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Highly Practical Catalytic Asymmetric 1,4-Addition of Arylboronic Acids in Water Using New Hydrophilic Chiral Bicyclo[3.3.0] Diene Ligands

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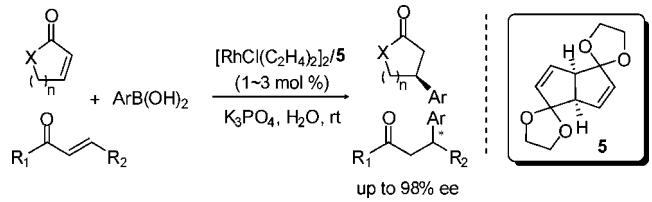
ABSTRACT



The first Rh−diene-catalyzed aqueous asymmetric 1,4-addition of α,β-unsaturated carbonyl compounds with arylboronic acids has been realized. By using a hydrophilic bicyclo[3.3.0] diene ligand, the reactions can be performed successfully in neat water at room temperature to afford the corresponding products in good yields and with very high enantioselectivities for both cyclic and linear substrates.

Organic reactions in aqueous media are currently receiving considerable attention in modern chemistry because of substantial environmental and economical advantages over conventional reactions in organic solvents.[1] Among them, catalytic asymmetric reactions that can be performed in water are of particular interest.[2] However, unlike the reactions in organic solvents, to achieve high stereoselectivity and yield by catalysis in water is usually difficult.[1h,i] Besides the solubility constraint reason, a major problem especially in asymmetric transition-metal catalysis is that water often disrupts the catalyst stability or decreases the catalyst activity and therefore influences the reaction stereoselectivity. In the field of transition-metal-catalyzed asymmetric carbon−carbon bond formation, rhodium-catalyzed 1,4-addition of organoboron reagents represents a powerful method.[3] In those reactions, water was used as cosolvent and found to be beneficial to the catalytic cycle. Although many attempts have been made to carry out catalysis in aqueous media,[4]

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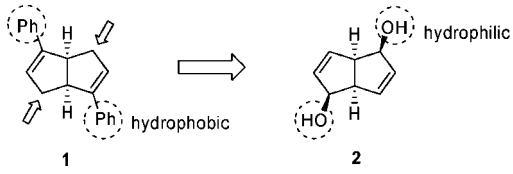
only one example of successful asymmetric addition in water is reported by using an amphiphilic resin-supported BINAP ligand at 100 °C.[5] In this paper, we disclose our development of a highly practical and efficient catalytic asymmetric 1,4-addition in water using an easily accessible new chiral diene ligand.[6,7]

In an earlier work, we reported our discovery of a new family of C_2-symmetric chiral diene ligands (represented by **1**) bearing a simple bicyclo[3.3.0] backbone and their successful application in the Rh-catalyzed enantioselective arylation of *N*-tosylarylimines with arylboronic acids.[8a] More recently, we described the use of these dienes in Rh-catalyzed asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated carbonyl compounds under mild conditions.[8b] Encouraged by this success, we envisioned exploring this bicyclo[3.3.0] system for further design of new chiral dienes with different catalytic properties. We hypothesized that incorporation of a hydrophilic group such as hydroxyl into the tetrahydropentalene framework may generate a hydrophilic or water-soluble chiral diene ligand, which should facilitate the related asymmetric catalysis in aqueous media (Scheme 1).

Scheme 1. New Hydrophilic Bicyclo[3.3.0] Diene Hypothesis



Synthesis of the designed 1,4-dihydroxy-substituted bicyclo[3.3.0] diene **2** was performed as depicted in Scheme 2. Following a literature procedure,[9] enantiomerically pure diketone (3a*R*,6a*R*)-**3**[10] was subjected to ketalization with ethylene glycol in refluxing toluene, followed by bromination with pyridinium tribromide in THF at −78 °C to give the dibromo diketal **4** in two simple steps. Treatment of **4** with NaOMe in DMSO afforded the elimination product **5**. Ketal removal and DIBAL-H reduction of the resulting carbonyls[11] provided the desired enantiopure diene (1*S*,3a*R*,4*S*,6a*R*)-**2** in good yield. Notably, intermediates (3a*R*,6a*R*)-**5** and **6** with a tetrahydropentalene framework may also be useful diene ligands for asymmetric catalysis.

