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Tetrahedron Letters 44 (2003) 6505–6508

TETRAHEDRON LETTERS

Bipyridyl-based diphosphine as an efficient ligand in the rhodium-catalyzed asymmetric conjugate addition of arylboronic acids to α,β-unsaturated ketones

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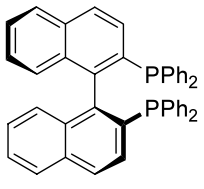
Received 2 May 2003; revised 28 May 2003; accepted 17 June 2003

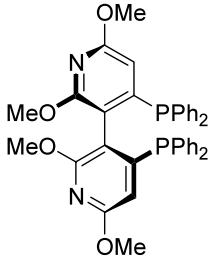
Abstract—Reactions of α,β-unsaturated ketones with excess arylboronic acids in the presence of a rhodium catalyst generated in situ from Rh(acac)(C_2H_4) and (*S*)-P-Phos in dioxane/water at 100°C gave high yields of the corresponding products in up to 99% ee.

The rhodium(I)-catalyzed 1,4-addition of aryl or alkenyl boronic acids to unsaturated compounds containing electron-deficient groups, first reported by Miyaura in 1997, is emerging as a new and powerful tool to introduce aryl or alkenyl groups to Michael acceptors.[1,2] By employing a BINAP-based rhodium complex as catalyst, Hayashi and his co-workers developed the asymmetric version of 1,4-addition of organoboronic acids to α,β-unsaturated ketones.[3] Extension of this methodology to α,β-unsaturated esters,[4a,d,g] 1-alkenylphosphonates,[4b] 1-nitroalkenes,[4c] and α,β-unsaturated amides[4e,f,g] also afforded good yields and high enantioselectivities. Among other chiral ligands examined, including water-soluble *Digm*-BINAP,[5] BINOL-based diphosphonites,[6] hemilabile bidentate amidomonophosphine[7] and other chelating diphosphines,[3d,4e] BINAP was found to give rise to the most active and enantioselective catalysts. Lately, the Hayashi group disclosed a detailed study of the reaction mechanism, and discovered an even more active rhodium(I) catalyst employing (*S*)-BINAP as a ligand.[8] More recently, Feringa et al. reported that monodentate phosphoramidites could be used as ligands in this reaction to give products in up to 89% ee.[9] It becomes obvious that the structure of the ligand has a significant effect on the reactivity of the metal complex and enantioselectivity of the products.

Recently metal complexes of bipyridyl-based diphosphine, e.g. P-Phos, and its derivatives have been shown to be highly active and enantioselective catalysts in asymmetric hydrogenations[10] and carbonylations,[11] suggesting that the rigidity of the bipyridyl backbone allows good transfer of chiral information. In this article, we wish to report results of P-Phos as a ligand in Rh(I)-catalyzed 1,4-addition of boronic acids to enones.



(*S*)-BINAP



(*S*)-P-Phos

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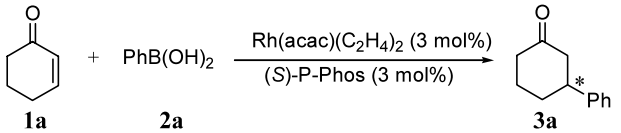
doi:10.1016/S0040-4039(03)01592-2

In the model reaction, 2-cyclohexenone **1a** was treated with phenylboronic acid **2a** in the presence of 3 mol% [Rh(acac)((*S*)-P-Phos)], which was generated in situ from equimolar of Rh(acac)($CH_2=CH_2$)$_2$ and (*S*)-P-Phos in dioxane/H_2O (10/1) at 100°C. Considering the possibility of the hydrolysis of arylboronic acid under the reaction conditions,[2b] an excess amount of phenylboronic acid (5 equiv.) was added. After stirring for 1 h, the reaction went to completion to give the adduct **3a** with almost quantitative yield (>99%) and excellent ee (99%).[13] The result compares favorably with those obtained with BINAP. According to Tomioka, the catalytic performance of BINAP strongly depends on the initial procedure.[7a] To test this effect, the same reaction promoted by Rh(I)/(*S*)-P-Phos was then conducted with a different initial procedure. Thus, the reaction mixture was first allowed to warm from ambient temperature to 100°C in 10 min, followed by stirring for a further 1 h. The same yield and enantioselectivity were obtained, implying that the catalytic performance of P-Phos is independent of the initial procedure. Table 1 summarizes the results obtained under the former reaction conditions at various temperatures. It was found that high chemical yield and enantioselectivity were dependent on the reaction temperature. As can be seen from Table 1, the reaction temperature of 100°C was found to be optimum. At room temperature, after stirring for 5 h, no product was observed. When the temperature was raised to 40°C, the 1,4-addition still remained sluggish, providing **3a** in less than 5% yield after 5 h. At 80°C, the yield increased to 70% after 5 h of stirring with 99% ee. Noticeably, a higher temperature (cf. 120°C, entry 5) decreased the otherwise good yield and ee. Similar temperature effect was noted with Rh(I)/BINAP as a catalyst.[3d]

