Methylene-Bridged P-Chiral Diphosphines in Highly Enantioselective Reactions

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Optically active diphosphines play a most important role as the chiral bidentate ligands in transition metal-catalyzed reactions.[1] Although numerous chiral diphosphines have been reported so far,[1,2] the design and synthesis of new chiral phosphine ligands are still a significant research subject in the field of asymmetric catalysis. Described here is the development of novel chiral diphosphines that are extremely simple and small but exhibit excellent enantioselectivity in representative catalytic asymmetric reactions.

The newly designed chiral diphosphine ligands **1a**−**1d** (abbreviated as MiniPHOS[3]) are shown in Figure 1. An important feature of these ligands is that they are methylene-bridged P-chiral diphosphines[4] possessing the smallest alkyl group (methyl group) and a bulky alkyl group at each phosphorus atom. These ligands would form highly strained four-membered C_2-symmetric chelates with metal, and this conformational rigidity together with the ideal asymmetric environment might lead to high enantioselectivity.

These ligands were synthesized in three steps from trichlorophosphine using phosphine−boranes as the intermediates (Scheme 1).[5] Thus, alkyldimethylphosphine−boranes **2a**−**2d** were obtained from trichlorophosphine in good to high yield. These compounds were reacted successively with *s*-BuLi/(−)-sparteine, alkyldichlorophosphines, methylmagnesium bromide, and BH_3−THF to afford optically active phosphine−boranes **3a**−**3d** and *meso* phosphine−boranes in a ratio of ca. 1:1.[6] The desired compounds **3a**−**3d** were easily obtained by recrystallization from methanol or ethanol (13−28%). The boranato groups were removed by the reaction with trifluoromethanesulfonic acid in toluene, followed by treatment with aqueous KOH, to provide the MiniPHOS **1a**−**1d** in almost quantitative yield.[7]

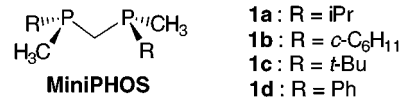
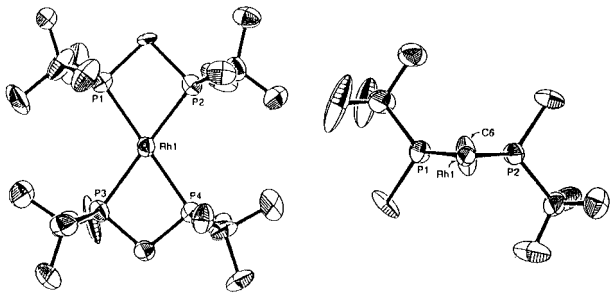


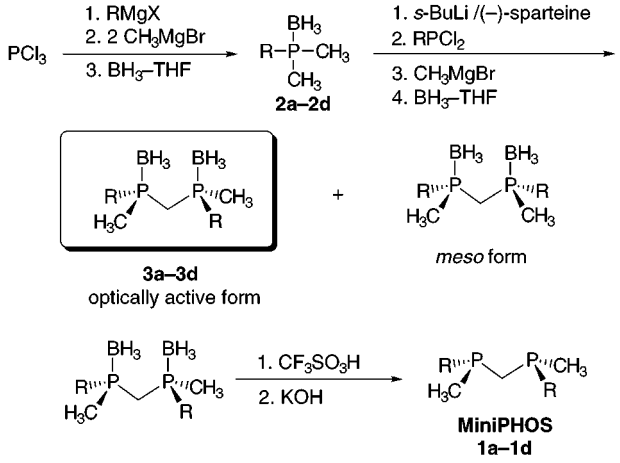
Figure 1.



(A) Top View (B) Side View

Figure 2. Top (A) and side (B) ORTEP drawings of [Rh((*R*,*R*)-*t*-Bu-MiniPHOS)$_2$]$^+$PF$_6^-$. The PF$_6^-$ anion and hydrogen atoms are omitted for clarity. In the side view, one *t*-Bu-MiniPHOS is omitted for clarity.

