# P-Chiral Bis(trialkylphosphine) Ligands and Their Use in Highly Enantioselective Hydrogenation Reactions

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Optically active phosphines play a most important role as the chiral ligands in various metal-catalyzed asymmetric reactions, and numerous chiral phosphines have been designed and synthesized over the past three decades.[1] Among them, some P-chiral phosphines such as (*R,R*)-1,2-bis[(*o*-methoxyphenyl)phenylphosphino]ethane (DIPAMP) were landmark discoveries at an early stage in the history of asymmetric hydrogenation reactions.[2,3] Thereafter, however, relatively less attention has been paid to P-chiral phosphine ligands in the field of asymmetric catalysis.[4] This is largely ascribed not only to the synthetic difficulty of highly enantiomerically enriched P-chiral phosphines but also to the fact that this class of phosphines, especially diaryl- and triarylphosphines, are configurationally unstable and gradually racemize at high temperatures.[5]

On the other hand, optically active trialkylphosphines are known to hardly racemize even at considerably high temperature.[6] On the basis of this fact, we designed a new class of P-chiral phosphine ligands, 1,2-bis(alkylmethylphosphino)ethanes (alkyl = *tert*-butyl, 1,1-diethylpropyl, 1-adamantyl, cyclopentyl, cyclohexyl) (abbreviated as BisP*) (Figure 1).[7] An important feature of these ligands is that a bulky alkyl group and the smallest alkyl group (methyl group) are bonded to each phosphorus atom. The ligands would form five-membered $C_2$-symmetric chelates, and this imposed asymmetric environment might lead to high enantioselectivity in asymmetric reactions. It is also anticipated that these electron-rich trialkylphosphine ligands provide very high catalytic efficiencies in transition-metal-catalyzed homogeneous hydrogenations.[8,9]

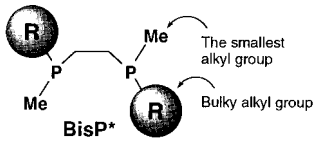
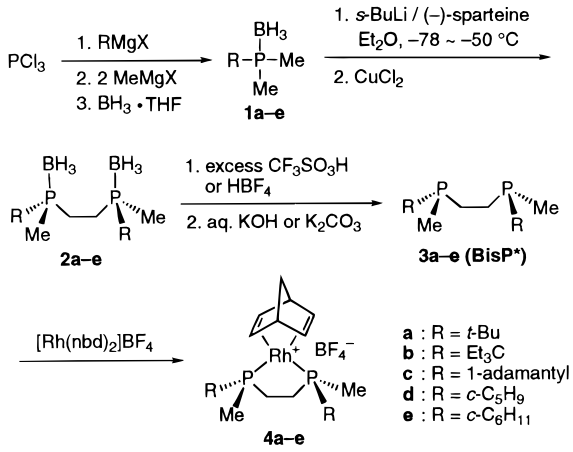



**Figure 1.**

**Scheme 1**




The preparation of the designed P-chiral phosphine ligands and their Rh-complexes has been accomplished using phosphine boranes as the intermediates (Scheme 1).[10] Evans et al. reported that aryldimethylphosphine boranes were subjected to enantioselective deprotonation by a *s*-BuLi−(−)-sparteine complex, followed by oxidative coupling using $Cu(OPiv)_2$, to afford $C_2$-symmetric bisphosphine boranes in excellent enantiomeric excesses (ee), but they did not describe the reactions of alkyldimethylphosphine boranes.[11] We applied their method to alkyldimethylphosphine boranes **1a**−**e** which were synthesized in one pot from phosphorus trichloride. The reactions of **1a**−**c** afforded highly enantiomerically enriched $C_2$-symmetric bisphosphines **2a**−**c** along with minor amounts of the meso diastereomers.[12] On the other hand, compounds **1d** and **1e** provided the corresponding $C_2$-symmetric products **2d** and **2e** with relatively low

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(1) For representative reviews, see the following: (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley & Sons: New York, 1994; Chapter 2. (b) Ojima, I., Ed. *Catalytic Asymmetric Synthesis*; VCH Publishers: Weinheim, 1993; Chapter 1. (c) Koenig, K. E. Applicability of Asymmetric Homogeneous Catalytic Hydrogenation. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 3.

