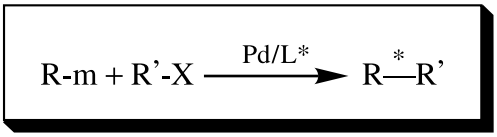


III.2.16 Palladium-Catalyzed Asymmetric Cross-Coupling

TAMIO HAYASHI

A. INTRODUCTION

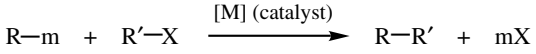
Palladium complexes as well as nickel complexes are known to catalyze the reaction of organometallic reagents (R—m) with alkenyl or aryl halides and related compounds (R′—X) to give cross-coupling products (R—R′), which provides one of the most useful synthetic means for making a carbon–carbon bond [1]–[5] (**Scheme 1**). The catalytic cycle of the reaction is generally accepted to involve an unsymmetrical diorganometal complex LnPd(II)(R)R′ as a key intermediate (**Sects. III.2.1–III.2.14**). From this intermediate the product R—R′ is released by reductive elimination to leave an LnPd(0) species that undergoes oxidative addition to R′—X, generating an intermediate LnPd(II)(X)R′. Transfer of an alkyl group from R—m to this intermediate by transmetallation reproduces the diorganometal complex. Since most of the palladium and nickel catalysts used successfully for the cross-coupling have tertiary phosphines as ligands, optically active phosphine ligands have conveniently been used to make the metal complexes function as chiral catalysts. As organometallic reagents (R—m), relatively reactive organomagnesium and organozinc reagents have often been used for asymmetric cross-coupling. Only a few examples have been reported on the application of cross-coupling with organoboron or organotin reagents to the asymmetric synthesis. The organic electrophiles (R′—X) used for the catalytic cross-coupling are aryl and alkenyl halides or pseudohalides, such as triflates, in which the new carbon–carbon bond is formed on the sp^2 carbon center, indicating that the creation of chiral carbon centers or chiral molecules by catalytic cross-coupling is not always easy. For asymmetric synthesis by this cross-coupling process, special systems have been designed. One is the reaction of secondary alkyl Grignard reagents, where a kinetic resolution of the racemic reagents is expected, and the other is enantioposition-selective asymmetric cross-coupling forming axially chiral and planar chiral molecules.

B. ASYMMETRIC CROSS-COUPLING OF SECONDARY ALKYL GRIGNARD AND ZINC REAGENTS

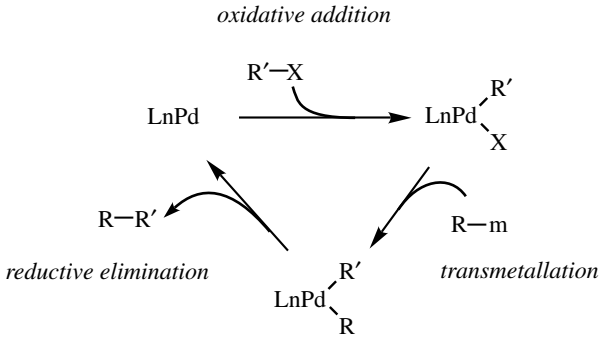
Asymmetric synthesis by the catalytic cross-coupling reaction has been studied most extensively with secondary alkyl Grignard reagents. Asymmetric cross-coupling with

Handbook of Organopalladium Chemistry for Organic Synthesis, Edited by Ei-ichi Negishi
ISBN 0-471-31506-0 © 2002 John Wiley & Sons, Inc.

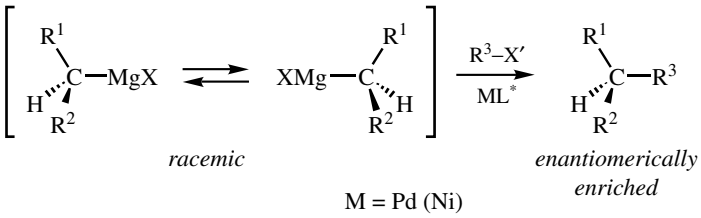
chiral catalysts allows transformation of a racemic mixture of the secondary alkyl Grignard reagent into an optically active product by kinetic resolution of the Grignard reagent. Since the secondary alkyl Grignard reagents usually undergo racemization at a rate comparable to the cross-coupling, the enantiomerically enriched coupling product is formed even if the conversion of the Grignard reagent is 100% (**Scheme 2**).



M = Pd (Ni)
m = Mg, Zn, Al, Zr, Sn, B, Si, etc.
R′ = aryl, alkenyl
X = Cl, Br, I, OSO_2CF_3, $OPO(OR)_2$, etc.



Scheme 1

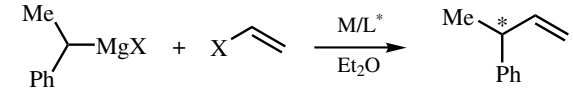


Scheme 2

In the first reported examples of asymmetric Grignard cross-coupling, a nickel complex coordinated with (−)-diop (**4**) was used as catalyst for the reaction of 1-phenylethyl Grignard reagent (**1**) with vinyl halide (**2**) giving (*R*)-3-phenyl-1-butene (**3**) and that of 2-butyl Grignard reagents with phenyl halides giving (*R*)-2-phenylbutane.[6],[7] The enantioselectivity was slightly dependent on the halide atoms of both the Grignard reagents and organic halides, the highest being 17% ee.

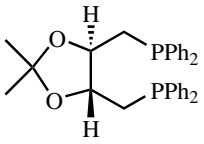
After these findings, asymmetric cross-coupling of the secondary alkyl Grignard reagents has been attempted using various kinds of optically active phosphine ligands. The reaction most extensively studied so far is that of 1-phenylethylmagnesium chloride

(**1**) with vinyl bromide (**2**) (**Scheme 3**). The cross-coupling proceeds generally in high yields in diethyl ether at 0 °C or lower temperature in the presence of not more than 1 mol% of the catalyst coordinated with chiral phosphine ligands. At an early stage, nickel complexes were mainly used. They are isolated nickel–phosphine complex $NiCl_2P^*$ or *in situ* catalyst generated from NiX_2 (X = Cl or Br) and a phosphine ligand L^*. The preformed palladium complex $PdCl_2L^*$ also catalyzes the asymmetric cross-coupling, although the examples of the use of palladium catalysts for this asymmetric Grignard cross-coupling are few. Some of the representative results obtained with nickel and palladium catalysts are summarized in **Scheme 3**.

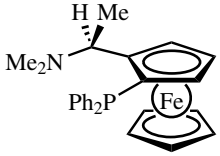


1: X = Cl, Br **2**: X = Br, Cl **3**

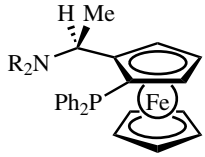
Enantiomeric purities of **3** obtained by nickel- (and palladium-) catalyzed cross-coupling of **1** with **2**. The ee values not specified are for the nickel-catalyzed reaction.

