Development of New 6-Membered Chelating Chiral Bisphosphine Ligands for Rhodium-Catalyzed Asymmetric Hydrogenation[1)]

Kiyoshi INOGUCHI, Naoto FUJIE, Kiyoshi YOSHIKAWA, and Kazuo ACHIWA*

School of Pharmaceutical Sciences, University of Shizuoka, Yada 52–1, Shizuoka 422, Japan. *Received March 24, 1992*

A new chiral 1,3-bisphosphine, (1*R*,2*R*)-1-diphenylphosphino-2-(diphenylphosphinomethyl)cyclopentane, which was designed to form the favorable skew conformation of the six-membered chelate with rhodium, was developed. Its rhodium complex was found to be one of the most efficient catalysts known for asymmetric hydrogenation of amino acid precursors. Further improvement of this ligand was also attempted for catalytic asymmetric hydrogenation of prochiral ketones to clarify the enantioselective mechanism.

Keywords catalytic asymmetric hydrogenation; rhodium complex; chiral bisphosphine; amino acid precursor; α-aminoketone; enantioselective mechanism

Though many chiral bisphosphine ligands have been prepared for rhodium-catalyzed asymmetric hydrogenations, useful 1,3-substituted chiral bisphosphine ligands have rarely been found except skewphos (**1**), which was developed by Marko *et al.*[2)] and Bosnich *et al.*[3)] According to Bosnich's group,[3)] it is necessary for the high enantioselecting ability of the 6-membered chelate system that the conformation of the chelate ring is stabilized in a skew conformation. Considering that a 6-membered ring tends to favor a chair conformation, it has been thought to be difficult to design new 1,3-bisphosphines of the desired form.

On the other hand, we have given much attention to the role of phosphino groups of pyrrolidinebisphosphine ligands and elucidated their electronic and steric effects for enhancing both the enantioselectivity and the activity of the rhodium catalyst.[4)] Based on a series of modifications of well-known bisphosphine ligands, we have developed a design concept for highly efficient rhodium catalysts in asymmetric hydrogenation.[5)] That is to say, by introduction of electron-donating groups into the bisphosphine ligands, higher catalytic activity and enantio-selectivity can be obtained. In order to test the general utility of our concept, the modification was applied to skewphos, and 4-methoxy-3,5-dimethyl (MOD)-skewphos (**2**) was prepared.[6)]

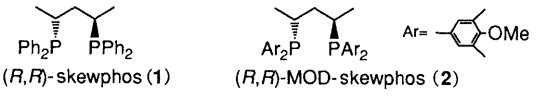


Chart 1. Skewphos (**1**) and MOD-Skewphos (**2**)

Asymmetric hydrogenation of (*Z*)-2-acetamidocinnamic acid catalyzed by cationic rhodium complexes of **1** and **2** was carried out (Table I).[6)] In the case of using **2**, a remarkable decrease of the enantioselectivity (entry 2; 81% ee, entry 3; 54% ee) with a reduction of the catalytic amount was found. It was considered that this was probably due to the generation of plural active species of the catalyst by conformational exchanges of the 6-membered chelate ring, for the reaction conditions were rather severe compared to Bosnich and Marko's cases. Bakos *et al.* described in detail both temperature and solvent dependence of the optical yield with the skewphos–rhodium complex and suggested that the conformational equilibrium of this complex is easily perturbed.[7)] Namely, there is an equilibrium between the skew and chair conformations, and so even the substitution of electron-donating phosphino groups could contribute to the higher catalytic activity but not retain the high enantioselectivity.

On the basis of the above consideration, we began to design a new 1,3-substituted bisphosphine ligand. As described, for high enantioselectivity, it is important for the 6-membered chelate ring to take the skew conformation. First, we considered two designs in which the ligand could