(2) Horner, L.; Siegel, H.; Buthe, H. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 942.

(3) (a) Knowles, W. S.; Sabacky, M. J. *J. Chem. Soc., Chem. Commun.* **1968**, 1445. (b) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D. *J. Chem. Soc., Chem. Commun.* **1972**, 10. (c) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 2567. (d) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946. (e) Knowles, W. S. *Acc. Chem. Res.* **1983**, *16*, 106.

(4) (a) Roberts, N. K.; Wild, S. B. *J. Am. Chem. Soc.* **1979**, *101*, 6254. (b) Horner, L. *Pure Appl. Chem.* **1980**, *52*, 843. (c) Knowles, W. S.; Christopfel, W. C.; Koenig, K. E.; Hobbs, C. F. *Adv. Chem. Ser.* **1982**, *196*, 325. (d) Yoshikuni, T.; Bailar, J. C., Jr. *Inorg. Chem.* **1982**, *21*, 2129. (e) Horner, L.; Simons, G. Z. *Naturforsch.* **1984**, *396*, 512. (f) Allen, D. G.; Wild, S. B.; Wood, D. L. *Organometallics* **1986**, *5*, 1009. (g) Johnson, C. R.; Imamoto, T. *J. Org. Chem.* **1987**, *52*, 2170. (h) Burgess, K.; Ohlmeyer, M. J.; Whitmire, K. H. *Organometallics* **1992**, *11*, 3588. (i) Corey, E. J.; Chen, Z.; Tanoury, G. J. *J. Am. Chem. Soc.* **1993**, *115*, 11000. (j) Nagel, U.; Krink, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1052. (k) Imamoto, T.; Tsuruta, H.; Wada, Y.; Masuda, H.; Yamaguchi, K. *Tetrahedron Lett.* **1995**, *36*, 8271. (l) Brenchley, G.; Fedouloff, M.; Mahon, M. F.; Molloy, K. C.; Wills, M. *Tetrahedron* **1995**, *51*, 10581. (m) Brenchley, G.; Fedouloff, M.; Merifield, E.; Wills, M. *Tetrahedron: Asymmetry* **1996**, *7*, 2809. (n) Vedejs, E.; Donde, Y. *J. Am. Chem. Soc.* **1997**, *119*, 9293.

(5) (a) Pietrusiewicz, K. M.; Zablocka, M. *Chem. Rev.* **1994**, *94*, 1375. (b) Imamoto, T. In *Handbook of Organophosphorus Chemistry*; Engel, R., Ed.; Marcel Dekker: New York, 1992; Chapter 1. (c) Kagan, H. B.; Sasaki, M. In *Chemistry of Organophosphorus Compounds*; Hartley, F. R., Ed.; Wiley & Sons: New York, 1990; Vol. 1, Chapter 3. (d) Valentine, D., Jr. In *Asymmetric Synthesis*; Morrison, J. D., Scott, J. W., Eds.; Academic Press: New York, 1984; Vol. 4, Chapter 3.

(6) Baechler, R. D.; Mislow, K. *J. Am. Chem. Soc.* **1970**, *92*, 3090.

(7) A similar bisphosphine ligand, (*S,S*)-1,2-bis(methylphenylphosphino)ethane, was previously synthesized and employed as a chiral ligand in rhodium-catalyzed asymmetric hydrogenation of *N*-benzoyl-α-aminocinnamic acid.[4e] The enantioselectivity of the reduction was reported to be 22% ee.

(8) Burk and co-workers have demonstrated that Rh and Ru catalysts bearing $C_2$-symmetric bis(trialkylphosphines), 1,2-bis(*trans*-2,5-dialkylphospholano)ethanes (BPE), exhibit not only very high enantioselectivities but also exceedingly high catalytic efficiencies in asymmetric hydrogenations of various olefinic and carbonyl substrates. (a) Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Organometallics* **1990**, *9*, 2653. (b) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518. (c) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125. (d) Burk, M. J.; Harper, T. G. P.; Kalberg, C. S. *J. Am. Chem. Soc.* **1995**, *117*, 4423. (e) Burk, M. J.; Gross, M. F.; Martinez, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 9375. (f) Burk, M. J.; Wang, Y. M.; Lee, J. R. *J. Am. Chem. Soc.* **1996**, *118*, 5142.

