Rhodium-catalyzed asymmetric 1,4-addition of organometallic reagents*

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Asymmetric 1,4-arylation and 1,4-alkenylation were achieved with the use of organoboronic acids or their derivatives in the presence of a rhodium catalyst coordinated with ligands of the *S*-2,2´-bis(diphenylphosphino)-1,1´-binaphthyl (*S*-binap) type. The scope of this asymmetric addition is very broad: α,β-unsaturated ketones, esters, amides, alk-1-enyl phosphonates, and 1-nitroalkenes are efficiently converted into the corresponding 1,4-addition products with enantioselectivity >95%. As shown by NMR spectroscopy, the catalytic cycle of the reaction in water involves three intermediates (aryl- or alkenylrhodium, (oxa-π-allyl)rhodium, and hydroxorhodium complexes). The asymmetric addition of *B*-Ar-9BBN and $ArTi(OPr^i)_3$ in aprotic solvents occurs with high enantioselectivity under mild conditions to give the corresponding metal enolates as the 1,4-addition products.

Key words: asymmetric catalysis, asymmetric 1,4-addition, rhodium catalyst.

Introduction

Catalytic asymmetric synthesis is a field of great interest in its practical usefulness as well as its scientific interest.[1] Although the asymmetric reduction and oxidation have been developed so well that some of the processes are used for industrial production of enantiomerically enriched compounds, the examples of high efficiency in terms of catalytic activity and enantioselectivity are still rare in the catalytic asymmetric carbon—carbon bond forming reactions. 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 non-asymmetric version is a basic synthetic reaction often used for the carbon—carbon bond formation, which allows us to introduce carbon nucleophiles to the β-position of electron-deficient olefins such as α,β-unsaturated ketones and esters.[2] Recently, two types of 1,4-addition reactions have been reported where high enantioselectivity is achieved.[3] One is the copper(I)-catalyzed addition of organozinc reagents with the use of copper(I) catalysts coordinated with chiral phosphorus ligands represented by phosphoramidite ligand based on the axially chiral 1,1´-binaphthol.[4] The other is the Michael addition to α,β-unsaturated ketones catalyzed by Shibasaki´s heterobimetallic catalysts consisting of chiral 1,1´-binaphthol and two types of metals.[5] In these two reactions, alkyl groups or soft carbon

nucleophiles are introduced at the stereogenic carbon center at the β-position of α,β-unsaturated ketones.

Miyaura´s report in 1997 describing the first example of rhodium-catalyzed 1,4-addition of aryl- and alkenylboronic acids to α,β-unsaturated ketones[6] stimulated us to modify the reaction conditions of the rhodium-catalyzed reaction for catalytic asymmetric 1,4-addition reactions. We succeeded in obtaining high catalytic activity and high enantioselectivity by carrying out the reaction in dioxane and water at 100 °C in the presence of a rhodium catalyst coordinated with the (*S*)-binap ligand, which was reported in 1998.[7] As a typical example, the reaction of cyclohex-2-enone with phenylboronic acid gave (*S*)-3-phenylcyclohexanone of 97% *ee*. After this publication, several reports appeared on the use of some other chiral phosphorus ligands for this type of rhodium-catalyzed 1,4-addition of organoboronic acids to α,β-unsaturated ketones under similar conditions.[8] We have successfully applied the rhodium-catalyzed asymmetric reaction to some other organometallic reagents and electron-deficient olefins. In this account, the recent development of the rhodium-catalyzed asymmetric 1,4-addition reactions recently studied in our research group is described.[9]

Catalytic asymmetric 1,4-addition of organoboronic acids and organoboroxines

In our first communication,[7] we reported that the rhodium-catalyzed asymmetric 1,4-addition of aryl- and alkenylboronic acids proceeded with high enantioselec-

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tivity for both cyclic and linear α,β-unsaturated ketones (Scheme 1). Important points for the high catalytic activity and the high enantioselectivity at this stage are (1) the use of Rh(acac)(C₂H₄)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. 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)(C₂H₄)₂ immediately generates Rh(acac)(binap) quantitatively, while Rh(acac)(CO)₂ generates two types of unidentified rhodium complexes together with a small amount of the Rh(acac)(binap) complex.

Scheme 1
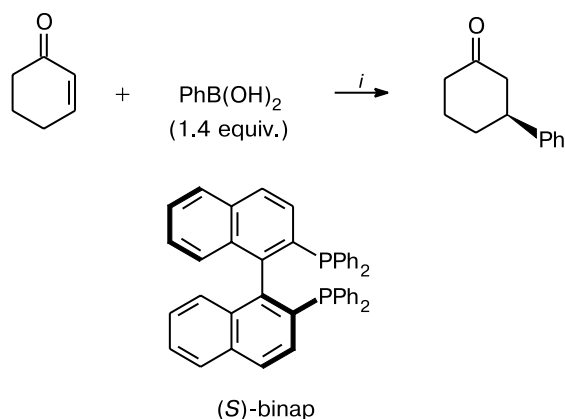
i. [Rhᴵ]/(*S*)-binap (3 mol.%), dioxane—water (10 : 1), 100 °C, 5 h.

Catalyst	Yield	*ee*
	%	
Rh(acac)(CO)₂/(*S*)-binap	15	43 (*S*)
Rh(acac)(C₂H₄)₂/(*S*)-binap	64	97 (*S*)
Rh(acac)((*S*)-binap)	62	96 (*S*)

The scope of this rhodium-catalyzed asymmetric 1,4-addition of organoboronic acids is very broad.[7] Some of the results obtained for the addition to α,β-unsaturated ketones are summarized in Scheme 2. Under standard conditions, that is, 3 mol.% of Rh(acac)(C₂H₄)₂ and binap in a dioxane—water (10 : 1) mixture at 100 °C, aryl groups substituted with either electron-donating or electron-withdrawing groups (4-MeC₆H₄, 4-CF₃C₆H₄, 3-MeOC₆H₄, and 3-ClC₆H₄) were introduced into cyclohex-2-enone with high enantioselectivity by the reaction with the corresponding boronic acids. Asymmetric addition of alk-1-enylboronic acids was as successful as that of arylboronic acids, the alkenylation product with hept-1-enylboronic acid being obtained with 94% enantioselectivity. Cyclo-

pentenone underwent the asymmetric addition of phenyl- and hept-1-enylboronic acids with high enantioselectivity under the same reaction conditions to give 3-substituted cyclopentanones with *ee* > 96% and in high yields. High enantioselectivity was also observed in the reaction of linear (*E*)-enones: 5-methylhex-3-en-2-one and non-3-en-2-one. 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. The procedures for the preparation of (*S*)-3-phenylcyclohexanone in several-gram scale has been published.[10]

