.03, activity = 64 g mmol-Zr^{-1} h^{-1}).[171] With this catalyst, they prepared di- and triblock co-polymers of *iso*-PH-*b*-PMCP and *iso*-PH-*b*-PMCP-*b*-*iso*-PH (*iso*-PH = isotactic poly(1-hexene); PMCP = poly-(methylene-1,3-cyclopentane)) from 1,5-hexadiene.[172]

A methyl cationic species such as $(C_5Me_5)[^tBuNC(Me)NCH_2CH_3]ZrMe^+[B(C_6F_5)_4]^-$ is conformationally more stable than a neutral dimethyl zirconium complex that is under facile racemization via amidinate ring flipping.[173] The observed isospecificity and living nature were built upon a subtle balance between the ligand substituents on the Cp ring and the amidinate [$R^1NC(R^3)NR^2$], and slight changes have measurable consequences. For example, non-substituted Cp causes a significant increase in activity for living 1-hexene polymerizations at the expense of loss in isospecificity (though it is isoselective for bulky vinyl cyclohexane).[174] Other combinations of the two *N*-amidinate substituents were found to be less active (R^1 = ^{t}Bu, R^2 = cyclohexyl; R^1 = ^{t}Bu, R^2 = 2,6-^{i}Pr$_2$-C$_6$H$_3$) or non-stereoselective (R^1 = R^2 = cyclohexyl),[171] and apparently remote R^3 other than Me caused a loss of stereocontrol (R^3 = H, Ph), of livingness (R^3 = H), and even a loss of activity (R^3 = ^{t}Bu).[175]

A unique feature of this catalyst was discovered under conditions where [B] < [Zr], that is, the molecular weight of the polymers is determined by the ratio of [1-hexene]$_0$/[Zr] (not by [1-hexene]$_0$/[B]), and PDI values below 1.10 are observed in all cases.[176] The authors clarified the mechanism whereby a methyl group was transferred from a neutral Zr(Me)–polymeryl species to a cationic Zr–polymeryl species through a putative Me-bridged cationic dinuclear species, causing extensive scrambling of the two species (Scheme 7). The equilibrium between these two species is much more rapid than monomer insertion, which allows all of the Zr to propagate at a constant rate, even though only a part of the Zr species are active at any given moment ([B] < [Zr]). The significant decrease in isoselectivity



Scheme 7 A proposed mechanism for a living polymerization involving rapid methyl group transfer.

observed under these conditions can be attributed to the racemization of the neutral alkyl–methyl species via the metal-centered amidinate ring-flip process mentioned above. Stereoblock poly(1-hexene) was synthesized by controlling the stoichiometry during polymerization, that is, an aspecific living chain under B < Zr was followed by isotactic chain growth by adding stoichiometric quantities of borate. The authors introduced chlorine instead of a methyl group as a mobile anionic group to utilize the stability of zirconium monoalkyl chlorides with respect to racemization.[177] Rapid chloride exchange establishes equilibrium between the active and dormant species, resulting in poly(1-hexene) with a low PDI from all of the Zr added in the reaction, and significantly, high isoselectivity is maintained, as expected.

Kol and co-workers found that a zirconium complex bearing a tetradentate bisphenoxy–bisamine [*ONNO*]-ligand, **F11-8**, promoted the living polymerization of 1-hexene with high isoselectivity at room temperature.[178] This complex is C_2-symmetric in an octahedral framework with a *cis*-N–Zr–N, *trans*-O–Zr–O disposition. Steric bulk on the alkyl substituents *ortho* to the phenoxy oxygen is crucial for high isoselectivity, for example, ^{t}Bu groups yield highly isotactic poly(1-hexene), but Me groups afford an atactic product. For propylene polymerization with the complex at 25 °C, isotactic polypropylene was formed with 80% [*mmmm*] via a site-control mechanism through 1,2-insertions.[179] Even more bulky adamantyl groups were found to enhance the isoselectivity up to 98.5% [*mmmm*], allowing the synthesis of a block co-polymer containing a highly isotactic polypropylene sequence and a polyethylene sequence.[180]

The bis(phenoxy–imine) Ti complexes **F11-9** are one of the rare examples that possess well-established living character for both ethylene and propylene, and even better, the living propylene polymerization is highly stereoselective.[181,182] Despite the fact that most of the bis(phenoxy–imine) complexes are considered to have a C_2-symmetric *cis*-N–Ti–N, *trans*-O–Ti–O, *cis*-Cl–Ti–Cl configuration as the main isomer, these Ti-complexes with MAO polymerize propylene monomers in a moderately to highly syndioselective manner rather than the expected isotactic one.[182,183] The syndioselectivity is chain-end controlled with 2,1-enchainments, which is unusual for group 4 metals.[184–186] When fluorinated phenyl groups that contain at least one *ortho*-fluorine are applied as R^1, the catalysts exhibit living nature for propylene polymerization with much enhanced syndioselectivity relative to the corresponding non-fluorinated catalysts at 0 °C or above.[187,188] The importance of the position and number of the fluorine substituents on the *N*-aryl groups is similar to that observed for the ethylene living polymerization, where an attractive interaction between *ortho*-F and β-H was proposed (Section 11.20.3.3.1). A similar interaction was presumed by researchers at Mitsui,[187] whereas calculations by Talarico *et al.* imply a rather pronounced steric effect of the *ortho*-F.[189] The polymerization characteristics with the bis(phenoxy–imine) Ti catalysts are apparently similar to those for soluble vanadium catalysts in terms of regiochemistry and stereocontrol mechanisms. However, the stereoselectivity and operating polymerization-temperature window of the Ti complexes are dramatically enhanced relative to the V catalysts at the cost of decreased activity. Steric modulation of the R^2 substituents gives a sharp increase in syndioregularity that is proportional to the volume of R^2, up to 94% of *rr* triad for the Me_3Si group (T_m = 156 °C, polymerization at 0 °C).[187] The observed chain-end-controlled R^2-sensitive syndioselectivity was explained theoretically by assuming a site inversion between the Δ and Λ forms that is driven by the chirality (*R* or *S*) at the α-carbon of the growing polymer chain.[190] Enantiofacial discrimination of an incoming propylene monomer seems to be induced by steric repulsion between the R^2 substituents and a methyl group on the monomer, which is consistent with the observed R^2 dependence. Although the postulated inversion between the Δ and Λ forms is not experimentally supported, bis(phenoxy–imine) complexes are likely to be fluxional in solution, as already reported for some Zr complexes.[191] By analogy, the presence of steric bulk at the R^2 position can also modulate co-monomer uptake in the co-polymerization of ethylene with α-olefins. By decreasing the steric demand at R^2, higher α-olefins (>C_6) are readily incorporated to afford diverse elastomers with high performance.[192] A wide array of block co-polymers have been synthesized by means of living polymerizations with bis(phenoxy–imine) Ti catalysts.[181,192]

Bis(phenoxy–ketimine) Ti complexes exhibit rather poor propylene-polymerization characteristics in their original forms. Ligand modifications aimed at affording increased activity have been implemented (reduction of steric bulk in the *ortho*-phenol substituents from ^{t}Bu (**F10-21**) to ^{i}Pr, Et, Me (**F11-10**), and H, and the introduction of perfluoro *N*-aryl groups), which resulted in the creation of isoselective living propylene polymerization catalysts.[193] Although the smaller *ortho*-phenol substituents of **F11-10** must be accompanied by lower selectivity, predominantly isotactic polypropylenes were obtained in a living fashion ([*mmmm*]: 61%, T_m = 96 °C, TOF = 138 h^{-1}, PDI = 1.11 at 0 °C polymerization). A site-control and 2,1-insertion mechanism seems to occur in these polymerizations, and it has been proposed that the site inversion assumed in the syndioselective chain-end-controlled polymerization of phenoxy–imine Ti complexes **F11-9** might be inhibited by the presence of phenyl groups at the ketimine functional sites.

11.20.3.5 Molecular Weight

Along with enabling technological advances in alkene polymerizations, the application of new ancillary ligands or co-catalysts has become significant in the field of alkene oligomerizations to obtain α-olefins. This research exploits a new phase in the development of known catalyst systems containing Cr, Ni, Pd, Ti metal centers, as well as Fe and Co as newcomers.

Figure 12 illustrates some catalysts that form ethylene oligomers with a Schulz–Froly distribution of chain lengths. Complexes **F12-1**–**F12-7** afford almost exclusively α-olefins,[194–201] while complexes **F12-8**[202] and **F12-9**[203] yield a mixture with inner olefins.

