# Highly Active and Enantioselective Rhodium-Catalyzed Asymmetric 1,4-Addition of Arylboronic Acid to $\alpha$ , $\beta$ -Unsaturated Ketone by using Electron-Poor MeO-F<sub>12</sub>-BIPHEP

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Abstract: The asymmetric 1,4-addition of phenylboronic acid to cyclohexenone were performed by using a low amount of rhodium/(R)-(6,6'-dimethoxybiphenyl-2,2'-diyl)bis[bis(3,4,5-trifluorophenyl)phosphine] (MeO-F<sub>12</sub>-BIPHEP) catalyst. Because the catalyst shows thermal resistance at 100°C, up to 0.00025 mol% Rh catalyst showed good catalytic activity. The highest turnover frequency (TOF) and turnover number (TON) observed were  $53,000 \text{ h}^{-1}$ and 320,000, respectively. The enantioselectivities of the products were maintained at a high level of 98% ee in these reactions. The Eyring plots gave the following kinetic parameters  $(\Delta\Delta H^{\neq} = -4.0 \pm$ 

# Introduction

The catalytic asymmetric conjugate addition of organometallic reagents to a, \beta-unsaturated carbonyl compounds is an important method for the preparation of chiral β-aryl-substituted carbonyl compounds. In particular, the Rh-catalyzed asymmetric 1,4-addition reaction of arylboron reagents has been studied intensively.<sup>[1]</sup> Recently, the kilogram scale Rh-catalyzed asymmetric 1,4-addition of arylboronic acid was reported.<sup>[2]</sup> Although 27 kg of substrate were used in the presence of 2 mol% Rh catalyst in that study, the amount of Rh precursor ([RhCl(COD)]<sub>2</sub>) was equivalent to ca. 480 g. Using less rhodium is highly desirable because it is very expensive. If the catalyst loading for the asymmetric catalysis is reduced to, for example, 0.01% or less, the asymmetric catalysis would increase in value. However, even though over one hundred studies of the asymmetric catalytic reaction have been reported, most of the chiral catalysts for the reaction require 1 to 3% Rh and those requiring 0.1% Rh or less are scarce.<sup>[3]</sup> Among the highly active cata0.1 kcalmol<sup>-1</sup> and  $\Delta\Delta S^{\neq} = -1.3 \pm 0.3$  calmol<sup>-1</sup>K<sup>-1</sup>), indicating that the entropy contribution is relatively small. Both the result and consideration of the transition state in the insertion step at the B3LYP/6-31G(d) [LANL2DZ for rhodium] levels indicated that the less  $\sigma$ -donating electron-poor (*R*)-MeO-F<sub>12</sub>-BIPHEP could be creating a rigid chiral environment around the rhodium catalyst even at high temperature.

**Keywords:** asymmetric catalysis; density function theory (DFT) calculations; fluorinated ligands; phosphane ligands; rhodium

lysts, Hayashi's chiral diene ligand shows outstanding catalytic activity with a turnover frequency (TOF) reaching 1,900  $h^{-1}$  at 30 °C for the asymmetric 1,4-addition of phenylboronic acid (1a) to cyclohexenone (2a).<sup>[3e]</sup> However, the 1,4-addition product was not formed when the catalyst loading was reduced to 0.01 mol%. The reason for this unsuccessful result is the small amount of phenol present in 1a, which was not removed by recrystallization, and therefore, led to the deactivation of the catalyst. Therefore, Hayashi et al. used 2,4,6-triphenylboroxin excluding the contaminant to give an impressive result (TOF= 14,000 h<sup>-1</sup> at 30 °C).<sup>[3e]</sup> Because of its high catalytic activity, the Rh/chiral diene catalyst system is one of the best catalytic systems for Rh-catalyzed asymmetric 1,4-addition. However, use of the commercially available 1a without modification in a highly active catalytic reaction would be more convenient for the Rhcatalyzed 1,4-addition. Recently, we reported that the highly electron-poor chiral ligand (R)-MeO-F<sub>12</sub>-BIPHEP (3),<sup>[3f]</sup> an electronically unique chiral diphosphane relative to the known chiral diphosphanes



**Figure 1.** Electronic properties of BINAP-type chiral ligands by measurement of carbonyl stretching frequencies of [RhCl(diphosphane)(CO)] complexes.