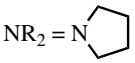


(–)-diop (**4**):
13% ee (*R*)[6],[7]

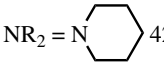


(*S*)-(*R*)-PPFA (**5**):
59–68% ee (*R*)[8],[9]
61% ee (*R*) (Pd)[9]

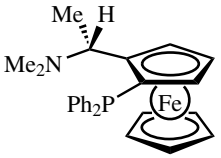




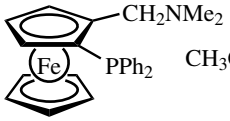
62% ee (*R*)[9]



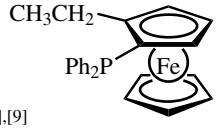
42% ee (*S*)[9]



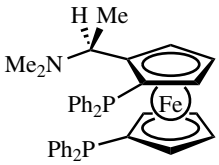
(*R*)-(*R*)-PPFA (**6**):
54% ee (*R*)[9]



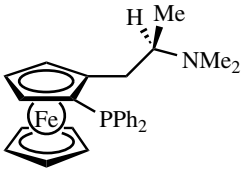
7: 65% ee (*S*)[8],[9]



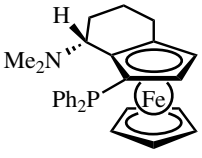
5% ee (*S*)[8],[9]



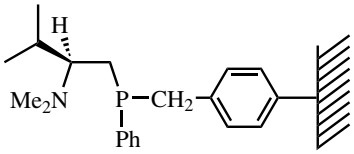
(*S*)-(*R*)-BPPFA (**8**):
65% ee (*R*)[9],[12]



17% ee (*R*)[10]

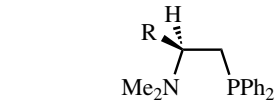


9: 79% ee (*R*) (Pd)[13]

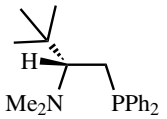


11: 49% ee (*S*)[16]

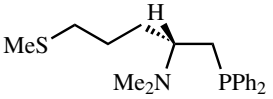
Scheme 3 (*Continued*)



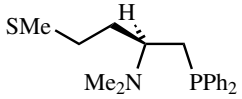
R = Me: (*S*)-alaphos (**10a**): 38% ee (*S*)[14],[15]
R = $PhCH_2$: (*S*)-phephos (**10b**): 71% ee (*S*)[14],[15]
R = *i*-Pr: (*S*)-valphos (**10c**): 81% ee (*S*)[14],[15]



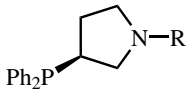
(*R*)-*t*-leuphos (**10d**):
83% ee (*R*)[14],[15]



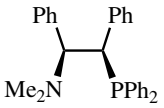
(*R*)-**12a**: 88% ee (*R*) [17]



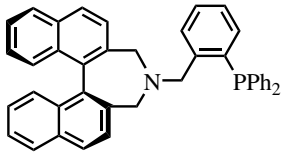
(*S*)-**12b**: 65% ee (*S*)[18]



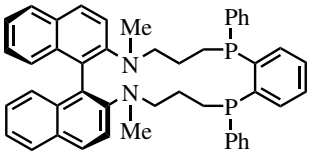
(*S*)-**13**
(R = CH_2Ph): 89% ee (*R*)[19],[20]



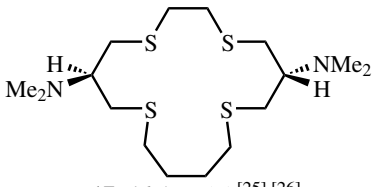
(1*R*,2*S*)-**14**:
66% ee[21] 65% ee (Pd)[21]



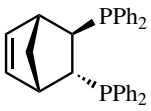
(*S*)-**15**: 46% ee (*R*)[22],[23]



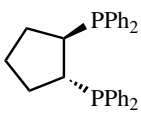
(*S*)-**16**: 16% ee (*R*)[24]



17: 46% ee (*R*)[25],[26]



(*R*,*R*)-norphos (**18**):
67% ee (*S*)[27]



19: 47% ee (*S*)[12],[28]

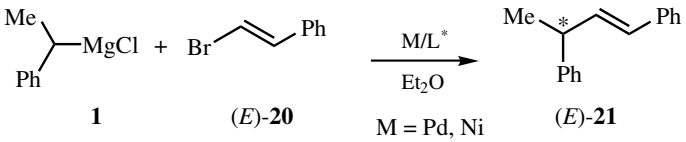
Scheme 3 (*Continued*)

It was found that the ferrocenylphosphines containing a (dialkylamino)alkyl group on the side chain are effective for the cross-coupling of **1** catalyzed by nickel complexes.[8]–[10] Ferrocenylmonophosphine, (*S*)-(*R*)-PPFA (**5**), and -bisphosphine, (*S*)-(*R*)-BPPFA (**6**), gave the coupling product **3** with 68% ee and 65% ee, respectively. The presence of the (dialkylamino)alkyl side chain is of primary importance for the high selectivity and the enantioselectivity is strongly affected by the structure of the dialkylamino group. The ferrocene planar chirality in **5** plays an important role in the enantiocontrol rather than the carbon central chirality on the ferrocene side chain, which is shown by comparison of the enantioselectivity with that observed with its diastereoisomer (*R*)-(*R*)-PPFA (**6**) or **7** that lacks the central chirality. A palladium catalyst coordinated with (*S*)-(*R*)-PPFA (**5**) ligand has been shown to have essentially the same enantioselectivity as the corresponding nickel catalyst.[9] The amino group is proposed to coordinate with the magnesium atom in the Grignard reagent at the transmetallation step in the catalytic cycle, where the coordination occurs selectively with one of the enantiomers of the racemic Grignard reagent to bring about high selectivity, although the coordination has not been supported by NMR studies of a palladium complex.[11] The influence of the extent of conversion on enantioselectivity has been studied in the reaction of the Grignard reagent **1** with **2** catalyzed by the nickel complex of (*S*)-(*R*)-BPPFA (**8**).[12] A ferrocenylphosphine **9**, which is

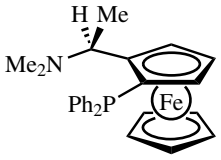
analogous to PPFA but has a tetrahydroindenyl moiety, was more enantioselective than PPFA (**5**) for Pd-catalyzed asymmetric cross-coupling of **1** with **2** to give (*R*)-**3** of 79% ee.[13]