Cr-based catalysts have been utilized for the synthesis of specific α-olefins, such as 1-hexene, and have been further developed by the use of ligands with novel structures.[204] Very recently, unprecedented selective tetramerization of ethylene was reported by Bollmann *et al.* to form 1-octene at >70% selectivity by using Cr(III) precursors in conjunction with diphosphinamine ligands activated with MAO **F12-10**.[205] Hessen and co-workers discovered that a hemilabile aryl group incorporated into the mono-Cp based Ti complexes **F12-11** induced the unusual transformation of Ti complexes from ethylene-polymerization catalysts to selective trimerization catalysts.[206]

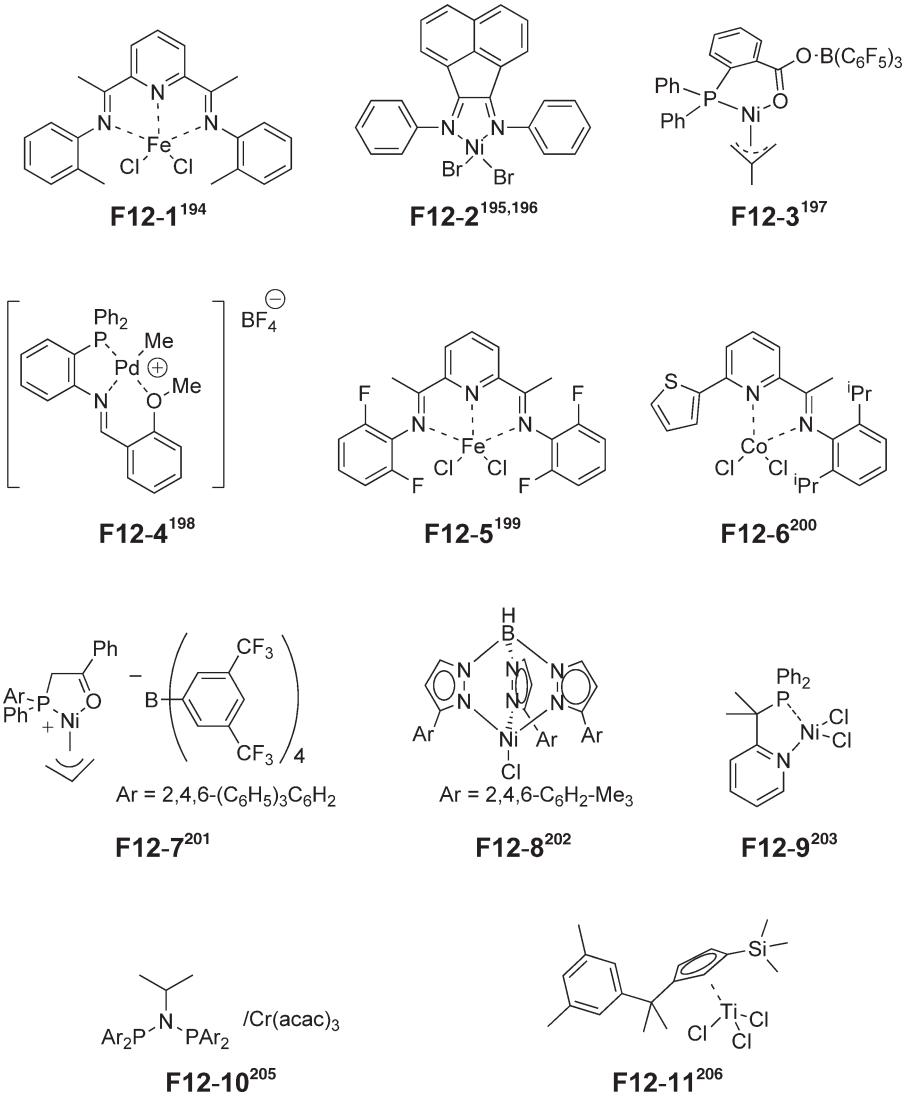


Figure 12 Catalysts for ethylene oligomerization.

11.20.4 Polymer Synthesis with Various Monomers

11.20.4.1 Polymers Containing Cyclic Olefins

Interest in cyclic olefin (co)polymers has increased dramatically over the past decade.[207,208] This is because this class of polymers displays many attractive properties such as high thermal stability, high optical transparency, low dielectric constants, and low moisture absorption. Thus, these polymers can potentially be utilized in many electronic and optical applications. Although cyclic olefin (co)polymers typically include ring-opening metathesis polymers, vinyl-addition homopolymers, and vinyl-addition co-polymers with acyclic co-monomers such as ethylene, we will mainly deal with vinyl-addition homo- and co-polymers in this section.

11.20.4.1.1 Homopolymers

Complexes of Ni and Pd combined with the appropriate co-catalysts are active for the polymerization of cyclic olefins such as cyclopentene and norbornene (NB). Recent reviews have summarized many of the catalytic properties of these complexes.[207,208] In 1999, Greiner and co-workers developed a highly active catalyst system composed of [NiBr(NPMe$_3$)$_4$] and MAO for the polymerization of NB.[209] The maximum activity reached 20.6 t-polymer mol-Ni^{-1} h^{-1} ($M_v = 647\,000$) at 20 °C. Additionally, it was reported by Li *et al.* that neutral Ni complexes bearing pyrrolide–imine ligands, **F13-1**, activated by MMAO can be used as highly active catalysts for NB polymerization; they display catalytic activities up to 42 t-polymer mol-Ni^{-1} h^{-1} and molecular weights (M_v) up to 920 000.[210] In 2001, Sen and Rhodes found a highly active cationic Pd-based catalyst that displayed an NB polymerization activity of 1000 t-polymer mol-Pd^{-1} h^{-1} at 25 °C.[211] With this catalyst, they successfully obtained NB and 5-ethylidene-2-NB or 5-vinyl-2-NB co-polymers that contain reactive olefinic groups.

Due to the lower oxophilicity and presumed greater functional group tolerance of Pd and Ni compared with early transition metals, much attention has recently been focused on the (co)polymerization of functionalized NB with non-functionalized NB. Risse *et al.*[212] and Heitz *et al.*[213] described the synthesis of functionalized NB (co)polymers based on NB with carboxylic acid or ester functionality using Pd-based catalysts. In 1995, Novak and co-workers demonstrated that Pd σ,π-alkyl complexes **F13-2** polymerize NB in a living fashion, and, moreover, yield block co-polymers from NB and diethyl 7-oxabicyclo[2.2.1]-hepta–2,5-diene–2,3-dicarboxylate.[214] Additionally, Rhodes and co-workers recently developed allyl Pd complexes that are highly active catalysts for the co-polymerization of 5-butyl–NB and 5-triethoxysilyl–NB, and are still active in aqueous media.[215] Conversely, the co-polymerization of ethylene or ethylene/α-olefin with functionalized NB using a neutral Ni complex **F13-3** was reported by Sen and Rhodes (e.g., ethylene NB–CO_2Et co-polymerization; NB–CO_2Et content 18 mol%, $M_w = 22\,900$, PDI = 1.69).[216]

Meanwhile, group 4 metallocene catalysts typically display low activities for the homopolymerization of cyclic olefins relative to those for conventional olefins. Recently, Wu and Lu described that CpTi(OCH$_2$Ph)$_3$ activated by MAO can be a high-activity catalyst for NB polymerization via vinyl addition below 80 °C.[217] Moreover, upon activation with dried MAO, Me$_2$Si(Flu)(^{t}BuN)TiMe$_2$ was shown by Shiono and co-workers to induce living NB polymerization at 20 °C and forming *o*-dichlorobenzene-soluble polymers with narrow molecular weight distributions (activity = 1087 kg-polymer mol-Ti^{-1} h^{-1}, $M_n = 296\,000$, PDI = 1.26).[218]

11.20.4.1.2 Co-polymers

The co-polymer of ethylene with a cyclic olefin represented by NB (cyclic olefin co-polymer; COC) is one of the most important engineering plastics, with many useful properties. While a number of Ni and Pd complexes have been demonstrated to catalyze vinyl-addition homopolymerization of NB, most of them are ineffective for the co-polymerization of ethylene and NB due to the fact that an ethylene-last-inserted species readily undergoes β-H transfer, resulting in the production of low molecular weight co-polymers. Conversely, early transition metal catalysts, such as V complexes and group 4 metallocene catalysts, can effectively co-polymerize ethylene with NB. Since Kaminsky *et al.* first described the preparation of ethylene/NB co-polymer using an ethylene-bridged metallocene catalyst in 1991,[219] a number of metallocene catalysts have been investigated as potential ethylene/NB co-polymerization catalysts.[220]

The ability of metallocene catalysts and Cp–amido type catalysts to co-polymerize NB with ethylene was investigated by Fink,[221–225] Tritto,[226–229] and Waymouth.[230] They systematically studied the co-polymerization behavior of these catalysts and thereafter elucidated the structure of the catalysts and their catalytic performance relationships. These findings have since formed the foundation of ethylene/NB co-polymerization research. Elsewhere, Nomura and co-workers revealed that non-bridged phenoxy–Cp-ligated Ti complexes **F13-4** with

