Asymmetric Conjugate 1,4-Addition of Arylboronic Acids to α,β-Unsaturated Esters Catalyzed by Rhodium(I)/(*S*)-binap

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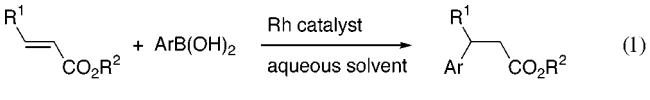
Received February 15, 2000

Arylboronic acids underwent the conjugate 1,4-addition to α,β-unsaturated esters to give β-aryl esters in high yields in the presence of a rhodium(I) catalyst. The addition of arylboronic acids to isopropyl crotonate resulted in high yields and high enantioselectivity exceeding 90% ee in the presence of 3 mol % of $Rh(acac)(C_2H_4)_2$ and (*S*)-binap at 100 °C. The rhodium/(*S*)-binap complex provided (*R*)-3-phenylbutanoate in the addition of phenylboronic acid to benzyl crotonate. The effects on the enantioselectivity of chiral phosphine ligands, rhodium precursors, and substituents on α,β-unsaturated esters are discussed, as well as the mechanistic aspect of the catalytic cycle.

Conjugate 1,4-addition reactions by rhodium−,[1] nickel−,[2] ruthenium−,[3] or copper[4] complexes are of great value in asymmetric synthesis since various chiral auxiliaries are now available for the metal-catalyzed reactions.[5] We have recently reported the rhodium-catalyzed 1,4-conjugate addition reactions of aryl- and 1-alkenylboronic acids to enones in an aqueous solvent, which proceeds through a sequence of boron−rhodium transmetalation, yielding an organorhodium(I) species and its addition to enones.[6] Hayashi[7] and the joint research with them[8] demonstrated asymmetric variants by using a rhodium(I)−chiral phosphine complex. Among the chiral phosphines examined, the binap ligand[9] developed by Noyori for asymmetric hydrogenation of alkenes was found to be the best chiral auxiliary, achieving over 90% ee for cyclic and acyclic enones. The efficiency of transmetalation from boron to rhodium was also demonstrated in catalytic 1,2-additions of organoboronic acids to aldehydes[10] and *N*-sulfonyl imines.[11] The utility of potassium organotrifluoroborates (RBF_3K) as the nucleophile for both rhodium-catalyzed 1,4- and 1,2-additions was recently reported by Batey.[12]

Here, we report a conjugate 1,4-addition of arylboronic acids (**2**) to α,β-unsaturated esters (**1**) yielding optically active β-aryl esters (**3**) in the presence of a rhodium(I)−binap catalyst (eq 1).[13]



(1)

1 **2** **3**

Reaction Conditions

The 1,4-addition reactions of phenylboronic acid to the representative α,β-unsaturated esters in the presence of $[Rh(cod)(MeCN)_2]BF_4$ (3 mol %) are summarized in Table 1.

The reaction was highly dependent on the substituent (R^1 in **1**), which may affect the rate of insertion of **1** into a rhodium−carbon bond. Thus, the additions to both dimethyl fumarate and diethyl maleate smoothly proceeded at room temperature (entries 1 and 2), whereas the additions to cinnamate, acrylate, and crotonate were heated to 50, 80, and 100 °C to complete the reactions

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10.1021/jo0002184 CCC: $19.00
Published on Web 08/23/2000

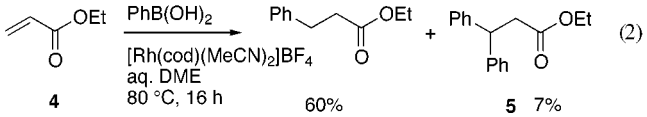
Table 1. Addition of Phenylboronic Acid to α,β-Unsaturated Esters with [Rh(cod)(MeCN)$_2$]BF$_4$[a]

