Asymmetric Conjugate Addition of Arylboronic Acids to Enones Catalyzed by Rhodium-Monodentate Phosphoramidite Complexes in the Presence of Bases

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Abstract: Rhodium(I)-catalyzed 1,4-addition of arylboronic acids to α,β-unsaturated carbonyl compounds was carried out in the presence of a chiral phosphoramidite ligand based on (*R*)-binol and dialkylamines. The reaction was significantly accelerated in the presence of a base such as KOH and Et_3N, allowing the reaction to be completed within 6 h at 50 °C. The addition to 2-cyclohexenone achieved enantioselectivities up to 99%, though they were less effective for 2-cyclopentenone (79% ee), 2-cycloheptenone (77% ee) and acyclic enones (31-43% ee).

Key words: arylboronic acids, rhodium catalyst, phosphoramidite, asymmetric, conjugate addition

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The conjugate addition of nucleophiles to activated alkenes such as Michael reaction of enolates or organocopper reagents to enones is a widely used process in organic chemistry.[1] It was recently demonstrated that rhodium(I) complexes are excellent catalysts for such conjugate additions of aryl- and alkenylboronic acids to α,β-unsaturated carbonyl compounds or other Michael acceptors.[2] Since various chiral phosphines are available for rhodium catalysts, the protocol was recently extended to asymmetric versions using chiral P-P ligands such as BINAP[3] and diphosphonites[4] and P-N ligands such as amidomonophosphines.[5] Although BINAP achieved high enantioselectivities practical for the addition to both cyclic and acyclic enones, the reactions often used large excesses of organoboronic acid because of a competitive hydrolytic B-C bond

cleavage of organoboronic acids due to a low catalyst efficiency requiring a temperature of over 100 °C in an aqueous solvent. This problem has recently been solved by the use of RhOH-binap catalyst that completes the reaction at 35 °C.[6] However, the substrates that can be used have been limited to relatively simple substrates because of the highly rigid coordination space of a BINAP ligand.

In connection with our interest in rhodium-catalyzed reactions of organoboronic acids, we report here the results of a preliminary study on the effects of monodentate phosphoramidite ligands (**4**) and bases in the 1,4-addition of arylboronic acids to α,β-unsaturated carbonyl compounds (Scheme 1).[7] Among the various phosphoramidite ligands extensively studied by Feringa and co-workers,[8] diethylamino derivative (**4a**) was found to be an excellent catalyst for cyclic enones. Since the enantioselectivity was reduced by raising the reaction temperature, the presence of a base was critical to carry out the reaction under mild conditions and to achieve high enantioselective. The reaction was completed within 6 h at 50 °C in the presence of 1 equivalent of KOH or Et_3N in striking contrast to the reaction occurring at 90 °C in the absence of a base.

<<Scheme 1>>

The effects of representative phosphoramidite ligands (**4**) and enones are summarized in Table 1. The catalyst was prepared *in situ* by mixing $Rh(acac)(C_2H_4)_2$ (3 mol%) and two equivalents of **4** at room temperature for 1 h. $Rh(acac)(coe)_2$, $[RhCl(C_2H_4)_2]_2$ and $[Rh(OH)(cod)]_2$ also gave analogous yields and enantioselectivities to those of $Rh(acac)(C_2H_4)_2$. The addition of phenylboronic acid to 2-cyclohexenone at 50 °C for 6 h in aqueous dioxane (6/1) resulted in 19% yield in the absence of a base (entry 1). In contrast, the yields were almost quantitative in the presence of 1 equivalent of Et_3N or KOH (entries 2 and 3). Phosphoramidites are sensitive to hydrolysis with water, but their rhodium complexes were sufficiently stable to be used in alkaline solution, whereas the yields decreased when a catalyst of less than 1 mol% was used. The enantioselectivities dramatically changed in a series of N,N-dialkylamino derivatives (entries 3-7). Among the ligands studied,

N,N-diethyl derivative (**4a**) exhibited the best enantioselectivity (98-99% ee, entries 2 and 3). The selectivities were reduced by increasing the bulkiness of amino groups (entries 4-6) except for the morpholine derivative (**4e**), which exceptionally showed a high selectivity comparable to that of the N,N-diethylamino derivative (entry 7). The phosphoramidites derived from (*R*)-(+)-binol generally afforded (*R*)-3-phenylcyclohexanone.