Alkenylcatecholboranes obtained by the hydroboration of alkynes with catecholborane were found to be good alkenylating reagents for the asymmetric 1,4-addition[11] (Scheme 3). For the high chemical yield in this reaction, triethylamine must be added, which probably neutralizes the catechol generated under the reactions conditions. The reaction of (*E*)-hept-1-enylborane, which is obtained by the hydroboration of hept-1-yne, with cyclohex-2-enone gave 92% yield of the 1,4-addition product, which is an (*S*)-isomer of 96% *ee*. 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 aryllithiums with trimethoxyborane, can be also used for the asymmetric 1,4-addition[12] (Scheme 4). 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. The highest yield was obtained in the reaction carried out in the presence of 1 equiv. (relative to aryl borate) of water. The enantioselectivity was high for the addition of several arylborate reagents. Using these *in situ* generated arylborate reagents, the amount of the catalyst was reduced without loss of enantioselectivity. For a typical example, in the reaction of cyclohex-2-enone with borate generated from 2-bromonaphthalene, 0.1 mol.% of the catalyst gave 96% yield of 3-(2-naphthyl)cyclohexanone which is 99% enantiomerically pure. In the addition to α,β-unsaturated ketones, 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.

α,β-Unsaturated esters are also good substrates for the rhodium-catalyzed asymmetric addition (Scheme 5).[13,14] The use of arylborates generated from aryllithiums and trimethoxyborane gave better results than that of the corresponding boronic acids. 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, ethyl,

Scheme 2

96—99% *ee* (*S*)

Ar = —⟨⟩—Me, —⟨⟩—CF$_3$, ⟨⟩(OMe), ⟨⟩(Cl)

94% *ee* (*S*)

97% *ee* (*S*)

96% *ee*

97% *ee*

92% *ee*
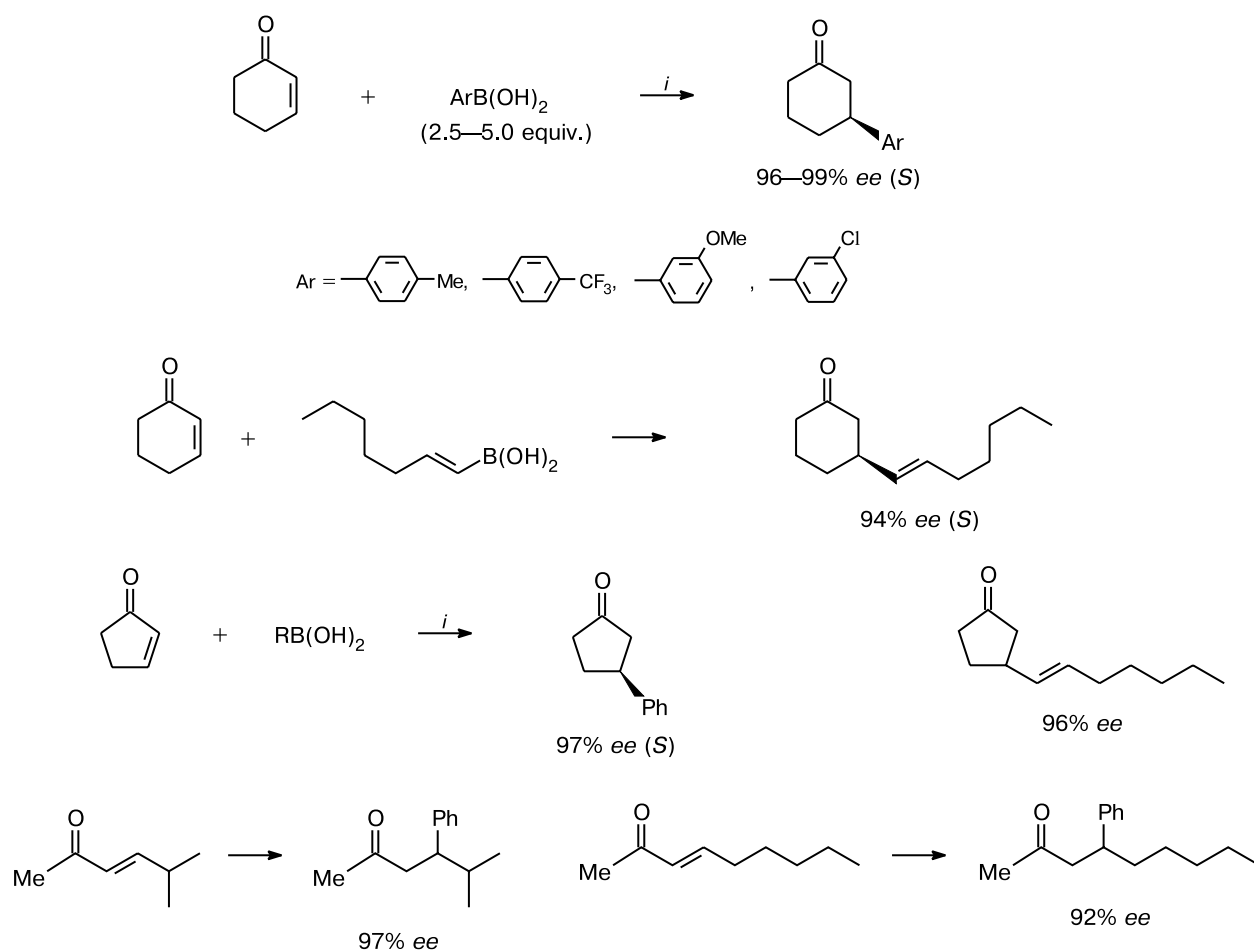
i. Rh(acac)(C$_2$H$_4$)$_2$ (3 mol.% Rh), (*S*)-binap (1 equiv. calculated per Rh), dioxane—water (10 : 1), 100 °C.

Scheme 3

R = *n*-C$_5$H$_{12}$

96% *ee*

98% *ee*
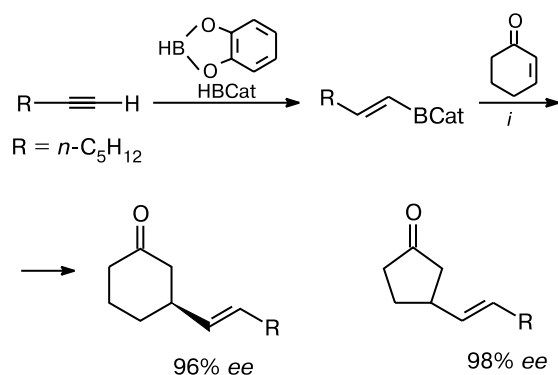
i. Rh(acac)(C$_2$H$_4$)$_2$ (3 mol.% Rh), (*S*)-binap (1 equiv. calculated per Rh), dioxane—water (10 : 1), Et$_3$N, 100 °C, 3 h.

