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Historical note

Catalytic asymmetric cross-coupling

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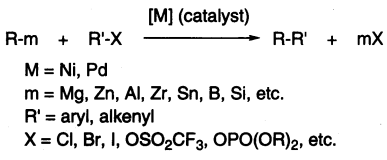
Abstract

Asymmetric cross-coupling of secondary alkylmagnesium and -zinc reagents with aryl and alkenyl halides in the presence of nickel or palladium catalysts coordinated with chiral phosphine ligands give optically active cross-coupling products. This asymmetric cross-coupling is applied to the asymmetric synthesis of chiral allylic silanes (95% ee). Axially chiral biaryls are prepared by asymmetric cross-coupling between two aryl groups (95% ee) or by enantioposition-selective cross-coupling (99% ee). © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Cross-coupling; Palladium catalyst; Nickel catalyst; Allylsilanes; Biaryls; Carbon–carbon bond formation

1. Introduction

Nickel and palladium complexes 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 (Scheme 1). Because the new carbon–carbon bond is formed on the sp^2 carbon center, the creation of chiral carbon centers or chiral molecules by the catalytic cross-coupling is not always easy. For the 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 the asymmetric synthesis of axially chiral molecules such as biaryls. To make the metal complexes function as chiral catalysts in the cross-coupling, optically active phosphine ligands can be conveniently used since most of the nickel and palladium catalysts used successfully for the cross-coupling have tertiary phosphines as ligands. This account outlines the catalytic asymmetric cross-coupling focusing on the results developed by our research group [1].



Scheme 1.

2. Asymmetric cross-coupling of secondary alkyl Grignard and zinc reagents

Asymmetric synthesis by the catalytic cross-coupling reaction has been most extensively studied with secondary alkyl Grignard reagents. The asymmetric cross-coupling with chiral catalysts allows transformation of a racemic mixture of the secondary alkyl Grignard reagent into an optically active product by a kinetic resolution of the Grignard reagent. Since the secondary alkyl Grignard reagents usually undergo racemization at a rate comparable to the cross-coupling, enantiomerically enriched coupling product is formed even if the conversion of the Grignard reagent is 100% (Scheme 2).

In the first reported examples of the asymmetric Grignard cross-coupling, a nickel complex coordinated with (−)-diop (**1**) was used as catalyst [2,3]. Reaction of 1-phenylethyl (**2**) and 2-butyl (**3**) Grignard reagents with vinyl chloride (**4a**) and phenyl halides (**5**), respectively, gave the corresponding coupling products, (*R*)-3-phenyl-1-butene (**6**) and (*R*)-2-phenylbutane (**7**) (Scheme 3).

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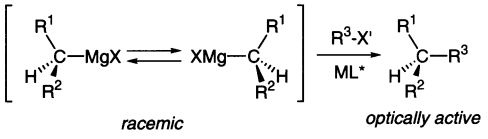
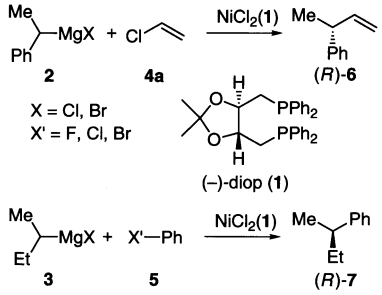
The enantioselectivity was dependent slightly on the halide atoms of both the Grignard reagents and organic halides, the highest being 13% ee for **6** and 17% ee for **7**.

