ELSEVIER

Journal of Molecular Catalysis A: Chemical 196 (2003) 117–124

JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL

www.elsevier.com/locate/molcata

# Preparation of an optically active bis(diethylphosphino)biphenyl ligand designed for highly reactive catalytic processes

Tomomi Shibata, Hideyuki Tsuruta, Hiroshi Danjo, Tsuneo Imamoto*

*Department of Chemistry, Faculty of Science, Chiba University, 1-33 Yayoi-cho, Inage-ku, Chiba 263-8522, Japan*

Received 25 April 2002; accepted 15 July 2002

**Abstract**

New optically active diphosphine ligands, (*S*)-2,2′-bis(diphenylphosphino)–3,3′,4,4′,5,5′,6,6′-octamethylbiphenyl (**2a**) and (*S*)-2,2′-bis(diethylphosphino)–3,3′,4,4′,5,5′,6,6′-octamethylbiphenyl (**2c**) were prepared via optical resolution of the corresponding phosphine oxides. The Rh complex of **2c** proved efficient in the catalytic asymmetric hydrogenation of a dehydroamino acid derivative even at −50 °C and gave 88% e.e. of hydrogenation product quantitatively.


*Keywords:* Optically active diphosphine ligand; Electron-rich phosphine; Axial chirality; Diethylphosphino group; Rh-catalyzed asymmetric hydrogenation

## 1. Introduction

Over the past three decades, an enormous number of optically active diphosphine ligands have been designed and prepared due to the spectacular development of transition metal-catalyzed asymmetric transformations [1–4]. Most of the ligands reported so far are based on backbone chirality and possess two same aryl or alkyl substituents on each phosphorus atom [5,6]. It is generally recognized that the two substituents become non-equivalent by the effect of the backbone chirality and the induced asymmetric environment regulates the enantioselection [7]. As for the two substituents on the phosphorus atom, phenyl or cyclohexyl group is most frequently employed, mainly because of synthetic reasons. It is also considered that these substituents fit for the construction of an effective asymmetric environment, owing to their moderately large steric bulkiness.

We have been interested in chiral diphosphines possessing two small alkyl groups on the phosphorus atoms. In such ligands the enantioselectivity of the reaction might be affected directly by the backbone chirality rather than the two non-equivalent small substituents. It was also anticipated that the reduced steric hindrance at the reaction center would enhance the catalytic activity. Herein we report the preparation of a new axially chiral diphosphine bearing two ethyl groups on the phosphorus atoms and its catalytic activity in Rh-catalyzed asymmetric hydrogenation of dehydroamino acid derivatives[1] [8].

* Corresponding author. Tel.: +81-43-290-2791; fax: +81-43-290-2791.
*E-mail address:* imamoto@scichem.s.chiba-u.ac.jp (T. Imamoto).

[1] (*R*)-2,2′-bis(Diethylphosphino)–6,6′-dimethylbiphenyl was prepared and used in Ru-catalyzed asymmetric hydrogenation as a chiral ligand.

1381-1169/02/$ – see front matter 
PII: S1381-1169(02)00640-4

## 2. Experimental section

### 2.1. General

All manipulations were carried out under nitrogen atmosphere. NMR spectra were recorded on a JEOL JMN-LA500 spectrometer (500 MHz for $^{1}H$ and 202 MHz for $^{31}P$) or a JEOL JMN-LA400 spectrometer (400 MHz for $^{1}H$ and 100 MHz for $^{13}C$). Chemical shifts are reported in $\delta$ (ppm) referenced to an internal tetramethylsilane standard for $^{1}H$ NMR, and to an external 85% $H_3PO_4$ standard for $^{31}P$ NMR. Residual chloroform ($\delta = 77.0$ ppm for $^{13}C$) was used as internal reference for $^{13}C$ NMR. $^{1}H$, $^{13}C$, and $^{31}P$ NMR spectra were recorded in $CDCl_3$ at 25 °C unless otherwise noted. Optical rotations were recorded on a JASCO DIP-370 polarimeter. MS (FAB) spectra were recorded on a JEOL HX-110 spectrometer. HPLC analyses were performed on a HITACHI L-6000 pump and a L-4000 UV detector with a chiral column.

### 2.2. Materials

THF was dried over sodium benzophenone ketyl and distilled prior to use. 2,2′,3,3′,4,4′,5,5′-Octamethyl–1,1′-biphenyl was prepared according to the reported procedure [9,10].

#### 2.2.1. 2,2′-Dibromo–3,3′,4,4′,5,5′,6,6′-octamethyl–1,1′-biphenyl (1)

To a suspension of 2,2′,3,3′,4,4′,5,5′-octamethyl–1,1′-biphenyl (13.32 g, 50 mmol) and iron powder (ca. 250 mg) in 200 ml of dry dichloromethane was added bromine (5.2 ml, 100 mmol) in 10 ml of dry dichloromethane dropwise (1 h) with vigorous stirring at 0 °C in the dark. The mixture was allowed to warm to room temperature and stirred for 12 h. The resulting red suspension was poured onto water (ca. 100 ml) and extracted with toluene (1500 ml). The organic layer was washed with 1 M NaOH aq., and dried over $Na_2SO_4$. After filtration, the solution was concentrated under reduced pressure, and the residue was recrystallized from toluene/hexane (200 ml/150 ml) to give **1** as white cubes (17.31 g, 82%); mp: >300 °C. $^{1}H$ NMR ($CDCl_3$, 400 MHz): $\delta$ (ppm) = 2.47 (s, 6H), 2.34 (s, 6H), 2.23 (s, 6H), 1.88 (s, 6H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ (ppm) = 140.9, 135.4, 134.3, 133.7, 133.5, 124.8, 21.2, 18.0, 17.8, 16.7. IR (KBr): 2920, 1445, 1214 $cm^{-1}$.