Scheme 4

ArBr →(Bu^{n}Li) →(B(OMe)$_3$) Li[ArB(OMe)$_3$] →(*i*)

Ar = Ph (99% *ee*), 4-CF$_3$C$_6$H$_4$ (98—99% *ee*), 2-naphthyl (99% *ee*)

Content of Rh (mol.%)	Yield (%)		
	Ph	4-CF$_3$C$_6$H$_4$	2-Naphthyl
3.0	>99	>99	>99
0.1	71	73	96

i. H$_2$O (1 equiv. calculated per ArBr); Rh(acac)(C$_2$H$_4$)$_2$/(*S*)-binap (binap/Rh = 1.2), dioxane, 100 °C, 5 h.

isopropyl, and *tert*-butyl esters, respectively, in the reaction of (*E*)-hexenoate esters. The sterically more bulky ester shows the higher enantioselectivity. Aryl groups

(4-ClC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-CF$_3$C$_6$H$_4$, 3-MeOC$_6$H$_4$, and 2-naphthyl) were also introduced at the β-position of iso-propyl ester with enantioselectivity ranging between 93 and 97% *ee* in high yields in the reactions with the corresponding lithium arylborates. Highest enantioselectivity (98% *ee*) was observed in the phenylation of isopropyl 4-methylpent-2-enoate with the phenylborate, although the yield was not high enough.
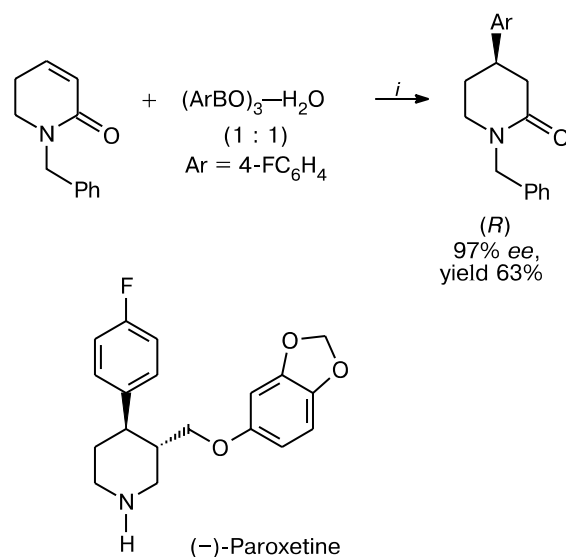
Scheme 5

R	Yield	*ee*
	(%)	
Me	>99	89
Et	>99	91
Pr^i	96	95
Bu^t	92	96

98% *ee*, yield 64%
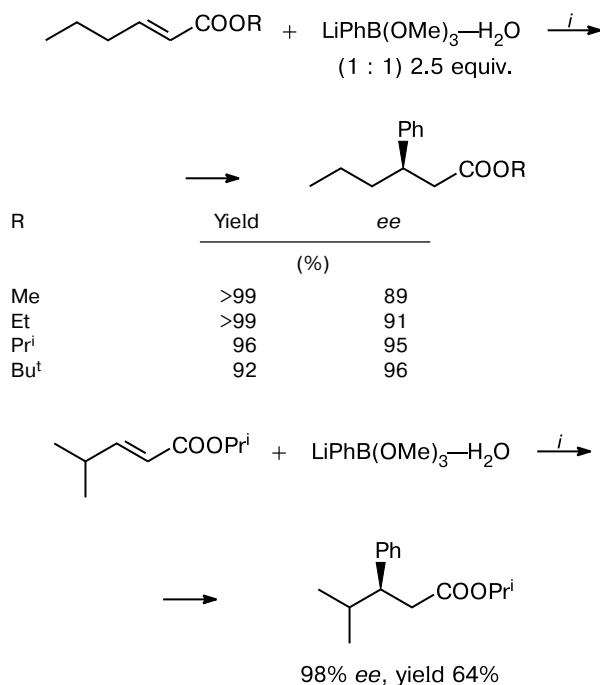
i. Rh(acac)(C$_2$H$_4$)$_2$ (3 mol.% Rh), (*S*)-binap (1 equiv. calculated per Rh), dioxane, 100 °C, 3 h.

Asymmetric 1,4-addition to cyclic α,β-unsaturated amides provides a new efficient route to enantiomerically enriched 4-aryl-2-piperidinones[15] (Scheme 6). For the 1,4-addition of 4-FC$_6$H$_4$B(OH)$_2$, which is related to asymmetric synthesis of (−)-Paroxetine, slightly modified conditions were required to obtain high yield of the arylation product. The main side reaction, that is, hydrolysis of the boronic acid giving fluorobenzene, was suppressed by use of a minimum amount of water. Thus the reaction with 4-fluorophenylboroxine and 1 equiv. (relative to boron) of water in the presence of Rh(acac)(C$_2$H$_4$)$_2$/(*R*)-binap catalyst in dioxane at 40 °C gave 63% yield of (*R*)-lactam with 97% enantioselectivity.

Alkenylphosphonates are less reactive toward 1,4-addition compared to α,β-unsaturated carbonyl compounds. Under the reaction conditions used for α,β-unsaturated ketones (phenylboronic acid in dioxane—water (10 : 1)), the yield of 1,4-addition was very low (44%) for diethyl