Based on the high efficiency of the (dialkylamino)alkyl side chain on the ferrocenylphosphines, a series of β-(dialkylamino)alkylphosphines **10** was prepared and used for Ni-catalyzed cross-coupling. Those substituted with a sterically bulky alkyl group at the chiral carbon center are more effective than the ferrocenylphosphine ligands. Valphos (**10c**) and *t*-leuphos (**10d**), which were prepared starting with valine and *tert*-leucine, respectively, gave the product **3** with over 81% ee.[14],[15] Use of polymer-supported β-(dialkylamino)alkylphosphine ligand **11**, which is analogous to valphos (**10c**), gave 3-phenyl-1-butene (**6**) in somewhat lower enantiomeric purity.[16] A comparable enantioselectivity was observed with the β-(dialkylamino)alkylphosphines **12** containing a sulfide group on the alkyl chain.[17],[18] The sulfur-bearing alkyl group is more effective than the simple alkyl side chain, the highest (88% ee) being obtained with **12a**, which is derived from homomethionine. Several 3-diphenylphosphinopyrrolidine-type ligands were prepared and used for the Ni-catalyzed Grignard cross-coupling of 1-phenylethylmagnesium chloride (**1**).[19],[20] The *N*-benzyl derivative **13** is most effective giving (*R*)-**3** of 89% ee in the reaction with vinyl chloride. An asymmetric amplification was observed to some extent in the asymmetric cross-coupling with ligands **13**. The enantioselectivities of palladium and nickel catalysts were shown to be the same (65–66% ee) in the reaction with the new chiral (β-aminoalkyl)phosphine ligand (1*R*,2*S*)-**14**, which was derived from *erythro*-2-amino-1,2-diphenylethanol.[21] Other (aminoalkyl)phosphines, based on the axially chiral 1,1′-binaphthyl skeleton, **15**[22],[23] and **16**,[24] have also been used for this Ni-catalyzed Grignard cross-coupling. Several chiral macrocyclic sulfides have been prepared and examined as chiral ligands for the Ni-catalyzed coupling reaction, although the enantioselectivity was not so high (46% ee with the tetrasulfide ligand **17**).[25],[26] Nickel catalyst complexed with unfunctionalized chelating bisphosphine ligands, (*R*,*R*)-norphos (**18**)[27] and **19**[12],[28], induced a high selectivity. Some other chiral ligands have also been used for the Ni-catalyzed reaction, but the enantioselectivities observed are generally low.[29]–[33]

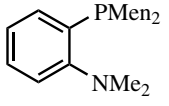
In the reaction of 1-phenylethylmagnesium chloride (**1**) with (*E*)-β-bromostyrene (**20**) forming (*E*)-1,3-diphenyl-1-butene (**21**) (**Scheme 4**), a palladium catalyst coordinated with PPFA (**5**) exhibited higher enantioselectivity (73% ee) than a nickel catalyst of the identical chiral ligand (52% ee).[9],[11] Palladium complexes of dimenthylphosphine **22**,[34] 1-phenylethylamine derivative **23**,[35] and norbornane derivative **24**[36] have also been examined, though the enantioselectivity was not always high. Phosphinoferrocenyloxazoline (*S*)-(*S*)-**25** was a more stereoselective ligand than its diastereomeric isomer for the Pd-catalyzed reaction of 1-phenylethylmagnesium chloride (**1**) with (*E*)-**20** to give (*E*)-**21** of 45% ee.[37] High enantioselectivity (94% ee) was reported by use of a nickel catalyst coordinated with (β-aminoalkyl)phosphine ligand (1*R*,2*S*)-**14**.[21] This is the highest selectivity for the cross-coupling of **1** with (*E*)-**20** in the presence of nickel or palladium catalyst. Nickel complexes coordinated with phosphinophenyloxazolines (*S*)-**26** were studied with regard to its structure and their use for asymmetric cross-coupling with (*Z*)-β-bromostyrene ((*Z*)-**21**).[38] Interestingly, the enantioselectivity in the reaction of (*E*)-**21** in the presence of (*S*)-**26a** was much lower (8% ee) than that (45% ee) of (*Z*)-**21**. Reverse of the enantioselection was observed with ligand **26b**, which contains a hydroxymethyl group in place of isobutyl.



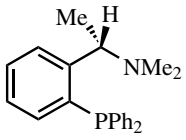
1 (*E*)-**20** M = Pd, Ni (*E*)-**21**



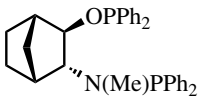
(*S*)-(*R*)-PPFA (**5**):
52% ee (*R*) (Ni)[9]
73% ee (Pd)[11]



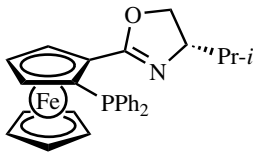
22: 11% ee (*R*) (Pd)[34]



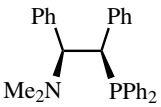
23: 40% ee (*R*) (Pd)[35]



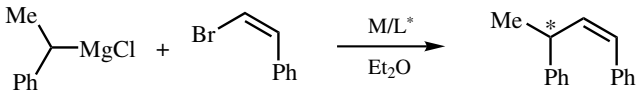
24: 13% ee (*S*) (Pd)[36]



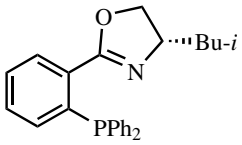
(*S*)-(*S*)-**25**: 45% ee (*S*) (Pd)[37]



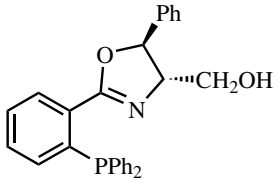
(1*R*,2*S*)-**14**: 94% ee (Ni)[21]



1 (*Z*)-**20** M = Pd, Ni (*Z*)-**21**



(*S*)-**26a**: 45% ee (*S*)[38]

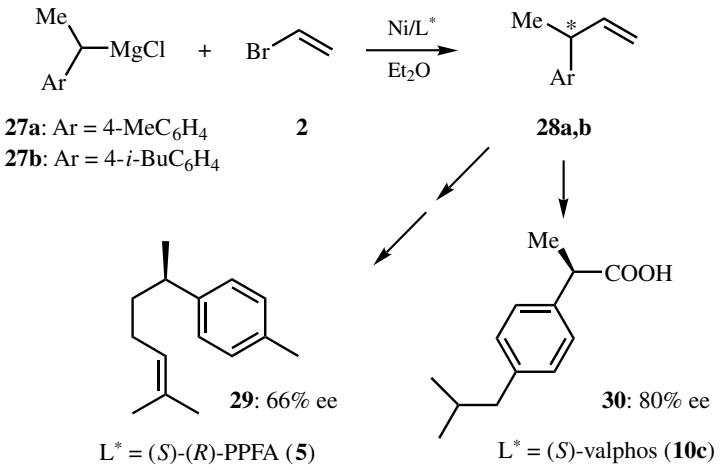


(*S,S*)-**26b**: 41% ee (*R*)[38]