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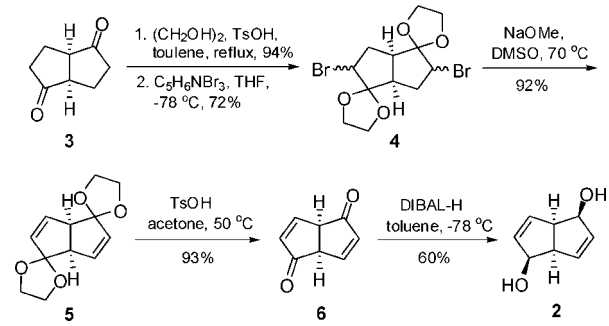
(7) For examples of Rh−diene catalysis in asymmetric 1,4-addition, see: (a) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, H. *J. Am. Chem. Soc.* **2003**, *125*, 11508. (b) Shintani, R.; Ueyama, K.; Yamada, I.; Hayashi, T. *Org. Lett.* **2004**, *6*, 3425. (c) Defieber, C.; Paquin, J.-F.; Serna, S.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 3873. (d) Paquin, J.-F.; Stephenson, C. R. J.; Defieber, C.; Carreira, E. M. *Org. Lett.* **2005**, *7*, 3821. (e) Shintani, R.; Okamoto, K.; Hayashi, T. *Org. Lett.* **2005**, *7*, 4757. (f) Paquin, J.-F.; Defieber, C.; Stephenson, C. R. J.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 10850. (g) Chen, F.-X.; Kina, A.; Hayashi, T. *Org. Lett.* **2006**, *8*, 341. (h) Helbig, S.; Sauer, S.; Cramer, N.; Laschat, S.; Baro, A.; Frey, W. *Adv. Synth. Catal.* **2007**, *349*, 2331. (i) Tokunaga, N.; Hayashi, T. *Adv. Synth. Catal.* **2007**, *349*, 513.

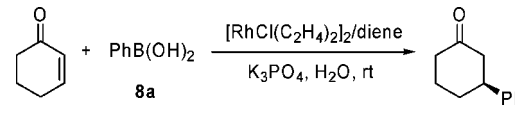
Scheme 2. Preparation of New Bicyclo[3.3.0] Dienes



To determine whether these dienes are hydrophilic or water soluble, we checked their solubilities in water. As expected, we found that diol diene **2** was highly soluble in water (>800 mg/mL). Interestingly, for dienes **5** and **6** that contain ketal and carbonyl groups, we also observed their solubilities in water of about 5 and 50 mg/mL, respectively. In comparison, the previously utilized diphenyl diene **1** is insoluble in water.[12]

To test our hypothesis of performing asymmetric catalysis in water, we examined these new C_2-symmetric bicyclo[3.3.0] dienes in the rhodium-catalyzed asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated carbonyl compounds. The reaction of 2-cyclohexenone (**7a**) with phenylboronic acid in water was first investigated, and the reslts are shown in Table 1. To our delight, aqueous catalysis

Table 1. Ligand Screening and Catalyst Loading[a]



entry	ligand	catalyst (mol %)	time (h)	yield[b] (%)	ee[c] (%)
1	**5**	3	0.5	96	93
2	**6**	3	0.5	62	86
3	**2**	3	0.5	94	89
4	**5**	1	6	94	93
5	**5**	0.5	12	81	93
6[d]	**5**	3	0.2	92	94
7	**1**	3	18	19	66

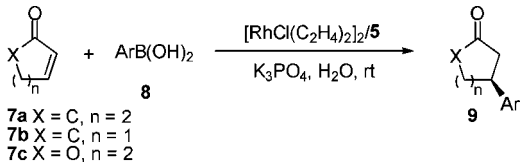
[a] The reaction was carried out with 2-cyclohexenone (0.50 mmol), phenylboronic acid (1.00 mmol), diene (1.1 equiv to Rh), and 1.5 M aq K_3PO_4 (0.17 mL) in H_2O (1.7 mL) at room temperature, unless otherwise noted. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Performed in dioxane/H_2O (10:1).

