Synthesis and Reactions of Optically Active Secondary Dialkylphosphine-Boranes

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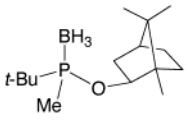
Introduction

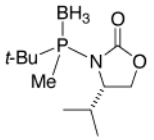
Optically active phosphines possessing a chiral center at the phosphorus atom have become increasingly important as the chiral ligands in various metal-catalyzed asymmetric reactions, and many phosphines of this class have been reported.[1−3] Among them, some P-chirogenic[4] trialkylphosphines have recently emerged as useful ligands that exhibit high catalytic activity, as well as excellent enantioselectivity in Rh(I)- or Ru(II)-catalyzed asymmetric hydrogenation.[5−7] However, despite the importance of P-chirogenic trialkylphosphines, the methodology for their syntheses remains relatively undeveloped.[8] For example, (*S*,*S*)-1,2-bis(alkylmethylphosphino)ethanes (BisP*) are readily obtained by the use of (−)-sparteine as a chiral source; however, synthesis of the corresponding (*R*,*R*)-enantiomers remains difficult.[5a] We envisioned that both enantiomers of such P-chirogenic trialkylphosphines might be effectively synthesized by the use of optically active secondary dialkylphosphine-boranes as the key intermediate. This idea led us to investigate the synthesis and reactions of optically active (*S*)- and (*R*)-*tert*-butylmethylphosphine-boranes (**5a** and **6a**), cyclohexylmethylphosphine-boranes (**5b** and **6b**), and 1-adamanthylmethylphosphine-boranes (**5c** and **6c**). In addition, we tried to prepare new C_2-symmetric P-chirogenic diphosphine-boranes by the use of these secondary phosphine-boranes.

Results and Discussion

Previously we reported that diastereomerically pure (menthyloxy)methylphenylphosphine-borane could be converted by reductive removal of the menthyloxy group into optically active secondary methylphenylphosphine-borane.[9] On the basis of these facts, bornyloxy(*tert*-butyl)-methylphosphine-borane (**1**) and *tert*-butyl(4′-isopropyl-2′-oxazolidinon-3′-yl)methylphosphine-borane (**2**) were synthesized, and these compounds could be separated into each diastereomer by preparative recycling HPLC or recrystallization. However, the reduction of these diastereomers with some single-electron reductants such as lithium naphthalenide, lithium 4,4′-di-*tert*-butylbiphenylide, lithium in liquid ammonia, or samarium iodide proceeded sluggishly even under more forcing conditions. Thus, the expected *tert*-butylmethylphosphine-borane was obtained in very low yields, and the enantiomeric purities of the product were disappointedly low (up to 23% ee).



1



2

Our attention was turned to the synthesis of phosphine-boranes bearing an alkylthio group in the expectation that they would be easily subjected to reduction

(1) For recent representative reviews on asymmetric catalysis, see: (a) Ojima, I., Ed. *Catalytic Asymmetric Synthesis*; VCH publishers: Wheinheim, 1993. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley & Sons: New York, 1994.

(2) For an excellent review of the preparation of P-chirogenic phosphines, see: (a) Pietrusiewicz, K. M.; Zablocka, M. *Chem. Rev.* **1994**, *94*, 1375−1411. For phosphine-borane reviews, see: (b) Imamoto, T. *Pure Appl. Chem.* **1993**, *65*, 655. (c) Ohff, M.; Holz, J.; Quirmbach, M.; Börner, A. *Synthesis* **1998**, 1391−1415. (d) Carboni, B.; Monnier, L. *Tetrahedron* **1999**, *55*, 1197−1248. (e) Imamoto, T. *Yuki Gosei Kagaku Kyokaishi*. **1998**, *56*, 511−520.