#### 2.2.2. 2,2′-bis(Diphenylphosphino)–3,3′,4,4′,5,5′,6,6′-octamethyl–1,1′-biphenyl (2a)

To a suspension of **1** (4.24 g, 10 mmol) in THF (17 ml) and ether (83 ml) was added *t*-BuLi in pentane (28 ml, 1.51 M, 42 mmol) at −45 °C within 20 min. The mixture was stirred at −45 °C for 90 min, and chlorodiphenylphosphine (5 ml, 27 mmol) was added at −45 °C. After stirring at −45 °C for 1 h, the reaction mixture was allowed to warm to room temperature and stirred for 12 h. The precipitate was collected by filtration and washed with ether (two times), water (four times), methanol, and ether (twice), then dried under reduced pressure to give **2a** as white powder (5.15 g, 81%); mp: 250 °C (dec.). $^{1}H$ NMR ($CDCl_3$, 400 MHz): $\delta$ (ppm) = 7.35–7.39 (m, 4H), 7.21–7.29 (m, 6H), 7.13–7.16 (m, 4H), 6.92–6.94 (m, 6H), 2.20 (s, 6H), 2.16 (s, 6H), 1.78 (s, 6H), 1.65 (s, 6H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ (ppm) = 150.2 (dd, $J_{C-P}$ = 41.4, 10.8 Hz), 140.0 (dd, $J_{C-P}$ = 2.5, 2.5 Hz), 137.2 (d, $J_{C-P}$ = 19.0 Hz), 135.4 (s), 133.6 (dd, $J_{C-P}$ = 7.0, 7.4 Hz), 132.6 (s), 132.6 (d, $J_{C-P}$ = 19.0 Hz), 130.1 (s), 130.1 (dd, $J_{C-P}$ = 2.5, 18.2 Hz), 127.9 (dd, $J_{C-P}$ = 2.5, 2.9 Hz) 127.6 (dd, $J_{C-P}$ = 1.7, 2.1 Hz), 126.6 (d, $J_{C-P}$ = 127.4 Hz), 22.2 (s), 18.8 (s), 17.2 (s). $^{31}P$ NMR ($CDCl_3$, 202 MHz): $\delta$ (ppm) = −10.4 (s). IR (KBr): 3045, 2910, 1435 $cm^{-1}$.

#### 2.2.3. 2,2′-bis(Dicyclohexylphosphino)–3,3′,4,4′,5,5′,6,6′-octamethyl–1,1′-biphenyl (2b)

To a suspension of **1** (5.09 g, 12 mmol) in THF (20 ml) and ether (100 ml) was added *t*-BuLi in pentane (33 ml, 1.51 M, 50 mmol) at −45 °C within 90 min. The mixture was stirred at −45 °C for 90 min, and a solution of chlorodicyclohexylphosphine (8.4 g, 36 mmol) in THF (10 ml) was added at −45 °C. After stirring at −45 °C for 15 min, the reaction mixture was allowed to warm to room temperature and stirred for 12 h. The precipitate was collected by filtration and washed with ether (twice), water (four times), methanol, and ether (twice), then dried under reduced pressure to give **2b** as white powder (6.37 g, 79%); mp: 247 °C. $^{1}H$ NMR ($C_6D_6$–$CD_2Cl_2$, 400 MHz): $\delta$ (ppm) = 2.33 (s, 6H), 2.23–2.33 (m, 2H), 2.10 (s, 6H), 2.08 (s, 6H), 1.62 (s, 6H), 0.96–2.00 (m, 42H). $^{13}C$ NMR ($C_6D_6$–$CD_2Cl_2$, 100 MHz): $\delta$ (ppm) = 149.8

(dd, $J_{C-P}$ = 23.6, 24.0 Hz), 139.0 (dd, $J_{C-P}$ = 2.5, 2.9 Hz), 136.0 (s), 133.8 (s), 133.4 (dd, $J_{C-P}$ = 6.2, 6.6 Hz), 132.2 (dd, $J_{C-P}$ = 9.4, 14.9 Hz), 38.6 (dd, $J_{C-P}$ = 8.3, 10.7 Hz), 37.7 (dd, $J_{C-P}$ = 9.1, 12.4 Hz), 33.8–34.5 (m), 32.7 (dd, $J_{C-P}$ = 5.8, 6.2 Hz), 30.1 (dd, $J_{C-P}$ = 6.6, 7.4 Hz), 28.7 (dd, $J_{C-P}$ = 6.6, 6.6 Hz), 28.5 (dd, $J_{C-P}$ = 4.1, 4.1 Hz), 28.0 (dd, $J_{C-P}$ = 3.3, 3.3 Hz) 27.7 (dd, $J_{C-P}$ = 7.9, 8.3 Hz), 26.9 (d, $J_{C-P}$ = 15.7 Hz), 21.0 (s), 19.3 (s), 17.1 (s), 17.0 (s). $^{31}$P NMR ($C_6D_6$–$CD_2Cl_2$, 202 MHz): $\delta$ (ppm) = 1.7 (s). MS (FAB): *m/z* 659 ($M + H^+$). IR (KBr): 2920, 1435 $cm^{-1}$.

