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Enantiomerically Pure 1,2-Bis(isopropylmethylphosphino)benzene and Its Use in Highly Enantioselective Rh-Catalyzed Asymmetric Hydrogenation

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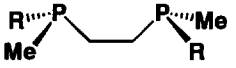
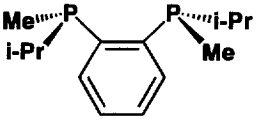
Abstract: A new P-chiral phosphine ligand with a 1,2-phenylene unit, (*S*,*S*)-1,2-bis(isopropylmethylphosphino)benzene, has been synthesized from 1,2-bis(methylphosphino)benzene. Its rhodium complex is highly effective in asymmetric hydrogenation of dehydroamino acid methyl esters to provide enantioselectivities of up to 98%.

The development of new chiral phosphine ligands has become very important due to expanded utility of transition mental-catalyzed asymmetric reactions, and more than one thousand optical active phosphine ligands have emerged over the past three decades.[1] Most of these ligands, possessing diaryl groups on the phosphorus atom, contain their chirality in the ligand backbone. In contrast, relatively little is known about P-chiral phosphine ligands bearing dialkyl or trialkyl phosphine moieties because of their synthetic difficulty.[2] We have recently shown that P-chiral trialkyl ligands, 1,2-bis(alkylmethylphosphino)ethanes (abbreviated as BisP*), are extremely effective in the asymmetric hydrogenation of various α,β-unsaturated α-amino acids and their esters.[3] These results prompted us to synthesize a new P-chiral phosphine ligand having the more rigid 1,2-phenylene backbone.[4] Herein we report the preparation of (*S*,*S*)-1,2-bis(isopropylmethylphosphino)benzene ((*S*,*S*)-**1**) and its use in rhodium-catalyzed asymmetric hydrogenation of dehydroamino acid methyl esters.



BisP*

R = *c*-C_5H_9, *c*-C_6H_{11}, *t*-Bu, Et_3C, 1-adamantyl



(*S*,*S*)-**1**

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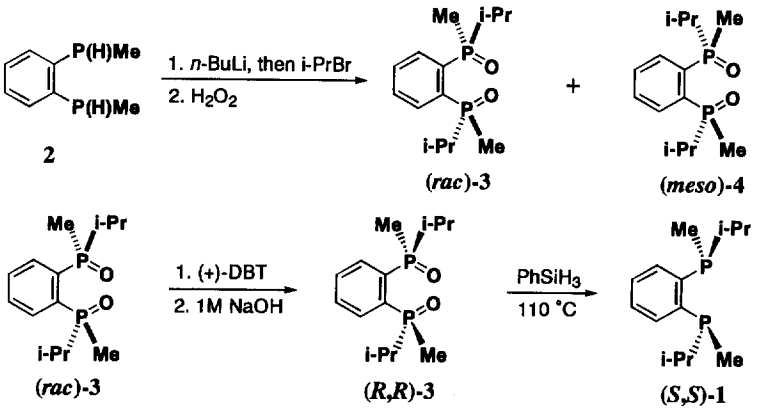
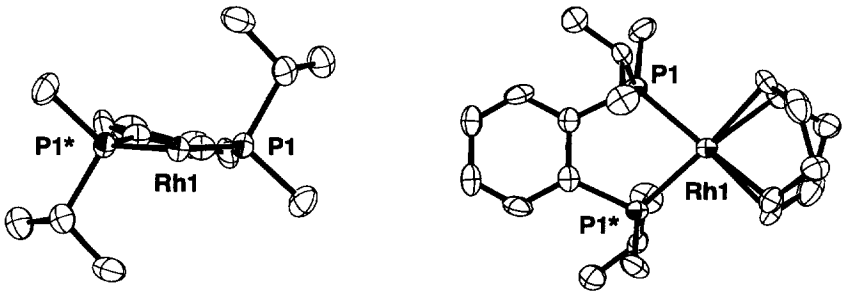
Enantiomerically pure ligand (*S,S*)-**1** was prepared starting from 1,2-bis(methylphosphino)benzene **2**[5] (Scheme1). Lithiation of **2** with *n*-BuLi, followed by slow addition of 2-bromopropane, afforded 1,2-bis(isopropylmethylphosphino)benzene in 79% isolated yield. Subsequent oxidation with hydrogen peroxide gave a mixture of phosphine oxides (*rac*)-**3** and (*meso*)-**4**, from which pure (*rac*)-**3** was obtained in 11% yield by repeated recrystallization from ethyl acetate. Optical resolution of (*rac*)-**3** was readily achieved by the use of a resolving reagent, dibenzoyl-D-tartaric acid ((+)-DBT).[6] Thus, treatment of (*rac*)-**3** with (+)-DBT (1 eq) in boiling ethyl acetate resulted in the formation of a diastereomeric complex of (*R,R*)-**3** and (+)-DBT as a crystalline solid, and its decomposition with aq. NaOH provided the desired compound (*R,R*)-**3** over with 99% ee in 35% yield.[7,8,9] Reduction of (*R,R*)-**3** with phenylsilane produced the chiral phosphine ligand (*S,S*)-**1** with 97% ee in good yield together with a small amount of the meso compound (10-15%).[10,11] Without further purification, the ligand **1** was treated with $[Rh(cod)_2]BF_4$ (cod = 1,5-cyclooctadiene) at –20 °C. The resulting cationic rhodium complex [Rh((*S,S*)-**1**)(cod)]BF_4 was purified by recrystallization from hot THF to give orange needles.

