Rhodium-Catalyzed Asymmetric 1,4-Addition of Organoboronic Acids and Their Derivatives to Electron Deficient Olefins

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This paper is decicated to Professor Ryoji Noyori for his distinguished achievements in chemistry.

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Abstract: Asymmetric 1,4-arylation and -alkenylation was achieved by use of organoboronic acids or their derivatives in the presence of a rhodium catalyst coordinated with binap ligand. The reaction conditions are unique in that it is usually carried out in an aqueous solvent at 100 °C. The scope of this asymmetric addition is very broad, α,β-unsaturated ketones, esters, 1-alkenylphosphonates, and 1-nitroalkenes being efficiently converted into the corresponding optically active 1,4-addition products with over 95% enantioselectivity. The catalytic cycle is proposed to involve the enantioselective addition of aryl- or alkenyl-rhodium intermediate to carbon-carbon double bond of the electron deficient olefins as a key step.

Key words: asymmetric catalysis, asymmetric 1,4-addition, rhodium complex, organoboronic acids, electron deficient olefins

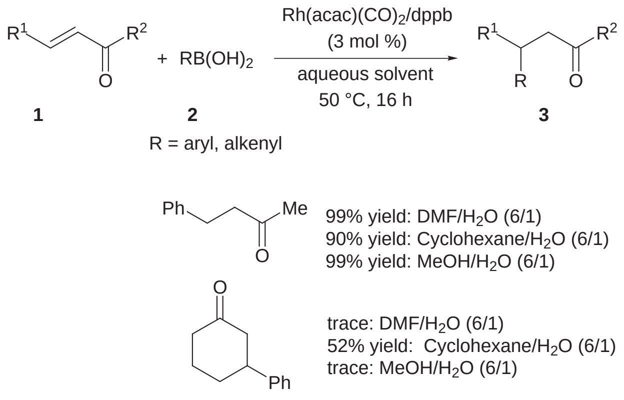
1 Introduction

The 1,4-conjugate addition of organometallic reagents to alkenes attached to an electron-withdrawing group represented by α,β-unsaturated ketones is widely used process for carbon-carbon bond formation giving β-substituted functionalized compounds, which are versatile synthons to further organic transformations.[1] Over the last twenty years, considerable efforts have been made to develop efficient chiral catalytic systems for the asymmetric 1,4-addition of organometallic reagents,[2] and high enantioselectivity of over 90% ee has been achieved in the addition of organomagnesium and -zinc reagents by use of copper(I) catalysts coordinated with chiral phosphorous ligands.[3,4] Typical examples are the reaction of Grignard reagents in the presence of a chiral amidophosphine ligand derived from (*S*)-proline[3g] and the reaction of diethylzinc in the presence of a phosphite or phosphorous amidite ligand based on the axially chiral 1,1'-binaphthol.[3a-d] In these 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. Recently, we found that the asymmetric 1,4-addition of organoboronic acids to α,β-unsaturated ketones is efficiently catalyzed by a chiral phosphine-rhodium complex in an aqueous solvent at 100 °C and we have been exploring the scope of this new catalytic asymmetric reaction.[5] The present account describes the development of the rhodium-catalyzed asymmetric 1,4-addition which has been studied in my laboratory these four years.

2 The Original Work by Miyaura on Rhodium-Catalyzed 1,4-Addition

In 1997, Miyaura reported a novel catalytic 1,4-addition reaction, that is, rhodium-catalyzed 1,4-addition of aryl- and alkenylboronic acids to enones (Scheme 1).[6] As a typical example, a rhodium complex generated from $Rh(acac)(CO)_2$ and 1,4-bis(diphenylphosphino)butane (dppb) catalyzes the reaction of methyl vinyl ketone with phenylboronic acid in an aqueous solvent (DMF/H_2O = 6/1) at 50 °C for 16 h to give over 90% yield of phenylation product, 4-phenylbutan-2-one. This Miyaura's new catalytic reaction has several advantages over other 1,4-addition reactions. (1) The organoboronic acids used in this reaction are stable to oxygen and moisture, 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 so far used, 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. (4) The reaction is 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,[2,7] one can use the accumulated knowledge of the chiral phosphine ligands for the asymmetric reaction.

In the report by Miyaura (Scheme 1),[6] the yields of the arylation products are generally high for β-unsubstituted



Scheme 1

enones such as methyl vinyl ketone, but the yields are not high for 2-cyclohexenone which is an enone often used for the asymmetric 1,4-addition. It follows that the improvement of the reaction conditions is first requisite for the reaction of this type of β-substituted enones. For the creation of a stereogenic carbon center in the 1,4-addition, we have to use β-substituted enones.