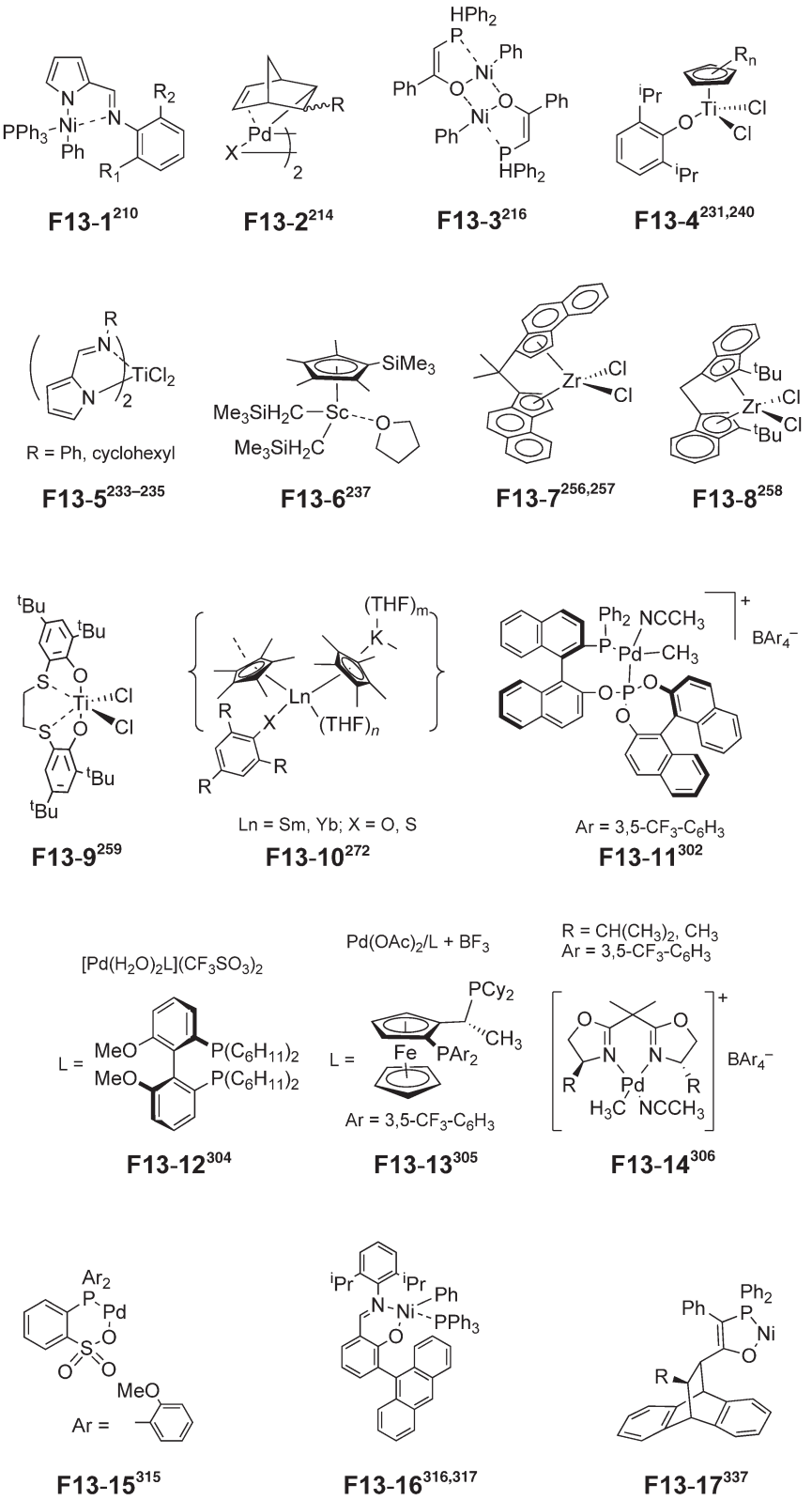
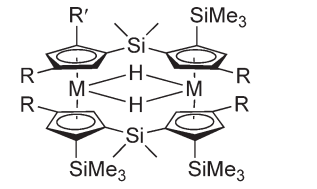


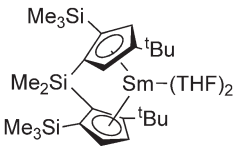
Figure 13 Catalysts for polymerizations using monomers other than ethylene or α-olefins.



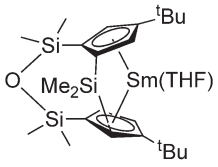
M = Y; R = $SiMe_2{}^tBu$; R′ = $SiMe_3$

M = Sm; R = ^tBu; R′ = H

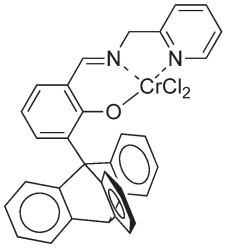
F13-18[342]



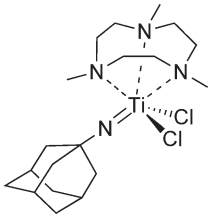
F13-19[343]



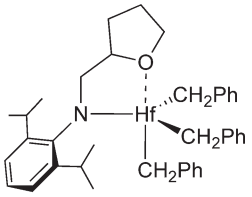
F13-20[343]



F13-21[381]



F13-22[382]



F13-23[384]

Figure 13 (*Continued*)

MAO activation were efficient catalysts for the co-polymerization of ethylene and NB (e.g., activity = 1,520 kg-polymer mol-Ti^{-1} h^{-1}, NB content = 48.9 mol%, M_n = 42 000, PDI = 2.1, T_g = 113.4 °C); the substituent on the Cp ring has an influence on both reactivity toward NB and NB sequence distribution.[231]

In general, conventional catalysts produce co-polymers with NB contents of less than 50 mol% with isolated or alternate NB units. Significantly, Shiono and co-workers demonstrated that $Me_2Si(Flu)(^tBuN)TiMe_2$ with dried MAO can form co-polymers with NB dyads and triads, and that the same complex in conjunction with $Ph_3CB(C_6F_5)_4$/Oct_3Al provided a co-polymer with an NB content of 82 mol% (T_g = 237 °C) under polymerization at 80 °C.[232]

Recently, much progress has been made in the living co-polymerization of ethylene and NB. In 2001, Tritto and co-workers reported that *rac*-$(C_2H_4)(Ind)_2ZrCl_2$ combined with MAO was capable of promoting quasi-living ethylene/NB co-polymerization and of forming narrow molecular weight distribution co-polymers (activity = 920 kg-polymer mol-Zr^{-1} h^{-1}, NB content = 59 mol%, M_n = 133 000, PDI = 1.16).[228] The presence of a large excess of NB with respect to ethylene (molar ratio: NB/ethylene > 28) in the polymerization medium is a requirement for achieving quasi-living co-polymerization, which implies that NB coordination to an active species plays a pivotal role in the realization of quasi-living co-polymerization.

Yoshida *et al.* recently found that upon activation with MAO, bis(pyrrolide–imine)Ti complexes **F13-5** could co-polymerize ethylene and NB in a highly controlled living manner at room temperature to yield co-polymers with very high molecular weights and narrow molecular weight distributions (M_n > 500 000, PDI < 1.2).[233–235] They concluded that the highly electrophilic as well as sterically open nature of the catalytically active species is responsible for the highly controlled living co-polymerization. This unique living nature has allowed the synthesis of a number of ethylene- and NB-based block co-polymers, which include PE-*b*-poly(ethylene-*co*-NB) and poly(ethylene-*co*-$NB)_1$-*b*-poly(ethylene-*co*-$NB)_2$, in which each segment features a different NB content. Li and co-workers developed a family of bis(*β*-enaminoketonato)Ti complexes **F10-23**. These complexes can induce living ethylene/NB co-polymerization and afford nearly monodisperse co-polymers and block co-polymers from ethylene and NB.[154,236] Very recently, cationic half-sandwich Sc complexes **F13-6**, as reported by Hou and co-workers, not only represent the first rare-earth metal catalysts for ethylene/NB co-polymerization, but can also produce (ethylene-*alt*-NB)-*b*-PE.[237]

In the case of co-polymers with cyclic olefins other than NB, Naga *et al.* performed the co-polymerizations of ethylene or propylene with cyclopentene by using a number of bridged metallocene catalysts, and then investigated the peak melting temperatures and crystalline structures of the resultant co-polymers, all containing cyclopentane units.[238] In 2004, Waymouth and Lavoie reported on the catalytic properties of a series of

Cp–amido-type catalysts for the alternating co-polymerization of ethylene and cyclic olefins.[239] Additionally, Coates and Fujita described the application of a bis(phenoxy–imine) Ti complex with fluorinated *N*-aryl groups for the synthesis of alternating atactic ethylene/cyclopentene co-polymers with *cis*-1,2-cyclopentane units and PE-*b*-poly(ethylene-*co*-cyclopentene), further demonstrating the utility of the living bis(phenoxy–imine) Ti catalysts for the preparation of unique polymers (see Section 11.20.3.3).[240] Very recently, the first successful ethylene/cyclohexene (CHE) co-polymerization using non-bridged phenoxy–Cp-ligated Ti complexes **F13-4**/MAO was reported by Nomura and co-workers, who prepared ethylene/CHE co-polymers with a fairly high CHE content (max. 16.2 mol%, 423 kg-polymer mol-Ti^{-1} h^{-1}).[241]