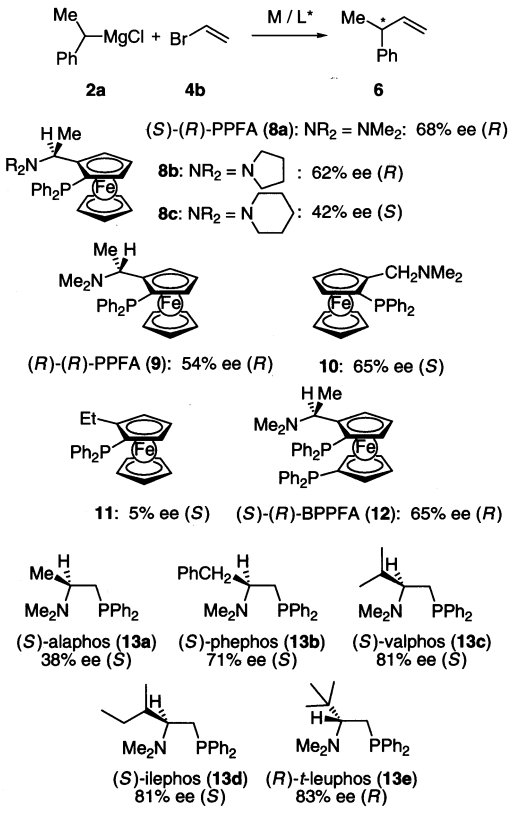
After these findings, asymmetric cross-coupling of the secondary alkyl Grignard reagents has been attempted using various kinds of optically active phosphine ligands. The reaction most extensively studied so far is that of 1-phenylethylmagnesium chloride (**2a**) with vinyl bromide (**4b**) forming 3-phenyl-1-butene (**6**) (Scheme 4).



Scheme 2.



Scheme 3.



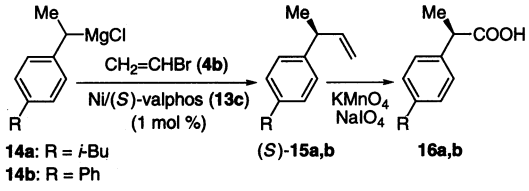
Scheme 4.

We found that the ferrocenylphosphines containing (dialkylamino)alkyl group on the side chain are effective for the cross-coupling of **2a** catalyzed by nickel or palladium complexes [4,5]. Ferrocenylmonophosphine, (*S*)-(*R*)-PPFA (**8a**) and -bisphosphine, (*S*)-(*R*)-BPPFA (**12**) gave the coupling product **6** 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 **8a** 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 (**9**) or **10** that lacks the central chirality. 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.

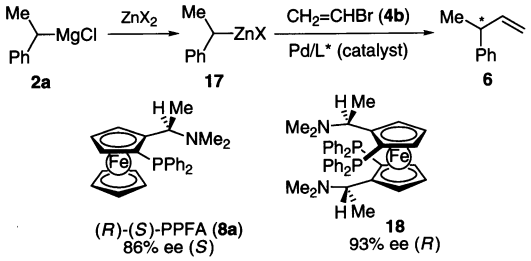
Based on the high efficiency of the (dialkylamino)alkyl side chain on the ferrocenylphosphines, a series of β-(dialkylamino)alkylphosphines (**13**) were prepared and used for the cross-coupling. Those substituted with sterically bulky alkyl group at the chiral carbon center are more effective than the ferrocenylphosphine ligands. Valphos (**13c**), ilephos (**13d**), and *t*-leuphos (**13e**), which were prepared starting with valine, isoleucine, and *t*-leucine, respectively, gave the product **6** with over 81% ee [6,7].

The chiral β-(dialkylamino)alkylphosphines (**13**) are used for the nickel-catalyzed asymmetric cross-coupling of 1-aryl-substituted ethyl Grignard reagents **14** with vinyl bromide (**4b**) (Scheme 5). The enantioselectivity is as high as that for the reaction of the 1-phenylethyl Grignard reagent (**2a**). Oxidation of the coupling products **15a** and **15b** gave optically active 2-(4-isobutylphenyl)propionic acid (ibuprofen) (**16a**, 80% ee) and its biphenyl analogue (**16b**, 82% ee), both of which are antiinflamatory agents [7].

Use of 1-phenylethylzinc reagents in place of the corresponding Grignard reagents sometimes increases the stereoselectivity (Scheme 6). The reaction of zinc reagents **17** prepared from **2a** with a zinc halide in THF in the presence of a palladium catalyst coordinated with a chiral ferrocenylphosphine [(*R*)-(*S*)-PPFA (**8a**)] pro-