### 2.2.4. 2,2′-bis(Boranatodiethylphosphino)–3,3′,4,4′,5,5′,6,6′-octamethyl–1,1′-biphenyl (3)

To a suspension of **1** (6.36 g, 15 mmol) in THF (30 ml) and ether (120 ml) was added *t*-BuLi in pentane (44 ml, 1.45 M, 64 mmol) at −45 °C within 90 min. The mixture was stirred at −45 °C for 90 min, and added to a solution of dry CuI (5.74 g, 30 mmol) in THF (100 ml) at −78 °C. After stirring for 4 h at −55 °C, dichloroethylphosphine (5.8 ml, 45 mmol) was added at −78 °C. The mixture was stirred at room temperature for 12 h, and borane–THF complex (75 ml, 1 M, 75 mmol) was added slowly at 0 °C. The reaction was quenched with 1 M HCl aq., and the suspension was filtered through Celite. The organic phase was separated from aqueous phase and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with 25% $NH_3$ aq. and brine, and dried over $Na_2SO_4$. After concentrated under reduced pressure, the residue was passed through silica gel and eluted with toluene/hexane (8:1). The combined eluent was concentrated and the remaining white solid was recrystallized from toluene/hexane (30 ml/60 ml) to give **3** as white cube (3.69 g, 60%); mp: 191–194 °C. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ (ppm) = 2.54 (s, 6H), 2.30 (s, 6H), 2.26 (s, 6H), 1.80–1.91 (m, 2H), 1.76 (s, 6H), 1.62–1.74 (m, 2H), 1.28–1.40 (m, 4H), 1.01–1.11 (m, 6H), 0.90–0.98 (m, 6H), 0.52–1.41 (brs, 6H). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ (ppm) = 141.5 (dd, $J_{C-P}$ = 2.1, 4.1 Hz), 138.0 (d, $J_{C-P}$ = 2.1 Hz), 137.9 (d, $J_{C-P}$ = 10.3 Hz), 137.0 (d, $J_{C-P}$ = 8.3 Hz), 134.6 (d, $J_{C-P}$ = 7.2 Hz), 127.5 (d, $J_{C-P}$ = 47.7 Hz), 22.0 (d, $J_{C-P}$ = 8.3 Hz), 19.4 (d, $J_{C-P}$ = 36.2 Hz), 18.7 (d, $J_{C-P}$ = 35.2 Hz), 18.3 (s), 17.0 (d, $J_{C-P}$ = 36.2 Hz), 9.1 (s), 8.4 (d, $J_{C-P}$ = 3.1 Hz). $^{31}$P NMR ($CDCl_3$, 202 MHz): $\delta$ (ppm) = 20.37 (d, $J_{P-B}$ = 48.4 Hz). IR (KBr): 2945, 2365, 1455, 1070 $cm^{-1}$.

### 2.2.5. 2,2′-bis(Diphenylphosphonyl)–3,3′,4,4′,5,5′,6,6′-octamethyl–1,1′-biphenyl (4a)

To a suspension of **2a** (4.00 g, 6.3 mmol) in toluene (320 ml) and ethanol (80 ml) was added 30% of hydrogen peroxide (2.0 g) at room temperature. After stirring at 50 °C for 1 h, the reaction was quenched with $Na_2S_2O_3$ aq. The organic phase was separated from aqueous phase, and the aqueous layer was extracted with toluene. The combined organic layer was washed with brine, dried over $Na_2SO_4$, and concentrated under reduced pressure to give **4a** as white powder (3.98 g, 95%); mp: >300 °C. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ (ppm) = 7.44–7.53 (m, 8H), 7.05–7.34 (m, 12H), 2.07 (s, 6H), 1.84 (brs, 12H), 1.71 (s, 6H). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ (ppm) = 141.7 (m), 139.2 (brs), 139.0 (brs), 138.5 (brs), 138.0 (s), 133.0 (d, $J_{C-P}$ = 11.5 Hz), 132.7 (d, $J_{C-P}$ = 9.8 Hz), 130.7 (d, $J_{C-P}$ = 9.0 Hz), 129.6 (s), 129.3 (d, $J_{C-P}$ = 114.9 Hz) 127.8 (d, $J_{C-P}$ = 11.5 Hz), 126.0 (d, $J_{C-P}$ = 12.3 Hz), 21.7 (m), 18.1 (d, $J_{C-P}$ = 9.8 Hz), 17.1 (d, $J_{C-P}$ = 6.6 Hz), 16.4 (d, $J_{C-P}$ = 7.4 Hz). $^{31}$P NMR ($CDCl_3$, 202 MHz): $\delta$ (ppm) = 30.0 (s). HRMS (FAB): Calcd. for $C_{44}H_{45}O_2P_2$ ($M + H^+$) 667.2895 found 667.2900. IR (KBr): 3155, 2920, 1435, 1175 $cm^{-1}$.