Scheme 6
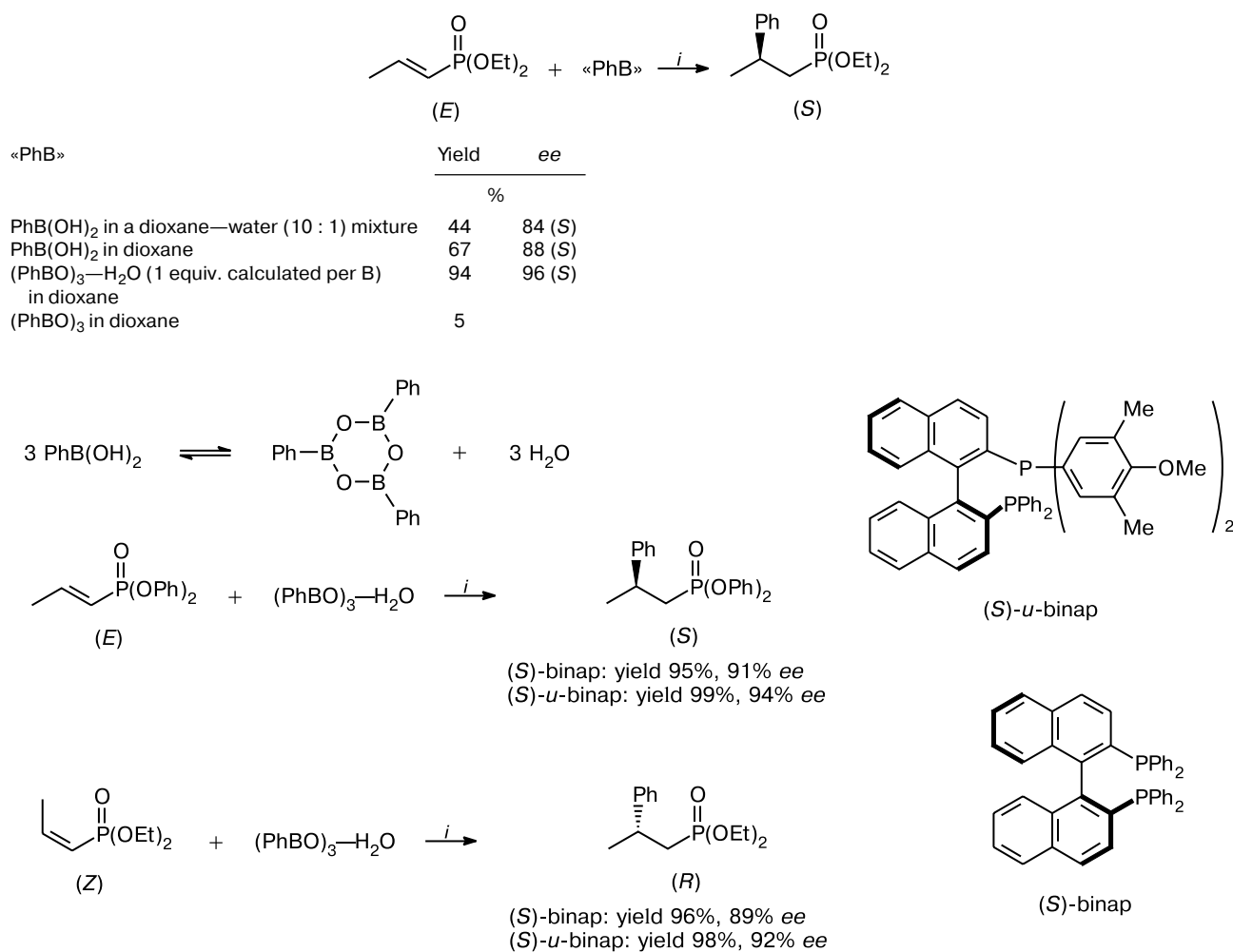

(*R*)
97% *ee*,
yield 63%

(−)-Paroxetine

i. Rh(acac)(C$_2$H$_4$)$_2$ (3 mol.% Rh), (*R*)-binap (1.1 equiv. calculated per Rh), dioxane.

(*E*)-propenylphosphonate. The asymmetric 1,4-addition was greatly improved (94% yield with 96% *ee*) by carrying out the reaction using phenylboroxine (PhBO)$_3$ and 1 equiv. of water (Scheme 7).[16] The addition of 1 equiv. of water is essential for the high yield, almost no reaction taking place in the absence of water. Boroxine and water should be in equilibration with a boronic acid under the reaction conditions[17] 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 with the rhodium catalyst coordinated with un-symmetrically substituted binap ligand, in particular, (*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. In the reaction of diphenyl (*E*)-propenylphosphonate with phenylboroxine, the (*S*)-*u*-binap ligand gave 99% yield of the 1,4-addition product with 94% *ee*, while the standard (*S*)-binap gave 95% yield with 91% *ee*. It is remarkable that the asymmetric phenylation of (*Z*)-isomer of diethyl 1-propenylphosphonate with phenylboroxine gave the *R*-isomer.

Nitroalkenes are good substrates for the rhodium-catalyzed asymmetric 1,4-addition of organoboronic acids.[18] The reaction of 1-nitrocyclohexene with phenylboronic acid in the presence of the Rh/(*S*)-binap catalyst at 100 °C for 3 h gave 89% yield of 2-phenyl-1-nitrocyclohexane

Scheme 7

«PhB»	Yield	*ee*
		%
PhB(OH)$_2$ in a dioxane—water (10 : 1) mixture	44	84 (*S*)
PhB(OH)$_2$ in dioxane	67	88 (*S*)
(PhBO)$_3$—H$_2$O (1 equiv. calculated per B) in dioxane	94	96 (*S*)
(PhBO)$_3$ in dioxane	5	

(*S*)-binap: yield 95%, 91% *ee*
(*S*)-*u*-binap: yield 99%, 94% *ee*

(*S*)-binap: yield 96%, 89% *ee*
(*S*)-*u*-binap: yield 98%, 92% *ee*

i. Rh(acac)(C$_2$H$_4$)$_2$ (3 mol.% Rh), (*S*)-binap (1 equiv. calculated per Rh), dioxane, 100 °C, 3 h.
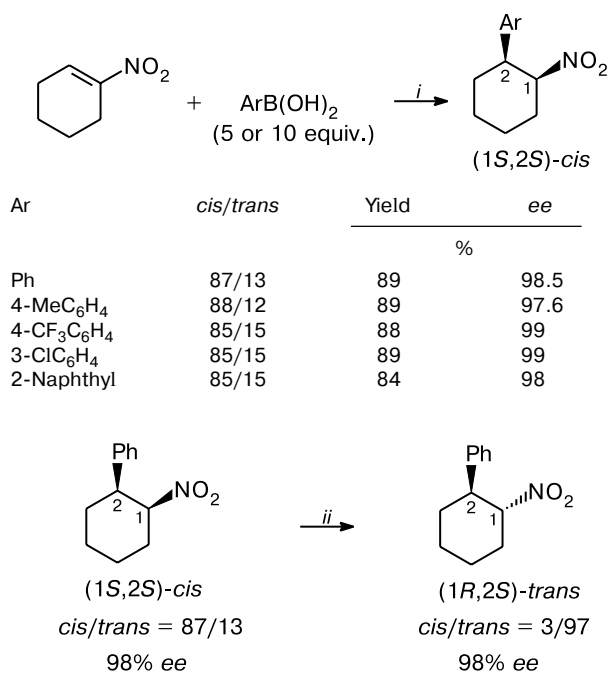
(Scheme 8). The main phenylation product is a *cis*-isomer (*cis* : *trans* = 87 : 13) and both of the *cis*- and *trans*-isomers are 98% enantiomerically pure. Treatment of the *cis*-rich mixture with sodium bicarbonate in refluxing ethanol caused *cis—trans*-equilibration giving thermodynamically more 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. Under similar reaction conditions, 1-nitrocyclohexene underwent asymmetric addition of some other arylboronic acids in good yields with high enantioselectivity. The corresponding *cis*-2-aryl-1-nitrocyclohexanes were produced with *cis*-selectivity >85% and with the enantioselectivity ranging between 97.6 and 99.0% *ee*. The optically active nitroalkanes obtained here 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.