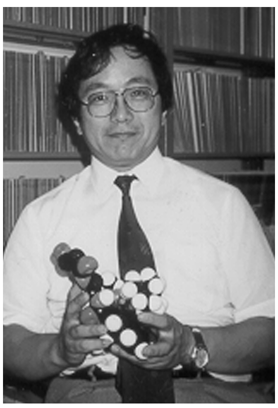
3 Catalytic Asymmetric 1,4-Addition of Organoboron Reagents to α,β-Unsaturated Ketones

3.1 Asymmetric 1,4-Addition of Organoboronic Acids

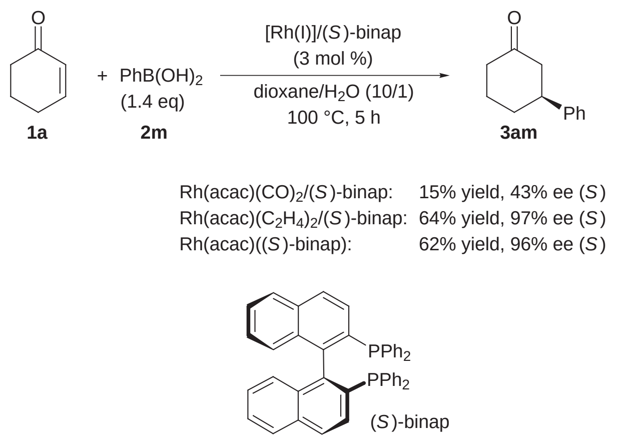
First we examined the reaction of 2-cyclohexenone (**1a**) with phenylboronic acid (**2m**) by use of (*S*)-2.2'-bis(diphenylphosphino)-1,1'-binaphthyl (binap),[8] which is one of the most effective chiral bisphosphine ligands developed by Noyori, in place of dppb under the same reaction conditions as reported by Miyaura.[6] As expected, the chemical yield of 1,4-addition product, 3-phenylcyclohexanone (**3am**), was very low. Thus, the reaction in the presence of a rhodium catalyst generated by mixing $Rh(acac)(CO)_2$ with binap in cyclohexane/H_2O or in methanol/H_2O at 50 °C gave only a trace amount (<2% yield) of **3am**. Heating the reaction at 100 °C in dioxane/H_2O (10/1) or in 1-propanol/H_2O (10/1) increased the yield of **3am** up to 15%, which was 43% enantiomerically pure. Although the yield is still low and the enantioselectivity is not high enough, the formation of the non-racemic product encouraged us because it demonstrates that the catalytic asymmetric synthesis is possible in this catalytic 1,4-addition. The reaction took place on the rhodium catalyst coordinated with the chiral phosphine ligand.

We examined several reaction conditions, and found that the reaction is efficiently catalyzed by a rhodium complex generated in situ by mixing $Rh(acac)(C_2H_4)_2$ with (*S*)-binap ligand (Scheme 2).[9] The rhodium precursor was changed from dicarbonyl complex to the bis(ethylene) complex. A mixture of 2-cyclohexenone (**1a**), 1.4 equiv of phenylboronic acid (**2m**), and 3 mol% of the rhodium catalyst was heated at 100 °C in dioxane and water (10/1) for 5 h to give 64% yield of 3-phenylcyclohexanone (**3am**) which turned out to be (*S*) isomer of 97% ee. NMR studies showed that the reaction of $Rh(acac)(C_2H_4)_2$ with 1 equiv of (*S*)-binap generates Rh(acac)(binap) complex quantitatively. In contrast, $Rh(acac)(CO)_2$ generates two kinds of unidentified rhodium complexes together with a small amount of the Rh(acac)(binap) complex. This must be one of the reasons why the catalyst generated from $Rh(acac)(CO)_2$ is less effective than that from $Rh(acac)(C_2H_4)_2$. It is reasonable that the ethylene is more readily replaced by the bisphosphine ligand than the carbon monoxide. Isolated rhodium-binap complex Rh(acac)[(*S*)-binap] was as effective as the in situ generated complex, 62% yield and 96% ee. For this asymmetric reaction binap is a chiral ligand of choice, some other chiral phosphine ligands being less enantioselective or less catalytically active.[10] The reaction of **1a** with **2m** proceeded with rhodium catalysts of chelating bisphosphine ligands, (*S*,*S*)-diop and (*S*,*S*)-chiraphos, but the enantioselectivity was much lower, 24% and 40% ee, respectively.