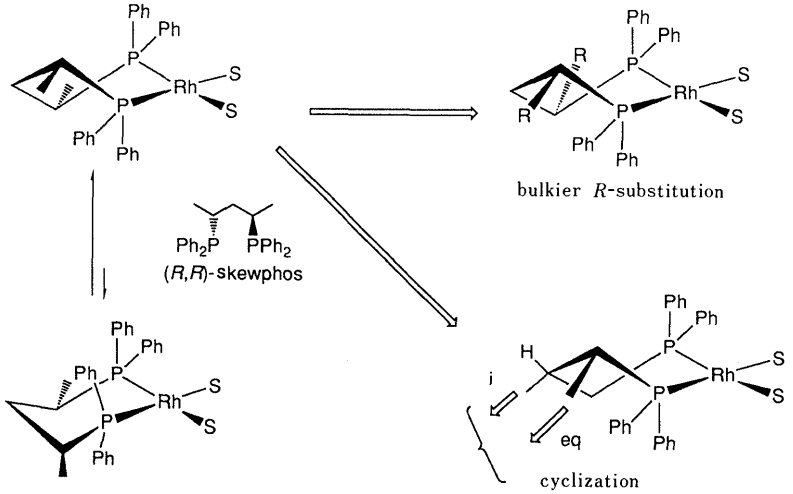


Chart 2. Some Methods to Fix the Skew Conformation

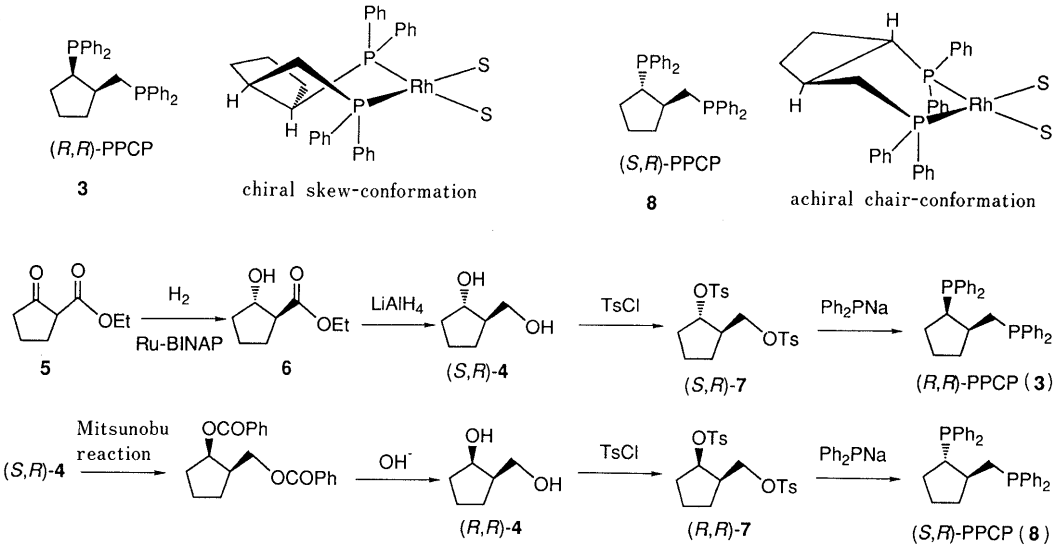


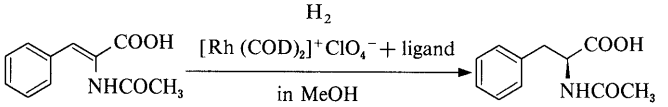
Chart 3. Preparation of (*R*,*R*)-PPCP (**3**) and (*S*,*R*)-PPCP (**8**)

be predominantly fixed in skew conformation, as shown in Chart 2. In one, the effect of the bulkier substituents C_1 and C_3 should hinder conformational exchange. But in this case, since the bulky substituents are close to the phenyl rings of the phosphino group, the chiral array of phenyl rings would be affected sterically by them. In this respect, the other design involving cyclization between C_1 and C_2 was thought to be more suitable. A 1,3-bisphosphine ligand having a cyclic structure derived from D-glucose has already been developed by Sunjic's group, but the conformational exchanges of the 6-membered glucose structure are considered to contribute many active species of catalyst, resulting in poor enantioselectivity.[8] So the rigid cyclopentane structure was expected to be more effective for the prevention of conformational exchange of the complex, because the cyclopentane structure, in which the configuration of the phosphino groups in *cis*, was fixed as equatorial at C_1 and isoclinal at that of C_2 of the 6-membered chelate ring. Thus, the new 1,3-bisphosphine ligand, named PPCP ((1*R*,2*R*)-1-(diphenylphosphino)-2-[(diphenylphosphino)methyl]-cyclopentane, (**3**)) was designed and prepared as shown in Chart 3.[6]

The chiral diol, (*S*,*R*)-**4**, was prepared by asymmetric hydrogenation of the cyclic β-ketoester (**5**) catalyzed by 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP)–ruthenium (II) complex, followed by reduction of the hydrogenation product (**6**) with $LiAlH_4$. Then (*S*,*R*)-**4** was tosylated to give (*S*,*R*)-**7** and optically pure (*S*,*R*)-**7** was obtained by recrystallization twice from ethanol. Next, (*S*,*R*)-**7** was phosphinated with sodium diphenylphosphide to give (*R*,*R*)-PPCP (**3**). To elucidate the effect of fixing the chelate conformation, (*S*,*R*)-PPCP (**8**), in which the phosphino groups are configurated *trans*, was also prepared, for this ligand–rhodium complex was considered to form a stabilized chair conformation. First (*S*,*R*)-**4** was converted to (*R*,*R*)-**4** by Mitsunobu reaction,[9] and then tosylated to give (*R*,*R*)-**7**. Then (*R*,*R*)-**7** was also made optically pure by recrystallization twice from ethanol and led to (*S*,*R*)-PPCP (**8**) by phosphination.

Using these ligands, asymmetric hydrogenations of (*Z*)-2-acetamidocinnamic acid were carried out, and the

Table I. Asymmetric Hydrogenation of (*Z*)-2-Acetamidocinnamic Acid



Ligand	Atm/°C/h	[Subst.]/[Rh]	Convn./%	ee/%
Skewphos (**1**)	5/50/20	1000	100	62 (*S*)
Skewphos (**1**)	5/50/20	10000	10	—
MOD-skewphos (**2**)	5/50/20	1000	100	81 (*S*)
MOD-skewphos (**2**)	5/50/20	10000	76	54 (*S*)
(*R*,*R*)-PPCP (**3**)	5/50/20	10000	100	94 (*S*)
(*R*,*R*)-PPCP (**3**)	5/50/20	20000	100	92 (*S*)
(*S*,*R*)-PPCP (**8**)	5/50/20	10000	100	20 (*S*)

results are also summarized in Table I.[6] (*R*,*R*)-PPCP (**3**)–rhodium cationic complex was found to have a very high enantioselectivity in spite of the decrease of the catalytic amount. This means that the chelate ring of this complex predominantly takes the skew conformation, as we expected. (*S*,*R*)-PPCP (**8**)–rhodium complex had a high catalytic activity but a poor enantioselectivity. Thus, it was very effective for the enantioselectivity and activity of the catalyst to fix the chelate conformation rigidly.

Possible conformations of the PPCP–Rh complex are illustrated in Chart 4. Since the two phosphino groups of PPCP are substrated *cis* on the cyclopentane ring, at least one of the alkyl chains of the cyclopentane must be axial to the 6-membered chelate ring in the cases of the chair conformation (B, C). In contrast, in the skew conformation (A), the substituted alkyl groups are equatorial at C_1 and isoclinal at C_2, and so the conformation A is thought to be more stable than B and C. The conformation D may be rather liable compared to the others, because this is the skew conformation in which, the substituted alkyl group on C_1 should be axial to the 6-membered chelate ring. Consequently, taking account of the fact that PPCP–Rh complex hydrogenated the amino acid precursor to the *S*-product with high optical yield, this complex is considered to be more strongly fixed in the skew conformation (A)