by 3 mol % of hydrophilic dienes **5**, **6**, and **2** were all successful, and the reactions went to completion within 0.5 h at room temperature without using any organic cosolvent, indicating that these dienes could act as efficient ligand and form highly active catalytic species in water. Most gratifyingly, the use of diketal diene **5** was found to be optimal,

giving the addition product **9aa** in 96% yield with 93% ee (entry 1). A slightly decreased enantiomeric excess of 89% was attained with initially designed water-soluble ligand **2** (entry 3). Taking advantage of the easy preparation of diene **5**, we decided to focus on this ligand for further studies. It is noted that water does not affect the catalyst activity and selectivity significantly (entries 1, 4, and 5). When the catalyst loading was reduced to 1 or even 0.5 mol %, the yield and enantioselectivity still remained high although a longer reaction time was required (entries 4 and 5). Moreover, the results of Rh/**5**-catalyzed reaction in water vs dioxane/H_2O (10/1) were essentially the same, suggesting no change in the efficiency of the metal catalyst in water; the reaction in dioxane/H_2O proceeded slightly faster than that in water (entry 1 vs 6). It should also be mentioned that water insoluble diene **1** gave poor results under the same conditions (entry 7).

With the optimal ligand **5**, we then evaluated its use in the aqueous rhodium-catalyzed 1,4-addition with cyclic α,β-unsaturated carbonyl compounds and arylboronic acids (Table 2). In all cases, the reactions proceeded smoothly at

Table 2. Asymmetric 1,4-Addition to Cyclic α,β-Unsaturated Carbonyl Compounds in Water[a]



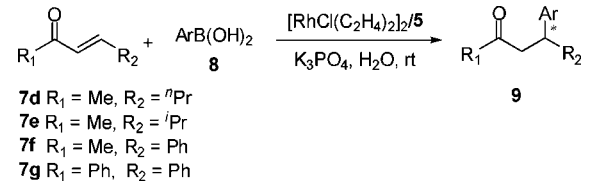
entry	7	Ar (8)	time (h)	yield[b] (%)	ee[c] (%)
1	**7a**	C_6H_5 (**8a**)	6	94	93
2	**7a**	4-BrC_6H_5 (**8b**)	4	90	95
3	**7a**	4-MeC_6H_5 (**8c**)	4	91	94
4	**7a**	4-$MeOC_6H_5$ (**8d**)	4	88	92
5	**7a**	4-$CF_3C_6H_5$ (**8e**)	4	88	95
6	**7a**	3-ClC_6H_5 (**8f**)	4	95	94
7	**7a**	3-MeC_6H_5 (**8g**)	4	94	94
8	**7a**	3-$MeOC_6H_5$ (**8h**)	8	82	93
9	**7a**	2-$MeOC_6H_5$ (**8i**)	4	93	69
10	**7a**	1-naphthyl (**8j**)	4	85	52
11[d]	**7b**	C_6H_5 (**8a**)	1.5	95	80
12[d]	**7b**	4-$CF_3C_6H_5$ (**8e**)	3	98	86
13[d]	**7c**	C_6H_5 (**8a**)	3	85	80
14[d]	**7c**	4-$CF_3C_6H_5$ (**8e**)	2	81	82

[a] The reaction was carried out with **7** (0.50 mmol), arylboronic acid (1.00 mmol), $[RhCl(C_2H_4)_2]_2$ (0.0025 mmol), dienes **5** (0.0055 mmol, 1.1 equiv to Rh), and 1.5 M aq K_3PO_4 (0.17 mL) in H_2O (1.7 mL) at room temperature. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Catalyst loading was increased to 3 mmol %.

room temperature in water to give the desired adducts in high yields. For 2-cyclohexenone (**7a**), high enantioselectivities (92−95% ee) were maintained when less hindered arylboronic acids were employed (entries 1−8). The electron-donating or -withdrawing groups on the phenyl ring of boronic acids did not seem to affect the reaction significantly. Very surprisingly, unlike the results found in our previous catalytic system using diene **1** in dioxane/H_2O,[8b] a dramatic drop of the selectivity was observed when sterically more hindered 2-methoxyphenylboronic acid or 1-naphthylboronic acid was used (entries 9−10). The Rh−diene **5** catalyst had also been examined in the asymmetric addition to other cyclic substrates such as 2-cyclopentenone (**7b**) and 5,6-dihydro-2-pyranone (**7c**), wherein a modest decrease of the selectivities were observed. Fortunately, the ees of the products remained at a good level (80−86%) (entries 11−14).

