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BINOL-Based Diphosphonites as Ligands in the Asymmetric Rh-Catalyzed Conjugate Addition of Arylboronic Acids

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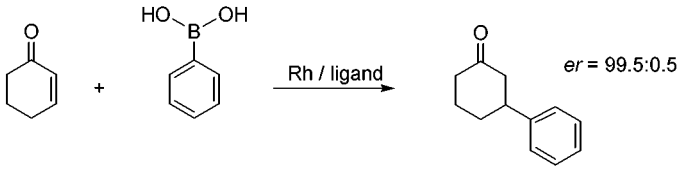
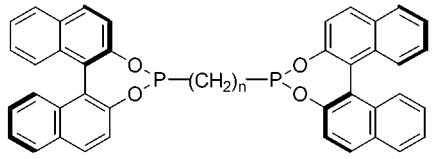
ABSTRACT

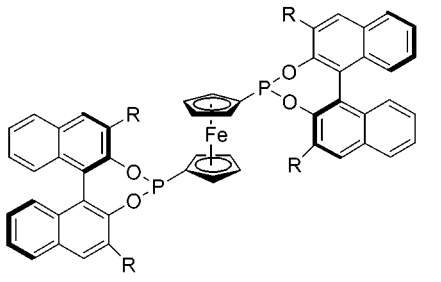


BINOL-based diphosphonites having achiral backbones are useful ligands in the Rh-catalyzed conjugate addition of arylboronic acids to α,β-unsaturated carbonyl compounds. The nature of the achiral backbone determines the direction and degree of enantioselectivity, with er values of up to 99.5:0.5 possible.

We have previously shown that BINOL-based diphosphonites of the type **1**−**2** are excellent ligands in the Rh-catalyzed asymmetric hydrogenation of prochiral olefins (er = 97:3 to 99:1).[1] It was therefore of interest to test these

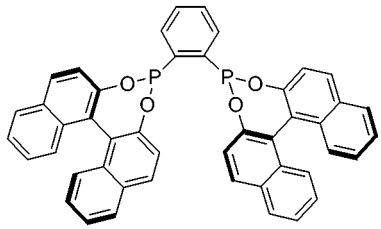


1 a n = 2
b n = 4



2 a R = H
b R = CH_3
c R = Br
d R = Ph

and related diphosphonites such as **3** and **4** in other types of transition metal catalyzed reactions. Herein we report their use in the asymmetric Rh-catalyzed conjugate addition of arylboronic acids to α,β-unsaturated carbonyl compounds, a reaction first reported by Hayashi and Miyaura using BINAP as the chiral ligand.[2]



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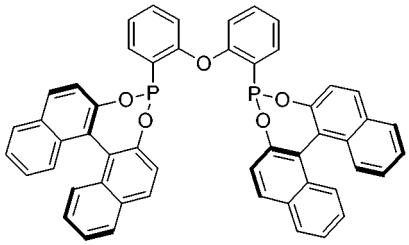

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The ligands **1**−**2** were prepared in good yields as previously reported.[1] The synthesis of the diphosphonites **3** and

(1) (a) Reetz, M. T.; Gosberg, A.; Goddard, R.; Kyung, S.-H. *Chem. Commun. (Cambridge)* **1998**, 2077−2078. (b) Reetz, M. T. *Pure Appl. Chem.* **1999**, *71*, 1503−1509. (c) Reetz, M. T.; Gosberg, A. German patent application 19840279.1 (04/09/1998).

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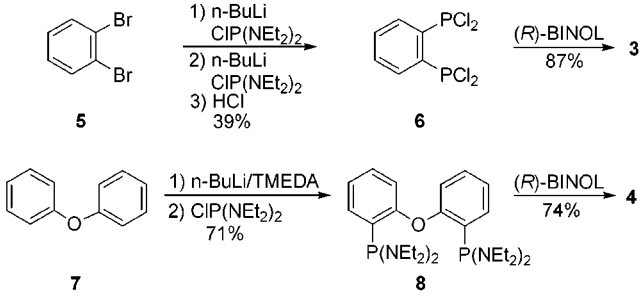
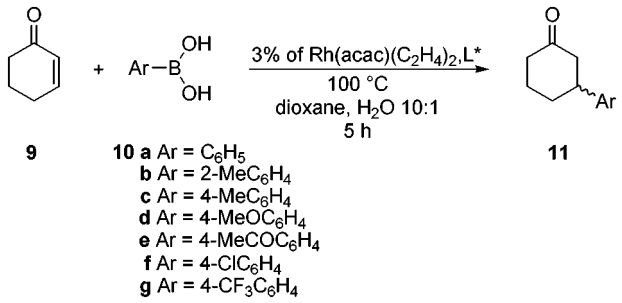
4 also posed no problems.[1c] In the present study all ligands were based on (*R*)-BINOL.



