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Rhodium-Catalyzed Asymmetric Conjugate Additions of Boronic Acids Using Monodentate Phosphoramidite Ligands

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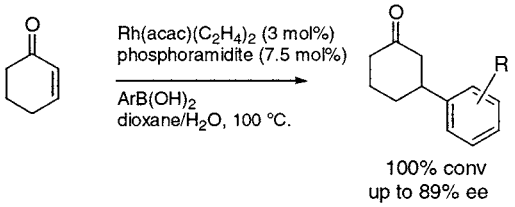
ABSTRACT



Monodentate phosphoramidites have been used for the first time as chiral ligands in the Rh-catalyzed enantioselective conjugate addition of arylboronic acids to enones, unsaturated esters, lactones, and nitro alkenes. High reaction rates and ee's up to 89% have been obtained.

The copper−phosphoramidite-catalyzed enantioselective conjugate addition of dialkylzinc reagents[1] has developed into a powerful methodology for introducing C−C bonds to prochiral centers.[2] The broad scope,[3] including the use of a variety of α,β-unsaturated ketones in combination with several (functionalized) organozinc reagents, and the excellent levels of stereocontrol add to its practicality in synthesis.[4] A drawback of the current system is that it is limited to aliphatic (functionalized) dialkylzinc reagents whereas the introduction of aryl groups via arylzinc halides gives racemic mixtures.

The rhodium-catalyzed conjugate addition of organoboronic acids developed by Hayashi and Miyaura is currently the method of choice to introduce aryl or alkenyl groups and is fully complementary to the copper−phosphoramidite method.[5] The introduction of alkyl groups is not suitable, whereas the 1,4-addition of aryl or alkenyl groups results in high yields and excellent ee's for a large number of enones and boronic acids.

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Rh-catalyzed conjugate additions of arylstannanes,[6] arylsilicon,[7] and aryltitanium[8] reagents have also been reported. Furthermore, a nonasymmetric catalytic coupling of phenylboronic acids to aldimines[9] as well as conjugate additions in aqueous media[10] have been described.

In all cases, BINAP[11] is used as a chiral ligand. Other diphosphines have been investigated, but these were found to result in catalysts showing lower activity and selectivity.[12] To the best of our knowledge the only other ligand types successfully employed in the asymmetric[13] conjugate addition of boronic acids to enones are binol-based diphosphonites developed by Reetz et al.[14] and amidomonophosphines introduced by Tomioka et al.[15]

All ligands used to date in the enantioselective conjugate addition of arylboronic acids to enones are bidentate in nature and phosphoramidites have not been reported as ligands. Furthermore, access to readily synthesized, cheap, and easily tunable chiral ligands becomes a key issue for practical application in asymmetric catalysis. We have already shown that in the asymmetric hydrogenation reaction, phosphoramidite ligands form stable and active complexes with rhodium.[16] It would be interesting to know if the monodentate phosphoramidite ligands could also be applied in the Rh-catalyzed conjugate addition of boronic acids. This would make these phosphoramidites a class of ligands suitable for the conjugate addition of both dialkylzinc reagents and arylboronic acids.

To test the stability of phosphoramidites under the conditions developed by Hayashi et al.[5c] for this type of reaction, **L1** (MonoPhos) was dissolved in dioxane/H_2O = 10/1 and heated to 100 °C for 5 h. As expected, the free ligand **L1** was completely hydrolyzed under these conditions. However, when 2 equiv of the ligand and 1 equiv of Rh(acac)-$(C_2H_4)_2$ were added to the same solvent mixture, as well as a large excess of phenylboronic acid, the ligand remained unchanged after heating to 100 °C for 16 h! This shows that the rhodium−phosphoramidite catalyst is stable under the standard reaction conditions for the boronic acid addition.