11.20.4.2 Polystyrene and Related Polymers

Since the first report on the synthesis of syndiotactic polystyrene (sPS) by researchers at Idemitsu in the mid-1980s,[242–244] a considerable amount of research has been directed toward the development of highly active, syndiospecific catalysts for the polymerization of styrene.[245] This is because sPS is crystalline and displays an exceptionally high peak melting temperature of 270 °C. As such, sPS could replace existing engineering plastics such as nylon, polycarbonate, and polyesters. While metallocene catalysts typically convert styrene to atactic or syndiotactic PS with low productivity, mono-Cp-based Ti catalysts (particularly mono-indenyl-type Ti catalysts) combined with MAO can be high-activity catalysts for syndiospecific styrene polymerization.[246] Mechanistic studies have revealed that the syndiospecific polymerization is mediated by a cationic trivalent Ti species,[247–251] which proceeds via a chain-end control mechanism with 2,1-insertion.[252,253] Recently, Hou and co-workers demonstrated that the mono-Cp scandium dialkyl complex **F13-6** could be activated with $Ph_3CB(C_6F_5)_4$ into a monoalkyl cationic species. This is similar to the Ti(III) species mentioned above and is more stable toward over-reduction; this serves as an excellent syndiospecific styrene polymerization and ethylene/styrene co-polymerization catalyst.[254]

Isotactic PS is industrially less valuable than sPS due to its difficult processing characteristics. Although this polymer was first reported by Natta some 50 years ago,[255] until recently, heterogeneous Ziegler–Natta catalysts were the best (albeit inadequate) catalytic performers. It has been shown recently that some bridged metallocene catalysts are capable of promoting the isospecific polymerization of styrene. Researchers at Denka described how the zirconocene **F13-7** in conjunction with MAO forms highly isotactic PS with high efficiency (activity = 1 kg-PS mmol-Zr^{-1} h^{-1}, $M_w = 36\,000$, PDI = 1.90, *mmmm* > 90%, $T_m = 222$ °C).[256,257]

A series of *rac*-$[CH_2(3\text{-R-1-Ind})_2]ZrCl_2$ compounds with various alkyl substituents were examined as styrene-polymerization catalysts in the presence of hydrogen by Izzo and co-workers.[258] They demonstrated that a sterically encumbered ^{t}Bu group in **F13-8** gives rise to isoselective oligomerization with 1,2-monomer insertion though H, Me, and Et groups induce syndioselective polymerization with 2,1-insertion. In 2003, Okuda and co-workers reported on bis(phenoxy-thioether) group 4 metal complexes **F13-9** that produced highly isotactic PS via a site-control mechanism.[259] The first insertion of styrene into the Ti–Me bond of an active species has been demonstrated to occur exclusively in a 2,1-fashion.

An interesting class of styrene-based polymers is ethylene/styrene co-polymers, which have many promising applications as films or foams, as compatibilizers, and as modifiers for bitumens and asphalts. The preparation of these co-polymers by a variety of catalysts has been reported, including both heterogeneous and homogeneous catalysts, but the co-polymers thus obtained typically contained low levels (<4 mol%) of styrene incorporation or were heterogeneous in nature.[260,261]

Researchers at Dow discovered that linked Cp–amido-type catalysts could be remarkable catalysts for the co-polymerization of ethylene and styrene to form atactic co-polymers with up to about 50 mol% of styrene content.[262–264] Sernetz and Mülhaupt examined ethylene/styrene co-polymerization with linked Cp–amido catalysts in detail, and proved the ligand's effects on the co-polymerization behavior.[265–267] In an extension of Sernetz's study, Xu prepared perfectly alternating co-polymers with isotactic structures using $Me_2Si(Flu)(^tBuN)TiMe_2/Ph_3CB(C_6F_5)_4$.[268] Nomura *et al.*[269,270] and Arai *et al.*[257] achieved the incorporation of more than 50 mol% of styrene with **F13-4**/MAO (74 mol%) and with **F13-7**/MAO (up to 100 mol%), respectively. Recently, Zhang and Nomura demonstrated that a complex of the type $Cp^*TiCl_2(N{=}C^tBu_2)$ with MAO catalyzed ethylene–styrene living co-polymerizations.[271]

In 2000, Hou and co-workers revealed that Sm(II) complexes such as a Cp^*/2,6-diisopropylphenoxy-ligated Sm(II) complex with a neutral Cp^*K ligand, **F13-10**, could polymerize both ethylene and styrene and, surprisingly, could convert them into PE-*b*-PS in the co-presence of ethylene and styrene.[272] They suggested that the co-polymerization was initiated by ethylene polymerization followed by the successive incorporation of styrene. Additionally, a stereospecific ethylene/styrene block co-polymerization using *rac*-$[CH_2(3\text{-}t\text{-Bu-1-Ind})_2]ZrCl_2$ **F13-8** with MAO

activation has been described by Oliva and co-workers.[273] They obtained co-polymers containing isotactic PS blocks from the co-polymerization of ethylene and styrene. Styrene is suggested to be incorporated into the Zr–C bond via 1,2-insertion, which may account for the generation of styrene homosequences.

11.20.4.3 Polybutadiene and Related Polymers

Poly(1,3-butadiene)s with high 1,4-*cis* contents are valuable materials that have a wide range of applications as synthetic rubbers. A variety of transition metal-based catalysts have been investigated so far for the polymerization of 1,3-butadiene (BD), and now poly(BD)s possessing high 1,4-*cis* contents (94–98%) are industrially available with high efficiency using both early and late transition metal-based catalysts, including $TiI_4/I_2/Al^iBu_3$, $CoCl_2$·pyridine/$AlEt_2Cl/H_2O$, $Ni(OCOR)_2/AlEt_3/BF_3{\cdot}OEt_2$, and $NdCl_3/EtOH/Al^iBu_3$.[274–276]

A recent remarkable outcome for BD polymerization is the realization of 1,4-*cis* stereospecific living polymerization. Wakatsuki and co-workers reported that an Sm(III)/Al(III) heterobimetallic complex, $(C_5Me_5)_2Sm(\mu\text{-}Me)_2AlMe_2$, after activation with Al^iBu_3 and $[Ph_3C][B(C_6F_5)_4]$ produced narrow molecular weight distribution poly(BD)s with very high 1,4-*cis* contents (e.g., −20 °C, 1,4-*cis*-selectivity = 99%, M_n = 12 600, PDI = 1.24).[277,278] The utility of this stereospecific and living catalyst is demonstrated in the synthesis of random BD/styrene co-polymers and BD- and styrene-based block co-polymers, which have very high 1,4-*cis*-poly(BD) microstructure contents.

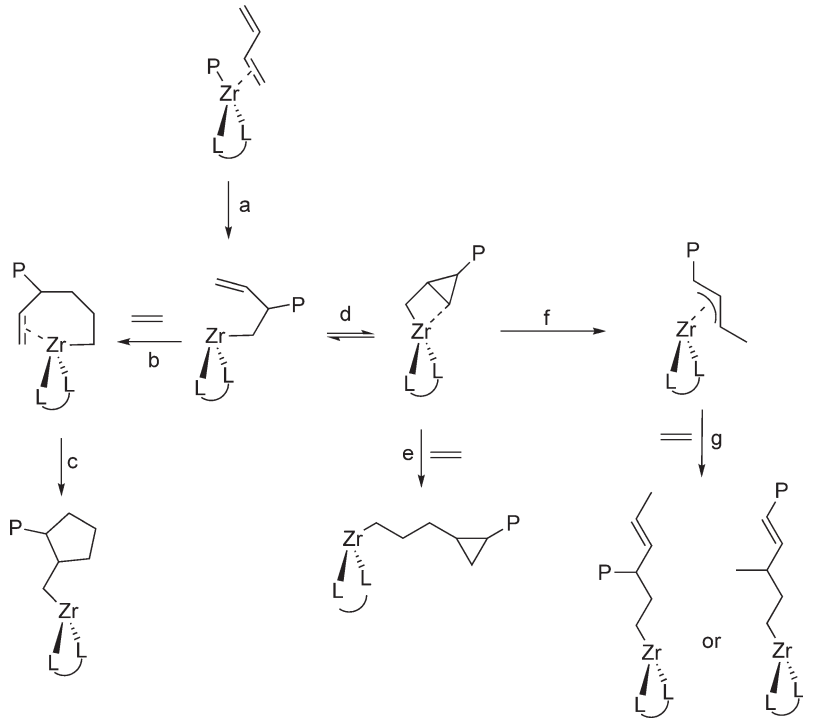
Alternatively, Soga and co-workers described how a series of $(C_5H_4R)TiCl_3$ compounds in association with MAO could mediate 1,4-*cis*-stereospecific living BD polymerization (e.g., R = ^{t}Bu, −25 °C, 1,4-*cis*-selectivity = 93.5%, M_n = 126 000, PDI = 1.04).[279] It was also revealed that an increase in the steric bulk of the substituent R results in an increase in both catalytic activity and 1,4-*cis*-selectivity.[280] Additionally, Shiono and co-workers found that stereospecific quasi-living BD polymerization could be catalyzed by a rather simple catalyst system composed of $CoCl_2$ and MAO (0 °C, 1,4-*cis*-selectivity = 98.2%, M_n = 361 000, PDI = 1.3).[280a]

Currently, non-metallocene group 4 metal complexes have been investigated for their potential as BD-polymerization catalysts. As Miyatake *et al.* reported, a bis(phenoxy)–thioether-ligated Ti complex converts BD into poly(BD) (activity = 52.8 kg-polymer mol-$Ti^{-1}\,h^{-1}$, 1,2-vinyl: 15%, 1,4-*trans*: 20%, 1,4-*cis*: 65%).[281] In addition, the BD-polymerization behavior of bis(phenoxy–imine) Ti catalysts was studied by Pellecchia *et al.*, who demonstrated that these catalysts displayed higher catalytic activity than $CpTiCl_3$/MAO and formed high molecular weight polymers with fairly high 1,4-*cis*-selectivity (79–86%).[282] Interestingly, these catalysts are also active for the polymerization of isoprene, unlike $CpTiCl_3$/MAO, which is inactive under analogous conditions.