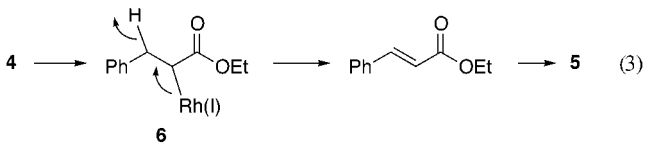
entry	α,β-unsaturated ester	*T*/°C	yield[b]/%
1	(*E*)-MeO$_2$CCH=CHCO$_2$Me	25	84
2	(*Z*)-EtO$_2$CCH=CHCO$_2$Et	25	79
3	(*E*)-PhCH=CHCO$_2$Me	50	87
4	(*E*)-4-NO$_2$C$_6$H$_4$CH=CHCO$_2$Me	50	97
5	CH$_2$=CHCO$_2$Me	80	60[c,d]
6	(*E*)-MeCH=CHCO$_2$Me	100	82[d]
7	MeCH=C(CO$_2$Et)$_2$	100	9[d]
8	MeCH=C(CO$_2$Et)$_2$	70	76[e]
9	(*Z*)-EtO$_2$CCH=C(Me)CO$_2$Et	100	trace[d]

[a] A mixture of α,β-unsaturated ester (1 mmol) and phenylboronic acid (2 mmol) in aqueous MeOH (6/1) was stirred for 16 h in the presence of [Rh(cod)(MeCN)$_2$]BF$_4$ (3 mol %). [b] Isolated yields. [c] The reaction was accompanied with methyl 3,3-diphenylpropionate (7%). [d] In aqueous dioxane (6/1). [e] The reaction was carried out in aqueous EtOH (5/2) at 70 °C for 24 in the presence of phenylboronic acid (4 mmol).

(entries 3−6). The relative reactivity is parallel to the order of rhodium/alkene complex stability or the insertion rate, which can be estimated by the LUMO energy level of alkenes.[14] However, the addition to trisubstituted alkenes was very slow, even at 100 °C, due to their large steric hindrance on the coordination to the rhodium metal center (entries 7 and 9). The prolongation of reaction time to 1 day improved the yield to 76% in the presence of 4 equiv of phenylboronic acid (entry 8). Similar to the results obtained in the addition to enones, aqueous solvents combining water and a weak donor solvent such as alcohols, dimethoxyethane (DME), or dioxane afforded good results. Judging from the recovery of the products, the saponification of the esters was very slow even at 100 °C.

The addition of phenylboronic acid to methyl acrylate (entry 5) was accompanied by 3,3-diphenylpropanoate (7%), which was derived from β-hydride elimination, giving ethyl cinnamate (eqs 2 and 3). A cinnamate intermediate was not detected in the reaction mixture since it is more reactive than the parent acrylate (entries 3 and 5).





The formation of a Heck-type product suggests the presence of a mechanism involving a rhodium species bound to the α-carbon (**6**). However, such byproducts were not observed, or were only observed in negligibly small amounts, in other substrates shown in entries 1−9.

Asymmetric Addition

The in situ preparation of a catalyst from rhodium complexes and (*S*)-binap was followed by the addition of phenylboronic acid to benzyl crotonate to reveal the effects of rhodium precursors on yields and enantioselectivities (Table 2).[15]

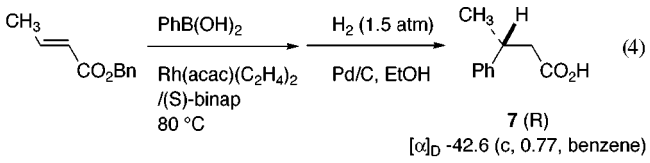
Table 2. Effect of Rhodium Precursor on the Asymmetric Addition of Phenylboronic Acid to Benzyl Crotonate[a]

entry	ligand	*T*/°C	time/h	yield[b]/%	% ee
1	[Rh(cod)(MeCN)$_2$]BF$_4$[c]	100	16	90	85
2	Rh(acac)(C$_2$H$_4$)$_2$	100	16	98	86
3	Rh(acac)(C$_2$H$_4$)$_2$	100	2	99	87
4	Rh(acac)(C$_2$H$_4$)$_2$	60	24	48	88
5	Rh(acac)(coe)$_2$[d]	100	16	98	86
6	Rh(acac)(CO)$_2$	100	16	98	86
7	[RhCl(cod)]$_2$	100	16	99	87
8	[RhCl(cod)]$_2$	60	24	64	33

[a] A mixture of benzyl crotonate (1 mmol) and phenylboronic acid (2 mmol) in aqueous dioxane was stirred in the presence of a rhodium complex (3 mol %) and (*S*)-binap (4.5 mol %). [b] Isolated yields. [c] cod = 1,5-cyclooctadiene. [d] coe = cyclooctene.