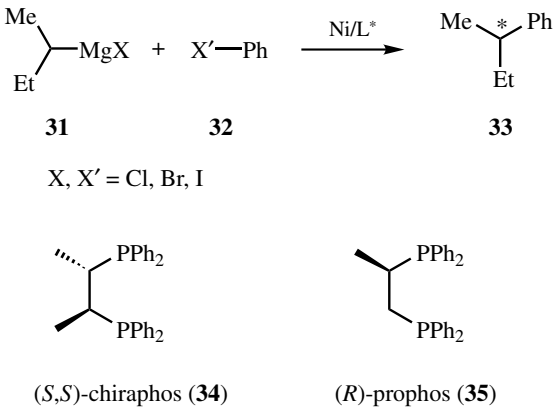
Scheme 4

For Ni-catalyzed asymmetric cross-coupling of 1-aryl-substituted ethyl Grignard reagents **27** with vinyl bromide (**2**), the chiral ferrocenylphosphine (*S*)-(*R*)-PPFA (**5**) and β-(dialkylamino)alkylphosphines **10** are used (**Scheme 5**). The enantioselectivity is as high as that for the reaction of the 1-phenylethyl Grignard reagent (**1**). The coupling product (*R*)-**28a** was converted by a sequence of reactions into α-curcumene (**29**) of 66% ee.[39] Oxidation of the coupling product **28b** gave optically active 2-(4-isobutylphenyl)propionic acid (ibuprofen) (**30**, 80% ee), which is an anti-inflammatory agent.[15]

Asymmetric cross-coupling of secondary alkyl Grignard reagents that do not contain an aryl group such as phenyl on the chiral carbon center has not been so successful in terms of enantioselectivity as that of the 1-arylethyl Grignard reagent. The reaction of the 2-butyl Grignard reagents **31** with phenyl halides **32** was studied with nickel catalysts complexed with chiral homologues of 1,2-bis(diphenylphosphino)ethane (**Scheme 6**).[27],[40],[41] Palladium catalysts have not been used for this type of Grignard



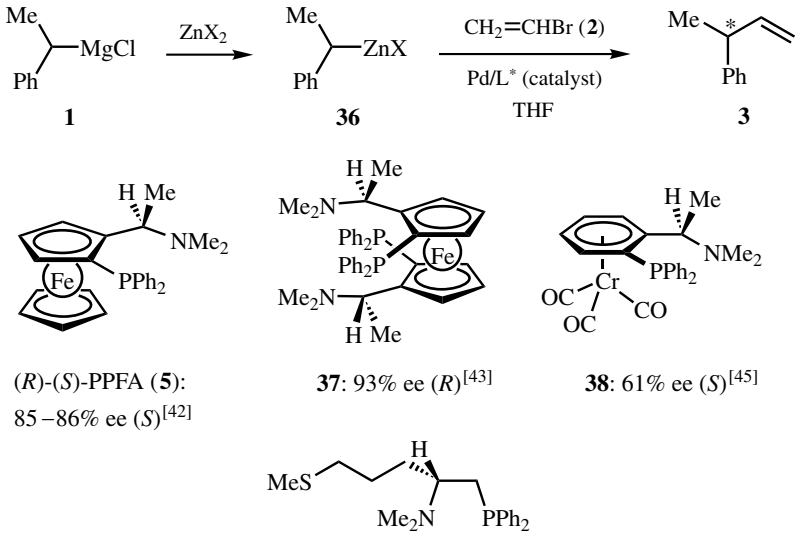
Scheme 5



Scheme 6

reagents. The highest enantiomeric purity (55% ee) of the product, 2-phenylbutane (**33**), was obtained in the reaction of **31** (X = Br) with **32** (X′ = Br) in the presence of a nickel complex coordinated with 1,2-bis(diphenylphosphino)cyclopentane (**19**). Use of (*S*,*S*)-chiraphos (**34**) as a chiral ligand produced (*S*)-**33** of 43% ee. Detailed studies on the reaction of **31** (X = Cl, Br, I) with **32** (X′ = Cl, Br, I) in the presence of nickel/(*R*)-prophos (**35**) catalyst revealed that the absolute configuration of the coupling product as well as the enantioselectivity is dependent on the halogen atoms in both the Grignard reagent and phenyl halides.

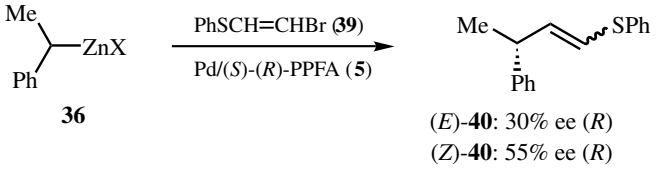
Use of 1-phenylethylzinc reagents in place of the corresponding Grignard reagents sometimes increases the stereoselectivity (**Scheme 7**). The reaction of zinc reagents is usually more efficiently catalyzed by palladium complexes than nickel complexes. The reaction of zinc reagents **36** prepared from **1** with a zinc halide in THF in the presence of a palladium catalyst coordinated with a chiral ferrocenylphosphine [(*R*)-(*S*)-PPFA (**5**)] proceeded with 85–86% enantioselectivity.[42] The selectivity is higher than that observed for the reaction with 1-phenylethyl Grignard reagent (see also **Scheme 3**). The highest



Scheme 7

enantioselectivity in the formation of (*R*)-**3**, 93% ee, was obtained with the C_2-symmetric ferrocenylphosphine ligand **37** containing two phosphorus atoms and two aminoalkyl side chains on the ferrocene skeleton.[43],[44] An aminoalkylphosphine **38** ligand, which is analogous to PPFA (**5**) but having the (η^6-benzene)chromium structure in place of ferrocene, showed a slightly lower selectivity (61% ee) in the reaction of 1-phenylethylzinc reagent.[45] Nickel catalysts of aminoalkylphosphines **12** have been used for asymmetric cross-coupling of the zinc reagent **36**,[46],[47] which gave (*R*)-**3** of 70% ee.