To explore the reaction scope further, we next investigated the aqueous addition to linear enones by the catalysis of Rh/**5**. Concerning the catalytic asymmetric addition to linear enones, there have been very limited examples known in the literature.[7] Previously, chiral diene ligand **1** was found to be ineffective toward α,β-unsaturated linear substrates.[8b] As summarized in Table 3, most of the reactions worked

Table 3. Asymmetric 1,4-Addition to Linear α,β-Unsaturated Ketones in Water[a]



entry	7	Ar (8)	time (h)	yield[b] (%)	ee[c] (%)
1	**7d**	C_6H_5 (**8a**)	1	92	73
2	**7d**	4-ClC_6H_5 (**8k**)	1.5	90	83
3	**7d**	4-$CF_3C_6H_5$ (**8e**)	1.5	87	86
4	**7d**	3-ClC_6H_5 (**8f**)	1.5	90	85
5[d]	**7d**	2-ClC_6H_5 (**8l**)	3	89	97
6	**7d**	2-MeC_6H_5 (**8m**)	1.5	91	98
7	**7d**	1-naphthyl (**8j**)	1.5	88	97
8	**7e**	C_6H_5 (**8a**)	1.5	92	77
9	**7e**	2-MeC_6H_5 (**8m**)	1.5	86	98
10	**7e**	1-naphthyl (**8j**)	1.5	84	97
11	**7f**	2-MeC_6H_5 (**8m**)	2.5	82	94
12	**7f**	1-naphthyl (**8j**)	2.5	83	91
13	**7g**	2-MeC_6H_5 (**8m**)	1.5	91	87
14	**7g**	1-naphthyl (**8j**)	1.5	89	82

[a] The reaction was carried out with **7** (0.50 mmol), arylboronic acid (1.00 mmol), $[RhCl(C_2H_4)_2]_2$ (0.0075 mmol), dienes (0.0165 mmol, 1.1 equiv to Rh), and 1.5 M aq K_3PO_4 (0.17 mL) in H_2O (1.7 mL) at room temperature. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The reaction was carried out at 50 °C.

well at room temperature in water with 3 mol % of catalyst, giving the expected addition products in high yields with good to excellent enantioselectivities. The reaction is also sensitive to sterics as found in the cases of cyclic substrates. In contrast, sterically encumbered arylboronic acids provided much higher enantioselectivities (entries 1−7 and 8−10). The best results of 97−98% ee were obtained for enones **7d** and **7e** with 2-chlorophenylboronic, 2-tolylboronic, and 1-naphthylboronic acids (entries 5−7, 9, and 10). Notably, for more challenging substrates **7f** and **7g** bearing a phenyl substituent at the double bond moiety, the reaction enanti-

oselectivities remained high when 2-tolylboronic acid and 1-naphthylboronic acid were used (entries 11−14).

To gain some structural information of the catalyst, crystalline solids of both (*R*,*R*)-**5** and Rh/(*R*,*R*)-**5** were obtained that were suitable for X-ray diffraction. The X-ray crystal structures are shown in Figure 1.[13,14] Not surprisingly, the rhodium−diene complex crystallized as a dimeric species in which two double bonds on the tetrahydropentalene framework of each ligand bind to one rhodium. Similar to the previously reported $[RhCl(\mathbf{1})]_2$ complex, the bite angle of the diene coordination in $[RhCl(\mathbf{5})]_2$ is 82.6° (83° in $[RhCl(\mathbf{1})]_2$), and the two double bonds are not parallel and twisted by 24.7° (24.9° in $[RhCl(\mathbf{1})]_2$). Interestingly, compared to that in the rhodium complex ($[RhCl(\mathbf{5})]_2$), a much larger angle of 33.2° was observed in the uncoordinated free diene ligand (*R*,*R*)-**5**.

In summary, an aqueous Rh-catalyzed asymmetric 1,4-addition of α,β-unsaturated carbonyl compounds with arylboronic acids was developed by using a hydrophilic bicyclo[3.3.0] diene ligand such as **5** at room temperature. The reactions can be performed successfully in neat water to afford the corresponding products in good yields and with very high enantioselectivities for both cyclic and linear substrates. To our knowledge, this is the first example employing a chiral diene−metal complex as an effective catalyst in asymmetric synthesis in water. We anticipate that these new chiral diene ligands will be applicable to other asymmetric transformations in either aqueous media or organic solvents.