Scheme 1



These ligands were allowed to react with [Rh(nbd)$_2$]$^+$X$^-$ (X = BF$_4$ or PF$_6$) to afford the bischelate complexes [Rh(MiniPHOS)$_2$]$^+$X$^-$, even with the use of [Rh(nbd)$_2$]$^+$X$^-$ and diphosphines in a 1:1 molar ratio. The molecular structure of a rhodium complex [Rh((*R*,*R*)-*t*-Bu-MiniPHOS)$_2$]$^+$-PF$_6^-$ was determined by single-crystal X-ray analysis.[8] The ORTEP drawing shown in Figure 2 clearly indicates the expected C_2-symmetric environment, where the bulky *tert*-butyl groups effectively shield two diagonal quadrants and the methyl groups are placed at the other quadrants.[9] This imposed asymmetric environment is expected to lead to high enantioselectivity in asymmetric catalysis.

These rhodium complexes were used as catalyst precursors in asymmetric hydrogenation of various dehydroamino acids and their methyl esters.[1,2,10] The results are summarized in Table 1. Almost complete enantioselectivity was achieved for the hydrogenation of 2-acetamidoacrylic acid

(1) For representative reviews, see the following: (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994. (b) Ojima, I., Ed. *Catalytic Asymmetric Synthesis*; VCH Publishers: Weinheim, 1993.

(2) For recently reported representative chiral diphosphines, see: (a) Pye, P. J.; Rossen, K.; Reamer, R. A.; Tsou, N. N.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1997**, *119*, 6207. (b) RajanBabu, T. V.; Ayers, T. A.; Halliday, G. A.; You, K. K.; Calabrese, J. C. *J. Org. Chem.* **1997**, *62*, 6012. (c) Zhang, F. Y.; Pai, C. C.; Chan, A. S. C. *J. Am. Chem. Soc.* **1998**, *120*, 5808. (d) Qiao, S.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 4168. (e) Jiang, Q.; Jiang, Y.; Xiao, D.; Cao, P.; Zhang, X. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1100.

(3) We abbreviate these chiral ligands as MiniPHOS, because they are quite small when compared with all the chiral diphosphines reported so far.

(4) A few chiral 1,1-diphosphines have been described in the literature, and there has been only one report dealing with Rh-catalyzed asymmetric hydrogenations with very low enantioselectivity. (a) Marinetti, A.; Menn, C. L.; Ricard, L. *Organometallics* **1995**, *14*, 4983. (b) Babu, R. P. K.; Krishnamurthy, S. S.; Nethaji, M. *Tetrahedron: Asymmetry* **1995**, *6*, 427. (c) Brunner, H.; Furst, J. *Tetrahedron* **1994**, *50*, 4303.

(5) (a) Imamoto, T.; Oshiki, T.; Onozawa, T.; Kusumoto, T.; Sato, K. *J. Am. Chem. Soc.* **1990**, *112*, 5244. (b) Jugé, S.; Stephane, M.; Laffitte, J. A.; Genêt, J. P. *Tetrahedron Lett.* **1990**, *31*, 6357. (c) Ohff, M.; Holz, J.; Quirmbach, M.; Börner, A. *Synthesis* **1998**, 1391. (d) Carboni, B.; Monnier, L. *Tetrahedron* **1999**, *55*, 1197 and references cited therein.

(6) Enantioselective deprotonation of aryl- or alkyldimethylphosphine−boranes with (−)-sparteine/*s*-BuLi complex was reported. (a) Muci, A. R.; Campos, K. R.; Evans, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 9075. (b) Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **1998**, *120*, 1635.

(7) McKinstry, L.; Livinghouse, T. *Tetrahedron Lett.* **1994**, *35*, 9319.

(8) Crystallographic Data for [Rh((*R*,*R*)-*t*-Bu-MiniPHOS)$_2$]PF$_6$: $C_{22}H_{52}F_6P_5Rh$; space group $P4_3$; $Z = 4$; $D = 1.356$ g/cm^{-3}; cell constants $a = 11.113(4)$ Å, $c = 27.301(5)$ Å, $V = 3371(1)$ Å^3; temperature of data collection 293 K; 1619 unique reflections ($I > 2.0\sigma(I)$); $R = 0.067$; Rw = 0.089; GOF = 1.41.