In exploratory experiments the model reaction of cyclohexenone **9** with phenylboronic acid **10a** was performed using $Rh(acac)(C_2H_4)_2$ as the rhodium source and a diphosphonite as the ligand (1:1) under conditions described by Hayashi and Miyaura[2] (3 mol % of Rh; 5 molar excess of **10a**; presence of H_2O in dioxane, 1:10; 100 °C; 5 h).



The immediate conclusion concerns the observation that diphosphonites, which are not as electron-rich as diphosphines (e.g., BINAP), are well suited for this transformation. Moreover, Table 1 shows that the nature of the achiral backbone of the ligands (all containing (*R*)-BINOL at phosphorus) influences the stereochemical outcome. Whereas in the previously reported Rh-catalyzed hydrogenation ferrocene-based ligands **2** are the best,[1] the ethano- and phenylene-bridged ligands **1a** and **3** are clearly superior in the present reaction, resulting in er values of 97.5:2.5 and 99.5:0.5, respectively, in favor of (*S*)-**11a** (Table 1). Thus, ligand **3** is as efficient as BINAP (er = 98.5:1.5).[2a] Surprisingly, ligand **4** leads to the *opposite* enantiomer (*R*) with excellent selectivity (er = 98.5:1.5; Table 1, entry 8). This means that it is possible to control the absolute configuration of the product either by the choice of (*R*)- or (*S*)-BINOL in the synthesis of the ligands or by the choice of the achiral backbone alone. Although the source of the stereochemical switch when going from **3** to **4** is difficult to pinpoint presently, it may to be related to increased flexibility of the backbone of the Rh-complex of ligand **4** and/or different bite angles. Indeed, ligand **1b**, which can be expected to be more flexible than **1a**, also shows opposite enantioselectivity (Table 1, entry 2), although the effect is less pronounced.

Table 1. Rh-Catalyzed Conjugate Addition of **10a** to **9** (5:1)

entry	ligand	mol % of Rh	conversion (%)	er	configuration of **11**[a]
1	**1a**	3	100	97.5:2.5	*S*
2	**1b**	3	100	71.5:28.5	*R*
3	**2a**	3	89	75.5:24.5	*S*
4	**2b**	3	84	91:9	*S*
5	**2c**	3	100	92.5:7.5	*S*
6	**2d**	3	77	89:11	*S*
7	**3**	3	100	99.5:0.5	*S*
8	**4**[b]	3	100	98.5:1.5	*R*
9	**3**	0.3	100	95.5:4.5	*S*
10	**4**	0.3	100	98.5:1.5	*R*

[a] Configurational assignment was made by comparison with authentic samples. [b] In this case 1.2 equiv of **10a**.

Several parameters were then varied in order to learn more about the reaction, especially concerning the role of water. Hayashi and Miyaura postulate a hydroxy-rhodium species as the actual catalysts.[2g,h] We therefore studied the influence of water on the reaction of **9** with **10a** using ligand **1a**. In the absence of any water, conversion was still complete, but the er value decreased from 97.5:2.5 to 92:8. This may well be due to different catalytic species. In other cases no significant influence on enantioselectivity was observed.

Another aspect of the original procedure based on BINAP has to do with the necessity of using an excess of phenylboronic acid (**10a**), with conversion to **11** decreasing from 99% to 64% upon lowering the **10**/**9** ratio from 5:1 to 1.4:1.[2a] This has been ascribed to protonation of a phenyl−rhodium intermediate with undesired formation of benzene.[2] In our case it is usually not necessary to use a great excess of reagent **10a**. For example, when employing ligand **4**, 99% conversion to the described product is observed by using just 1.2 equiv of **10a**. Another advantage of the diphosphonite ligand system concerns the fact that several of these ligands lead to catalysts which are particularly active, the reaction of **9** with **10a** requiring only 0.3 mol % of Rh/**3** or Rh/**4** (Table 1, entries 9 and 10). Although a reaction time of 5 h was chosen for all reactions in the standard protocol, many of them are over within half an hour. Alternatively, the reaction can even be run at room temperature/36 h, leading to 100% conversion and 95.5:2.5 to 98.5:1.5 er values using 3 mol % of Rh/**4**. In the case of the reaction using 3 mol % of Rh/BINAP, only 41% conversion (99.5:0.5 er) is observed.

The conjugate addition was then extended to include arylboronic acids **10b**−**g**. Although not all of the ligands were tested, the generality of the process was demonstrated (Table 2). In some of the cases the er values are slightly lower than in the BINAP system.[2] However, it needs to be pointed out that upon using Rh/BINAP the electron-rich

(2) (a) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579−5580. (b) Hayashi, T.; Senda, T.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **1999**, *121*, 11591−11592. (c) Hayashi, T.; Senda, T.; Ogasawara, M. *J. Am. Chem. Soc.* **2000**, *122*, 10716−10717. (d) Sakuma, S.; Sakai, M.; Itooka, R.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 5951−5955. (e) Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron: Asymmetry* **1999**, *10*, 4047−4056. (f) Kuriyama, M.; Tomioka, K. *Tetrahedron Lett.* **2001**, *42*, 921−923. (g) Hayashi, T. *Synlett* **2001**, 879−887. (h) Itooka, R.; Iguchi, Y.; Miyaura, N. *Chem. Lett.* **2001**, *7*, 722−723.