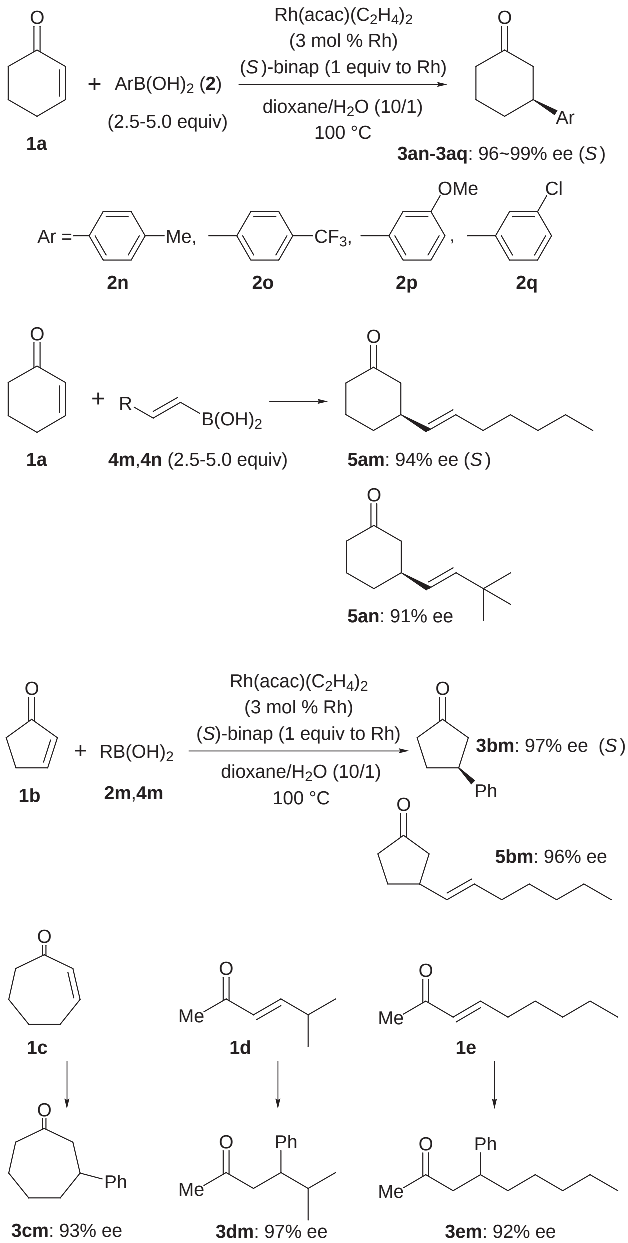
Biographical Sketch



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 is "Catalytic Asymmetric Hydrosilylation of Olefins and Ketones". Then he was appointed 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 Catalysis Research Center, Hokkaido University. Since 1994, he has been Full Professor in Faculty of Science, Kyoto University. He received the Award for Young Chemists of the Society of Synthetic Organic Chemistry, Japan in 1983. He has been interested in development of new reactions catalyzed by transition metal complexes, especially in catalytic asymmetric reactions.



Scheme 2



Scheme 3

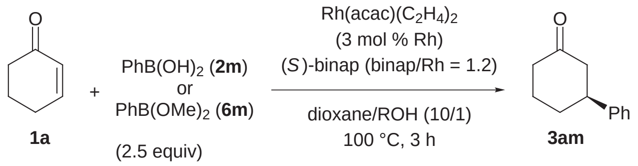
It was found that phenylboronic acid (**2m**) undergoes hydrolysis giving benzene as a competing reaction under the reaction conditions. The yield of addition product **3am** was improved by use of an excess of the boronic acid. Thus, with 2.5 equivalents of **2m**, the yield was 93% and a quantitative yield of **3am** was obtained even in the presence of 1 mol% of the catalyst without loss of enantioselectivity. The reaction temperature is also important for high chemical yield. At 60 °C or lower the 1,4-addition was very slow, giving **3am** in not higher than 3% yield. The highest yield was achieved at 100 °C.

The scope of this catalytic asymmetric addition is very broad (Scheme 3). 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**. Asymmetric addition of 1-alkenylboronic acids was also successful, (*E*)-1-heptenylboronic acid (**4m**) and (*E*)-3,3-dimethyl-1-butenylboronic acid (**4n**) giving the corresponding alkenylation products **5am** and **5an** of over 90% ee. Cyclopentenone (**1b**) also underwent the asymmetric addition of phenyl- and 1-heptenylboronic acids with high enantioselectivity under similar reaction conditions to give 3-substituted cyclopentanones, **3bm** [97% ee (*S*)] and **5bm** (96% ee), in high yields. High enantioselectivity was also observed in the reaction of linear enones **1d** and **1e** which have *trans* olefin geometry. Thus, 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.

3.2 Mechanistic Studies

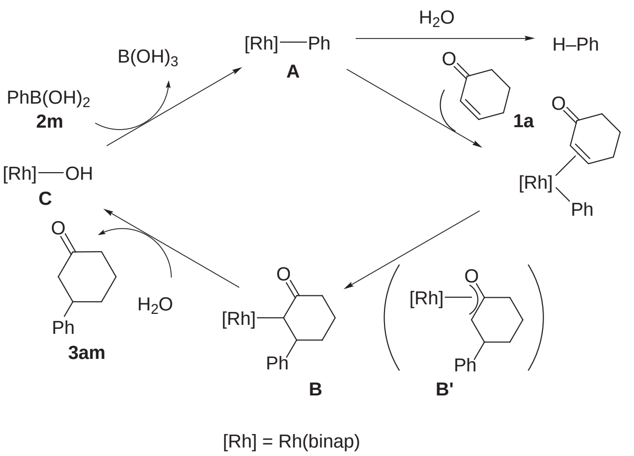
It should be noted that the presence of water or a proton source is important for the rhodium-catalyzed 1,4-addition. In the reaction of phenylboronic acid (**2m**), the addition of water or alcohol is not always necessary because the boronic acid itself can be the proton source. In the reaction of dimethyl ester **6m**, if water or alcohol is not added, the 1,4-addition does not take place. It is assumed that proton is playing a key role in the catalytic cycle giving the 1,4-addition product (Scheme 4).[11]

Our studies on the mechanism of the rhodium-catalyzed 1,4-addition are still in progress. At this moment, we propose the catalytic cycle shown in Scheme 5 which involves the insertion of carbon-carbon double bond of enone into aryl-rhodium bond giving an oxo-π-allyl species as a key step. Thus, in the reaction of **1a** with **2m**, a phenyl-rhodium complex coordinated with binap **A**, which is generated by transmetallation of phenyl group from boron to rhodium, adds to cyclohexenone (**2m**) to form alkyl-rhodium intermediate **B**. It may be isomerized into oxo-π-allyl species **B’**, which undergoes protonolysis by water to give 1,4-addition product **3am** and hydroxo-