## Catalytic cycle for the rhodium-catalyzed 1,4-addition of organoboronic acids

We succeeded in characterizing the important intermediates involved in the catalytic cycle of the rhodium-catalyzed 1,4-addition by use of RhPh(PPh$_3$)(binap) as a key intermediate.[19] The catalytic cycle illustrated for the reaction of phenylboronic acid with cyclohex-2-enone is shown in Scheme 9. 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 10).

Scheme 8

Ar	cis/trans	Yield	ee
		%	
Ph	87/13	89	98.5
4-MeC$_6$H$_4$	88/12	89	97.6
4-CF$_3$C$_6$H$_4$	85/15	88	99
3-ClC$_6$H$_4$	85/15	89	99
2-Naphthyl	85/15	84	98

(1S,2S)-cis

cis/trans = 87/13

98% ee

(1R,2S)-trans

cis/trans = 3/97

98% ee

i. Rh(acac)(C$_2$H$_4$)$_2$ (3 mol.% Rh), (*S*)-binap (1.1 equiv. calculated per Rh), solvent—water (10 : 1), 100 °C, 3 h; *ii*. NaHCO$_3$, EtOH, refluxing.
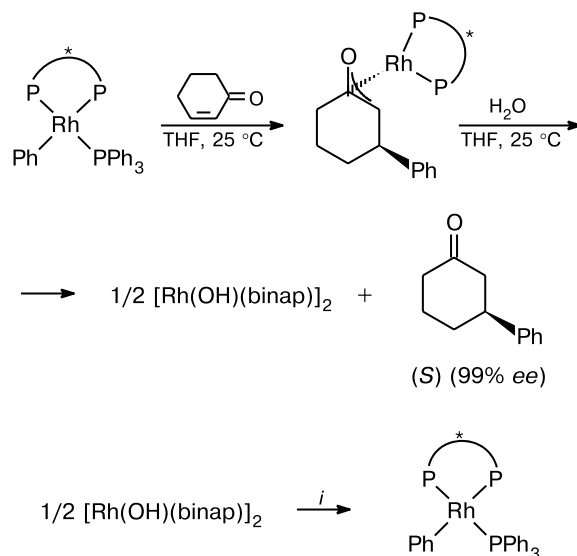
Scheme 9
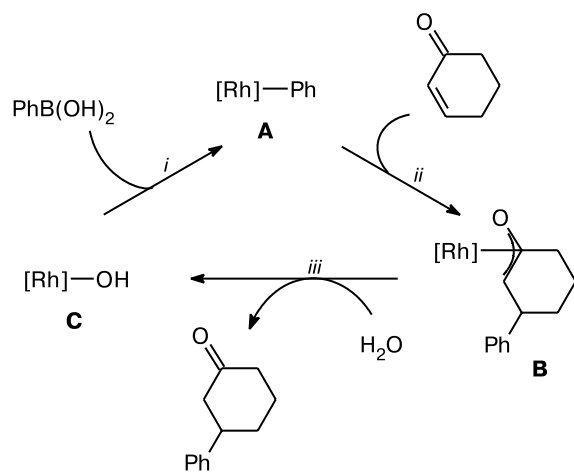
[Rh] = Rh(binap)

i. Transmetallation; *ii*. Insertion (addition of phenylrhodium); *iii*. Hydrolysis.

The reaction of the phenylrhodium complex RhPh(PPh$_3$)(binap) with cyclohex-2-enone gave oxa-π-allylrhodium, 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. The oxa-π-allyl-rhodium complex was converted immediately into the hydroxorhodium complex [Rh(OH)(binap)]$_2$ on addition of water, liberating the phenylation product. Trans-metallation of the phenyl group from boron to rhodium takes place by addition of phenylboronic acid in the presence of triphenylphosphine to regenerate the phenyl-rhodium RhPh(PPh$_3$)(binap).

Scheme 10


(S) (99% ee)

1/2 [Rh(OH)(binap)]$_2$

i. PhB(OH)$_2$ (2 equiv.), PPh$_3$, THF, 25 °C, 30 min.

All the three transformations in Scheme 10 was found to proceed at 25 °C but the catalytic reaction in the presence of a rhodium catalyst generated from Rh(acac)(C$_2$H$_4$)$_2$ does not proceed at 60 °C or lower. It turned out that the acetylacetonato ligand retards the transmetallation step because of the high stability of the Rh—acac moiety. The use of the hydroxo complex [Rh(OH)(binap)]$_2$ as a catalyst made it possible to run the reaction at lower temperature[19] (Scheme 11). Thus the addition of phenylboronic acid or phenylboroxine to cyclohex-2-enone is catalyzed by [Rh(OH)(binap)]$_2$ at 35 °C to give a quantitative yield of 3-phenylcyclo-hexanone, which is ≥99% enantiomerically pure. This catalyst system is also applicable to the reaction of other enones and organoboron reagents. 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.

Scheme 12 shows the stereochemical pathway in the reaction catalyzed by the rhodium complex coordinated
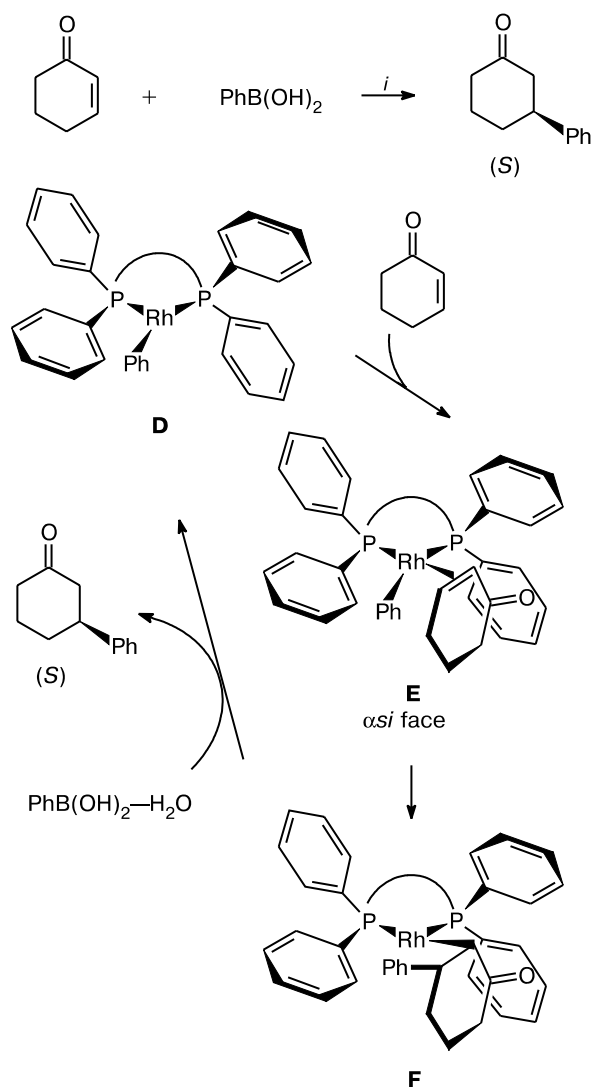
Scheme 11
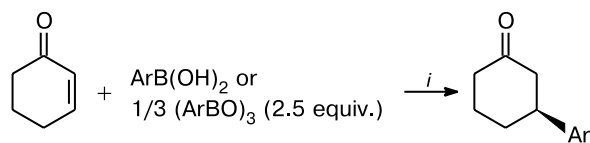
i. [Rh(OH)((*S*)-binap)]$_2$ (3 mol.% Rh), dioxane—water (10 : 1), 35 °C, 3 h (Rh(acac)((*S*)-binap) (3 mol.% Rh), dioxane—water (10 : 1), 100 °C, 5 h).