All of the cationic and neutral rhodium complexes examined, such as [Rh(cod)(CH$_3$CN)$_2$]BF$_4$, Rh(acac)(CH$_2$=CH$_2$)$_2$, Rh(acac)(coe)$_2$, Rh(acac)(CO)$_2$, and [Rh(cod)Cl]$_2$, were highly effective at 100 °C (entries 1−8). There were no large differences in yields or enantioselectivities (% ee) between cationic and neutral rhodium complexes, but neutral complexes were superior to cationic rhodiums because a combination of Rh(acac)(CH$_2$=CH$_2$)$_2$/(*S*)-binap revealed higher enantioselectivity (1−3% ee) than [Rh(cod)(CH$_3$CN)$_2$]BF$_4$/(*S*)-binap (entry 1). The reaction was completed within 2 h at 100 °C and overnight at 60 °C (entries 2 and 3). The enatioselectivity was not affected by the reaction temperatures or by the reaction times, although the RhCl complex resulted in significantly low enantioselectivity at 60 °C (entry 8). The isolated Rh(acac)[(*S*)-binap][15] showed essentially the same enatioselectivity as that of the in situ preparation.

The enatiomeric excess (% ee) was determined by HPLC analysis using a chiral stationary column (Dicel Chiralcel OD-H or OB-H). The addition of PhB(OH)$_2$ to benzyl crotonate with a cationic rhodium/(*S*)-binap catalyst (entry 1) provided benzyl 3-phenylbutanoate ([α]$_D$ −14.5 (*c* 1.02, CHCl$_3$), whose saponification with H$_2$ (1.5 atm, 10% Pd/C in EtOH at room temperature for 3 h) gave 3-phenylbutanoic acid ([α]$_D$ −42.6 (*c* 0.77, benzene) (eq 4). Thus, the absolute configuration of the ester (**7**) obtained from (*S*)-binap was established to be (*R*) by the specific rotation reported for (*R*)-3-phenylbutanoic acid ([α]$_D$ −45.8 (*c* 0.77, benzene).[16]



The effects of commercially available chiral ligands on the enantioselectivity in the addition of 3-methoxyphenylboronic acid to isopropyl crotonate are summarized in Table 3 and Figure 1.

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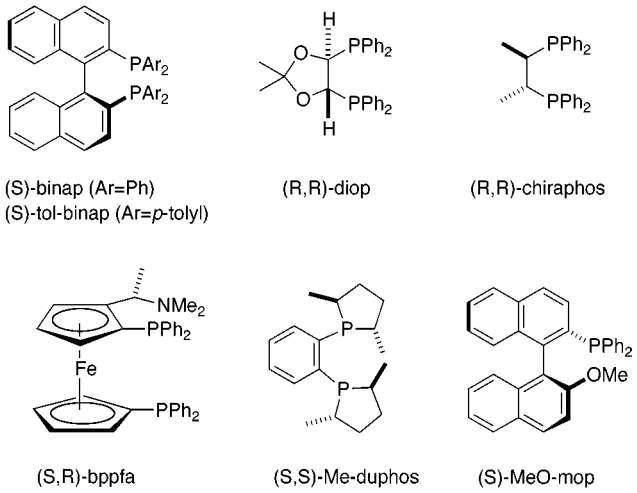


Figure 1. Chiral ligands.

Table 3. Effect of Ligand on the Asymmetric Addition of 3-Methoxyphenylboronic Acid to Isopropyl Crotonate[a]

entry	ligand	yield[b]/%	% ee
1	(*S*)-binap	91	91
2	(*S*)-tol-binap	43	91
3	(*R*,*R*)-diop	45	7
4	(*R*,*R*)-chiraphos	97	75
5	(*S*,*R*)-bppfa	9	0
6	(*S*,*S*)-Me-duphos	92	29
7	(*S*)-MeO-mop	trace	

[a] A mixture of isopropyl crotonate (1 mmol) and 3-methoxyphenylboronic acid (2 mmol) in aqueous dioxane was stirred for 16 h at 100 °C in the presence of $Rh(acac)(C_2H_4)_2$ (3 mol %) and ligand (4.5 mol %). [b] Isolated yields.