### 2.2.6. 2,2′-bis(Dicyclohexylphosphonyl)–3,3′,4,4′,5,5′,6,6′-octamethyl–1,1′-biphenyl (4b)

To a suspension of **2b** (4.28 g, 6.5 mmol) in toluene (80 ml) and ethanol (20 ml) was added 30% of hydrogen peroxide (2.0 g) at room temperature. After stirring for 1 h, the reaction was quenched with $Na_2S_2O_3$ aq. The organic phase was separated from aqueous phase, and the aqueous layer was extracted with toluene. The combined organic layer was washed with brine, dried over $Na_2SO_4$, and concentrated under reduced pressure to give **4b** as white powder (4.15 g, 95%); mp: 242–244 °C (dec.). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ (ppm) = 2.26 (s, 6H), 2.22 (s, 6H), 2.20 (s, 6H), 1.64 (s, 6H), 1.41–2.17 (m, 30H), 1.09–1.30 (m, 14H). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ (ppm) = 147.1 (dd, $J_{C-P}$ = 2.5, 5.7 Hz), 137.3 (d, $J_{C-P}$ = 2.5 Hz), 133.3 (d, $J_{C-P}$ = 12.3 Hz), 133.0 (d, $J_{C-P}$ = 3.3 Hz), 132.9 (d, $J_{C-P}$ = 3.3 Hz), 127.4 (d, $J_{C-P}$ = 85.3 Hz), 42.8 (s), 42.5 (s), 41.8 (s), 41.1 (s), 26.2–28.7 (m), 21.0 (m), 18.7 (m), 17.3 (m), 16.7

(s). $^{31}$P NMR ($CDCl_3$, 202 MHz): $\delta$ (ppm) = 48.8 (s). HRMS (FAB): Calcd. for $C_{44}H_{69}O_2P_2$ ($M + H^+$) 691.4773 found 691.4754. IR (KBr): 2920, 1435, 1180 $cm^{-1}$.

### 2.2.7. 2,2′-bis(Diethylphosphonyl)–3,3′,4,4′,5,5′,6,6′-octamethyl–1,1′-biphenyl (**4c**)

A solution of **3** (3.00 g, 6.37 mmol) in pyrrolidine (15 ml) was stirred at 60 °C for 3 h, and then the volatiles were removed under reduced pressure. The residue was passed through a short silica gel column and eluted with toluene under nitrogen. The eluent was concentrated under reduced pressure, and the residual white solid was dissolved in a mixed solvent of toluene (100 ml) and ethanol (20 ml) under nitrogen. To the solution was added 30% of hydrogen peroxide (2.8 g) at room temperature. After stirring for 1 h, the reaction was quenched with $Na_2S_2O_3$ aq. The organic phase was separated from aqueous phase, and the aqueous layer was extracted with toluene. The combined organic layer was washed with brine, dried over $Na_2SO_4$, and concentrated under reduced pressure to give **4c** as white powder (2.69 g, 89%); mp: 188–189 °C (dec.). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ (ppm) = 2.45 (s, 6H), 2.25 (s, 6H), 2.23 (s, 6H), 1.96–2.18 (m, 2H), 1.76–1.87 (m, 6H), 1.70 (s, 6H), 1.00–1.09 (m, 12H). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ (ppm) = 143.9 (dd, $J_{C-P}$ = 3.3, 6.6 Hz), 138.1 (d, $J_{C-P}$ = 3.3 Hz), 134.9 (d, $J_{C-P}$ = 4.9 Hz), 134.8 (d, $J_{C-P}$ = 4.1 Hz), 132.8 (d, $J_{C-P}$ = 10.7 Hz), 128.5 (d, $J_{C-P}$ = 91.9 Hz), 20.6 (d, $J_{C-P}$ = 4.9 Hz), 17.9 (s), 17.4 (s), 16.7 (s), 6.6 (dd, $J_{C-P}$ = 4.9, 27.9 Hz). $^{31}$P NMR ($CDCl_3$, 202 MHz): $\delta$ (ppm) = 45.0 (s). MS (FAB): 475 ($M + H^+$). IR (KBr): 2938, 2345, 1458, 1143 $cm^{-1}$.

### 2.2.8. Optical resolution of **4a**

A mixture of **4a** (2.00 g, 3.0 mmol) and (1*S*)-(+)-camphorsulfonic acid ((+)-CSA; 1.4 g, 6.0 mmol) was dissolved in hot chloroform (90 ml). To the solution was added acetic acid (ca. 0.5 ml) and hot ethyl acetate (210 ml), and the mixture was gradually cooled to ca. −18 °C. The precipitate was collected by filtration, washed with ethyl acetate, and dried under reduced pressure to give the diastereomerically pure complex of (*S*)-(+)-**4a** and (+)-CSA as colorless needles (2.57 g, 82%). $[\alpha]_D^{20}$ + 172.3 (*c* = 0.47, chloroform). The complex was treated with 1 M NaOH aq., extracted with chloroform, dried over $Na_2SO_4$, and concentrated under reduced pressure to give (*S*)-(+)-**4a** as white powder (mp: 297 °C (dec.)). $[\alpha]_D^{23}$ + 347.0 (*c* = 0.79, dichloromethane). The e.e. value was determined to be >99% e.e. by HPLC analysis with chiral stationary phase column: DAICEL CHIRALCED OD-H; hexane/ethanol = 9/1, 0.25 ml/min, (*S*) $t_1$ = 22.8 min, (*R*) $t_2$ = 27.0 min.

