Rhodium-Catalyzed Asymmetric 1,4-Addition of Aryl- and Alkenylboronic Acids to Enones

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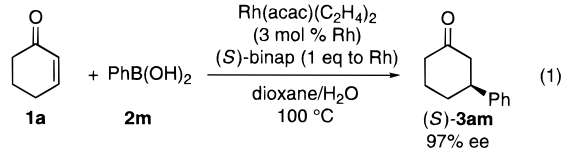
The 1,4-conjugate addition of organometallic reagents to enones is widely used process for carbon−carbon bond formation giving β-substituted carbonyl compounds which are versatile synthons to further organic transformations. Although considerable efforts have been made to develop efficient chiral catalytic systems for asymmetric 1,4-addition, the successful examples are rare in terms of enantioselectivity, catalytic activity, and generality.[1−4] Very recently, a part of the authors discovered the rhodium-catalyzed 1,4-conjugate addition of aryl- and alkenylboronic acids to enones.[5] This new catalytic reaction has several advantages over other 1,4-addition reactions. (1) The organoboronic acids used in this reaction are stable to oxygen and moisture, permitting us to run the reaction in protic media or even in an aqueous solution. (2) The organoboronic acids are much less reactive toward enones in the absence of a rhodium catalyst than the organometallic reagents so far used, such as organomagnesium or -lithium reagents, and no 1,2-addition to enones takes place in the presence or absence of the catalyst. (3) The reaction is catalyzed by transition-metal complexes coordinated with phosphine ligands. Since chiral phosphine ligands are the chiral auxiliaries most extensively studied for transition-metal-catalyzed asymmetric reactions,[6] one can use the accumulated knowledge of the chiral phosphine ligands for the asymmetric reaction. Here we report asymmetric 1,4-addition of aryl- and alkenylboronic acids which proceeds with high enantioselectivity in the presence of a chiral phosphine−rhodium catalyst.[7]

Our initial studies were focused on the development of reaction conditions including reaction temperature, solvent, rhodium precursor, and chiral ligand for the asymmetric addition of phenylboronic acid (**2m**) to 2-cyclohexenone (**1a**) producing 3-phenylcyclohexanone (**3am**). Under the conditions reported



previously,[5] that is, in the presence of rhodium catalyst generated from Rh(acac)$(CO)_2$ and a phosphine ligand at 50 °C for 16 h, the reaction is very slow with any chiral ligands examined,[8] giving only <2% yield of **3am**. It was found that the reaction is efficiently catalyzed by a rhodium complex generated in situ by mixing Rh(acac)$(C_2H_4)_2$ with 1 equiv of (*S*)-binap in an aqueous solvent at 100 °C (eq 1). Thus, a mixture of **1a** (39 mg, 0.40 mmol), **2m** (68 mg, 0.56 mmol, 1.4 equiv), Rh(acac)$(C_2H_4)_2$ (3.1 mg, 0.012 mmol, 3 mol %), and (*S*)-binap (7.5 mg, 0.012 mmol) in dioxane/H_2O (1.0 mL/0.1 mL) was heated at 100 °C for 5 h. After aqueous workup, silica gel chromatography (hexane/EtOAc = 5/1) gave 44 mg (64% yield) of (*S*)-3-phenylcyclohexanone (**3am**) whose enantiomeric excess is 97% (entry 1 in Table 1). The absolute configuration of (*S*) was determined by comparison of the specific rotation ($[\alpha]^{20}_D$ −21 (*c* 0.96, chloroform)) with that reported for (*R*)-**3am**,[9] and the enantiomeric excess was determined by HPLC analysis using a chiral stationary phase column (Chiralcel OD-H, hexane/2-propanol = 98/2). Use of Rh(acac)$(CO)_2$ in place of Rh(acac)$(C_2H_4)_2$ as a catalyst precursor significantly lowered both catalytic activity and enantioselectivity (entry 2). ^{1}H and ^{31}P NMR studies revealed that Rh(acac)$(C_2H_4)_2$ reacts immediately with 1 equiv of (*S*)-binap in C_6D_6 to give Rh(acac)[(*S*)-binap] quantitatively.[10] The isolated Rh(acac)[(*S*)-binap] complex showed essentially the same catalytic activity and stereoselectivity (entry 3) as the in situ catalyst generated from Rh(acac)$(C_2H_4)_2$ and (*S*)-binap, indicating that Rh(acac)[(*S*)-binap] is a catalytically active species or a key precursor. In contrast, addition of (*S*)-binap to Rh(acac)$(CO)_2$ in the same solvent gave a complex mixture consisting of two main species, Rh(acac)[(*S*)-binap] and an unidentified species. The lower selectivity of the catalyst generated from Rh(acac)$(CO)_2$ is attributed to the formation of the complex mixture.