Table 2. Rh-Catalyzed Conjugate Addition of **10b−g** to **9**[a]

entry	reagent[b]	ligand	conversion (%)	er
1	**10d**	**1a**	88	95.5:4.5
2	**10e**	**1a**	82	93.5:6.5[c]
3	**10b**	**3**	96	96.5:3.5
4	**10c**	**3**	100	97:3
5	**10d**	**3**	87	97.5:2.5
6	**10e**	**3**	88	97:3
7	**10f**	**3**	75	95.5:4.5
8	**10g**	**3**	93	94.5:5.5

[a] 3 mol % of Rh. [b] 5 equiv. [c] Determined by HPLC on Chiralcel OD-H.

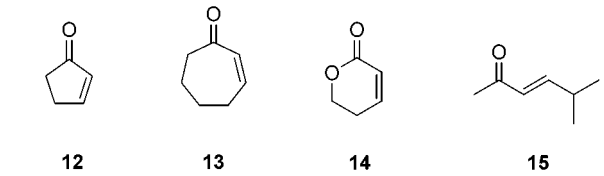
arylboronic acid **10d** affords none of the desired adduct **11d** (only protonation with formation of anisol),[2] whereas Rh/**3** results in excellent conversion and enantioselectivity (entry 5, Table 2).

We then studied the reaction of phenylboronic acid (**10a**) with other substrates, **12**−**15**. Again, although not all ligands were tested, it was found that **3** and **4** are usually the most active and selective, leading to products having opposite absolute configuration (Table 3). Noteworthy is the fact that both cyclic and acyclic substrates react rapidly and selectively. In two cases the absolute configuration is presently unknown, which means that only the polarimetrically determined sign of the specific rotation is given, as was reported by Hayashi and Miyaura.[2a]

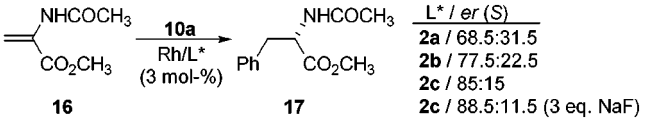
Table 3. Rh-Catalyzed Conjugate Reactions of **10a**[a]

entry	substrate	ligand	conversion (%)	er	configuration
1	**12**	**1a**	63	91:9	*S*
2	**12**	**2a**	100	76.5:23.5	*S*
3	**12**	**3**	58	94.5:5.5	*S*
4	**13**	**1a**	100	92.5:7.5	(−)[b]
5	**13**	**2a**	100	79.5:20.5	(−)[b]
6	**13**	**3**	100	92.5:7.5	(−)[b]
7	**13**	**4**	100	98:2	(+)[b]
8	**14**	**1a**	83	96:4	*S*
9	**14**	**2c**	100	85:15	*S*
10	**14**	**3**	100	97:3	*S*
11	**15**	**3**	82	98:2	(−)[b]
12	**15**	**4**	85	66:34	(+)[b]

[a] All reactions were carried out in dioxane/H_2O (10:1) at 100 °C for 5 h using 3 mol % of Rh/L*. Configurational assignment was made by comparison with authentic samples. [b] Sign of specific rotation.



Finally, it was of interest to test the α-acetamido acrylic acid ester **16** because stereochemistry is not only determined in the phenyl insertion step but also in the protonation. This type of transformation is known using phenyltin reagents,[3] but an asymmetric catalytic version has not been reported. Using the BINAP-based Rh catalyst,[2] we observed 100% conversion to the phenylalanine derivative **17**, but the product turned out to be racemic. In the case of phosphonites, conversion under the standard conditions was also quantitative. Moreover, significant albeit not perfect enantioselectivity resulted. The best er was observed with ligand **2c** (85:15 in favor of (*S*)-**17**) which was increased to 88.5:11.5 in the presence of 3 equiv of NaF:



In conclusion, BINOL-based diphosphonites are useful ligands in the Rh-catalyzed conjugate addition reactions. Advantages include simple synthesis, high catalyst activity, and useful levels of enantioselectivity. It is also clear that variation of the achiral backbone can be used to tune the ligands, with even reversal of enantioselectivity being observed. Since the trends in the present reaction are quite different from those observed previously in the case of hydrogenation,[1] the question regarding the universal chiral diphosphonite cannot be answered. We are currently studying other types of transition metal catalyzed processes using BINOL-based diphosphonites.[1c]

Supporting Information Available: Experimental procedures and full characterization for typical compounds **3** and **11a**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL010219Y

(3) Huang, T.-S.; Li, C.-J. *Org. Lett.* **2001**, *3*, 2037−2039 and references therein.