(9) Inoguchi, K.; Sakuraba, S.; Achiwa, K. *Synlett* **1992**, 169.

(10) (a) Imamoto, T.; Kusumoto, T.; Suzuki, N.; Sato, K. *J. Am. Chem. Soc.* **1985**, *107*, 5301. (b) Imamoto, T.; Oshiki, T.; Onozawa, T.; Kusumoto, T.; Sato, K. *J. Am. Chem. Soc.* **1990**, *112*, 5244. (c) Juge, S.; Stephan, M.; Laffitte, J. A.; Genet, J. P. *Tetrahedron Lett.* **1990**, *31*, 6357. (d) Yang, H.; Lugan, N.; Mathieu, R. *Organometallics* **1997**, *16*, 2089.

(11) Muci, A. R.; Campos, K. R.; Evans, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 9075.

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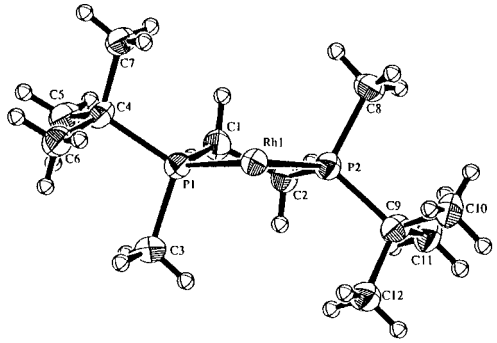
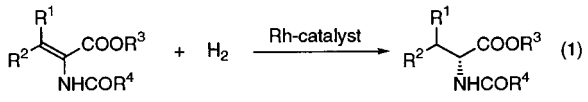



**Figure 2.** ORTEP drawing of rhodium complex [Rh((*S*,*S*)-**3a**)(nbd)]$BF_4$ (**4a**): the NBD and the $BF_4^-$ anion are omitted for clarity.

enantiomeric purity.[13] Enantiomerically pure **2a**−**e** were obtained by direct recrystallization of the crude products or by recrystallization after removal of the meso diastereomers by HPLC or flash chromatography. Subsequent removal of the boranato group was difficult by our conventional method,[10a,b] even with the use of highly reactive cyclic amines such as 1,4-diazabicyclo[2.2.2]-octane or pyrrolidine. An alternative method developed by McKinstry and Livinghouse was found to be effective for this transformation.[14] Thus, the reactions with trifluoromethanesulfonic acid in toluene or tetrafluoroboric acid in dichloromethane, followed by treatment with aqueous KOH or $K_2CO_3$, provided the desired bisphosphines **3a**−**e** in high yields.[15] These bisphosphines were converted to the cationic Rh complexes **4a**−**e** by the reactions with [Rh(nbd)$_2$]$BF_4$.

The crystal structure of rhodium complex **4a** was determined by single-crystal X-ray analysis.[16] The ORTEP drawing shown in Figure 2 clearly confirms the expected $C_2$-symmetric environment, where the bulky *tert*-butyl groups occupy the quasi-equatorial positions and the methyl groups are located at the quasi-axial positions to form a $\lambda$-chelate structure.

For the purpose of comparison, the rhodium complexes **4a**−**e** were employed as the catalyst precursors in asymmetric hydrogenation of α-(acylamino)acrylic derivatives including $\beta$-disubstituted ones (eq 1). The reductions of $\beta$-monosubstituted