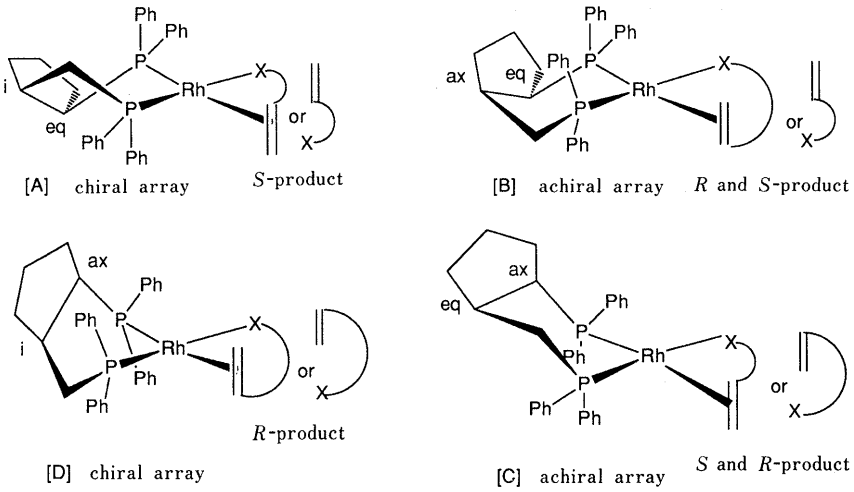


Chart 4. Possible Conformations of (*R*,*R*)-PPCP (**3**)–Rhodium Complex

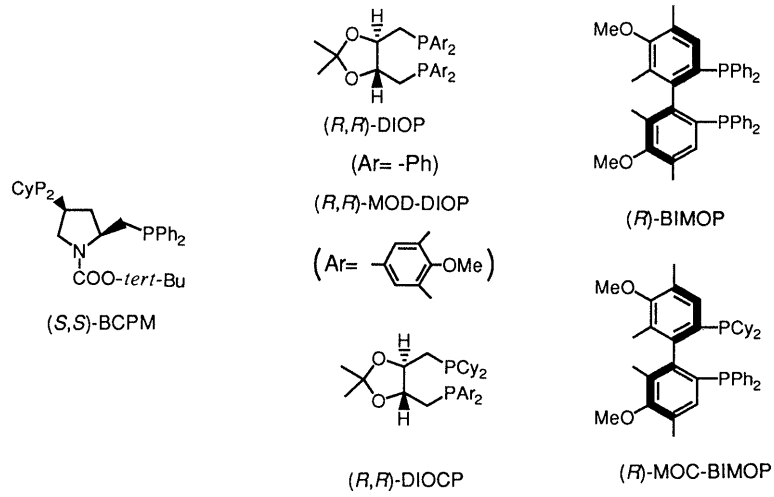
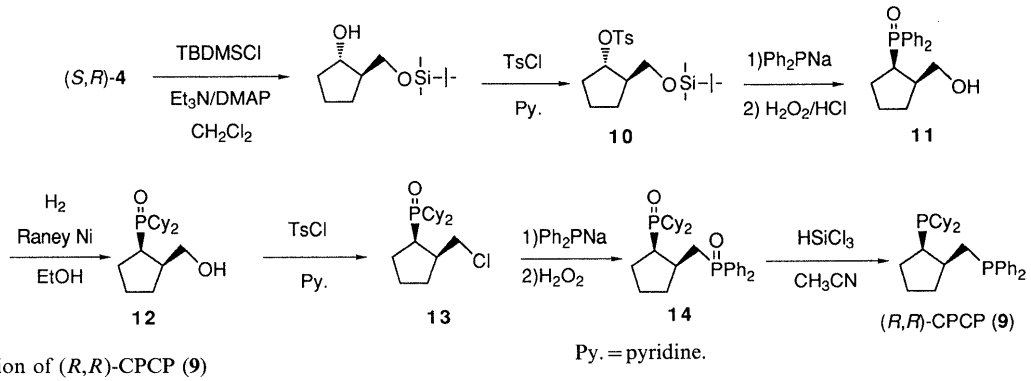


Chart 5. Chiral Bisphosphine Ligands



Py. = pyridine.

Chart 6. Preparation of (*R*,*R*)-CPCP (**9**)

because of the steric hindrance of the cyclopentane ring than skewphos–Rh complex, which contains only 1,3-dimethyl substituents on the ligand structure.

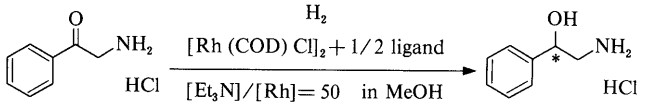
Thus, we could develop a very efficient C_2-unsymmetric 1,3-bisphosphine ligand, PPCP, for catalytic asymmetric hydrogenation of amino acid precursors. On the other hand, asymmetric hydrogenation of prochiral ketones is important for the synthesis of optically active secondary alcohols, and so the development of more effective methods is desirable. We have already developed several chiral bisphosphines bearing a dicyclohexylphosphino group, *N*-(*tert*-butoxycarbonyl)-4-(dicyclohexylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine (BCPM)[4a] and 4-[(dicyclohexylphosphino)methyl]-5-[(diphenylphosphino)methyl]-2,2-dimethyl-1,3-dioxolane (DIOCP),[10] for rhodium-catalyzed asymmetric hydrogenation. BCPM and its *N*-substituted analogues were found to be potentially suitable ligands for catalytic asymmetric hydrogenation of prochiral ketones.[11] The reason why the BCPM–rhodium complex was so effective was considered to be not only its electron-

rich phosphino group but also its unsymmetric ligand structure.[12] In the case of asymmetric hydrogenation of ketopantolactone, DIOCP, an unsymmetralized bis-[(diphenylphosphino)methyl]-2,2-dimethyl-1,3-dioxolane (DIOP) analogue, has a lower enantioselectivity (72% ee)[10] than BCPM (91% ee)[4a] because of its C_2-symmetric ligand structure. New atropisomeric biarylbisphosphine, 6,6′-bis-(diphenylphosphino)-3,3′-dimethoxy-2,2′,4,4′-tetramethyl-1,1′-biphenyl (BIMOP),[13] has been similarly modified to monocyclohexyl (MOC)–BIMOP[14] for rhodium-promoted asymmetric hydrogenation. In the asymmetric hydrogenation of aminoacetophenone using MOC–BIMOP–rhodium complex, a very high enantioselectivity was achieved (93% ee)[14] but its catalytic activity was found to be much lower than that of BCPM–rhodium complex.[11a]

We considered that the same modification as employed for BCPM should be applied to PPCP for effective asymmetric hydrogenations of prochiral ketones.