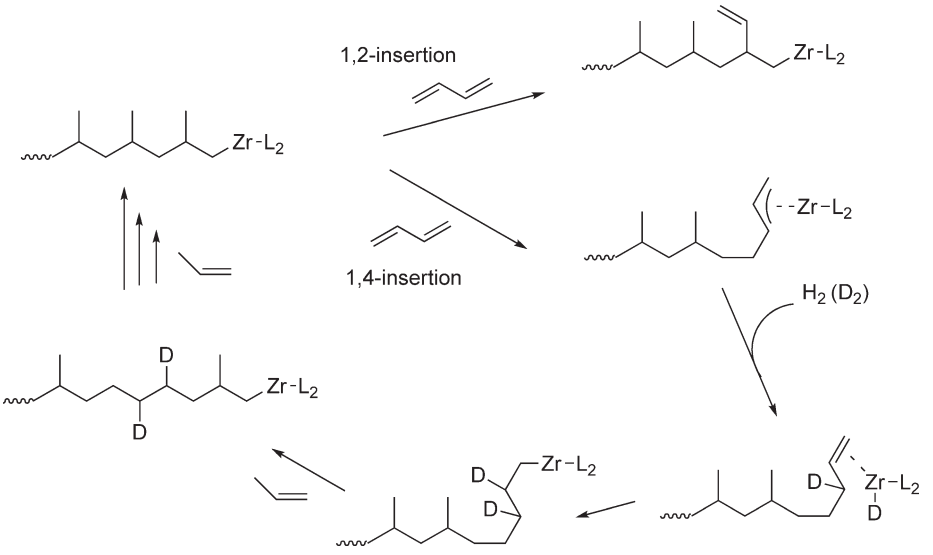
Recent advances in Cp-based catalyst technology made it possible to produce unique microstructure polymers from ethylene and BD. Longo and co-workers have reported in a series of publications the unprecedented cyclo-co-polymerization of ethylene and BD using a sterically encumbered isospecific metallocene **F13-8** with MAO, which affords 1,2-cyclopropane rings together with 1,2-cyclopentane rings in the polymer chain, both with high *trans*-selectivity (Scheme 8).[283–287] η^2-Primary BD coordination and insertion, which are induced by the steric hindrance exerted by the 3-*tert*-butyl group, followed by cyclization leads to the generation of a cyclopropane ring (Scheme 8, a–d–e). Interestingly, the same catalyst furnishes co-polymers containing only the unprecedented 1,1- and 1,3-constitutional units from BD, both presenting the (*E*)-configuration of a double bond, under high-temperature and low ethylene concentration conditions. The 1,1- and 1,3-constitutional units are formed through cyclopropane cleavage and consequent carbon skeleton isomerization followed by ethylene insertion (Scheme 8, a–d–f–g).

Waymouth and Choo revealed that $Me_2Si(1\text{-}Ind)(Flu)ZrCl_2$ in conjunction with MAO promoted ethylene/BD co-polymerization to yield a unique alternating co-polymer comprised of 1,2-cyclopentane and trimethylene units.[288] Alternatively, $[Me_2Si(Cp)(Flu)]NdCl$ in the presence of butyloctylmagnesium was reported by Boisson *et al.* as being capable of catalyzing alternating ethylene/BD co-polymerization to yield high molecular weight poly(ethylene-*alt*-*trans*-1,4-BD) with high efficiency.[289–293]

With respect to the preparation of vinyl group-containing polyolefins, Shiono and Ishihara succeeded in the selective synthesis of poly(propylene-*ran*-BD)s with pendant vinyl groups by the co-polymerization of propylene and BD using an isospecific zirconocene, *rac*-$Me_2Si(2\text{-}Me\text{–}4\text{-}Ph\text{–}1\text{-}Ind)_2ZrCl_2$, with MAO in the presence of hydrogen.[294] In this co-polymerization, hydrogen selectively transforms the π-allyl zirconocene species generated by the 1,4-inserted BD to the Zr–alkyl species, resulting in the realization of high catalytic activity and selectivity for the formation of polymers with pendant vinyl groups (BD content = 5.3–11.8 mol%, activity = 0.5–2.3 kg-polymer mol-$Zr^{-1}\,h^{-1}$, T_m = 94–125 °C) (Scheme 9). These vinyl group-containing polymers are useful precursors for functionalized polyolefins.



Scheme 8 Several pathways in ethylene/butadiene co-polymerizations leading to unique-structure polymers.



Scheme 9 A proposed mechanism for co-polymerization of propylene and butadiene to form isotactic polypropylenes with pendant vinyl groups.

11.20.4.4 Co-polymers of CO and Olefins

Alternating co-polymerization of olefins with carbon monoxide (CO), typically by using Pd-based catalysts, produces 1,4-polyketones (γ-polyketones) that exhibit unique material properties (e.g., high crystallinity, excellent mechanical properties, and high chemical resistance). Whereas Shell suspended their efforts to commercialize these polyketones,

research into olefin/CO alternating co-polymerization with Pd-based catalysts has still drawn considerable attention due to the attractive material properties and the great possibilities of this class of polymers as new materials.[295–297]

For ethylene/CO co-polymerization, perfect alternation is retained even in the presence of a very low concentration of CO, due to the fact that a stable Pd alkyl species chelated by the β-carbonyl group kinetically favors strongly coordinating and sterically less demanding CO insertion over ethylene insertion. Therefore, only when the CO is consumed does the catalyst start promoting the dimerization of ethylene to butenes. Interestingly, non-perfect alternating ethylene/CO co-polymerization with neutral Pd catalysts containing *o*-alkoxy derivatives of diphenylphosphinobenzene sulfonic acid was recently reported by Pugh and co-workers.[298]

Alternating co-polymers of α-olefin and CO can be isotactic or syndiotactic, depending on the direction of the alkyl substituent on the polymer backbone. Unlike regioregular α-olefin homopolymers, α-olefin/CO alternating co-polymers possess directionality along the polymer backbone due to the incorporation of CO. Accordingly, isotactic regioregular polyketones are chiral by virtue of their main-chain stereochemistry, whereas the syndiotactic congeners are achiral.

In the early 1980s, cationic Pd complexes bearing bidentate tertiary phosphine ligands were discovered to promote propylene/CO co-polymerization to form alternating co-polymers.[299,300] However, with the initial catalysts, the regioselectivity of the propylene was not well-controlled, and thus three kinds of regioisomers were present in the polymer backbone. It was later revealed that bidentate alkylphosphine and/or chiral phosphine-ligated complexes formed polyketones with high stereoregularity. A chiral catalyst is capable of selecting one of the two enantiofaces of α-olefins, and hence an isotactic alternating co-polymer can be produced using these catalysts.

In 1990, Wong disclosed in a patent literature that a propylene/CO alternating co-polymer arising from a Pd-based catalyst and (−)-4,5-bis(dibutylphosphinomethyl)–2,2-dimethyl–1,3-dioxolane as a chiral ligand displayed a specific rotation of $[\alpha]_D^{25} + 10.4$ in $(CF_3)_2CHOH$.[301] This represents the first example of asymmetric alternating co-polymerization of propylene with CO. While a number of excellent catalyst systems for the enantioselective alternating co-polymerization of α-olefins with CO have been developed to date, two of the most promising complexes concerning propylene are the chiral bidentate phosphine–phosphite-ligated Pd complex and the chiral bisphosphine-ligated Pd complex created by Nozaki **F13-11**[302,303] and Consiglio **F13-12**,[304] respectively. With these catalysts, the absolute configurations of the chirotopic carbon atoms are controlled with at least 95% ee (*S*) (Nozaki) and 98% ee (*R*) (Consiglio), respectively. Recently, Consiglio and co-workers showed that a Pd complex with a chiral ferrocene-based bisphosphine ligand **F13-13** affords extremely high catalyst productivity with nearly perfect regio- and stereoselectivity (50 °C, CO pressure = 7.5 MPa, 1.8 kg-polymer g-Pd^{-1} h^{-1}, $M_w = 14\,000$, dyad: 97.5%, $[\alpha]_D = -34.6$ in $(CF_3)_2CHOH$).[305]

In addition to the asymmetric co-polymerization of α-olefins with CO, similar reactions of styrenic monomers and CO have also been achieved with several catalyst systems. The major difference between an α-olefin co-polymerization and a styrenic monomer co-polymerization is the regiochemistry of the monomer insertion; an α-olefin is incorporated by 1,2-insertion, while a styrenic monomer is incorporated by 2,1-insertion. In 1994, Brookhart and co-workers first demonstrated the asymmetric alternating co-polymerization of 4-*tert*-butyl-styrene with CO using a chiral bisoxazoline-ligated Pd complex **F13-14** to provide a highly isotactic and optically active polymer.[306] Brookhart and Wagner subsequently prepared an isotactic–syndiotactic stereoblock polyketone using a ligand exchange, whereby the chiral bisoxazoline ligand is replaced with an achiral bipyridine ligand during the chain formation.[307]

The synthesis of syndiotactic alternating styrene/CO co-polymers with bidentate nitrogen-ligated Pd complexes has already been reported,[308–310] but thus far, there have never been any reports of α-olefin and CO-based congeners. Syndioselective alternating co-polymerization is believed to proceed via a chain-end control mechanism.