	ROH	yield (%)	% ee
PhB(OH)$_2$ (**2m**)	H_2O	94	98.5 (*S*)
	MeOH	94	98.5 (*S*)
	none	85	98.6 (*S*)
PhB(OMe)$_2$ (**6m**)	H_2O	94	98.7 (*S*)
	MeOH	92	98.6 (*S*)
	none	6	98.5 (*S*)

Scheme 4



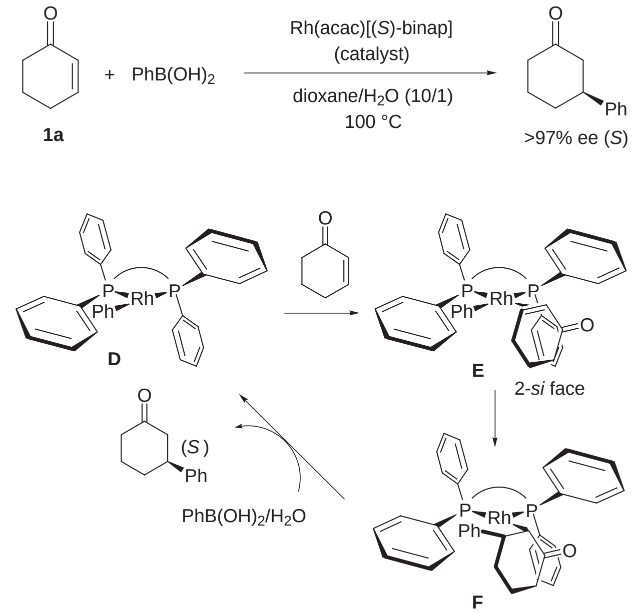
Scheme 5

rhodium complex **C**. The main side reaction, hydrolysis of phenylboronic acid giving benzene, is probably caused by the protonolysis of the phenyl-rhodium species **A**.

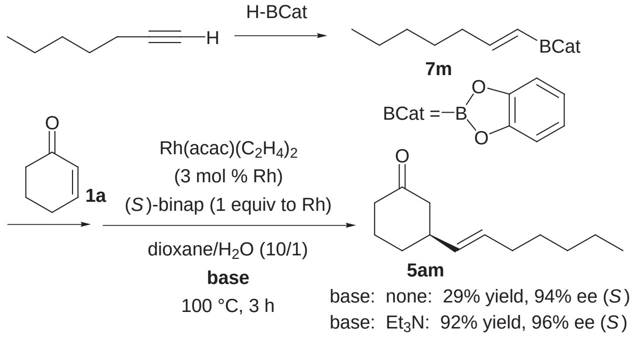
Scheme 6 shows the stereochemical pathway forming the products of *S* configuration, which is exemplified by the reaction of 2-cyclohexenone (**1a**).[9] According to the highly skewed structure known for transition metal complexes coordinated with a binap ligand,[12] (*S*)-binap–rhodium intermediate **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 **1a** coordinates to rhodium with its 2*si* face forming **E** rather than with its 2*re* face, which undergoes migratory insertion to form a stereogenic carbon center in **F** whose absolute configuration is *S*. All the 1,4-addition products **3** obtained have the absolute configuration resulting from the attack of 2*si* face of enones.

3.3 Asymmetric 1,4-Addition of Alkenylcatecholboranes and Arylborates

In the previous Section, it was shown that aryl- and alkenylboronic acids can be successfully used for the rhodium-catalyzed asymmetric 1,4-addition. Unfortunately, however, the preparation, isolation, and purification of the boronic acids are not always easy. Organoboronic acids are usually prepared by the reaction of organometallic reagents such as organolithium reagents with a trialkoxyborane and hydrolysis, recrystallization, and so on.[13] It would be more practically useful if boronic acid esters were used for the asymmetric 1,4-addition. We found that alkenylcatecholboranes obtained by the hydroboration of alkynes with catecholborane are good alkenylating reagents for this asymmetric 1,4-addition.[14] For the reaction of (*E*)-1-heptenylborane (**7m**), which is obtained by the hydroboration of 1-heptyne, with 2-cyclohexenone (**1a**), several reaction conditions were examined (Scheme 7). The chemical yield of 1,4-addition product **5am** was low (29%) under the conditions used for the reaction of aryl- and alkenylboronic acids, that is, in dioxane/H_2O (10/1) at 100 °C, though 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.