The modified ligand, named CPCP (1-(dicyclohexylphosphino)-2-[(diphenylphosphino)methyl]cyclopentane (**9**)), bearing a dicyclohexylphosphino group, was synthesized as shown in Chart 6. The primary hydroxy group of (*S*,*R*)-**4** was protected by the *tert*-butyldimethylsilyl group and then the remaining hydroxy group was tosylated to give **10**. The monophosphinyl compound (**11**) was obtained by the phosphination of **10** with sodium diphenylphosphide followed by treatment with hydrogen peroxide and 6 N HCl. Compound **11** was catalytically reduced to the dicyclohexylphosphinyl compound (**12**) with Raney Ni. The tosylation of **12** afforded the unexpected 2-chloromethyl compound (**13**), but it could be phosphinated by sodium diphenylphosphide and subsequently oxidized to the corresponding bisphosphinyl compound (**14**). Compound **14** was reduced with trichlorosilane to give CPCP (**9**).

TABLE II. Asymmetric Hydrogenation of α-Aminoacetophenone Hydrochloride



Entry	Ligand	Chirality[b]	Atm/°C/h	[Subst.]/[Rh]	Convn./%	ee/%
1	(*S*,*S*)-BCPM	M	20/50/20	1000	100	81 (*S*)
2	(*S*,*S*)-MOD-DIOP	P	50/50/96	100	100	21 (*S*)
3[a]	(*R*,*R*)-DIOCP	M	20/50/20	1000	100	73 (*S*)
4	(*R*)-BIMOP	P	50/50/100	500	61	8 (*S*)
5	(*R*)-MOC-BIMOP	P	90/50/170	1000	100	93 (*R*)
6	(*R*,*R*)-PPCP	P	50/50/72	100	100	15 (*S*)
7	(*R*,*R*)-CPCP	P	20/50/24	1000	62	29 (*R*)

a) Substrate; *N*,*N*-diethyl derivative, No Et_3N. *b*) P/M chirality; ref. 12.

The results of asymmetric hydrogenation of 2-aminoacetophenone hydrochloride using the rhodium complexes of our modified ligands are summarized in Table II. Unfortunately, CPCP (**9**)–rhodium complex was found to be less effective than BCPM–rhodium complex both catalytic activity and enantioselectivity. But the results using PPCP and CPCP–rhodium complexes (entries 6 and 7) are interesting, since opposite enantiomers were provided, though these catalysts should construct the same chirality (P-chirality[12]). We have already described this phenomenon using BIMOP analogs (entries 4 and 5).[14] Similar results were obtained with DIOP analogs (entries 2 and 3).

In general, asymmetric hydrogenation of prochiral ketones using rhodium catalysts is not efficient and so has not been well-investigated. On the basis of Halpern's mechanism of asymmetric hydrogenation of olefin,[15] we have already attempted to explain the enantioselective mechanism derived from steric factors in the cases of BCPM[12] and MOC–BIMOP.[14] Namely, in the case of PPCP, as shown in Chart 7, it is general that the less stable diastereomer should be hydrogenated more smoothly to give the corresponding enantiomer of the product. But with the dicyclohexylphosphino group on the ligand (CPCP), its steric hindrance should affect the oxidative addition of a hydrogen molecule and define the direction of the addition.

Since the hydrogen molecule should approach the metal from the c-*endo* direction with respect to the prochiral carbonyl group, the more stable diastereomer would be hydrogenated predominantly, yielding the opposite en-

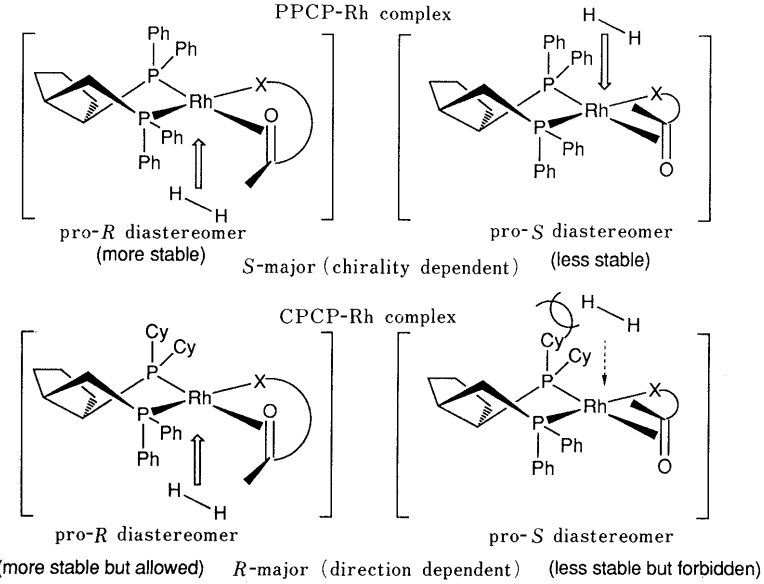


Chart 7. Enantioselective Mechanism in Asymmetric Hydrogenation of Aminoketones

antiomer, contrary to the cases of original ligands. The results with DIOP analogs and PPCP analogs have substantiated the above considerations.

In other words, asymmetric hydrogenation of prochiral ketones can be also explained on the basis of Halpern's mechanism, but there should be small differences in the potential energy between the diastereomers provided by catalyst–substrate adducts. For enhancing the catalytic activity for ketone reduction, a strongly electron-donating phosphino group, such as a dicyclohexylphosphino group, is thought to be neccessary, and moreover, was found to play an important role to determine the absolute configuration of the hydrogenation product independently of the chirality of the catalyst.

Experimental

General Procedures All melting points were determined with a micro-melting point apparatus (Yanagimoto) and are uncorrected. Optical rotations were measured on a JASCO DIP-140 digital polarimeter. Infrared (IR) spectra were measured on a JASCO A-202 IR spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on JEOL JNM-GX270 and JNM-GX500 spectrometers using tetramethylsilane (TMS) as an internal standard, and ^{31}P-nuclear magnetic resonance (^{31}P-NMR) spectra were taken on a JEOL JNM-GX500 spectrometer (^{31}P, 202.35 MHz) using 85% H_3PO_4 as an external standard; the abbreviations of signal pattern are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Column chromatography was carried out on silica gel (Kiesel gel 60, 70—230 mesh, Merck).