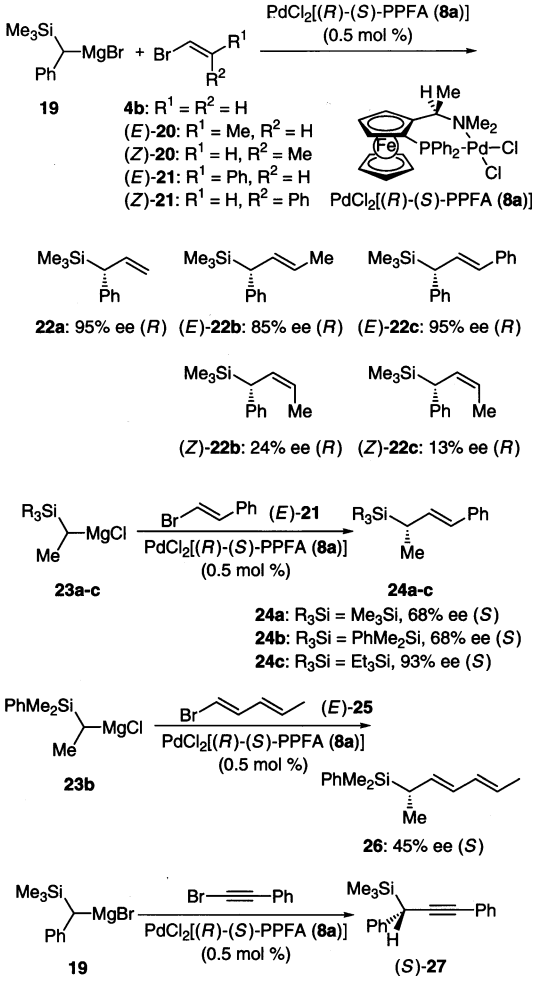
Scheme 5.



Scheme 6.

ceeded with 85–86% enantioselectivity [8]. The selectivity is higher than that observed for the reaction with 1-phenylethyl Grignard reagent (see Scheme 4). The highest enantioselectivity in forming (*R*)-**6** of 93% ee was obtained with C_2-symmetric ferrocenylphosphine ligand **18** that has two phosphorus atoms and two aminoalkyl side chains on the ferrocene skeleton [9,10].

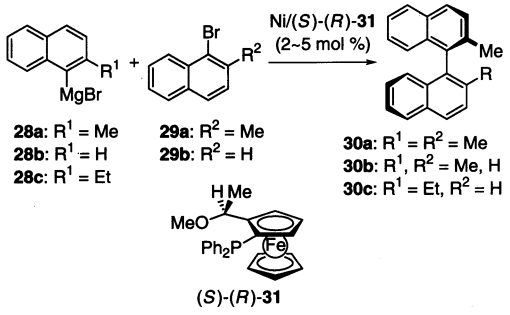
The asymmetric cross-coupling was successfully applied to the synthesis of optically active allylsilanes [11,12] (Scheme 7). The reaction of α-(trimethylsilyl)benzylmagnesium bromide (**19**) with vinyl bromide (**4b**), (*E*)-bromopropene ((*E*)-**20**), and (*E*)-bromostyrene ((*E*)-**21**) in the presence of 0.5 mol% of palladium complex coordinated with chiral ferrocenylphosphine, (*R*)-(*S*)-PPFA (**8a**), gave the corresponding (*R*)-allylsilanes (**22**) 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. Lower stereoselectivity was observed with (*Z*)-alkenyl bromides (*Z*)-**20** and (*Z*)-**21**. The palladium/PPFA catalyst was also effective for the reaction of 1-(trialkylsilyl)ethylmagneium chlorides (**23**) with (*E*)-bromostyrene ((*E*)-**21**). The enantioselectivity was dependent on the trialkylsilyl group, triethylsilyl being best to produce (*S*)-1-phenyl-3-silyl-1-butene (**24c**) of 93% ee. Dienylsilane (*S*)-**26** which is 45% enantiomerically pure was also prepared by the asymmetric cross-coupling with dienyl bromide (*E*)-**25**. The palladium-catalyzed asymmetric cross-coupling of α-(trimethylsilyl)benzylmagnesium bromide (**19**) was also applied to the synthesis of optically active propargylsilane **27** (18% ee) by using 1-bromo-2-phenylacetylene as a coupling partner [13].



Scheme 7.

