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Enantiopure 1,2-Bis(*tert*-butylmethylphosphino)benzene as a Highly Efficient Ligand in Rhodium-Catalyzed Asymmetric Hydrogenation

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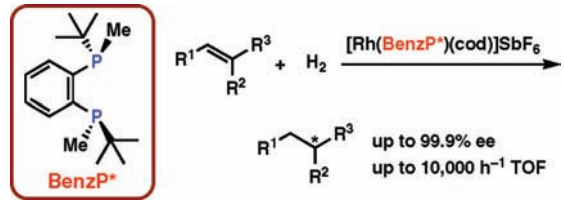
ABSTRACT



An electron-rich P-stereogenic bisphosphine ligand named "BenzP*" was conveniently prepared from *o*-dibromobenzene and enantiopure *tert*-butylmethylphosphine-borane. Its rhodium complex exhibited excellent enantioselectivities of up to 99.9% and high catalytic activity of up to 10 000 h^{-1} TOF in asymmetric hydrogenations of various functionalized alkenes.

Chiral phosphine ligands have played an important role in transition metal-catalyzed asymmetric reactions, and numerous ligands have been designed and synthesized over the past four decades.[1] Many of the reported chiral phosphine ligands exhibit excellent enantioinduction abilities in various asymmetric transformations. However, the ligands that are practically useful for the production of chiral compounds are limited to several outstanding ligands[2] and hence, the exploration of more efficient and widely applicable chiral phosphine ligands is still a vital research topic.[3]

Previously, we synthesized P-stereogenic phosphine ligands using phosphine-boranes as the key intermediate. Among the ligands, BisP*, MiniPHOS, QuinoxP*, and AlkynylP* were found to exhibit very high to almost perfect enantioselectivities in some representative transition metal-catalyzed asymmetric reactions.[4] One of the features of the ligands is that they possess a bulky substituent, such as a *tert*-butyl group, and a small group, such as a methyl group on the stereogenic phosphorus atoms. We envisioned that enantiopure 1,2-bis(*tert*-butylmethylphosphino)benzene (named BenzP*) (**1**) would exhibit excellent enantioselectivities and

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(1) For representative reviews, see: (a) Börner, A., Ed. *Phosphorus Ligands in Asymmetric Catalysis*; Wiley-VCH; Weinheim, Germany, 2008;Vols. 1−3. (b) Guiry, P. J.; Saunders, C. P. *Adv. Synth. Catal.* **2004**, *346*, 497. (c) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029–3069. (d) Ohkuma, T.; Kitamura, M.; Noyori, R. *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: Weinheim, Germany, 2000, Chapter 1.

(2) (a) Zhang, W.; Tongxiang, C.; Zhang, X. *Acc. Chem. Res.* **2007**, *40*, 1278–1290. (b) Shimizu, H.; Nagasaki, I.; Matsumura, K.; Sayo, N.; Saito, T. *Acc. Chem. Res.* **2007**, *40*, 1385–1393. (c) de Vries, J. G.; Elsevier, C. J., Eds. *The Handbook of Homogeneous Hydrogenation*; Wiley-VCH: Weinheim, Geramny, 2007; Vol. 1−3. (d) Blaser, H.-U.; Schmidt, E. *Asymmetric Catalysis on Industrial Scale*; Wiley-VCH: Weinheim, Germany, 2004. Genet, J.-P. *Acc. Chem. Res.* **2003**, *36*, 908–918.