Scheme 1. Asymmetric 1,4-addition by using Rh/(R)-3.

(Figure 1),<sup>[4]</sup> is highly effective for Rh-catalyzed asymmetric 1,4-additions (Scheme 1).<sup>[3f]</sup> Although its TOF value reached 750 h<sup>-1</sup> with high enantioselectivity (>99% *ee*) at 20 °C in the asymmetric 1,4-addition of **1a** to **2a**, the reaction conditions were not fully optimized. Therefore, we studied the appropriate reaction conditions required to achieve a highly effective asymmetric 1,4-addition in the presence of 0.01 mol% or less Rh/(*R*)-**3**, even with the use of commercially available **1a**. Firstly, the stability of Rh complexes bearing (*R*)-**3** was investigated to obtain relevant information for the catalysis. It is also beneficial to understand the highly electron-poor chiral diphosphanemetal complexes that are not well-known.

## **Results and Discussion**

The  $[RhCl(diphosphane)]_2$  complex is a catalyst precursor for the asymmetric 1,4-addition of **1a** to **2a**. In this reaction, the complex is usually generated in situ from  $[RhCl(C_2H_4)_2]_2$  and diphosphane, <sup>[3f,5]</sup> followed by the conversion to  $[RhOH(diphosphane)]_2$  as the active (or resting)<sup>[6]</sup> species with base and  $H_2O$ . If the  $[RhCl{(R)-3}]_2$  complex can be stored as a pre-catalyst and used directly for the catalysis, handling in the experiment will be facilitated. Therefore, we checked the air stability of the  $[RhCl{(R)-3}]_2$  complex. Unfortunately,  $[RhCl{(R)-3}]_2$  was very air-sensitive and decomposed readily even after careful weighing. When the solid state of  $[RhCl{(R)-3}]_2$  was allowed to stand in the air for  $2 \min$ , diphosphane dioxide (R)-5 was observed by <sup>31</sup>P NMR in toluene- $d_8$  (Figure 2). The dioxide (R)-5 would be generated via oxidation of Rh.<sup>[7]</sup> This result is unexpected because electronpoor (R)-3 and its ligated metal should be resistant to air oxidation. Interestingly,  $[RhCl{(R)-BINAP}]_2$  is air stable, although (R)-BINAP is a more electron-donating diphosphane than (R)-3. When these crystal structures<sup>[3f,7]</sup> were compared, the difference was confirmed in the Rh…Rh distance [Figure 3; 3.511 Å for Rh/(R)-3 vs. 3.287 Å for Rh/(R)-BINAP]. The elongation of Rh…Rh in  $[RhCl{(R)-3}]_2$  results from the weak interaction between filled  $d_z^2$  and empty p orbitals in the two Rh atoms, because the interaction is unfavorable for the less  $\sigma$ -donating (R)-3 (Figure 3).<sup>[9]</sup> This weak interaction between Rh atoms suggests that the filled  $d_{z}^{2}$  orbital of Rh did not achieve stabilization by interaction with the empty p orbital of the other Rh; in other words, the orbital energy of  $d_z^2$  is maintained at a high level. Therefore,  $[RhCl{(R)-3}]_2$ would be susceptible to oxidation with  $O_2$  in the air. Because  $[RhCl{(R)-3}]_2$  cannot be weighed in air, it is difficult to use the complex as a storble precatalyst. The active species of  $[Rh(OH)\{(R)-3\}]_2$  are also unstable in air. Therefore, the rhodium species are required to be prepared in situ in our catalytic system.