3. Asymmetric cross-coupling of aryl Grignard reagents forming axially chiral biaryls

Preparation of axially chiral binaphthyls is one of the most exciting applications of the catalytic asymmetric cross-coupling reaction to organic synthesis. The reaction of 2-methyl-1-naphthylmagnesium bromide (**28a**) with 1-bromo-2-methylnaphthalene (**29a**) forming 2,2′-dimethyl-1,1′-binaphthyl (**30a**) has been examined with nickel catalysts coordinated with several chiral phosphine ligands (Scheme 8). Initial studies with (−)-diop (**1**), (*S*)-(*R*)-BPPFA (**12**), and a binaphthyl–bisphosphine ligand gave rather poor enantioselectivity [14,15]. Use of ferrocenylphosphine ligand (*S*)-(*R*)-**31**, which is a chiral monophosphine ligand containing methoxy group on the side chain, dramatically increased the selectivity to produce a high yield of (*R*)-**30a** with 95% ee [16]. High enantioselectivity was also attained in



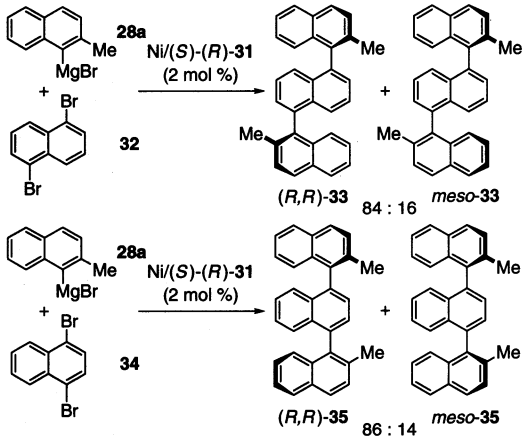
Scheme 8.

the reaction of **28a** with 1-bromonaphthalene (**29b**) which gave (*R*)-2-methyl-1,1′-binaphthyl (**30b**) with 83% ee. Binaphthyl (*R*)-**30b** with a much lower % ee was produced in the reaction of the other combination, that is, cross-coupling of 1-naphthylmagnesium bromide (**28b**) with 1-bromo-2-methylnaphthalene (**29a**). The 2-ethyl-1-naphthyl Grignard reagent **28c** was also successfully used for the reaction with **29b**, which gives **30c** of 77% ee.

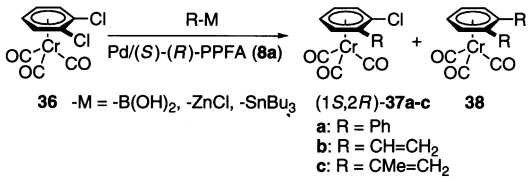
The nickel-catalyzed cross-coupling of 2-methyl-1-naphthylmagnesium bromide (**28a**) was extended to the asymmetric synthesis of ternaphthalenes [17] (Scheme 9). Reaction of 1,5-dibromonaphthalene (**32**) with two equivalents of **28a** in the presence of nickel catalyst coordinated with (*S*)-(*R*)-**31** gave a high yield of ternaphthalene (**33**) consisting of chiral and meso isomers in a ratio of 84/16. The chiral isomer turned out to be 98.7% enantiomerically pure with (*R*,*R*) configuration. The very high enantiomeric excess can be rationalized by the double asymmetric induction at the first and second cross-coupling. The reaction of **28a** with 1,4-dibromonaphthalene (**34**) gave ternaphthalene (*R*,*R*)-**35** of 95.3% ee together with a small amount of meso-**35**.

4. Enantioposition-selective asymmetric cross-coupling

Planar chiral tricarbonyl(η^6-arene)chromium complexes were prepared by catalytic asymmetric cross-coupling of tricarbonyl(η^6-*o*-dichlorobenzene)chromium (**36**) with alkenyl- or arylmetals [18,19] (Scheme 10). In the presence of 10 mol% of a palladium catalyst generated from [PdCl(η^3-C_3H_5)]$_2$ and ferrocenylmonophosphine (*S*)-(*R*)-PPFA (**8a**), an enantioposition-selective substitution of one of the chloride atoms takes place to give planar chiral monosubstitution products **37** together with a minor amount of disubstitution products **38** which are achiral. The highest enantiomeric