(1*S*,2*S*)-2-(Ethoxycarbonyl)cyclopentan-1-ol (6) A solution of [RuI_2(*p*-cymene)](80 mg, 0.08 mmol) and (*S*)-BINAP (80 mg, 0.12 mmol) in CH_2Cl_2 (10 ml) was stirred for 30 min at 50 °C under an argon atmosphere. This catalyst solution was added to a solution of ethyl 2-oxocyclopentanecarboxylate (**5**, 6.5 g, 40 mmol) in degassed CH_2Cl_2 (30 ml). The mixture was placed in an autoclave (200 ml), pressurized with hydrogen to 100 atm and stirred for 4 d at 50 °C. The reaction mixture was concentrated and distilled (bulb-to-bulb) under reduced pressure to give **6** (6.2 g, colorless oil). Yield 80%, bp 150 °C (14 mmHg).

(1*S*,2*R*)-2-(Hydroxymethyl)cyclopentan-1-ol ((*S*,*R*)-4) A solution of **6** (5.4 g, 34 mmol) was added dropwise to a suspension of $LiAlH_4$ (2.3 g, 60 mmol) in tetrahydrofuran (THF) (20 ml) under ice cooling, then the mixture was stirred for 4 h at room temperature. The reaction mixture was quenched with H_2O (10 ml) and the whole was treated with 2 N NaOH (20 ml) under ice cooling, then filtered through Celite. The Celite was washed with boiled THF (100 ml). The filtrate was dried over $MgSO_4$ and then evaporated to give (*S*,*R*)-**4** (4.0 g, colorless oil). Yield 99%, $[\alpha]_D^{22}$ +38.6° (*c* = 1.0, methanol).

(1*S*,2*R*)-1-(4-Methylphenyl)sulfonyloxy-2-[(4-methylphenyl)-sulfonyloxymethyl]cyclopentane ((*S*,*R*)-7) A solution of *p*-toluensulfonylchloride (19 g, 100 mmol) in anhydrous pyridine (40 ml) was added dropwise to a stirred solution of (*S*,*R*)-**4** (4.0 g, 34 mmol) in anhydrous pyridine (25 ml), under ice cooling then the mixture was stirred for 2 h at room temperature. The reaction mixture was acidified with 10% HCl under ice cooling and then the aqueous solution was extracted with AcOEt (100 ml × 3). The organic layer was washed with saturated aqueous $NaHCO_3$, H_2O and saturated aqueous NaCl (each 100 ml), and dried over $MgSO_4$ and then evaporated. The residue was recrystallized twice from ethanol to obtain (*S*,*R*)-**7** (9.4 g, colorless needles). Yield 65%, mp 69 °C, $[\alpha]_D^{22}$ +19.0° (*c* = 0.89, toluene). ^{1}H-NMR δ ($CHCl_3$): 1.22—1.91 (6H, m, $-CH_2CH_2CH_2-$), 2.30—2.46 (1H, m, –CH–), 2.46 (6H, s, *p*-CH_3–), 3.82—3.92 (2H, m, $-CH_2O-$), 4.61 (1H, q, *J* = 5.5 Hz, –OCH–), 7.32—7.38 and 7.72—7.77 (8H, m, Ar-H).

(1*R*,2*R*)-1-(Diphenylphosphino)-2-[(diphenylphosphino)methyl]cyclopentane ((*R*,*R*)-PPCP, 3) Under an argon atmosphere, sodium (400 mg, 18 mmol), degassed 1,4-dioxane (5 ml) and diphenylphosphine (Ph_2PH, 3.2 g, 18 mmol) were refluxed for 12 h. Then the mixture was allowed to cool to room temperature and concentrated under reduced pressure. The residue was taken up in degassed dimethylformamide (DMF) (5 ml) under an argon atmosphere and the solution was cooled to −30 °C. Then a solution of (*S*,*R*)-**7** (1.0 g, 2.3 mmol) of degassed DMF (10 ml) was added dropwise and the reaction mixture was stirred for 17 h at −20 °C. The mixture was allowed to warm to room temperature and filtered through Celite, which was then washed with degassed toluene (60 ml). The filtrate was washed with degassed H_2O (30 ml × 2), dried over $MgSO_4$ with ice cooling under an argon atmosphere for 20 min and then evaporated. The residue was chromatographed on a silica gel with degassed *n*-hexane–toluene (1 : 1) as an eluent to give (*R*,*R*)-PPCP (**3**, 750 mg, colorless crystals) after recrystallization from degassed ethanol. Yield 43%, mp 85 °C, $[\alpha]_D^{22}$ +114.0° (*c* = 0.67, toluene). ^{1}H-NMR δ ($CDCl_3$): 1.52—2.05 (7H, m, $-CH_2CH_2CH_2CH-$), 2.06—2.26 (1H, m, P–CH–), 2.52—2.75 (2H, m, P–CH_2–), 7.15—7.54 (20H, m, Ar-H).

(1*R*,2*R*)-2-(Hydroxymethyl)cyclopentan-1-ol ((*R*,*R*)-4) A solution of diethyl azodicarboxylate (6.8 g, 20 mmol) in anhydrous THF (30 ml) was added dropwise during 30 min to a stirred mixture of (*S*,*R*)-**4** (2.3 g, 10 mmol), triphenylphosphine (10.4 g, 20 mmol), benzoic acid (4.8 g, 20 mmol) and anhydrous THF (30 ml). And the reaction mixture was stirred at ambient temperature for 12 h, then evaporated, and the residue was washed with ether (30 ml × 3) on Celite. The filtrate was evaporated and then chromatographed on silica gel with toluene as the eluent to give the corresponding dibenzoate as a crystalline solid. This was recrystallized from ice cooled methanol to give colorless crystal (3.2 g, yield 50%). This product was dissolved in aqueous 5% NaOH/methanol (1 : 1) and the solution was stirred at room temperature for 20 h, then concentrated, extracted with AcOEt (50 ml × 2), washed with saturated, aqueous NaCl, dried over anhydrous $MgSO_4$, and evaporated. The residue was chromatographed on a silica gel column with AcOEt as a eluent to give (*R*,*R*)-**4** (900 mg, colorless oil). Yield 40% from (*S*,*R*)-**4**, $[\alpha]_D^{22}$ −37.7° (*c* = 0.68, methanol). ^{1}H-NMR δ ($CDCl_3$): 1.26—2.11 (7H, m, $-CH_2CH_2CH_2CH-$), 3.42 (2H, br d, *J* = 5.4 Hz, –OH), 3.70—3.83 (2H, m, $O-CH_2-$), 4.35—4.38 (1H, m, O–CH–).

