Rhodium-Catalyzed Asymmetric 1,4-Addition and Its Related Asymmetric Reactions

Tamio Hayashi* and Kaori Yamasaki

Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan

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1. Introduction

It has been well-documented that catalytic asymmetric synthesis is a field of great importance in its practical usefulness as well as its scientific interest.[1] Among several types of the catalytic asymmetric reactions, the asymmetric reduction and oxidation have been developed so well that some of the processes are used for industrial production of enantiomerically enriched compounds.[1] On the other hand, the examples of high efficiency in terms of catalytic activity and enantioselectivity are still rare in the catalytic asymmetric carbon−carbon bond forming reactions.[1] Among the asymmetric carbon−carbon bond forming reactions catalyzed by chiral transition metal complexes, the asymmetric 1,4-addition is one of the most promising reactions because its nonasymmetric version is a basic synthetic reaction often used for the carbon−carbon bond formation.[2] Over the last 20 years, considerable efforts have been made to develop efficient chiral catalytic systems for the asymmetric 1,4-addition of organometallic reagents,[3,4] and high enantioselectivity has been recently achieved in the addition of organozinc reagents by use of copper(I) catalysts coordinated with chiral phosphorus ligands.[5] A typical example is the addition of diethylzinc to 2-cyclohexenone in the presence of a phosphoramidite ligand based on the axially chiral 1,1′-binaphthol. In the copper-catalyzed reactions, the organic groups introduced are limited to primary alkyl groups in most cases, and the reaction must be carried out at very low temperature, usually below 0 °C.

In 1997, Miyaura reported the first nonasymmetric 1,4-addition of aryl- and alkenyl-boronic acids to α,β-unsaturated ketones using a phosphine-rhodium complex as a catalyst system.[6] This new rhodium-catalyzed reaction has stimulated the synthetic organic chemists who are interested in asymmetric catalysis to modify the reaction conditions of the rhodium-catalyzed 1,4-addition and to achieve high enantioselectivity. Recent developments of the rhodium-catalyzed carbon−carbon bond forming reactions by use of organometallic reagents, which include the 1,4-addition of both nonasymmetric and asymmetric versions, were reviewed earlier this year by Lautens.[7] The scope of this review is more narrow, focusing sharply on asymmetric 1,4-addition catalyzed by chiral rhodium complexes and its related asymmetric reactions whose catalytic cycle generally involves enantioselective carbo-rhodation of multiple bonds.[8]

2. Asymmetric Addition of Organoboron Reagents

2.1. A Short History

In his first report,[6] Miyaura used a rhodium catalyst generated from $Rh(acac)(CO)_2$ and 1,4-bis(diphenylphosphino)butane (dppb) in an aqueous solvent at 50 °C for the addition of aryl- and alkenylboronic acids to α,β-unsaturated ketones. Although the yields are generally high for β-unsubstituted enones such as methyl vinyl ketone, the yields are moderate for β-substituted enones such as 2-cyclohexenone (Scheme 1). The reaction conditions for β-substituted substrates must be improved before this new reaction is extended to catalytic asymmetric synthesis. Nevertheless, the reaction has several advantages over other 1,4-addition reactions. (1) The organoboronic acids used in this reaction are relatively stable to oxygen and moisture compared with some other organometallic reagents, permitting us to run the reaction in protic media or even in an aqueous solution. (2) The organoboronic acids are much less reactive toward enones in the absence of a rhodium catalyst than the organometallic reagents

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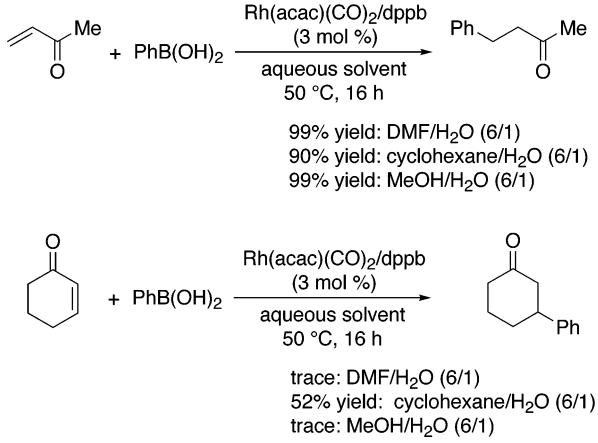
Tamio Hayashi was born in Gifu, Japan, in 1948. He graduated from Kyoto University in 1970. He received his Ph.D. degree in 1975 from Kyoto University under the direction of Professor Makoto Kumada. The title of his thesis was "Catalytic Asymmetric Hydrosilylation of Olefins and Ketones". Then he was appointed as a Research Associate in Faculty of Engineering, Kyoto University. He spent the year 1976–1977 as a postdoctoral fellow at Colorado State University with Professor Louis S. Hegedus. He was promoted to Full Professor in 1989 in the Catalysis Research Center, Hokkaido University. Since 1994, he has been Full Professor in the Faculty of Science, Kyoto University. His awards include the Award for Young Chemists of the Society of Synthetic Organic Chemistry, Japan, in 1983, the IBM (Japan) Prize in 1991, and The Chemical Society of Japan Award in 2003. He has been interested in the development of new reactions catalyzed by transition metal complexes, especially in catalytic asymmetric reactions.

Kaori Yamasaki was born in Wakayama, Japan. She studied chemistry at Kobe University under the supervision of Professor Akira Sera, where she received her B.Sc. in 1987. She spent the year 1987–1995 at the Sumitomo Chemical Company as a research chemist. After working as a secretary for two years, she became a research assistant to Professor Tamio Hayashi in the Faculty of Science, Kyoto University.

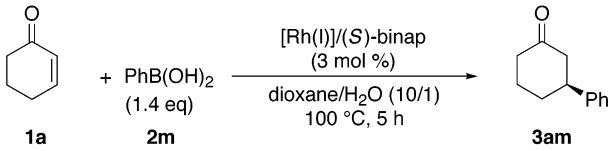
used so far, such as organo-magnesium or -lithium reagents, and no 1,2-addition to enones takes place in the presence or absence of the catalyst. (3) Aryl and alkenyl groups can be introduced at the β position. In the copper-catalyzed reaction, there have been no successful examples of the introduction of sp^2 carbons with high enantioselectivity.[9] (4) The reaction is mainly catalyzed by transition metal complexes coordinated with phosphine ligands. Since chiral phosphine ligands are the chiral auxiliaries most extensively studied for transition metal-catalyzed asymmetric reactions,[1] one can use the accumulated knowledge of the chiral phosphine ligands for the asymmetric reaction.

In 1998, Hayashi and Miyaura reported the first example of the rhodium-catalyzed asymmetric 1,4-addition,[10] which was realized by successful modification of the reaction conditions used in the Miyaura's original paper.[6] Important points modified for high catalytic activity and high enantioselectivity are (1) the use of $Rh(acac)(C_2H_4)_2$ as a rhodium catalyst precursor, (2) binap as a chiral bisphosphine ligand, (3) high reaction temperature (100 °C), and (4) the use of a mixture of dioxane and water in a ratio of 10 to 1 as a solvent. As a typical example, the reaction of 2-cyclohexenone (**1a**) with 1.4 equiv of phenylboronic acid (**2m**) in the presence of 3 mol % of $Rh(acac)(C_2H_4)_2$ and (*S*)-binap in dioxane/H_2O (10/1) at 100 °C for 5 h gave 64% yield of (*S*)-3-phenylcyclohexanone (**3am**) which is 97% enantiomerically pure (Scheme 2).[11] The modest yield is due to the side reaction causing hydrolysis of phenylboronic acid (**2m**) giving benzene at this high reaction temperature, and use of a large excess of **2m** (2.5 equiv) improved the yield of **3am** up to 93%. The high reaction temperature is essential, almost no reaction taking place at 60 °C or lower. With $Rh(acac)(CO)_2$ as a catalyst precursor, the reaction is slower and the enantioselectivity is much lower. NMR studies showed that the addition of 1 equiv of binap ligand to $Rh(acac)(C_2H_4)_2$ immediately generates Rh(acac)(binap) quantitatively, while $Rh(acac)(CO)_2$ generates two kinds of unidentified rhodium complexes together with a small amount of the Rh(acac)(binap) complex. The weaker coordination of ethylene than carbon monoxide supplies a reason for the higher enantioselectivity of $Rh(acac)(C_2H_4)_2$. Isolated rhodium−

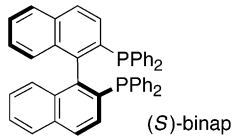
Scheme 1



Scheme 2



Rh(acac)$(CO)_2$/(*S*)-binap: 15% yield, 43% ee (*S*)
Rh(acac)$(C_2H_4)_2$/(*S*)-binap: 64% yield, 97% ee (*S*)
Rh(acac)((*S*)-binap): 62% yield, 96% ee (*S*)
Rh(acac)$(C_2H_4)_2$/(*S*)-binap: 93% yield, 97% ee (*S*) ($PhB(OH)_2$: 2.5 eq)



Scheme 3

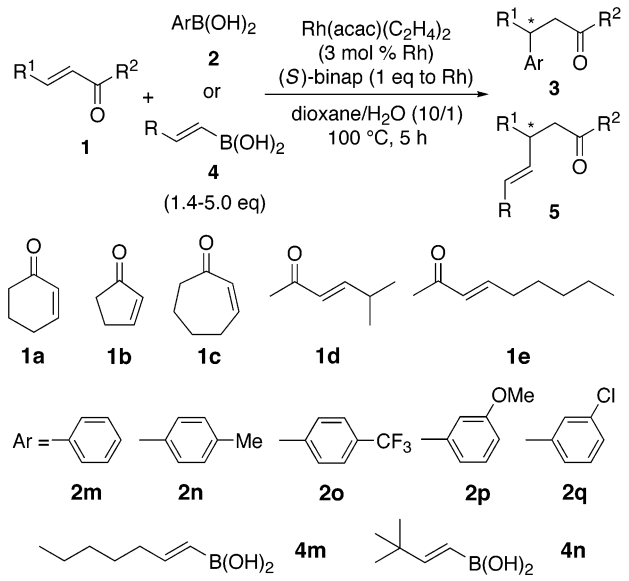


Table 1. Asymmetric 1,4-Addition of Boronic Acids 2 or 4 to Enones 1 Catalyzed by (*S*)-Binap−Rhodium(I) (Scheme 3)[a]

entry	enone **1**	boronic acid **2** or **4** (eq to **1**)	ketone **3** or **5**	yield (%)	% ee	
1	**1a**	**2m** (5.0)	**3am**	>99	97	(*S*)
2	**1a**	**2n** (5.0)	**3an**	>99	97	(−)
3[b]	**1a**	**2o** (2.5)	**3ao**	70	99	(−)
4	**1a**	**2p** (5.0)	**3ap**	97	96	(−)
5	**1a**	**2q** (5.0)	**3aq**	94	96	(−)
6	**1b**	**2m** (1.4)	**3bm**	93	97	(*S*)
7	**1c**	**2m** (1.4)	**3cm**	51	93	(−)
8	**1d**	**2m** (5.0)	**3dm**	82	97	(−)
9	**1e**	**2m** (2.5)	**3em**	88	92	(−)
10	**1a**	**4m** (2.5)	**5am**	88	94	(−)
11	**1a**	**4n** (5.0)	**5an**	76	91	(−)
12	**1b**	**4m** (2.5)	**5bm**	64	96	(−)

[a] The reaction was carried out in dioxane/H_2O (10/1) at 100 °C for 5 h in the presence of 3 mol % of the catalyst generated from Rh(acac)$(C_2H_4)_2$ and (*S*)-binap unless otherwise noted. [b] In 1-propanol/H_2O (10/1).

