Rhodium(I)-Catalyzed Asymmetric 1,4-Addition of Arylboronic Acids to α,β-Unsaturated Amides

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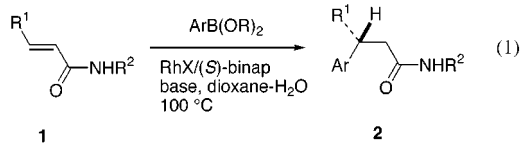
The conjugate addition of arylboronic acids to α,β-unsaturated amides was carried out in the presence of a chiral rhodium catalyst and an aqueous base. The catalyst prepared in situ from Rh(acac)(CH_2═CH_2)$_2$ and (*S*)-binap provided (R)-*N*-benzyl-3-phenylbutanamide with 93% ee in the addition of phenylboronic acid to *N*-benzyl crotonamide. The reaction suffered from incomplete conversion resulting in moderate yields, but addition of an aqueous base, such as K_2CO_3 (10−50 mol%) was found to be highly effective to improve the chemical yields. The role of the base giving a RhOH species active for transmetalation with arylboronic acids was discussed.

The conjugate addition of organometallic reagents to α,β-unsaturated carbonyl compounds is a widely used process for carbon−carbon bond formation.[1] Although such intermolecular transfer reactions are rare for organoboronic acids, various rhodium(I) complexes catalyze the 1,4-addition of aryl- and alkenylboronic acids to α,β-unsaturated carbonyl compounds.[2−4] The additions of arylboronic acids to unactivated alkenes such as norbornene[5] and vinylarenes[6] were also recently found to be catalyzed by rhodium(I) complexes. The additions to α,β-unsaturated ketones,[7] esters,[8] nitroalkenes,[9] and alkenylphosphonates[10] were extended to asymmetric versions by using a rhodium(I)-binap complex. Here, we report a conjugate addition of arylboronic acids to α,β-unsaturated amides (**1**) yielding optically active β-aryl amides (**2**) in the presence of a rhodium(I)-binap catalyst (eq 1).[11]



1 **2** (1)

Although the reaction suffered from incomplete conversion resulting in moderate chemical yields, the presence of an aqueous base was found to be very effective for completing the reaction. Such effects of bases were recently demonstrated in the addition of arylboronic acids to aldehydes catalyzed by a rhodium(I)-carbene complex.[12]

The effects of catalysts on yields and enantioselectivities in the addition of phenylboronic acid to *N*-benzyl crotonamide are summarized in Table 1. All catalysts were prepared in situ by stirring a rhodium precursor (3 mol %) and a chiral ligand (4.5 mol %). There were no large differences in enantioselectivities (% ee) between cationic and neutral rhodium precursors, since two cationic rhodium(I) complexes (entries 1 and 2), Rh(acac) (entry 3), and RhCl complex (entry 4) yielded *N*-benzyl-3-phenylbutanamide with 91−93% ee. Among the ligands employed, binap[13] again exhibited the best enantioselectivity (entries 5−8), as was the case in related reactions with α,β-unsaturated ketones and esters.[7−10]

The absolute configuration of the product was established by using the reaction of phenylboronic acid with crotonamide (**1**, R^1 = Me, R^2 = H) since the *N*-benzyl derivative strongly resisted the acid-catalyzed hydrolysis. The reaction catalyzed by the (*S*)-binap complex provided 3-phenylbutanamide ($[\alpha]_D$ −30.9 (*c* 1.01, $CDCl_3$)), which was then converted into (*R*)-3-phenylbutanoic acid ($[\alpha]_D$ −44.8 (*c* 0.76, benzene))[14] via the acid-catalyzed hydrolysis. Thus, the stereochemical pathway in the insertion of an unsaturated amide into the Rh−C bond can be rationalized by the same mechanism as that of α,β-unsaturated ketones[7] or other Michael acceptors.[8−10]

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Table 1. Effect of Catalyst in the Asymmetric Addition of Phenylboronic Acid to *N*-Benzyl Crotonamide[a]

entry	Rh(I) precursor	ligand	yield[b] (%)	% ee
1	$[Rh(cod)(MeCN)_2]BF_4$[c]	(*S*)-binap[d]	53	91
2	$[Rh(cod)_2]BF_4$[c]	(*S*)-binap[d]	60	93
3	$Rh(acac)(C_2H_4)_2$	(*S*)-binap[d]	67	93
4	$[RhCl(cod)]_2$[c]	(*S*)-binap[d]	64	93
5	$Rh(acac)(C_2H_4)_2$	(*R*,*R*)-chiraphos[e]	82	48
6	$Rh(acac)(C_2H_4)_2$	(*S*,*S*)-Me-duphos[f]	36	43
7	$Rh(acac)(C_2H_4)_2$	(*R*,*R*)-diop[g]	10	7

