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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 Et₃N, 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

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 BINAP³ and diphosponites⁴ 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 Et₃N 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)(C₂H₄)₂ (3 mol%) and two equivalents of **4** at room temperature for 1 h. Rh(acac)(coe)₂, [RhCl(C₂H₄)₂]₂ and [Rh(OH)(cod)]₂ also gave analogous yields and enantioselectivities to those of Rh(acac)(C₂H₄)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 Et₃N 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).

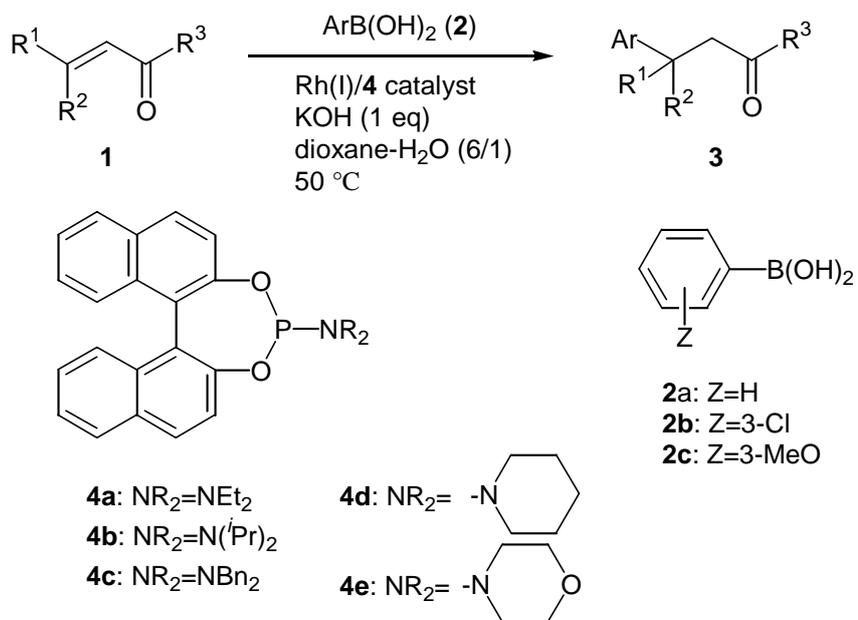
In conclusion, Feringa's phosphoramidites were found to be excellent ligands for the rhodium-catalyzed conjugate addition of arylboronic acids to cyclic enones. High reaction rates and enantioselectivities up to 99% were obtained for 2-cyclohexenone when the reactions were carried out at 50 °C in the 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)(C₂H₄)₂ (0.03 mmol), **4a** (0.06 mmol) and PhB(OH)₂ (1.5 mmol) was flushed with argon. 1,4-Dioxane-H₂O (6/1, 3 ml) and KOH (10 M in H₂O, 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, [α]_D²⁰ +21.4 (c 0.95, CHCl₃). 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

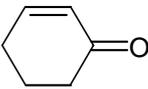
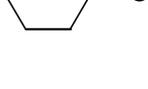
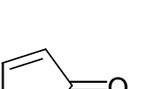
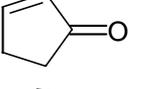
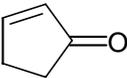
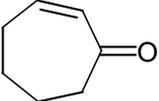
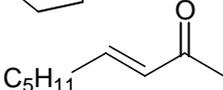
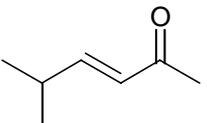
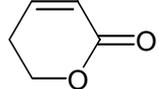
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9. Addition of phenylboronic acid to 3-nonen-2-one (entry 12) showed the enantioselectivities suggesting the superiority of bulky dialkylamino ligands; **4a** (1% ee), **4b** (43% ee), **4c** (7% ee), **4d** (26% ee) and **4e** (12% ee).



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

^aA mixture of enone (1 mmol), ArB(OH)₂ (1.5 mmol), Rh(acac)(C₂H₄)₂ (0.03 mmol), ligand (0.06 mmol) and KOH (1 mmol) in dioxane-H₂O (6/1, 3 ml) was stirred for 6 h at 50 °C, unless otherwise noted. ^bThe reaction was conducted in the absence of KOH. ^cEt₃N (1 mmol) was used in place of KOH.