A variety of α,β-unsaturated ketones as well as arylboronic acids were coupled in the Rh(I)/(*S*)-P-Phos catalyzed 1,4-conjugate addition under conditions similar to the addition of phenylboronic acid to 2-cyclohexenone **1a**. The results are summarized in Table 2.

Table 1. Asymmetric 1,4-addition of phenylboronic acid **2a** to 2-cyclohexenone **1a** catalyzed by Rh(I)/(*S*)-P-Phos[a]



1a **2a** **3a**

Entry	Temp. (°C)	Time (h)	Yield (%)	Ee (%)[b]
1	100	1	>99	99
2	25	5	0	–
3	40	5	5	97
4	80	5	70	99
5	120	5	79	97

[a] Reactions were carried out with **1a** (0.40 momol), **2a** (2.0 mmol) under N_2 in dioxane (1 ml)/H_2O (0.1 ml).

[b] Determined by HPLC analysis using a Daicel Chiralcel OD-H chiral stationary phase column.

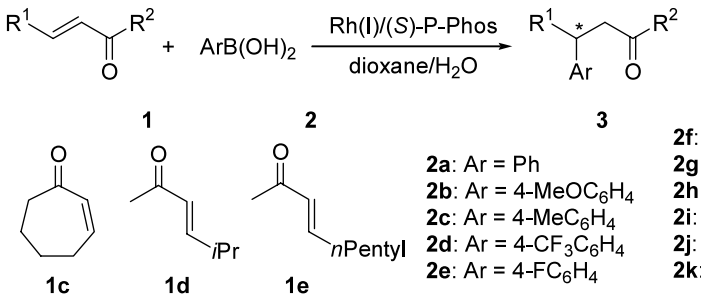
Enones **1b–e** underwent the reaction with phenylboronic acid **2a** smoothly, providing high yields and enantioselectivites (entries 1–4). For example, asymmetric addition of phenylboronic acid to enone **1c** catalyzed by the Rh(I)/(*S*)-P-Phos complex led to 88% yield and 98% ee. Yet, when the (*S*)-BINAP-Rh(I) was used for this addition, the yield and enantioselectivity were reported to be 51 and 93%, respectively.[3a] In the reaction of arylboronic acid **2b**, it was found that a reduced amount of water favored the addition, affording higher yield (entry 5 versus 6). Using 5 equiv. of **2b** and 3 mol% Rh(I)/(*S*)-P-Phos in dioxane/H_2O (20/1) at 100°C for 5 h, 90% yield and 99% ee were achieved, whereas no addition product was formed using the Rh(I)/BINAP catalyst.[2b,3c] Both the yield and ee suggest that P-Phos may efficiently retard the competing hydrolysis of the boronic acid giving methoxybenzene. In the presence of a reduced amount of water, similarly good results were also found in the reactions of **2b** with enones **1b** and **1c** (entry 7 versus 8 and entry 9 versus 10). Excellent enantioselectivities and yields were also observed in the reactions of 2-cyclohexenone **1a** with a wide array of arylboronic acids **2c–i** (entries 11–17). It is worth noting that in the addition of arylboronic acid **2e** to 2-cyclohexenone **1a** catalyzed by Rh(I)/(*S*)-BINAP the yield was disappointingly low.[8] In contrast, when Rh(I)/(*S*)-P-Phos catalyst was employed, the yield rose to 97% (entry 13). For the *ortho*-substituted arylboronic acid **2j**, high yield and enantioselectivity were obtained with lower-water-content solvent system, indicating that steric hindrance does not cause great disturbance to the reaction (entry 18 versus 19). In the case of **2k**, the reduced amount of water did improve the reaction as indicated by an increase of yield from 15% to 44% (entry 20 versus 21). Further reduction of the water-to-dioxane ratio did not lead to improved yield beyond 45%. Two possible intervening events may be operative: (1) Because of the similar π-releasing property of MeO in **2k** and **2b** (versus the *meta*-analog **2f**), hydrolysis of **2k** to produce methoxybenzene may just be as facile. (2) Considering the oxophilicity of Rh(I), the low yield may be ascribed to the existence of intramolecular chelation, which has been observed in the coordination chemistry of rhodium complexes.[12]