11.20.4.5 Functionalized Polyolefins

The addition of functionality to a polyolefin that is otherwise non-polar can greatly enhance the range of attainable properties (e.g., adhesion, wettability, dyeability, printability, and compatibility with other polymers), which widens the field to which polyolefin materials can be applied. Industrially, functionalized polyolefins are mainly produced using a high-temperature and high-pressure free-radical process. Thus, the products are limited to ethylene-based, relatively random-branched co-polymers. Therefore, the development of new methods that provide a wider range of functionalized polyolefins under milder conditions in a more controlled manner is a scientific challenge and an industrial goal. A number of methods have been investigated for producing functionalized polyolefins. These include the co-polymerization of hydrocarbon monomers with polar monomers,[311] a β-H transfer reaction (plus the

subsequent functionalization of olefinic moieties), a chain-transfer reaction involving a reactive chain-transfer agent, and living olefin polymerization. The following is a summary of recent advances in the methods mentioned above for the synthesis of functionalized polyolefins.

11.20.4.5.1 Co-polymerization of hydrocarbon monomers with polar monomers

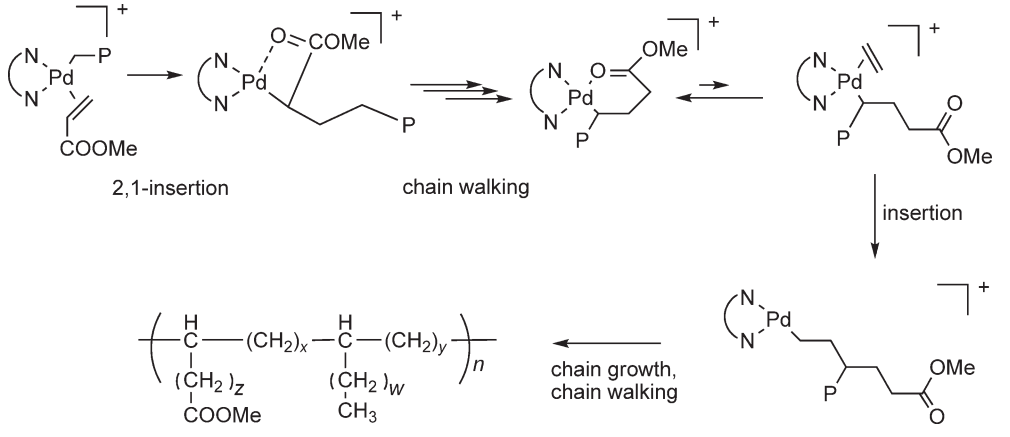
Regarding the co-polymerization of hydrocarbon and polar monomers, late transition metal catalysts have provided the most significant advances to date because of their lower oxophilicity and thus greater functional-group tolerance than early transition metal catalysts, although group 4 metallocene catalysts are known to promote the co-polymerization of olefins and non-vinyl polar monomers with masked functional groups.[312,313]

Ni phosphorus–ylide complexes were reported by Ittel and co-workers to be active for the co-polymerization of ethylene and non-vinyl-functionalized monomers, yielding functionalized polyethylenes (PEs). These results demonstrate the high potential of late transition metal complexes for the production of co-polymers from hydrocarbon and polar monomers.

In 1996, Brookhart and co-workers developed a remarkable class of Pd complexes with sterically encumbered diimine ligands (Scheme 4, **S4-1**, **S4-2**, **S4-4**, and **S4-5**). These examples are capable of mediating the co-polymerization of ethylene with methyl acrylate (MA) to furnish highly branched PE with ester groups on the polymer chain ends by a chain-walking mechanism (Scheme 10).[84] This represents the first example of transition metal-catalyzed ethylene/MA co-polymerization via an insertion mechanism. The mechanism for co-polymerization is by 2,1-insertion of MA and subsequent chelate-ring expansion, followed by the insertion of ethylene units.[314] The discovery of these diimine Pd catalysts has stimulated a resurgence of activity in the area of late transition metal-based molecular catalysis. Recently, the random incorporation of MA into linear PE by Pd-catalyzed insertion polymerization was reported by Pugh and co-workers.[315] They revealed that a neutral Pd catalyst **F13-15** generated *in situ* in combination with $Pd(OAc)_2$ or Pd(dibenzylideneacetone)$_2$ and di(2-methoxyphenyl)phosphinobenzene–2-sulfonic acid can co-polymerize ethylene with MA to provide co-polymers with linear structures (e.g., activity = 9 g-polymer mmol-Pd^{-1} h^{-1}, MA content = 17 mol%, M_n = 6400, PDI = 1.8).

Grubbs and co-workers have developed a new class of neutral Ni complexes incorporating bulky phenoxy–imine ligands **F13-16** that show considerable tolerance toward functional groups and even remain active in the presence of water.[316,317] These complexes can co-polymerize ethylene with functionalized NBs such as 5-norbornen-2-ol to provide cyclic olefin co-polymers with hydroxy or ester functionality. It has been reported that these Ni complexes are ineffective for the polymerization of MA due to β-H transfer from the enolate–Ni complex to the Ni metal.

Although much work on the development of transition metal catalysts for the co-polymerization of hydrocarbon and polar monomers has been reported (particularly in the patent literature), so far no effective means seems to exist for directly incorporating functionality into a polyolefin chain by using an industrially feasible process. With respect to polar monomer co-polymerization, Jordan *et al.*[318,319] and Boone *et al.*[320] thoroughly investigated ethylene and vinyl chloride, methyl methacrylate (MMA) and acrylonitrile co-polymerization by experimental and theoretical methods, and showed why these co-polymerizations were difficult to achieve.



Scheme 10 Co-polymerization of ethylene and methyl acrylate with a palladium–α-diimine complex.

11.20.4.5.2 β-H Transfer reaction

Polyolefins with vinyl end groups can be readily transformed into end-functionalized polyolefins by post-polymerization functionalization to yield a wide variety of end-functionalized polyolefins, which include epoxy-, amine-, and hydroxy-terminated polyolefins. Brookhart, Gibson, and co-workers reported on diimine–pyridine-ligated Fe complexes incorporating sterically less hindered alkyl substituents such as a methyl group *ortho* to the imine-*N*'s, **F12-1**, that selectively converted ethylene to oligomers, affording linear α-olefin mixtures (>99%) (see also Section 11.20.3.5).[194,321]

Effective catalyst systems for the production of polyolefins with vinyl groups were developed by Weng *et al.*[322] and by Ishii *et al.*[323] It was found by Weng and co-workers that *rac*-[Me_2Si(2-Me–4-Ph–1-Ind)$_2$]$ZrCl_2$ with MAO and *rac*-[$Me_2Si(Ind)_2$]$HfMe_2$ with [Me_2PhNH][$B(C_6F_5)_4$] produced vinyl-terminated isotactic PPs through β-Me elimination (vinyl selectivity = 60–80%, T_m = 140–150 °C). Additionally, bis(phenoxy–imine) Zr complexes with cycloalkyl groups on the imine-*N*'s in association with MAO were demonstrated by Ishii *et al.* to provide vinyl-terminated low molecular weight PEs with high efficiency (M_w = 2000–5000, vinyl selectivity > 90%).

These vinyl group-containing polymers may serve as new building blocks in the synthesis of functionalized polyolefins and polyolefin- and polar polymer-based block and graft co-polymers.

11.20.4.5.3 Chain-transfer reaction to a reactive chain-transfer agent

A reasonable synthetic procedure for functionalized polyolefins using a chain-transfer reaction would be direct synthesis by chain transfer to the aluminum species (which is typically used as a co-catalyst and/or a scavenger in a polymerization medium) during the course of the polymerization. Shiono and co-workers showed that propylene polymerization with $Me_2Si(Flu)(^tBuN)TiMe_2$ using MAO as a co-catalyst at 40 °C selectively formed Al-terminated moderately syndiotactic PP (*rr* = 60%).[324] Kim and Byun also reported that ethylene polymerization catalyzed by zirconocenes/MAO in the presence of allylbenzene produced Al-terminated PEs.[325] Michiue and Jordan demonstrated that a Ti(III) tris(pyrazolyl)borate complex in association with MAO exclusively formed Al-terminated PEs, which were readily converted to hydroxy-terminated PEs by air oxidation.[326,327] Likewise, very recently, Saito *et al.* reported on a bis(phenoxy–imine) Zr complex incorporating a 2-isopropylphenyl group on the imine-*N*, which, in combination with MAO or MAO/trimethylaluminum, afforded a wide variety of Al-terminated PEs with narrow to broad molecular weight distributions over a range of molecular weights.[328] These Al-terminated polyolefins can be transformed to a wide array of functionalized polyolefins and polyolefin- and polar polymer-based block and graft co-polymers by using established methods.