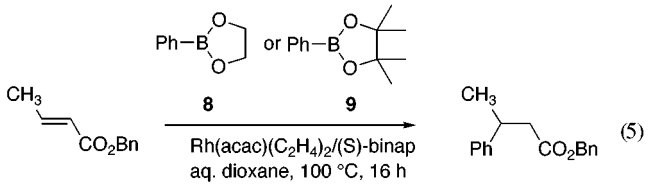
The complexes in situ obtained from binap, chiraphos, and Me-duphos afforded high yields of the addition product (entries 1, 4, and 6), but binap was again found to be the best ligand giving both high yields and high asymmetric induction, similar to those obtained by the 1,4-addition to enones (entry 1). Other bidentate ligands resulted in low yields or low enantioselectivities (entries 2, 3, and 5). The chiral monodentate ligand MeO-mop, reported in asymmetric hydrosilylation,[17] did not catalyze the reaction (entry 7).

The results of 1,4-addition of representative arylboronic acids to α,β-unsaturated esters in the presence of $Rh(acac)(C_2H_4)$/(S)-binap are summarized in Table 4.

3-Methoxyphenylboronic acid was added to a series of crotonates to reveal the effect of the ester group (R^2 in **1**) (entries 1−6). The bulkiness of the ester group improved the enantioselectivity in the order of ethyl ∼ isobutyl ∼ benzyl < isopropyl ∼ cyclohexyl < *tert*-butyl, thus suggesting the superiority of secondary and tertiary alkyl esters, whereas the reaction was very slow for the *tert*-butyl ester (entry 6). Various arylboronic acids having ortho, meta, and para substituents smoothly underwent the addition to isopropyl crotonate with high enantioselectivity exceeding 90% ee (entries 4 and 7−12). There was no appreciable difference in yields or enantioselectivity between meta- and para-functionalized arylboronic acids (entries 4 and 7−9). However, ortho-substitution caused a significant increase in the enantioselectivity, though both reactions were very slow, even in the presence of a large excess of boronic acid (entries 10 and 11). The *o*-methoxy group in $Rh(2\text{-}MeOC_6H_4)(PMe_3)_3$ coordinates to the rhodium metal center,[18] but it is not obvious at present whether the significant effect of an *o*-methoxy group is derived not only from steric interaction but also from intramolecular chelation.

Together with the effect of the ester group (R^2), the β-substitution (R^1) significantly affected the yields and enantioselectivities. The enantioselectivity improved to 97% ee in the β-isopropyl derivative (entry 12), but the increase in steric interaction significantly reduced the chemical yield, which was not improved in the presence of a large excess of arylboronic acids or by prolongation of the reaction time. More flexible chiraphos was better ligand for improving the chemical yield, but the enantioselectivity was not sufficient for practical purposes (entry 13). Although bulky β-alkyl groups caused an increase in the enantioselectivity, all attempts at high-enantioselective addition to β-aryl derivatives such as cinnamate were unsuccessful (entries 14 and 15).

Under similar reaction conditions, arylboronic esters **8** and **9** also underwent the conjugate addition (eq 5).



The pinacol ester **9** resulted in a slightly lower yield, but the enantioselectivity thus obtained was the same as that of phenylboronic acid (entry 3). Various arylboronic pinacol esters are now accessible by the palladium-catalyzed cross-coupling reaction of bis(pinacolato)-diboron with aryl halides or triflates or by a similar coupling reaction of pinacolborane with aryl halides in the presence of triethylamine.[19] Thus, the stepwise bond-forming reactions catalyzed by palladium and rhodium may allow one-pot synthesis of β-aryl esters.

Mechanism

Although work on mechanistic details is still in progress, it is thought that the present transformation may have resulted from a catalytic cycle that involves the transmetalation of arylboronic acid to a rhodium(I) species **10** to give an arylrhodium(I) complex **11**, the coordination of an unsaturated ester to rhodium followed by insertion into the Rh−C bond to afford an equilibrium mixture of **12** and **13** and, finally, the hydrolysis of the rhodium enolate **13** with water to provide **14** and **10** (Figure 2).