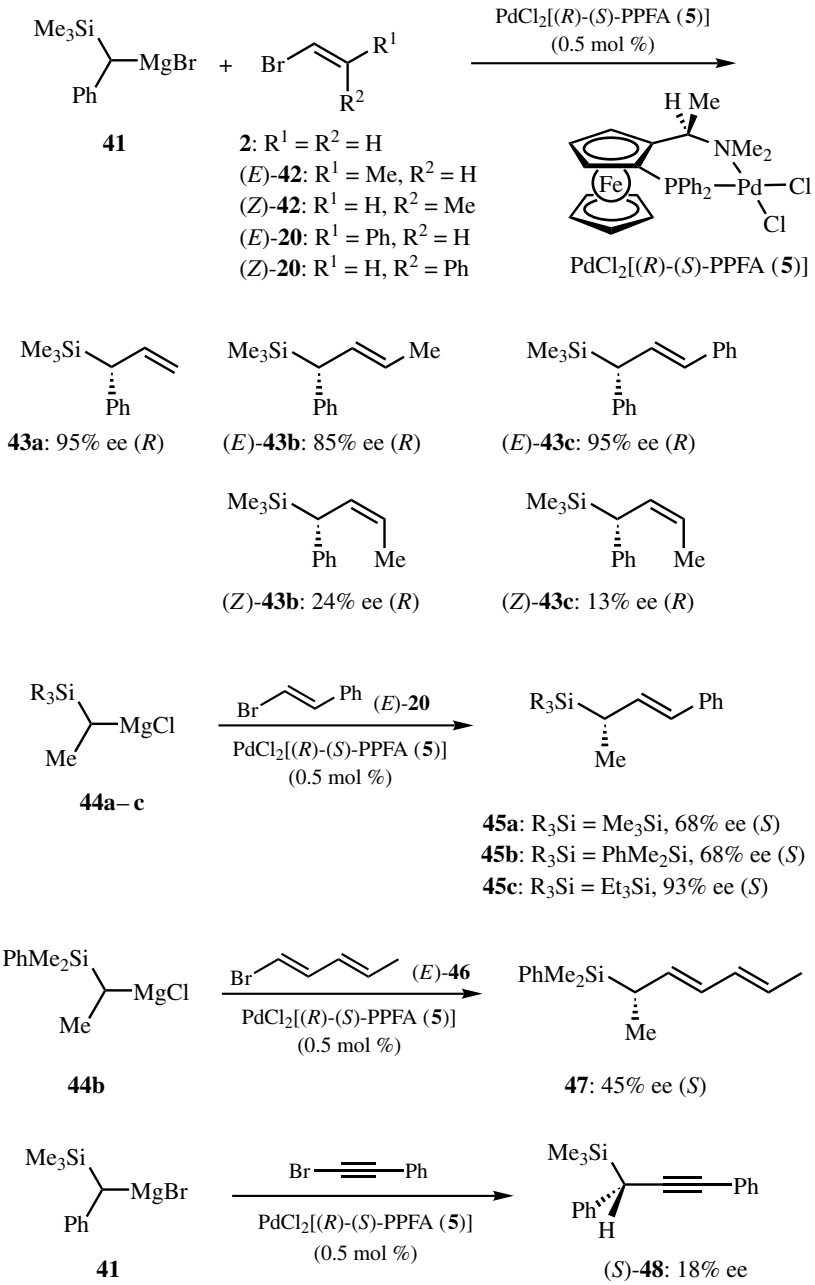
In the asymmetric cross-coupling of the zinc reagent **36** catalyzed by Pd/(*S*)-(*R*)-PPFA (**5**), (*E*)-β-bromostyrene (**20**)[42] and (*E*)- and (*Z*)-1-bromo-2-(phenylthio)ethenes (**39**) have also been used. Enantiomerically enriched alkenyl sulfides **40** could undergo the second cross-coupling, the sulfide being replaced by the Grignard reagent in the presence of a nickel catalyst (**Scheme 8**).[48]



Scheme 8

As a coupling partner of 1-phenylethyl Grignard reagent **1**, allyl phenyl ether gave (*R*)-4-phenyl-1-butene of 58% ee in the reaction catalyzed by $NiCl_2$[(*S*,*S*)-chiraphos (**34**)].[49]

Pd-catalyzed asymmetric cross-coupling was successfully applied to the synthesis of optically active allylsilanes (**Scheme 9**).[50],[51] The reactions of α-(trimethylsilyl)benzylmagnesium bromide (**41**) with vinyl bromide (**2**), (*E*)-bromopropene ((*E*)-**42**), and



Scheme 9

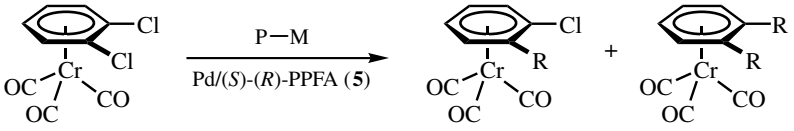
(*E*)-bromostyrene ((*E*)-**20**) in the presence of 0.5 mol % of a palladium complex coordinated with chiral ferrocenylphosphine, (*R*)-(*S*)-PPFA (**5**), gave the corresponding (*R*)-allylsilanes (**43**) with 95%, 85%, and 95% ee, respectively, which were substituted with phenyl group at the chiral carbon center bonded to the silicon atom. These allylsilanes were used for the $S_{E'}$ reactions forming optically active homoallyl alcohols and π-allylpalladium complexes.

A lower stereoselectivity was observed with the (*Z*)-alkenyl bromides (*Z*)-**42** and (*Z*)-**20**. The palladium/PPFA catalyst was also effective for the reaction of 1-(trialkylsilyl)ethylmagnesium chlorides **44** with (*E*)-bromostyrene ((*E*)-**20**). The enantioselectivity was dependent on the trialkylsilyl group, triethylsilyl being the best to produce (*S*)-1-phenyl-3-silyl-1-butene (**45c**) of 93% ee. The dienylsilane (*S*)-**47**, which is 45% enantiomerically pure, was also prepared by asymmetric cross-coupling with the dienyl bromide (*E*)-**46**. Pd-catalyzed asymmetric cross-coupling of α-(trimethylsilyl)benzylmagnesium bromide (**41**) was also applied for the synthesis of the optically active propargylsilane **48** (18% ee) by using 1-bromo-2-phenylacetylene as a coupling partner.[52]

C. ENANTIOPOSITION-SELECTIVE ASYMMETRIC CROSS-COUPLING

Pd-catalyzed asymmetric cross-coupling has been applied to asymmetric synthesis of planar chiral tricarbonyl(η^6-*o*-dichlorobenzene)chromium complexes and axially chiral biaryl molecules by an enantioposition-selective reaction.

Planar chiral tricarbonyl(η^6-arene)chromium complexes were prepared by catalytic asymmetric cross-coupling of tricarbonyl(η^6-*o*-dichlorobenzene)chromium (**49**) with alkenyl- or arylmetal reagents (**Scheme 10**).[53],[54] In the presence of 10 mol % of a palladium catalyst generated from $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and ferrocenylmonophosphine (*S*)-(*R*)-PPFA (**5**), an enantioposition-selective substitution of one of the chloride atoms takes place to give the planar chiral monosubstitution products **50** together with a minor amount of the disubstitution products **51**, which are achiral. The highest enantiomeric excess of the monosubstitution product is 69% ee, which was reported for the phenylation of **49** with phenylboronic acid to afford (1*S*,2*R*)-**50a**. Alkenylation with ethenylboronic acid or propen-2-ylboronic acid also proceeded enantioselectively to give the corresponding monoalkenylation product **50b** (38% ee) or **50c** (44% ee). Interestingly, use of ethenyltributyltin as the vinylation reagent in place of ethenylboronic acid resulted in the formation of the racemic product **50b** while use of ethenylzinc chloride gave **50b** of 42% ee.



