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A new C_2-symmetric chiral bisphosphine ligand containing a bioxazole backbone: highly enantioselective hydrosilylation of ketones

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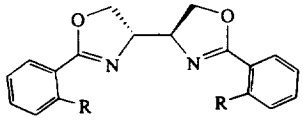
Abstract: C_2-Symmetric (4*S*,4′*S*)-2,2′-bis(*o*-diphenylphosphinophenyl)-4,4′,5,5′-tetrahydro-4,4′-bi(1,3-oxazole) (**1**, Phos-Biox) has been designed and synthesized as a chiral ligand for metal-catalyzed reactions. The Phos-Biox **1** was found to be an efficient ligand for rhodium(I)-catalyzed asymmetric reduction of prochiral acetophenones with diphenylsilane to give optically active secondary alcohols of up to 97% ee. © 1997 Elsevier Science Ltd. All rights reserved.

The design and synthesis of new chiral ligands for transition metals have played a significant role in the development of catalytic asymmetric reactions, and there have been many efforts devoted to the preparation of efficient ligands.[1] In particular, to reduce the number of stereochemical permutations within the catalytic ensemble, a series of C_2-symmetric chiral bisphosphine (*P*,*P*-chelation)[2] and bisoxazoline (*N*,*N*-chelation)[3] ligands have attracted considerable attention as chiral ligands for metal-catalyzed asymmetric reactions. Recently, an introduction of phosphine–oxazoline hybrid ligands opened up a new path to the development of chiral ligands, and are demonstrated to be efficient in various metal-catalyzed asymmetric reactions.[4] However, in sharp contrast with the *P*,*P*- and *N*,*N*-ligands, C_2-symmetric phosphine–oxazoline hybrid ligands have not received much attention.[5] During our studies on the design of new C_2-symmetric bioxazole (Biox) derivatives as chiral ligands,[6] we have prepared optically active C_2-symmetric bisphosphine ligand, (4*S*,4′*S*)-2,2′-bis(*o*-diphenylphosphinophenyl)-4,4′,5,5′-tetrahydro-4,4′-bi(1,3-oxazole) **1** (abbreviated (*S*,*S*)-Phos-Biox) which is expected to be effective as a chiral ligand for several types of transition metal-catalyzed asymmetric reactions. Here we report the results of its application in rhodium(I)-catalyzed enantioselective hydrosilylation of acetophenone derivatives.



1 : R = PPh_2 (*S*,*S*)-Phos-Biox
2 : R = F (*S*,*S*)-F-Biox
3 : R = H (*S*,*S*)-Ph-Biox

The key feature of this bisphosphine ligand is that the conformationally rigid chiral bioxazole ring can restrict the flexibility of the ligand bound to a transition metal. Thus, the chiralities of the backbone could be transferred efficiently to the phosphine. Moreover, this ligand may provide a wide bite angle for the metal chelation, and create a deep chiral pocket. The C_2-symmetric bisphosphine–bioxazole hybrid ligand **1** was readily synthesized by the reaction of the potassium diphenylphosphide with fluorobioxazole **2** which was prepared according to our previously reported method using *o*-fluorobenzoyl chloride instead of benzoyl chloride for Ph-Biox **3**.[6]

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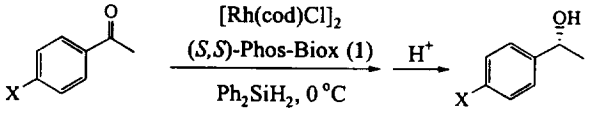
Table 1. Enantioselective hydrosilylation of acetophenones using (*S,S*)-Phos-Biox **1** as a ligand

Entry[a]	4	Rh/1/ketone[b]	Reaction Time (h)[c]	5/4[d]	% ee[e] (config)[f]
1	**a**	1/10/100	3	98/2	95(*R*)
2	**a**	1/2/400	7	98/2	97(*R*)
3	**b**	1/2/400	7	98/2	93(*R*)
4	**c**	1/2/400	3	97/3	91(*R*)
5	**d**	1/2/400	4	99/1	21(*R*)