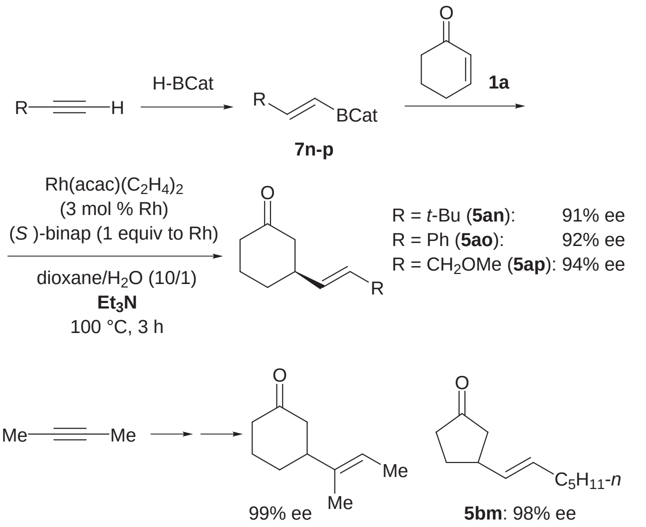
Scheme 6



Scheme 7

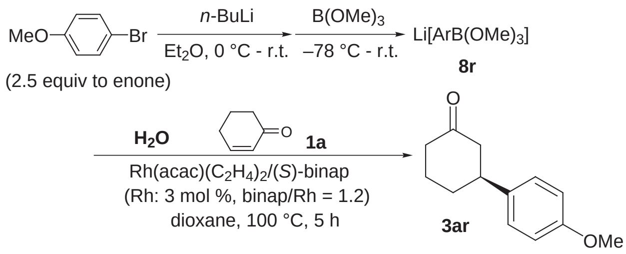
The yield was greatly improved by addition of triethylamine, giving 92% yield of **5am** which is an (*S*) isomer of 96% ee.

Some other alkenylcatecholboranes were also successfully used for the catalytic asymmetric 1,4-addition (Scheme 8). The 1-alkenylboranes **7n-7p** derived from terminal acetylenes containing *t*-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.



Scheme 8

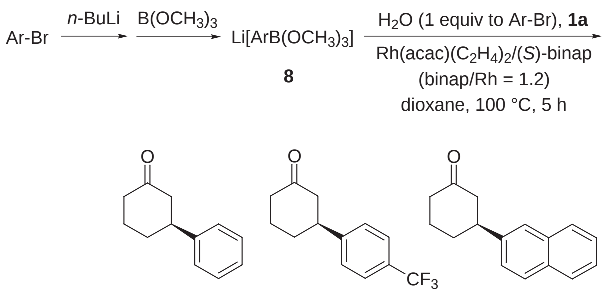
Arylborates, readily generated in situ by treatment of aryl bromides with butyllithium and trimethoxyborane, can be used for the asymmetric 1,4-addition.[15] This is another one-pot reaction, and the yields are generally higher than those obtained with arylboronic acids. The arylation of 2-cyclohexenone (**1a**) with lithium trimethyl 4-methoxyphenylborate (**8r**) generated from 4-methoxyphenyl bromide was examined under several reaction conditions (Scheme 9). It should be noted that 4-methoxyphenylboronic acid does not give the 1,4-addition product at all under the conditions used for the reaction of arylboronic acids in dioxane/H_2O[9] because the hydrolysis giving methoxybenzene is very fast. The experimental results show that 1,4-addition product **3ar** is obtained on addition of water to the rhodium-catalyzed reaction of **8r** and the yield of **3ar** is strongly dependent on the amount of water added. The highest yield was obtained in the reaction carried out in the presence of one equiv (to **8r**) of water, which gave **3ar** of 98% ee in 80% yield. Addition of excess water lowered the yield though the enantioselectivity was kept constant. In the absence of water, the reaction does not take place.



H_2O (equiv to Li[ArB(OMe)$_3$])	yield (%)	% ee
10	19	98 (*S*)
2	51	98 (*S*)
1	80	98 (*S*)
0.5	74	98 (*S*)
0	4	97 (*S*)

Scheme 9

By use of the in situ generated arylborate reagents, we succeeded in reducing the amount of the catalyst (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 (**3as**) which is 99% enantiomerically pure. The ee was the same as that observed with 3 mol% of the catalyst. 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.



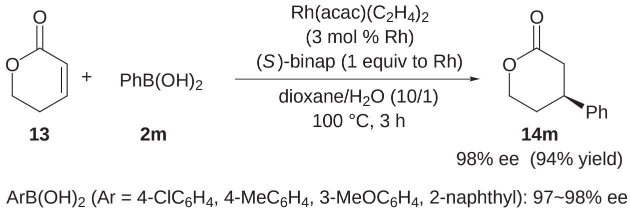
	3am (99% ee)	**3ao** (98~99% ee)	**3as** (99% ee)
3 mol % Rh	>99% yield	>99% yield	>99% yield
0.1 mol % Rh	71% yield	73% yield	96% yield