(1*R*,2*R*)-1-(4-Methylphenyl)sulfonyloxy-2-[(4-methylphenyl)sulfonyloxymethyl]cyclopentane ((*R*,*R*)-7) A solution of tosyl chloride (1.9 g, 10 mmol) in anhydrous pyridine (4 ml) was added dropwise to a stirred solution of (*R*,*R*)-**4**(400 mg, 3.4 mmol) in anhydrous pyridine (2.5 ml) under ice cooling. The mixture was stirred at room temperature for 30 h, then worked up in the usual manner, and the product was isolated by column chromatography on silica gel. This material was recrystallized twice from ice cooled ethanol to give optically pure (*R*,*R*)-**7** (1.0 g, colorless crystals). Yield 68%, mp 56 °C, $[\alpha]_D^{22}$ −40.5° (*c* = 0.72, toluene). ^{1}H-NMR δ ($CDCl_3$): 1.35—1.92 (6H, m, $-CH_2CH_2CH_2-$), 2.46 (6H, s, *p*-CH_3–), 3.97 (2H, dd, *J* = 5.5, 4.4 Hz, $-CH_2-O$), 4.88—4.94 (1H, br, O–CH–), 7.30—7.37 and 7.72—7.82 (8H, m, Ar-H).

(1*S*,2*R*)-1-(Diphenylphosphino)-2-[(diphenylphosphino)methyl]cyclopentane ((*S*,*R*)-PPCP, 8) Under an argon atmosphere, sodium (230 mg, 10 mmol), degassed 1,4-dioxane (2 ml) and diphenylphosphine (1.9 g, 10 mmol) were refluxed for 12 h. Then the mixture was allowed to cool to room temperature and concentrated under reduced pressure. The residue was taken up in degassed DMF (5 ml) under an argon atmosphere and the solution was cooled to −30 °C. To this mixture, a solution of (*R*,*R*)-**7** (1.0 g, 2.3 mmol) in degassed DMF (10 ml) was added dropwise, and the reaction mixture was stirred for 10 h at −20 °C, then worked up in the usual manner, and the product was isolated by column chromatography on silica gel with degassed *n*-hexane/toluene (1 : 1) as an eluent to give (*S*,*R*)-PPCP (**8**, 690 mg, colorless oil). Yield 65%, $[\alpha]_D^{22}$ +65.8° (*c* = 0.54, toluene). ^{1}H-NMR δ ($CDCl_3$): 1.37—2.18 (8H, m, $-CH_2CH_2CH_2CHCH-$P), 2.42—2.55 (2H, m, P–CH_2–), 7.15—7.60 (20H, m, Ar-H).

(1*S*,2*R*)-2-[(*tert*-Butyldimethylsilyloxy)methyl]-1-[(4-methylphenyl)-sulfonyloxy]cyclopentane (10) A solution of *tert*-butyldimethylsilyl chloride (6.5 g, 43.1 mmol) in anhydrous THF (80 ml) was added to a mixture of (*S*,*R*)-**4** (4.5 g, 38.8 mmol), 4-dimethylaminopyrrolidine (190 mg, 1.56 mmol), anhydrous THF (70 ml) and triethylamine (4.8 g, 47.4 mmol) at room temperature and the mixture was stirred at room temperature for 16 h, then evaporated to dryness. The residue was dissolved in AcOEt (400 ml). The solution was washed with H_2O (50 ml) and saturated aqueous NaCl (50 ml × 2), dried over $MgSO_4$ and evaporated. Then 6 g of the residue was dissolved in anhydrous pyridine (25 ml) and stirred under ice cooling. To this solution, a solution of tosyl chloride (7.4 g, 39 mmol) in anhydrus pyridine (25 ml) was added dropwise, and the mixture was stirred at room temperature for 20 h, then worked up in the usual manner. The product was isolated by chromatography on silica gel with toluene as an eluent to give **10** (8.8 g, colorless oil). Yield 82%, $[\alpha]_D^{22}$ +29.8° (*c* = 1.1, toluene). ^{1}H-NMR δ ($CDCl_3$): −0.029 (6H, d, *J* = 1.95 Hz, Si–CH_3), 0.83 (9H, s, $C(CH_3)_3$), 1.21—1.89 (6H, m, $-CH_2CH_2CH_2-$), 2.16—2.28 (1H, m, –CH–), 2.24 (3H, s, *p*-CH_3–), 3.38 (2H, qd, *J* = 10.3, 5.4 Hz, $-CH_2-O$), 4.76 (1H, q, *J* = 4.1 Hz, –CH–O), 7.32 (2H, d, *J* = 8.3 Hz, H_a of Ar-H), 7.79 (2H, d, *J* = 8.4 Hz, H_b of Ar-H).

(1*R*,2*R*)-1-(Diphenylphosphinyl)-2-(hydroxymethyl)cyclopentane (11) Chlorodiphenylphosphine ($ClPPh_2$, 8.8 g, 40 mmol), sodium (1.8 g,