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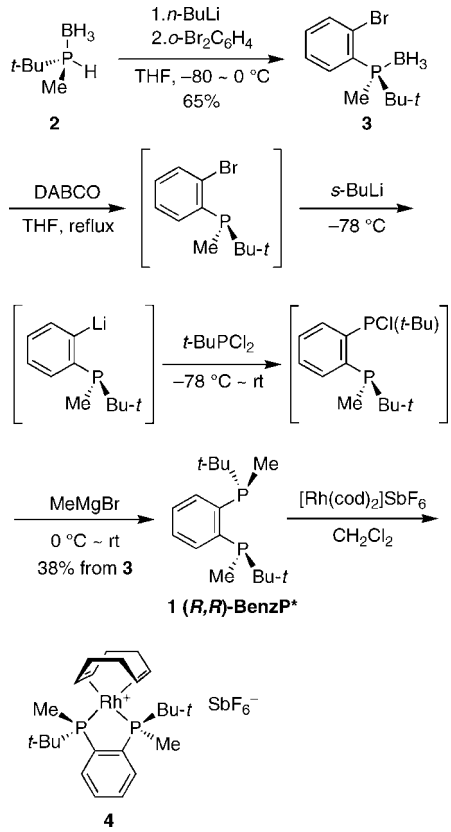
high catalytic activities because it has similar structural motif to *t*-Bu-BisP* and is expected to form a more rigid five-membered chelate ring owing to the *o*-phenylene backbone, as in the case of DuPHOS.[5] This ligand was previously synthesized by using a BH_2-bridged phosphonium salt.[6] However, the method required considerable skill for the separation of the enantiomerically enriched intermediates and the synthetic difficulty hampered even the evaluation of its enantioinduction ability. Herein, we report an efficient method for the preparation of this ligand and its high utility in rhodium-catalyzed asymmetric hydrogenation.

A new synthetic route to chiral diphosphine ligand **1** is depicted in Scheme 1. The reaction of the lithium derivative

Scheme 1. Preparation of Chiral Phosphine Ligand **1** and Its Rhodium Complex **4**



of (*S*)-*tert*-butylmethylphosphine-borane (**2**) with *o*-dibromobenzene afforded (*R*)-(2-bromophenyl)(*tert*-butyl)methylphosphine-borane (**3**) as a crystalline compound with complete retention of configuration at the phosphorus atom in 65% yield.[7−9] This compound was reacted successively with 1,4-diazabicyclo[2.2.2]octane (DABCO), *sec*-butyllithium, *tert*-butyldichlorophosphine, and methylmagnesium bromide to give desired ligand **1** in 38% yield.[11] It should be noted that these four reaction steps were carried out in one pot without isolation of the intermediates and ligand **1** was readily separated as a crystalline solid without chromatographic separation from other byproduct, such as a *meso*-diphosphine isomer. The counter enantiomer ligand

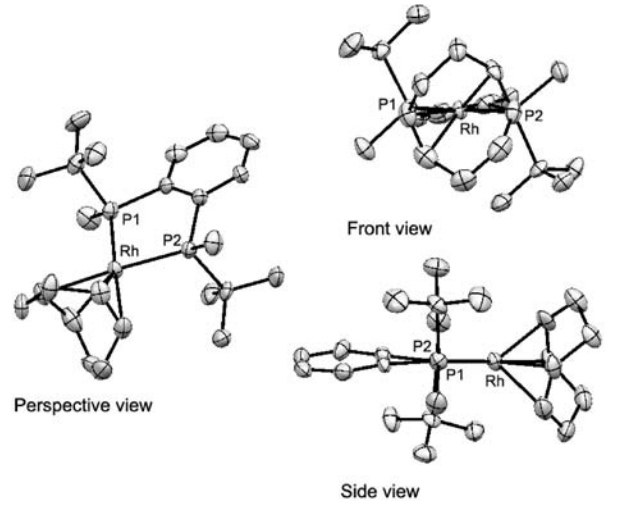


Figure 1. ORTEP drawing of complex **4**. Hydrogen atoms, SbF_6^- anion, and ethyl acetate molecule are omitted for clarity.