The arylrhodium(I)/arylphosphine complexes are unstable, making isolation in pure form impossible, but they

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Table 4. Asymmetric Addition of Arylboronic Acids to α,β-Unsaturated Esters[a]

entry	α,β-unsaturated ester	$ArB(OH)_2$	yield[b]/%	% ee	$[\alpha]^{20}_D$ (*c* in $CHCl_3$)
1	(*E*)-$CH_3CH{=}CHCO_2C_2H_5$	3-$MeOC_6H_4B(OH)_2$	81	87	−20.3 (1.01)
2	(*E*)-$CH_3CH{=}CHCO_2CH_2CH(CH_3)_2$	3-$MeOC_6H_4B(OH)_2$	98	88	−21.7 (1.01)
3	(*E*)-$CH_3CH{=}CHCO_2CH_2Ph$	3-$MeOC_6H_4B(OH)_2$	97	87	−12.3 (1.00)
4	(*E*)-$CH_3CH{=}CHCO_2i$-C_3H_7	3-$MeOC_6H_4B(OH)_2$	91	91	−21.2 (1.02)
5	(*E*)-$CH_3CH{=}CHCO_2cyclo$-C_6H_{11}	3-$MeOC_6H_4B(OH)_2$	97	91	−18.4 (1.01)
6	(*E*)-$CH_3CH{=}CHCO_2t$-C_4H_9	3-$MeOC_6H_4B(OH)_2$	54	92	−19.5 (1.01)
7	(*E*)-$CH_3CH{=}CHCO_2i$-C_3H_7	4-$MeC_6H_4B(OH)_2$	89	92	−23.5 (1.01)
8	(*E*)-$CH_3CH{=}CHCO_2i$-C_3H_7	4-$MeOC_6H_4B(OH)_2$	55	92	
9	(*E*)-$CH_3CH{=}CHCO_2i$-C_3H_7	4-$MeOC_6H_4B(OH)_2$	82[c]	92	−21.6 (0.99)
10	(*E*)-$CH_3CH{=}CHCO_2i$-C_3H_7	2-$MeC_6H_4B(OH)_2$	35[c]	94	−8.5 (1.00)
11	(*E*)-$CH_3CH{=}CHCO_2i$-C_3H_7	2-$MeOC_6H_4B(OH)_2$	43[c]	98	−2.0 (1.00)
12	(*E*)-$(CH_3)_2CHCH{=}CHCO_2i$-C_3H_7	3-$MeOC_6H_4B(OH)_2$	26	97	−17.5 (1.02)
13	(*E*)-$(CH_3)_2CHCH{=}CHCO_2i$-C_3H_7	3-$MeOC_6H_4B(OH)_2$	92[d]	77	
14	(*E*)-$PhCH{=}CHCO_2i$-C_3H_7	4-$MeC_6H_4B(OH)_2$	28	77	
15	(*E*)-$PhCH{=}CHCO_2i$-C_3H_7	4-$MeC_6H_4B(OH)_2$	37[c]	78	+2.9 (0.99)

[a] A mixture of α,β-unsaturated ester (1 mmol) and arylboronic acid (2 mmol) in aqueous dioxane was stirred for 16 h at 100 °C in the presence of $Rh(acac)(C_2H_4)_2$ (3 mol %) and (*S*)-binap (4.5 mol %). [b] Isolated yields by chromatography over silica gel. [c] Arylboronic acid (5 mmol) was used. [d] (*R*,*R*)-Chiraphos was used in place of (*S*)-binap.

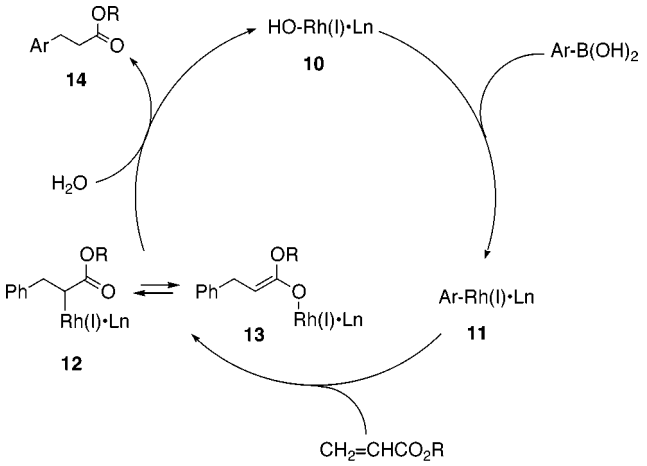
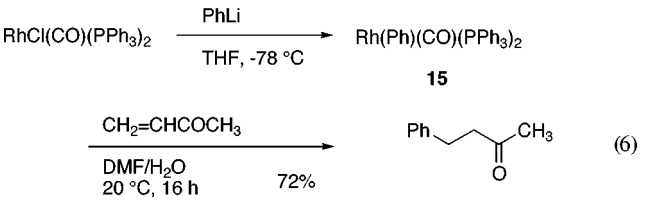


