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High Performance of a Chiral Diene–Rhodium Catalyst for the Asymmetric 1,4-Addition of Arylboroxines to α,β-Unsaturated Ketones

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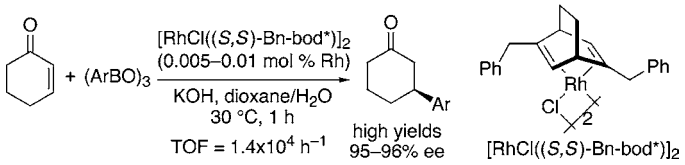
ABSTRACT



A rhodium complex coordinated with (*S*,*S*)-2,5-dibenzylbicyclo[2.2.2]octa-2,5-diene (Bn-bod*) showed high catalytic activity and high enantioselectivity in the asymmetric 1,4-addition of arylboroxines to cyclic α,β-unsaturated ketones, 0.005–0.01 mol % of the catalyst giving high yields of the addition products with not lower than 94% ee. The turnover frequency of the catalyst is up to 1.4×10^4 h^{-1}.

The recent development of chiral diene ligands opened new research fields in transition-metal-catalyzed asymmetric reactions.[1−3] They have been demonstrated to be highly effective ligands, especially in rhodium-catalyzed aryl-transfer reactions. Their rhodium complexes have displayed higher catalytic activity and/or higher enantioselectivity than the chiral phosphine−rhodium complexes in asymmetric 1,4-addition of arylboronic acids to electron-deficient olefins and the related asymmetric carbon−carbon bond-forming reactions.[1,2] Here, we report the results obtained for our studies inquiring into the decrease of catalyst loading of the chiral diene−rhodium complex for the asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated ketones.[4,5] Although high turnover frequency (TOF) has been reported in the catalytic asymmetric hydrogenation,[6] the decrease of the catalyst amount is still challenging in other catalytic asymmetric reactions.[7,8]

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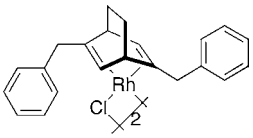
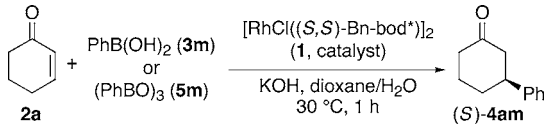


[RhCl((*S*,*S*)-Bn-bod*)]$_2$ (**1**)

The catalytic activity of the rhodium complex [RhCl((*S*,*S*)-Bn-bod*)]$_2$ (**1**),[9] where (*S*,*S*)-Bn-bod* stands for (*S*,*S*)-2,5-dibenzylbicyclo[2.2.2]octa-2,5-diene,[1c,d] was examined for the asymmetric 1,4-addition of phenylboronic acid (**3m**) to 2-cyclohexenone (**2a**). In the first set of experiments (entries 1−4 in Table 1), the loading of catalyst **1** was decreased from 1.0 to 0.01 mol % for the reaction of enone **2a** (0.60 mmol) with boronic acid **3m** (1.2 mmol, 2 equiv to **2a**) in the presence of aqueous KOH (1.5 M, 0.20 mL, 0.30 mmol) in dioxane (1.8 mL) at 30 °C for 1 h. The phenylboronic acid (**3m**) used for the present experiments is the commercially available sample received from Tokyo Kasei Kogyo. While the reaction in the presence of 1.0 or 0.10 mol % of the catalyst **1** gave a quantitative yield of the 1,4-addition product **4am**, further decrease of the catalyst caused lower yields of **4am**. Thus, the yield was 79% in the presence of 0.05 mol % of catalyst **1** and no **4am** was produced with the catalyst loading of 0.01 mol %. The enantiomeric purity of **4am** was kept high (96% ee (*S*)) whenever it was obtained. In the second set of experiments (entries 5−7), the loading of catalyst **1** was kept constant (0.05 mol %) and the effects of the amount of boronic acid **3m** were studied. To our surprise, the use of a larger amount of the boronic acid resulted in a lower yield of the product. The reaction with 3.0 and 5.0 equiv of the boronic acid gave **4am** in 37% and 0% yield, respectively. Consistent with this tendency, the yield was higher (95%) with a smaller amount of boronic acid (1.2 equiv). In the case of low yields, the starting enone **2a** was recovered in the corresponding amounts. These rather unusual results may suggest that the phenylboronic acid used here contains a small amount of a contaminant which deactivates the catalyst.