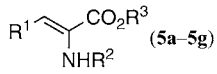
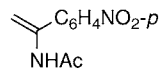
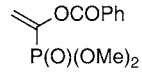
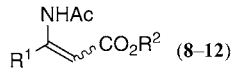
(*S*,*S*)-BenzP* can be also prepared by using (*R*)-*tert*-butylmethylphosphine-borane, which is produced in a large scale from (S_P,*S*)-*tert*-butyl(methyl)(1-phenylethylcarbamoyl)phosphine-borane.[12]

The obtained ligand **1** was converted into rhodium complex **4** by the reaction with $[Rh(cod)_2]SbF_6$. Recrystallization of the complex from ethyl acetate afforded cubic crystals suitable for single-crystal X-ray analysis. The crystal structure shown in Figure 1 clearly indicates that the bulky *tert*-butyl groups effectively shield two diagonal quadrants and the methyl groups are positioned in the other quadrants. This imposed asymmetric environment would lead to excellent enantioselectivity in asymmetric catalysis.

The enantioinduction ability and the catalytic efficiency of the rhodium complex were examined in the hydrogenation of various functionalized alkenes. The results are summarized in Table 1. A typical experiment with methyl 2-acetamidoacrylate

(3) For recent representative examples, see: (a) Deng, J.; Duan, Z.-C.; Huang, J.-D.; Hu, X.-P.; Wang, D.-Y.; Yu, S.-B.; Xu, X.-F.; Zheng, Z. *Org. Lett.* **2007**, *9*, 4825–4828. (b) Xie, J.-H.; Zhou, Q.-L. *Acc. Chem. Res.* **2008**, *41*, 581–593. (c) Stephan, M.; Sterk, D.; Mohar, B. *Adv. Synth. Catal.* **2009**, *351*, 2779–2786. (d) Schrems, M. G.; Pfaltz, A. *Chem. Commun.* **2009**, 6210–6212. (e) Gschwend, B.; Pugin, B.; Bertogg, A.; Pfaltz, A. *Chem.—Eur. J.* **2009**, *15*, 12993–13007. (f) Korenaga, T.; Osaki, K.; Maenishi, R.; Sakai, T. *Org. Lett.* **2009**, *11*, 2325–2328. (g) Oki, H.; Oura, I.; Nakamura, T.; Ogata, K.; Fukuzawa, S. *Tetrahedron: Asymmetry* **2009**, *20*, 2185–2191. (h) Tang, W.; Qu, B.; Capacci, A. G.; Rodriguez, S.; Wei, X.; Haddad, N.; Narayanan, B.; Ma, S.; Grinberg, N.; Yee, N. K.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2010**, *12*, 176–179. (i) Fandrick, D. R.; Fandrick, K. R.; Reeves, J. T.; Tan, Z.; Tang, W.; Capacci, A. G.; Rodriguez, S.; Song, J. J.; Lee, H.; Yee, N. K.; Senanayake, C. H. *J. Am. Chem. Soc.* **2010**, *132*, 7600–7601. (j) Tang, W.; Capacci, A. G.; White, A.; Ma, S.; Rodriguez, S.; Qu, B.; Savoie, J.; Patel, N. D.; Wei, X.; Haddad, N.; Grinberg, N.; Yee, N. K.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2010**, *12*, 1104–1107. (k) Zhang, X.; Cao, B.; Yan, Y.; Yu, S.; Ji, B.; Zhang, X. *Chem.—Eur. J.* **2010**, *16*, 871–877. (l) Zupancic, B.; Mohar, B.; Stephan, M. *Org. Lett.* **2010**, *12*, 1296–1299. (m) Zupancic, B.; Mohar, B.; Stephan, M. *Org. Lett.* **2010**, *12*, 3022–3025. (n) Xie, J.-B.; Xie, J.-H.; Liu, X.-Y.; Kong, W.-L.; Li, S.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2010**, *132*, 4538–4539. (o) Shi, S.-L.; Xu, L.-W.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 6638–6639. (p) Zhang, X.; Huang, K.; Hou, G.; Cao, B.; Zhang, X. *Angew. Chem., Int. Ed.* **2010**, *49*, 6421–6424.