(b) In the case of [RhCl{(R)-binap}],



**Figure 3.** Comparison of oxidative resistance between  $[RhCl\{(R)-3\}]_2$  and  $[RhCl\{(R)-binap\}]_2$ .

Next, we investigated the thermal stability of the Rh complex bearing (R)-3. Although catalytic activity is generally improved by increasing the reaction temperature, thermal decomposition of the catalyst into metal and ligand sometimes occurs, especially in the case of a less electron-donating ligand. For example, the 1,5-cyclooctadiene (COD) ligand in the achiral [RhCl(COD)]<sub>2</sub> complex is dissociated at temperatures higher than 90 °C.<sup>[9]</sup> Therefore, an additional 45,000fold amount of COD ligand was required for rhodium to achieve high turnover numbers (TON = 375,000) in the 1,4-addition of *p*-tolylboronic acid to **2a** at 100°C for 36 h catalyzed by  $[RhCl(COD)]_2$  with NaHCO<sub>3</sub>.<sup>[9]</sup> Such thermal decomposition of the catalyst and corresponding addition of a large quantity of ligand represent a great disadvantage for asymmetric catalysis because the decomposed achiral metal catalyst may reduce the enantioselectivity of the reaction product. Also, a large quantity of the expensive chiral ligand is required. In the case of Rh/(R)-3 catalyst, a lack of the thermal stability is suspected because the electron-poor (R)-3 has a weak  $\sigma$ -donating ability, showing a relatively weak Rh-P bond in BINAP-like diphosphanes.<sup>[10]</sup> Therefore, we confirmed the thermal stability of the active species of  $[Rh(OH)\{(R)-3\}]_2$  complex. The complex was allowed to stir in toluened<sub>8</sub> solution at 100 °C for 12 h. Although an ultra-low volume of black precipitate was generated, only the [Rh(OH){(R)-3}]<sub>2</sub> ( $\delta$ =56.6) signal was observed by <sup>31</sup>P NMR. Hence, the [Rh(OH){(R)-3}]<sub>2</sub> catalyst was found to have a thermal stability up to 100 °C in toluene. Furthermore, the Rh–P bond possibly does not show weakening at such high temperatures because the coupling constant remained at  $J_{\text{Rh,P}}$ =186 Hz at temperatures between 20 and 100 °C. Although the thermal stability of the other labile species in the catalysis could not be ascertained, improvement in the catalytic activity may be possible by increasing the reaction temperature without the addition of a large amount of (R)-3.

Following the successful investigation of the stability of Rh complexes bearing (R)-3, optimization of the reaction conditions for the asymmetric 1,4-addition of 1a to 2a was performed. Previously, the reaction catalyzed by Rh/(R)-3 was found to be accelerated by changing the solvent from 1,4-dioxane to toluene.[3f] Therefore, we first investigated the solvent effect. The Rh-catalyzed asymmetric 1,4-addition to 2a was optimized by using 1.0 equivalent of 1a, without purification, in the presence of 0.05 mol%  $[RhCl(C_2H_4)_2]_2$ with 0.1 mol% (R)-3 (3/Rh = 1.0) and 40% KOH in solvent/H<sub>2</sub>O at 30°C for 30 min. Although several solvents containing 1,4-dioxane were used for the catalytic reaction, a solvent system exceeding the performance of toluene<sup>[3c]</sup> was not found (Table 1). The solvent effect did not affect the enantioselectivities of (R)-4aa.

Next, we optimized the added base (Table 2), which mainly plays a role in the transformation of [RhCl-(ligand)]<sub>2</sub> into [Rh(OH)(ligand)]<sub>2</sub>.<sup>[5]</sup> The addition of 10 or 40 mol% KOH to the reaction of **1a** and **2a** in the presence of 0.05 mol% Rh/(R)-**3** catalyst at 30 °C for 30 min gave 79% (R)-**4aa** with over 99.5% *ee* (en-

Table 1. Solvent effect of asymmetric 1,4-addition.

	[F (0.1	RhCl(C <sub>2</sub> H <sub>4</sub> ) <sub>2</sub> ] <sub>2</sub> /( <i>R</i> )- <b>3</b> mol% Rh, <b>3</b> /Rh = 1.0)	0 	
2a +	PnB(OH) <sub>2</sub>	base toluene/H <sub>2</sub> O 30 °C, 30 min		
Entry	Solvent	Yield [%]	% ee	
1	toluene	79	>99	
2	1,4-dioxane	24	>99	
3	hexane	18	99	
4	$CH_2Cl_2$	23	>99	
5	Et <sub>2</sub> O	15	>99	
6	THF	12	>99	
7	DMF	24	>99	
8	EtOH	5	99	

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0 + 2a		[RhCl(C₂H₄)₂]₂ (0.1 mol% Rh, <b>3</b>	$\overset{\circ}{\vdash}$	
	• PnB(OH) <sub>2</sub> ·	base toluene/H 30 °C, 30	<sub>2</sub> O min	,'Ph ( <i>R</i> )- <b>4aa</b>
Entry	Base	(mol%)	Yield [%]	% ee
1	none		20	98
2 <sup>[a]</sup>	none		78	>99
2	VOU	(10)	70	00

 Table 2. Study of additional base for asymmetric 1,4-addition.