[a] All reactions were carried out in THF at 0 °C. [b] mol ratio. [c] The reaction time in which all of the ketone was consumed. [d] Determined by ^{1}H NMR ($CDCl_3$) of the products after hydrolysis. [e] Determined by ^{1}H NMR of the corresponding (*R*)-MTPA ester. [f] Determined by major (CH_3O) signal of its (*R*)-(+)-MTPA ester in ^{1}H NMR ($CDCl_3$) spectrum: the methoxy signal of (*R*)-enantiomer was appeared at up field than that of the (*S*)-enantiomer.[7]

The efficiency of (*S,S*)-Phos-Biox **1** as a chiral ligand for the asymmetric hydrosilylation of acetophenones was examined. Thus, to a solution of the catalyst precursor prepared *in situ* by mixing $[Rh(cod)Cl]_2$ (cod=cyclooctadiene) and (*S,S*)-Phos-Biox in THF at room temperature was added ketone **4** and diphenylsilane at −10°C. The mixture was stirred at 0°C until the reaction was complete, and the resulting silyl ether was then hydrolyzed to give optically active alcohol **5**. The results are summarized in Table 1.



4a : X = H
4b : X = CH_3
4c : X = Cl
4d : X = OCH_3

5a : X = H
5b : X = CH_3
5c : X = Cl
5d : X = OCH_3

Although, Ito *et al.* recently reported alkyldiphosphanes as efficient chiral ligands,[2n] most of the chiral bisphosphine ligands afforded only low to moderate enantioselectivities in Rh(I)-catalyzed hydrosilylations of ketones.[2a–e] With respect to enantioselectivity, *N,N*-ligands such as bisoxazolines or pyridyl-oxazolines have so far proved superior to bidendate phosphine ligands. However, to obtain high levels of enantioselectivity with *N,N*-ligands, large excess amount of ligands, up to tenfold with respect to rhodium metal, were generally required.[3a,8b] Surprisingly, as shown in Table 1, all reactions using bisphophine ligand, Phos-Biox **1**, proceeded highly enantioselectively (91–97% ee, *R*) and the starting ketones were converted to the corresponding optically active secondary alcohols almost quantitatively (entries 1–4). The only exception was ketone **4d** containing the *p*-OMe substituent, for which a so-called '*p*-methoxy effect'[8b] diminished the enantioselectivity to 21% ee (entry 5). Such a '*p*-methoxy effect' on the enantioselectivity was also observed in the $[Rh(cod)Cl]_2$/(−)-DIOP[8a] and $[Rh(cod)Cl]_2$-(*R*)-Pythia[8b] catalyzed hydrosilylations and in the baker's yeast catalyzed reduction of **4d**.[8c] Under the standard conditions the rhodium:ligand:ketone ratio was 1:2:400. When the rhodium:ligand:ketone ratio was changed to a typical ratio (1:10:100) used in $[Rh(cod)Cl]_2$-Pythia[8b] catalyzed reactions, there was no change in product enantioselectivity (entry 1). This result suggests that the complex between rhodium and Phos-Biox **1** may have a higher binding stability than that of the $[Rh(cod)Cl]_2$-Pythia complex. Although the chelation mode is unclear at the present time, it should be noted here that, to the best of our knowledge, (*S,S*)-Phos-Biox **1** is the most effective chiral bisphosphine ligand for the rhodium(I)-catalyzed asymmetric hydrosilylation of acetophenone derivatives.[9]

In conclusion, the new C_2-symmetric chiral bisphosphine ligand, Phos-Biox **1**, is an excellent ligand for the rhodium(I)-catalyzed asymmetric hydrosilylation of ketones. This ligand is expected to have many applications in asymmetric catalysis. Further work aimed at the elucidation of the coordination mode and broadening the scope of this ligand to other catalysis are currently in progress and will be reported in due course.