Table 1. Asymmetric Hydrogenation of Prochiral Substrates Catalyzed by Rhodium Complex **4**

entry[a]	substrate	s/c	H_2 (atm)	time (h)	ee (%) of product (configuration)
	 (**5a**–**5g**)				
1	**5a**: R^1 = H, R^2 = Ac, R^3 = Me	1000	3	0.3	99.9 (*R*)
2	**5a**: R^1 = H, R^2 = Ac, R^3 = Me	10000	5	1	99.9 (*R*)
3	**5b**: R^1 = Ph, R^2 = Ac, R^3 = Me	1000	3	0.3	99.9 (*R*)
4	**5b**: R^1 = Ph, R^2 = Ac, R^3 = Me	10000	5	5	99.8 (*R*)
5	**5c**: R^1 = Ph, R^2 = Ac, R^3 = H	1000	3	0.5	99.5 (*R*)
6	**5d**: R^1 = *m*-FC_6H_4, R^2 = Ac, R^3 = H	1000	3	0.7	99.4 (*R*)
7	**5e**: R^1 = 3-MeO-4-$AcOC_6H_3$, R^2 = Ac, R^3 = Me	500	3	0.3	99.9 (*R*)
8	**5f**: R^1 = 2-Furyl, R^2 = Cbz, R^3 = Me	200	3	3	99.1 (*R*)
9	**5g**: R^1 = 2-pyrrolyl, R^2 = Cbz, R^3 = Me	200	3	3	94.1 (*R*)
10	 (**6**)	1000	3	0.5	99.2 (*R*)
11	 (**7**)	1000	6	3	97.6 (*S*)
	 (**8**–**12**)				
12	(*E*)-**8**: R^1 = Me, R^2 = Me	1000	3	0.8	99.6 (*R*)
13	(*Z*)-**8**: R^1 = Me, R^2 = Me	1000	3	0.8	97.6 (*R*)
14	(*E*)-**8**:(*Z*)-**8** = 1:1	1000	3	0.8	98.7 (*R*)
15	(*E*)-**8**:(*Z*)-**8** = 1:1	5000	5	20	97.9 (*R*)
16	(*E*)-**9**: R^1 = Pr, R^2 = Et	1000	3	4	99.9 (*R*)
17	(*Z*)-**9**: R^1 = Pr, R^2 = Et	1000	3	3	94.0 (*R*)
18	(*Z*)-**10**: R^1 = *i*-Pr, R^2 = Et	1000	3	12	86.3 (*S*)
19	(*Z*)-**11**: R^1 = Ph, R^2 = Me	1000	3	0.5	97.2 (*S*)
20	(*Z*)-**12**: R^1 = *p*-$MeOC_6H_4$, R^2 = Et	1000	2	2	98.5 (*S*)

[a] All reactions were carried out in methanol at room temperature.

(**5a**) shows that the hydrogenation with a 1000 substrate/catalyst (s/c) ratio under 3 atm hydrogen pressure was completed within 0.3 h to give the product with 99.9% ee (entry 1). The reaction with a 10 000 s/c ratio under 5 atm hydrogen pressure was also completed within a short time (1 h) to give the product without any decrease of the enantioselectivity (entry 2). Other α-dehydroamino acid derivatives (**5b**−**g**) were also subjected to hydrogenation under similar reaction conditions. All reactions except that of 2-pyrrolyl derivative (**5g**) afforded excellent ee values of the corresponding products (entries 3−9). The high enantioinduction ability of this catalyst was proved also in the hydrogenation of 1-acetamido-1-(*p*-nitrophenyl)ethene (**6**) and dimethyl α-benzoyloxyethenephosphonate (**7**) (entries 10 and 11).