### 2.2.9. X-ray crystallographic analysis of **4a**-(+)-CSA

Absolute configuration of the titled compound was determined to be *S* by single crystal X-ray analysis. Crystallographic data for $C_{44}H_{44}O_2P_2{\cdot}2C_{10}H_{16}O_4S{\cdot}CHCl_3$: $C_{65}H_{77}O_{10}P_2S_2Cl_3$; monoclinic, space group $P2_1$ (# 4); $Z$ = 2; $D$ = 1.334 g $cm^{-1}$; cell constants $a$ = 12.401(4), $b$ = 12.783(2), $c$ = 20.220(8) Å; $\beta$ = 103.776(3)°; $V$ = 3113(1) Å$^3$; temperature of data collection 301 K; 5502 reflections measured, 5489 unique reflections ($I > 1.00\sigma(I)$); 740 variables; $R$ = 0.071; $R_w$ = 0.098; GOF = 1.86.

### 2.2.10. Optical resolution of **4b**

A mixture of **4b** (2.07 g, 3.0 mmol) and (2*R*,3*R*)-(−)-*O*,*O*′-dibenzoyltartaric acid monohydrate ((−)-DBTA; 1.13 g, 3.0 mmol) was dissolved in chloroform (90 ml) with heating. To the solution was added hot ethyl acetate (60 ml), and the mixture was gradually cooled to ca. −20 °C. The precipitate was collected by filtration, washed with ethyl acetate, and dried under reduced pressure to give the diastereomerically pure complex of (+)-**4b** and (−)-DBTA (770 mg, 48%). $[\alpha]_D^{24}$ + 5.6 (*c* = 0.44, chloroform). The complex was treated with 1 M NaOH aq., extracted with chloroform, dried over $Na_2SO_4$, and concentrated under reduced pressure to give (+)-**4b** as white powder (mp: 297 °C (dec.)). $[\alpha]_D^{25}$ + 41.4 (*c* = 0.46, chloroform).

### 2.2.11. Optical resolution of **4c**

A mixture of **4c** (953 mg, 2.0 mmol) and (−)-DBTA (752 mg, 2.0 mmol) was dissolved in dry dichloromethane (20 ml) with heating. To the solution was added hot ethyl acetate (20 ml), and the mixture was gradually cooled to room temperature. The precipitate was collected by filtration, washed with ethyl acetate, and dried under reduced pressure to give diastereomerically pure complex of (*S*)-(+)-**4c** and (−)-DBTA (733 g, 86%). $[\alpha]_D^{23}$ + 0.09 (*c* = 0.66, chloroform). This complex was treated with 1 M

NaOH aq., extracted with chloroform, dried over $Na_2SO_4$, and concentrated under reduced pressure to give (*S*)-(+)-**4c** as white powder (mp: 188–189 °C (dec.)). $[\alpha]_D^{25} + 53.5$ ($c = 0.48$, chloroform). The e.e. value was determined to be >99% e.e. by HPLC analysis with chiral stationary phase column: DAICEL CHIRALPAK AD; hexane/ethanol = 9/1, 0.5 ml/min, (*S*) $t_1 = 9.2$ min, (*R*) $t_2 = 19.4$ min.

### 2.2.12. X-ray crystallographic analysis of *4c*-(−)-DBTA

Absolute configuration of the titled compound was determined to be *S* by single crystal X-ray analysis. Crystallographic data for $C_{28}H_{44}O_2P_2 \cdot [C_6H_5CO_2CH(CO_2H)]_2 \cdot CH_2Cl_2$: $C_{47}H_{60}O_{10}P_2Cl_2$; orthorhombic, space group $P222_1$ (# 20); $Z = 4$; $D = 1.315\ g\,cm^{-1}$; cell constants $a = 12.236(4)$, $b = 13.401(3)$, $c = 26.301(3)$ Å; $V = 4634(1)$ Å$^3$; temperature of data collection 173 K; 2789 reflections measured, 2766 unique reflections ($I > 1.50\sigma(I)$); 281 variables; $R = 0.090$; $R_w = 0.168$; GOF = 2.34.

### 2.2.13. Reduction of (S)-*4a*

To a mixture of (*S*)-**4a** (111 mg, 0.17 mmol), cerium(III) chloride (245 mg, 1.0 mmol), and lithium aluminum hydride (51 mg, 1.34 mmol) was added THF (5 ml), and the suspension was stirred at 60 °C for 90 min. The reaction was quenched with 1 M HCl aq., and extracted with ethyl acetate. The organic layer was washed with $NaHCO_3$ aq. and brine, and dried over $Na_2SO_4$. The solution was concentrated under reduced pressure to give (*S*)-**2a** as white powder (67 mg, 63%).

### 2.2.14. Reduction of (S)-*4c*

Methyl nonafluorobutanesulfonate (76.3 ml, 0.4 mmol) was added to a solution of **4c** (47.0 mg, 0.1 mmol) and tricyclohexylphosphine oxide (2.8 mg, 0.01 mmol) in degassed dimethoxyethane (3 ml) under nitrogen, and the mixture was stirred at 30 °C for 18 h. To the mixture was added lithium aluminum hydride (39.0 mg, 0.8 mmol) at 0 °C, and stirred at 80 °C for 24 h. Borane–THF complex (2 ml, 1 M) was then added to the suspension at 0 °C and stirred at room temperature for 3 h. The reaction was quenched with 1 M HCl aq. and extracted with ethyl acetate. The combined organic layer was washed with $NaHCO_3$ aq. and brine, and dried over $Na_2SO_4$. After concentrated under reduced pressure, the residue was chromatographed on silica gel (hexane/EtOAc = 5/1) to give (*S*)-**3** (36 mg, 77%) (mp: 230 °C (dec.)). $[\alpha]_D^{23} + 31.8$ ($c = 0.42$, chloroform).