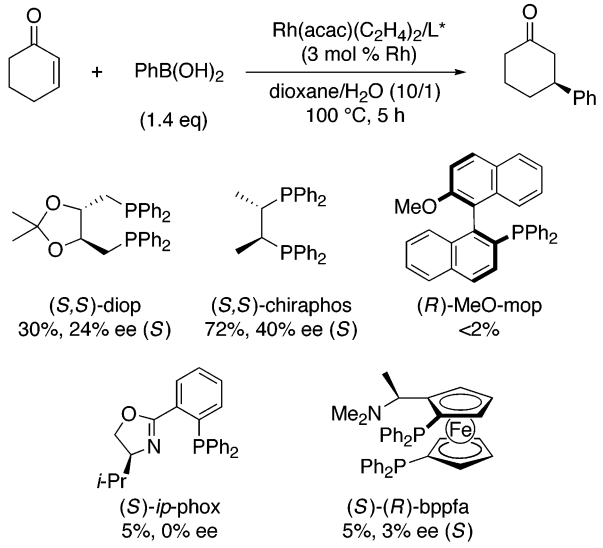
binap complex Rh(acac)((*S*)-binap) was as effective as the in situ generated complex. After this report by Hayashi and Miyaura,[10] the reaction conditions described above have been often used as the standard conditions for the rhodium-catalyzed asymmetric reactions.

2.2. α,β-Unsaturated Ketones

2.2.1. Asymmetric Addition of Boronic Acids

The scope of this rhodium-catalyzed asymmetric 1,4-addition of organoboronic acids is very broad[10] (Scheme 3). Some of the results obtained for the addition to α,β-unsaturated ketones are summarized in Table 1. Under standard conditions, that is, 3 mol % of Rh(acac)$(C_2H_4)_2$ and binap in dioxane/H_2O (10/1) at 100 °C, aryl groups substituted with either electron-donating or -withdrawing groups, 4-MeC_6H_4, 4-$CF_3C_6H_4$, 3-$MeOC_6H_4$, and 3-ClC_6H_4, were introduced onto 2-cyclohexenone (**1a**) with high enantioselectivity by the reaction with the corresponding boronic acids **2n**−**q** (entries 2−5). Asymmetric addition of 1-alkenylboronic acids, **4m** and **4n**, was as successful as that of arylboronic acids. Thus, the corresponding alkenylation products **5am** and **5an** were obtained with enantioselectivities up to 94% ee (entries 10 and 11). Cyclopentenone (**1b**) underwent the asymmetric addition of phenyl- and 1-heptenylboronic acids with high enantioselectivity under the same reaction conditions to give 3-substituted cyclopentanones, **3bm** (97% ee (*S*)) and **5bm** (96% ee), in high yields (entries 6 and 12). High enantioselectivity was also observed in the reaction of linear enones **1d** and **1e**, which have trans olefin geometry (entries 8 and 9). In summary, the rhodium-catalyzed asymmetric 1,4-addition proceeds with high enantioselectivity for both cyclic and linear α,β-unsaturated ketones with a variety of aryl- and alkenylboronic acids.

Scheme 4



For this rhodium-catalyzed asymmetric 1,4-addition, binap is one of the most enantioselective ligands, showing over 90% enantioselectivity for various types of enones and organoboronic acids. With diop and chiraphos, which are chelating bisphosphine ligands, the 1,4-addition occurs, but the enantioselectivity is much lower (Scheme 4). The yields of 1,4-addition product are very low with MeO-mop, *ip*-phox, and bppfa, which are monodentate phosphine, phosphines containing an oxazoline, and an amino group, respectively.[12]

Tomioka recently reported that amidomonophosphine ligand **6** derived from L-proline is a good ligand for the asymmetric addition to cyclic enones[13] (Scheme 5, Table 2). The enantioselectivity is comparable to binap in the 1,4-addition to 2-cyclohexenone (**1a**), although it is somewhat lower for cyclopentenone (**1b**) and cycloheptenone (**1c**). The amidomonophosphine ligand is proposed to behave as a hemilabile ligand. The amido carbonyl oxygen has a fluxional process involving dissociation from rhodium and recoordination. The chelate coordination is important for high activity and enantioselectivity of the rhodium/**6** complex as a catalyst. Analogous amidophosphine ligands **7** and **8**, where the coordination of the amido group is less likely due to the sterically bulky

Scheme 5

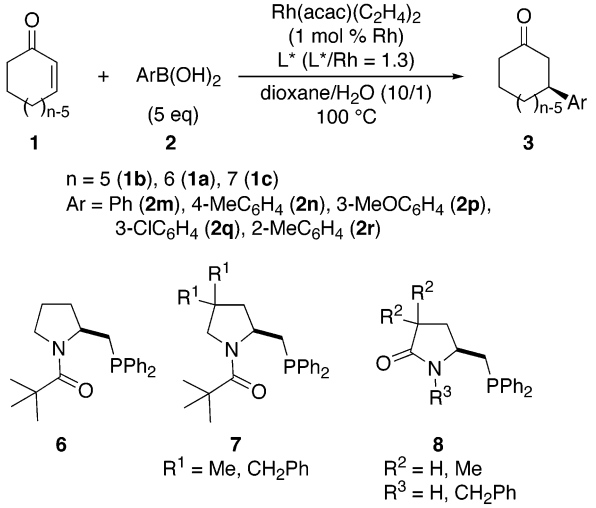
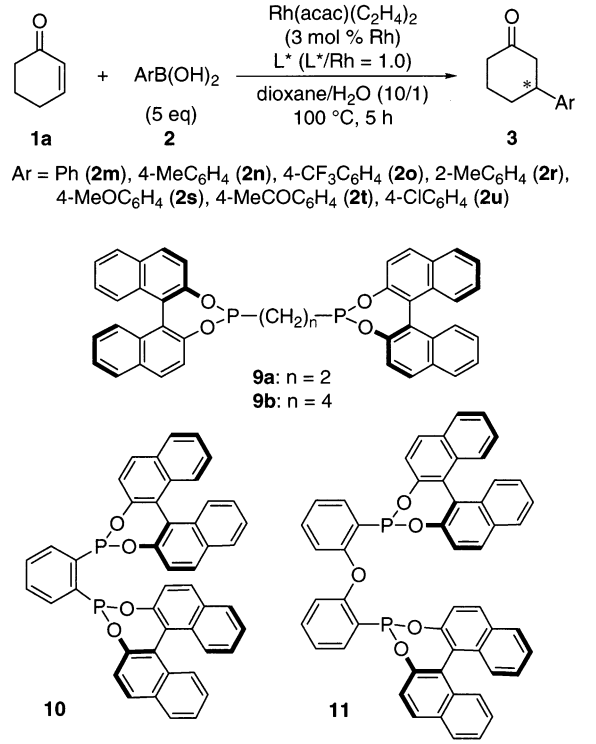


Table 2. Asymmetric 1,4-Addition of Arylboronic Acids 2 to Cycloalkenones 1 Catalyzed by 6−Rhodium(I) (Scheme 5)[a]

entry	enone 1	boronic acid 2	time (h)	ketone 3 yield (%)		% ee	
1	**1a**	**2m**	1	**3am**	99	96	(*S*)
2	**1b**	**2m**	6	**3bm**	90	83	(*S*)
3	**1c**	**2m**	24	**3cm**	95	91	
4	**1a**	**2n**	1	**3an**	99	92	
5	**1a**	**2p**	1	**3ap**	99	93	
6	**1a**	**2q**	3	**3aq**	90	91	
7	**1a**	**2r**	1	**3ar**	99	91	(*S*)

[a] The reaction was carried out in dioxane/H_2O (10/1) at 100 °C. **1**/**2**/Rh(acac)$(C_2H_4)_2$/**6** = 1.0/5.0/0.01/0.013.

Scheme 6



alkyl substituents or the wrong orientation of the amido group, showed much lower catalytic activity and enantioselectivity, supporting the importance of the coordination of the amido group for high performance of the ligand **6**.

Table 3. Asymmetric 1,4-Addition of Arylboronic Acids 2 to Cyclohexenone 1a Catalyzed by Diphosphinite−Rhodium Complexes (Scheme 6)[a]

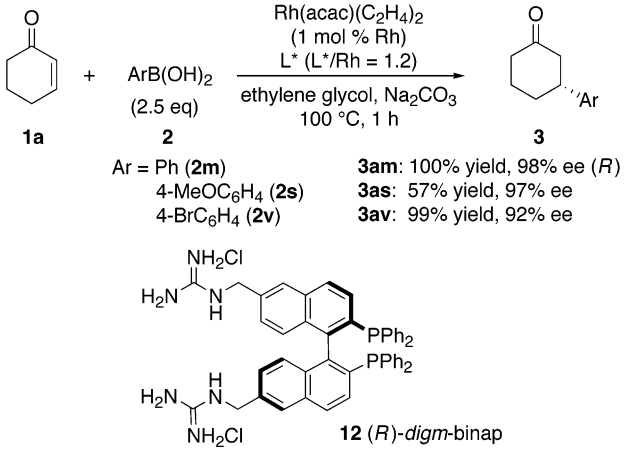
entry	enone 1	boronic acid 2	ligand	ketone 3 conversion (%)		% ee	
1	**1a**	**2m**	**9a**	**3am**	100	95	(*S*)
2	**1a**	**2m**	**9b**	**3am**	100	43	(*R*)
3	**1a**	**2m**	**10**	**3am**	100	99	(*S*)
4	**1a**	**2m**	**11**	**3am**	100	97	(*R*)
5	**1a**	**2n**	**10**	**3an**	100	94	
6	**1a**	**2o**	**10**	**3ao**	93	89	
7	**1a**	**2r**	**10**	**3ar**	96	93	
8	**1a**	**2s**	**10**	**3as**	87	95	
9	**1a**	**2t**	**10**	**3at**	88	94	
10	**1a**	**2u**	**10**	**3au**	75	91	

[a] The reaction was carried out in dioxane/H_2O (10/1) at 100 °C for 5 h. **1a**/**2**/Rh(acac)$(C_2H_4)_2$/ligand = 1.0/5.0/0.03/0.03.

Reetz reported the use of 1,1′-binaphthol-based diphosphonites **9**−**11** for the asymmetric 1,4-addition[14] (Scheme 6, Table 3). The enantioselectivity is strongly dependent on the achiral backbone. Thus, for example, in the asymmetric phenylation of 2-cyclohexenone (**1a**), ethylene ligand **9a** gave (*S*)-**3am** of 95% ee while tetramethylene ligand **9b** gave (*R*)-**3am** of 43% ee (entries 1 and 2). The enantioselectivity of this type of diphosphonite ligands, especially **10**, is generally very high, as high as binap ligand, for several combinations of enones and arylboronic acids (entries 5−10). They also succeeded in decreasing the amount of the rhodium catalyst to 0.3 mol % without significant loss of enantioselectivity.

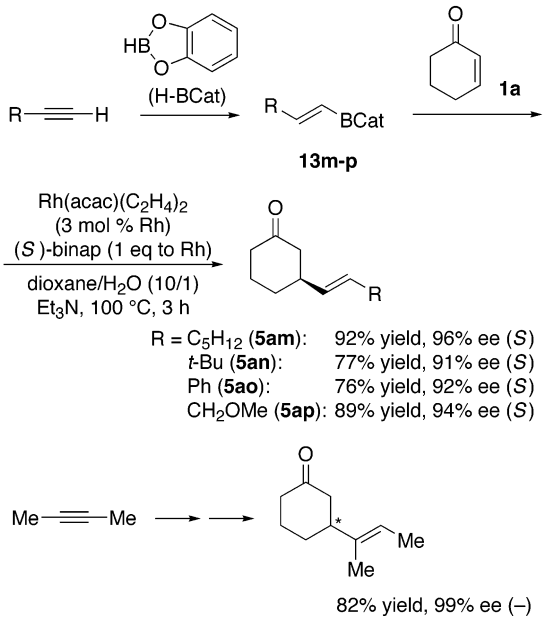
A water-soluble ligand **12** which has a binap skeleton as a basic structure and contains two guanidinium salts on the binaphthyl was used by Michelet and Genet for the asymmetric 1,4-addition[15] (Scheme 7). Although attempts to use this catalyst

Scheme 7



system in neat water were not successful because of low enantioselectivity, they found that the phenylation of 2-cyclohexenone (**1a**) in ethylene glycol in the presence of sodium carbonate proceeds with high yields and enantioselectivity (98% ee). They also reported that the catalyst amount was decreased to 0.005% with acceptable enantioselectivity (88% ee).