(3) For recent reports of new P-chirogenic phosphines, see: (a) Imamoto, T.; Tsuruta, H.; Wada, Y.; Masuda, H.; Yamaguchi, K. *Tetrahedron Lett.* **1995**, *36*, 8271−8274. (b) Airey, A. L.; Swiegers, G. F.; Willis, A. C.; Wild, S. B. *J. Chem. Soc., Chem. Commun.* **1995**, 693−694. (c) Bianchini, C.; Cicchi, S.; Peruzzini, M.; Pietrusiewicz, K. M.; Brandi, A. *J. Chem. Soc., Chem. Commun.* **1995**, 833−834. (d) Brenchley, G.; Fedouloff, M.; Merifield, E.; Wills, M. *Tetrahedron: Asymmetry* **1996**, *7*, 2809−2812. (e) Robin, F.; Mercier, F.; Ricard, L.; Mathey, F.; Spagnol, M. *Chem. Eur. J.* **1997**, *3*, 1365−1369. (f) Yang, H.; Lugan, N.; Mathieu, R. *Organometallics* **1997**, *16*, 2089−2095. (g) Hamada, Y.; Matsuura, F.; Oku, M.; Hatano, K.; Shioiri, T. *Tetrahedron Lett.* **1997**, *38*, 8961−8964. (h) Stoop, R. M.; Mezzetti, A.; Spindler, F. *Organometallics* **1998**, *17*, 668−675. (i) Nettekoven, U.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Widhalm, M.; Spek, A. L.; Lutz, M. *J. Org. Chem.* **1999**, *64*, 3996−4004. (j) Carmichael, D.; Doucet, H.; Brown, J. M. *J. Chem. Soc., Chem. Commun.* **1999**, 261−262. (k) Miura, T.; Imamoto, T. *Tetrahedron Lett.* **1999**, *40*, 4833−4836. (l) Tsuruta, H.; Imamoto, T. *Tetrahedron: Asymmetry* **1999**, *10*, 877−882. (m) Song, Y.; Vittal, J. J.; Chan, S. H.; Leung, P. H. *Organometallics* **1999**, *18*, 650−655.

(4) Many researchers including ourselves have used a conventional term "P-chiral" to express a chirality whose stereogenic center exists at the phosphorus atom. However, a referee of this paper recommended the use of "P-chirogenic" or "P-stereogenic" rather than "P-chiral", since chirality is a property of the molecule as a whole and not of a single atom. We agree with the referee's proposal and use the term "P-chirogenic" in this paper.

(5) (a) Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **1998**, *120*, 1635−1636. (b) Yamanoi, Y.; Imamoto, T. *J. Org. Chem.* **1999**, *64*, 2988−2989. (c) Yamano, T.; Taya, N.; Kawada, M.; Huang, T.; Imamoto, T. *Tetrahedron Lett.* **1999**, *40*, 2577−2580.

(6) Burk and co-workers have also demonstrated that bistrialkylphosphine ligands, 1,2-bis(*trans*-2,5-dialkylphospholano)ethanes (BPE), exhibit not only high enantioselectivity but also high catalytic efficiency in asymmetric hydrogenation. Burk, M. J. In *Handbook of Chiral Chemicals*; Ager, D. J., Ed.; Marcel Dekker: New York, 1999; Chapter 18 and references therein.

(7) Electronic effects of trialkylphosphines in Rh-catalyzed hydrogenation were reported with some electronically modified ligands: (a) Inoguchi, K.; Sakuraba, S.; Achiwa, K. *Synthesis* **1992**, 169−178. (b) RajanBabu, T. V.; Ayers, T. A.; Casalnuovo, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 4101−4102.

(8) For new synthetic approaches of P-chirogenic phosphines bearing an aromatic substituent, see: (a) Juge, S.; Stephan, M.; Laffitte, J. A.; Genet, J. P. *Tetrahedron Lett.* **1990**, *31*, 6357−6360. (b) Corey, E. J.; Chen, Z.; Tanoury, G. J. *J. Am. Chem. Soc.* **1993**, *115*, 11000−11001. (c) Muci, A. R.; Campos, K. R.; Evans, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 9075−9076. (d) Vedejs, E.; Donde, Y. *J. Am. Chem. Soc.* **1997**, *119*, 9293−9294. (e) Wolfe, B.; Livinghouse, T. *J. Am. Chem. Soc.* **1998**, *120*, 5116−5117.