### 2.2.15. Deboranation of (S)-*3*

A solution of **3** (82.4 mg, 0.2 mmol) in pyrrolidine (2.5 ml) was stirred at 60 °C for 3 h. The volatiles were removed under reduced pressure, and the residue was passed through a short silica gel column with toluene elution under nitrogen. The eluent was concentrated under reduced pressure to give quantitative yield of (*S*)-**2c** as white solid.

### 2.2.16. General procedure for the preparation of rhodium complexes

To a suspension of $[Rh(cod)_2]OTf$ or $[Rh(nbd)_2]BF_4$ (1 mmol) in THF (9 ml) was added a solution of diphosphine (*S*)-**2** (1 mmol) in THF (4 ml) under nitrogen at room temperature, and the mixture was stirred at intact temperature for 30 min. The mixture was filtered under nitrogen and the filtrate was concentrated under reduced pressure. The residue was washed with degassed hexane under nitrogen, and dried under reduced pressure to give a rhodium complex of diphosphine (*S*)-**2**.

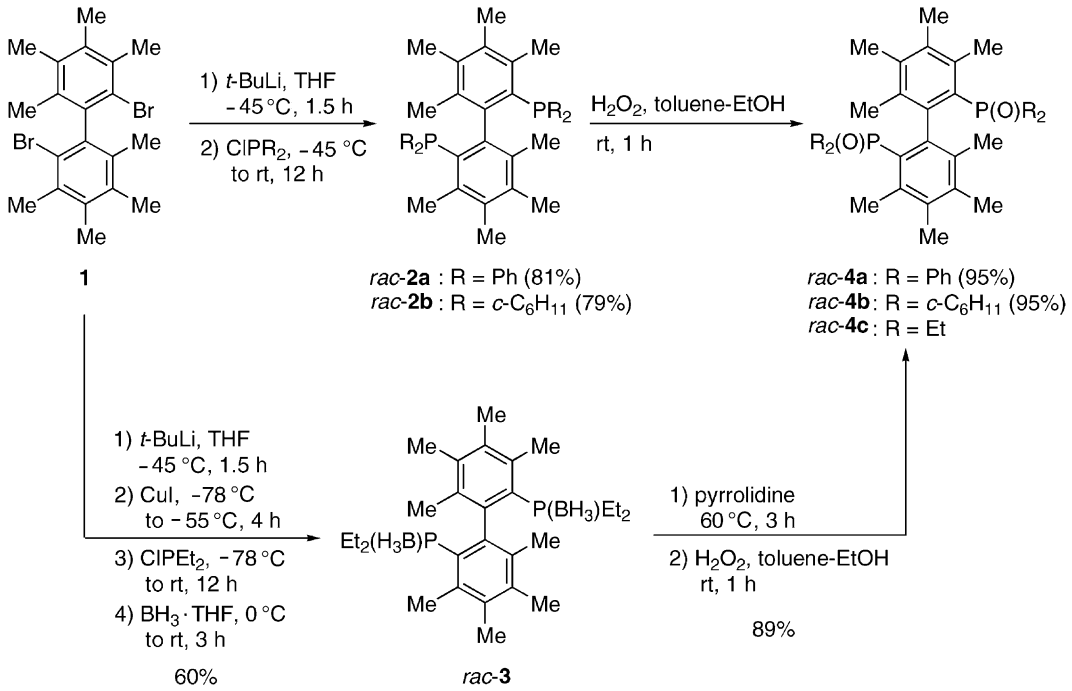
### 2.2.17. General procedure for Rh-catalyzed asymmetric hydrogenation of methyl acetaminocinnamate

A 50 ml Fisher–Porter tube was charged with methyl acetaminocinnamate (205 mg, 1 mmol) and 5 mmol of the Rh-catalyst. The tube was connected to the hydrogen tank via stainless steel tubing. The vessel was evacuated and filled with hydrogen gas (Nippon Sanso, 99.9999%) to a pressure of about 2 atm. This operation was repeated and the bottle was immersed in a dry ice–ethanol bath. The upper cock of the bottle was opened and anhydrous methanol (2 ml) was added quickly using a syringe. After four vacuum/$H_2$ cycles, the tube was pressurized to an initial pressure of 3–50 atm. The tube was closed off and the cooling bath was removed. The solution was stirred at appropriate temperature until no further hydrogen uptake was observed. The resulting solution was submitted to direct analysis for the enantiomeric excess values by HPLC or GC.