(9) Knowles, W. S. *Acc. Chem. Res.* **1983**, *16*, 106.

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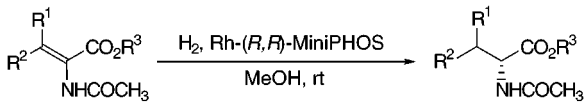
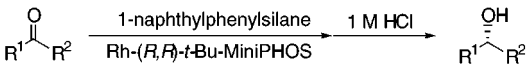
Table 1. Rh-Catalyzed Enantioselective Hydrogenation of Dehydroamino Acids and Their Methyl Esters[a]



entry	R^1	R^2	R^3	MiniPHOS	H_2 (atm)	ee (%)[b]
1	H	H	H	*t*-Bu	1	>99.9
2				c-C_6H_{11}	1	99.1
3				*i*-Pr	1	98
4				Ph	1	26
5	H	H	Me	*t*-Bu	1	>99.9
6				c-C_6H_{11}	1	98.9
7				*i*-Pr	1	98
8	H	Ph	H	*t*-Bu	1	97
9	H	Ar[c]	H	*t*-Bu	2	95
10	H	Ph	Me	*t*-Bu	1	98
11	H	Ar[c]	Me	*t*-Bu	2	95
12	$-(CH_2)_5-$		Me	*t*-Bu	6	97
13				c-C_6H_{11}	6	94
14				*i*-Pr	6	83
15	$-(CH_2)_4-$		Me	*t*-Bu	6	94
16				c-C_6H_{11}	6	90
17				*i*-Pr	6	88
18	Me	Me	Me	*t*-Bu	6	87
19				c-C_6H_{11}	6	85

[a] All reactions were carried out with a molar ratio of Rh-MiniPHOS/dehydroamino acid derivatives 1/500. The reactions were complete within 24−48 h. [b] Enantiomeric excesses were determined by GC or HPLC using chiral columns, as described in the Supporting Information. [c] Ar = 3-MeO-4-$AcOC_6H_3$.

Table 2. Rh-Catalyzed Asymmetric Hydrosilylation of Ketones[a]



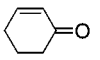
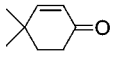
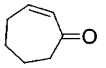
entry	R^1	R^2	temp (°C)	yield (%)[b]	ee (%)[c]
1	Ph	Me	−40	86	91
2	1-naphthyl	Me	−40	90	97
3	2-naphthyl	Me	−40	99	94
4	*o*-$CH_3C_6H_4$	Me	−40	96	95
5	*m*-$CH_3C_6H_4$	Me	0	83	89
6	*o*-$MeOC_6H_4$	Me	−15	88	90
7	Ph	Et	−20	81	83
8	$PhCH_2CH_2$	Me	−20	93	80

[a] All reactions were carried out in THF with a molar ratio of Rh-(*R*,*R*)-*t*-Bu-MiniPHOS/ketone/1-naphthylphenylsilane 1/100/150. The reactions were complete with 3−4 days. [b] Isolated yield. [c] Determined by GC or HPLC using chiral columns.

and its methyl ester (entries 1−3 and 5−7). It is noted that the ligands having *tert*-butyl, cyclohexyl, and isopropyl groups exhibited very high enantioselectivities, while a ligand possessing phenyl groups leads to low selectivity (entry 4). Excellent enantioselectivity was obtained for several α-acetamidocinnamic acid derivatives (entries 8−11). Moreover, these catalysts were also found to be effective for the *β*,*β*-disubstituted enamides in the reduction of which it has been notoriously difficult to achieve high enantioselectivity (entries 12−19).[11−15]

To extend the utilization of the present catalyst precursors, asymmetric hydrosilylation of simple ketones was examined. Despite extensive experimentation in this area, most of the chiral diphosphine ligands afforded only low to moderate enantioselectivity in rhodium(I)-catalyzed hydrosilylation of ketones. The use of the *t*-Bu-MiniPHOS−Rh complex as a catalyst precursor in asymmetric hydrosilylation of simple ketones afforded very high enantioselectivities (Table 2). These results are comparable to the enantioselectivity obtained previously by use of the most effective ligands.[16]