Entry	Base	(mol%)	Yield [%]	% ee
1	none		20	98
$2^{[a]}$	none		78	>99
3	KOH	(10)	79	>99
4	KOH	(40)	79	>99
5	KOH	(70)	16	_
6	KOH	(100)	0	_
7	NaHCO <sub>3</sub>	(10)	80	>99
8	NaHCO <sub>3</sub>	(40)	86	>99
9 <sup>[a]</sup>	NaHCO <sub>3</sub>	(40)	86	>99
10	NaHCO <sub>3</sub>	(70)	82	>99
11	NaHCO <sub>3</sub>	(100)	82	>99
12	$Na_2CO_3$	(40)	76	>99
13	$K_2CO_3$	(40)	52	>99
14	K <sub>3</sub> PO <sub>4</sub>	(40)	32	>99
15	KO-t-Bu	(40)	36	99
16	KF	(40)	62	99
17	LiOH	(40)	30	99
18	$(i-Pr)_2NEt$	(40)	18	>99
19	Et <sub>3</sub> N	(40)	16	98
20 <sup>[a]</sup>	Et <sub>3</sub> N	(40)	20	99

<sup>[a]</sup>  $[Rh(OH){(R)-3}]_2$  was used instead of  $[RhCl(C_2H_4)]_2/(R)-3$ .

tries 3 and 4). However, when the amount of KOH was increased to 70 or 100 mol%, the yield of (R)-4aa decreased (16%, 0%) because of hydrolysis of 1a or the [Rh–Ph] species with KOH (entries 5 and 6).<sup>[9,11]</sup> The use of NaHCO<sub>3</sub> as a base gave (R)-4aa in yields of 80% and higher with >99% ee (entries 7-11, except for 9). In particular, addition of 40 mol% NaHCO<sub>3</sub> gave the best result (86%, entry 8). It is interesting to note that the decrease in the yield of (R)-4aa was not observed when using 100 mol% NaHCO<sub>3</sub>, suggesting that hydrolysis of **1a** or the [Rh-Ph] species under harsher conditions such as high reaction temperatures is avoidable with this base. It is clear that the role of the added base is to form  $[Rh(OH)\{(R)-3\}]_2$ , because the reaction without the base in the presence of  $[RhCl(C_2H_4)]_2/(R)$ -3 gave a poor yield (entry 1) and in the presence of  $[Rh(OH)\{(R)-3\}]_2$  afforded 78% yield of (R)-4aa (entry 2). The latter reaction was slightly improved by the addition of NaHCO<sub>3</sub> (entry 9), suggesting that the added base somewhat accelerated the transmetalation of **1a** to the Rh catalyst.<sup>[3f,9]</sup> The other bases, Na<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, K<sub>3</sub>PO<sub>4</sub>, KO-t-Bu, KF, LiOH, Et<sub>3</sub>N and (i-Pr)<sub>2</sub>NEt, were less effective relative to NaHCO<sub>3</sub> (entries 12-19). From the viewpoint of basicity, including KOH and NaHCO<sub>3</sub>, no tendency was observed. Interestingly, the yield of (R)-**4aa** in the presence of  $[Rh(OH)\{(R)$ -**3**}]\_2 with Et<sub>3</sub>N was similar to that achieved by using  $[RhCl\{(R)$ -**3**}]\_2/Et<sub>3</sub>N (entry 20 vs. 19), and the result also showed that the addition of Et<sub>3</sub>N dramatically decreased the catalytic activity of  $[Rh(OH)\{(R)$ -**3**}]\_2 (entry 20 vs. 2). These results suggest that Et<sub>3</sub>N deactivated the catalytic cycle rather than inhibited the formation of  $[Rh(OH)\{(R)$ -**3**}]\_2. From the results of these experiments, we chose 40 mol% of NaHCO<sub>3</sub> as the additional base for further studies.

