Synthesis and Application of Chiral Phospholane Ligands Bearing a Sterically and Electrically Adjustable Moiety

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Dedicated to Professor Ryoji Noyori on the occasion of his receiving a Nobel Prize.

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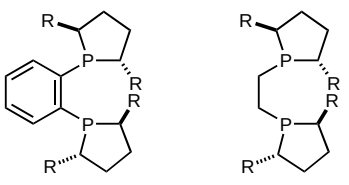
Abstract: A series of C_1-symmetric phosphine-phospholane ligands, 1-(disubstituted phosphino)-2-(phospholano)benzenes (**5**), which are called UCAPs, with an achiral phosphino group and a chiral phospholane which can be sterically and electrically adjustable, has been designed and synthesized. In the asymmetric hydrogenation of (*Z*)-*N*-benzoyl-1-phenylpropenamine (**3**), the stereorecognition abilities of the **5d** – **e**–Rh catalysts which have a bulkier aryl substituent on the achiral phosphorus are superior to that observed with the DuPHOS-Rh catalyst. The effects of varying substituents on the achiral phosphorus atom are discussed.

Keywords: Asymmetric catalysis; hydrogenation; ligand design; P-ligands; rhodium

Chiral phosphine ligands play a most important role in transition metal-catalyzed enantioselective transformations,[1] and many successful chiral phosphines such as DIOP,[2] DIPAMP[3] and BINAP[4] have been designed and synthesized. Among them, DuPHOS (**1**) and BPE (**2**) (Figure 1),[5,6] developed by Burk and coworkers, are the most superior classes of the ligands that afford excellent selectivity in Rh(I)-catalyzed asymmetric hydrogenation of olefins. However, sometimes further development of a new ligand is required to obtain the best result. For example, (*Z*)-*N*-benzoyl-1-phenylpropenamine (**3**) is one of the substrates that the ligand fails to hydrogenate in high conversion and ee (25% conversion, 78% ee, Table 1, entry 10). We have set substrate **3** as the target molecule for our study (Scheme 1).

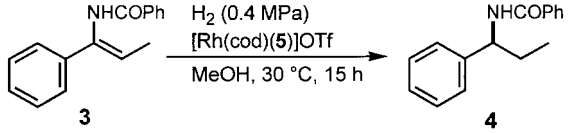
We started our studies to search new ligands by considering reaction intermediates. The dominant factor of enantioselectivity in asymmetric hydrogenation has often been explained using simple quadrant diagrams.[7] In the asymmetric control of C_2-symmetric ligands like **1** or **2**, only the two essential intermediates need to be considered [(a) = (c), (b) = (d)] as seen in Figure 2.

However, if we can control the coordination mode by changing the steric and electronic properties of the phosphino moiety without using a C_2-symmetric system, one can design a molecular catalyst to select two essential modes, (a) and (d). That idea led us to design the C_1-symmetric (achiral phosphine)-(chiral phospholane) ligands, 1-(disubstituted phosphino)-2-(phospholano)benzenes (**5a – i**; Figure 3), which are called UCAPs.[8,9] The existence of the phosphino group is expected to block (1) and (4), which may make it difficult to coordinate a substrate *via* mode (b) or (c), while the phospholane group is expected to determine enantioselectivity between (a) and (d) utilizing the excellent asymmetric environment caused by the phospholane moiety (Figure 2). Recently, 1-(2,5-dimethylphospholano)-2-(diphenylphosphino)benzene (**5a**) itself was reported by Stelzer et al. through a different approach.[10] However, our interest is in the adjustability of **5**. The di(substituted)phosphino moiety can consist of a variety of groups, which should make it possible for the



1 2

Figure 1. Structures of ligands **1** and **2.**



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Scheme 1. Hydrogenation of (*Z*)-*N*-benzoyl-l-phenylpropenamine **3** catalyzed by Rh complexes (see Table 1).