Reactive chain-transfer agents other than alkylaluminum compounds are also used for the synthesis of end-functionalized polyolefins. Marks and co-workers showed that primary and secondary silanes (e.g., $PhSiH_3$, $PhMeSiH_2$, Et_2SiH_2) could work as effective chain-transfer agents in early transition metal-catalyzed homogeneous[329] and heterogeneous[330] olefin-polymerization systems to control molecular weight and to selectively form silyl-capped and/or silyl-linked polyolefins. For example, they synthesized PhH_2Si-capped atactic PP with $Me_2Si(Me_4C_5)(^tBuN)TiMe^+B(C_6F_5)_4^-$ in the presence of $PhSiH_3$ (activity = 1.06 kg-polymer mmol-Ti^{-1} h^{-1}, M_n = 20 300, PDI = 2.0). Recently, Kawaoka and Marks demonstrated that this chemistry could be applicable to organolanthanide-catalyzed synthesis of phosphine-terminated polyethylenes.[331]

An analogous approach that provides polyolefins having terminal reactive groups with high productivity was developed by Chung and co-workers, who employed dialkylborane ($H–BR_2$) and *p*-methylstyrene/hydrogen (*p*-MS/H_2) as a reactive chain-transfer agent during metallocene-catalyzed olefin polymerization, and synthesized polyolefins with terminal borane and *p*-MS groups. These functionalized polyolefins were successfully converted to various block co-polymers (e.g., iPP-*b*-PS, PE-*b*-PMMA).[332–335]

Hessen and co-workers discovered that the reaction of ethylene with [$Cp^*_2La(C_4H_3S)$]$_2$ (prepared from [Cp^*_2LaH]$_2$ and thiophene) in the presence of thiophene formed thienyl-capped PE, $H(CH_2CH_2)_n$(2-C_4H_3S) (e.g., 80 °C, ethylene: 7.5 atm, activity = 27 g-polymer mmol-La^{-1} h^{-1}, M_w = 1300, PDI = 1.4). They revealed that C–H activation of thiophene was the only chain-transfer mechanism that is in operation, and that all of the PE chains produced under the conditions they examined were capped on one side by a thienyl group.[336]

MMA can function as a chain-transfer agent for late transition metal-catalyzed ethylene polymerization. Gibson and Tomov revealed that Ni complexes with bulky phosphino–enolate ligands, **F13-17**, were capable of polymerizing ethylene in the presence of MMA to afford MMA-end-capped PEs through immediate β-H transfer after MMA insertion.[337]

11.20.4.5.4 Living olefin polymerization

Living olefin polymerization allows the synthesis of end-functionalized polyolefins if appropriate initiation and/or quenching methods are used. Doi *et al.* first showed the utility of living olefin-polymerization catalysts for the preparation of end-functionalized polyolefins. They synthesized iodine-, amine-, aldehyde-, hydroxy-, and methacryl-terminated PPs using living V–PP species and appropriate reagents.[144]

Brookhart and co-workers have contributed significantly to the preparation of functionalized polyolefins with living olefin polymerization as well as polar monomer co-polymerization. In 1995, they reported the synthesis of functionalized benzene- and silyl-capped PEs using a β-agostic Co complex with an alkyl group including a functional group, **F10-6**.[147] It was subsequently demonstrated by Brookhart *et al.* that living ethylene polymerization with diimine-ligated Pd complexes, coupled with the use of a functionalized initiator and/or cleavage of the living Pd–polymer bond with an appropriate agent, yielded mono- and difunctionalized branched, amorphous PEs. For example, they prepared methyl ester-capped PE and telechelic PEs bearing one methyl ester and one ethyl ester, or one methyl ester and one aldehyde. The aldehyde functionality is achieved through 4-penten-1-ol insertion into the Pd–polymer bond, followed by Pd migration down the chain and β-H elimination.[159] Recently, ethylene- and/or α-olefin-based monodisperse (co)polymers that possess terminal reacting groups such as hydroxy and amine (e.g., HO–sPP–NH_2, $M_n = 9600$, PDI = 1.08) were successfully obtained using a living bis(phenoxy–imine) Ti complex.[153]

While living olefin polymerization is a useful tool for the synthesis of functionalized monodisperse polyolefins, this approach has a significant disadvantage in that only one polymer chain is made from one catalyst complex. Therefore, it is essential to develop a method that allows a considerable increase in the polymer/catalyst ratio. In 2003, Mitani *et al.* reported a unique strategy for the enhancement of catalyst productivity for the production of living polymers. They demonstrated that the combination of a living bis(phenoxy–imine) Ti complex and $ZnEt_2$ allowed the catalytic production of Zn-terminated monodisperse PEs.[338] Gibson and co-workers showed that ethylene polymerization with a diimine–pyridine-ligated Fe complex in the presence of $ZnEt_2$ resulted in the formation of Zn-terminated ethylene oligomers with narrow molecular weight distributions, thereby offering a method that enabled to generate monodisperse polyolefins efficiently.[339] The functionalized polyolefins described in this section can be used as macro-initiators for the synthesis of block co-polymers.

With respect to the synthesis of block co-polymers consisting of polyolefin and polar polymer segments, Yasuda and co-workers developed a new strategy for the synthesis of PE and polar polymer diblock co-polymers, which includes the sequential block co-polymerization of ethylene (insertion mechanism) followed by a polar monomer (non-insertion mechanism).[340] It should be pointed out that, due to the change of mechanism during the course of the polymerization, the reversal of monomer addition does not result in block co-polymer formation. With the above strategy, Yasuda and co-workers prepared linear diblock co-polymers, such as PE-*b*-PMMA (PE segment: $M_n = 10\,300$, PDI = 1.42; PMMA segment: $M_n = 24\,200$, PDI = 1.37) and PE-*b*-poly(ε-caprolactone) [PE segment: $M_n = 6600$, PDI = 1.40; poly(ε-caprolactone) segment: $M_n = 23\,900$, PDI = 1.76] using a Cp^*-based Sm complex.[341] Likewise, poly(1-hexene)-*b*-PMMA [poly(1-hexene) segment: $M_n = 21\,000$, PDI = 1.86; PMMA segment: $M_n = 35\,900$, PDI = 1.99] and poly(1-hexene)-*b*-poly(ε-caprolactone) [poly(1-hexene) segment: $M_n = 21\,000$, PDI = 1.86; poly(ε-caprolactone) segment: $M_n = 174\,800$, PDI = 2.52] were successfully synthesized using bridged binuclear Y and Sm complexes **F13-18**.[342] Additionally, a triblock co-polymer, PMMA-*b*-PE-*b*-PMMA, was obtained by Yasuda and co-workers using a Si-bridged Cp-based Sm complex (**F13-19** and **F13-20**) through a telechelic ethylene-bridged dinuclear species.[343]

Group 4 metallocene catalysts are also applicable to the above sequential block co-polymerization method to furnish polyolefin and polar polymer block co-polymers. Frauenrath *et al.*[344] and Chen and Jin[345] reported the synthesis of PE-*b*-PMMA and PP-*b*-PMMA, respectively, using metallocene catalysts (e.g., *rac*-$(C_2H_4)(Ind)_2ZrMe_2$/$B(C_6F_5)_3$, iPP-*b*-iPMMA; PP segment: $M_n = 8900$, PDI = 1.90; block co-polymer: $M_n = 10\,900$, PDI = 1.66, MMA content = 17.1 mol%).

11.20.4.5.5 Other methods

The (co)polymerization of dienes can be a good method for the preparation of polymers with reactive vinyl groups, a method that enables the preparation of polymers possessing plural vinyl groups per polymer chain. A fluorinated bis(phenoxy–imine) Ti complex was shown by Coates and co-workers to convert 1,5-hexadiene to poly(methylene–1,3-cyclopentane-*co*-3-vinyl tetramethylene), which contained multiple vinyl groups.[346] As already discussed, Saito *et al.* and others revealed that bis(phenoxy–imine) Ti complexes favored secondary insertion.[184–186] This is probably responsible for the formation of 3-vinyl tetramethylene units. Likewise, the same catalyst system can form sPP-*b*-poly(methylene–1,3-cyclopentane-*co*-3-vinyl tetramethylene) from propylene and 1,5-hexadiene. Very recently,

Shiono and co-workers developed a unique method for the preparation of polymers with pendant vinyl groups with an isospecific metallocene catalyst from propylene and BD in the presence of H_2. This method is introduced in Section 11.20.4.3.[294]

11.20.5 Miscellaneous

11.20.5.1 Heterogenization of Soluble Single-site Catalysts

Supported catalysts normally possess the technological advantages of good morphology control, high polymer bulk density, and little reactor fouling. Since most existing olefin-polymerization plants run as slurry or gas-phase processes with heterogeneous catalysts represented by $MgCl_2$-supported $TiCl_4$ catalysts, the immobilization of homogeneous molecular catalysts onto a support is essential for their applications to these processes. The most widely applied method of immobilizing homogeneous catalysts such as metallocene catalysts is to anchor them onto SiO_2 that has been pre-treated with MAO (SiO_2-supported MAO). Likewise, the immobilization of metallocene catalysts onto a SiO_2-supported borate compound has been studied extensively, much of which was disclosed in the patent literature. In addition to SiO_2, a number of organic as well as inorganic substrates (e.g., Al_2O_3, $CaCO_3$, $MgCl_2$, zeolites, clays, polypropylene, polystyrene, cyclodextrins) were examined as potential supports for MAO or borate compounds. It seems that catalyst leaching and decreasing in catalytic activity still remain a problem in these systems. Recent reviews cover much of the work described above.[347,348] Marks and co-workers have investigated the activation of transition metal alkyl complexes on a solid surface. For example, they showed that $(C_5Me_5)_2ThMe_2$ could be activated by $MgCl_2$, where the Lewis acidity of $MgCl_2$ led to the abstraction of a methide anion, generating a catalytically active actinide center for ethylene polymerization.[349] Alternatively, they have also studied sulfated metal oxides as an extremely strong Brønsted acidic surface.[350–354] Protonolysis of an M–C bond of transition metal complexes leads to the formation of cation-like species, which serve as highly active hydrogenation and olefin-polymerization catalysts.