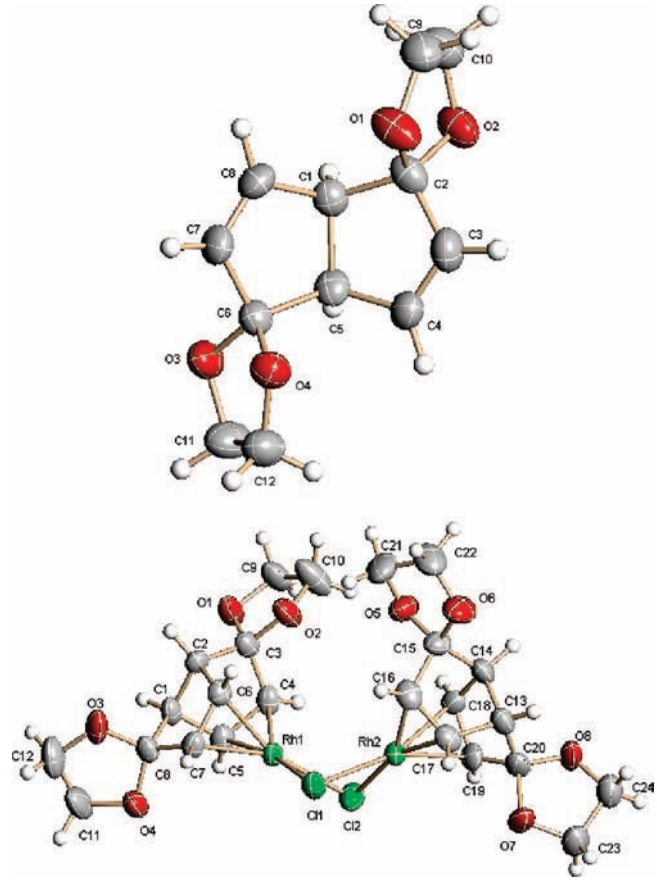


Figure 1. X-ray crystal structure of **5** (upper) and $[RhCl(\mathbf{5})]_2$ (lower).

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Supporting Information Available: Experimental procedures, characterization data, and copies of HPLC and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Prepared from the corresponding (1*S*,3a*R*,4*S*,6a*R*)-octahydropentalene-1,4-diol using the method reported in ref 8.

(11) Farnum, D. G.; Hagedorn, A. A., III *Tetrahedron Lett.* **1975**, *16*, 3987.

(12) No peak signal was detected by ^{1}H NMR in D_2O.

(13) Crystallographic data for (*R*,*R*)-**5** ($C_{12}H_{14}O_2$): T = 293 (2) K; wavelength: 0.71073 Å; crystal system: orthorhombic, space group: mdit > $P2_12_12_1$; unit cell dimensions: a = 6.1336(7) Å, b = 11.7280(14) Å, c = 14.5571(17) Å, α = 90°, β = 90°, γ = 90°; V = 1047.2 (2) Å^3; Z = 4; ρ_{calc} = 1.410 Mg/m^3; $F(000)$ = 472; final R indices [$I > 2\sigma(I)$]: R_1 = 0.0392, wR_2 = 0.0616; R indices (all data), R_1 = 0.0564, wR_2 = 0.0655; 6189 reflections mesured, 1337 were unique ($R_{(int)}$ = 0.0711).

(14) The rhodium complex was obtained by treatment of (*R*,*R*)-**5** with $[RhCl(C_2H_4)_2]_2$ in THF at room temperature for 48 h. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.76 (s, 2H), 3.74−3.79 (m, 2H), 3.89 (dd, J = 6.5, 14.0 Hz, 2H), 4.01−4.17 (m, 4H), 4.19−4.30 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 48.1, 65.4, 65.6, 68.0, 68.1, 82.3, 82.4, 119.6. Crystallographic data for $[RhCl(R,R)\text{-}\mathbf{5}]_2$ ($C_{24}H_{28}Cl_2O_8Rh_2$): T = 293(2) K; wavelength: 0.71073 Å; crystal system: orthorhombic, space group: $P2_12_12_1$; unit cell dimensions: a = 9.7534(10) Å, b = 9.9312(10) Å, c = 28.882(3) Å, α = 90°, β = 90°, γ = 90°; V = 2797.6(5) Å^3; Z = 4; ρ_{calc} = 1.848 Mg/m^3; $F(000)$ = 1572; final R indices [$I > 2\sigma(I)$]: R_1 = 0.0470, wR_2 = 0.1192; R indices (all data), R_1 = 0.0501, wR_2 = 0.1206; 16478 reflections mesured, 6011 were unique ($R_{(int)}$ = 0.0938).