**5a** : $R^1$ = H, $R^2$ = Ph, $R^3$ = Me, $R^4$ = Me
**5b** : $R^1$ = H, $R^2$ = Ph, $R^3$ = H, $R^4$ = Me
**5c** : $R^1$ = H, $R^2$ = Ph, $R^3$ = Me, $R^4$ = Ph
**5d** : $R^1$ = H, $R^2$ = Ph, $R^3$ = H, $R^4$ = Ph
**5e** : $R^1$ = H, $R^2$ = 3-MeO-4-AcOC$_6$H$_3$, $R^3$ = Me, $R^4$ = Me
**5f** : $R^1$ = H, $R^2$ = 3-MeO-4-AcOC$_6$H$_3$, $R^3$ = H, $R^4$ = Me
**5g** : $R^1$ = H, $R^2$ = H, $R^3$ = Me, $R^4$ = Me
**5h** : $R^1$, $R^2$ = -(CH$_2$)$_6$-, $R^3$ = Me, $R^4$ = Me
**5i** : $R^1$ = Me, $R^2$ = Me, $R^3$ = Me, $R^4$ = Me

derivatives (**5a**−**f**) and $\beta$-unsubstituted one (**5g**) were carried out at room temperature and an initial $H_2$ pressure of 2 atm in the presence of the catalyst (0.2 mol %). The reactions proceeded rapidly and were complete within 0.2−2 h. On the other hand, the $\beta$-disubstituted ones (**5h** and **5i**) required a higher $H_2$ pressure (6 atm) and a longer time (10−24 h) for completion of the reactions. These results are summarized in Table 1.

**Table 1.** Rh-Catalyzed Enantioselective Hydrogenation of α-(Acylamino)acrylic Derivatives (Eq 1)

| entry[a] | cat. precursor | substrate | solvent | % ee (config)[b] | entry[a] | cat. precursor | substrate | solvent | % ee (config)[b] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **4a** | **5a** | MeOH | 99.9[c] (*R*) | 12 | **4b** | **5h** | MeOH | 20.1[g] (*R*) |
| 2 | **4a** | **5b** | MeOH | 98.4[d] (*R*) | 13 | **4c** | **5a** | MeOH | 99.9[c] (*R*) |
| 3 | **4a** | **5c** | MeOH | 97.7[c] (*R*) | 14 | **4c** | **5b** | MeOH | 98.6[d] (*R*) |
| 4 | **4a** | **5d** | MeOH | 95.9[d] (*R*) | 15 | **4c** | **5g** | MeOH | >99.9[g] (*R*) |
| 5 | **4a** | **5e** | MeOH | 99.8[e] (*R*) | 16 | **4c** | **5h** | MeOH | 82.4[g] (*R*) |
| 6 | **4a** | **5f** | MeOH | 97.3[f] (*R*) | 17 | **4d** | **5a** | MeOH | 43.0[c] (*R*) |
| 7 | **4a** | **5g** | MeOH | 98.1[g] (*R*) | 18 | **4d** | **5h** | MeOH | 93.0[g] (*R*) |
| 8 | **4a** | **5h** | MeOH | 83.6[g] (*R*) | 19 | **4e** | **5a** | MeOH | 47.1[c] (*R*) |
| 9 | **4a** | **5h** | $C_6H_6$ | 84.1[g] (*R*) | 20 | **4e** | **5h** | MeOH | 89.3[g] (*R*) |
| 10 | **4a** | **5i** | $C_6H_6$ | 55.3[g] (*R*) | 21 | **4e** | **5i** | MeOH | 90.9[g] (*R*) |
| 11 | **4b** | **5a** | MeOH | 94.7[c] (*R*) | | | | | |

[a] Reactions were carried out at room temperature and an initial $H_2$ pressure of 2 atm (for substrates **5a**−**g**) or 6 atm (for substrates **5h** and **5i**) using the catalyst precursors (**4a**−**e**) (0.2 mol %). [b] Absolute configurations were confirmed by comparison of sign of optical rotation and chiral HPLC or GC elution order, with configurationally defined examples. [c] The ee (%) values were determined by HPLC using a Daicel Chiral OJ column. [d] The ee (%) values were determined by HPLC using a Daicel Chiral OJ column on the corresponding methyl ester. [e] The ee (%) values were determined by HPLC using a Daicel Chiral OD-H column. [f] The ee (%) values were determined by HPLC using a Daicel Chiral OD-H column on the corresponding methyl ester. [g] The ee (%) values were determined by chiral capillary GC using Chrompack's Chiral-L-Val column (25 m).