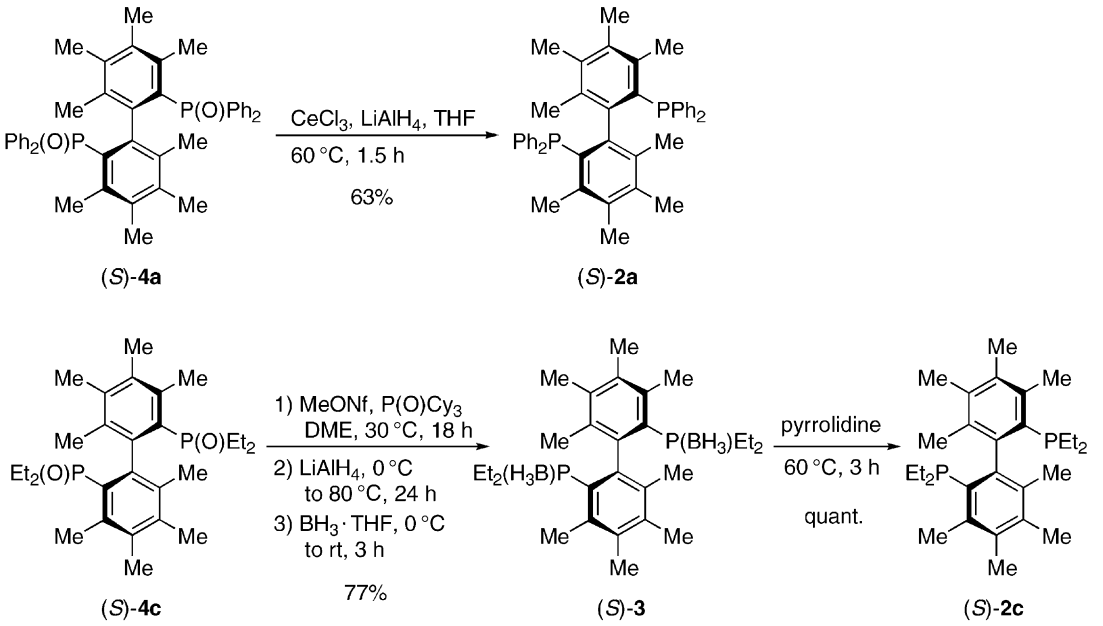
## 3. Results and discussion

We first planned to prepare diphosphines possessing several types of substituents on phosphorus atoms in order to discuss the substituent effect on the reactivity and selectivity in transition metal-catalyzed asymmetric reactions. As an axially chiral backbone, 3,3′,4,4′,5,5′,6,6′-octamethyl–1,1′-biphenyl unit was chosen owing to its accessibility and high electron-donating ability toward the phosphorus atoms. We considered also that the enantioselection would be largely affected by the methyl groups at 3 and 3′ positions of biphenyl. The diphosphines were prepared from 2,2′-dibromo–3,3′,4,4′,5,5′,6,6′-octamethyl–1,1′-biphenyl (**1**) as outlined in Schemes 1 and 2. Dilithiation of **1** with *t*-butyllithium, followed by reaction with chlorodiphenylphosphine or chlorodicyclohexylphosphine resulted in the formation of diphosphines *rac*-**2a** and *rac*-**2b**, respectively. In the case of the reaction with chlorodiethylphosphine [11], the dilithio intermediate was converted into a dicopper derivative via transmetallation with CuI to avoid deprotonation from chlorodiethylphosphine. The product was isolated as bis(phosphine-borane) *rac*-**3**. These compounds were converted into the corresponding phosphine oxides for optical resolution. Diphosphines *rac*-**2a** and *rac*-**2b** were easily oxidized by treatment with hydrogen peroxide. The same oxidation conditions were also applicable to phosphine-borane *rac*-**3** after deboranation with pyrrolidine. Successful optical resolution of *rac*-**4a** was realized by diastereoselective complexation with (1*S*)-(+)-10-camphorsulfonic acid ((+)-CSA) [12]. The CSA complex was isolated as a single diastereomer by recrystallization, and the absolute configuration of the axial chirality was determined to be *S* by X-ray crystallographic analysis. On the other hand, (2*R*,3*R*)-(−)-*O*,*O*′-dibenzoyl tartrate ((−)-DBTA) was used for diastereoselective complexation with *rac*-**4b** and *rac*-**4c** [13]. Treatment of the obtained diastereomerically pure complexes with NaOH aq. afforded the respective optically pure phosphine oxides.

Diphosphine oxide (*S*)-**4a** was readily reduced by lithium aluminum hydride in the presence of cerium(III) chloride to afford optically pure diphosphine (*S*)-**2a** (Scheme 2). In the case of racemic **4c**,




Scheme 1.

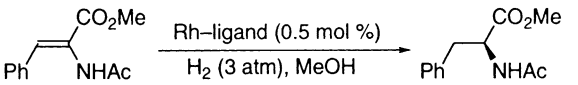



Scheme 2.

prior methylation of the phosphine oxide oxygen with methyl nonafluorobutanesulfonate was required, probably due to the increased electron density of the phosphorus atoms [14]. However, subsequent reduction of optically active **4c** by this method only gave rise to the monoreduced product. In order to overcome this difficulty we examined the reaction conditions using several types of additives, and found that tricyclohexylphosphine oxide facilitated the reduction to give the desired diphosphine. Thus, the reduction of optically active **4c** was carried out in the presence of tricyclohexylphosphine oxide to afford optically active bis(phosphine-borane) (*S*)-**3** in 77% yield after complexation with borane. Deboranation of (*S*)-**3** was easily achieved by treatment with pyrrolidine. Finally, reduction of optically active **4b** did not proceed at all probably owing to strong oxygen affinity of the phosphorus atoms and large steric hindrance around the reaction centers. These diphosphines were converted into the corresponding cationic Rh complexes by mixing with $[Rh(cod)_2]OTf$ or $[Rh(nbd)_2]BF_4$.