Compound	Yield	*ee*
	%	
	98 (93)	99.3 (97)
	96 (0)	99.1 (—)
	95 (93)	98 (97)
	94 (51)	96.3 (93)
	85 (75)	99.1 (97)
	92 (88)	97.8 (92)

Scheme 12

i. Rh(acac)((*S*)-binap) (catalyst), dioxane—water (10 : 1), 100 °C.

with (*S*)-binap.[7] According to the highly skewed structure known for transition metal complexes coordinated with a binap ligand,[20] (*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 cyclohex-2-enone 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 1,4-addition products can be predicted by this type of stereocontrol model, (*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.

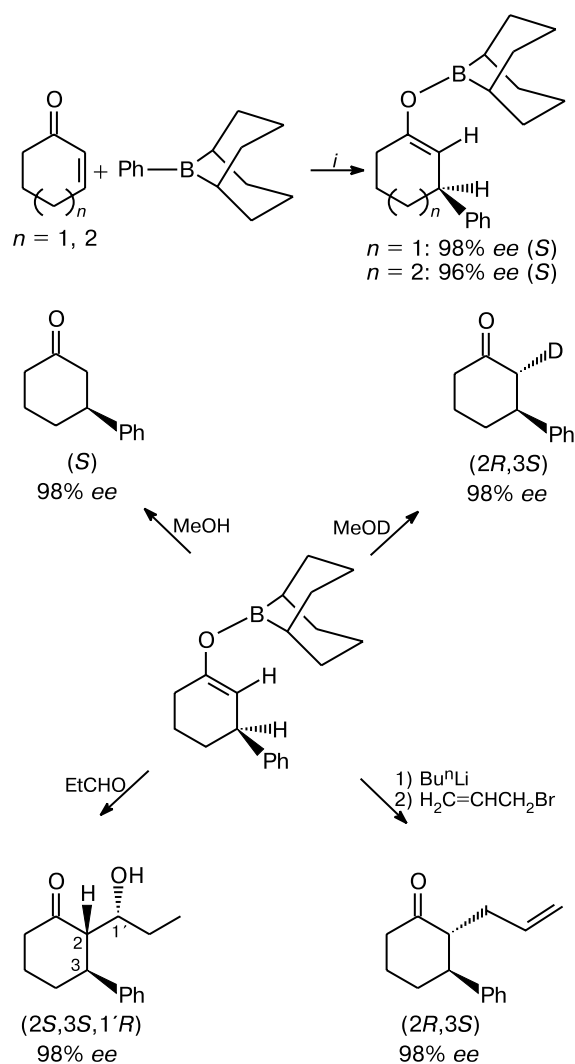### Asymmetric 1,4-addition of organoboron and organotitanium reagents forming metal enolates

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-allyl-rhodium giving hydroxorhodium species and the hydrolyzed 1,4-addition product (*cf.* Scheme 9). The use of water as a co-solvent 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 it was found that the use of *B*-Ar-9-BBN realizes the catalytic asymmetric 1,4-addition forming chiral boron enolates (Scheme 13).[21] As a typical example, the reaction of cyclohex-2-enone with 1.1 equiv. of *B*-Ar-9-BBN in the presence 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 which is an *S*-isomer of 98% ee. Unfortunately, this reaction forming chiral boron enolate is observed only for cyclohex-2-enone and cyclohept-2-enone. The reaction of boron enolate with electrophiles provides us with a chance for the further transformation as expected.

Scheme 13

n = 1, 2

n = 1: 98% *ee* (*S*)
n = 2: 96% *ee* (*S*)

(*S*)
98% *ee*

(2*R*,3*S*)
98% *ee*

MeOH   MeOD

EtCHO   1) Bu^{n}Li
               2) H$_2$C=CHCH$_2$Br

(2*S*,3*S*,1′*R*)
98% *ee*

(2*R*,3*S*)
98% *ee*

cod is cycloocta-1,5-diene

i. [Rh(OMe)(cod)]$_2$/(*S*)-binap (3 mol.% Rh), toluene, 80 °C, 1 h.

A new type of catalytic tandem 1,4-addition—aldol reaction has been also found with the use of