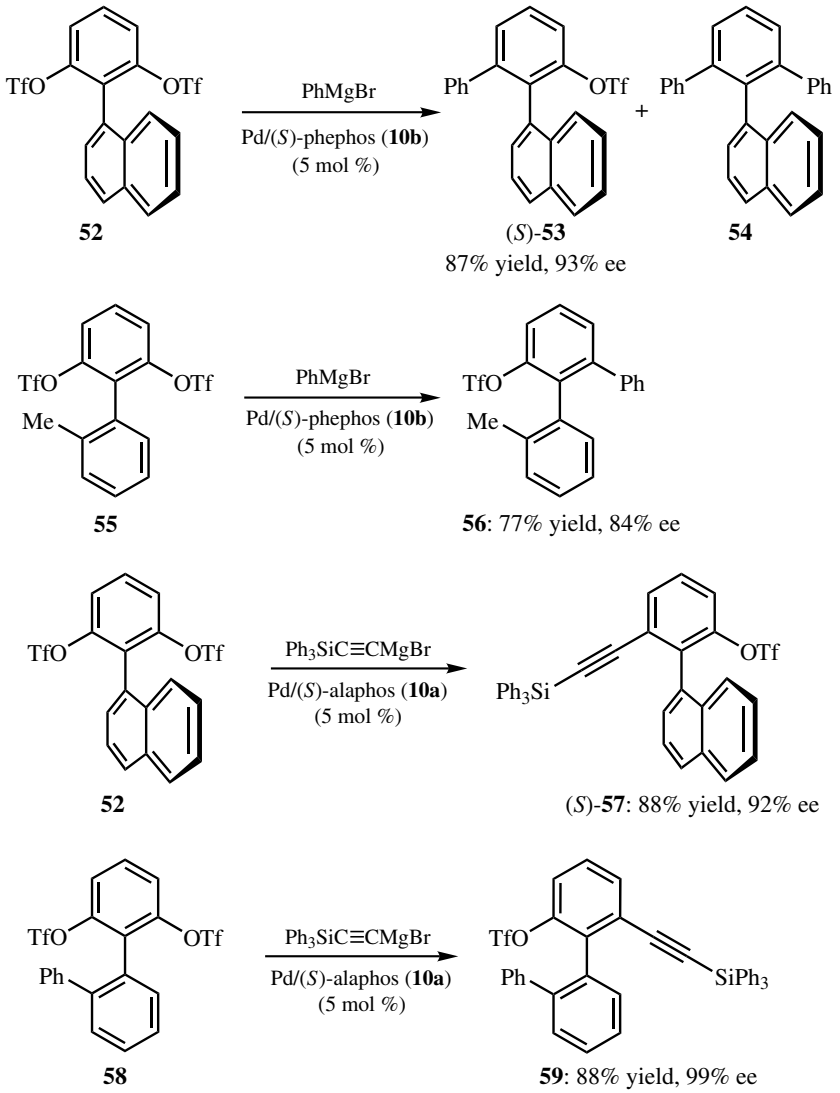
49 —M = —$B(OH)_2$, —ZnCl, —$SnBu_3$ (1*S*,2*R*)-**50a–c** **51**

a: R = Ph
b: R = CH=CH_2
c: R = CMe=CH_2

Scheme 10

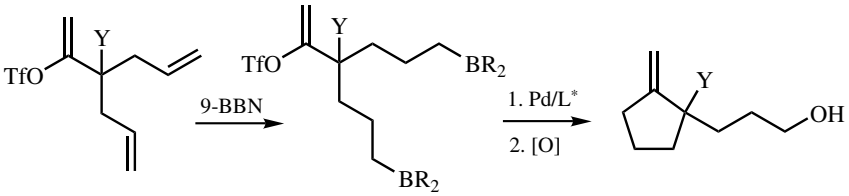
Enantioposition-selective asymmetric cross-coupling has also been successfully applied to the synthesis of axially chiral biaryl molecules (**Scheme 11**).[55],[56] Reaction of the achiral ditriflate **52** with 2 equiv of phenylmagnesium bromide in the presence of lithium bromide and 5 mol % of $PdCl_2$[(*S*)-phephos (**10b**)] at −30 °C for 48 h gave an 87% yield of the monophenylation product (*S*)-**53**, which is 93% ee, and a 13% yield of diphenylation product **54**. The enantiomeric purity of the monophenylation product

(*S*)-**53** is dependent on the yield of the diphenylation product **54**. A kinetic resolution is demonstrated to take place at the second cross-coupling forming **54**. The minor isomer at the first cross-coupling, that is, (*R*)-**53**, is consumed five times faster than the major isomer (*S*)-**53** at the second cross-coupling, which causes an increase in the enantiomeric purity of (*S*)-**53** as the amount of **54** increases. High enantioselectivity was also reported in the reaction of *o*-tolyl analog **55**, which gave the monophenylation product **56** of 84% ee. For enantioposition-selective alkynylation, the (*S*)-alaphos (**10a**) ligand is more enantioselective than (*S*)-phephos (**10b**).[57] For examples, the reaction of achiral ditriflates **52** and **58** with (triphenylsilyl)ethynylmagnesium bromide in the presence of a palladium catalyst coordinated with (*S*)-alaphos (**10a**) gave the corresponding monoalkynylation products (*S*)-**57** (92% ee) and **59** (99% ee), respectively.



Scheme 11

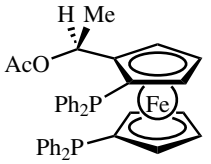
Intramolecular cross-coupling of prochiral triflate **61a**, which contains a pair of enantiotopic alkylboranes and is generated by hydroboration of prochiral diene **60a**, was examined with palladium catalysts coordinated with several chiral phosphine ligands (**Scheme 12**).[58] Highest enantioselectivity in forming cyclopentane derivative (*R*)-**62a** of 28% ee was observed with ferrocenylbisphosphine **63**. In the cyclization of **60b**, which has a quaternary carbon center, the enantioselectivity was a little higher, PPFA (**5**) giving **62b** of 31% ee.



60a: Y = H
60b: Y = CH_2OSiMe_2Bu-*t*

61

62a: 28% ee (*R*)
62b: 31% ee (*R*)



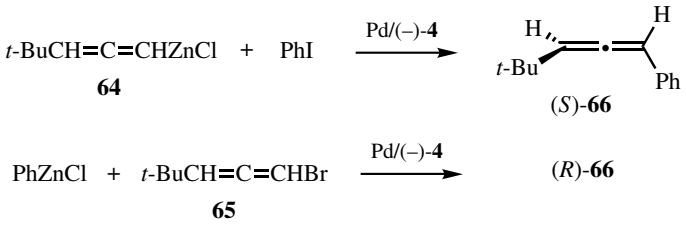
(*S*)-(*R*)-BPPFOAc (**63**)

Scheme 12

D. OTHERS

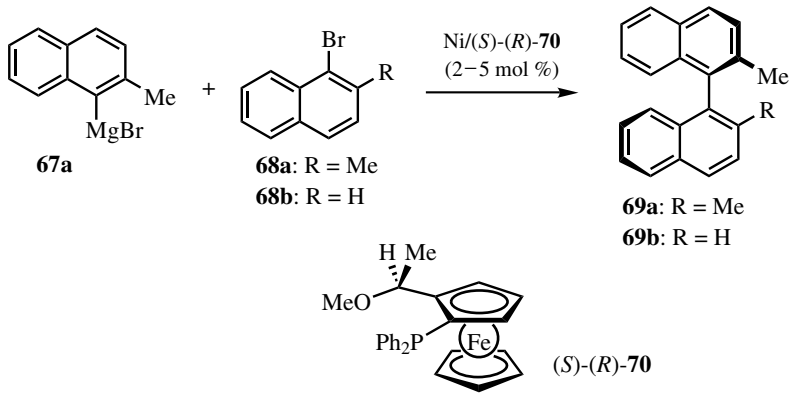
A chiral allene compound has been prepared by a Pd-catalyzed cross-coupling reaction of 4,4-dimethylpenta-1,2-dienylzinc chloride (**64**) with phenyl iodide or of 1-bromo-4,4-dimethylpenta-1,2-diene (**65**) with phenylzinc chloride (**Scheme 13**).[59] The highest enantiomeric purity (25% ee) of the allene (*S*)-**66** was obtained in the former coupling with (*R*,*R*)-diop (**4**) as chiral ligand. Interestingly, the enantiomeric purity was independent of the ratio of the reagents although the reaction seems to involve a kinetic resolution of the racemic **64**.