Scheme 1.



The crystal structure of the rhodium complex was determined by X-ray crystallography.[12] The ORTEP diagram shown in Figure 1 clearly confirms that bulky isopropyl groups are located close to the C_2-symmetric Rh coordination sphere due to the rigid conformation of the 1,2-phenylene unit.

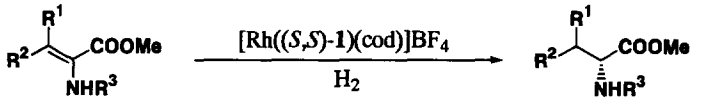


(A) Front View **(B) Top View**

Figure 1. ORTEP drawing of [Rh((*S,S*)-**1**)(cod)]BF_4: COD in front view, BF_4^- counterion, and all hydrogen atoms are omitted for clarity.

The asymmetric hydrogenation of dehydroamino acid methyl esters, using [Rh((*S,S*)-**1**)(cod)]BF_4 as a precursor catalyst, was examined in order to evaluate the effectiveness of the ligand **1**.[13] The results are summarized in Table 1. It is noted that these substrates, including β,β-disubstituted ones, were reduced with excellent enantioselectivity.

Table 1. Rh-Catalyzed Asymmetric Hydrogenation of Dehydroamino Acid Methyl Esters



entry[a]	R^1	R^2	R^3	ee % (config)[b,c]
1	H	H	Ac	97 (*S*)
2	H	Ph	Ac	97 (*S*)
3	H	Ph	Bz	96 (*S*)
4	H	Ar[d]	Ac	98 (*S*)
5	Me	Me	Ac	87 (*S*)
6	-$(CH_2)_5$-		Ac	89 (*S*)
7	-$(CH_2)_4$-		Ac	77 (*S*)

[a] Reactions were carried out at 0 °C and an initial H_2 pressure of 2 atm (for entries 1, 2, 3, 4 and 6) or 6 atm (for entries 5 an 7) for 20–180 min using the catalyst precursor (0.2 mol %). [b] The ee % values were determinded by HPLC using Daicel Chiralcel OJ, OD-H, or chiral capillary GC using Chromapack's Chiral-L-Val Column (25 m). [c] Absolute configurations were confirmed by comparison of chiral HPLC or GC elution orders with those reported in literature.[3] [d]Ar = 3-MeO-4-$AcOC_6H_3$.