<<Table 1>>

Although hydrolytic B-C bond cleavage is a serious side-reaction at 100 °C, a 50% excess of arylboronic acids was a sufficient amount to complete the reaction at 50 °C. Indeed, both 3-chloro- (**2b**) and 3-methoxyphenylboronic acid (**2c**) afforded 75% and 84% yields of products with 98-99% ee (entries 8 and 9). In contrast to the excellent enantioselectivities for 2-cyclohexenone, the ligand was highly sensitive to enones. The selectivities decreased to 79% ee for 2-cyclopentenone and to 77% ee for 2-cycloheptenone (entries 10 and 11). Acyclic enones such as 3-nonen-2-one and 5-methyl-3-hexen-2-one resulted in 1% ee and 11% ee, respectively. Although reoptimization of the ligands for acyclic enones showed that the N,N-diisopropyl derivative (**4b**) increases the selectivity to 31-43% ee (entries 12 and 13), all attempts at an enantioselective reaction practical for acyclic enones failed.[9] An extension of the protocol to α,β-unsaturated lactones suffered from a slow addition and a high sensitivity to saponification. Finally, an 84% ee was achieved by heating the mixture at 90 °C in the absence of bases (entry 14).

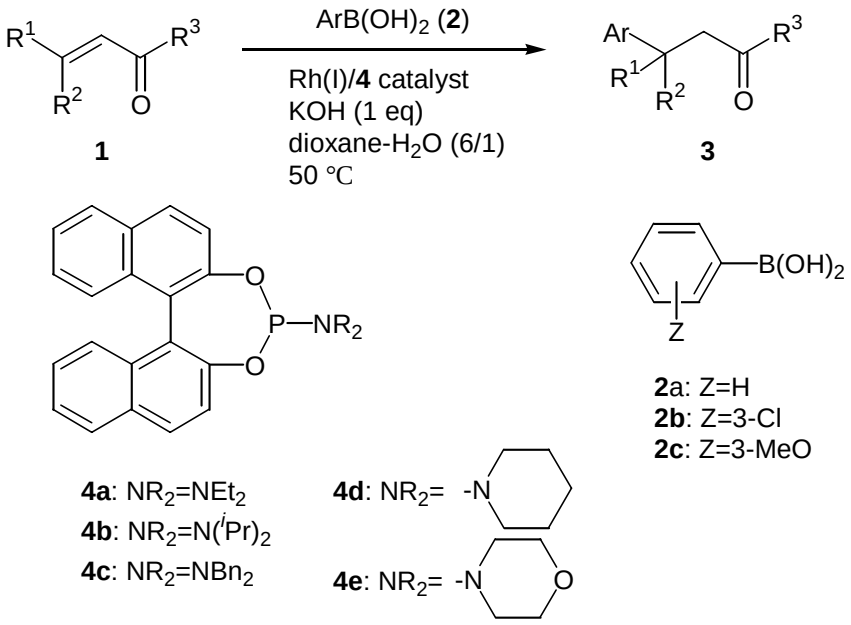
In conclusion, Feringa's phosphoramidites were found to be excellent ligands for the rhodium-catalyzed conjugate addition of arylboronic acids to cyclic enones. High reaction rates and enantioselectivities up to 99% were obtained for 2-cyclohexenone when the reactions were carried out at 50 °C in the presence of a base. Because of the availability of various derivatives by a simple synthetic route, phosphoramidites are practical chiral ligand that are easily variable depending upon the substrates.

Representative procedure (entry 3 in Table 1): A flask charged with $Rh(acac)(C_2H_4)_2$ (0.03 mmol), **4a** (0.06 mmol) and $PhB(OH)_2$ (1.5 mmol) was flushed with argon. 1,4-Dioxane-H_2O (6/1, 3 ml) and KOH (10 M in H_2O, 0.1 ml, 1 mmol) were successively added. After being stirred for 1 h, 2-cyclohexenone (1 mmol) was added. The resulting mixture was then stirred for 6 h at 50 °C. Chromatography over silica gel gave (R)-3-phenylcyclohexanone: 95% yield, 98% ee, $[\alpha]^{20}_D$ +21.4 (c 0.95, $CHCl_3$). The enantiomer excess was determined by HPLC analysis using a chiral stationary phase column (Daicel Chiralpak AD) with hexane/2-propanol = 98/2.