[a] A mixture of *N*-benzyl crotonamide (1 mmol) and phenylboronic acid (2 mmol) in aqueous dioxane was stirred at 100 °C for 16 h in the presence of a rhodium(I) precursor (3 mol %) and a phosphine ligand (4.5 mol %). [b] Isolated yields. [c] cod = 1,5-cyclooctadiene. [d] (*S*)-(−)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl. [e] (2*R*,3*R*)-(+)-2,3-Bis(diphenylphosphino)butane. [f] (+)-1,2-Bis[(2*S*,5*S*)-2,5-dimethylphospholano]benzene. [g] (2*S*,3*S*)-(+)-4,5-Bis(diphenylphosphinomethyl)-1,2-dimethyl-2,3-dioxolane.

Table 2. Effects of Acids and Bases in the Addition of Phenylboronic Acid to *N*-Benzyl Crotonamide[a]

entry	additive	equiv	yield[b] (%)
1	none		67
2	AcOH	0.05	15
3	$MeSO_3H$	0.05	0
4	TsOH	0.05	0
5	HCl	0.05	0
6	CF_3SO_3H	0.05	0
7	$B(OH)_3$	1.00	75
8	$Eu(OTf)_3$	0.05	tr
9	$Yb(OTf)_3$	0.05	tr
10	Et_3N	2.00	59
11	KF	2.00	71
12	NaOAc	2.00	tr
13	$KHCO_3$	0.05	85
14	K_2CO_3	0.05	82
15	K_3PO_4	0.05	88
16	KOH	0.05	85

[a] A mixture of *N*-benzyl crotonamide (1 mmol) and phenylboronic acid (2 mmol) in aqueous dioxane (6/1, 6 mL) was stirred at 100 °C for 16 h in the presence of an acid or a base (0.05−1.0 equiv), $Rh(acac)(C_2H_4)_2$ (3 mol %), and (*S*)-binap (4.5 mol %). [b] GC yields based on the amide. The enantioselectivities were in a range of 93−94% ee.

Although the rhodium-binap complex achieved high enantioselectivities, the addition to the unsaturated amides suffered from incomplete conversion resulting in moderate chemical yields (<70%). It was found that various acids strongly retard the reaction and, reversely, that the addition of a base accelerates the reaction (Table 2). The inhibitory effect of acids can be in the order of acid strength since it was smaller for acetic acid (entry 2) and very large for $MeSO_3H$, TsOH, HCl, and CF_3SO_3H (entries 3−6). Water-stable Lewis acids such as $Eu(OTf)_3$ and $Yb(OTf)_3$ were also found to be strong inhibitors (entries 8 and 9). On the other hand, the addition of an inorganic base exerts a remarkable accelerating effect (entries 13−16). The effect was independent of the basic strengths of $NaHCO_3$, K_2CO_3, K_3PO_4, and KOH or the stoichiometry in a range of 5 to 200 mol %, except that NaOAc exceptionally resulted in no reaction (entry 12). The presence of a base did not influence the high enantioselectivity of the rhodium/binap complex.

The effect of added bases on the reaction rate is shown in Figure 1. The addition of phenylboronic acid to *N*-benzyl crotonamide at 100 °C in the presence of Rh(acac)/(*S*)-binap (3 mol %) resulted in 76% yield after 4 h. Further prolongation to 16 h was no longer effective to complete the reaction (solid line and ■). In contrast,

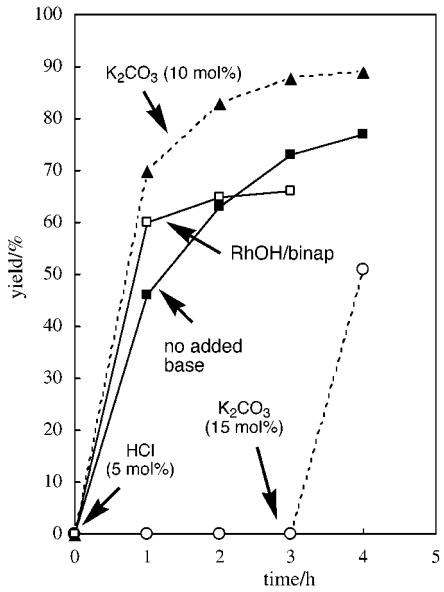
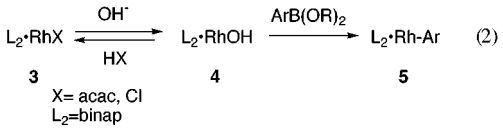