To our surprise, the hydrogenation of didehydro-*N*-acetyl-α-cyclohexylglycine methyl ester (entry 6) was particularly fast under these mild conditions (2atm, 0°C), and it was completed whithin 45 min. This result may be attributed to the "steric matching" between the ligand **1** and the substrate olefin.

In conclusion, we have prepared a new P-chiral phosphine ligand, (*S,S*)-1,2-bis(isopropylmethylphosphino)benzene. Its rhodium complex was highly effective in asymmetric hydrogenation of α-(acylamino)acrylic derivatives. Synthesis of related phosphine ligands and their use in various catalytic asymmetric reductions are currently being investigated in our laboratory.

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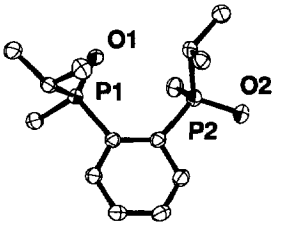
7. (*R,R*)-**3**: colorless prism; mp 209-210 °C; $[\alpha]^{27}_{D}$ +10.2 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (dd, $^3J_{HP}$ = 16.6, 7.3 Hz, 6H), 1.33 (dd, $^3J_{HP}$ = 16.6, 7.1 Hz, 6H), 1.87 (d, $^2J_{HP}$ = 12.9 Hz, 6H), 2.64–2.80 (m, 2H), 7.59–7.65 (m, 2H), 8.04 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1 (d, J_{CP} = 5.0 Hz), 16.3 (d, J_{CP} = 68.6 Hz), 28.9 (d, J_{CP} = 72.0 Hz), 130.7, 130.8, 133.6; ^{31}P NMR (160 MHz, $CDCl_3$) δ 48.0; IR (KBr) 2970, 2880, 1300, 1190, 1170, 1120, 890; FAB MS (rel intensity) 287 (M^++H, 100). Anal. Calcd for $C_{14}H_{24}O_2P_2$: C, 58.73; H, 8.45. Found: C, 58.78; H, 8.44.
8. The absolute stereochemistry on the phosphorus atom was determined by X-ray analysis of the (*R,R*)-**3**. Crystal data for the (*R,R*)-**3**: formula $C_{14}H_{24}P_2O_2$, F.W. 286.29, orthorhombic, space group $P2_12_12_1$, a = 11.509(5) Å, b = 16.319(3) Å, c = 8.505(2) Å, V = 1597.4(7) Å^3, Z = 4, d_{calc} = 1.190 gcm^{-3}, $F(000)$ = 616, μ(Mo Kα) = 2.66 cm^{-1}, λ(Mo Kα) = 0.71070 Å, 2555 reflections measured, 2440 observed ($I > 3.00\sigma(I)$), 163 variables, R = 0.034, R_w = 0.050, GOF 1.11, Flack parameter = 0.089(10).



(*R,R*)-**3**

9. Enantiomeric excess was determined by HPLC analysis with Daicel Chiralcel OD-H using *n*-hexane–2-propanol (9:1) as the eluant (flow rate 1.0 min/ml, (*S,S*) t_1 = 9.05, (*R,R*) t_2 = 10.70).
10. The other isomer, (*R,R*)-**1**, was also prepared in a similar manner using dibenzoyl-L-tartaric acid ((–)-DBT).
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12. Crystal data for the cationic rhodium complex: formula $C_{22}H_{36}BF_4P_2Rh$, F.W. 552.18, orthorhombic, space group $C222_1$, a = 13.35(1) Å, b = 16.84(1) Å, c = 10.975(3) Å, V = 2467(2) Å^3, Z = 4, d_{calc} = 1.486 gcm^{-3}, $F(000)$ = 1136, μ(Mo Kα) = 8.57 cm^{-1}, λ(Mo Kα) = 0.71070 Å, 1159 reflection measured, 1157 observed ($I > 1.00\sigma(I)$), 126 variables, R = 0.080, R_w = 0.107, GOF 2.23.
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