Scheme 10

4 Catalytic Asymmetric 1,4-Addition of Organoboron Reagents to α,β-Unsaturated Esters

It has been shown that α,β-unsaturated ketones successfully undergo the rhodium-catalyzed asymmetric 1,4-addition to give the corresponding β-substituted ketones with high enantioselectivity. In situ generated alkenylcatecholboranes and lithium arylborates as well as isolated boronic acids can be used for the 1,4-addition. α,β-Unsaturated esters are also good substrates for this asymmetric addition.[16] The results obtained for the phenylation of (*E*)-hexenoate esters **9a-9d** are shown in Scheme 11, where phenyl boronic acid (**2m**) in dioxane/H_2O (10/1) (Method A) or phenylborate (**8m**) generated from bromobenzene, butyllithium, and trimethoxyborane (Method B) was used as the phenylation reagent. In the reaction of methyl ester **9a** and ethyl ester **9b**, Method A gave high yields of the phenylation products, but in the reaction of isopropyl ester **9c** and tert-butyl ester **9d** the yields were much lower (<42% yield). The low yield is ascribed to the competing hydrolysis of the boronic acid giving benzene before completion of the rhodium-catalyzed 1,4-addition. The yields were greatly improved by use of Method B, which gave the phenylation products, **10cm** and **10dm**, in 96% and 92% yield, respectively. 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 (**10am**), ethyl (**10bm**), isopropyl (**10cm**), and tert-butyl (**10dm**) esters, respectively, in the reactions using Method B. The sterically more bulky ester shows the higher enantioselectivity. Aryl groups, 4-ClC_6H_4, 4-MeC_6H_4, 4-$CF_3C_6H_4$, 3-$MeOC_6H_4$, and 2-naphthyl, were also introduced at the β position of isopropyl ester **9c** with enantioselectivity ranging between 93% and 97% ee in high yields in the reactions with the corresponding lithium arylborates starting from aryl bromides. Highest enantioselectivity (98% ee) was observed in the phenylation of isopropyl 4-methyl-2-pentenoate (**11**) under Method B conditions, though the yield was not high enough.

The reaction of cyclic α,β-unsaturated esters also proceeded with high enantioselectivity (Scheme 12). The reaction of 6-membered cyclic ester **13** with arylboronic acids including phenyl and substituted phenyls gave the corresponding arylation products **14** of 97−98% ee in high yields, which are useful chiral synthons for biologically important molecules.

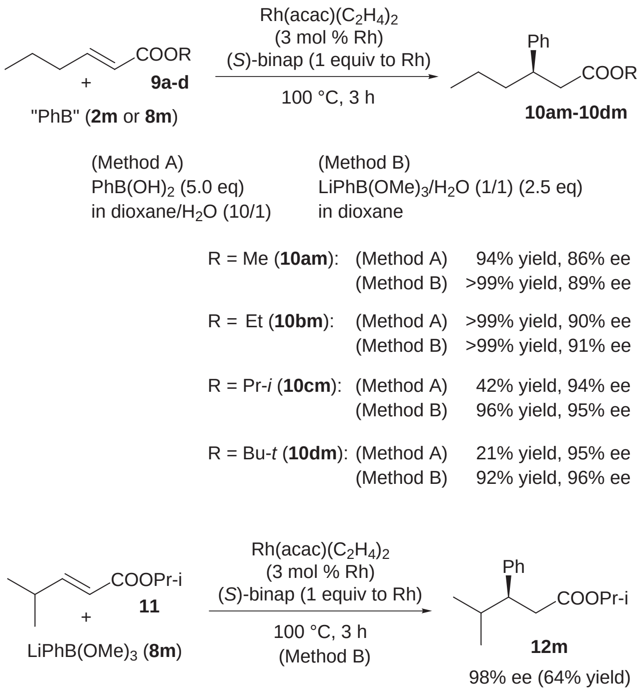


Scheme 12

Similar results for the asymmetric 1,4-addition to α,β-unsaturated esters has been independently reported by Miyaura. In their reaction of crotonate esters using arylboronic acids, the enantioselectivity is higher with the more bulky ester groups.[17]

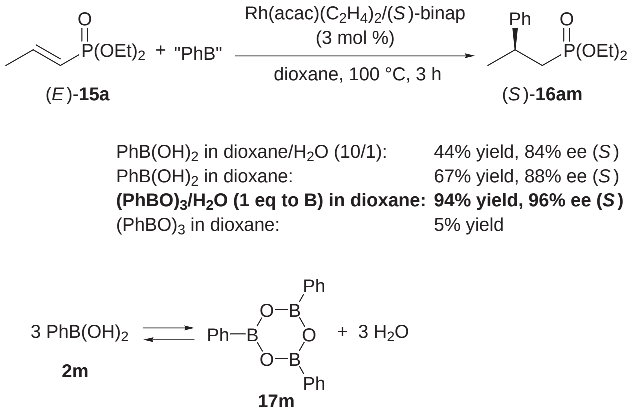
5 Catalytic Asymmetric 1,4-Addition of Organoboroxines to 1-Alkenylphosphonates

Optically active phosphonic acid derivatives are important compounds because of their synthetic utility as chiral building blocks as well as their potential biological activity. Although many reports have appeared on the topic of catalytic asymmetric 1,4-addition to α,β-unsaturated carbonyl compounds with high enantioselectivity, the enantioselective reaction to α,β-unsaturated phosphonates not been reported yet, probably due to their low reactivity toward the 1,4-addition.[1] It was found that the rhodium-catalyzed asymmetric 1,4-addition was applied to the addition to phosphonate esters by use of triarylcyclotriboroxanes as arylating reagents in place of arylboronic acids.[18] The reaction of diethyl (*E*)-propenylphosphonate (**15a**) with phenylboronic acid under the reaction conditions used for that of α,β-unsaturated ketones was slow, giving a low yield (44%) of the phenylation product **16am**. Studies on reaction period and solvent effects showed that the rhodium catalyst loses its catalytic activity within 30 min under the conditions using phenylboronic acid in dioxane and water, and that the presence of a large amount of water as a cosolvent causes the catalyst deactivation. The asymmetric 1,4-addition was greatly improved by carrying out the reaction with triphenylcyclotriboroxane (phenylboroxine $(PhBO)_3$) (**17m**) in place of phenylboronic acid (Scheme 13). The best result was obtained in the reaction of (*E*)**-15a** with phenylboroxine (**17m**) and 1 equiv (to boron) of water in the presence of rhodium/(*S*)-binap catalyst in dioxane at 100 °C for 3 h, which gave 94% yield of (*S*)**-16am** with 96% enantioselectivity. The addition of 1 equiv of water is essential for the high yield, almost no reaction taking place in the absence of water. Under similar reaction conditions, (*E*)**-15a** underwent asymmetric arylation with some other aryl-