(9) Oshiki, T.; Hikosaka, T.; Imamoto, T. *Tetrahedron Lett.* **1991**, *32*, 3371−3374.

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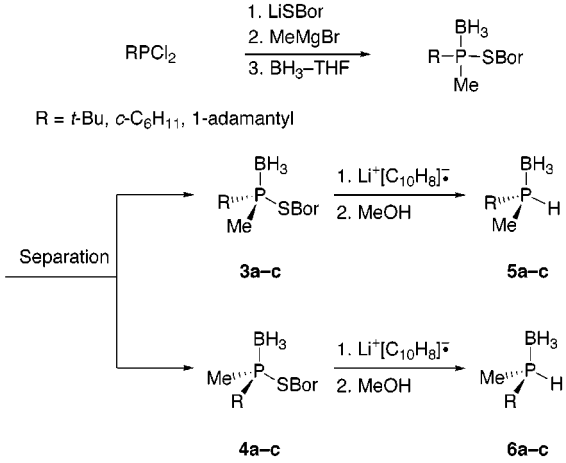
Scheme 1



under mild conditions. (1*S*)-*exo*-2-Bornanethiol (BorSH) was selected as a chiral auxiliary,[10,11] and the synthesis of the desired secondary phosphine-boranes was tried according to the synthetic route shown in Scheme 1. First, *tert*-butyldichlorophosphine was treated in one pot with lithium 2-bornanethiolate, methylmagnesium bromide, and borane−THF complex to furnish the diastereomeric mixtures of bornylthio(*tert*-butyl)methylphosphine-boranes (**3a** and **4a**) in 93% combined yield. Both diastereomers were separated by the use of preparative recycling HPLC, and they were identified as the expected diastereomers from spectroscopic data together with elemental analysis. The separated diastereomers were reduced by lithium naphthalenide with cleavage of the P−S bond in THF at −78 °C. The resulting reaction mixtures were treated with methanol at the same temperature to afford the desired (*S*)- and (*R*)-*tert*-butylmethylphosphine-boranes (**5a** and **6a**) in high yield with virtually net retention of the configuration at the phosphorus atom.[12] These compounds were stereochemically stable and could be stored without any loss of enantiomeric purities at room temperature for 1 week. In a similar manner, other secondary phosphine-boranes (**5b**, **6b**, **5c**, and **6c**) were synthesized in high yield from bornylthiocyclohexylmethylphosphine-boranes (**3b** and **4b**) and 1-adamantyl(bornylthio)methylphosphine-boranes (**3c** and **4c**), respectively. An important feature of the synthesized secondary phosphine-boranes is that a bulky alkyl group (*tert*-butyl, cyclohexyl, 1-adamantyl) and the smallest alkyl group (methyl group) bond to the phosphorus atom. This steric contrast may be an important factor in effecting high enantioselection in asymmetric reactions. The molecular structure of **4a** was determined by X-ray crystallographic analysis. It is clear that this compound has the *S* configuration at the phosphorus atom and, therefore, the other diastereomer **3a** must possess the *R* configuration. The geometry of the phosphorus atom is approximately tetrahedral with a slightly opened S−P−B angle (116.8(3)°). The bond length (1.94 Å) between the phosphorus and the boron atoms is almost the same as those of other phosphine-borane complexes.[13]

The lithiated secondary phosphine-boranes bearing an aromatic substituent are known to readily racemize at room temperature.[14] We measured the racemization rates of lithiated optically active *tert*-butylmethylphosphine-borane and obtained the following kinetic data: $k_{rac} \times 10^5$ (sec^{-1}) = 2.68 (40.0 °C), 11.2 (50.0 °C), and 44.9 (60.0 °C); E_a = 29.2 kcal/mol and ln A = 36.4.[15] From these data, the racemization half-life of the lithiated species at 20.0 °C is calculated to be 7.4 days. This stereochemical stability is in sharp contrast to that of lithiated secondary phosphine-boranes bearing an aromatic substituent, and it is consistent with the results on the racemization of tertiary phosphines.[16] These stereochemical properties indicate that optically active secondary dialkylphosphine-boranes are potentially useful in these syntheses of various chiral trialkylphosphine ligands.