Scheme 8

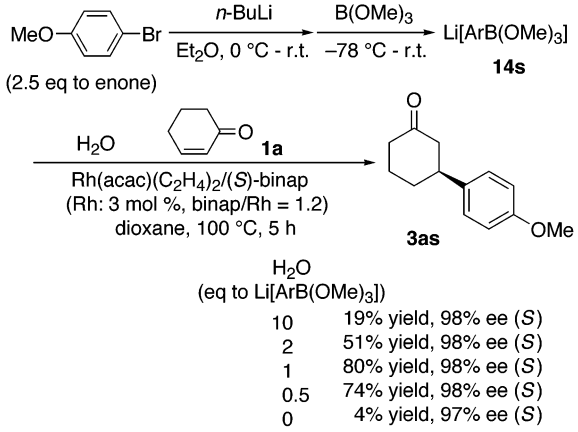


2.2.2. Asymmetric Addition of Other Borane Sources

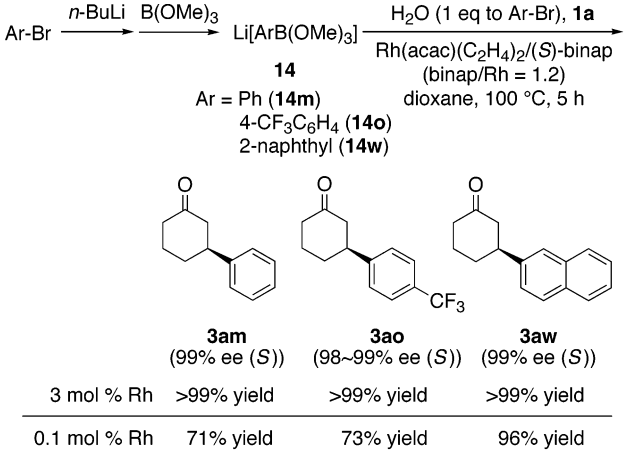
Hayashi reported that alkenylcatecholboranes obtained by the hydroboration of alkynes with catecholborane are good alkenylating reagents for the asymmetric 1,4-addition[16] (Scheme 8). Under the conditions used for the reaction of aryl- and alkenylboronic acids, that is, in the presence of 3 mol % of $Rh(acac)(C_2H_4)_2$ and binap in dioxane/H_2O (10/1) at 100 °C, the reaction of (*E*)-1-heptenylborane (**13m**), which is obtained by the hydroboration of 1-heptyne, with 2-cyclohexenone (**1a**) gave only 29% yield of 1,4-addition product **5am**, although the enantioselectivity is high (94% ee). Considering that the alkenylcatecholborane undergoes hydrolysis in the aqueous solvent generating alkenylboronic acid and catechol which makes the reaction media acidic, several bases were added to the reaction mixture. The yield was greatly improved by addition of triethylamine, giving 92% yield of **5am**, which is an (*S*) isomer of 96% ee. Some other alkenylcatecholboranes were also successfully used for the catalytic asymmetric 1,4-addition. The 1-alkenylboranes **13n**−**13p** derived from terminal acetylenes containing *tert*-butyl, phenyl, and methoxymethyl groups gave high yields of the corresponding 3-(1-alkenyl)cyclohexanones **5an**−**5ap** with over 90% ee. High enantioselectivity (99% ee) was observed in the reaction starting from 2-butyne, which is an internal acetylene. One-pot synthesis of the optically active β-alkenyl ketones is possible from alkynes and catecholborane without isolation of the alkenylcatecholboranes.

Lithium trimethyl arylborates, readily generated in situ by treatment of aryl bromides with butyllithium and trimethoxyborane, can be used for the asymmetric 1,4-addition[17] (Scheme 9). This is another one-pot reaction. In general this reaction provides higher yields than those obtained with arylboronic acids. Studies of the reaction conditions indicated that the amount of water has an effect on the yields remaining the enantioselectivity unaffected. Thus,

Scheme 9



Scheme 10



the highest yield was obtained in the reaction carried out in the presence of 1 equiv (to **14s**) of water, which gave **3as** with 98% ee in 80% yield. Using these in situ generated arylborate reagents, the amount of the catalyst was reduced without loss of enantioselectivity (Scheme 10). For a typical example, in the reaction of borate generated from 2-bromonaphthalene, 0.1 mol % of the catalyst gave 96% yield of the 3-(2-naphthyl)cyclohexanone (**3aw**) which is 99% enantiomerically pure. In summary, this one-pot reaction is superior to the reaction of arylboronic acids both in higher catalytic activity resulting in higher chemical yield and in easier manipulation avoiding the isolation of arylboronic acids.[11]

Potassium organotrifluoroborates **15** and **16**, which are generally more stable than the corresponding organoboronic acids, were shown by Darses and Genet to promote the rhodium-catalyzed asymmetric 1,4-addition[18] (Scheme 11, Table 4). In the presence of a cationic rhodium catalyst generated from $[Rh(cod)_2][PF_6]$ and (*R*)-binap in a mixed solvent of toluene/H_2O (4/1), the 1,4-addition of phenyltrifluoroborate **15m** to 2-cyclohexenone (**1a**) proceeded at 105−110 °C to give a high yield of the phenylation product **3am** with 98% ee (entry 1). The reaction of organotrifluoroborates has some characteristic features which are different from that of organoboronic acids. Thus, the reaction is not catalyzed well by the neutral rhodium complex generated from $Rh(acac)(C_2H_4)_2$, and the enantioselectivity is strongly de-

Scheme 11

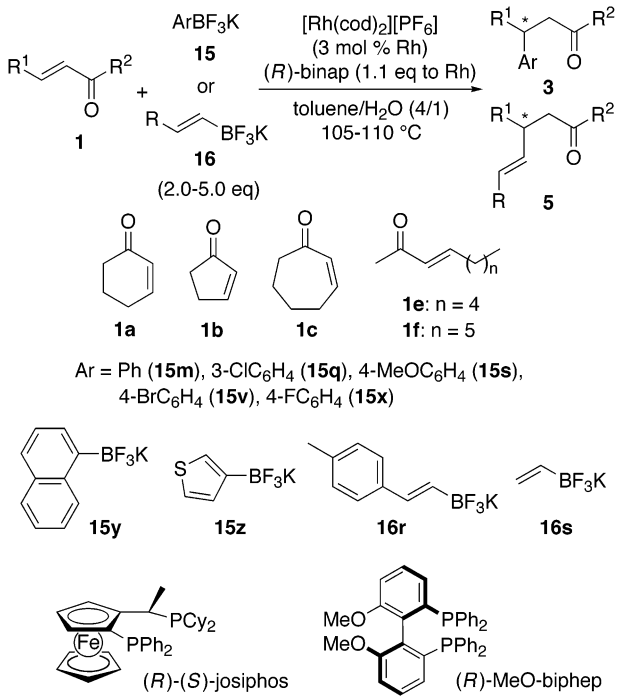


Table 4. Asymmetric 1,4-Addition of Organotrifluoroborates 15 or 16 to Enones 1 Catalyzed by (*R*)-Binap−Rhodium(I) (Scheme 11)[a]

entry	enone **1**	**15** or **16** (eq to **1**)	time (h)	ketone **3** or **5** yield (%)		% ee	
1	**1a**	**15m** (2.0)	1	**3am**	99	98	(*R*)
2	**1b**	**15m** (2.0)	1	**3bm**	98	95	(+)
3	**1c**	**15m** (2.0)	1	**3cm**	99	95	(+)
4	**1e**	**15m** (2.0)	1	**3em**	99	92	(+)
5	**1f**	**15m** (2.0)	1	**3fm**	95	95	(+)
6	**1a**	**15q** (3.0)	3	**3aq**	96	97	(*R*)
7	**1a**	**15s** (3.0)	6	**3as**	97	90	(+)
8	**1c**	**15s** (2.0)	3	**3cs**	75	94	(+)
9	**1a**	**15v** (2.0)	6	**3av**	90	96	(+)
10	**1a**	**15x** (5.0)	2	**3ax**	95	98	(+)
11	**1a**	**15y** (5.0)	20	**3ay**	90	98	(+)
12	**1e**	**15z** (2.0)	2	**3ez**	84	90	(−)
13	**1a**	**16r** (3.0)	7	**5ar**	93	95	(−)
14	**1c**	**16r** (2.0)	1	**5cr**	70	95	(−)
15	**1a**	**16s** (4.0)	2	**5as**	99	92	(+)
16[b]	**1a**	**15m** (2.0)	2	**3am**	100	99	(*R*)
17[c]	**1a**	**15m** (2.0)	2	**3am**	100	98	(*R*)

[a] The reaction was carried out in toluene/H_2O (4/1) at 105−110 °C. **1**/[Rh(cod)$_2$][PF_6]/(*R*)-binap = 1.0/0.03/0.033. [b] (*R*)-(*S*)-josiphos. [c] (*R*)-MeO-biphep.

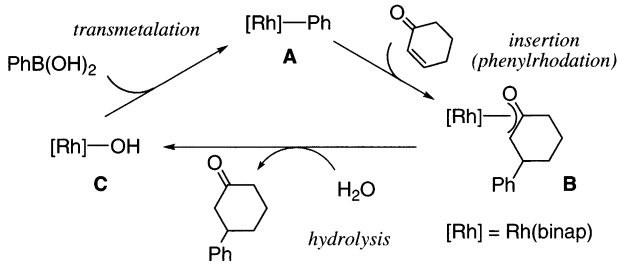
pendent on the solvent employed. The use of toluene as an organic part of the mixed solvent, and an excess amount of water is important for the high enantioselectivity. It is remarkable that an unsubstituted vinyl group can be introduced in a high yield by use of the vinyltrifluoroborate **16s** (entry 15). The corresponding boronic acid cannot be used because of its instability under the reaction conditions. They have also examine several other chiral bisphosphines for the reaction of **1a** with **15m**. The enantioselectivity was high with (*R*)-(*S*)-josiphos (99% ee) (entry 16) and (*R*)-MeO-biphep (98% ee) (entry 17), while it was low with (*R*,*R*)-dipamp (3% ee) and (*R*,*R*)-diop (26% ee).[18b]

2.3. Catalytic Cycle and the Origin of the Enantioselectivity

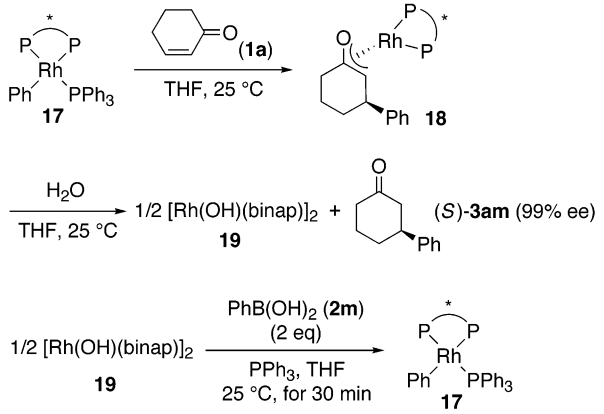
Recently Hayashi has characterized the important intermediate involved in the catalytic cycle of the rhodium-catalyzed 1,4-addition by use of RhPh(PPh_3)(binap) (**17**) as a key intermediate.[19] The catalytic cycle illustrated for the reaction of phenylboronic acid (**2m**) with 2-cyclohexenone (**1a**) is shown in Scheme 12. The reaction proceeds by way of three intermediates, phenylrhodium **A**, oxa-π-allylrhodium **B**, and hydroxorhodium **C** complexes. All of the intermediates and transformations between the three complexes were observed in NMR spectroscopic studies (Scheme 13). The reaction of phenylrhodium complex **17** with 2-cyclohexenone (**1a**) gave oxa-π-allylrhodium **18** which is formed by insertion of the carbon−carbon double bond of enone into the phenyl−rhodium bond followed by isomerization into the thermodynamically stable complex. Oxa-π-allylrhodium complex (**18**) was converted immediately into hydroxorhodium complex **19** on addition of water, liberating the phenylation product **3am**. Transmetalation of phenyl group from boron to rhodium takes place by addition of phenylboronic acid (**2m**) in the presence of triphenylphosphine to regenerate the phenylrhodium **17**.