It was found that phenylboronic acid (**2m**) undergoes hydrolysis giving benzene as a competing reaction under the reaction

(1) For reviews, see: (a) Schmalz, H.-G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, Chapter 1.5. (b) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771. (c) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley and Sons: New York, 1994; pp 207−212. (d) Nógrádi, M. *Stereoselective Synthesis*; VCH Publishers: New York, 1995; pp 213−224. (e) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley and Sons: New York, 1995.

(2) For recent examples for asymmetric addition of organozinc or magnesium reagents in the presence of nickel or copper catalysts, see: (a) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2620. (b) Knöbel, A. K. H.; Escher, I. H.; Pfaltz, A. *Synlett* **1997**, 1429. (c) Alexakis, A.; Burton, J.; Vastra, J.; Mangeney, P. *Tetrahedron: Asymmetry* **1997**, *8*, 3987. (d) De Vries, A. H. M.; Imbos, R.; Feringa, B. L. *Tetrahedron: Asymmetry* **1997**, *8*, 1467. (e) De Vries, A. H. M.; Meetsma, A.; Feringa, B. L. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2374. (f) Kanai, M.; Tomioka, K. *Tetrahedron Lett.* **1995**, *36*, 4275. (g) Van Klaveren, M.; Lambert, F.; Eijkelkamp, D. J. F. M.; Grove, D. M.; van Koten, G. *Tetrahedron Lett.* **1994**, *35*, 6135. (h) Asami, M.; Usui, K.; Higuchi, S.; Inoue, S. *Chem. Lett.* **1994**, 297. (i) Soai, K.; Okudo, M.; Okamoto, M. *Tetrahedron Lett.* **1991**, *32*, 95. (j) Bolm, C. *Tetrahedron: Asymmetry* **1991**, *2*, 701.

(3) Asymmetric addition of aryllithiums catalyzed by a chiral ligand has been reported: Tomioka, K.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1993**, *34*, 681.

(4) For recent examples for catalytic asymmetric Michael addition of malonate esters, see: (a) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *J. Org. Chem.* **1996**, *61*, 3520. (b) Arai, T.; Sasai, H.; Aoe, K.; Okamura, K.; Date, T.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 104 and references therein.

(5) Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229.

(6) For a review, see: Ojima, I. *Catalytic Asymmetric Synthesis*; VCH Publishers: New York, 1993.

(7) Asymmetric Michael addition forming a chiral carbon center on the nucleophile has been reported to be catalyzed by a chiral bis(phosphine)−rhodium complex: (a) Sawamura, M.; Hamashima, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 8295. (b) Sawamura, M.; Hamashima, H.; Ito, Y. *Tetrahedron* **1994**, *50*, 4439.

(8) The following chiral ligands were examined: 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (binap), 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (diop), 2,3-bis(diphenylphosphino)butane (chiraphos), 2,2′-bis[4-(isopropyl)oxazolyl]-1,1′-binaphthyl (boxax), 2-[2-(diphenylphosphino)phenyl]-4-(isopropyl)oxazoline (phox), 2-diphenylphosphino-2′-methoxy-1,1′-binaphthyl (mop).

(9) The specific rotation of (*R*)-3-phenylcyclohexanone (**3am**, 98.7% ee) has been reported to be $[\alpha]^{20}_D$ +20.5 (*c* 0.58, chloroform): Schultz, A. G.; Harrington, R. E. *J. Am. Chem. Soc.* **1991**, *113*, 4926.

(10) Rh(acac)[(*S*)-binap]: ^{1}H NMR (C_6D_6, 23 °C) δ 1.54 (s, 6H, MeCO), 5.35 (s, 1H, COCHCO), 6.45 (br, 4H), 6.52 (t, J = 7.2 Hz, 2H), 6.65−6.68 (m, 2H), 6.72 (d, J = 8.3 Hz, 2H), 6.97−7.00 (m, 2H), 7.15−7.20 (m, 9H), 7.23 (d, J = 8.1 Hz, 2H), 7.64 (quint, J = 4.3 Hz, 2H), 8.03 (br, 4H), 8.21 (br, 3H); ^{31}P{^{1}H} NMR (C_6D_6, 23 °C) δ 55.3 (d, J_{Rh-P} = 193 Hz). Anal. Calcd for $RhC_{49}H_{39}O_2P_2$: C, 71.36; H, 4.77. Found: C, 71.07; H, 4.76. It has been reported that the addition of a bisphosphine to Rh(acac)(cod) forms Rh(acac)(bisphosphine): Fennis, P. J.; Budzelaar, P. H. M.; Frijns, J. H. G.; Orpen, A. G. *J. Organomet. Chem.* **1990**, *393*, 287.