To evaluate the effect of the substituents on the phosphorus atoms, these Rh complexes were employed in catalytic asymmetric hydrogenation of a dehydroamino acid derivative. The reduction of methyl (*Z*)-2-acetamidocinnamate, typical dehydroamino acid derivative, was carried out in methanol at various temperatures and initial $H_2$ pressures. These results are summarized in Table 1. The Rh complex of diphosphine (*S*)-**2a**, bearing phenyl groups at phosphorus donor atoms, exhibited low catalytic activity, requiring high $H_2$ pressure (50 atm) and temperature (50 °C) for completion of the reaction (entry 1). In contrast, the hydrogenation catalyzed by the Rh

Table 1
Rh-catalyzed asymmetric hydrogenation of methyl (*Z*)-2-acetaminocinnamate




| Entry | Ligand | Temperature (°C) | Time | e.e. (%) |
|---|---|---|---|---|
| 1[a] | (*S*)-**2a** | 50 | 15 h | 88 |
| 2 | *rac*-**2b** | RT | 15 h | – |
| 3 | (*S*)-**2c** | RT | <10 min | 74 |
| 4 | (*S*)-**2c** | −20 | 36 h | 84 |
| 5 | (*S*)-**2c** | −40 | 60 h | 89 |
| 6[b] | (*S*)-**2c** | −50 | 60 h | 88 |

[a] The reaction was carried out under 50 atm of $H_2$.
[b] The reaction was carried out with 1 mol% of catalyst.

complex of *rac*-**2b**, with cyclohexyl groups on donor atoms, proceeded under mild conditions (room temperature, 3 atm of $H_2$; entry 2). These results clearly indicate that electron-donating ability of the substituents on phosphorus strongly affects the catalytic activity of the complexes in Rh-catalyzed hydrogenation. Electron-rich donor atoms may accelerate the oxidative addition of Rh(I) to hydrogen. Remarkable rate acceleration was observed by the Rh complex of ligand (*S*)-**2c** (entry 3). The hydrogenation completed within 10 min at ambient temperature under 3 atm of $H_2$, and 74% e.e. of hydrogenation product was obtained in quantitative yield. The reaction proceeded even at −50 °C and the enantioselectivity was increased to 88% (entry 6) [15]. The high reactivity observed here implies that introduction of less hindered alkyl groups on the donor atoms led to reduced steric repulsion between the substrate and the catalyst. Furthermore, there was almost no loss of enantioselectivity in comparison with the case of the ligand possessing larger substituents, i.e. phenyl groups, on phosphorus. It should be noted that efficient enantioinduction was realized by axial chirality derived from rigid octamethylbiphenyl backbone even in the case of the ligand possessing ethyl groups on the donor atoms. Another interesting fact is that Rh-(*S*)-BINAP provided (*R*)-hydrogenation product, whereas Rh-(*S*)-**2a** lead to (*S*)-product. The existence or non-existence of the methyl groups at 3 and 3′ positions are responsible for these opposite enantioselections.

## 4. Conclusion

Diphosphines **2a** and **2c** were designed and prepared as new optically active diphosphine ligands for transition metal-catalyzed processes. Ligand (*S*)-**2c** exhibited high reactivity in Rh-catalyzed hydrogenation of a dehydroamino acid derivative, owing to reduced steric hindrance between the substrate and the catalyst.

## References

[1] R. Noyori, Asymmetric Catalysis in Organic Synthesis, Wiley, New York, 1994.
[2] I. Ojima (Ed.), Catalytic Asymmetric Synthesis, VCH Publishers, Weinheim, 1993.
[3] K.E. Koenig, in: J.D. Morrison (Ed.), Asymmetric Synthesis, Academic Press, New York, 1985.
[4] E.N. Jacobsen, A. Pfaltz, H. Yamamoto (Ed.), Comprehensive Asymmetric Catalysis, Springer, Berlin, 1999.
[5] H. Brunner, W. Zettlmeier, Handbook of Enantioselective Catalysis with Transition Metal Compounds, Products and Catalysis, vol. 1, VCH, Basel, 1993.
[6] H. Brunner, W. Zettlmeier, Handbook of Enantioselective Catalysis with Transition Metal Compounds, Ligands—References, vol. 2, VCH, Basel, 1993.
[7] J. Halpern, in: J.D. Morrison (Ed.), Asymmetric Synthesis, vol. 5, Academic Press, New York, 1985, Chapter 2, p. 41.
[8] Y. Crameri, J. Foricher, M. Scalone, R. Schmid, Tetrahedron: Asym. 8 (1997) 3617.
[9] H.M. Reginald, Y.-H. Lai, V.W. Richard, V. Williams, J. Org. Chem. 44 (1979) 4733.
[10] H. Hart, A. Teuerstein, Synthesis 9 (1979) 693.
[11] H.E. Ulmer, L.C.D. Groenweghe, L. Maier, J. Inorg. Nucl. Chem. 20 (1961) 84.
[12] H. Takaya, K. Mashima, K. Koyano, M. Yagi, H. Kumobayashi, T. Taketomi, S. Akutagawa, R. Noyori, J. Org. Chem. 51 (1986) 629.
[13] A. Miyashita, H. Karino, J. Shimamura, T. Chiba, K. Nagano, H. Nohira, H. Takaya, Chem. Lett. (1989) 1849.
[14] T. Imamoto, S. Kikuchi, T. Miura, Y. Wada, Org. Lett. 3 (2001) 87.
[15] P.J. Pye, K. Rossen, R.A. Reamer, N.N. Tsou, R.P. Volante, P.J. Reider, J. Am. Chem. Soc. 119 (1997) 6207.