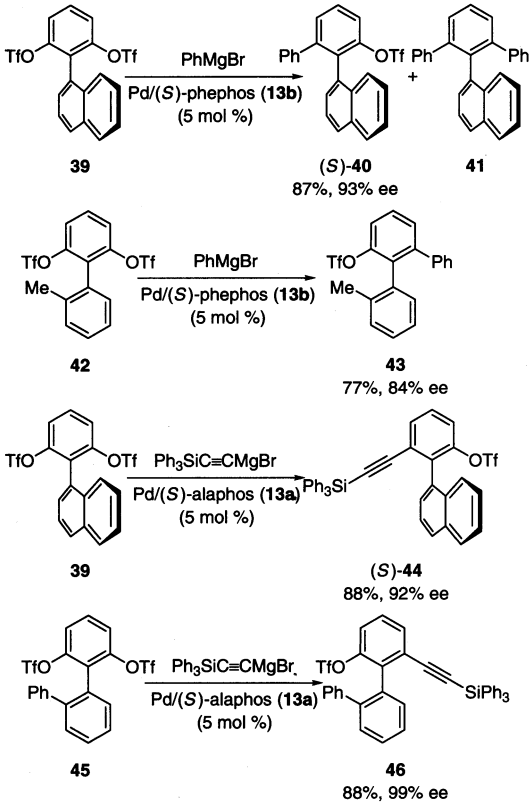
Scheme 9.



Scheme 10.

excess of the monosubstitution product is 69% ee which was reported for the phenylation of **36** with phenylboronic acid forming (1*S*,2*R*)-**37a**. Alkenylation with ethenylboronic acid or propen-2-ylboronic acid also proceeded enantioselectively to give the corresponding monoalkenylation product **37b** (38% ee) or **37c** (44% ee). Interestingly, use of ethenyltributyltin as the vinylation reagent in place of ethenylboronic acid resulted in the formation of racemic product **37b** while ethenylzinc chloride gave **37b** of 42% ee.

The enantioposition-selective asymmetric cross-coupling has been also successfully applied to the synthesis of axially chiral biaryl molecules [20] (Scheme 11). Reaction of achiral ditriflate **39** with two equivalents of phenylmagnesium bromide in the presence of lithium bromide and 5 mol% of $PdCl_2$[(*S*)-phephos (**13b**)] at −30 °C for 48 h gave 87% yield of monophenylation product (*S*)-**40** which is 93% ee and 13% yield of diphenylation product **41**. The enantiomeric purity of the monophenylation product (*S*)-**40** is dependent on



Scheme 11.

the yield of diphenylation product **41**. A kinetic resolution is demonstrated to take place at the second cross-coupling forming **41**. Minor isomer at the first cross-coupling, that is (*R*)-**40**, is consumed five times faster than major isomer (*S*)-**40** at the second cross-coupling, which causes an increase of enantiomeric purity of (*S*)-**40** as the amount of **41** increases. High enantioselectivity was also reported in the reaction of *o*-tolyl analogue **42** which gave monophenylation product **43** of 84% ee. For the enantioposition-selective alkynylation, (*S*)-alaphos (**13a**) ligand is more enantioselective than (*S*)-phephos (**13b**) [21]. For examples, the reaction of achiral ditriflates **39** and **45** with (triphenylsilyl)ethynylmagnesium bromide in the presence of palladium catalyst coordinated with (*S*)-alaphos (**13a**) gave the corresponding monoalkynylation products (*S*)-**44** (92% ee) and **46** (99% ee), respectively.

5. Conclusions and perspectives

Catalytic asymmetric cross-coupling has held a unique position in the field of asymmetric synthesis. Development of asymmetric reactions by use of the cross-coupling as a key step is not always easy, because the cross-coupling is a substitution reaction on the sp^2 carbon center. As is different from the addition reactions to carbon–carbon or carbon–heteroatom double bonds, it is difficult to create a new stereogenic carbon center during the coupling reaction. On the other hand, the cross-coupling reaction has opened a new and convenient route to planar chiral or axially chiral molecules such as biaryls, which cannot be readily obtained by other catalytic asymmetric reactions. Hopefully, the catalytic asymmetric cross-coupling will find wide applications in synthetic organic chemistry.

Acknowledgements

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