B-Ar-9-BBN.[22] The reaction of *B*-Ar-9BBN, vinyl ketone, and aldehyde catalyzed by [Rh(OMe)(cod)]$_2$ proceeded in toluene at 20 °C to give high yield of the aldol-type product with high *syn*-selectivity (Scheme 14). Asymmetric reaction using [Rh(OH)((*S*)-binap)]$_2$ as a catalyst gave optically active products, *syn*-(4*S*,5*R*)-aldol of 41% *ee* and *anti*-(4*R*,5*R*)-aldol of 94% *ee*, although the *syn/anti*-selectivity is low.
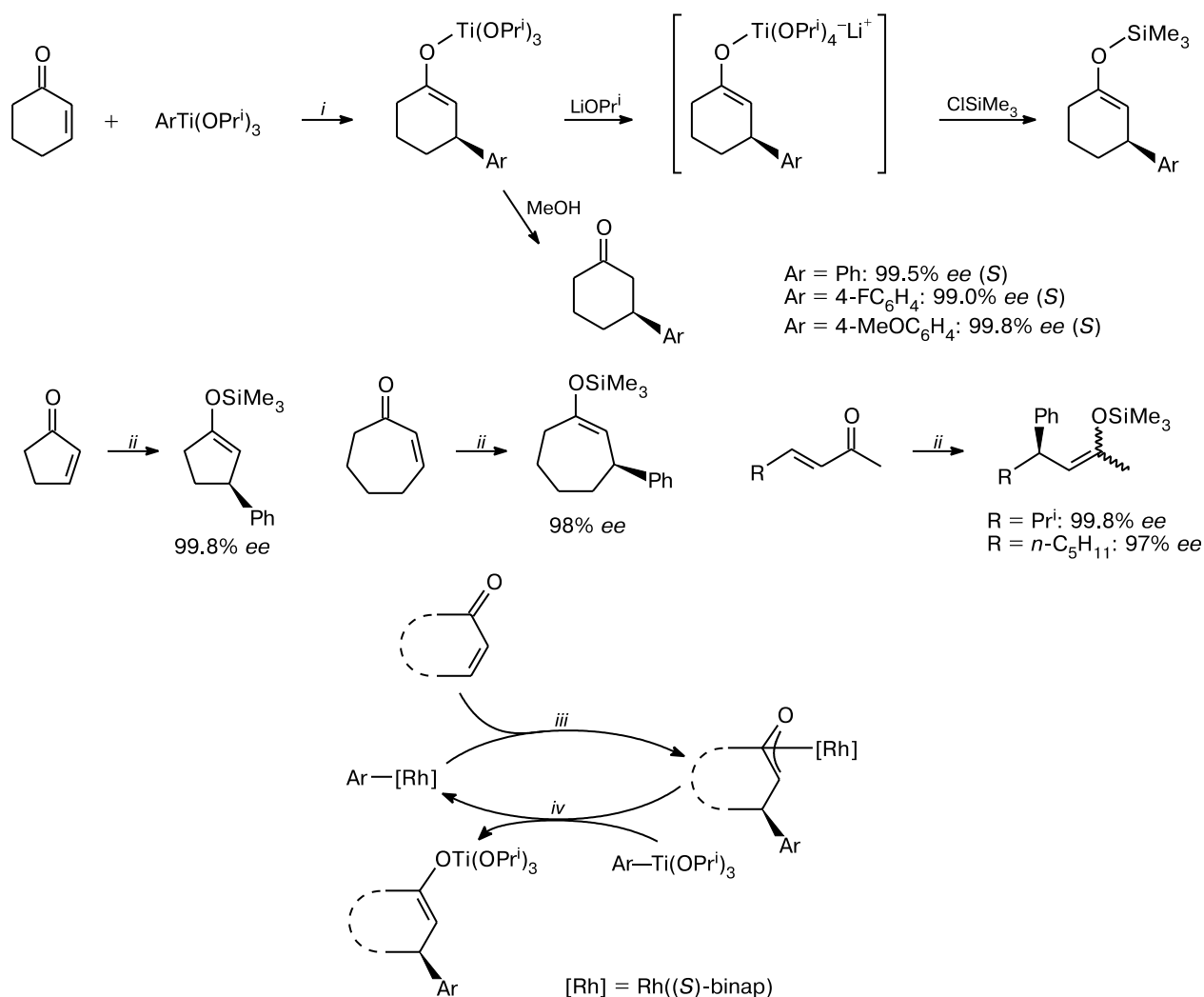
Scheme 14

syn/anti = 21/1—6/1

syn (41% *ee*)   *anti* (94% *ee*)
syn/anti = 0.8/1
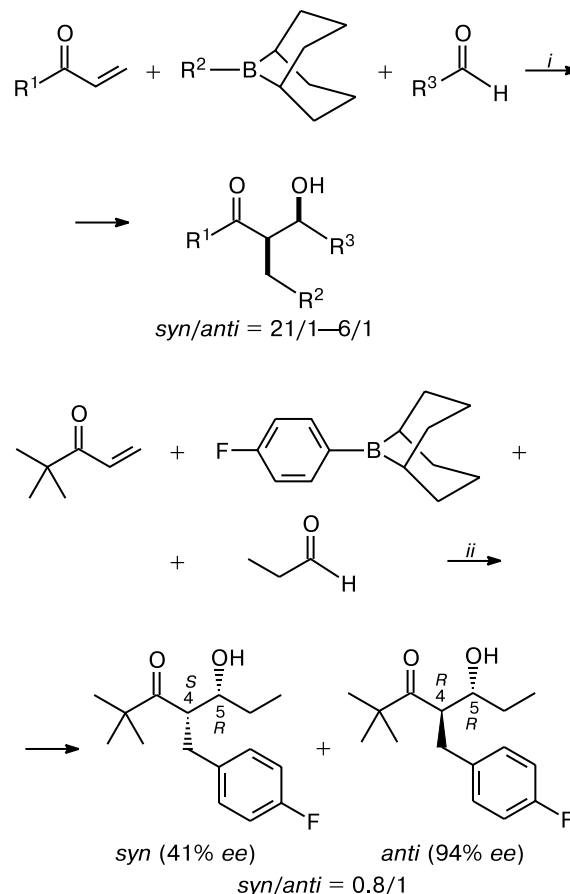
R^1 = Bu^t, Ph, Me; R^2 = Ph, 4-FC$_6$H$_4$, 4-MeOC$_6$H$_4$, Me(CH$_2$)$_4$CH=CH; R^3 = Ph, Et, Pr^i

i. 1) [Rh(OMe)(cod)]$_2$ (3 mol.% Rh), toluene, 20 °C, 2 h;
2) H$_2$O$_2$/NaOH; *ii*. 1) [Rh(OH)((*S*)-binap)]$_2$, DMF, 20 °C, 12 h;
2) H$_2$O$_2$/NaOH.

Recently, we found that a rhodium catalyst and aryltitanium triisopropoxide (ArTi(OPr^i)$_3$) is a good combination for the asymmetric 1,4-addition to α,β-unsaturated ketones in an aprotic solvent (Scheme 15).[23] The addition of ArTi(OPr^i)$_3$ to cyclohex-2-enone 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 as 1,4-addition products. The

Scheme 15

Ar = Ph: 99.5% *ee* (*S*)
Ar = 4-FC$_6$H$_4$: 99.0% *ee* (*S*)
Ar = 4-MeOC$_6$H$_4$: 99.8% *ee* (*S*)

99.8% *ee*

98% *ee*

R = Pr^i: 99.8% *ee*
R = *n*-C$_5$H$_{11}$: 97% *ee*

[Rh] = Rh((*S*)-binap)

i. [Rh(OH)((*S*)-binap)]$_2$ (3 mol.% Rh), THF, 20 °C, 1 h; *ii*. 1) PhTi(OPr^i)$_3$, [Rh(OH)((*S*)-binap)]$_2$ (3 mol.% Rh), THF, 20 °C, 5 min; 2) LiOPr^i, ClSiMe$_3$; *iii*. Insertion; *iv*. Transmetallation.

enantioselectivity is very high: 99.5, 99.0, and 99.8% *ee*, for Ar = Ph, 4-FC$_6$H$_4$, and 4-MeOC$_6$H$_4$, respectively. The titanium enolates were converted into silyl enol ethers by treatment with chlorotrimethylsilane and lithium isopropoxide. Other cyclic enones (cyclopent-2-enone and cyclohept-2-enone) and some linear enones are also good substrates for the asymmetric 1,4-addition of phenyltitanium triisopropoxide giving the corresponding arylation products with enantioselectivity ≥97%. The catalytic cycle was demonstrated by NMR studies to involve the transmetallation of the aryl group from titanium to rhodium of the (oxa-π-allyl)rhodium intermediate leaving an arylrhodium species and the titanium enolate.