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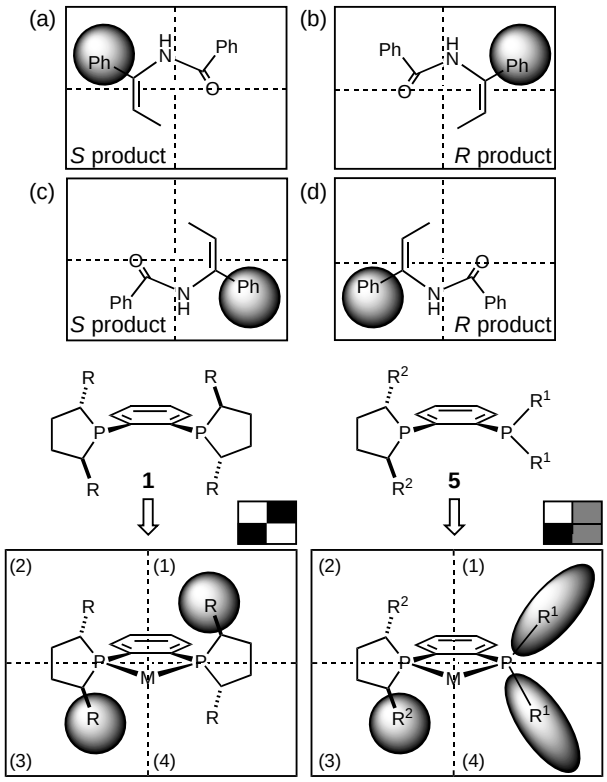
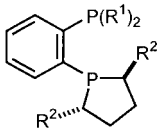


Figure 2. Possible coordination modes in intermediate [(**3**)][Rh(P–P)]$^+$ complex and the dominant factor of enantioselectivity in the diphosphine with 1,2-phenylene backbone.



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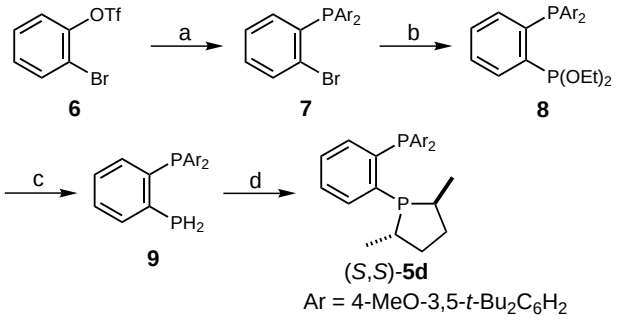
a: (*S*,*S*)-Me-UCAP-Ph;	R^1 = Ph;	R^2 = Me
b: (*S*,*S*)-Et-UCAP-Ph;	R^1 = Ph;	R^2 = Et
c: (*S*,*S*)-Me-UCAP-DM;	R^1 = 3,5-Me_2-C_6H_3;	R^2 = Me
d: (*S*,*S*)-Me-UCAP-DTBM;	R^1 = 4-MeO-3,5-*t*-$Bu_2C_6H_2$;	R^2 = Me
e: (*S*,*S*)-Me-UCAP-(1-Nap);	R^1 = 1-naphthyl;	R^2 = Me
f: (*S*,*S*)-Me-UCAP-(*p*-MeO-Ph);	R^1 = 4-MeO-C_6H_4;	R^2 = Me
g: (*S*,*S*)-Me-UCAP-(*p*-CF_3-Ph);	R^1 = 4-CF_3-C_6H_4;	R^2 = Me
h: (*S*,*S*)-Me-UCAP-*i*-Pr;	R^1 = $CH(CH_3)_2$;	R^2 = Me
i: (*S*,*S*)-Me-UCAP-Cy;	R^1 = *c*-C_6H_{11};	R^2 = Me

Figure 3. Structures of ligands **5**.

ligand to be fit to the substrate, giving high enantioselectivity. Herein, we report the preparation of UCAPs **5** and the use of these ligands for Rh-catalyzed hydrogenation.

The synthesis of 1-bis(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino-2-[(2*S*,5*S*)-2,5-dimethylphospholano]-benzene [(*S*,*S*)-Me-UCAP-DTBM: **5d**], one of the UCAP ligands, is shown in Scheme 2. Phosphinylation of triflate **6** with the aid of a Pd catalyst followed by



a: i) $Ar_2P(O)H$, $Pd_2(dba)_3$•$CHCl_3$, dppp, EtN(*i*-Pr)$_2$, toluene, reflux
ii) $HSiCl_3$, $PhNMe_2$, toluene, reflux
b: i) *n*-BuLi, THF, -78 °C, ii) $(EtO)_2PCl$
c: $LiAlH_4$, TMSCl, THF
d: i) *n*-BuLi, THF, 0 °C, ii) (2*R*,5*R*)-2,5-Hexanediol cyclic sulfate
iii) *n*-BuLi, 0 °C - room temp.