All the three transformations in Scheme 13 was found to proceed at 25 °C, but the catalytic reaction in the presence of a rhodium catalyst generated from Rh(acac)(C_2H_4)$_2$ does not proceed at 60 °C or lower. It turned out that the acetylacetonato ligand retards the transmetalation step because of the high stability of the rhodium−acac moiety. Use of the hydroxo complex [Rh(OH)(binap)]$_2$ as a catalyst made it possible to run the reaction at lower temperature[19] (Scheme 14, Table 5). Thus, the addition of phenyl-

Scheme 12



Scheme 13



Scheme 14

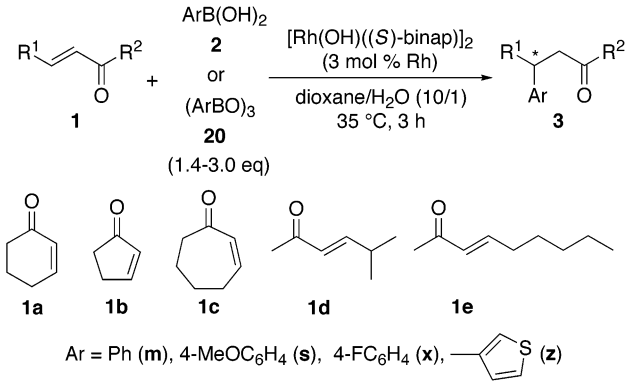


Table 5. Asymmetric 1,4-Addition of Organoboron Reagents $RB(OH)_2$ 2 or $(RBO)_3$ 20 to Enones 1 Catalyzed by [Rh(OH)((*S*)-binap)]$_2$ (Scheme 14)[a]

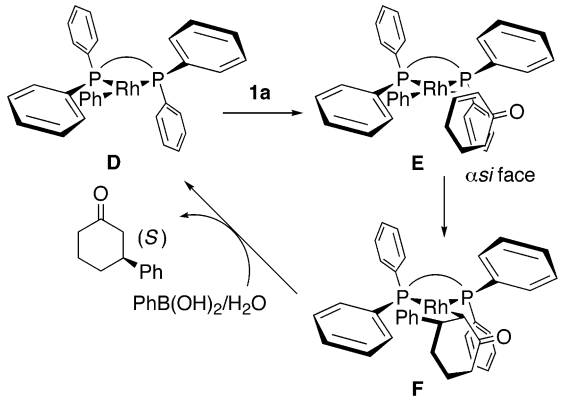
entry	enone 1	2 or 20 (eq to 1)	ketone 3	yield (%)	% ee	
1	**1a**	**2m** (2.5)	**3am**	96	99.3	(*S*)
2	**1a**	**20m** (2.5)	**3am**	98	99.3	(*S*)
3	**1a**	**20m** (1.4)	**3am**	94	99.2	(*S*)
4	**1a**	**20s** (2.5)	**3as**	96	99.1	
5	**1a**	**20x** (2.5)	**3ax**	96	99.1	(*S*)
6	**1b**	**20m** (2.5)	**3bm**	95	98	(*S*)
7	**1c**	**20m** (2.5)	**3cm**	94	96	(*S*)
8	**1d**	**20m** (2.5)	**3dm**	89	98	(*S*)
9	**1e**	**20m** (2.5)	**3em**	92	98	(*R*)
10[b]	**1a**	**2z** (3.0)	**3az**	67	99	(*S*)
11[b]	**1c**	**2z** (3.0)	**3cz**	81	99	(*S*)

[a] The reaction was carried out in dioxane/H_2O (10/1) at 35 °C for 3 h in the presence of 3 mol % (Rh) of [Rh(OH)((*S*)-binap)]$_2$. [b] At 40 °C for 24 h.

boronic acid (**2m**) or phenylboroxine (**20m**) to 2-cyclohexenone (**1a**) is catalyzed by [Rh(OH)(binap)]$_2$ at 35 °C to give a quantitative yield of **3am** which is over 99% enantiomerically pure (entries 1−3). This catalyst system is also applicable to the reaction of other enones and organoboron reagents (entries 4−9). The enantioselectivity is always higher than that in the reaction catalyzed by the rhodium−acac complex at 100 °C because the reaction temperature is lower. The chemical yields are higher and less boron reagent is used because the hydrolysis of the boronic acids, which is the main side reaction, is suppressed at the lower temperature. The higher efficiency of the [Rh(OH)(binap)]$_2$ catalyst was also observed in the asymmetric addition of 3-thiopheneboronic acid (**2z**) to enones (entries 10 and 11).[20]

Scheme 15 shows the stereochemical pathway in the reaction catalyzed by the rhodium complex coordinated with (*S*)-binap.[10] According to the highly skewed structure known for transition metal complexes coordinated with a binap ligand,[21] (*S*)-binap−rhodium intermediate **D** should have an open space at the lower part of the vacant coordination site, the upper part being blocked by one of the phenyl rings of the binap ligand. The olefinic double bond of 2-cyclohexenone (**1a**) coordinates to rhodium with its α*si* face forming **E** rather than with its α*re* face, which undergoes migratory insertion to form a stereogenic carbon center in **F**, whose absolute configuration is *S*. The absolute configurations of all the

Scheme 15



1,4-addition products can be predicted by this type of stereocontrol model, with the (*S*)-binap−rhodium intermediate attacking the α*si* face of α,β-unsaturated ketones, both cyclic and linear ones, and other electron deficient olefins, including α,β-unsaturated esters and alkenylphosphonates (vide infra).

2.4. α,β-Unsaturated Esters and Amides

It has been shown that α,β-unsaturated esters are good substrates for the rhodium-catalyzed asymmetric 1,4-addition of organoboron reagents to give the corresponding β-substituted esters with high enantioselectivity. As observed for the α,β-unsaturated ketones,[17] the lithium arylborates generally give better results than the corresponding arylboronic acids (Scheme 16).[22] Table 6, which summarizes the results obtained for the phenylation of (*E*)-hexenoate esters **21a**−**21d** in the presence of the Rh(acac)-$(C_2H_4)_2$/(*S*)-binap catalyst, shows that the yields of 3-phenylhexanoates **22** are higher, especially for esters of sterically bulky alcohols, with the lithium phenylborate **14m**. In the addition to isopropyl ester **21c** and *tert*-butyl ester **21d**, the lithium phenylborate **14m** gave 96% and 92% yields, respectively, while phenylboronic acid **2m** gave 42% and 21% yields, respectively (entries 5−8). Interestingly, the enantioselectivity increases as the steric bulkiness of the ester moiety increases. The enantiomeric purities of the phenylation products are 89%, 91%, 95%, and 96% ee for methyl (**22am**), ethyl (**22bm**), isopropyl (**22 cm**), and *tert*-butyl (**22dm**) esters, respectively, in the reactions with the lithium phenylborate **14m** (entries 1, 3, 5, and 7). Substituted phenyl and 2-naphthyl groups were introduced at the β position of isopropyl ester **21c** with enantioselectivity ranging between 93% and 97% ee in high yields in the reactions with the corresponding lithium arylborates (entries 9−12). Highest enantioselectivity (98% ee) was observed in the phenylation of isopropyl 4-methyl-2-pentenoate (**21e**), though the yield was moderate (entry 13).

The reaction of cyclic α,β-unsaturated esters also proceeds with high enantioselectivity[22] (Scheme 17). The reaction of six-membered cyclic ester **21f** with arylboronic acids including phenyl and substituted phenyls gave the corresponding arylation products **22f** of 97−98% ee in high yields.

Similar results for the asymmetric 1,4-addition to α,β-unsaturated esters has been independently re-

Scheme 16

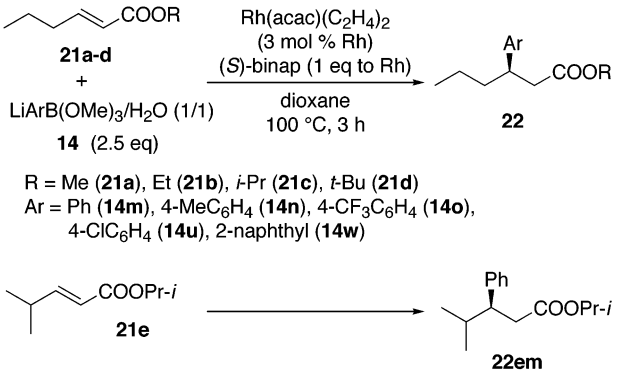
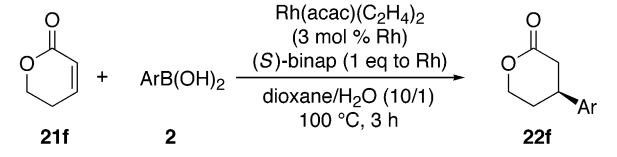


Table 6. Asymmetric 1,4-Addition of Arylboron Reagents 14 or 2 to α,β-Unsaturated Esters 22 Catalyzed by (*S*)-Binap−Rhodium(I) (Scheme 16)[a]

entry	ester **21**	borate **14** or boronic acid **2**	ester **22**	yield (%)	% ee	
1	**21a**	**14m**	**22am**	>99	89	(−)
2[b]	**21a**	**2m**	**22am**	94	86	(−)
3	**21b**	**14m**	**22bm**	>99	91	(−)
4[b]	**21b**	**2m**	**22bm**	>99	90	(−)
5	**21c**	**14m**	**22cm**	96	95	(−)
6[b]	**21c**	**2m**	**22cm**	42	94	(−)
7	**21d**	**14m**	**22dm**	92	96	(−)
8[b]	**21d**	**2m**	**22dm**	21	95	(−)
9	**21c**	**14n**	**22cn**	88	97	(−)
10	**21c**	**14o**	**22co**	98	96	(−)
11	**21c**	**14u**	**22cu**	95	97	(−)
12	**21c**	**14w**	**22cw**	96	93	(−)
13	**21e**	**14m**	**22em**	64	98	(*S*)

[a] The reaction was carried out in dioxane at 100 °C for 3 h. **21**/**14**/H_2O/Rh(acac)$(C_2H_4)_2$/(*S*)-binap = 1.0/2.5/2.5/0.03/0.03. [b] With arylboronic acid **2** (5.0 equiv to **21**) in dioxane/H_2O (10/1).

Scheme 17

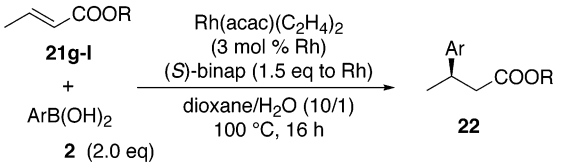


Ar = Ph (**2m**) **22fm**: 94% yield, 98% ee (*S*)
4-MeC_6H_4 (**2n**) **22fn**: 91% yield, 97% ee (+)
4-$CF_3C_6H_4$ (**2o**) **22fo**: 75% yield, 97% ee (*S*)
3-$MeOC_6H_4$ (**2p**) **22fp**: 91% yield, 98% ee (+)
4-ClC_6H_4 (**2u**) **22fu**: 95% yield, 97% ee (+)
2-naphthyl (**2w**) **22fw**: 93% yield, 98% ee (+)

ported by Miyaura[23] (Scheme 18, Table 7). As observed in the reaction of esters **21a**−**21d**,[22] the enantioselectivity is higher with the more bulky ester groups in the reaction of crotonate esters **21g**−**21l**. Phenylboronic esters of 1,2-diols **23** and **24** can participate in the asymmetric addition to benzyl crotonate (**21g**) to give the corresponding phenylation product **22gm** with the same enantioselectivity as phenylboronic acid (Scheme 19).