80 mmol), and degassed anhydrous 1,4-dioxane (100 ml) were refluxed under an argon atmosphere for 5 h. The mixture was allowed to cool to room temperature, diluted with degassed, anhydrous THF (40 ml) and then cooled with ice. To this mixture, a solution of **10** (7.5 g, 20 mmol) in degassed, and anhydrous THF (40 ml) was added dropwise and the whole was stirred for 3 h under ice cooling and then for 16 h at room temperature. The reaction mixture was filtered through Celite, which was then washed with toluene. The organic layer was evaporated. The residue was taken up in saturated aqueous NaCl (50 ml) and extracted with toluene (100 ml) and AcOEt (50 ml × 3). The organic layer was washed with H_2O (100 ml), dried over anhydrous $MgSO_4$, and then evaporated. The residue was dissolved in methanol (100 ml) and the solution was stirred under ice cooling. To this solution, 10% aqueous H_2O_2 (20 ml) and then saturated HCl in methanol (10 ml) were added dropwise. The mixture was stirred for 2 h under ice cooling and evaporated to dryness. The residue was taken up in H_2O (50 ml) and extracted with AcOEt (100 ml × 2). The organic layer was washed with saturated aqueous $NaHCO_3$ (50 ml × 2), H_2O (50 ml) and saturated aqueous NaCl (50 ml), then dried over anhydrous $MgSO_4$ and evaporated. The residue was chromatographed on silica gel with AcOEt as an eluent to give the product, which was recrystallized twice from ethanol–isopropyl ether (IPE) to obtain optically pure **11** (3.2 g, colorless needles). Yield 53%, mp 141 °C, $[\alpha]_D^{22}$ −21.9° (c=0.62, methanol). ^{1}H-NMR δ ($CDCl_3$): 1.49—2.17 (7H, m, $-CH_2CH_2CH_2-$ and –OH), 2.41—2.54 (1H, m, –CH–), 2.70—2.79 (1H, m, –CH–P), 3.47 (1H, dd, J=12.7, 5.9 Hz, H_a of $-CH_2-O$), 3.62 (1H, dd, J=12.7, 3.0 Hz, H_b of $-CH_2-O$), 7.26—7.54 and 7.68—7.93 (10H, m, Ar-H). FAB-MS: $(M+H)^+$ 301. *Anal.* Calcd for $C_{18}H_{21}O_2P$: C, 71.99; H, 7.05. Found: C, 71.89; H, 7.05.

(1*R*,2*R*)-1-(Dicyclohexylphosphinyl)-2-(hydroxymethyl)cyclopentane (12) A mixture of **11** (1.2 g, 4.0 mmol), 5% Raney Ni (W6) (2.0 g, Nikkourika) and absolute ethanol (20 ml) was placed in a autoclave (100 ml). The autoclave was pressurized with hydrogen to 100 atm at 80 °C and stirring was continued for 5 d. The reaction mixture was cooled to 0 °C and filtered through Celite. The filtrate was evaporated and the residue was recrystallized from IPE to obtain **12** (1.0 g, colorless crystals). Yield 76%, mp 133 °C, $[\alpha]_D^{22}$ +5.3° (c=0.68, methanol). ^{1}H-NMR δ ($CDCl_3$): 1.05—2.20 (29H, m, $-CH_2CH_2CH_2CH-$ and cyclohexyl-H), 2.54 (1H, br s, P–CH–), 3.48—3.63 (2H, m, $-CH_2O$), 5.69 (1H, br s, –OH). FAB-MS: $(M+H)^+$ 313. *Anal.* Calcd for $C_{18}H_{33}O_2P$: C, 69.20; H, 10.65. Found: C, 69.40; H, 10.74.

(1*R*,2*R*)-2-(Chloromethyl)-1-(dicyclohexylphosphinyl)cyclopentane (13) A solution of **12** (800 mg, 2.6 mmol) in anhydrous pyridine (10 ml) was added dropwise, to a stirred solution of tosyl chloride (1.5 g, 7.8 mmol) in anhydrous pyridine (10 ml) under ice cooling, then the mixture was stirred at room temperature for 30 h. The reaction mixture was worked up in the usual manner, and the crude product was chromatographed on a silica gel with AcOEt as an eluent. The product was recrystallized from IPE to obtain **13** (460 mg, colorless crystals). Yield 54%, mp 138 °C, $[\alpha]_D^{22}$ +26.9° (c=0.64, methanol). ^{1}H-NMR δ ($CDCl_3$): 1.15—2.24 (29H, m, $-CH_2CH_2CH_2CH-$, cyclohexyl-H), 2.66 (1H, br s, P–CH–), 3.30—3.55 (1H, m, H_a of $-CH_2-Cl$), 4.20—4.26 (1H, m, H_b of $-CH_2-Cl$). FAB-MS: $(M+H)^+$ 331. *Anal.* Calcd for $C_{18}H_{33}ClOP$: C, 65.34; H, 9.75. Found: C, 65.40; H, 10.04.

(1*R*,2*R*)-1-(Dicyclohexylphosphinyl)-2-[(diphenylphosphinyl)-methyl]-cyclopentane (14) The phosphination was carried out in the same manner as for the preparation of (*R*,*R*)-PPCP (**3**). The reaction product was isolated by chromatography on silica gel with AcOEt as an eluent and recrystallized with methanol–IPE to obtain **14** (colorless crystals). Yield 21%, mp 109—111 °C, $[\alpha]_D^{22}$ +16.8° (c=0.46, methanol). ^{1}H-NMR δ ($CDCl_3$): 0.84—2.30 (29H, m, $-CH_2CH_2CH_2CH-$ and cyclohexyl-H), 2.71—2.79 (1H, m, P–CH–), 3.48—3.52 (1H, m, P–CH_2–), 7.39—7.52 and 7.75—7.88 (10H, m, Ar-H). ^{31}P-NMR δ (CD_3OD); 36.54 (s), 56.00 (s). FAB-MS: $(M+H)^+$ 497. *Anal.* Calcd for $C_{30}H_{42}O_2P_2$: C, 72.56; H, 8.52. Found: C, 71.94; H, 8.85.