Figure 1. Effect of base in the addition of phenylboronic acid to *N*-benzyl crotonamide.

the reaction was significantly accelerated by the addition of 10 mol % of aqueous K_2CO_3, resulting in 89% yield after 6 h (dotted line and ▲). The reaction, which was inhibited by the addition of HCl (5 mol %) to Rh(acac)-$(C_2H_4)_2$/(S)-binap (3 mol %), restarted spontaneously when the mixture was treated with aqueous K_2CO_3 (15 mol %) (dotted line and ○). All of these results are consistent with the view that bases act for the conversion of the RhCl or Rh(acac) complex **3** to the corresponding RhOH complex **4**,[15] which has been proposed to be an active intermediate for transmetalation with organoboronic acids (eq 2).[2,3,8,11,16] Although the addition of (*S*)-



binap to $[RhOH(cod)]_2$ is a convenient alternative for the preparation of RhOH/binap complex (solid line and □), the slow ligand exchange resulting in incomplete complexation decreased the enantioselectivities.

Representative results of asymmetric additions of arylboronic acids to α,β-unsaturated amides in the presence of K_2CO_3 (50 mol %), as well as RhCl/(*S*)-binap catalyst (3 mol %), are summarized in Table 3. Phenylboronic acid was added to a series of crotonamides to evaluate the effect of *N*-substituents on yields or enantioselectivity (entries 1−4). Under basic conditions using K_2CO_3 (50 mol %), crotonamide and its *N*-phenyl, *N*-cyclohexyl, and *N*-benzyl derivatives provided the addition products with 89% ee, 90% ee, 93% ee, and 93% ee, respectively (entries 1−4), though no reaction was observed for *N*,*N*-dialkyl derivatives such as the piperidine amide. A series of reactions of *para*-substituted arylboronic acids showed the superiority of electron-deficient arylboronic acids. Phenylboronic acid and its 4-trifluoromethyl derivative reacted much faster, and much better yields and enantioselectivities were obtained (entries 4

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Table 3. Asymmetric Addition of Phenylboronic Acid to α,β-Unsaturated Amides[a]

entry	amides	$ArB(OR)_2$	yield[b] (%)	% ee	$[\alpha]^{20}_D$ ($CDCl_3$)
1	(*E*)-CH_3CH=$CHCONH_2$	$PhB(OH)_2$	62	89	−30.9 (1.01)
2	(*E*)-CH_3CH=$CHCONHPh$	$PhB(OH)_2$	88	90	−51.8 (1.01)
3	(*E*)-CH_3CH=$CHCONHc$-C_6H_{11}	$PhB(OH)_2$	80	93	−30.1 (1.01)
4	(*E*)-CH_3CH=$CHCONHCH_2Ph$	$PhB(OH)_2$	85	93	−12.1 (1.00)
5	(*E*)-CH_3CH=$CHCONHCH_2Ph$	4-$CF_3C_6H_4B(OH)_2$	82	92	−5.3 (1.03)
6	(*E*)-CH_3CH=$CHCONHCH_2Ph$	4-$MeC_6H_4B(OH)_2$	74	87	−11.6 (1.00)
7	(*E*)-CH_3CH=$CHCONHCH_2Ph$	4-$MeOC_6H_4B(OH)_2$	50	77	−11.6 (1.00)
8	(*E*)-$PhCH$=$CHCONHCH_2Ph$	$PhB(OH)_2$	tr		
9	(*E*)-$C_5H_{11}CH$=$CHCONHCH_2Ph$	$PhB(OH)_2$	89	91	−4.6 (1.00)
10	(*E*)-$(CH_3)_2CHCH$=$CHCONHCH_2Ph$	$PhB(OH)_2$	19	95	−8.0 (1.00)
11	(*E*)-CH_3CH=$CHCONHCH_2Ph$	$PhB(O_2C_2H_4)$[c]	90	91	
12	(*E*)-CH_3CH=$CHCONHCH_2Ph$	$PhB(O_2C_2Me_4)$[d]	88	91	