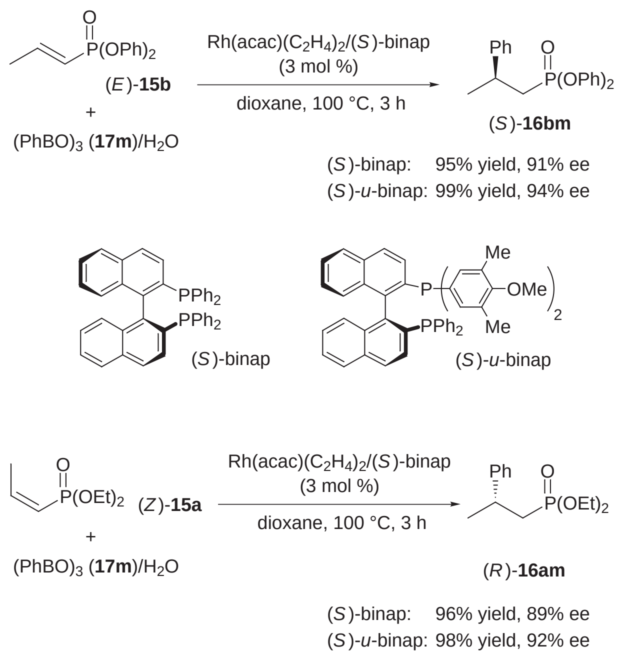


Scheme 11

boroxines ($(ArBO)_3$: Ar = 4-MeC_6H_4, 4-$CF_3C_6H_4$, 3-$MeOC_6H_4$) to give the corresponding arylation products of around 96% ee in high yields. The arylboroxines can be obtained by dehydration of arylboronic acids by azeotropic removal of water from their toluene or xylene solution or heating at 300 °C in vacuo.[19]



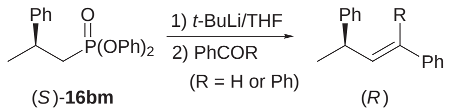
Scheme 13



Scheme 14

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 14). In the reaction of diphenyl (*E*)-propenylphosphonate (**15b**) with **17m**, (*S*)-*u*-binap ligand gave 99% yield of **16bm** with 94% ee while the standard (*S*)-binap gave 95% yield of **16bm** with 91% ee. It is interesting that the asymmetric phenylation of *Z* isomer of diethyl 1-propenylphosphonate (*Z*)-**15a** with phenylboroxine **17m** gave *R* isomer of **16am**. The opposite absolute configuration of **16am** observed for (*E*)-**15a** and (*Z*)-**15a** indicates that the dialkoxyphosphinyl moiety on the 1-alkenylphosphonate plays a key role in the enantioface selection (cf. Scheme 6). The (*S*)-binap-rhodium catalyst recognizes the enantioface of 1-propenylphosphonate by the steric bulkiness of the phosphinyl group, both (*E*)-**15a** and (*Z*)-**15a** being phenylated on the rhodium from 1*si* face irrespective of the *E*,*Z* geometry of the 1-propenyl moiety.

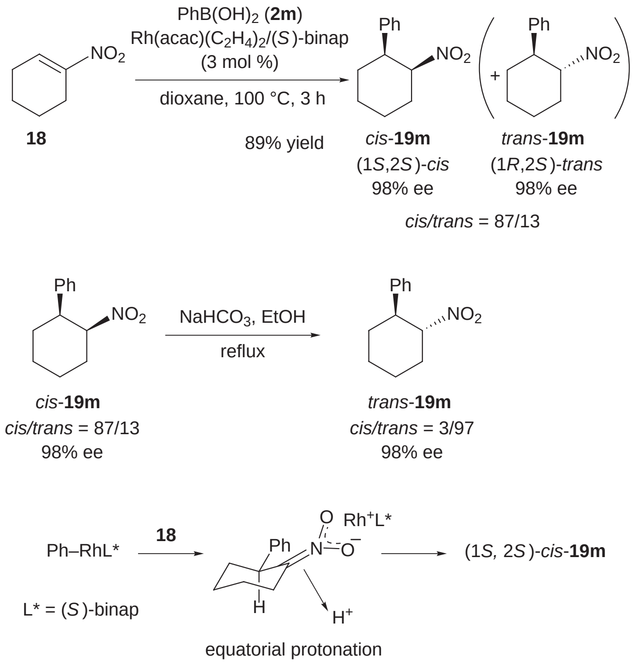
The optically active alkylphosphonates **16** containing the stereogenic carbon center at β-position can be used as chiral building blocks for the synthesis of optically active alkenes by the Horner-Emmons type reaction (Scheme 15). The olefination examined for benzaldehyde or benzophenone with diphenyl phosphonate **16bm** proceeded without loss of enantiomeric purity.