^dat 90 °C for 6 h in the absence of KOH.

Graphical abstract

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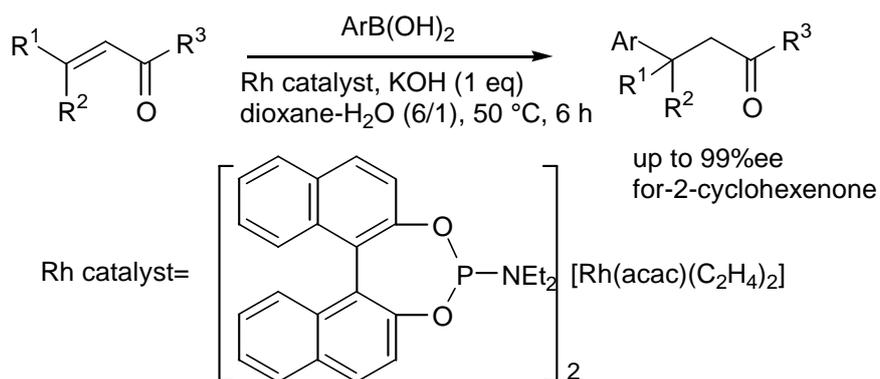
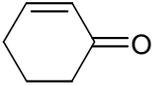
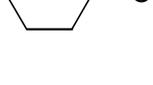
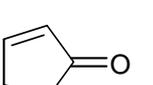
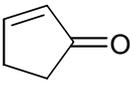
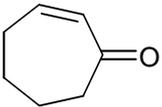
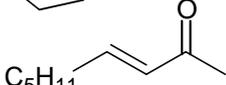
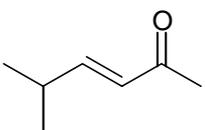
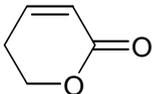
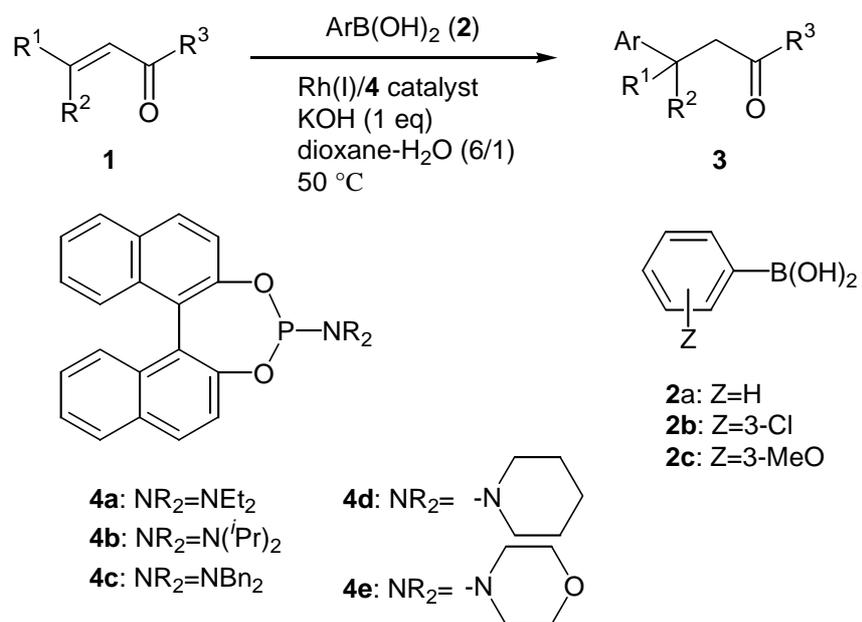


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13		2a	4b	39	31
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^aA mixture of enone (1 mmol), ArB(OH)₂ (1.5 mmol), Rh(acac)(C₂H₄)₂ (0.03 mmol), ligand (0.06 mmol) and KOH (1 mmol) in dioxane-H₂O (6/1, 3 ml) was stirred for 6 h at 50 °C, unless otherwise noted. ^bThe reaction was conducted in the absence of KOH. ^cEt₃N (1 mmol) was used in place of KOH.

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