We studied the asymmetric 1,4-addition of 1a to 2a in the presence of Rh/(R)-3 catalyst under the optimized conditions (toluene solvent with 40 mol% aqueous NaHCO<sub>3</sub>) to decrease the catalyst loading (Table 3). The asymmetric 1,4-addition of 1a to 2a in the presence of 0.02 mol% Rh catalyst, prepared from 0.01 mol% [RhCl( $C_2H_4$ )<sub>2</sub>]<sub>2</sub> and 0.02 mol% (*R*)-3, gave a 41% yield of product (R)-4aa with >99% ee, indicating that the TOF is  $2,100 \text{ h}^{-1}$  (entry 1). Under similar conditions, the reaction using Rh/(R)-BINAP or Rh/(R)-MeO-BIPHEP catalyst did not proceed (entries 2 and 3).<sup>[3f]</sup> Additionally, the use of presynthesized  $[RhOH\{(R)-BINAP\}]_2$  did not yield a product under these conditions (entry 4). The reason for the very high catalytic activity of Rh/(R)-3 is the achievement of optimized reaction conditions for this catalyst and its acceleration of the transmetalation and insertion steps of the asymmetric 1,4-addition by the electronic effect of (R)-**3**.<sup>[3f,12,13]</sup> By increasing the temperature to 50°C and using the same quantity of Rh/ (R)-3, the yield was improved to 92% (TOF =  $4,600 h^{-1}$ ) without any loss of enantioselectivity (entry 5). The reaction at 80°C could reduce the catalyst loading to 0.005% Rh/(*R*)-3. Although only a stoichiometric amount of 1a was used at 80°C, (R)-4aa was obtained in 90% yield with 99% ee and a TOF value of  $18,000 \text{ h}^{-1}$  (entry 6). Increasing the reaction temperature to 100 °C could reduce the catalyst loading down to 0.0025% Rh/(R)-3. Under these conditions, a slight excess of PhB(OH)<sub>2</sub> was required to provide a high yield of (R)-4aa. The product was obtained in 96% yield with a TOF of  $38,000 \text{ h}^{-1}$ (entry 7).<sup>[14]</sup> When Rh/(R)-3 catalyst was reduced to 0.001%, the TOF value further increased up to 53,000  $h^{-1}$  with 98% *ee* (entry 8). To the best of our knowledge, the highest TOF value was established in the catalytic asymmetric carbon-carbon bond forming reactions.<sup>[3d,e,15]</sup> As a result, although boronic acid **1a** was used, the amount of Rh/(R)-3 catalyst could be reduced below 0.01 mol%, raising its high catalytic activity up to a TOF of  $53,000 \text{ h}^{-1}$  in the asymmetric 1.4-addition by increasing the reaction temperature. The TOF values in the case of other substrates were estimated. An electron-donating or electron-withdrawing functional group on the phenylboronic acid

Table 3. Low catalyst loading and high TOF of Rh/(R)-3 catalyst for asymmetric 1,4-addition of 1 to 2.





Entry	Rh [%]	2	<b>1</b> [equiv.]	Temperature [°C]	Yield [%]	TOF $[h^{-1}]$	% ее
1	0.02	2a	<b>1a</b> [1.0]	30	41	2,100	>99
2 <sup>[a]</sup>	0.02	2a	<b>1a</b> [1.0]	30	0	_	_
3 <sup>[b]</sup>	0.02	2a	<b>1a</b> [1.0]	30	0	_	-
4 <sup>[c]</sup>	0.02	2a	<b>1a</b> [1.0]	30	0	_	_
5	0.02	2a	<b>1a</b> [1.0]	50	92	4,600	99
6	0.005	2a	<b>1a</b> [1.0]	80	90	18,000	99
7	0.0025	2a	<b>1a</b> [1.3]	100	96	38,000	98
8	0.001	2a	<b>1a</b> [1.3]	100	53	53.000	98
9	0.0025	2a	<b>1b</b> [1.3]	100	79	32,000	97
10	0.0025	2a	<b>1c</b> [1.3]	100	55	22,000	98
11	0.0025	2a	<b>1d</b> [1.3]	100	54	22.000	96
12	0.005	2b	<b>1a</b> [1.3]	100	52	10,000	95

[a]  $[RhCl(C_2H_4)_2]_2/(R)$ -MeO-BIPHEP was used.