Ni-catalyzed asymmetric cross-coupling has been applied to the synthesis of axially chiral binaphthyls by the cross-coupling of two 1-naphthyl fragments. Unfortunately, no palladium complexes have been used for this type of reaction, probably due to their lower catalytic activity for the reaction of sterically bulky substrates. The reaction of



Scheme 13

2-methyl-1-naphthylmagnesium bromide (**67**) with 1-bromo-2-methylnaphthalene (**68a**) forming 2,2′-dimethyl-1,1′-binaphthyl (**69a**) has been examined using nickel catalysts coordinated with several chiral phosphine ligands (**Scheme 14**). Initial studies with (−)-diop (**4**), (*S*)-(*R*)-BPPFA (**8**), and (*S*)-2,2′-bis(diphenylphosphinomethyl)-1,1′-binaphthyl, gave rather poor enantioselectivities (2%, 5%, and 13% ee, respectively).[29],[60] Use of the ferrocenylphosphine ligand (*S*)-(*R*)-**70**, which is a chiral monophosphine ligand containing a methoxy group on the side chain, dramatically increased the selectivity to produce a high yield of (*R*)-**69a** with 95% ee.[61] High enantioselectivity was also attained in the reaction of **67** with 1-bromonaphthalene (**68b**), which gave (*R*)-2-methyl-1,1′-binaphthyl (**69b**) with 83% ee. Ni-catalyzed cross-coupling of the naphthyl Grignard reagent **67** was extended to the asymmetric synthesis of ternaphthalenes.[62] Reaction of 1,5-dibromonaphthalene with 2 equiv of **67** in the presence of nickel/(*S*)-(*R*)-**70** catalyst gave a high yield of ternaphthalene consisting of chiral and meso isomers in a ratio of 84:16. The chiral isomer turned out to be 98.7% enantiomerically pure with the (*R*,*R*) configuration. The very high enantiomeric excess can be rationalized by the double asymmetric induction at the first and the second cross-couplings.



Scheme 14

By Ni-catalyzed asymmetric cross-coupling, the Grignard reagents 2-phenylpropylmagnesium chloride and 2-norbornylmagnesium chloride that do not undergo the racemization have been resolved kinetically in the reaction with less than 1 equiv of vinyl bromide, although the efficiency of the resolution is not high.[63] Several chiral ferrocenylsulfides, which are analogous to PPFA (**5**) or BPPFA (**8**) but have a sulfide group instead of diphenylphosphino group, were used for the reaction of allylmagnesium chloride with 1-phenylethyl chloride in the presence of nickel or palladium catalysts to give 4-phenyl-1-pentene with up to 28% ee.[64],[65]

E. SUMMARY

1. Palladium as well as nickel complexes coordinated with chiral phosphine ligands, especially those containing a dialkylamino side chain, have been used for asymmetric cross-coupling.

2. Asymmetric cross-coupling of secondary alkyl Grignard reagents represented by 1-phenylethylmagnesium chloride, which undergo racemization under the reaction conditions, produces enantiomerically enriched alkenes of up to 94% ee. The reaction has been studied mainly with nickel catalysts rather than palladium catalysts.

3. For asymmetric cross-coupling with organozinc reagents, palladium complexes are more catalytically active than nickel catalysts and the reaction of organozinc reagents usually proceeds with higher enantioselectivity than that of the corresponding organomagnesium reagents.

4. Optically active allylic silanes (up to 95% ee) are prepared by Pd-catalyzed asymmetric cross-coupling of α-silylalkyl Grignard reagents.

5. Pd-catalyzed enantioposition-selective cross-coupling has been applied to the asymmetric synthesis of planar chiral and axially chiral molecules.

6. The mechanism of enantioselection in asymmetric cross-coupling is not well understood. A detailed understanding will open more efficient catalytic systems for this type of reaction.

REFERENCES

[1] V. Farina, *Comp. Organomet. Chem. II*, **1995**, *12*, 161–240.

[2] J. Tsuji, *Palladium Reagents and Catalysts*, Wiley, Chichester, **1995**.

[3] R. F. Heck, *Palladium Reagents in Organic Synthesis*, Academic Press, New York, **1985**.

[4] B. M. Trost and T. R. Verhoeven, *Comp. Organomet. Chem.*, **1982**, *8*, 799–938.

[5] P. W. Jolly, *Comp. Organomet. Chem.*, **1982**, *8*, 713–797.

[6] G. Consiglio and C. Botteghi, *Helv. Chim. Acta.*, **1973**, *56*, 460.

[7] Y. Kiso, K. Tamao, N. Miyake, K. Yamamoto, and M. Kumada, *Tetrahedron Lett.*, **1974**, 3.

[8] T. Hayashi, M. Tajika, K. Tamao, and M. Kumada, *J. Am. Chem. Soc.*, **1976**, *98*, 3718.

[9] T. Hayashi, M. Konishi, M. Fukushima, T. Mise, M. Kagotani, M. Tajika, and M. Kumada, *J. Am. Chem. Soc*., **1982**, *104*, 180.

[10] T. Hayashi, M. Konishi, T. Hioki, M. Kumada, A. Ratajczak, and H. Niedbala, *Bull. Chem. Soc. Jpn.*, **1981**, *54*, 3615.

[11] K. V. Baker, J. M. Brown, N. A. Cooley, G. D. Hughes, and R. J. Taylor, *J. Organomet. Chem.*, **1989**, *370*, 397.

[12] A. Indolese and G. Consiglio, *J. Organomet. Chem.*, **1993**, *463*, 23.

[13] B. Jedlicka, C. Kratky, W. Weissensteiner, and M. Widhalm, *J. Chem. Soc. Chem. Commun.*, **1993**, 1329.

[14] T. Hayashi, M. Fukushima, M. Konishi, and M. Kumada, *Tetrahedron Lett.*, **1980**, *21*, 79.

[15] T. Hayashi, M. Konishi, M. Fukushima, K. Kanehira, T. Hioki, and M. Kumada, *J. Org. Chem.*, **1983**, *48*, 2195.