It is noted that catalyst precursors **4a**−**c** exhibited excellent enantioselectivity in the hydrogenations of $\beta$-monosubstituted derivatives and $\beta$-unsubstituted one (entries 1−7, 11, and 13−15). However, use of these catalysts in the reactions of $\beta$-disubstituted derivatives resulted in disappointingly low enantioselectivity (entries 8−10, 12, and 16). On the other hand, **4d** and **4e** afforded low enantioselectivities in the reduction of the $\beta$-monosubstituted derivatives (entries 17 and 19). Surprisingly, these catalysts were effective for the $\beta$-disubstituted derivatives to provide remarkably high enantioselectivity up to 93.0% ee (entries 18, 20, and 21).[17] The "steric matching" between the ligands (**3d** and **3e**) and the substrate olefins is considered responsible for these results.

In summary, we have prepared a new class of P-chiral phosphine ligands, 1,2-bis(alkylmethylphosphino)ethanes (**3a**−**e**). The resulting Rh catalysts **4a**−**e** are highly reactive, facilitating the reduction of α-(acylamino)acrylic derivatives in excellent enantioselectivity. Further applications of these ligands to other catalytic asymmetric reactions are in progress in our laboratory.

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**Supporting Information Available:** Experimental details for preparation of **3a**−**e** and **4a**−**e** and procedures for hydrogenation and enantiomeric excess determinations (10 pages). An X-ray crystallographic file, in CIF format, is available through the Web only. See any current masthead page for ordering information and Web access instructions.

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(12) For example, the reaction of **1a** afforded $C_2$-symmetric product **2a** (67%, >99% ee) and the meso diastereomer (13%). Enantiomerically pure **2a** was obtained by direct recrystallization of the crude product containing the meso diastereomer from hot toluene one or two times.

(13) For example, the reaction of **1d** afforded $C_2$-symmetric product **2d** (46%, 75% ee) accompanied by the meso diastereomer (29%).

(14) (a) McKinstry, L.; Livinghouse, T. *Tetrahedron Lett*. **1994**, *35*, 9319. (b) McKinstry, L.; Livinghouse, T. *Tetrahedron* **1994**, *50*, 6145.

(15) **3a**−**d** were obtained as crystalline solids or oil: **3a**, mp 23.5−25.5 °C; **3b**, oil; **3c**, mp 124−126 °C; **3d**, oil; **3e**, mp 21−23 °C. The absolute configuration of **3a** was determined by the single-crystal X-ray analyses of its TfOH salt (**3a**·2TfOH) and Rh complex **4a**. The absolute configuration of **3e** was determined by X-ray analysis of Ru complex **3e**·Ru($C_4H_7$)$_2$. The configurations of other three phosphine ligands **3b**−**d** were estimated by analogy.

(16) Crystal data for **4a**: orthorhombic, $P2_12_12_1$; $a$ = 20.500(8), $b$ = 9.826(5), and $c$ = 11.517(3) Å; $V$ = 2319(1) Å$^3$; $Z$ = 4; $d_{calcd}$ = 1.478 g cm$^{-3}$; $F$(000) = 1064; $\mu$(Mo Kα) = 9.06 cm$^{-1}$; $\lambda$(Mo Kα) = 0.71069 Å; 3519 reflections measured, 3482 observed ($I > 2.0\sigma(I)$); 244 variables; $R$ = 0.032, $R_w$ = 0.040, GOF = 1.49. Flack parameter = 0.010(1).

(17) The following are the highest ee values for the enantioselective hydrogenations of $\beta$-disubstituted derivatives. Me-DuPHOS (99.4% ee);[8e] Me-BPE (98.6% ee);[8e] BuTRAP (88% ee);[18] DIPAMP (55% ee);[19] [2.2]-PHANEPHOS (51% ee).[20]

(18) Sawamura, M.; Kuwano, R.; Ito, Y. *J. Am. Chem. Soc*. **1995**, *117*, 9602.

(19) Scott, J. W.; Keith, D. D.; Nix, G., Jr.; Parrish, D. R.; Remington, S.; Roth, G. P.; Townsend, J. M.; Valentine, D., Jr.; Yang, R. *J. Org. Chem*. **1981**, *46*, 5086.

(20) Pye, P. J.; Rossen, K.; Reamer, R. A.; Tsou, N. N.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc*. **1997**, *119*, 6207.