[b]  $[RhCl(C_2H_4)_2]_2/(R)$ -BINAP was used.

[c]  $[RhOH\{(R)-BINAP\}]_2$  was used.

(1b-1d) slightly diminished the catalytic activity of Rh/(R)-3 (entries 9–11). Although Rh/(R)-3 show relatively low catalytic activity in the case of straightchain  $\alpha,\beta$ -unsaturated ketone **2b** (entry 12), the TOF value exceeded 10,000  $h^{-1}$ .

The catalytic system was applicable to a larger scale of asymmetric 1,4-addition in the presence of a small quantity of Rh/(R)-3 catalyst (Scheme 2). A mixture of 19.4 mL (0.2 mol) 2a and 36.6 g (1.5 equiv.) 1a in the presence of 0.00025% Rh/(R)-3  $[97 \ \mu g \quad (0.25 \ \mu mol) \quad [RhCl(C_2H_4)_2]_2 \quad and \quad 400 \ \mu g$  $(0.50 \,\mu\text{mol}) (R)$ -3 catalyst in toluene with 40% aqueous NaHCO<sub>3</sub> was stirred at 100°C for 24 h to give



Scheme 2. Asymmetric 1,4-addition of 1a to 2a on a gramscale.

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27.9 g (R)-4aa (80%) with 98% ee. The TON reached 320.000.

In the asymmetric 1,4-addition, our catalyst achieved both high activity and high enantioselectivity. Performing the reaction at several temperatures



Figure 4. Eyring plot's of the reaction of 2a with 1a catalyzed by Rh/(R)-3.



Figure 5. DFT calculations at insertion step.

enabled us to evaluate kinetic parameters in the transition state. Figure 4 shows the Eyring plots<sup>[16]</sup> of ln- $(k_{\rm R}/k_{\rm S})$ , whose enantioselectivities were average values of three times experiments, as a function of 1/ T for the Rh/(R)-3-catalyzed asymmetric 1,4-addition of 1a to 2a. The Eyring plots show a straight line with a high correlation coefficient ( $r^2 > 0.99$ ), indicating that the decreasing % ee of (R)-4aa is followed by the theory of kinetics. Therefore, the slight decrease in % ee of (R)-4aa with increasing reaction temperature is not attributed to decomposition of the catalyst. The kinetic parameters  $\Delta\Delta H^{\neq}$  (-4.0±0.1 kcalmol<sup>-1</sup>) and  $\Delta\Delta S^{\neq}$  (-1.3±0.3 calmol<sup>-1</sup>K<sup>-1</sup>) were obtained from the Eyring plots. The entropy contribution is relatively small because  $T\Delta\Delta S^{\neq}$  at 373 K is calculated to be  $-0.47 \text{ kcal mol}^{-1}$ ,<sup>[17]</sup> suggesting that the electronpoor (R)-3 ligand coordinates relatively more tightly to the Rh and creates a rigid chiral environment around the Rh, as explained above. The asymmetric introduction occurs in the insertion of 2a to the (R)-3-Rh-Ph complex. We calculated the insertion step, including the transition states, by DFT calculations (Figure 5).<sup>[18,19]</sup> The favorable transition state, which gave (R)-enantiomer of **4aa**, was more stable by 1.9 kcalmol<sup>-1</sup> than the unfavorable one, which gave the (S)-enantiomer of 4aa (Figure 6). Although the relative energy is estimated incompletely as compared to the experimental  $\Delta\Delta H^{\neq}$  value (-4.0 kcal mol<sup>-1</sup>), the difference in their characters becomes very apparent. In the favorable transition state, 2a coordinated to an open space at the lower part of the vacant coordination site in Figure 6a, as expected from the preceding paper.<sup>[11]</sup> In contrast, the steric repulsion arises from the aromatic rings on phosphorous and 2a coordinated to the upper part being blocked in the unfavorable transition state (Figure 6b). Although the electron-poor (R)-3 has lower  $\sigma$ -donating ability for a metal catalyst, this chiral environment in the transia) Favorable transition state (B)



b) Unfavorable transition state (B)



Figure 6. Transition state in insertion step.

tion state was sustained even under high-temperature conditions.