The asymmetric addition of arylboronic acids was found by Miyaura to take place for α,β-unsaturated amides in the presence of the Rh(acac)$(C_2H_4)_2$/(*S*)-binap catalyst[24] (Scheme 20, Table 8). The enantioselectivity is comparable to that in the addition to the corresponding esters. The reaction suffered from

Scheme 18



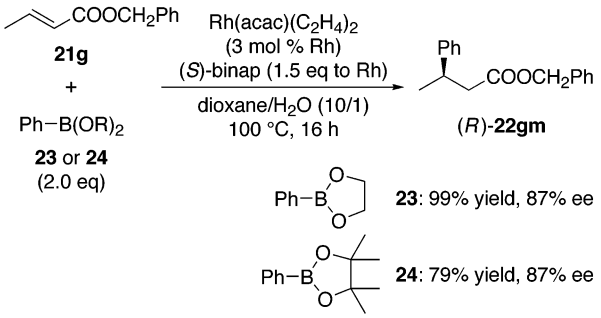
R = Ch_2Ph (**21g**), *i*-Pr (**21h**), Et (**21i**), *i*-Bu (**21j**), *c*-Hex (**21k**), *t*-Bu (**21l**)
Ar = Ph (**2m**), 3-$MeOC_6H_4$ (**2p**)

Table 7. Asymmetric 1,4-Addition of Arylboronic Acids 2 to α,β-Unsaturated Esters 22 Catalyzed by (*S*)-Binap−Rhodium(I) (Scheme 18)[a]

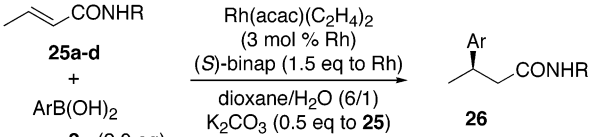
entry	ester **21**	boronic acid **2**	ester **22**	yield (%)	% ee	
1[b]	**21g**	**2m**	**22gm**	99	87	(*R*)
2	**21g**	**2p**	**22gp**	97	87	(−)
3	**21h**	**2p**	**22hp**	91	91	(−)
4	**21i**	**2p**	**22ip**	81	87	(−)
5	**21j**	**2p**	**22jp**	98	88	(−)
6	**21k**	**2p**	**22kp**	97	91	(−)
7	**21l**	**2p**	**22lp**	54	92	(−)

[a] The reaction was carried out in dioxane/H_2O (10/1) at 100 °C for 16 h. **21**/**2**/Rh(acac)$(C_2H_4)_2$/(*S*)-binap = 1.0/2.0/0.03/0.045. [b] Reaction time was 2 h.

Scheme 19



Scheme 20



R = CH_2Ph (**25a**), *c*-Hex (**25b**), H (**25c**), Ph (**25d**)
Ar = Ph (**2m**), 4-MeC_6H_4 (**2n**), 4-$CF_3C_6H_4$ (**2o**), 4-$MeOC_6H_4$ (**2s**)

incomplete conversion, resulting in moderate yields, but addition of an aqueous base such as potassium carbonate improved the chemical yields.

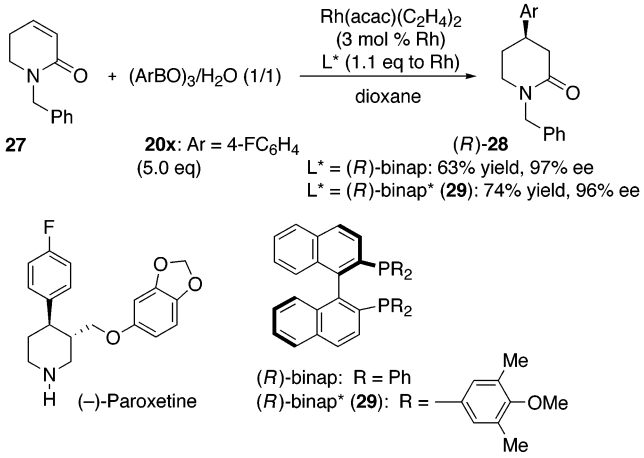
Asymmetric 1,4-addition to cyclic α,β-unsaturated amides provides a new efficient route to enantiomerically enriched 4-aryl-2-piperidinones **28**[25] (Scheme 21). For the 1,4-addition of 4-$FC_6H_4B(OH)_2$ (**2x**), which is related to asymmetric synthesis of (−)-paroxetine, slightly modified conditions were required to obtain a high yield of the arylation product **28**. The main side reaction, that is, hydrolysis of **2x** giving fluorobenzene, was suppressed by use of a minimum amount of the water. Thus, the reaction of lactam **27** with 4-fluorophenylboroxine (**20x**) and 1 equiv (to boron) of water in the presence of Rh(acac)$(C_2H_4)_2$/(*R*)-binap catalyst in dioxane at 40

Table 8. Asymmetric 1,4-Addition of Arylboronic Acids 2 to α,β-Unsaturated Amides 25 Catalyzed by (*S*)-Binap−Rhodium(I) (Scheme 20)[a]

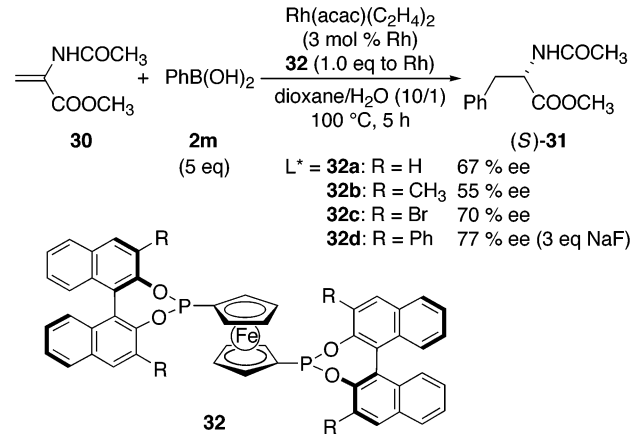
entry	amide **25**	boronic acid **2**	amide **26**	yield (%)	% ee	
1[b]	**25a**	**2m**	**26am**	67	93	(*R*)
2	**25a**	**2m**	**26am**	85	93	(*R*)
3	**25b**	**2m**	**26bm**	89	93	(−)
4	**25c**	**2m**	**26cm**	62	89	(−)
5	**25d**	**2m**	**26dm**	88	90	(−)
6	**25a**	**2n**	**26an**	74	87	(−)
7	**25a**	**2o**	**26ao**	82	92	(−)
8	**25a**	**2s**	**26as**	50	77	(−)

[a] The reaction was carried out in dioxane/H_2O (6/1) at 100 °C for 16 h. **25**/**2**/Rh(acac)$(C_2H_4)_2$/(*S*)-binap/K_2CO_3 = 1.0/2.0/0.03/0.045/0.5. [b] Without K_2CO_3.

Scheme 21



Scheme 22



°C gave 63% yield of (*R*)-**28x** with 97% enantioselectivity. This is much better than the reaction carried out under the usual reaction conditions.

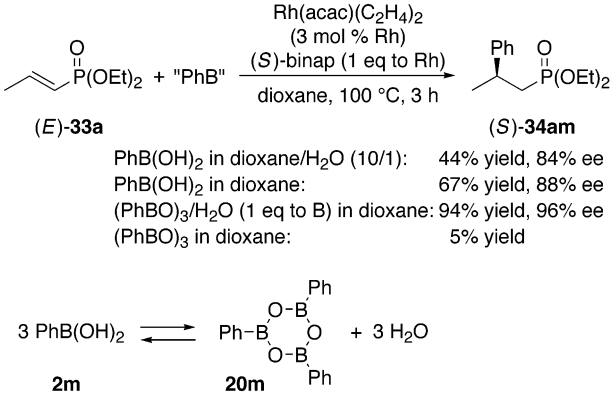
An interesting asymmetric transformation is the 1,4-addition to α-acetamidoacrylic ester **30** giving phenylalanine derivative **31** reported by Reetz[14] (Scheme 22). The addition of phenylboronic acid (**2m**) catalyzed by the rhodium complex of 1,1′-binaphthol-based diphosphinite ligand **32** gave a quantitative yield of **31** with up to 77% ee. In this asymmetric reaction, stereochemical outcome is determined at the hydrolysis step of an oxa-π-allylrhodium intermediate, not at the insertion step (cf. Scheme 15).

2.5. Other Electron Deficient Olefins

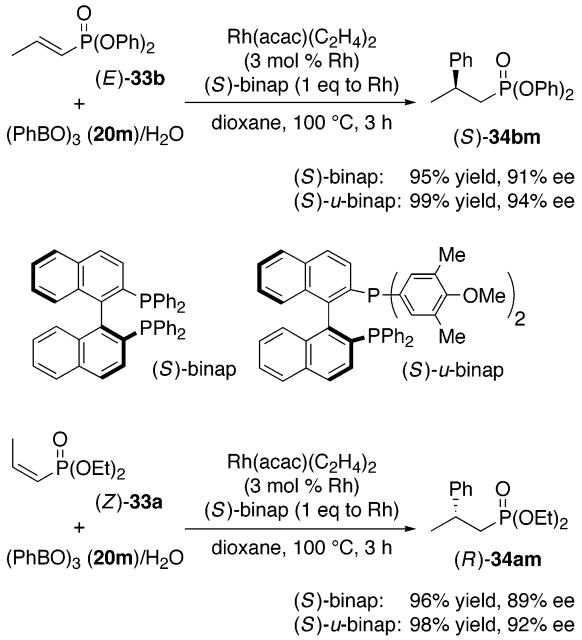
Alkenylphosphonates are less reactive toward 1,4-addition compared to α,β-unsaturated carbonyl compounds. Hayashi found that the rhodium-catalyzed asymmetric 1,4-addition can be improved by using arylboroxines as arylating reagents instead of arylboronic acids[26] (Scheme 23). For example, the reaction of diethyl (*E*)-propenylphosphonate (**33a**) with phenylboronic acid in dioxane/H_2O (10/1) under the reaction conditions used for α,β-unsaturated ketones was slow (44% yield). The asymmetric 1,4-addition was greatly improved (94% yield with 96% ee) by carrying out the reaction using phenylboroxine (PhBO)$_3$ (**20m**) with 1 equiv of water. The addition of 1 equiv of water is essential for the high yield, almost no reaction taking place in the absence of water. A boroxine and water should be in equilibration with a boronic acid under the reaction conditions,[27] and hence the use of arylboroxine in combination with 1 equiv of water for the asymmetric 1,4-addition should result in the same outcome, as using the corresponding arylboronic acid with no water added. Nevertheless, the results of the catalytic reactions are better with the combination of boroxine and water.

The enantioselectivities and chemical yields were slightly higher in the reaction catalyzed by rhodium complex coordinated with unsymmetrically substituted binap ligand, (*S*)-*u*-binap, which has diphenylphosphino and bis(3,5-dimethyl-4-methoxyphenyl)-phosphino groups at the 2 and 2′ positions on the 1,1′-binaphthyl skeleton (Scheme 24). In the reaction of diphenyl (*E*)-propenylphosphonate (**33b**) with **20m**, (*S*)-*u*-binap ligand gave 99% yield of **34bm** with 94% ee, while the standard (*S*)-binap gave 95% yield of **34bm** with 91% ee. It is remarkable that the asymmetric phenylation of (*Z*) isomer of diethyl 1-propenylphosphonate (*Z*)-**33a** with phenylboroxine **20m** gave *R* isomer of **34am**. The opposite absolute configuration of **34am** observed for (*E*)-**33a** (Scheme 23) and (*Z*)-**33a** (Scheme 24) indicates that the dialkoxyphosphinyl moiety on the 1-alkenylphosphonate plays a key role in the enantioface selection (Scheme 25). The (*S*)-binap−rhodium catalyst recognizes the enantioface of 1-propenylphosphonate by the steric bulkiness of the phosphinyl group, both (*E*)-**33a** and (*Z*)-**33a** being phenylated on the rhodium from 1*si* face irrespective of the *E*,*Z* geometry of the 1-propenyl moiety.