Experimental

General

^{1}H NMR, ^{13}C NMR and ^{31}P NMR were recorded on a Varian Gemini 300 MHz spectrometer and optical rotations were measured with an Autopol® polarimeter. Chemical analyses were carried out by the Advanced Analysis Center at the Korea Institute of Science and Technology. Melting points were taken on a Thomas–Hoover capillary melting point apparatus and are uncorrected. HRMS (FAB) analysis was carried out by the Mass Spectrometry Analysis Group at Korea Basic Science Institute. THF was distilled prior to use from sodium/benzophenone under nitrogen. Column chromatography was performed on Kieselgel 60 (230–400 mesh) and TLC was carried out using glass sheets precoated with silica gel 60F254 purchased from Merck.

(4S,4′S)-2,2′-Bis(o-diphenylphosphinophenyl)-4,4′,5,5′-tetrahydro-4,4′-bi(1,3-oxazole) 1

To a solution of (4*S*,4′*S*)-2,2′-bis(*o*-fluorophenyl)-4,4′,5,5′-tetrahydro-4,4′-bi(1,3-oxazole) **2** (1.5 g, 4.57 mmol) in anhydrous THF (20 mL) was added potassium diphenylphosphide (9.14 mmol, as a 0.5 M solution in THF) at 0°C via syringe under an argon atmosphere. The mixture was then stirred for 30 min at the same temperature, whereupon the red solution of the phosphide fades to a pale yellow. The reaction was quenched by addition of water (10 mL), and extracted with methylene chloride (3×15 mL). The combined organic layer was dried with anhydrous $MgSO_4$, filtered and concentrated under rotavap. The residue was purified by column chromatography on silica gel (ethyl acetate:hexane=1:2) to give pure **1** (1.4 g, 46%) as white solid. R_f 0.54; $[\alpha]_D^{24}$ +53.2 (*c* 0.5, $CHCl_3$); m.p. 132–133°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (m, 2H), 7.38–7.20 (m, 24H), 6.89 (m, 2H), 4.22 (m, 2H), 3.57 (pseudo d, *J*=8.2 Hz, 4H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 11.62; HRMS (FAB) Calcd for $C_{32}H_{35}N_2O_2P_2[(M+H)^+]$: 661.2173. Found: 661.2170.

(4S,4′S)-2,2′-Bis(o-fluorophenyl)-4,4′,5,5′-tetrahydro-4,4′-bi(1,3-oxazole) 2

Prepared according to our previously reported method using *o*-fluorobenzoyl chloride instead of benzoyl chloride for Ph-Biox **3**.[6] $[\alpha]_D^{24}$ −29.1 (*c* 0.9, $CHCl_3$); m.p. 58–59°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (t, *J*=7.0 Hz, 2H), 7.47 (m, 2H), 7.17 (m, 4H), 4.93 (m, 2H), 4.47 (dd, *J*=9.6, 9.0 Hz, 2H), 4.37 (dd, *J*=9.6, 6.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.21, 161.05 (d, $J_{C,F}$=258.9 Hz), 132.0 (d, $J_{C,F}$=9.7 Hz), 131.02, 123.87, 116.55 ($J_{C,F}$=21.9Hz), 115.76. Anal. Calcd for $C_{18}H_{14}N_2O_2F_2$: C, 65.85; H, 4.30; N, 8.53. Found: C, 65.8; H, 4.32; N, 8.58.

Typical procedure for the rhodium-catalyzed hydrosilylation of acetophenone derivatives