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Table 1. Asymmetric 1,4-Addition of Boronic Acids **2** to Enones **1** Catalyzed by (*S*)-binap-Rhodium(I)[a]

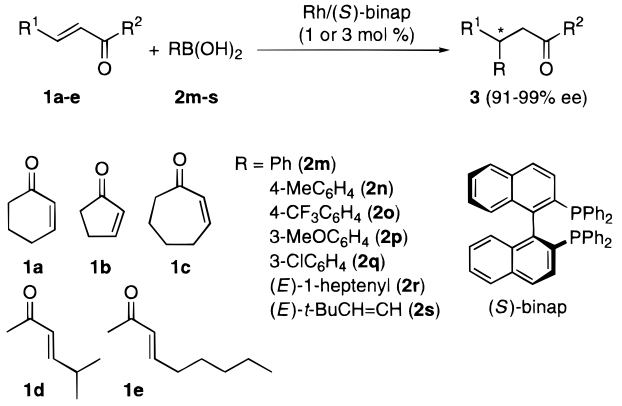
entry	enone **1**	$RB(OH)_2$ **2** (equiv to **1**)	temp (°C)	yield[b] (%) of **3**	% ee[c]	$[\alpha]^{20}_D$ (*c* in $CHCl_3$)
1	**1a**	**2m** (1.4)	100	64 (**3am**)	97 (*S*)	−21 (0.96)
2[d]	**1a**	**2m** (1.4)	100	15 (**3am**)	43 (*S*)	
3[e]	**1a**	**2m** (1.4)	100	62 (**3am**)	97 (*S*)	
4	**1a**	**2m** (2.5)	100	93 (**3am**)	97 (*S*)	
5	**1a**	**2m** (5.0)	100	>99 (**3am**)	97 (*S*)	
6[f]	**1a**	**2m** (5.0)	100	>99 (**3am**)	96 (*S*)	
7	**1a**	**2m** (1.4)	40	<2 (**3am**)	97 (*S*)	
8	**1a**	**2m** (1.4)	60	3 (**3am**)	97 (*S*)	
9	**1a**	**2m** (1.4)	80	42 (**3am**)	97 (*S*)	
10	**1a**	**2m** (1.4)	120[g]	59 (**3am**)	97 (*S*)	
11	**1a**	**2n** (5.0)	100	>99 (**3an**)	97	−17 (0.95)
12[h]	**1a**	**2o** (2.5)	100	70 (**3ao**)	99	−11 (0.97)
13	**1a**	**2p** (5.0)	100	97 (**3ap**)	96	−13 (0.91)
14	**1a**	**2q** (5.0)	100	94 (**3aq**)	96	−9.5 (1.13)
15	**1a**	**2r** (2.5)	100	88 (**3ar**)	94	−12 (0.88)
16	**1a**	**2s** (5.0)	100	76 (**3as**)	91	−19 (0.86)
17	**1b**	**2m** (1.4)	100	93 (**3bm**)	97 (*S*)	−92 (0.82)
18	**1b**	**2r** (2.5)	100	64 (**3br**)	96	−79 (0.45)
19	**1c**	**2m** (1.4)	100	51 (**3cm**)	93	−58 (0.75)
20	**1d**	**2m** (5.0)	100	82 (**3dm**)	97	−33 (1.12)
21	**1e**	**2m** (2.5)	100	88 (**3em**)	92	−17 (1.26)

[a] The reaction was carried out in dioxane/H_2O (10/1) for 5 h in the presence of 3 mol % of the catalyst generated from $Rh(acac)(C_2H_4)_2$ and (*S*)-binap unless otherwise noted. [b] Isolated yield by silica gel chromatography. [c] Determined by HPLC analysis with chiral stationary phase columns: Daicel Chiralcel OD-H (**3am**, **3ao**, **3ap**, **3cm**, **3dm**, **3em**), AD (**3an**, **3aq**), OB-H (**3bm**) (eluent, hexane/2-propanol = 98/2), and AS (**3ar**, **3as**, **3br**) (eluent, hexane/2-propanol = 90/10). [d] $Rh(acac)(CO)_2$ was used in place of $Rh(acac)(C_2H_4)_2$. [e] Isolated Rh(acac)[(*S*)-binap] was used as a catalyst. [f] In the presence of 1 mol % of the catalyst. [g] In a pressure-resistant reactor. [h] Reaction in 1-propanol/H_2O (10/1).