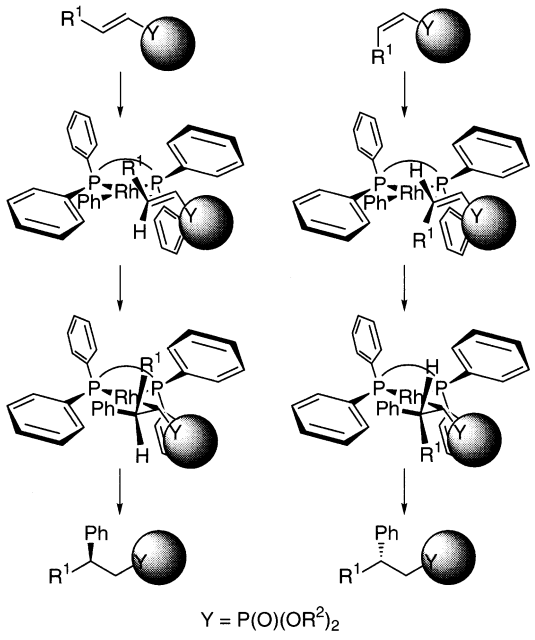
Scheme 23



Scheme 24

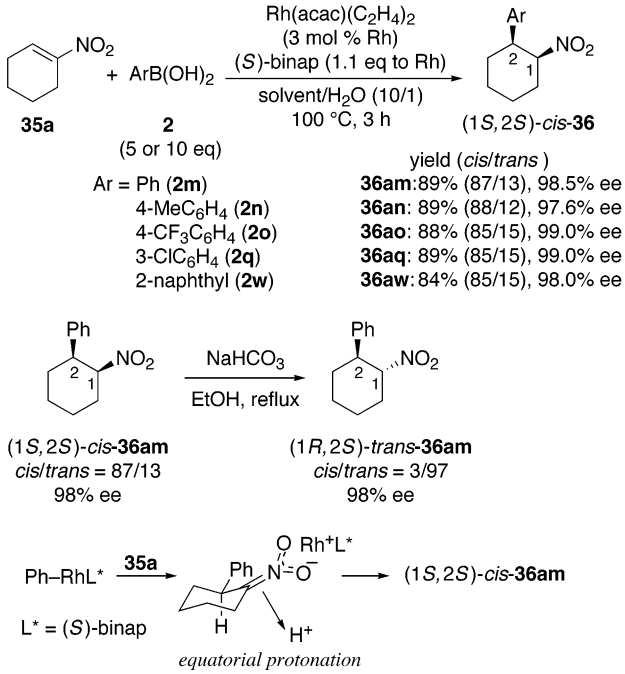


Scheme 25



Nitroalkenes are good substrates for the rhodium-catalyzed asymmetric 1,4-addition of organoboronic acids.[28] Hayashi reported that the reaction of 1-nitrocyclohexene (**35a**) with phenylboronic acid (**2m**) in the presence of the rhodium/(*S*)-binap catalyst at 100 °C for 3 h gave 89% yield of 2-phenyl-1-nitrocyclohexane (**36am**) (Scheme 26). The main phenylation product **36am** is a cis isomer (cis/trans = 87/13), and both of the cis and trans isomers are 98% enantiomerically pure. Treatment of the *cis*-rich mixture with sodium bicarbonate in refluxing ethanol caused cis−trans equilibration, giving thermodynamically more stable trans isomer (trans/cis = 97/3). It should be noted that this rhodium-catalyzed asymmetric phenylation produced thermodynamically less stable cis isomer of high enantiomeric purity and it can be isomerized, if one wishes, into

Scheme 26



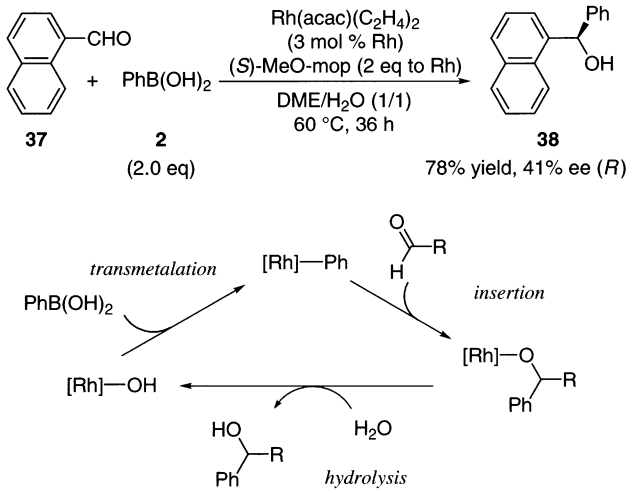
trans isomer without loss of its enantiomeric purity. The preferential formation of *cis*-**36am** in the catalytic phenylation may indicate the protonation of a rhodium nitronate intermediate in the catalytic cycle. Under similar reaction conditions, 1-nitrocyclohexene (**35a**) underwent asymmetric addition of some other arylboronic acids in good yields with high enantioselectivity. The corresponding *cis*-2-aryl-1-nitrocyclohexanes were produced with over 85% cis selectivity and with the enantioselectivity ranging between 97.6% and 99.0% ee. The optically active nitroalkanes obtained by the present method are useful chiral building blocks which can be readily converted into a wide variety of optically active compounds by taking advantages of the versatile reactivity of nitro compounds.

2.6. Other Substrates

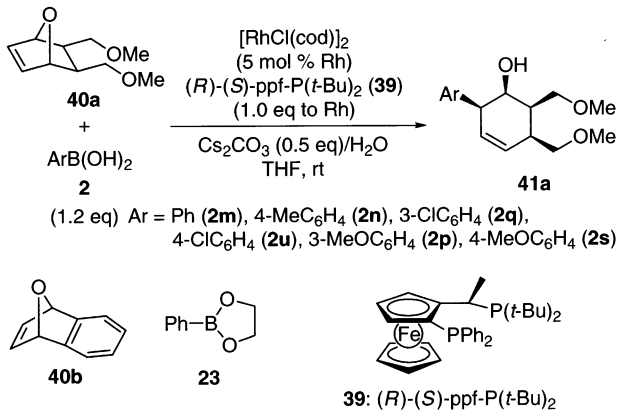
Arylboronic acids are known to add to aldehydes in the presence of a rhodium catalyst.[29] However, unfortunately, there has been only one example of the asymmetric version of the rhodium-catalyzed asymmetric arylation of aldehydes. In the report by Miyaura,[29a] a rhodium complex coordinated with axially chiral monodentate phosphine ligand, (*S*)-MeO-mop, catalyzes the addition of phenylboronic acid (**2m**) to 1-naphthoaldehyde (**37**) in DME/H_2O at 60 °C for 36 h to give 78% yield of diarylmethanol (*R*)-**38** with 41% ee (Scheme 27). Use of chiral chelating bisphosphine ligands such as diop and binap gave the racemic product. A catalytic cycle involving addition of phenyl-rhodium species to aldehyde forming alkoxy-rhodium is proposed.

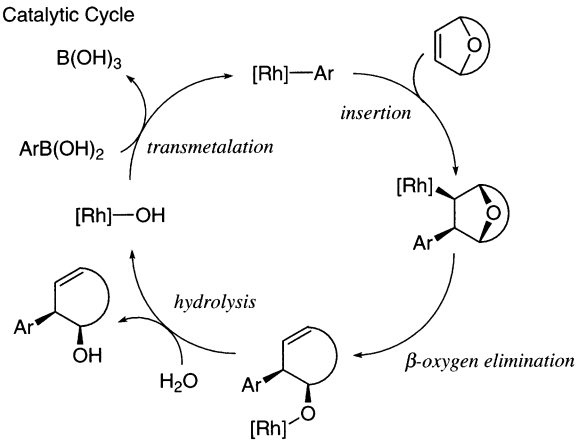
Lautens reported the asymmetric ring-opening reaction of oxanorbornene derivatives **40** with arylboronic acids or arylboronate esters catalyzed by a chiral rhodium complex[30] (Scheme 28, Table 9). The efficiency of the catalytic asymmetric synthesis was dependent on several factors of the reaction condi-

Scheme 27



Scheme 28





tions. High enantioselectivity (up to 99% ee) was observed with chiral ferrocenylbisphosphine ligand **39** in a THF solution containing aqueous cesium carbonate. In the reaction of oxabenzonorbornadiene (**40b**), the ring-opening proceeded in a higher yield with the phenylboronate of ethylene glycol than with phenylboronic acid (entries 7 and 8). The catalytic cycle has been suggested[31] to involve a β-oxygen elimination as a key step. Thus, insertion of the double bond of oxanorbornene into the aryl-rhodium bond forms an alkylrhodium intermediate, which undergoes β-oxygen elimination to give alkoxyrhodium intermediate, and then hydrolysis and transmetalation regenerates the aryl-rhodium intermediate. Stereochemical outcome is determined at enantioposition-selective carborhodation of the meso-type alkene.

Table 9. Rh-Catalyzed Asymmetric Ring Opening of Oxabicycles 40 with Arylboronic Acids 2 (Scheme 28)[a]

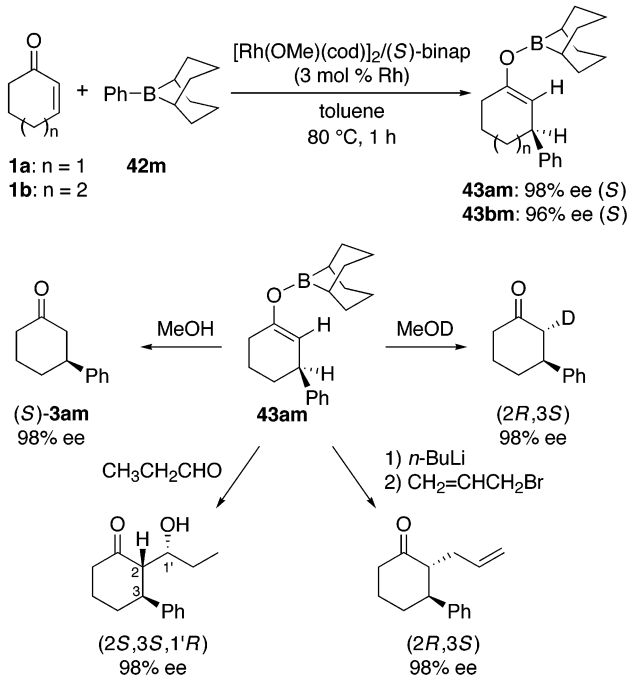
		boron reagent	product **41**		
entry	40	**2** or **23**	yield (%)	% ee	
1	**40a**	**2m**	**41am**	91	95 (+)
2	**40a**	**2n**	**41an**	88	95 (+)
3	**40a**	**2q**	**41aq**	73	99 (+)
4	**40a**	**2u**	**41au**	95	95 (+)
5	**40a**	**2p**	**41ap**	91	95 (+)
6	**40a**	**2s**	**41as**	87	96 (+)
7	**40b**	**2m**	**41bm**	28	92 (−)
8	**40b**	**23**	**41bm**	78	92 (−)

[a] The reaction was carried out in THF with Cs_2CO_3 (5 M in H_2O, 0.5 equiv to **40a**) at room temperature for 14 h. **40**/**2**/$[RhCl(cod)]_2$/**39** = 1.0/1.2/0.025/0.05.

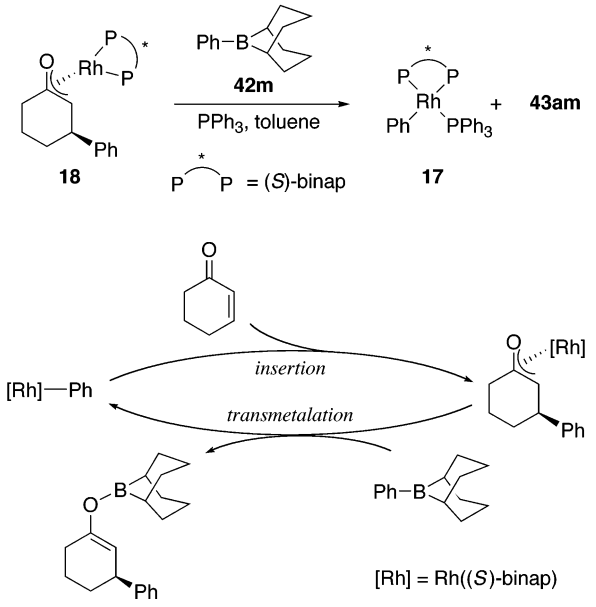
2.7. Reactions in Aprotic Solvents

In the rhodium-catalyzed 1,4-addition of organoboron reagents to electron deficient alkenes described above, protic solvents represented by water play a key role in the catalytic cycle which involves hydrolysis of oxo-π-allylrhodium giving hydroxorhodium species and the hydrolyzed 1,4-addition product (cf. Scheme 12). The use of water as a cosolvent is one of the advantages of this reaction over other 1,4-addition reactions, but one major drawback is that the 1,4-addition product is obtained as the hydrolyzed product. A catalytic asymmetric 1,4-addition giving boron enolates as the products would be more useful. Recently Hayashi found that the use of *B*-Ar-9BBN (**42**) realizes the catalytic asymmetric 1,4-addition forming chiral boron enolates[32] (Scheme 29). As a typical example, the reaction of 2-cyclohexenone (**1a**) with 1.1 equiv of *B*-Ph-9BBN (**42m**) in the presence