A solution of acetophenone **4a** (1 mmol), $[Rh(cod)Cl]_2$ (1.2 mg, 0.25×10^{-2} mmol), and (*S*,*S*)-Phos-Biox **1** (3.3 mg, 0.5×10^{-2} mmol) was degassed, and then stirred for 1 h at room temperature under an argon atmosphere. After diphenylsilane (0.3 mL, 1.6 mmol) was added to the solution at −10°C, the reaction mixture was stirred at 0°C until ketone **4a** disappeared by TLC analysis (ethyl acetate:hexane=1:6, R_f 0.4). The reaction was quenched with methanol (5 mL), and then 1 N hydrochloric acid (10 mL) at 0°C. After stirring the solution for 1 h at 0°C, the organic layer was extracted with methylene chloride (4×10 mL). The combined organic layer was washed with saturated aqueous NaCl solution, dried with anhydrous $MgSO_4$, filtered and concentrated at 0°C using rotavap (30 mmHg) to give a yellowish oil. The ratio of **5a**:**4a** was determined by comparison of the methyl signals at 2.55 (s) and 1.43 (d, *J*=6.5 Hz) in the ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of the crude product. For measuring enantiomeric excess, the product was purified by column chromatography on silica gel (ethyl acetate:hexane=1:6, R_f 0.2), and then converted to the MTPA ester of **5a** with (*R*)-(+)-MTPA and $(COCl)_2$ to give (CH_3O) δ 3.46 for (*R*)-enantiomer (major) and 3.55 for (*S*)-enantiomer (minor) in ^{1}H NMR (300 MHz, $CDCl_3$) spectrum, 97% ee. **5b**: δ 3.47 (major) and 3.55 (minor), 93% ee: **5c**: δ 3.47 (major) and 3.56 (minor), 91% ee: **5d**: δ 3.45 (major) and 3.54 (minor), 21% ee.