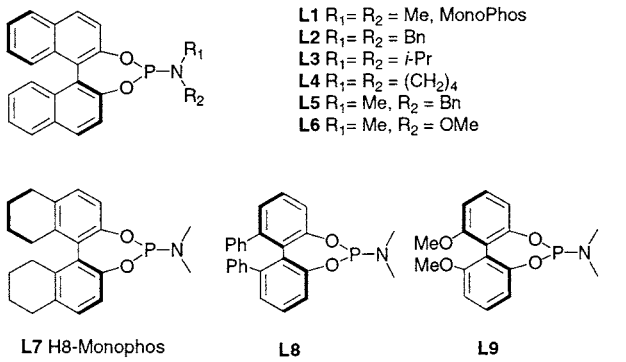
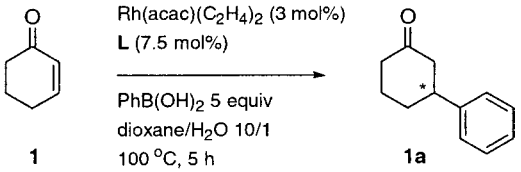


Figure 1. (*S*)-Bisphenol-based monodentate ligands used in the conjugate addition of $PhB(OH)_2$ to cyclohexenone.

A variety of phosphoramidite ligands[17] (Figure 1) were prepared and tested in the rhodium-catalyzed conjugate addition of phenylboronic acid to cyclohexenone **1** (Scheme 1).

Scheme 1



[a] Determined by ^{1}H NMR. [b] Determined by chiral HPLC or GC.

The conditions reported earlier were used,[5c] i.e., 3 mol % of Rh(acac)$(C_2H_4)_2$[18] as catalyst precursor, 7.5 mol % of phosphoramidite ligand, dioxane/H_2O = 10/1 as solvent, 5 equiv of phenylboronic acid, and reaction times of 5 h at 100 °C.[19] A workup involving dilution with saturated aqueous $NaHCO_3$, followed by extraction with EtOAc and filtration over silica gel yielded the product (*S*)-**1a** that was used for characterization and ee determination.

The most effective ligands turned out to be MonoPhos **L1** and the structurally related phosphoramidites **L4**, **L5**, **L7**, **L8**, and **L9**. For these ligands, full conversion was achieved, and ee's of 83%−89% were obtained. The other ligands showed lower reactivity or selectivity. Characteristic of the more successful ligands in this study is the presence of at least one small substituent (a methyl group) on the nitrogen. This requirement has previously been noted in the rhodium-catalyzed asymmetric hydrogenation.[20,21]

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(12) Takaya, Y.; Ogasawara, M.; Hayashi, T. *Chirality* **2000**, *12*, 469−471.

(13) The rhodium−$P(OEt)_3$-catalyzed addition of arylboronic acids to oxabenzonorbornadienes has been reported very recently: Murakami, M.; Igawa, H. *Chem. Commun.* **2002**, 390−391.

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(16) van den Berg, M.; Minnaard, A. J.; Schudde, E. P.; Van Esch, J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2000**, *122*, 11539−11540.

(17) Synthesized according to known procedures, see refs 1 and 20. For **L6**, **L8**, and **L9**, see the Supporting Information.

(18) After a first screening, Rh(acac)$(C_2H_4)_2$ was selectioned as the rhodium source of choice. See the Supporting Information.

(19) (a) The use of 2.5 equiv of ligand relative to rhodium was chosen for convenience as it was observed that the reaction proceeds better with a slight excess of phosphoramidite (compared to the 1:2 Rh/L ratio). (b) Replacing water by methanol provides the same conversion and ee although reaction time increases.

Surprisingly, modification of the bisphenol part of the ligand did not effect to a major extent the high level of ee, since the structurally different ligands **L1**, **L7**, **L8**, and **L9** gave almost the same results (84−89% ee).