Scheme 2. Synthesis of the (*S*,*S*)-Me-UCAP-DTBM ligand.

reduction with $HSiCl_3$ gave the tertiary phosphine **7**. Halogen-metal exchange of **7** with *n*-butyllithium followed by quenching with diethyl chlorophosphonite gave the tertiary phosphine-phosphonite **8**. Reduction of **8** with $LiAlH_4$/TMSCl gave the tertiary-primary phosphine **9**. According to the literature,[5c] **9** was reacted with 1 equivalent of (2*R*,5*R*)-2,5-hexanediol cyclic sulfate in the presence of *n*-butyllithium to give pure **5d**. Other UCAP ligands which have various substituents on the phosphorus atom were similarly prepared from the corresponding tertiary-primary phosphines. However, **5g – i** should be better synthesized *via* the borane complexes of the final products or intermediates (see Supporting Information).

The asymmetric hydrogenation of **3** was performed at 30 °C with 0.4 MPa of hydrogen for 15 h in the presence of the isolated cationic **5**–Rh(I) complexes (0.2 mol %), [Rh(cod)(**5**)]OTf, as shown in Scheme 1 and Table 1. Although the use of the **5a**–Rh(I) catalyst gave (*S*)-**4** with complete conversion, the enantioselectivity was still unsatisfactory (94% ee, entry 1). Electronic variation of the substituent on an achiral phosphorus atom such as **5f – i** did not give higher enantioselectivity (entries 6 – 9). RajanBabu et al. have reported that an electron-deficient phosphorus in the chiral DIOP derivatives gives lower enantioselectivities in Rh(I)-catalyzed enamide reductions.[11] As expected, when the electron-withdrawing ligand **5g**–Rh(I) complex was used, the enantioselectivity and catalytic activity were strikingly low (entry 7). Contrary to this, remarkable increases in enantioselection were observed with the more bulky aryl substituent on the achiral phosphorus atom. In particular, when **5d**– or **5e**–Rh(I) catalysts were used, the highest enantioselectivity, 99% ee, was achieved (entries 4, 5). On the other hand, the **5a**–Rh(I) catalyst afforded higher enantioselectivity than that of the **5b**–Rh(I) catalyst (entries 1, 2).[12]

Hydrogenation of *N*-acetyl-1-phenylpropenamine (*E*/*Z* = *ca.* 2/1) catalyzed by the UCAP-Rh(I) complex

Table 1. Rh-catalyzed asymmetric hydrogenation of (*Z*)-*N*-benzoy-l-phenylpropenamine **3**.[a]

Entry	Ligand	Conversion[b] [%]	% ee[c] (config.[d])
1	**5a**	>99	94 (*S*)
2	**5b**	>99	81 (*S*)
3	**5c**	>99	95 (*S*)
4	**5d**	>99	99 (*S*)
5	**5e**	56	99 (*S*)
6	**5f**	>99	90 (*S*)
7	**5g**	4	6 (*S*)
8	**5h**	>99	69 (*R*)
9	**5i**	>99	40 (*R*)
10	(*R*,*R*)-Me-DuPHOS	25	78 (*R*)

[a] Reactions were carried out at 30 °C and an initial hydrogen pressure of 0.4 MPa using a 0.3 M solution of substrate in methanol and the catalyst precursors [Rh(cod)(P–P)]OTf (0.2 mol %). Reaction time was 15 h.
[b] Determined by capillary GLC analysis using an SPB-1 column.
[c] Determined by HPLC analysis using a CHIRALCEL OD-H column.
[d] Determined by the sign of rotation of the isolated product.

also gave the corresponding (*S*)-amine with good enantioselectivity: **5a** (94% ee), **5c** (92% ee), **5d** (91% ee), and **5e** (95% ee) (cf., Me-DuPHOS, 95% ee). In the case of the hydrogenation of this enamide, it was found that the stereorecognition abilities of the present catalysts are almost the same as that of Me-DuPHOS-Rh(I) catalysts.

The senses of enantioselection with **5a**–**g**-Rh(I) catalysts were identical with that of the DuPHOS: the (*S*,*S*)-phospholane afforded *S* enantiomer of **4** (entries 1–7). Surprisingly, **5h**–**i** showed the opposite mode of enantioselection: the same (*S*,*S*)-phospholanes gave the *R* enantiomer of **4** in moderate enantioselectivity (entries 8, 9). These results indicate that the enantioselection is swayed not only by the chirality of the phospholane, but also by the substituents at the achiral phosphorus atom. The further mechanistic studies in the enamides reduction are required to establish the dominant factor of the enantioselection in the UCAP–Rh(I) catalysts.