Covalently attaching molecular catalysts to supports is a method that can minimize catalyst leaching. In 1998, a PS-supported titanocene was prepared by Barrett and de Miguel, which displayed 41 g-PE mmol-Ti^{-1} h^{-1} of activity.[355] Soga and co-workers reported a series of poly(siloxane)-supported metallocene catalysts. These supported catalysts combined with MAO were found to have high activity for the (co)polymerization of ethylene, propylene, and ethylene/1-octene, though the reaction products typically displayed broad molecular weight distributions.[356,357]

Miller and O'Hare demonstrated that a Si-bridged isospecific zirconocene grafted onto a mesoporous silica such as MCM-41 using a pendant Si–Cl anchor could produce an iPP with higher tacticity and molecular weight than its corresponding homogeneous counterpart, albeit exhibiting lower activity.[358] This is of great significance, since supported molecular catalysts normally display lower stereoselectivity than those of their solution-phase analogs. Notably, Sita and co-workers reported on a supported living-catalyst system consisting of a Cp^*–amidinate Zr complex (which behaves as a homogeneous living higher α-olefin catalyst with MAO activation, see Section 11.20.3.4) that was chemically tethered to a lightly cross-linked PS–divinylbenzene support, which polymerized higher α-olefins in a living and isospecific manner, and, moreover, created isotactic poly(1-hexene)-*b*-isotactic poly(1-octene).[359]

A unique immobilization strategy was developed by Alt, who synthesized metallocenes with alkene functionalities and employed these functionalized metallocene catalysts for polymerization.[360] During the polymerization process, the metallocene catalysts are consumed as a co-monomer, leading to the generation of polymer-supported metallocene catalysts.

In addition to the heterogenization of Cp-based catalysts, the heterogenization of recently emerging non-metallocene catalysts has attracted attention both in academia and in industry. Herrmann and co-workers reported that the immobilization of alkenyl-functionalized diimine–pyridine Fe complexes onto SiO_2 via hydrosilation resulted in the formation of highly active and temperature-stable catalysts that did not undergo any reactor fouling.[361] Recently, diimine Ni complexes covalently attached to SiO_2 were prepared by Brookhart and co-workers, which, in combination with $Et_3Al_2Cl_3$ (non-MAO system), displayed 10-fold higher activities than the corresponding SiO_2/MAO-supported systems and provided PE particles with good morphology.[362]

Jin and co-workers applied the self-immobilization method developed by Alt to group 4 bis(phenoxy–imine) complexes.[363] They demonstrated that Ti and Zr bis(phenoxy–imine) complexes with allyl-substituted phenoxy–imine ligands upon activation with MAO showed high ethylene-polymerization activity and form good morphology PEs. The same research group also demonstrated that this self-immobilization method was applicable to

phenoxy–imine-ligated single-component Ni catalysts.[364] Regarding group 5 metal catalysts, Chan *et al.* reported a PS imidovanadium catalyst that exhibited dramatically improved kinetic profiles for ethylene polymerization compared to its corresponding unsupported counterpart.[365]

Nakayama *et al.* have made seminal contributions in the field of the heterogenization of molecular catalysts. They developed a new and effective method for the immobilization and simultaneous activation of heteroatom-based molecular catalysts, resulting in the realization of MAO- and borate-free single-site catalysts capable of controlling polymer morphology.[366–369] Their catalysts are comprised of transition metal complexes with heteroatom-containing ligands, such as group 4 and 5 bis(phenoxy–imine) complexes, diimine-ligated Ni complexes and diimine–pyridine-ligated Fe complexes, and $MgCl_2/R^1{}_nAl(OR)_{3-n}$, prepared by the de-alcoholysis of an $MgCl_2$/alcohol adduct with alkylaluminum. With the above catalyst combinations, highly active, thermally robust V-based catalysts have been successfully developed. In addition, the $MgCl_2$-supported molecular catalysts allow access to unique polymers, such as sPP with exceptionally high T_m (155 °C), ethylene/propylene co-polymers in which the longer co-polymer chains possess higher propylene content, and ultra-high molecular weight non-coherent spherical PE particles of 10 μm in size.

The $MgCl_2$ support/activator technology was further developed by Chadwick *et al.*[370–372] and Mao *et al.*,[373,374] who reported on a similar $MgCl_2$-based compound, [$MgCl_2/R_nAl(OEt)_{3-n}$; R = Et, *i*-Bu], that could also work as a good support and activator for bis(phenoxy–imine) Ti complexes, diimine-ligated Ni complexes, and diimine–pyridine-ligated Fe complexes. The results obtained by Nakayama, Chadwick, and Mao clearly demonstrate the very high potential of $MgCl_2$-based compounds as support/activators for molecular catalysts incorporating heteroatom-containing ligands.

11.20.5.2 Combinatorial Approach for Finding New Catalysts

An important new technology to emerge in the field of chemistry over the past decade has been combinatorial chemistry, which was originally developed for the discovery of peptide-based drugs. Given the recent significant advances in rapid-synthesis and high-throughput screening techniques, using robotics as well as analysis systems, combinatorial chemistry offers numerous opportunities for both the discovery and optimization of drugs, agricultural chemicals, materials, and catalysts.[375,376]

The first combinatorial approach relevant to the development of olefin polymerization catalysts was reported in 1998 by researchers at Symyx, who carried out the screening of Ni and Pd complexes bearing a variety of diimine ligands (Brookhart catalysts), which were synthesized in the solid phase (using 1% cross-linked PS as a support) and tested for ethylene polymerization.[377] Subsequently, Chen and Hinderling performed the rapid screening of diimine-ligated Pd complexes for ethylene polymerization using electrospray-ionization tandem mass spectrometry (ESI-MS/MS). The ESI-MS/MS is shown to be a powerful tool for a combinatorial approach.[378] Combinatorial chemistry is also used for the efficient optimization of SiO_2 supports for metallocene catalysts, focusing on the morphology of the resultant polymers.[379]

Coates and co-workers extended a combinatorial approach to the screening of stereoselective propylene-polymerization catalysts using the bis(phenoxy–imine) Ti complexes. In consequence, they have identified one complex as a stereoselective catalyst (0 °C, *rr* = 88%, T_m = 108 °C) out of 78 possible complexes.[183] Additionally, Coates and Mason investigated the propylene-polymerization behavior of heteroligated bis(phenoxy–imine) Ti complexes using gel permeation chromatography (GPC) as a combinatorial-screening method, revealing that heteroligated catalysts could exhibit higher activity than their parent homoligated catalysts.[380]

Gibson and co-workers demonstrated the utility of combinatorial methods for discovering a highly active ethylene-polymerization catalyst.[381] Using a high-throughput screening methodology based on an empirically found bidentate phenoxy–imine Cr complex, they identified a tridentate phenoxy–imine–pyridine-ligated Cr complex **F13-21** that, in conjunction with MAO, gives an ethylene polymerization activity of 6.97 kg-PE mmol-Cr^{-1} h^{-1} at room temperature. This activity constitutes one of the highest activities exhibited by Cr-based catalysts. Similarly, the discovery of high-activity ethylene-polymerization catalysts based on imido–Ti complexes with Me_3[9]aneN_3 **F13-22** was reported by Mountford and co-workers, representing the first highly active group 4 imido–ethylene-polymerization catalysts (max. activity = 10.3 kg-PE mmol-$Ti^{-1}h^{-1}$, 100 °C).[382]

Scientists at Symyx and Dow have developed amide–ether Hf complexes **F13-23** using an integrated high-throughput screening methodology established by Symyx,[383] and shown outstanding catalytic properties for ethylene/1-octene co-polymerization in a high-temperature solution process.[384] Notably, the Hf catalysts equal or exceed the performance of the prototypical linked Cp–amido complex in terms of product molecular weight and co-monomer

incorporation, albeit displaying lower activity. With a further extension of this methodology, they discovered a significant class of C_1-symmetric catalysts for isospecific propylene polymerization.[139,140] The catalysts are composed of group 4 metals (Zr, Hf) and non-symmetric amide–pyridine ligands **F9-6**, which produce highly isotactic PPs with extremely high efficiency, even under solution-polymerization conditions. The discovery of such unique structure-catalysts appears to be more difficult without the use of the combinatorial approach.

With the remarkable outcomes that were introduced above, a large number of industrial chemical companies now view combinatorial chemistry as important to the future of catalyst development, though it is very expensive to sustain substantial investment both in capital and in resources in order to establish an advanced combinatorial capability.

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