## Conclusions

In conclusion, we have developed a highly active and enantioselective Rh-catalyzed asymmetric 1,4-addition of phenylboronic acid to cyclohexenone using the electron-poor MeO-F<sub>12</sub>-BIPHEP. Because of its pronounced catalytic activity, the Rh/(R)-**3** catalyst is suitable for practical use as a catalyst for asymmetric 1,4-additions. In fact, we have already reported the efficient reaction of a less reactive coumarin substrate using Rh/(R)-**3** catalyst.<sup>[20]</sup> In the near future, we would like to synthesize a biologically active agent using Rh/(R)-**3** catalyst.

We also studied the properties of the electron-poor diphosphane-ligated Rh complex. We found that the chiral electron-poor diphosphane acts effectively even at high temperatures and promises to exceed the use of other related asymmetric catalysts.

## **Experimental Section**

#### **General Experimental Methods**

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Solvents, which were purchased as dehydrated solvents grade commercial products from Kanto Chemical Co., Inc., were stored in Schlenk tubes under an argon atmosphere after argon bubbling. µ-Dichlorotetraethylenedirhodium(I) was purchased from Sigma-Aldrich® and was used without purification. 2-Cyclohexenone was purchased from Sigma-Aldrich® and was stored under argon atmosphere after a degassing operation. Phenylboronic acid was purchased from Tokyo Chemical Industry Co., Ltd. and was used without purification. Other reagents were purchased at the highest commercial quality and used without further purification, unless otherwise noted. Preparative column chromatography was carried out by using silica gel (Fuji Silysia BW-127 ZH, 100-270 mesh). <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were measured at 300 MHz or 500 MHz and 75 MHz or 125 MHz or 150 MHz, respectively, and chemical shifts are given relative to tetramethylsilane (TMS). <sup>19</sup>F NMR spectra were measured at 282 or 376 Hz MHz, and chemical shifts are given relative to CCl<sub>3</sub>F using C<sub>6</sub>F<sub>6</sub> as a secondary reference (-162.9 ppm). <sup>31</sup>P NMR spectra were measured at 121 MHz, and chemical shifts are given relative to 85%  $H_3PO_4$  as an external standard.

#### Synthesis of [RhCl{(*R*)-3}]<sub>2</sub>

A 20-mL Schlenk flask was flushed with argon and charged with (*R*)-**3** (9.6 mg, 12 µmol), µ-dichlorotetraethylenedirhodium(I) (2.3 mg, 6.0 µmol), and 0.50 mL of deoxygenated dichloromethane. The mixture was stirred at room temperature for 5 min. Removal of the solvent under vacuum gave [RhCl{(*R*)-**3**]]<sub>2</sub> as a red solid: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$ =3.52 (s, 12 H), 6.52–6.58 (m, 8 H), 7.04–7.61 (m, 20 H); <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):  $\delta$ =-157.8 to -157.7 (m, 4F), -157.3 to -157.1 (m, 4F), -134.6 to -134.5 (m, 8F), -134.3 (br s, 8F); <sup>31</sup>P NMR (121 MHz, CDCl<sub>3</sub>):  $\delta$ =50.0 (d, <sup>1</sup>J<sub>Rh,P</sub>=196 Hz).

#### Synthesis of [RhOH{(R)-3}]<sub>2</sub>

A 20-mL Schlenk flask was flushed with argon and charged with (*R*)-3 (4.1 mg, 5.1  $\mu$ mol),  $\mu$ -dichlorotetraethylenedirhodium(I) (1.0 mg, 2.5 µmol), KOH (0.9 mg) and 1.0 mL of deoxygenated dioxane with 0.5 mL of water. The mixture was stirred at room temperature for 10 min. After removal of the solvent under vacuum, the resulting orange solid was dissolved in toluene, and then the solution was filtered through Celite<sup>®</sup> to give a yellowish-orange solution. Removal of the solvent under vacuum gave  $[RhOH\{(R)-3\}]_2$  as an orange solid: <sup>1</sup>H NMR (300 MHz, toluene- $d_8$ ):  $\delta = -2.84$  (s, 2H), 3.01 (s, 12H), 5.94 (d, J=7.85 Hz, 4H), 6.29-6.35 (m, 4H), 6.56 (t, J=7.85 Hz, 4H), 7.28-7.36 (m, 8H), 7.78 (br, 8H); <sup>19</sup>F NMR (282 MHz, toluene- $d_8$ ):  $\delta = -157.6$  to -157.4(m, 4F), -156.7 to -156.5 (m, 4F), -134.5 (br s, 8F), -132.4 to -132.3 (m, 8F); <sup>31</sup>P NMR (121 MHz, toluene- $d_8$ ):  $\delta = 56.6 \text{ (d, } {}^{1}J_{\text{Rh,P}} = 186 \text{ Hz}).$ 