Table 1. Rhodium-Catalyzed Asymmetric 1,4-Addition of Phenylboronic Acid (**3m**)[a] or Phenylboroxine (**5m**)[b] to 2-Cyclohexenone (**2a**) Catalyzed by [RhCl((*S*,*S*)-Bn-bod*)]$_2$ (**1**)[c]



2a (*S*)-**4am**

entry	**3m** or **5m** (equiv B to **2a**)	catalyst **1** (mol % Rh)	yield (%) of **4am**[d]	% ee[e]
1	$PhB(OH)_2$ (2.0)	1.0	100	96 (*S*)
2	$PhB(OH)_2$ (2.0)	0.10	100	96 (*S*)
3	$PhB(OH)_2$ (2.0)	0.05	[79]	96 (*S*)
4	$PhB(OH)_2$ (2.0)	0.01	[0]	
5	$PhB(OH)_2$ (3.0)	0.05	[37]	96 (*S*)
6	$PhB(OH)_2$ (5.0)	0.05	[0]	
7	$PhB(OH)_2$ (1.2)	0.05	95	96 (*S*)
8[f]	$(PhBO)_3$ (1.2)	0.01	96	96 (*S*)
9[f]	$(PhBO)_3$ (2.0)	0.01	100	96 (*S*)
10[g]	$(PhBO)_3$ (1.2)	0.005	71	96 (*S*)

[a] Commercially available boronic acid was used as received. [b] Prepared and purified by us (see text). [c] The reaction was carried out with enone **2a** (0.60 mmol) and aqueous KOH (1.5 M, 0.20 mL, 0.30 mmol) in dioxane (1.8 mL) at 30 °C for 1 h. [d] Isolated yield of **4am** by silica gel chromatography. The yields in brackets are those obtained by ^{1}H NMR with nitromethane as an internal standard. [e] Determined by HPLC analysis with a chiral stationary-phase column (Chiralcel OD-H). [f] Enone **2a** (3.0 mmol) and aqueous KOH (5 M, 0.30 mL, 1.5 mmol) in dioxane (3.0 mL). [g] The reaction of 1.73 g (18 mmol) of enone **2a**.

Attempts to remove the impurity by recrystallization of the boronic acid were not successful, no 1,4-addition product being obtained with the catalyst loading of 0.01 mol %. It was found that the use of phenylboroxine ($(PhBO)_3$, **5m**) in place of phenylboronic acid (**3m**) greatly improved the present catalytic reaction. The boroxine **5m**, which was obtained by dehydration of the commercially available boronic acid **3m** by azeotropic removal of water from its benzene solution and purified by washing the crude boroxine repeatedly with hexane,[10] gave high yields of the 1,4-addition product **4am** (96% ee) in the presence of 0.01 mol % of the catalyst **1** (entries 8 and 9). Under the same conditions (0.01 mol % of Rh catalyst), the 1,4-addition did not proceed at all with phosphorus ligands such as binap or phosphoramidites, demonstrating the high catalytic activity of the diene rhodium catalyst. A larger scale reaction is possible with 0.005 mol % of the catalyst, which gave 71% yield of **4am** in the reaction period of 1 h (entry 10), the turnover frequency (TOF) of the catalyst being calculated to be 1.4×10^4 h^{-1}. To the best of our knowledge, this TOF number is highest for the catalytic asymmetric carbon−carbon bond-forming reactions[8] including asymmetric 1,4-addition reactions.[11,12]

Arylboroxine and water are known to be in a fast equilibrium with arylboronic acid,[13] and hence, the reaction

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(8) For reports describing high TOF: (a) Long, J.; Hu, J.; Shen, X.; Ji, B.; Ding, K. *J. Am. Chem. Soc.* **2002**, *124*, 10 (TOF = 1.0×10^2 h^{-1}). (b) Yoshida, T.; Morimoto, H.; Kumagai, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3470 (TOF = 2.4×10^2 h^{-1}). (c) Kina, A.; Shimada, T.; Hayashi, T. *Adv. Synth. Catal.* **2004**, *346*, 1169 (TOF = 3.5×10^2 h^{-1}). (d) Matsunaga, S.; Kinoshita, T.; Okada, S.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 7559 (TOF = 3.1×10^3 h^{-1}). (e) Davies, H. M. L.; Venkataramani, C. *Org. Lett.* **2003**, *5*, 1403 (TOF = 3.8×10^3 h^{-1})

(9) The rhodium complex was obtained by treatment of (*S*, *S*)-Bn-bod* with $[RhCl(C_2H_4)_2]_2$ in chloroform. ^{1}H NMR ($CDCl_3$): δ 0.24 (m, 4H), 0.52 (m, 4H), 2.76 (d, J = 14.1 Hz, 4H), 3.52 (br, 4H), 3.54 (d, J = 14.0 Hz, 4H), 4.03 (d, J = 5.4 Hz, 4H), 7.21 (t, J = 7.3 Hz, 4H), 7.29 (t, J = 7.4 Hz, 8H), 7.35 (d, J = 7.4 Hz, 8H).