Table 3. Cu-Catalyzed Asymmetric Michael Reaction of Diethylzinc to α,*β*-Unsaturated Ketones[a]

entry	enone	MiniPHOS	yield (%)[b]	ee (%)[c]	config.[d]
1		*t*-Bu	73	70	(*R*)
2		c-C_6H_{11}	79	83	
3		*t*-Bu	89	73	(−)[e]
4		c-C_6H_{11}	86	81	
5		*t*-Bu	91	97	(−)[e]
6		c-C_6H_{11}	88	90	
7		iPr	94	82	
8	chalcone	*t*-Bu	96	71	(*R*)

[a] All reactions were carried out in toluene at −80 °C with a molar ratio $Cu(OTf)_2$/MiniPHOS/α,*β*-unsaturated ketone/diethylzinc 1/1/100/110. These reactions were complete within 24 h. [b] Isolated yield. [c] Determined by GC or HPLC using chiral columns. [d] The absolute configurations were determined by comparing the observed optical rotations with the literature values. [e] The absolute configurations were not determined.

It was also found that these chiral diphosphines were successfully used for catalytic asymmetric carbon−carbon bond-forming reactions. Namely, the catalytic asymmetric Michael reaction of diethylzinc to α,*β*-unsaturated ketones in the presence of MiniPHOS-coordinated copper(II) triflate afforded the corresponding addition products with high enantiomeric excesses (Table 3).[17,18]

In conclusion, we have explored novel methylene-bridged P-chiral diphosphines. These ligands exhibit excellent to almost perfect levels of enantioselectivity in representative catalytic asymmetric reactions, even though they are quite simple and small in comparison with the previously reported chiral diphosphines.

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Supporting Information Available: Synthetic procedures, characterization data for new compounds, and enantiomeric excess determinations. An X-ray crystallographic file, in CIF format, is available through the Web only. This material is available free of charge via the Internet at http://pubs.acs.org.

JO990131M

(10) Burk et al. have demonstrated that Rh and Ru catalysts bearing DuPHOS or BPE exhibit very high enantioselectivities in various asymmetric hydrogenations. (a) Burk, M. J.; Gross, M. F.; Harper, T. G. P.; Kalberg, C. S.; Lee, J. R.; Martinez, J. P. *Pure Appl. Chem.* **1996**, *68*, 37. (b) Burk, M. J.; Wang, Y. M.; Lee, J. R. *J. Am. Chem. Soc.* **1996**, *118*, 5142. (c) Burk, M. J.; Kalberg, C. S.; Pizzano, A. *J. Am. Chem. Soc.* **1998**, *120*, 4345. (d) Burk, M. J.; Bienewald, F.; Harris, M.; Zanotti-Gerosa, A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1931.

(11) Hoerrner et al. reported asymmetric hydrogenation of *β*,*β*-disubstituted dehydroamino acid derivatives to prepare *β*-methyltryptophan with excellent enantiomeric excess. Hoerrner, R. S.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 3455.

(12) The following are the highest ee values for the enantioselective hydrogenations of *β*,*β*-disubstituted derivatives. Me-DuPHOS (99.4% ee);[10b] Me-BPE (98.6% ee);[10b] BisP* (93.0% ee);[6b] BuTRAP (88% ee).[13]

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

(14) The same rhodium catalysts were employed also for the asymmetric hydrogenation of itaconic acid. Almost perfect enantioselectivities (*t*-Bu-MiniPHOS >99.9%; c-C_6H_{11}-MiniPHOS >99.9%; *i*-Pr-MiniPHOS 98%) were observed in this reaction.

(15) It is reasonable to consider that under the reaction conditions the bischelate rhodium complexes dissociate to the free diphosphines and the monochelate complexes which act as the actual catalyst species.

(16) Kuwano, R.; Uemura, T.; Saitoh, M.; Ito, Y. *Tetrahedron Lett.* **1999**, *40*, 1327 and references cited therein.

(17) (a) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771. (b) Krause, N. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 283.

(18) (a) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2620. (b) Knöbel, A. K. H.; Escher, I. H.; Pfaltz, A. *Synlett* **1997**, 1429.