In conclusion, we have prepared a new class of C_1-symmetric phosphine-phospholane ligands UCAP **5a**–**i** which demonstrated the higher enantioselectivity in certain asymmetric hydrogenations than C_2-symmetric DuPHOS by adjusting the di(substituted)phosphine moiety. That is, the more bulky aryl substituent on the achiral phosphorus atom such as **5d**–**e** gave the higher enantioselectivity in the case of asymmetric hydrogenation of enamide **3**. Through this study, we showed the extent to which the enantioselection is changed by adjustment of the structures of a chiral diphosphine, which may help in the development of catalysts for new substrates. Further applications of the UCAP ligands in asymmetric reactions are continuing to be examined.

Experimental Section

2-(Trifluoromethanesulfonyloxy)bromobenzene (6)

Trifluoromethanesulfonic anhydride (448.5 g, 1.59 mol) was added dropwise to a solution of 2-bromophenol (250.0 g, 1.45 mol) and pyridine (171.4 g, 2.17 mol) in dichloromethane (1.5 L) at 0 °C for 2 h. The mixture was allowed to warm to room temperature and stirred for 2 h. The resulting mixture was poured into 2 N hydrochloric acid (500 mL) and stirred at room temperature for 30 min, and then the two layers were separated. The organic layer was washed with water (500 mL × 2) and brine (500 mL), and then dried over magnesium sulfate. After evaporation of dichloromethane, the residue was distilled under reduced pressure to give **6** as a colorless oil; yield: 425.3 g (97%); bp 112–113 °C/15–16 mmHg; ^{1}H NMR ($CDCl_3$): δ = 7.20–7.40 (3H, m), 7.60–7.80 (1H, m).

Bis(3,5-di-*tert*-butyl-4-methoxyphenyl) (2-bromophenyl)phosphine Oxide

Under a nitrogen atmosphere, a solution of **6** (15.00 g, 49.2 mmol), bis(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphine oxide[13] (28.71 g, 59.0 mmol), *N*,*N*-diisopropylethylamine (12.85 mL, 73.8 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (1.27 g, 2.5 mmol), and 1,3-bis(diphenylphosphino)propane (1.01 g, 2.5 mmol) in toluene (150 mL) was stirred at 110 °C for 15 h. The reaction mixture was then cooled to room temperature and poured into 1 N hydrochloric acid (150 mL). The mixture was stirred at room temperature for 30 min, and the two layers were separated. The aqueous layer was extracted with ethyl acetate (100 mL). The combined organic layer was washed with water (100 mL) and brine (100 mL), and then dried over magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (hexane/ethyl acetate = 2/1) to give the title compound as a white, waxy solid; yield: 30.83 g (98%); ^{1}H NMR ($CDCl_3$): δ = 1.35 (36H, s), 3.69 (6H, s), 7.35–7.45 (2H, m), 7.50 (2H, s), 7.53 (2H, s), 7.65 (1H, ddd, J = 1.2, 3.9, 7.7 Hz), 7.73 (1H, ddd, J = 1.9, 7.7, 12.5 Hz); ^{31}P NMR ($CDCl_3$): δ = 33.3 (s); EI-MS: m/z = 642 (M^+).

Bis(3,5-di-*tert*-butyl-4-methoxyphenyl) (2-bromophenyl)phosphine (7)

A mixture of bis(3,5-di-*tert*-butyl-4-methoxyphenyl)(2-bromophenyl)phosphine oxide (28.81 g, 44.9 mmol), *N*,*N*-dimethylaniline (31.30 mL, 247.0 mmol) and trichlorosilane (22.66 mL, 224.5 mmol) was stirred in toluene (300 mL) at 110 °C for 15 h. The reaction mixture was cooled to 5 °C, and then 25% aqueous sodium hydroxide (180 mL) was added carefully. The mixture was stirred at room temperature for 30 min. The aqueous layer was separated and extracted with toluene (100 mL). The combined organic layer was washed with 1 N

hydrochloric acid (200 mL × 2), water (100 mL), and brine (100 mL). The solvent was removed under reduced pressure, and the residue was recrystallized from toluene – methanol to give **7** as a white solid; yield: 24.30 g (87%); mp 142 – 143 °C; ^{1}H NMR ($CDCl_3$): δ = 1.31 (36H, s), 3.68 (6H, s), 6.71 – 6.74 (1H, m), 7.07 (4H, d, J = 7.6 Hz), 7.15 – 7.23 (2H, m), 7.57 – 7.60 (1H, m); ^{31}P NMR ($CDCl_3$): δ = – 3.1 (s); EI-MS: m/z = 626 (M^+).