#### **General Procedure of Asymmetric 1,4-Addition**

A 20-mL Schlenk flask was flushed with argon and charged with (R)-MeO-F<sub>12</sub>-BIPHEP (3) (400 μg, 0.501 μmol), μ-dichlorotetraethylenedirhodium(I) (97 µg, 0.25 µmol; 0.001% Rh for 2a) and 0.1 mL of deoxygenated toluene. The mixture was stirred at room temperature for 5 min, and then the solvent was removed under vacuum. To the Schlenk flask were added sodium hydrogen carbonate (1.68 g, 20.0 mmol), phenylboronic acid (1a) (7.93 g, 65.0 mmol), 2cyclohexen-1-one (2a) (4.8 mL, 50 mmol), 7.5 mL of deoxygenated toluene, and 5.0 mL of deoxygenated water. The resulting mixture was then stirred at 100 °C for 1 h. To the solution was added saturated aqueous NaHCO3 solution. The resulting mixture was extracted with EtOAc (three times). The organic layer was dried over MgSO<sub>4</sub>, filtrated with suction, and then concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane/ EtOAc = 5/1) to give (R)-3-phenylcyclohexanone (4aa) as a colorless oil; yield: 4.57 g (53%); 98% ee;  $TOF = 53,000 h^{-1}$ . <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 1.74 - 1.92$  (m, 2H), 2.07-2.19 (m, 2H), 2.32-2.63 (m, 4H), 2.96-3.06 (m, 1H), 7.20-7.25 (m, 3H), 7.31–7.36 (m, 2H); <sup>13</sup>C NMR (75 MHz,  $CDCl_3$ ):  $\delta = 25.4$ , 32.7, 41.1, 44.6, 48.8, 126.4, 126.6, 128.6, 144.2, 211.0; IR (neat): v = 3061, 3028, 2937, 2866, 1713, 1603, 1497, 1452, 1421, 1344, 1315, 1250, 1223, 1030, 756, 700, and 538 cm<sup>-1</sup>;  $[\alpha]_D^{23.5}$ : +19.9° (*c* 1.0, CHCl<sub>3</sub>); HPLC (Daicel Chiralcel OD-H, hexane/i-PrOH = 100/1, flow rate =  $0.7 \text{ mLmin}^{-1}$ ):  $t_{\rm R}$  of (S)-4aa; 20.0 min (0.86%),  $t_{\rm R}$  of (R)-4aa; 21.3 min (99.14%).

#### Asymmetric 1,4-Addition for TON Experiment

A 20-mL Schlenk flask was flushed with argon and charged with (R)-MeO-F<sub>12</sub>-BIPHEP (3) (400  $\mu$ g, 0.501  $\mu$ mol),  $\mu$ -dichlorotetraethylenedirhodium(I) (97 μg, 0.25 µmol; 0.00025% Rh for 2a) and 0.1 mL of deoxygenated toluene. The mixture was stirred at room temperature for 5 min, and then the solvent was removed under vacuum. To the Schlenk flask were added sodium hydrogen carbonate (6.72 g, 80.0 mmol), phenylboronic acid (1a) (36.6 g, 300 mmol), 2-cyclohexen-1-one (2a) (19.4 mL, 200 mmol), 30 mL of deoxygenated toluene, and 20 mL of deoxygenated water. The resulting mixture was then stirred at 100 °C for 24 h. To the solution was added saturated aqueous NaHCO<sub>3</sub> solution. The resulting mixture was extracted with EtOAc (three times). The organic layer was dried over MgSO<sub>4</sub>, filtrated with suction, and then concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5/1) to give (R)-4aa as a colorless oil; yield: 27.9 g (80%); 98% ee; TON = 320,000 h<sup>-1</sup>.

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