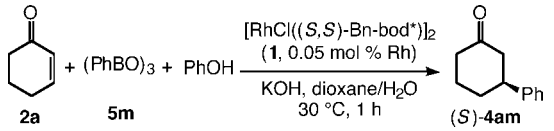
(10) Washing the solid boroxine with hexane is essential for the required high purity.

(11) Examples of low catalyst loadings in rhodium-catalyzed asymmetric 1,4-addition: (a) Amengual, R.; Michelet, V.; Genêt, J.-P. *Synlett.* **2002**, 1791. (b) Takaya, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron Lett.* **1999**, *40*, 6957. (c) Reetz, M. T.; Moulin, D.; Gosberg, A. *Org. Lett.* **2001**, *3*, 4083.

(12) In the nonasymmetric 1,4-addition of an arylboronic acid, high TOF (up to 1.0×10^4 h^{-1}) of $[Rh(OH)(cod)]_2$ as a catalyst has been reported: Itooka, R.; Iguchi, Y.; Miyaura, N. *J. Org. Chem.* **2003**, *68*, 6000.

(13) Tokunaga, Y.; Ueno, H.; Shimomura, Y.; Seo, T. *Heterocycles* **2002**, *57*, 787.

Table 2. Effects of Phenol on Rhodium-Catalyzed Asymmetric 1,4-Addition of Phenylboroxine (**5m**)[a] to 2-Cyclohexenone (**2a**) Catalyzed by Rh/(*S*,*S*)-Bn-bod* Complex **1** or **6**[b]



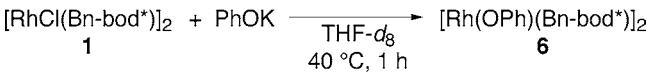
entry	phenol (equiv to Rh)	catalyst (0.05 mol % Rh)	yield (%) of **4am**[c]	% ee[d]
1	0	1	95	96 (*S*)
2	2.0	1	[56]	96 (*S*)
3	3.0	1	[24]	92 (*S*)
4	5.0	1	[0]	
5	0	6	[11]	94 (*S*)

[a] Prepared and purified by us (see text). [b] The reaction was carried out with enone (**2a**, 0.60 mmol), phenylboroxine (**5m**, 1.2 equiv B to **2a**), aqueous KOH (1.5 M, 0.20 mL, 0.30 mmol), and **1** or **6** (0.05 mol % Rh) in dioxane (1.8 mL) at 30 °C for 1 h. [c] Isolated yield of **4am** by silica gel chromatography. The yields in brackets are those obtained by ^{1}H NMR with nitromethane as an internal standard. [d] Determined by HPLC analysis with a chiral stationary-phase column (Chiralcel OD-H).

starting from phenylboronic acid and that starting from arylboroxine in water should result in the same outcome. The much higher yield observed here with phenylboroxine **5m** than with boronic acid **3m** indicates that the impurity present in the boronic acid was removed during the preparation and purification of the boroxine. ^{1}H NMR analysis of the commercially available phenylboronic acid revealed that it contains 0.05 ± 0.02 mol % of phenol, and it was supposed that the phenol is the impurity that deactivates the rhodium catalyst. To verify the deactivation caused by phenol, control experiments were carried out by addition of phenol to the reaction system consisting of 2-cyclohexenone (**2a**), phenylboroxine (**5m**), and [RhCl((*S*,*S*)-Bn-bod*)]$_2$ (**1**, 0.05 mol % Rh), which otherwise gives a high yield of the 1,4-addition product **4am** (entry 1 in Table 2). As more phenol was added, the yield of **4am** was decreased. Thus, the addition of 2.0 and 3.0 equiv (to Rh) of phenol gave **4am** in 56% and 24% yield, respectively (entries 2 and 3), and the reaction was completely suppressed by the addition of 5.0 equiv of phenol (entry 4). These results are in very good agreement with those observed in the reaction using phenylboronic acid (**3m**) in the presence of 0.05 mol % (Rh) of the catalyst (entries 3, 5, and 6 in Table 1), where the boronic acid contains 0.05 ± 0.02 mol % of phenol.