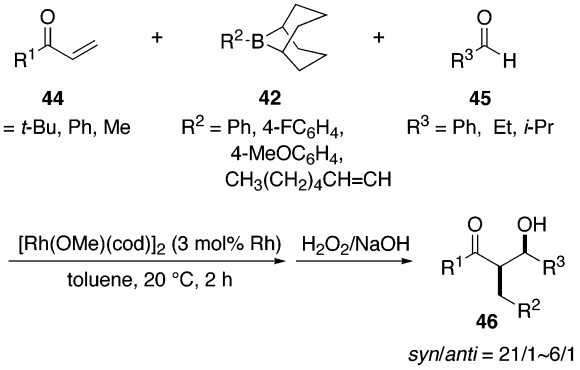
Scheme 29



Scheme 30



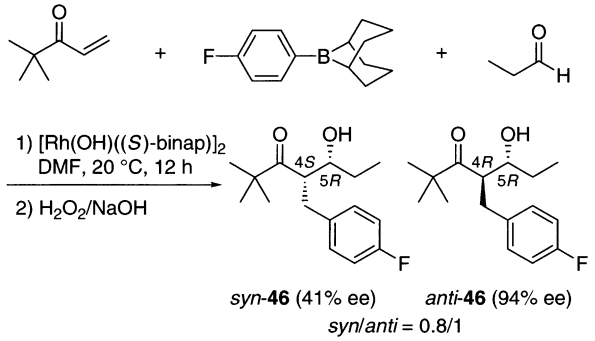
Scheme 31



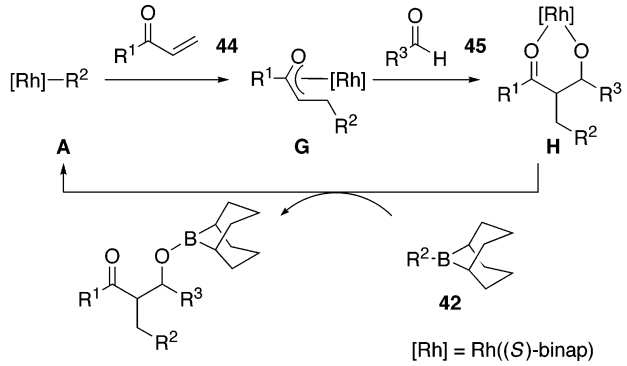
of 3 mol % of a rhodium catalyst generated from $[Rh(OMe)(cod)]_2$ and (*S*)-binap in toluene at 80 °C for 1 h gave a high yield of the boron enolate **43**, which is an *S* isomer of 98% ee. The boron enolate formation was not observed in the reaction with phenylboronate esters, phenylboroxine, or tetraphenylborate. Unfortunately, this reaction forming chiral boron enolate is observed only for 2-cyclohexenone and 2-cycloheptenone. The reaction of boron enolate **43** with electrophiles provides us with a chance for the further transformation as expected. ^{31}P NMR studies revealed that a direct transmetalation of the phenyl group from boron to rhodium of the (oxa-π-allyl)-rhodium complex is involved in the present reaction (Scheme 30). The catalytic cycle consists of two steps. One is insertion of the enone into the aryl−rhodium bond, and the other is transmetalation to the (oxa-π-allyl)rhodium complex, forming an arylrhodium species and the boron enolate.

A new type of catalytic tandem 1,4-addition-aldol reaction has been reported by Hayashi.[33] The reaction of *B*-Ar-9BBN (**42**), vinyl ketone **44**, and aldehyde **45** catalyzed by 3 mol % of $[Rh(OMe)(cod)]_2$ proceeded in toluene at 20 °C to give high yield of the aldol-type product **46** with high syn selectivity (Scheme 31). Asymmetric reaction using $[Rh(OH)((S)\text{-binap})]_2$

Scheme 32



Scheme 33

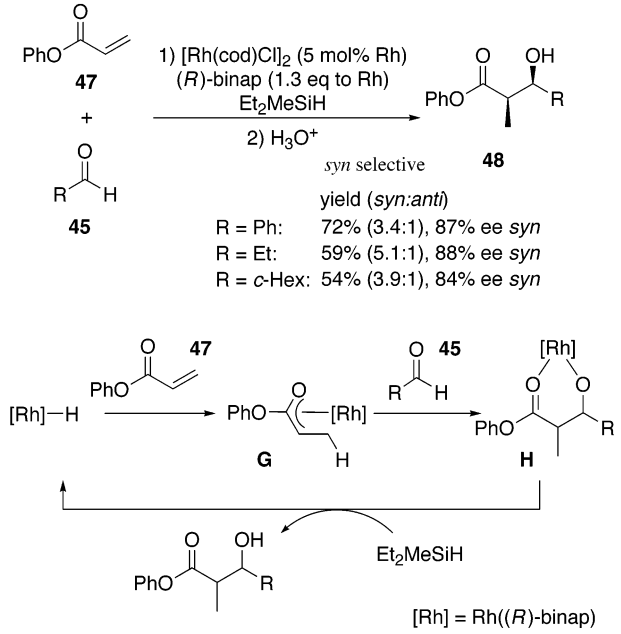


as a catalyst gave optically active products, *syn*-(4*S*,5*R*)-**46** of 41% ee and *anti*-(4*R*,5*R*)-**46** of 94% ee, though the syn/anti selectivity is low (Scheme 32). The formation of the enantiomerically enriched products demonstrates that the reaction proceeds through (oxa-π-allyl)rhodium complex **G** coordinated with (*S*)-binap ligand which is formed by the carbo-rhodation of the vinyl ketone and undergoes aldol-type reaction, with aldehyde forming rhodium aldolate **H** (Scheme 33). The boron enolate as an intermediate is ruled out, which would lead to a racemic aldol product.

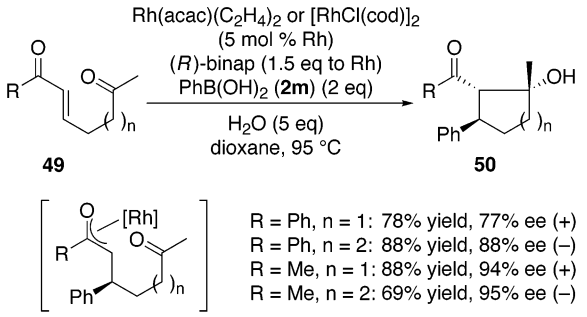
The rhodium-catalyzed asymmetric reductive aldol reaction starting with phenyl acrylate (**47**), diethylmethylhydrosilane, and aldehydes **45**, which has been reported by Morken,[34] is considered to proceed in a manner similar to the 1,4-addition-aldol reaction (Scheme 34). The reaction gives aldol-type product with moderate *syn* selectivity with up to 88% enantioselectivity for various types of aldehydes. The key enantioselective step is probably the aldol reaction of (oxa-π-allyl)rhodium complex **G**, generated by hydro-rhodation of acrylate, with aldehyde giving rhodium aldolate **H**.

Intramolecular tandem 1,4-addition-aldol reaction of enone−ketone **49** with phenylboronic acid **2m** was reported to occur in the presence of an excess of water[35] (Scheme 35). This cyclization should proceed through the (oxa-π-allyl)rhodium intermediate. Because the intramolecular reaction of the intermediate with ketone moiety is faster than protonolysis with water, the aldol product is obtained in high yields even in the presence of water. Binap is a ligand of choice, which gave the 1,4-addition-aldol product of up to 95% ee. The product was racemic with Josiphos or MeDuphos.

Scheme 34



Scheme 35



3. Asymmetric Addition of Organosilicon Reagents

Although there have been several reports on the use of organosilicon compounds for the rhodium-catalyzed 1,4-addition,[36] only one report has appeared so far on the asymmetric version of this reaction. Oi and Inoue reported that the asymmetric 1,4-addition of aryl- and alkenyltrialkoxysilanes **51** to α,β-unsaturated ketones takes place in the presence of 2 mol % of a cationic rhodium catalyst generated from $[Rh(cod)(MeCN)_2]BF_4$ and (*S*)-binap in dioxane/H_2O (10/1) at 90 °C[37] (Scheme 36, Table 10). The use of 1.5 equiv of binap ligand relative to the rhodium catalyst precursor is important for high enantioselectivity, because the cationic precursor $[Rh(cod)(MeCN)_2]BF_4$ is more catalytically active than the complex coordinated with binap. The chemical yields of the 1,4-addition products are generally a little lower than those with the corresponding boronic acids. The enantioselectivity is almost the same as that with the boronic acids, which is probably because the reaction pathway is similar. Both (*E*) and (*Z*) isomers of styrylsilanes **52u** and **52v** gave the corresponding 1,4-addition products without isomerization of the *E*/*Z* geometry (entries 10 and 11). The asymmetric 1,4-addition of phenyltrimethoxysilane (**51m**) was applied to α,β-unsaturated ester **21m** and

Scheme 36

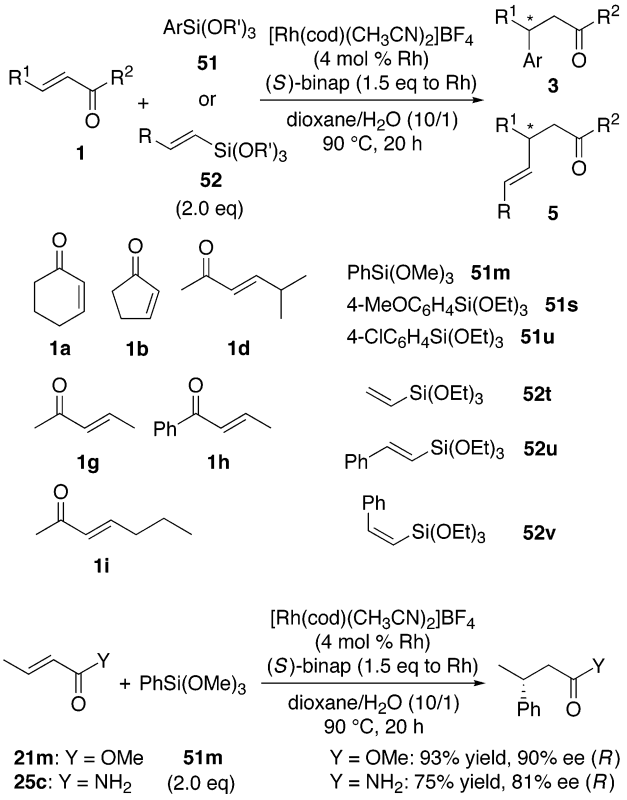


Table 10. Asymmetric 1,4-Addition of Organosilanes 51 or 52 to Enones 1 Catalyzed by (*S*)-Binap−Rhodium(I) (Scheme 36)[a]

entry	enone **1**	silane **51** or **52**	ketone **3** or **5**	yield (%)	% ee	
1	**1a**	**51m**	**3am**	76	98	(*S*)
2	**1b**	**51m**	**3bm**	89	94	(*S*)
3	**1d**	**51m**	**3dm**	62	98	(−)
4	**1g**	**51m**	**3gm**	90	75	(*R*)
5	**1h**	**51m**	**3hm**	90	75	(*R*)
6	**1i**	**51m**	**3im**	87	91	(−)
7	**1a**	**51s**	**3as**	73	96	(−)
8	**1a**	**51u**	**3au**	56	96	(−)
9	**1a**	**52t**	**5at**	54	96	(*S*)
10	**1a**	**52u**	**5au**	85	91	(*S*)
11	**1a**	**52v**	**5av**	88	87	(−)

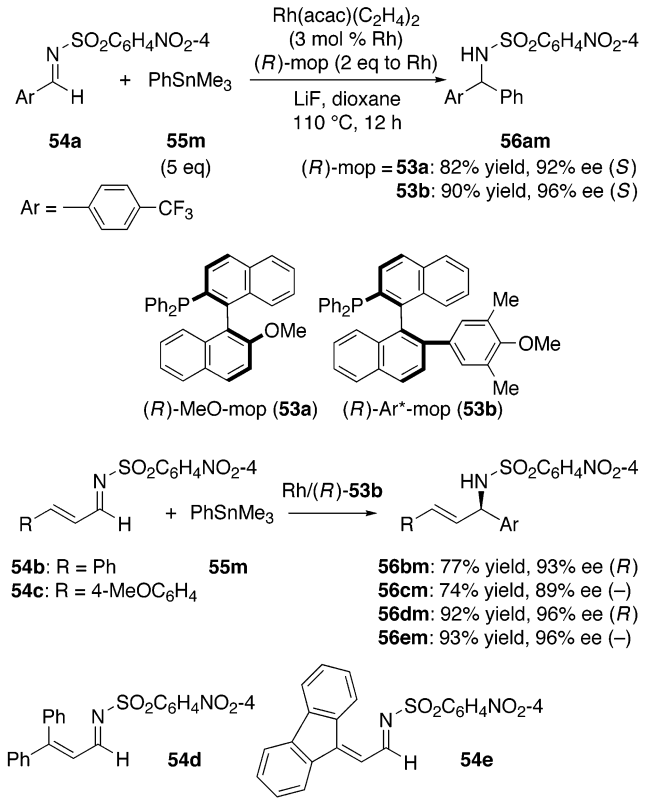
[a] The reaction was carried out in dioxane/H_2O (10/1) at 90 °C for 20 h. **1**/organosilane/$[Rh(cod)(CH_3CN)_2]BF_4$/(*S*)-binap = 1.0/2.0/0.04/0.06.

amide **25c**, which gave the corresponding β-phenylation products with good selectivity.