The optically active secondary dialkylphosphine-boranes, *tert*-butylmethylphosphine-boranes, cyclohexylmethylphosphine-boranes, and 1-adamanthylmethylphosphine-boranes, were used for the synthesis of several P-chirogenic trialkylphosphine-borane derivatives.[17] They were readily subjected to deprotonation with butyllithium at −78 °C, and the generated lithium derivatives underwent reaction with benzyl chloride or 2-picolyl chloride at the same temperature through to room temperature. All reactions proceeded smoothly to afford the corresponding P-chirogenic trialkylphosphine-borane derivatives with high enantiomeric purities in high yields. These results are summarized in Table 1. One advantage of this new synthetic route is that both enantiomers can

(10) (1*S*)-*exo*-2-Bornanethiol was easily prepared from (−)-borneol in three steps and 60% overall yield: Blanco, J. M.; Caamaño, O.; Eirín, A.; Fernández, F.; Medina, L. *Synthesis*, **1990**, 584−586.

(11) (−)-Menthol, (+)-isomenthol, (+)-fenchyl alcohol, (−)-isopinocamphenol, (*R*)-1-phenylethylamine, and menthyltiol were also employed as chiral auxiliaries, but the obtained diastereomers were not separated completely.

(12) The direct determination of ee values was not successful by chiral HPLC, and therefore their alkylated derivatives were used for the ee determinations.

(13) (a) Bradley, D. C.; Hursthouse, M. B.; Motevalli, M.; Zheng, D. H. *J. Chem. Soc., Chem. Commun*. **1991**, 7−8. (b) Schmidbaur, H.; Wimmer, T.; Lachmann, J.; Müeller, G. *Chem. Ber*. **1991**, *124*, 275−278. (c) Schmidbaur, H.; Stüetzer, A.; Bissinger, P.; Schier, A. *Z. Anorg. Allg. Chem*. **1993**, *619*, 1519−1525 (d) Gourdel, Y.; Pellon, P.; Toupet, L.; Le Corre, M. *Tetrahedron Lett*. **1994**, *35*, 1197−4294. (e) Imamoto, T.; Hirakawa, E.; Yamanoi, Y.; Inoue, T.; Yamaguchi, K.; Seki, H. *J. Org. Chem*. **1995**, *60*, 7697−7700. (f) Imamoto, T.; Yoshizawa, T.; Hirose, K.; Wada, Y.; Masuda, H.; Yamaguchi, K.; Seki, H. *Heteroatom. Chem*. **1995**, *6*, 99−104. (g) Bader, A.; Pabel, M.; Willis, A. C.; Wild, S. B. Inorg. Chem. **1996**, *35*, 3874−3877.

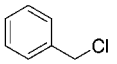
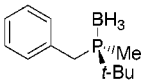
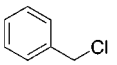
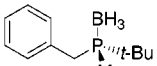
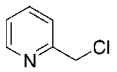
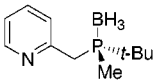
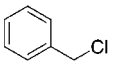
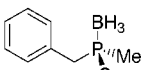
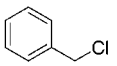
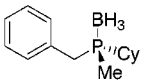
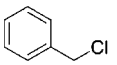
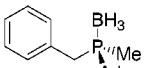
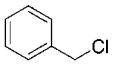
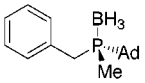
(14) (a) Valentine, D., Jr. In *Asymmetric Synthesis*; Morrison, J. D., Scott, J. W., Eds.; Academic Press: New York, 1984; Vol. 4, Chapter 3. (b) Kagan, H. B.; Sasaki, M. In *The Chemistry of Organophosphorus Compounds*; Hartley, F. R., Ed.; Wiley & Sons: New York, 1990; Vol. 1, Chapter 3. (c) Imamoto, T. In *Handobook of Organophosphorus Chemistry*; Engel, R., Ed.; Marcel Dekker: New York, 1992; Chapter 3.