References and Notes

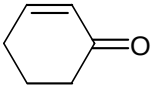
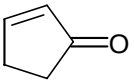
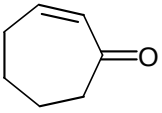
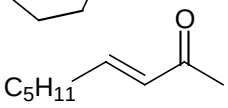
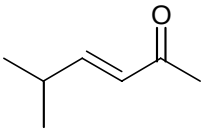
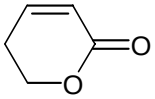
1. For reviews; (a) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171. (b) Shibasaki, M.; Gröger, H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Chapter 29.3. (c) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.
2. (a) Yamamoto, Y.; Fujita, M.; Miyaura, N. *Synlett* **2002**, 767. (b) Amengual, R.; Michelet, V.; Genêt, J-P. *Tetrahedron Lett*. **2002**, *43*, 5905. (c) Pucheault, M.; Darses, S.; Genêt, J-P. *Tetrahedron Lett*. **2002**, *43*, 6155. (d) Itooka, R.; Iguchi, Y.; Miyaura, N. *Chem. Lett*. **2001**, 722. (e) Ramnaulth, J.; Poulin, O.; Bratovanov, S. S.:Rakhit, S.; Maddaford, S. P. *Org. Lett*. **2001**, *3*, 2571. (f) Batey, R. A.; Thadani, A. N.; Smil, D. V. *Org. Lett.* **1999**, *1*, 1683. (g) Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229.
3. (a) Hayashi, T.; Senda, T.; Ogasawara, M.; *J. Am. Chem. Soc.* **2000**, *122*, 10716. (b) Senda, T.; Ogasawara, M.; Hayashi, T. *J. Org. Chem*. **2001**, *66*, 6852. (c) Sakuma, S.; Miyaura, N. *J. Org. Chem***. 2001**, *66*, 8944. (d) Sakuma, S.; Sakai, M.; Itooka, R.; Miyaura, N. *J. Org. Chem*. **2000**, *65*, 5951.(e) Hayashi, T.; Senda, T.; Ogasawara, M. *J. Am. Chem. Soc*. **2000**, *122*, 10716. (f) Hayashi, T.; Senda, T.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **1999**, *121*, 11591. (g) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.*, **1998**, *120*, 5579. (h) For a review, see: Fagnou, K.; Lautens, M. *Chem. Rev*., **2003**, *103*, 169.

4. (a) Chan, A. S. C. *Tetrahedron Asymmetry*, **1999**, *10*, 3259. (b) Reetz, M.; T.; Moulin, D.; Gosberg, A. *Org. Lett*. **2001**, *3*, 4083.
5. (a) Kuriyama, M.; Nagai, K.; Yamada, K.; Miwa, Y.; Taga, T.; Tomioka, K. *J. Am. Chem. Soc*. **2002**, *124*, 8932. (b) Kuriyama, M.; Tomioka, K. *Tetrahedron Lett*. **2001**, *42*, 921.
6. Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc*. **2002**, *124*, 5052.
7. During the course of our study, analogous reaction was carried out at 100 °C in the absence of bases: Boiteau, J-G.; Imbos, R.; Minnaard, A. J.; Feringa, B. L. *Org. Lett*. **2003**, *5*, 681.
8. (a) de Vries, A. H. M.; Meetsma, A.; Feringa, B. L. *Angew. Chem. Int. Ed. Engl*. **1996**, *35*, 2374. (b) Arnold, L. A.; Imbos, R.; Mandoli, A.; Vries, A. H. M.; Naasz, R.; Heringa, B. L. *Tetrahedron* **2000**, *56*, 2865. (c) For a review, Feringa, B. L. *Acc. Chem. Res*. **2000**, *33*, 346. see also references cited in 7.
9. Addition of phenylboronic acid to 3-nonen-2-one (entry 12) showed the enantioselectivities suggesting the superiority of bulky dialkylamino ligands; **4a** (1% ee), **4b** (43% ee), **4c** (7% ee), **4d** (26% ee) and **4e** (12% ee).



Scheme 1. Asymmetric 1,4-Addition of Arylboronic Acids to Enones

Table 1. Asymmetric 1,4-Addition of Arylboronic Acids to Enones (Scheme 1)[a]

entry	enone	$ArB(OH)_2$ **2**	ligand **3**	yield/%	ee%
1[b]		**2a**	**4a**	19	-
2[c]		**2a**	**4a**	90	99 (R)
3		**2a**	**4a**	95	98 (R)
4		**2a**	**4b**	38	22 (S)
5		**2a**	**4c**	5	24 (R)
6		**2a**	**4d**	67	51 (R)
7		**2a**	**4e**	68	89 (R)
8		**2b**	**4a**	75	99
9		**2c**	**4a**	84	98
10		**2b**	**4a**	97	79
11		**2a**	**4a**	67	77
12		**2a**	**4b**	50	43
13		**2a**	**4b**	39	31
14[d]		**2a**	**4a**	55	84

[a]A mixture of enone (1 mmol), $ArB(OH)_2$ (1.5 mmol), $Rh(acac)(C_2H_4)_2$ (0.03 mmol), ligand (0.06 mmol) and KOH (1 mmol) in dioxane-H_2O (6/1, 3 ml) was stirred for 6 h at 50 °C, unless otherwise noted. [b]The reaction was conducted in the absence of KOH. [c]Et_3N (1 mmol) was used in place of KOH.
[d]at 90 °C for 6 h in the absence of KOH.