Figure 2. Proposed catalytic cycle.

are key intermediates for carrying out various coupling reactions with organic halides[20] and additions to alkenes and alkynes.[21] Preliminary results suggested a sequence of the formation of the ArRh(I) species and its addition to unsaturated esters because the Michael adduct was obtained when the in situ preparation of phenylrhodium(I) (**15**) from a Vaska complex was followed by the addition to methyl vinyl ketone (eq 6). The sequence involves insertion of the alkene double bond into the Rh−C bond and hydrolysis of the rhodium intermediate (**11** → **14**).



(6)

The synthesis of rhodium enolate and its applications to catalytic Aldol chemistry was extensively studied by Heathcock.[22] The η^1 oxygen-bound rhodium enolate complexes, synthesized from $RhCl(CO)(PMe_3)_2$ and potassium enolates or silyl enolates, exhibit a dynamic equilibrium between the O-bound and the C-bound forms, which are sufficiently nucleophilic to condense with carbonyl compounds. Thus, the hydrolysis of the rhodium enolate **13** with water lead to **14**, which avoids the β-hydride elimination from **12** giving the Heck-coupling product (eq 3) or Aldol-type condensation of **13**. Although there is no clear evidence that (hydroxo)rhodium(I)[24] exists as an active species for transmetalation (**10** → **11**), results of present study implied that there is a mechanism that involves transmetalation as a crucial step in the catalytic cycle. The high oxophilicity of the boron center and the basicity of transition metal hydroxides would induce transmetalation, which can be rationalized by the related catalyzed reactions by palladium and platinum complexes whereby organic groups on the boron atom readily transfer to $Pd(acac)_2$,[25] $[\eta^3\text{-}C_3H_5PdOAc]_2$,[26] $\eta^3\text{-}C_3H_5Pd(acac)$,[26] $RPd(OR)L_2$ (R = H, Me, Ac)[26,27,28] and $[Pt(OR)(S)L_2]^+$ (R = H, Me)[29] under neutral conditions. The reaction of phenylboronic acid with benzyl crotonate with the Rh(acac)/(S)-binap complex (entry 2 in Table 2) was retarded completely by the addition of a 3 mol % of acid such as HBF_4, AcOH, or HCl, thus suggesting that neutralization of the (hydroxo)rhodium species inhibits transmetalation.

The stereochemical pathway in the insertion of the C−C double bond of **1** into the Rh−aryl bond can be explained by a mechanism similar to that of the 1,4-addition to enones.[6] The binap ligand was originally

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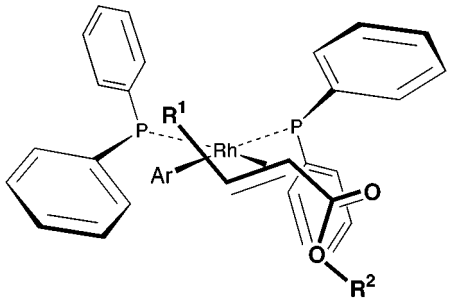
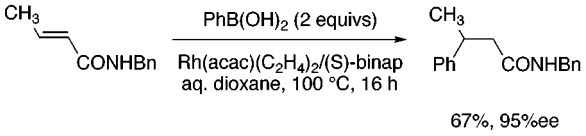


Figure 3. Transition state.

designed for asymmetric hydrogenation, but it also works well in the Heck reaction[30] and the conjugate addition because those reactions involve a similar molecular recognition mechanism. The configuration of a speculated intermediate of the rhodium−(*S*)-binap[30] and α,*β*-unsaturated ester coordinated is shown in Figure 3.