4. Asymmetric Addition of Organotin Reagents

It has been reported by Oi that aryl(trimethyl)stannanes can participate in the rhodium-catalyzed 1,4-addition to α,β-unsaturated ketones[38] and 1,2-addition to aldehydes,[39] but these reactions have not been applied to asymmetric synthesis. The active rhodium catalyst used for these addition reactions is $[Rh(cod)(MeCN)_2]BF_4$, and the addition of phosphine ligands has been reported to inhibit the reactions. The low catalytic activity of the phosphine-rhodium complexes has probably made the catalytic asymmetric synthesis difficult. The addition of aryl(trimethyl)stannanes to imines[40] was successfully

Scheme 37



developed to catalytic asymmetric synthesis of chiral diarylmethylamines by use of axially chiral monodentate phosphine ligand MOP **53**[41] (Scheme 37). The reaction of *N*-alkylidenesulfonamides **54** with aryltrimethylstannane **55** in the presence of 3 mol % of $Rh(acac)(C_2H_4)_2$ and one of the mop ligands **53** in dioxane at 110 °C for 12 h gave modest to high yields of chiral diarylmethylamine sulfonamides **56**. The arylation is very slow with chelating bisphosphine ligands such as binap. Of the mop ligands, the one substituted with 3,5-dimethyl-4-methoxyphenyl group **53b** is more enantioselective than the standard MeO−mop **53a**. The imine **54** which contains a 4-nitro group on the phenyl of sulfonamide is more reactive than others to give higher yields of the arylation products. As the best example, the sulfonamide of phenyl(4-trifluoromethylphenyl)methylamine (*S*)-**56am** with 96% ee was obtained in 90% yield in the reaction of 4-nitrobenzenesulfonamide **54a** with phenyltrimethylstannane (**55m**) catalyzed by Rh/(*R*)-**53b**. Interestingly, imines of α,β-unsaturated aldehydes **54b**−**54c** undergo 1,2-addition to the imine moiety selectively to give arylated allylamines, the formation of the 1,4-addition products being not observed. The enantioselectivity forming the allylamines was high, ranging between 89% and 96% ee, in the phenylation with the mop ligand **53b**.[42]

5. Asymmetric Addition of Organotitanium Reagents

Recently Hayashi found that a rhodium catalyst and aryltitanium triisopropoxide ($ArTi(OPr\text{-}i)_3$, **57**) is a good combination for the asymmetric 1,4-addition to α,β-unsaturated ketones in an aprotic solvent[43]

Scheme 38

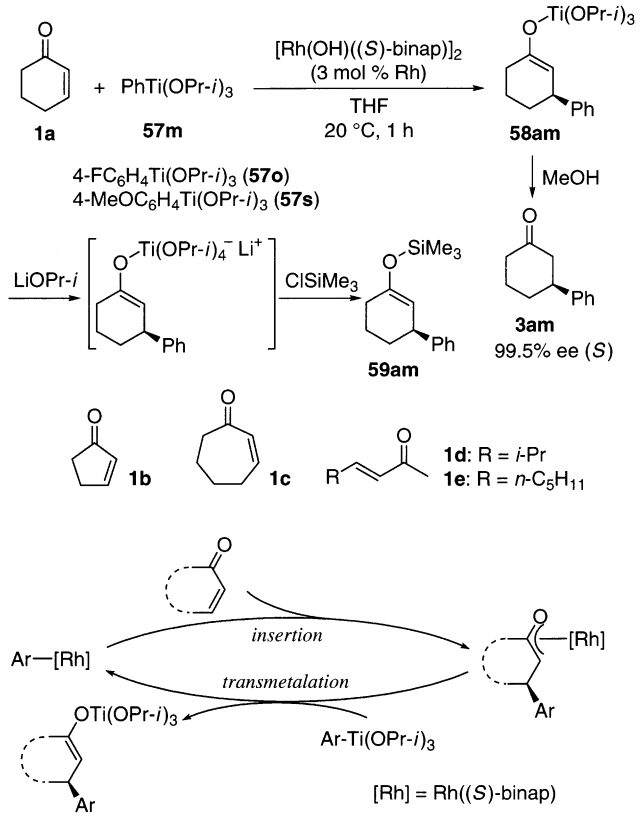


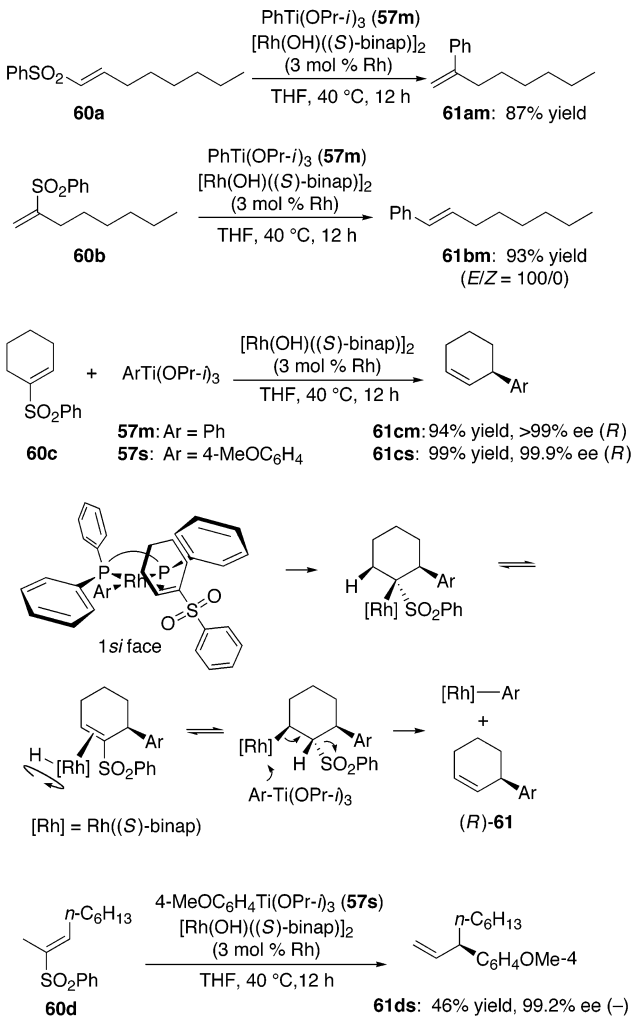
Table 11. Asymmetric 1,4-Addition of Aryltitanium Triisopropoxides 57 to Enones 1 Catalyzed by [Rh(OH)((*S*)-binap)]$_2$ (Scheme 38)[a]

entry	enone **1**	$ArTi(OPr\text{-}i)_3$ **57**	silyl ether **59**	yield (%)	% ee	
1	**1a**	**57m**	**59am**	84	99.5	(*S*)
2	**1a**	**57o**	**59ao**	68	99.0	(*S*)
3	**1a**	**57s**	**59as**	84	99.8	(*S*)
4	**1b**	**57m**	**59bm**	62	99.8	(*S*)
5	**1c**	**57m**	**59cm**	89	98	(*S*)
6	**1d**	**57m**	**59dm**	77	99.8	(*S*)
7	**1e**	**57m**	**59em**	84	97	(*R*)

[a] The reaction was carried out with enone **1** (1.00 mmol) and $ArTi(OPr\text{-}i)_3$ **57** (1.60 mmol) in 5.0 mL of THF at 20 °C for 1 h in the presence of 3 mol % (Rh) of [Rh(OH)((*S*)-binap)]$_2$. To the reaction mixture, were added LiOPr-*i* (1.60 mmol) and $ClSiMe_3$ (2.00 mmol).

(Scheme 38, Table 11). The addition of $ArTi(OPr\text{-}i)_3$ (**57**) to 2-cyclohexenone (**1a**) was completed within 1 h in the presence of 3 mol % of [Rh(OH)((*S*)-binap)]$_2$ in THF at 20 °C to give high yields of the titanium enolates **58** as 1,4-addition products. The enantioselectivity is very high, 99.5%, 99.0%, and 99.8% ee, for Ar = Ph, 4-FC_6H_4, and 4-$MeOC_6H_4$, respectively (entries 1−3). The titanium enolates were converted into silyl enol ethers by treatment with chlorotrimethylsilane and lithium isopropoxide. Other cyclic enones **1b** and **1c** and linear enones **1d** and **1e** are also good substrates for the asymmetric 1,4-addition of phenyltitanium triisopropoxide giving the corresponding arylation products with over 97% enantioselectivity (entries 4−7). The catalytic cycle was demonstrated by NMR studies to involve the transmetalation of the aryl group from titanium to rho-

Scheme 39



dium of the (oxa-π-allyl)rhodium intermediate leaving an arylrhodium species and the titanium enolate.

The use of alkenyl sulfones **60** for the rhodium-catalyzed addition of aryltitanium reagents (ArTi(OPr-*i*)$_3$, **57**) was found to give us an interesting result[44] (Scheme 39). The addition to linear alkenyl sulfones **60a** and **60b** resulted in a cine substitution reaction, where the sulfonyl group is substituted with the phenyl group on the next carbon of the double bond took place regioselectively. The catalytic cycle was established by deuterium labeling studies to proceed through anti elimination of rhodium and sulfonyl group from an alkyl−rhodium intermediate. In the addition reaction to cyclic alkenyl sulfone **60c**, the asymmetric carbon center created at the carborhodation step is retained in the substitution product. Thus, the reaction of **60c** with aryltitanium triisopropoxides (ArTi(OPr-*i*)$_3$, **57**) in the presence of 3 mol % of [Rh(OH)((*S*)-binap)]$_2$ in THF at 40 °C gave a quantitative yield of 1-arylcyclohexenes **61c** with over 99% enantioselectivity. The reaction of sulfone of internal alkene **60d** also proceeded with high enantioselectivity to give allylarene **61ds** of 99.2% ee.

6. Conclusion

The rhodium-catalyzed asymmetric 1,4-addition of organoboron reagents, which was started by Hayashi and Miyaura in 1998, has been developing quickly. The reaction can be carried out in an aqueous solvent and the enantioselectivity is very high, in most cases over 90% ee, at a reaction temperature of around 100 °C. The substrates for the asymmetric addition have covered α,β-unsaturated ketones, esters, amides, phosphonates, nitroalkenes, and so on. This reaction provides the best method for enantioselective introduction of aryl and alkenyl groups to β position of these electron deficient olefins. Considering the reactivity of the transition metal−carbon bond toward various types of carbon−carbon or carbon-heteroatom multiple bonds, the rhodium intermediate is expected to add to some unsaturated bonds other than the electron deficient olefins. Actually, the addition of organoboron reagents to unactivated alkenes[45] and alkynes[46] as well as aldehydes[29] and imines[47] has been reported to be catalyzed by a rhodium complex. Unfortunately, the carbon atoms successfully introduced by this rhodium-catalyzed reaction have been limited to sp^2 carbons. Since it has been reported that the insertion of an olefin into rhodium−sp^3 carbon bond takes place in an intramolecular system,[48] the asymmetric 1,4-addition of alkyl groups will be realized in the future. The catalytic asymmetric introduction of alkynyl groups is another challenging subject. One of the significant recent developments is the finding that organo-silicon, -tin, and -titanium reagents can participate in the rhodium-catalyzed 1,4-addition. In particular, the reactions of aryltitanium reagents in an aprotic solvent are promising, whose catalytic cycle is different from that for the reactions in protic solvents such as water. Many new catalytic reactions of synthetic value will be developed by combination of various types of organometallic reagents and unsaturated molecules, and some of them will be extended to catalytic asymmetric reactions of high enantioselectivity by proper tuning of the chiral catalyst.

7. References

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