The asymmetric hydrogenation of *β*-dehydroamino acid derivatives and related substrates is one of the most efficient methods for the production of chiral *β*-amino acids, and considerable effort has been made in this area.[13] In most

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(6) Yamamoto, Y.; Koizumi, T.; Katagiri, K.; Furuya, Y.; Danjo, H.; Imamoto, T.; Yamaguchi, K. *Org. Lett.* **2006**, *8*, 6103–6106.

(7) Bayardon, J.; Laureano, H.; Chaux, F.; Leroux, F.; Henry, J. C.; Jugé, S. 2010, patent pending. Professor Sylvain Jugé of the University of Bourgogne informed T. Imamoto before their publication that the reaction of *o*-dibromobenzene with (*o*-methoxyphenyl)phenylphosphine-borane in the presence of *n*-butyllithium afforded (*o*-bromophenyl)(*o*-methoxyphenyl)phenylphosphine-borane. We deeply thank Professor Jugé for his personal communication.

(8) It is noted that the use of *o*-dichlorobenzene in place of *o*-dibromobenzene provided no trace of the desired compound but the borane adduct of (*R*,*R*)-1,3-bis(*tert*-butylmethylphosphino)benzene as the major product.

(9) To determine the enantiomeric excess of compound **3** by HPLC analysis using a chiral column, (±)-2-(boranato-*tert*-butylmethylphosphino)bromobenzene was prepared by the successive reactions of *o*-dibromobenzene with *i*-PrMgCl·LiCl,[10] *tert*-butyldichlrophosphine, methylmagnesium bromide, and BH_3·THF. See details in the Supporting Information.

(10) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed* **2004**, *43*, 3333–3336.

cases, the hydrogenation of (*E*)-derivatives gives rise to high enantioselectivity compared with that of (*Z*)-derivatives; the reactions of the latter require high hydrogen pressure and/or a long reaction time, and the enantioselectivity is considerably low.[3l,14] We employed the rhodium catalyst with the BenzP* ligand in the hydrogenation of several β-dehydroamino acid derivatives, and the results are added in Table 1. The hydrogenation of methyl (*E*)-3-acetamido-2-butenoate ((*E*)-**8**) in the presence of 0.1 mol % catalyst under 3 atm of hydrogen pressure was completed within 0.8 h to give a product with 99.6% ee (entry 12). We are pleased to find that the (*Z*)-isomer ((*Z*)-**8**) reacted under the same conditions to afford a product with a slightly lower ee (97.6%) (entry 13). A 1:1 mixture of (*E*)-**8** and (*Z*)-**8** was also subjected to hydrogenation and excellent enantioselectivity (98.7%) was achieved (entry 14). The reaction with a 5000 s/c ratio furnished a product with 97.9% ee (entry 15). Similarly high to excellent enantioselectivities were observed in the hydrogenation of propyl, isopropyl, phenyl, and *p*-methoxyphenyl derivatives (**9**−**12**) (entries 16−20). In regard to enantioselectivity and turnover frequency (TOF), these results are comparable to the highest values reported so far.[3h,15]

In conclusion, we have developed a convenient method for the preparation of enantiopure 1,2-bis(*tert*-butylmethylphosphino)benzene (BenzP*) from *tert*-butylmethylphosphine-borane and *o*-dibromobenzene. Its rhodium complex exhibited excellent enantioselectivities of up to 99.9% and activities of up to 10 000 h^{-1} TOF in the asymmetric hydrogenation of various functionalized alkenes, including β-dehydroamino acid esters. In addition to the catalytic efficiency, the handling ease in air indicates the versatile utility of the ligand in a wide variety of transition metal-catalyzed asymmetric reactions.

Further study on the preparation of related ligands and their application to the production of useful enantiopure compounds is in progress in our laboratory and the results will be published in due course.

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Supporting Information Available: Detailed descriptions of experimental procedures and X-ray crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) While the chiral ligand BenzP* is an electron-rich diphosphine, its crystalline solid was robust in air; it was not readily oxidized on exposure to air for one week.

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