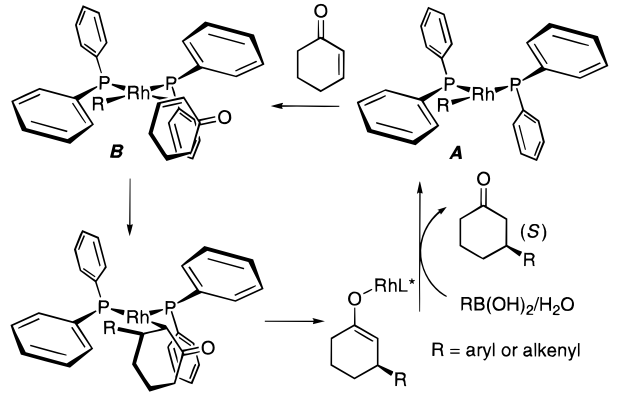
conditions. The yield of the addition product **3am** was greatly improved by use of a large excess of the boronic acid (entries 4 and 5). With 5 times excess of phenylboronic acid (**2m**), a quantitative yield of **3am** was obtained even in the presence of 1 mol % of the catalyst without loss of enantioselectivity (entry 6). The reaction temperature is also important for the high chemical yield (entries 7−10). At 60 °C or lower, the 1,4-addition was very slow giving **3am** in not higher than 3% yield. The highest yield was achieved at 100 °C. Interestingly, the enantioselectivity was kept constant at the reaction temperature ranging between 40 and 120 °C.[11]

The scope of the present catalytic asymmetric addition is broad (Scheme 1). Aryl groups substituted with either electron-donating or -withdrawing groups, 4-MeC_6H_4, 4-$CF_3C_6H_4$, 3-$MeOC_6H_4$, and 3-ClC_6H_4, were introduced onto 2-cyclohexenone with high enantioselectivity by the reaction with the corresponding boronic acids **2n**−**q** (entries 11−14). Asymmetric addition of 1-alkenylboronic acids was also successful, (*E*)-1-heptenylboronic acid (**2r**) and (*E*)-3,3-dimethyl-1-butenylboronic acid (**2s**) giving the corresponding products of over 90% ee (entries 15 and 16). Cyclopentenone (**1b**) also underwent the asymmetric addition of phenyl- and 1-heptenylboronic acids with high enantioselectivity under similar reaction conditions to give the corresponding 3-substituted cyclopentanones, **3bm**[12] (97% ee (*S*)) and **3br** (96% ee), respectively, in high yields (entries 17 and 18). High enantioselectivity was also observed in the reaction of linear enones **1d** and **1e** which have trans olefin geometry (entries 20 and 21). Thus, the present catalytic asymmetric 1,4-addition proceeds with high enantioselectivity for both cyclic and linear α,β-unsaturated ketones with a variety of aryl- and alkenylboronic acids.

Scheme 1



Scheme 2[a]



[a] The binaphthylene moiety in (*S*)-binap is omitted for clarity.

The catalytic cycle has been proposed to involve the insertion of carbon−carbon double bond of enone into aryl−rhodium bond as a key step.[5] Scheme 2 shows the stereochemical pathway forming the products of (*S*) configuration, which is exemplified by the reaction of 2-cyclohexenone. According to the highly skewed structure known for transition-metal complexes coordinated with a binap ligand,[13] (*S*)-binap−rhodium intermediate **A** should have an open space at the lower part of the vacant coordination site, the upper part being blocked by one of the phenyl rings of the binap ligand. The olefinic double bond of 2-cyclohexenone coordinates to rhodium with its 2*si* face forming **B** rather than with its 2*re* face, which undergoes migratory insertion to form a stereogenic carbon center whose absolute configuration is (*S*). All the 1,4-addition products **3** obtained here are expected to have the absolute configuration resulting from the attack of 2*si* face of enones.

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data for the products (3 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(11) For some other substrates, the higher enantioselectvity was observed at the higher reaction temperature.

(12) The specific rotation of (*S*)-3-phenylcyclopentanone (**3bm**, 70% ee) has been reported to be $[\alpha]^{RT}_D$ −67.7 (*c* 1.0, chloroform): Barnhart, R. W.; Wang, X.; Noheda, P.; Bergens, S. H.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1994**, *116*, 1821.

(13) Ozawa, F.; Kubo, A.; Matsumoto, Y.; Hayashi, T. *Organometallics* **1993**, *12*, 4188 and references therein.