The coordination of **1** with its 2re face to a vacant orbital of the rhodium−(*S*)-binap complex provides (R)-**3** (Ar = Ph, R = Me, R′ = CH_2Ph) on the migratory insertion of the C−C double bond into the rhodium−carbon bond (eq 4). A comparison of a series of crotonic esters (entries 1−6 in Table 4) revealed the superiority of bulky R^2, which may interact with the upper phenyl group of the binap ligand at the coordination from its 2 si face.

In addition to our previous reports[6] on 1,4-additions of aryl- and 1-alkenylboronic acids to enones, the reaction with α,*β*-unsaturated esters was found to be efficiently catalyzed by a rhodium-binap catalyst. Because of the simple experimental procedure using a catalytic amount of a rhodium−binap complex, we anticipate the feasibility of conjugate additions to other Michael acceptors. Preliminary results for the addition of phenylboronic acid to *N*-benzyl crotonamide are shown in eq 7. Under reaction conditions similar to those used for the esters, various amides showed a higher enantioselectivity than that of the corresponding ester derivatives, the results of which will be reported elsewhere (eq 7).[13]



(7)

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Experimental Section

$Rh(acac)(CH_2{=}CH_2)_2$, $Rh(acac)(CO)_2$, and $[Rh(cod)Cl]_2$ are commercially available. $[Rh(cod)(CH_3CN)_2]BF_4$[31] and $Rh(acac)(coe)_2$[32] were synthesized by the reported procedures. HPLC analysis was directly performed with a chiral stationary phase column, Chiralcel OD-H and OB-H, purchased from Dicel Co., Ltd.

General Procedure. Rhodium complex (0.03 mmol), ligand (0.045 mmol), and arylboronic acid (2 or 5 mmol) were added to a flask containing a magnetic stirring bar, a septum inlet, and a reflux condenser. The flask was flashed with argon and charged with 1,4-dioxane (6 mL) and water (1 mL). After being stirred for 30 min, α,*β*-unsaturated ester (1.0 mmol) was added. The mixture was then stirred for 16 h at the temperature shown in Tables 1−4. The product was extracted with benzene, washed with brine, and dried over $MgSO_4$. Chromatography over silica gel gave the desired product.

(*R*)-3-Phenylbutanoic Acid (Eq 4). $(acac)Rh(C_2H_4)_2$ (0.03 mmol), (*S*)-binap (0.045 mmol), and phenylboronic acid (2 mmol) were placed in a flask. The flask was flashed with argon and then charged with 1,4-dioxane (6 mL) and water (1 mL). After being stirred for 30 min, benzyl crotonate was added. The mixture was then stirred for 16 h at 100 °C. Chromatography over silica gel yielded benzyl 3-phenylbutanoate: yield 0.252 g (99%); 86% ee (HPLC, OD-H; hexane/2-propanol = 98:2).

To a glass pressure bottle containing a magnetic stirring bar and 10% Pd−C (10 mg) were added EtOH (3 mL) and benzyl 3-phenylbutanoate (1 mmol). The resulting mixture was stirred for 3 h at room temperature under 1.5 atmospheres of hydrogen. The catalyst was removed by filtration through Celite, and the acid was then extracted with 1 M NaOH (50 mL). The aqueous phase was treated with 1 M HCl (100 mL), and the product was then extracted with diethyl ether. Evaporation of solvent yielded 3-phenylbutanoic acid: yield 0.118 g (72%); $[\alpha]_D$ −42.6 (*c* 0.77, benzene).

Addition of Phenylrhodium(I) Complex to Methyl Vinyl Ketone (Eq 6). To a solution of Vaska complex $RhCl(CO)(PPh_3)_2$ (0.03 mmol) in THF (0.5 mL) was added phenyllithium (0.832 M in diethyl ether, 0.3 mmol) at −78 °C. After the misture was stirred for 1.5 h at −78 °C, DMF (6 mL), H_2O (1 mL) and methyl vinyl ketone (1 mmol) were added. The resulting mixture was stirred overnight at room temperature. GC analysis revealed the formation of 4-phenyl-2-butanone in 72% yield based on the Vaska complex.

Supporting Information Available: Text describing experimental details and spectral and/or analytical data of the products. This material is available free of charge via Internet at http://pubs.acs.org.

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