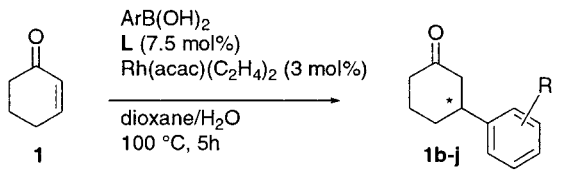
During most reactions, homogeneous and brightly yellow colored solutions were observed. Upon repeating some of the reactions we found Rh-black formed in one of the flasks that contained **L1** as ligand after only 15 min of reaction time. Analysis of the mixture showed that full conversion and 84% ee had been achieved. This means that the catalyst based on **L1** shows a considerably faster reaction (15 min vs 5 h with BINAP),[22] but a less selective one than with the Rh−BINAP-based catalyst applied by Hayashi.

This particular reaction was studied in more detail. Increasing the ligand-to-rhodium ratio did not affect the conversion or the ee. Surprisingly, the use of an excess of $PhB(OH)_2$ turned out to be unnecessary.[23] A 1.2 equiv portion of $PhB(OH)_2$ provided 100% conversion and 84% ee at 100 °C in 15 min.[24] An experiment on a larger scale (2 g of cyclohexenone, 21 mmol) using 0.6 mol % of an in situ generated catalyst from $Rh(acac)(C_2H_4)_2$ and 2.5 equiv of **L1** and 1.2 equiv of phenylboronic acid, resulted in complete conversion within 1 h at 100 °C. The product was isolated in 92% yield with an ee of 84%.

In an attempt to improve the ee, we screened a number of water miscible solvents in the conjugate addition of phenylboronic acid to cyclohexenone. Several solvents turned out to be suitable for this reaction and the conversion was usually very selective affording the desired product **1a**. Dioxane remained the solvent of choice, although MeOH and *i*-PrOH also gave full conversion. With the latter solvents reaction times of >4 h are needed to complete the reaction but ee's are comparable (80−85%).

To examine the scope of the conjugate addition, several substituted arylboronic acids, and catalysts based on the ligands **L1** and **L7**, were used (Scheme 2). In all experiments, **L7** afforded higher enantioselectivity than **L1**. Compared to phenylboronic acid, all substituted boronic acids gave a slower conversion to the product as full conversion was not achieved in 5 h at 100 °C.

Scheme 2. Conjugate Addition of Substituted Phenylboronic Acids, Using Catalysts Based on **L1** or **L7**



[a] Determined by ^1H NMR. [b] Determined by chiral HPLC or GC; all reactions are performed with 2 equiv of boronic acid.

It turned out that the nature and the position of the substituent on the phenyl ring has an effect on both the reactivity and the enantioselectivity. In all cases, ortho-substituted boronic acids gave a slow conversion and lower ee's, probably due to steric hindrance. This decrease in reactivity was also observed with *o*-fluoro-substituted phenylboronic acid, but in that case, a good enantioselectivity (ee = 73%) was achieved. This is probably due to the small size of the fluorine. The moderate conversions obtained with the fluorine-substituted boronic acids can also be explained by the fast hydrolysis reaction observed by Hayashi in similar cases.[5g]

Apparently, substituents at the meta position do not have an effect on the enantioselectivity of the reaction. Ee's up to 89% are achieved, which is comparable to values found in the unsubstituted case.

Interestingly, the addition of 4-methoxyphenylboronic acid occurs (entries 8 and 9), although complete conversion is not achieved. It should be noted that for this substrate, Hayashi reports under the present conditions (dioxane/water, Rh−BINAP at 100 °C) formation of only anisole[5i] whereas Reetz reports full conversion for this compound and an ee of 95%.[14] 2-Thiopheneboronic acid, 2-furanboronic acid, and 2,6-dimethylphenylboronic acid did not give any conversion.

To further investigate the scope of this reaction, a number of α,β-unsaturated ketones, esters, lactones, and nitroalkenes were investigated in the Rh-**L1**- and Rh-**L7**-catalyzed conjugate addition of phenylboronic acid (Figure 2, Table 1).