1-Bis(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino-2-[(2*S*,5*S*)-2,5-dimethylphospholano]benzene (5d)

Under a nitrogen atmosphere, a 1.6 M solution of *n*-butyllithium in hexane (16.2 mL, 25.2 mmol) was added dropwise to a solution of **7** (15.00 g, 24.0 mmol) in THF (150 mL) at – 78 °C for 30 min. The solution was stirred at – 78 °C for 1 h and then diethyl chlorophosphonite (4.15 g, 25.2 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and then stirred for 15 h. After evaporation of the solvent, the residue was dissolved in diethyl ether (50 mL) and the insoluble material was filtered off. The filtrate was evaporated and the residue was purified by chromatography through a short alumina column (hexane/ethyl acetate = 4/1) to give a 77:23 mixture of **8** and bis(3,5-di-*tert*-butyl-4-methoxyphenyl)phenylphosphine as a pale yellow, waxy solid. The ratio of a mixture was determined by ^{1}H NMR. The crude product **8** was used for the next reaction without further purification; yield: 14.03 g.

8: ^{1}H NMR (CD_2Cl_2): δ = 1.00 (6H, t, J = 7.0 Hz), 1.29 (36H, s), 3.51 – 3.57 (2H, m), 3.65 (6H, s), 3.78 – 3.82 (2H, m), 7.03 (4H, d, J = 7.7 Hz), 7.30 – 7.34 (2H, m), 7.39 – 7.40 (1H, m), 7.86 – 7.89 (1H, m); ^{31}P NMR (CD_2Cl_2): δ = – 17.5 (d, J = 149 Hz), 150.1 (d, J = 149 Hz).

Bis(3,5-di-*tert*-butyl-4-methoxyphenyl)phenylphosphine): ^{1}H NMR (CD_2Cl_2): δ = 1.32 (36H, s), 3.67 (6H, s), 7.13 (4H, d, J = 8.2 Hz), 7.24 – 7.29 (2H, m), 7.30 – 7.35 (3H, m); ^{31}P NMR (CD_2Cl_2): δ = – 4.3 (s).

Under a nitrogen atmosphere, trimethylsilyl chloride (4.89 g, 45.0 mmol) was added to a suspension of lithium aluminum hydride (1.71 g, 45.0 mmol) in THF (75 mL) at – 30 °C. The resulting mixture was allowed to warm to room temperature and then stirred for 1.5 h. A solution of the crude **8** (10.00 g) in THF (50 mL) was then added dropwise to the reducing mixture at – 30 °C over 30 min. The resulting mixture was allowed to warm to room temperature and then stirred for 16 h. A solution of water (20 mL) in THF (20 mL) followed by 1 N aqueous sodium hydroxide (30 mL) was added slowly dropwise, and the two layers were separated. After the organic layer was concentrated, diethyl ether (50 mL) and water (20 mL) were added to the residue and then the two layers were separated. The organic layer was washed with water (20 mL × 2) and dried over sodium sulfate. The solvent was removed under reduced pressure to give a 70:30 mixture of **9** and bis(3,5-di-*tert*-butyl-4-methoxyphenyl)phenylphosphine as a white, waxy solid. The ratio of the mixture was determined by ^{1}H NMR. The crude product **9** was used for the next reaction without further purification; yield: 8.20 g.

9: ^{1}H NMR (CD_2Cl_2): δ = 1.31 (36H, s), 3.67 (6H, s), 3.95 (2H, dd, J = 12.3, 205.3 Hz), 6.86 – 6.89 (1H, m), 7.07 (4H, d, J = 8.2 Hz), 7.21 – 7.22 (2H, m), 7.53 – 7.57 (1H, m); ^{31}P NMR (CD_2Cl_2): δ = – 124.3 (d, J = 92 Hz), – 9.6 (d, J = 92 Hz).