(15) The (*S*)-*tert*-butylmethylphosphine-borane possessing 89% ee was lithiated by butyllithium at 0 °C, and the flask was immersed in a constant-temperature bath. After intervals ranging from 15 min to 2 h, a part of the solution was taken out and quenched with benzyl chloride. The enantiomeric excess of the derivative was determined by chiral HPLC (Daicel CHIRALCEL OD-H).

(16) Baechler and Mislow reported that in tertiary phosphines the planar transition state of racemization was stabilized, relative to the ground state, by (p−p)π delocalization involving the lone pair of electrons on phosphorus: Baechler, R. D.; Mislow, K. *J. Am. Chem. Soc*. **1970**, *92*, 3090−3093.

(17) (a) Imamoto, T.; Kusumoto, T.; Suzuki, N.; Sato, K. *J. Am. Chem. Soc*. **1985**, *107*, 5301−5302. (b) Imamoto, T.; Oshiki, T.; Onozawa, T.; Kusumoto, T.; Sato, K. *J. Am. Chem. Soc*. **1990**, *112*, 5244−5252. (c) Imamoto, T.; Oshiki, T.; Onozawa, T.; Matsuo, M.; Hikosaka, T.; Yanagawa, M. *Heteroatom. Chem*. **1992**, *3*, 563−575. (d) Imamoto, T.; Matsuo, M.; Nonomura, T.; Kishikawa, K.; Yanagawa, M. *Heteroatom. Chem*. **1993**, *4*, 475−486. (e) Soulier, E.; Clement, J. C.; Yaouanc, J. J.; des Abbayes, H. *Tetrahedron Lett*. **1998**, *39*, 4291−4294.

Table 1. Alkylation of Optically Active Secondary Phosphine-Boranes with Electrophiles

entry	substrate	electrophile	product[a]	yield(%)[b]	ee (%)[c]
1	**5a**		 **7a**	93	90
2	**6a**		 **7b**	90	91
3	**6a**		 **8**	85	96
4	**5b**		 **9a**	83	92
5	**6b**		 **9b**	80	89
6	**5c**		 **10a**	75	98[d]
7	**6c**		 **10b**	80	99[d]

[a] Cy = cyclohexyl, Ad = 1-adamantyl. [b] Isolated yield. [c] The ee was determined by HPLC analysis employing a Daicel CHIRALCEL OD-H or CHIRALPAC AD and AS. [d] Substrates were used after recrystallization from 2-propanol.

be synthesized from each optically active secondary phosphine-borane.[18]

On the basis of the experimental facts mentioned above, we tried to synthesize several C_2-symmetric P-chirogenic diphosphine-boranes, including the precursors to 1,2-bis(alkylmethylphosphino)ethanes (BisP*).[19,20] In most cases, P-chirogenic diphosphine-boranes could be isolated by column chromatography from the crude products contaminated with small amounts of the corresponding *meso*-isomers.[21] The results are illustrated in Table 2.

α,α′-Dichloro-*o*-xylene and bis(bromomethyl)mesitylene were alkylated in low yield (entries 1 and 2), whereas 2,6-bis(chloromethyl)pyridine provided the diphosphine-borane in 84% yield (entry 3). The reaction of **6a** and **6b** with 1,2-dichloroethane at −78 °C afforded the undesired monophosphine-borane species as the major products. To prevent the formation of these species, the lithium derivatives were allowed to react at higher temperature (20−40 °C) to provide the corresponding diphosphine-boranes in good yield (entries 4 and 5). Moreover, the treatment with 1,3-dichloropropane and 1,4-dichlorobutane gave the desired C_2-symmetric diphosphine-boranes in 69% and 80% yields, respectively (entries 6 and 7).

In summary, we have developed a new synthetic route to P-chirogenic trialkylphosphine-boranes by employing optically active secondary dialkylphosphine-borane as the synthetic intermediate. One principal advantage of this new synthetic route is that both enantiomers can be synthesized from each optically active secondary phosphine-borane; also, this method is applicable to the synthesis of other analogous phosphine-boranes and phosphine ligands.