[a] A mixture of an amide (1 mmol), $ArB(OR)_2$ (2 mmol), and K_2CO_3 (0.5 mmol) in aqueous dioxane (6/1. 3.5 mL) was stirred at 100 °C for 16 h in the presence $Rh(acac)(C_2H_4)_2$ (3 mol %), and (*S*)-binap (4.5 mol %). [b] Isolated yields. [c] 2-Phenyl-1,3−2-benzodioxaborole. [d] 2-Phenyl-4,4,5,5-tetramethyl-1,3,2-benzodioxaborole.

and 5) than those of 4-methyl- and 4-methoxyphenylboronic acid (entries 6 and 7). Such an effect of substituents was also observed in the addition to α,β-unsaturated ketones or esters, though it was not as significant as those of the amides. As seen in many of our previous reactions with enones and α,β-unsaturated esters,[8] the bulkiness of β-substituents significantly affected chemical yields (entries 8−10). The rhodium-binap catalyst can be limitedly used for β-methyl and β-primary alkyl unsaturated amides (entries 4 and 9) because analogous reactions were very slow for phenyl and isopropyl derivatives (entries 8 and 10). Under similar reaction conditions using a base, both ethylenegycol and pinacol ester of phenylboronic acid smoothly added to the amides with enantioselectivities comparable to that of phenylboronic acid (entries 11 and 12). The reaction can be applied to the synthesis of more functionalized derivatives, since various pinacol arylboronic esters are now accessible by the palladium-catalyzed cross-coupling reaction of haloarenes or triflates with bis(pinacolato)diboron[17−19] or by the analogous coupling reaction of haloarenes with pinacolborane,[20,21] and both reactions tolerate various functional groups.

Experimental Section

Effect of Bases (Figure 1). $Rh(acac)(C_2H_4)_2$ (0.06 mmol), (*S*)-binap (0.09 mmol), phenylboronic acid (4 mmol), and N-benzyl crotonamide (2 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 *(12* mL*)*, water (2 mL), and pentadecane (0.72 mmol) as an internal standard. The mixture was then stirred for 16 h at *100* °C. At suitable time intervals, portions of solution were sampled with a syringe (ca. 0.1 mL) and poured into a stirred mixture of ethyl acetate and water. The yields of *N*-benzyl-3-phenylbutanamide determined by GC analysis are shown in the figure by the solid line and ■.

A mixture of $Rh(acac)(C_2H_4)_2$ (0.06 mmol), (S)-binap (0.09 mmol), phenylboronic acid (4 mmol), *N*-benzyl crotonamide (2 mmol), and K_2CO_3 (0.2 mmol, 10 mol %) in 1,4-dioxane (12 mL) and water (2 mL) was stirred at 100 °C. The yields at specific intervals are shown by the dotted line and ▲. An analogous reaction using K_2CO_3 (1 mmol, 50 mol %) resulted in yields identical to that when using 10 mol % K_2CO_3.

A mixture of $Rh(acac)(C_2H_4)_2$ (0.06 mmol), (*S*)-binap (0.09 mmol), phenylboronic acid (4 mmol), and *N*-benzyl crotonamide (2 mmol) in dioxane (12 mL) and H_2O (2 mL) was treated with 1 N HCl (0.1 mL, 0.1 mmol) at room temperature. No reaction was observed during 3 h at 100 °C. Aqueous K_2CO_3 (2 M, 0.15 mL, 0.3 mmol) was then added to the mixture. The yields at specific intervals are plotted in the figure by the dotted line and ○.

A mixture of $[RhOH(cod)]_2$ (0.03 mmol) and (*S*)-binap (0.09 mmol) in dioxane (2 mL) was stirred for 2 h at room temperature. Phenylboronic acid (4 mmol), *N*-benzyl crotonamide (2 mmol), dioxane (10 mL), and H_2O (2 mL) were then added, and the mixture was stirred at 100 °C. The yields determined by GC analysis are shown in the figure by the solid line and □.

General Procedure for 1,4-Addition to α,β-Unsaturated Amides (Table 3). $Rh(acac)(C_2H_4)_2$ (0.03 mmol), (*S*)-binap (0.045 mmol), arylboronic acid (2 mmol), K_2CO_3 (0.5 mmol), and α,β-unsaturated amide (1 mmol) were added to the flask containing a magnetic stirring bar, a septum inlet, and a reflux condenser. The flask was flashed with argon and then charged with 1,4-dioxane (3 mL) and water (0.5 mL). The mixture was stirred for 16 h at 100 °C. The product was extracted with ethyl acetate, washed with brine, and dried over anhydrous magnesium sulfate. Chromatography over silica gel gave the desired product. HPLC analysis was directly performed with chiral stationary phase column, Chiralcel OD-H, OB-H and AD, purchased from Dicel.

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

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