Scheme 15

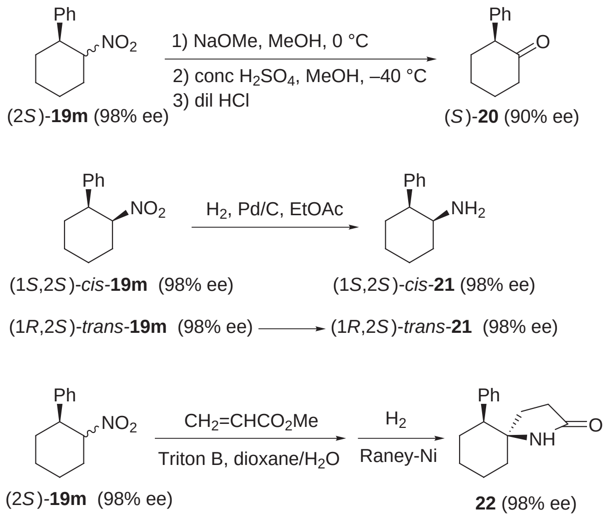
6 Catalytic Asymmetric 1,4-Addition of Organoboronic Acids to 1-NitroAlkenes

Nitroalkenes are also good substrates for the rhodium-catalyzed asymmetric 1,4-addition of organoboronic acids.[20] Although some successful results have been achieved on the asymmetric addition to α,β-unsaturated carbonyl compounds, there have been very few reports on the asymmetric addition to 1-nitroalkenes,[21] in spite of the wide applicability of nitro compounds to organic transformations.[22] It was found that 1-nitroalkenes undergo the 1,4-addition of boronic acids by the rhodium catalysis and the asymmetric reaction of 1-nitrocyclohexene (**18**) proceeds with high enantioselectivity and with high diastereoselectivity giving thermodynamically less stable *cis* isomer preferentially (Scheme 16). Thus, the reaction of **18** 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 (**19m**). The main phenylation product **19m** 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 *trans* isomer without loss of its enantiomeric purity. The preferential formation of *cis*-**19m** in the catalytic phenylation may indicate the protonation of a rhodium nitronate intermediate[23] in the catalytic cycle.



Scheme 16

Under similar reaction conditions, 1-nitrocyclohexene (**18**) underwent asymmetric addition of some other arylboronic acids (**2n-2p**) 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 asymmetric addition of phenylboronic acid was also successful for other cyclic nitroalkenes, 1-nitrocycloheptene and 1-nitrocyclopentene, which gave the corresponding phenylation products with high enantioselectivity, though the diastereoselectivity forming *cis* or *trans* isomer is low. The optically active nitroalkanes obtained by the present rhodium-catalyzed asymmetric addition 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. Three of the examples are shown in Scheme 17. Exposure of (2*S*)**-19m** (98% ee) to the Nef reaction conditions gave (*S*)-2-phenylcyclohexanone (**20**) of 90% ee. Reduction of the nitro group in *cis***-19m** (>99% *cis*) and *trans***-19m** (>99% *trans*) by hydrogenation catalyzed by palladium on charcoal gave the corresponding optically active 2-phenyl-1-aminocyclohexanes, *cis***-21** and *trans***-21**, respectively, without *cis/trans* isomerization or loss of their enantiomeric purity. Michael addition of (2*S*)**-19m** to methyl acrylate followed by reduction of the nitro group gave spiro amide **22** as a single isomer in a high yield. Thus, the optically active nitro compounds obtained here are synthetically very useful, the nitro functionality being readily converted into other functional groups such as carbonyl and amino.



Scheme 17

7 Conclusion

The rhodium-catalyzed asymmertric 1,4-addition reaction of organoboron reagents, which provides a highly efficient method of enantioselective transfer of aryl and alkenyl groups onto the β position of electron deficient olefins, is complementary to the copper-catalyzed reactions where alkyl organometallic reagents are incorporated with high enantioselectivity.[3] The rhodium-catalyzed reaction involves a rhodium-aryl or -alkenyl species as an intermediate in the catalytic cycle. Considering the reactivity of the transition metal-carbon bond toward carbon-carbon or carbon-hetero atom 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 aldehydes[24] and imines[25] has been reported to be catalyzed by a rhodium complex. The addition to aldehydes is applyed to asymmetric synthesis of diarylmethanols, though the enantioselectivity is not high enough.[24a] An interesting reaction of arylboronic acids with norbornene has been recently reported, which involves the addition of rhodium-aryl bond to the norbornene double bond.[26] The arylrhodium species can be also generated by transmetalation from organostannanes. The addition of arylstannanes to aldehydes,[27] imines,[28,29] and α,β-unsaturated carbonyl compounds[30] catalyzed by a rhodium complex giving alcohols and amines, respectively, is thought to proceed through a similar catalytic cycle. High enantioselectivity has been achieved in the arylation of imines with arylstannanes, which is catalyzed by a rhodium complex coordinated with an axially chiral monodentate phosphine ligand (MOP).[29,31] 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.

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