Under a nitrogen atmosphere, a 1.6 M solution of *n*-butyllithium in hexane (5.67 mL, 9.1 mmol) was added dropwise to a solution of the crude **9** (5.00 g) in THF (100 mL) at 0 °C. The solution was stirred at 0 °C for 1 h and then a solution of (2*R*,5*R*)-2,5-hexanediol cyclic sulfate (1.64 g, 9.1 mmol)[5c] in THF (30 mL) was added dropwise at 0 °C. The reaction mixture was allowed to warm to room temperature and then stirred for 1 h. A 1.6 M solution of *n*-butyllithium in hexane (5.67 mL, 9.1 mmol) was again added dropwise to the reaction mixture at 0 °C. The reaction mixture was stirred at room temperature for 15 h. Methanol (1 mL) was added to quench any excess *n*-butyllithium remaining and the solvents were evaporated under reduced pressure. The residue was dissolved in diethyl ether (60 mL) and the insoluble material was filtered off. The filtrate was evaporated and the residue was purified by flash chromatography on silica gel (hexane/dichloromethane = 3/1 to 1/1) to give **5d** as a white solid; yield: 2.41 g (36% from **7**); mp 65 – 66 °C; $[\alpha]_D^{29}$: + 118.8 (c 1.00, CH_2Cl_2); ^{1}H NMR (CD_2Cl_2): δ = 0.73 (3H, dd, J = 7.2, 9.3 Hz), 1.05 (3H, J = 7.1, 13.7 Hz), 1.29 (18H, s), 1.30 (18H, s), 1.49 – 1.61 (2H, m), 2.00 – 2.06 (1H, m), 2.15 – 2.35 (2H, m), 2.48 – 2.58 (1H, m), 3.65 (3H, s), 3.65 (3H, s), 6.92 – 6.95 (1H, m), 7.05 (2H, d, J = 7.1 Hz), 7.09 (2H, d, J = 7.1 Hz), 7.21 – 7.24 (1H, m), 7.28 – 7.31 (1H, m), 7.50 – 7.52 (1H, m); ^{31}P NMR (CD_2Cl_2): δ = – 1.80 (d, J = 160 Hz), – 13.0 (d, J = 160 Hz); EI-MS: m/z = 660 (M^+).

[Rh(cod)(5d)]OTf

Under a nitrogen atmosphere, a solution of **5d** (100.0 mg, 0.151 mmol) in dichloromethane (3 mL) was added dropwise to a stirred solution of $[Rh(cod)_2]OTf$ (67.5 mg, 0.144 mmol) in dichloromethane (2 mL) at room temperature. The mixture was stirred for 30 min, and the solvent was removed under reduced pressure. The residue was recrystallized from dichloromethane-diethyl ether to give the title complex as a orange-yellow solid; yield: 140.0 mg (95%); ^{1}H NMR (CD_2Cl_2): δ = 1.12 (3H, dd, J = 7.1, 15.3 Hz), 1.29 – 1.35 (3H, m), 1.33 (18H, s), 1.35 (18H, s), 1.52 – 1.64 (1H, m), 1.90 – 2.02 (1H, m), 2.08 – 2.18 (1H, m), 2.23 – 2.76 (11H, s), 3.71 (3H, s), 3.73 (3H, s), 4.68 – 4.75 (1H, m), 5.04 – 5.11 (1H, m), 5.42 – 5.54 (2H, m), 7.30 (2H, d, J = 12.1 Hz), 7.37 (2H, d, J = 12.1 Hz), 7.50 – 7.54 (1H, m), 7.56 – 7.61 (1H, m), 7.65 – 7.71 (1H, m), 7.73 – 7.77 (1H, m); ^{31}P NMR (CD_2Cl_2): δ = 61.4 (dd, J = 27, 148 Hz), 74.8 (dd, J = 27, 148 Hz).

Asymmetric Hydrogenation of (*Z*)-*N*-Benzoyl-1-phenylpropenamine (3)

[Rh(cod)(**5d**)]OTf (1.8 mg, 0.0018 mmol), (*Z*)-*N*-benzoyl-1-phenylpropenamine **3** (214 mg, 0.90 mmol) and methanol (3 mL) were charged to a 100 mL stainless steel autoclave under a nitrogen stream. Hydrogen (0.4 MPa) was introduced and the mixture was stirred for 15 h at 30 °C. The conversion and ee of (*S*)-*N*-benzoyl-1-phenylpropylamine **4** were determined by capillary GLC analysis using an SPB-1 column and by HPLC analysis using a CHIRALCEL OD-H column (> 99% conversion, 99% ee).

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