In conclusion, P-Phos has been shown to be an efficient ligand in the rhodium-catalyzed 1,4-addition of arylboronic acids. The activity and stereorecognition ability of Rh(I)/P-Phos catalyst in this addition reaction is comparable to, or at times better than, those observed with BINAP, BINOL-based diphosphonites and hemilabile bidentate amidomonophosphine.

Acknowledgements

We thank The Hong Kong Research Grants Council Central Allocation Fund (Project ERB003), The University Grants Committee Areas of Excellence Scheme in Hong Kong (AoE P/10-01) and The Hong Kong Polytechnic University ASD Fund for financial support of this study.

Table 2. Asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated ketones catalyzed by Rh(I)/(*S*)-P-Phos[a]



Entry	Ketone **1**	$ArB(OH)_2$ (equiv. to **1**)	Time (h)	Yield (%)	Ee (%)[c]
1	**1b**	**2a** (1.4)	5	89	97
2	**1c**	**2a** (1.4)	5	88	98
3	**1d**	**2a** (2.5)	5	90	90
4	**1e**	**2a** (5.0)	5	86	96
5	**1a**	**2b** (5.0)	5	82	99
6[b]	**1a**	**2b** (5.0)	5	90	99
7	**1b**	**2b** (5.0)	5	77	99
8[b]	**1b**	**2b** (5.0)	5	90	99
9	**1c**	**2b** (5.0)	5	62	99
10[b]	**1c**	**2b** (5.0)	5	86	99
11	**1a**	**2c** (5.0)	4	>99	99
12	**1a**	**2d** (5.0)	4	97	99
13	**1a**	**2e** (5.0)	4	97	96
14	**1a**	**2f** (5.0)	4	95	99
15	**1a**	**2g** (5.0)	4	97	99
16	**1a**	**2h** (5.0)	4	94	99
17	**1a**	**2i** (5.0)	4	98	97
18	**1a**	**2j** (5.0)	5	74	99
19[b]	**1a**	**2j** (5.0)	5	90	99
20	**1a**	**2k** (5.0)	5	15	99
21[b]	**1a**	**2k** (5.0)	5	44	99

[a] Reactions were carried out under N_2 in dioxane (1 ml)/H_2O (0.1 ml) at 100°C in the presence of 3 mol% of the catalyst generated from $Rh(acac)(C_2H_4)_2$ and (*S*)-P-Phos.
[b] Dioxane (1 ml)/H_2O (0.05 ml).
[c] Determined by HPLC analysis using Daicel Chiralcel chiral stationary phase columns.

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13. *Typical procedure for the Rh(I)-catalyzed 1,4-conjugate addition of arylboronic acid to enones*: A flask charged with $[Rh(acac)(C_2H_4)_2]$ (3.1 mg, 12 μmol), (*S*)-P-Phos (7.7 mg, 12 μmol) and $PhB(OH)_2$ (224 mg, 2.00 mmol) was flushed with nitrogen. To the flask was added successively 2-cyclohexenone (39 mg, 0.40 mmol), 1,4-dioxane (1.0 mL) and water (0.1 mL). The mixture was stirred at 100°C for 1 h. After evaporation of the solvent, the residue was diluted with ethyl acetate and then washed with saturated $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4, concentrated under reduced pressure, and chromatographed on silica gel (hexane/EtOAc = 5/1) to give 3-phenylcyclohexanone (70 mg, >99%). The ee value of the product was determined by HPLC analysis.