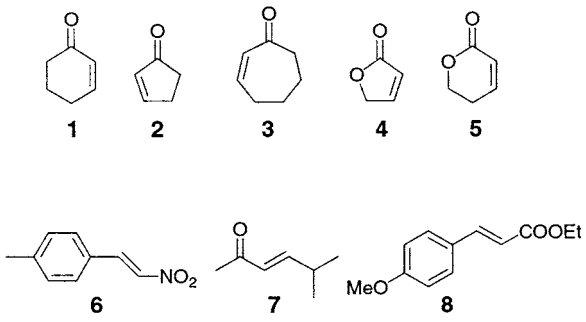


Figure 2. Substrates for the conjugate addition of phenylboronic acid.

The smaller and less flexible cyclopentenone **2** gives full conversion but the product is isolated with a disappointing 15% ee using **L1** as the ligand. The use of **L7** resulted in an increase in ee to 50%. This trend continues for the other substrates: higher ee's are obtained when **L7** is used as a ligand. Cycloheptenone **3** and 5,6-dihydro-2*H*-pyran-2-one **5** in combination with **L7** resulted in the 1,4-adducts with 78% ee and 62% ee, respectively. For 2(5*H*)-furanone **4**,

(20) Peña, D.; Minnaard, A. J.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 14552−14553. See also ref 16.

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(22) At 25 °C, 63% conversion (84% ee) was reached in 16 h.

(23) For the BINAP-catalyzed conjugate addition, 5 equiv of $PhB(OH)_2$ are employed to achieve complete conversion, since considerable amounts of benzene are formed; see ref 5c.

(24) Hayashi recently reported a similar result using a preformed BINAP hydroxorhodium complex; see ref 5i.

Table 1. Conjugate Addition of Phenylboronic Acid to Several Alkenones, Using Catalysts Prepared from **L1** or **L7**

entry	substrate	ligand	adduct	conv,[a] %	ee,[b] %
1	**1**	**L1**	**1a**	100	84
2	**1**	**L7**	**1a**	100	89
3	**2**	**L1**	**2a**	100	15
4	**2**	**L7**	**2a**	100	50
5	**3**	**L1**	**3a**	64	71
6	**3**	**L7**	**3a**	80	78
7	**4**	**L1**	**4a**	50	38
8	**4**	**L7**	**4a**	45	14
9	**5**	**L1**	**5a**	100	29
10	**5**	**L7**	**5a**	100	62
11	**6**	**L1**	**6a**	100	44
12	**7**	**L1**	**7a**	100	16
13	**8**	**L1**	**8a**	87	23

[a] Determined by ^{1}H NMR. [b] Determined by chiral HPLC or GC.

however, the opposite is observed: a change from **L1** to **L7** results in a drop in ee from 38% to 14%. The origin of this effect is not clear. Linear nitro alkene **6** and acyclic alkenones **7** and **8** afforded the products with 44% ee, 16% ee, and 23% ee, respectively, when **L1** was used as a ligand.

This study demonstrates that monodentate ligands can be applied successfully in the rhodium-catalyzed conjugate addition of arylboronic acids to enones, unsaturated esters, lactones, and nitroalkenes. The applied phosphoramidite ligands are surprisingly stable under the reaction conditions and lead to moderate to high ee in the 1,4-adduct. The ligand of choice is H8-MonoPhos **L7** as it is superior in selectivity compared to related ligands. The best results obtained to date are with cyclohexenone **1**, as the 1,4-adduct is formed with an ee of 89%. A remarkable finding is the rate of the conjugate addition. Using H8-MonoPhos **L7** at 100 °C, full conversion is reached within 15 min. A comparison of substrate range studied so far between the present catalyst and the systems developed by Hayashi, Reetz and Tomioka shows that the bidentate ligand-based catalytic systems are superior in scope at present. Our preliminary results using simple, cheap monodentate phosphoramidites for this reaction will stimulate the development of a widely applicable monodentate ligand for rhodium-catalyzed conjugate addition. Investigations to enhance the enantioselectivity and to obtain insight into factors governing the fast reaction observed during the Rh-catalyzed asymmetric conjugate addition of arylboronic acid to enones using phosphoramidites are currently in progress.

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Supporting Information Available: Selected experimental procedures and ^{1}H NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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