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References

1. For reviews, see: (a) Ojima, I. (Ed), *Catalytic Asymmetric Synthesis*, VCH Publisher Inc., New York, 1993, 159. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*, John Wiley & Sons, New York, 1994.
2. Selected papers: (a) Kagan, H. B.; Dang, T.-P. *J. Am. Chem. Soc.* **1972**, *94*, 6429. (b) Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1977**, *99*, 6262. (c) Brunner, H.; Pieronzyk, W.; Schonhammer, B.; Streng, K.; Bernal, I.; Korp, J. *Chem. Ber.* **1981**, *114*, 1137. (d) McNeil, P. A.; Roberts, N. K.; Bosnich, B. *J. Am. Chem. Soc.* **1981**, *103*, 2273. (e) Allen, D. L.; Gibson, V. C.; Green, M. L. H.; Skinner, J. F.; Bashkin, J.; Grebenik, P. D. *J. Chem. Soc., Chem. Commun.* **1983**, 895. (f) Nagel, U.; Kinzel, E.; Andrade, J.; Prescher, G. *Chem. Ber.* **1986**, *119*, 3326. (g) Takaya, H.; Akutagawa, S.; Noyori, R. *Org. Synth.* **1988**, *67*, 20. (h) Schmid, R.; Cereghetti, M.; Heiser, B.; Schonholzer, P.; Hansen, H.-J. *Helv. Chim. Acta* **1988**, *71*, 897. (i) Miyasita, A.; Karino, H.; Shimamura, J.-I.; Chiba, T.; Nagano, K.; Nohira, H.; Takaya, H. *Chem. Lett.* **1989**, 1849. (j) Hayashi, T.; Yamamoto, A.; Hojo, M.; Ito, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 495. (k) Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Organometallics*, **1990**, *9*, 2653. (l) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518. (m) Trost, B. M.; Van Vranken, D. L. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 228. (n) Sawamura, M.; Kuwano, R.; Ito, Y. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 111. (o) Trost, B. M.; Breit, B.; Peukert, S.; Zambrano, J.; Ziller, J. W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2386. (p) Trost, B. M.; Van Vranken, D. L. *Chem Rev.* **1996**, *96*, 395 and references cited therein. (q) Zhu, G.; Cao, P.; Jiang, Q.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 1799.
3. Selected papers: (a) Nishiyama, H.; Sakaguchi, H.; Nakamura, T.; Horihata, M.; Kondo, M.; Itoh, K. *Organometallics* **1989**, *8*, 846. (b) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005. (c) Muller, D.; Umbricht, G.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232. (d) Helmchen, G.; Krotz, A.; Ganz, K.-T.; Hansen, D. *Synlett* **1991**, 257. (f) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726. (g) Nishiyama, H.; Yamaguchi, S.; Park, S.-B.; Itoh, K. *Tetrahedron: Asymmetry* **1993**, *4*, 143. (h) Ito, K.; Katsuki, T. *Tetrahedron Lett.* **1993**, *34*, 2661. (i) Park, S.-B.; Murata, K.; Matsumoto, H.; Nishiyama, H. *Tetrahedron: Asymmetry* **1995**, *6*, 2487. (j) Zhang, W.; Adschi, Y.; Hirao, T.; Ikeda, I. *Tetrahedron: Asymmetry* **1996**, *7*, 451. (k) Evans, D. A.; Murry, J.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 5814. (l) Bedekar, A.; Andersson, P. G. *Tetrahedron Lett.* **1996**, *37*, 4073. (m) Imai, Y.; Zhang, W.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Tetrahedron: Asymmetry* **1996**, *7*, 2453. (n) Uozumi, Y.; Kyota, H.; Kishi, E.; Kitayama, K.; Hayashi, T. *Tetrahedron: Asymmetry* **1996**, *7*, 1603. (o) Uozumi, Y.; Kato, K.; Hayashi, T. *J. Am. Chem. Soc.* **1997**, *119*, 5063. (p) Davies, O. W.; Gerena, L.; Cai, D.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1997**, *38*, 1145. (q) Kim, S.-G.; Cho, C.-W.; Ahn, K. H. *Tetrahedron: Asymmetry* **1997**, *8*, 1023.
4. (a) Matt, P. V.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566. (b) Dawson, G. J.; Frost, C. G.; Williams, J. M. *Tetrahedron Lett.* **1993**, *34*, 3149. (c) Eichelmann, H.; Gais, H. J. *Tetrahedron: Asymmetry* **1995**, *6*, 643. (d) Lloyd-Jones, G. C.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 462. (e) Nishibayashi, Y.; Segawa, K.; Ohe, K.; Uemura, S. *Organometallics* **1995**, *14*, 5486. (f) Nishibayashi, Y.; Segawa, K.; Takada, H.; Ohe, K.; Uemura, S. *Chem. Commun.* **1996**, 847. (g) Newman, L. M.; Williams, J. M. J.; McCague, R.; Potter, G. A. *Tetrahedron: Asymmetry* **1996**, *7*, 1597. (h) Sudo, A.; Saigo, K. *J. Org. Chem.* **1997**, *62*, 5508.
5. C_2-Symmetric diphenylphosphino(oxazolinyl)ferrocenes have been reported: (a) Zhang, W.; Hirao, T.; Ikeda, I. *Tetrahedron Lett.* **1996**, *37*, 4545. (b) Ahn, K. H.; Cho, C.-W.; Park, J.; Lee, S. *Tetrahedron: Asymmetry* **1997**, *8*, 1179.
6. Lee, S.; Lim, C. W.; Song, C. E.; Kim, I. O.; Jun, C. H. *Tetrahedron: Asymmetry* **1997**, *8*, 2927.
7. Nishiyama, H.; Kondo, M.; Nakamura, T.; Itoh, K. *Organometallics* **1991**, *10*, 500.

8. (a) Peyronel, J. F.; Fiaud, J. C.; Kagan, H. B. *J. Chem. Res.* **1980**, 4057. (b) Brunner, H.; Kürzinger, A. *J. Organomet. Chem.* **1988**, *346*, 413. (c) Eichberger, G.; Faber, K.; Griengl, H. *Monatsh. Chem.* **1985**, *116*, 1233.
9. Selected papers in which high enantioselectivities have been achieved in the Rh-catalyzed hydrosilylation of ketones: (a) Brunner, H.; Becker, R.; Riepl, G. *Organometallics* **1984**, *3*, 1354. (b) Brunner, H.; Obermann, U. *Chem. Ber.* **1989**, *122*, 499. (c) Brunner, H.; Brandl, P. *J. Organomet. Chem.* **1990**, *390*, C81. (d) see Refs 8b, 3a, 7, 2n, 3g and 4e.

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