On addition of 1 equiv of KOPh to [RhCl((*S*,*S*)-Bn-bod*)]$_2$ (**1**) at 40 °C in THF-d_8, we observed (^{1}H NMR) exclusive formation of a new rhodium species which is assigned to be phenoxy complex [Rh(OPh)((*S*,*S*)-Bn-bod*)]$_2$ (**6**)[14] (Scheme 1). The use of phenoxy complex **6** as a catalyst (0.05 mol % of Rh) for the reaction of **2a** with boroxine **5m** gave 11% yield of the 1,4-addition product **4am** (entry 5 in Table 2).

Scheme 1

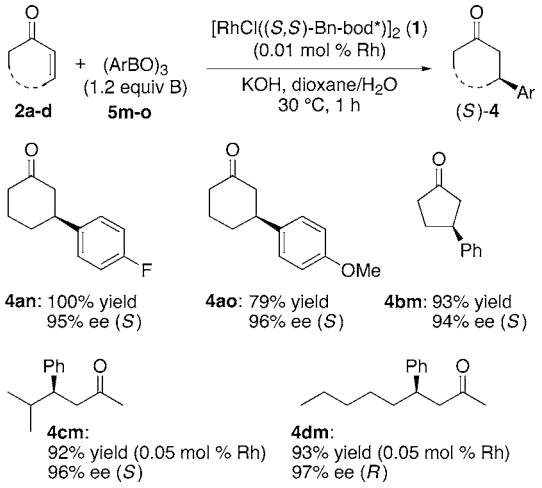


Although the 1,4-addition was not completely suppressed, we suppose that the formation of phenoxy complex **6** is responsible for the deactivation of the catalyst.

Considering that the phenoxy complex **6** is likely to undergo the ligand exchange under the reaction conditions with H_2O (or OH^-) giving [Rh(OH)((*S*,*S*)-Bn-bod*)]$_2$, which is assumed to be a catalytically active species,[15] the low yield (11%) does not contradict our supposition that the phenoxy complex is not catalytically active for the 1,4-addition.

As shown in Scheme 2, the addition of phenylboroxine

Scheme 2



(**5m**) to 2-cyclopentenone (**2b**) was also efficiently catalyzed by 0.01 mol % of the Rh/(*S*,*S*)-Bn-bod* catalyst to give 93% yield of (*S*)-3-phenylcyclopentanone (**4bm**) with 94% enantioselectivity. Arylboroxines substituted with 4-fluoro and 4-methoxy groups, which were prepared and purified in a manner similar to **5m**, were successfully applied to the asymmetric addition to 2-cyclohexenone as well. The corresponding 1,4-addition products **4an** and **4ao** were obtained in high yields with high enantioselectivity. Linear enones were less reactive than cyclic ones, but 0.05 mol % of the chiral diene−rhodium complex **1** efficiently catalyzed the asymmetric addition of boroxine **5m** to 5-methyl-3-hexen-2-one (**2c**) and 3-nonen-2-one (**2d**).[16]

In summary, the rhodium complex coordinated with chiral diene ligand (*S*,*S*)-Bn-bod* showed its high performance as a catalyst in the asymmetric 1,4-addition of arylboroxines

(14) ^{1}H NMR (THF-d_8): δ 0.26 (m, 4H), 0.37 (m, 4H), 1.76 (d, J = 13.8 Hz, 4H), 2.78 (d, J = 6.1 Hz, 4H), 2.98 (d, J = 14.0 Hz, 4H), 3.90 (d, J = 5.6 Hz, 4H), 6.72 (t, J = 7.2 Hz, 2H), 7.09 (d, J = 7.6 Hz, 4H), 7.15 (t, J = 7.6 Hz, 4H), 7.31 (t, J = 7.4 Hz, 4H), 7.41 (t, J = 7.6 Hz, 8H), 7.46 (d, J = 7.8 Hz, 8H).

(15) A hydroxorhodium complex, [Rh(OH)(binap)]$_2$, was reported to be an active catalyst for the asymmetric 1,4-addition (ref 5b).

(16) The use of 0.05 mol % of catalyst **1** for the addition of boroxine **5m** to α,β-unsaturated esters and amides failed probably due to their lower reactivity.

to α,β-unsaturated ketones. The catalyst loading of 0.005−0.01 mol % efficiently catalyzed the reaction without loss of enantioselectivity. The deactivation of catalyst caused by a small amount of phenol, which is found during this study, provides us with a significant information on the mechanism of rhodium-catalyzed 1,4-addition reactions.

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Supporting Information Available: Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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