The use of alkenyl sulfones for the rhodium-catalyzed addition of aryltitanium reagents (ArTi(OPr^i)$_3$) was found to give us an interesting result (Scheme 16).[24] The addi-

tion to linear alkenyl sulfones, 1-phenylsulfonyloct-1-ene and 2-phenylsulfonyloct-1-ene, resulted in a *cine*-substitution reaction, where the sulfonyl group is substituted with the phenyl group on the next carbon of the double bond, the substitution took place regioselectively. The catalytic cycle was established by deuterium labeling studies to proceed through *anti*-elimination of rhodium and sulfonyl group from an alkylrhodium intermediate. In the addition reaction to cyclic alkenyl sulfone, 1-phenylsulfonylcyclohexene, the asymmetric carbon center created at the carborhodation step is retained in the substitution product. Thus, the reaction with aryltitanium triisopropoxides (ArTi(OPr^i)$_3$) in the presence of 3 mol.% of [Rh(OH)((*S*)-binap)]$_2$ in THF at 40 °C gave a quantitative yield of 1-arylcyclohexenes with enantioselectivity >99%.

Scheme 16
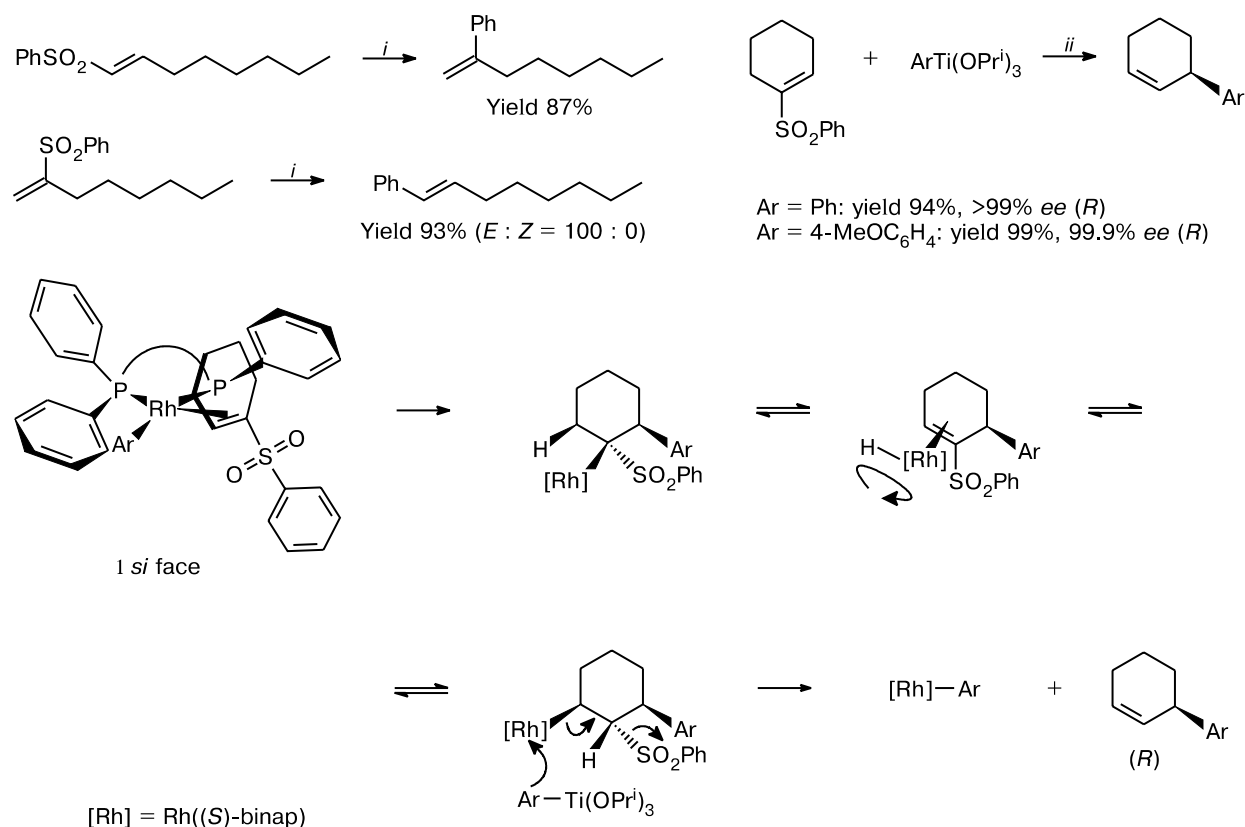
i. PhTi(OPr^i)$_3$, [Rh(OH)((*S*)-binap)]$_2$ (3 mol.% Rh), THF, 40 °C, 12 h; *ii*. [Rh(OH)((*S*)-binap)]$_2$ (3 mol.% Rh), THF, 40 °C, 12 h.

Conclusion

The rhodium-catalyzed reaction shown here involves an arylrhodium or alkenylrhodium species as an intermediate in the catalytic cycle. Considering the reactivity of the transition metal—carbon bond toward 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 aldehydes[25] and imines[26] has been reported to be catalyzed by a rhodium complex. The addition to aldehydes is applied to asymmetric synthesis of diarylmethanols, although the enantioselectivity is not high enough.[25] An interesting reactions of arylboronic acids with norbornene and oxanorbornene derivatives have been reported by Miura[27] and Lautens,[28] respectively, which involve the addition of the rhodium—aryl bond to the norbornene double bond. In the reaction of oxanorbornene derivatives forming chiral functionalized cyclohexenes as ring-opening products, over 90% enantioselectivity has been achieved.[28] The arylrhodium species can also be generated by transmetallation from some other organometallic reagents. The addition of aryltin,[29] arylsilicon,[30] and arylbismuth[31] reagents to α,β-unsaturated carbonyl compounds catalyzed by a rhodium complex proceeds through a similar catalytic cycle. The addition of arylsilanes has recently been applied to the catalytic asymmetric synthesis.[32] 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). 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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