[16] T. Hayashi, N. Nagashima, and M. Kumada, *Tetrahedron Lett.*, **1980**, *21*, 4623.

[17] B. K. Vriesema and R. M. Kellogg, *Tetrahedron Lett.*, **1986**, *27*, 2049.

[18] J. H. Griffin and R. M. Kellogg, *J. Org. Chem.*, **1985**, *50*, 3261.

[19] U. Nagel and H. G. Nedden, *Chem. Ber.*, **1997**, *130*, 535.

[20] U. Nagel and H. G. Nedden, *Chem. Ber.*, **1997**, *130*, 989.

[21] M. Hayashi, K. Takaoki, Y. Hashimoto, and K. Saigo, *Enantiomer*, **1997**, *2*, 293.

[22] P. Wimmer and M. Widhalm, *Tertrahedron: Asymmetry*, **1995**, *6*, 657.
[23] P. Wimmer and M. Widhalm, *Monatsh. Chem.*, 1996, *127*, 669.
[24] M. Widhalm, P. Wimmer, and G. Klintschar, *J. Organomet. Chem.*, 1996, *523*, 167.
[25] M. Lemaire, B. K. Vriesema, and R. M. Kellogg, *Tetrahedron Lett.*, 1985, *26*, 3499.
[26] B. K. Vriesema, M. Lemaire, J. Buter, and R. M. Kellogg, *J. Org. Chem.*, 1986, *51*, 5169.
[27] H. Brunner and M. Pröbster, *J. Organomet. Chem.*, 1981, *209*, C1.
[28] G. Consiglio and A. Indolese, *J. Organomet. Chem.*, 1991, *417*, C36.
[29] K. Tamao, H. Yamamoto, H. Matsumoto, N. Miyake, T. Hayashi, and M. Kumada, *Tetrahedron Lett.*, 1977, 1389.
[30] M. E. Wright and M.-J. Jin, *J. Organomet. Chem.*, 1990, *387*, 373.
[31] H. Brunner and S. Limmer, *J. Organomet. Chem.*, 1991, *413*, 55.
[32] H. Brunner, W. Li, and H. Weber, *J. Organomet. Chem.*, 1985, *288*, 359.
[33] H. Brunner, H.-J. Lautenschlager, W. A. König, and R. Krebber, *Chem. Ber.*, 1990, *123*, 847.
[34] C. Döbler and A. Kinting, *J. Organomet. Chem.*, 1991, *401*, C23.
[35] H.-J. Kreuzfeld, C. Döbler, and H.-P. Abicht, *J. Organomet. Chem.*, 1987, *336*, 287.
[36] C. Döbler and H.-J. Kreuzfeld, *J. Organomet. Chem.*, 1988, *344*, 249.
[37] C. J. Richards, D. E. Hibbs, and M. B. Hursthouse, *Tetrahedron Lett.*, 1995, *36*, 3745.
[38] G. C. Lloyd-Jones and C. P. Butts, *Tetrahedron*, 1998, *54*, 901.
[39] K. Tamao, T. Hayashi, H. Matsumoto, H. Yamamoto, and M. Kumada, *Tetrahedron Lett.*, 1979, *23*, 2155.
[40] G. Consiglio, O. Piccolo, and F. Morandini, *J. Organomet. Chem.*, 1979, *177*, C13.
[41] G. Consiglio, F. Morandini, and O. Piccolo, *Tetrahedron*, 1983, *39*, 2699.
[42] T. Hayashi, T. Hagihara, Y. Katsuro, and M. Kumada, *Bull. Chem. Soc. Jpn.*, 1983, *56*, 363.
[43] T. Hayashi, A. Yamamoto, M. Hojo, and Y. Ito, *J. Chem. Soc. Chem. Commun.*, 1989, 495.
[44] T. Hayashi, A. Yamamoto, M. Hojo, K. Kishi, Y. Ito, E. Nishioka, H. Miura, K. Yanagi, *J. Organomet. Chem.*, 1989, *370*, 129.
[45] M. Uemura, R. Miyake, H. Nishimura, Y. Matsumoto, and T. Hayashi, *Tetrahedron: Asymmetry*, 1992, *3*, 213.
[46] G. Cross and R. M. Kellogg, *J. Chem. Soc. Chem. Commun.*, 1987, 1746.
[47] G. Cross, B. K. Vriesema, G. Boven, and R. M. Kellogg, *J. Organomet. Chem.*, 1989, *370*, 357.
[48] C. Cardellicchio, V. Fiandanese, and F. Naso, *Gazz. Chim. Ital.*, 1991, *121*, 11.
[49] G. Consiglio, O. Piccolo, L. Roncetti, and F. Morandini, *Tetrahedron*, 1986, *42*, 2043.
[50] T. Hayashi, M. Konishi, H. Ito, and M. Kumada, *J. Am. Chem. Soc.*, 1982, *104*, 4962.
[51] T. Hayashi, M. Konishi, Y. Okamoto, K. Kabeta, and M. Kumada, *J. Org. Chem.*, 1986, *51*, 3772.
[52] T. Hayashi, Y. Okamoto, and M. Kumada, *Tetrahedron Lett.*, 1983, *24*, 807.
[53] M. Uemura, H. Nishimura, and T. Hayashi, *Tetrahedron Lett.*, 1993, *34*, 107.
[54] M. Uemura, H. Nishimura, and T. Hayashi, *J. Organomet. Chem.*, 1994, *473*, 129.
[55] T. Hayashi, S. Niizuma, T. Kamikawa, N. Suzuki, and Y. Uozumi, *J. Am. Chem. Soc.*, 1995, *117*, 9101.
[56] T. Kamikawa and T. Hayashi, *Tetrahedron*, 1999, *55*, 3455.
[57] T. Kamikawa, Y. Uozumi, and T. Hayashi, *Tetrahedron Lett.*, 1996, *37*, 3161.
[58] S. Y. Cho and M. Shibasaki, *Tetrahedron: Asymmetry*, 1998, *9*, 3751.
[59] W. de Graaf, J. Boersma, G. van Koten, and C. J. Elsevier, *J. Organomet. Chem.*, 1989, *378*, 115.

[60] K. Tamao, A. Minato, N. Miyake, T. Matsuda, Y. Kiso, and M. Kumada, *Chem. Lett.*, 1975, 133.

[61] T. Hayashi, K. Hayashizaki, T. Kiyoi, and Y. Ito, *J. Am. Chem. Soc.*, 1988, *110*, 8153.

[62] T. Hayashi, K. Hayashizaki, and Y. Ito, *Tetrahedron Lett.*, 1989, *30*, 215.

[63] T. Hayashi, K. Kanehira, T. Hioki, and M. Kumada, *Tetrahedron Lett.*, 1981, *21*, 137.

[64] M. O. Okoroafor, D. L. Ward, and C. H. Brubaker, Jr., *Organometallics*, 1988, *7*, 1504.

[65] A. A. Naiini, C.-K. Lai, D. L. Ward, and C. H. Brubaker, Jr., *J. Organomet. Chem.*, 1990, *390*, 73.