(1*R*,2*R*)-1-(Dicyclohexylphosphino)-2-[(diphenylphosphino)-methyl]-cyclopentane((*R*,*R*)-CPCP, 9) Trichlorosilane (400 mg, 2.0 mmol) was added to a stirred mixture of **14** (100 mg, 0.2 mmol), triethylamine (230 mg, 2.2 mmol) and degassed acetonitrile (5 ml) in an argon atmosphere under ice cooling. The reaction mixture was refluxed for 3 h. The mixture was cooled with ice, then 30% aqueous NaOH (20 ml) and degassed toluene (40 ml) were added and the whole was heated to 60 °C with stirring under an argon atmosphere for 30 min. The organic layer was separated and further extraction of the aqueous layer with degassed toluene (20 ml × 2) was carried out. The combined organic layer was washed with degassed H_2O, degassed saturated aqueous $NaHCO_3$, and degassed saturated aqueous NaCl (each 20 ml) and then dried over anhydrous $MgSO_4$ in an argon atmosphere under ice cooling for 30 min. The organic layer was evaporated and the residue was chromatographed on silica gel with *n*-hexane–toluene (1 : 1) to give **9** (68 mg, colorless oil). Yield 73%, $[\alpha]_D^{22}$ +57.1° (c=0.24, toluene). ^{1}H-NMR δ ($CDCl_3$): 0.78—2.63 (32H, m, $-CHCH_2CH_2CH_2CH-CH_2-$, cyclohexyl-H), 7.18—7.82 (10H, m, Ar-H). *Anal.* Calcd for $C_{30}H_{42}P_2$: C, 77.56; H, 9.11. Found: C, 77.35; H, 8.93.

Asymmetric Hydrogenation of (*Z*)-2-Acetamidocinnamic Acid (General Procedure) A mixture of $[Rh(cod)_2]^+$ ClO_4^- (bis(1,5-cyclooctadiene)-rhodium (I) perchlorate, 2.3 mg, 0.5×10^{-2} mmol), chiral bisphosphine ((*R*,*R*)-PPCP, 2.7 mg, 0.6×10^{-2} mmol), and degassed methanol (2 ml) was stirred at room temperature under an argon atmosphere for 20 min. This solution, together with (*Z*)-acetamidocinnamic acid (1.026 g, 5.0 mmol ([cat.]/[subst.] = 1000)) and degassed methanol (8 ml) was placed in an autoclave (100 ml), pressurized with hydrogen to 5 atm, and stirred at 50 °C for 20 h. The reaction mixture was evaporated and the residue was dissolved in 0.5 N NaOH (20 ml) under ice cooling. The solution was filtered. The filtrate was acidified with 6 N HCl (5 ml) under ice cooling, extracted with ether (200 ml × 2), dried with anhydrous $MgSO_4$ and then evaporated to give *N*-acetylphenylalanine as a colorless solid. Conversion was measured by ^{1}H-NMR analysis and optical yield was calculated from the optical rotation using the value for optically pure *N*-acetylphenylalanine ($[\alpha]_D^{20}$ +40.1° (c=1.0, methanol)).

Asymmetric Hydrogenation of α-Aminoacetophenone Hydrochloride (General Procedure) A mixture of $[Rh(cod)Cl]_2$ (chloro (1,5-cyclooctadiene) rhodium (I) dimer, 2.4 mg, 0.5×10^{-2} mmol), chiral bisphosphine ((*R*,*R*)-PPCP, 5.4 mg), 1.2×10^{-2} mmol), and degassed methanol (2 ml) was stirred at room temperature under an argon atmosphere for 20 min. This solution, together with α-aminoacetophenone hydrochloride (171 mg, 1.0 mmol ([cat.]/[subst.] = 100)), triethylamine (50 mg, 0.5 mmol) and degassed methanol, (18 ml) was placed in an autoclave (100 ml), pressurized with hydrogen to 50 atm, and stirred at 50 °C for 72 h. The reaction mixture was brought to ambient temperature, and active carbon powder (300 mg) was added. The mixture was stirred for 1 h and filtered. The filtrate was evaporated to give 2-amino-1-phenylethanol hydrochloride as a solid. Conversion was measured by ^{1}H-NMR analysis. Part of the product was led to the *N*-benzoyl compound, and optical yield was determined by HPLC analysis using a column packed with Chiralcel OD (Daicel; eluent; *n*-hexane : isopropanol = 9 : 1).

References

1) Asymmetric Reactions Catalyzed by Chiral Metal Complexes. LIII.
2) J. Bakos, I. Toth, and L. Marko, *J. Org. Chem.*, **46**, 5427 (1981).
3) P. A. NacNail, N. K. Roberts, and B. Bosnich, *J. Am. Chem. Soc.*, **103**, 2273 (1981).
4) *a*) H. Takahashi, M. Hattori, M. Chiba, T. Morimoto, and K. Achiwa, *Tetrahedron Lett.*, **27**, 4477 (1986); *b*) H. Takahashi and K. Achiwa, *Chem. Lett.*, **1989**, 305; *c*) K. Inoguchi, T. Morimoto, and K. Achiwa, *J. Organomet. Chem.*, **370**, C9 (1989).
5) K. Inoguchi, S. Sakuraba, and K. Achiwa, *Synlett*, **1992**, 169.
6) K. Inoguchi and K. Achiwa, *Synlett*, **1991**, 49.
7) J. Bakos, I. Toth, B. Heil, G. Szalontai, L. Parkanyi, and V. Fulop, *J. Organomet. Chem.*, **370**, 263 (1989).
8) V. Sunjic, I. Habus, and G. Snatzke, *J. Organomet. Chem.*, **370**, 295 (1989).
9) O. Mitsunobu and M. Eguchi, *Bull. Chem. Soc. Jpn.*, **44**, 3427 (1971).
10) M. Chiba, H. Takahashi, H. Takahashi, T. Morimoto, and K. Achiwa, *Tetrahedron Lett.*, **28**, 3675 (1987).
11) *a*) H. Takeda, T. Tachinami, M. Aburatani, H. Takahashi, T. Morimoto, and K. Achiwa, *Tetrahedron Lett.*, **30**, 363 (1989); *b*) H. Takahashi, S. Sakuraba, H. Takeda, and K. Achiwa, *J. Am. Chem. Soc.*, **112**, 5876 (1990).
12) S. Sakuraba, T. Morimoto, and K. Achiwa, *Tetrahedron; Asymmetry*, **2**, 597 (1991).
13) N. Yamamoto, M. Murata, T. Morimoto, and K. Achiwa, *Chem. Pharm. Bull.*, **39**, 1085 (1991).
14) K. Yoshikawa, N. Yamamoto, M. Murata, K. Awano, T. Morimoto, and K. Achiwa, *Tetrahedron; Asymmetry*, **3**, 13 (1992).
15) J. Halpern, "Asymmetric Synthesis," Vol. 5, ed. by J. D. Morrison, Academic Press, New York, 1985.