Experimental Section

General Procedure for the Preparation of Compounds 5a−6c. A representative experimental procedure is described for the preparation of (*S*)-*tert*-butylmethylphosphine-borane (**5a**). To a stirred, cooled (−78 °C) solution of **3a** (721 mg, 2.5 mmol) in THF (10 mL) was slowly added lithium naphthalenide (7.5 mL of a 1.0 M THF solution, 7.5 mmol) under Ar atmosphere. After 30 min, the reaction mixture was rinsed with MeOH (2 mL) at −78 °C, and 1 M HCl (5 mL) was added. The aqueous layer was extracted with Et_2O, and the combined extracts were washed with brine, dried ($MgSO_4$), and concentrated at low pressure (20−30 mmHg). The residue was purified by chromatography on silica gel (hexane−AcOEt, 20:1) to give **5a** (286 mg, 97%) as a colorless solid. If further purification is desired, the product may be distilled in vacuo.

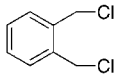
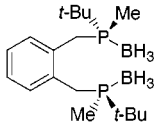
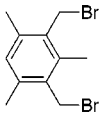
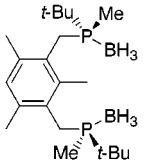
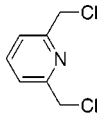
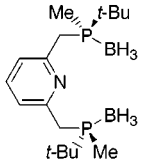
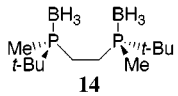
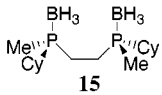
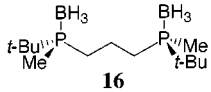
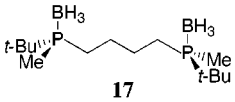
(18) Recently Wolfe and Livinghouse showed a direct synthesis of many P-chirogenic phosphine-boranes via dynamic resolution of lithiated racemic *tert*-butylphenylphosphine-borane with (−)-sparteine.[8e] However, this method was limited to the synthesis of one enantiomer.

(19) McKinstry and Livinghouse reported that the P−B bond of trialkylphosphine-boranes could be readily cleaved by reactions with acids, followed by treatment with KOH or K_2CO_3 to afford the corresponding phosphines: (a) McKinstry, L.; Livinghouse, T. *Tetrahedron Lett.* **1994**, *35*, 9319−9322. (b) McKinstry, L.; Livinghouse, T. *Tetrahedron* **1995**, *51*, 7655−7666.

(20) We have shown that BisP* are highly effective ligands in asymmetric hydrogenation of α-(acylamino)acrylic derivatives to provide enantioselectivities of up to 99.9% ee.[5a]

(21) Secondary phosphine-boranes used in these experiments were not enantiomerically pure, and hence small amounts of *meso*-isomers were produced.

Table 2. Bisphosphinylation of Several Electrophiles with Optically Active Secondary Phosphine-Boranes

entry	substrate	electrophile	product[a]	yield(%)[b]	ee (%)[c]
1	**5a**		 **11**	30	–[d]
2	**5a**		 **12**	35	98
3	**6a**		 **13**	84	99
4	**6a**	$Cl(CH_2)_2Cl$	 **14**	60	99
5	**6b**	$Cl(CH_2)_2Cl$	 **15**	58	–[d]
6	**5a**	$Cl(CH_2)_3Cl$	 **16**	69	98
7	**5a**	$Cl(CH_2)_4Cl$	 **17**	80	–[d]

[a] Cy = cyclohexyl. [b] Isolated yield. [c] The ee was determined by HPLC analysis employing a Daicel CHIRALCEL OD-H or CHIRALPAC AD and AS. [d] The ee values couldn't be determined by chiral HPLC analysis.

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Supporting Information Available: Experimental procedure for the preparation of **3a**−**4c**; characterization data of **3a**−**17**; ^1H and ^{13}C NMR spectra for compounds **3b**, **4b**, **5a**, **5b**, **8**, and **13**; ORTEP diagram and X-ray crystallographic data for **4a** (30 pages). This material is available free of charge via the Internet at http://pubs. acs. org.

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