Graphical abstract

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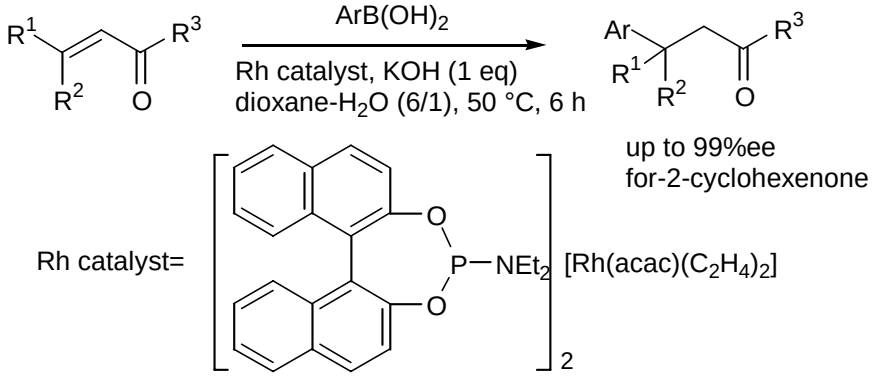
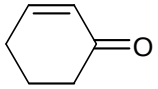


Table 1. Asymmetric 1,4-Addition of Arylboronic Acids to Enones (Scheme 1)[a]

entry	enone	$ArB(OH)_2$ **2**	ligand **3**	yield/%	ee%
1[b]		**2a**	**4a**	19	-
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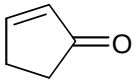
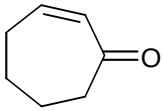
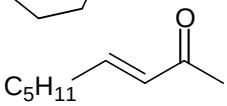
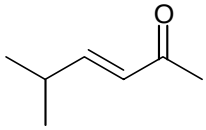
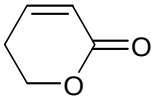
10		**2b**	**4a**	97	79
11		**2a**	**4a**	67	77
12		**2a**	**4b**	50	43
13		**2a**	**4b**	39	31
14[d]		**2a**	**4a**	55	84

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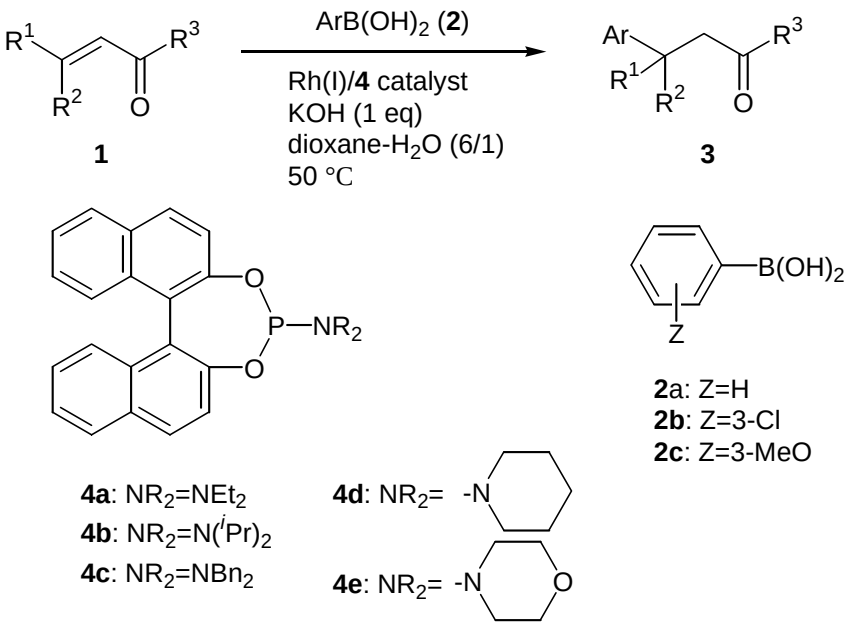

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