Efficient Asymmetric Hydrogenation of β- and γ-Amino Ketone Derivatives Leading to Practical Synthesis of Fluoxetine and Eprozinol[1)]

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***N*-(Methylcarbamoyl)-4-(dicyclohexylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine (MCCPM)- and *N*-(*tert*-butoxycarbonyl)-4-(dicyclohexylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine (BCPM)–rhodium(I) complexes were efficient catalysts for asymmetric hydrogenations of β- and γ-amino ketone hydrochloride derivatives. Utilizing this methodology, we have developed efficient syntheses of fluoxetine and eprozinol from intermediate optically active amino alcohols.**

Key words catalytic asymmetric hydrogenation; rhodium complex; chiral bisphosphine; β-amino ketone; γ-amino ketone

In the course of our research on asymmetric catalysis by use of *N*-substituted 4-(dicyclohexylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidines (CPMs) ligands (**1a—c**, **2**) as a chiral chelating bisphosphine ligand, we found that their rhodium(I) complexes are highly efficient catalysts for asymmetric hydrogenation of various α-amino ketone derivatives.[2)] Although some other chiral catalysts, *e.g.*, 1-[1′,2-bis(diphenylphosphino)ferrocenyl]-ethanol (BPPFOH)[3)]–, 4,5-bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolane (DIOP)[4)]–rhodium complex and 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP)[5)]–rhutenium complex, are also effective for asymmetric hydrogenation of α-amino ketone derivatives, little attention has been given to asymmetric hydrogenations of β- and γ-amino ketone derivatives catalyzed by chiral phosphine–rhodium complex. We report here efficient asymmetric hydrogenations of β- and γ-amino ketone hydrochloride derivatives catalyzed by **1**– and **2**–rhodium-(I) complexes.

We initiated our present studies with the asymmetric hydrogenation of β-amino ketones.[6)] The results are summarized in Table 1. The best optical purity (90.8% ee) was obtained with (2*S*,4*S*)-*N*-(methylcarbamoyl)-4-(dicyclohexylphosphino)-2-[(diphenylphosphino)methyl]-pyrrolidine ((2*S*,4*S*)-MCCPM) (**1a**)–rhodium(I) complex as a catalyst and 3-(*N*-benzyl-*N*-methylamino)propiophenone hydrochloride (**3a**) as a substrate (entry 1).

Catalytic hydrogenation of γ-amino ketones was also examined, and the results are summarized in Table 2.[7)] When **5b** was hydrogenated in the presence of **1a**–rhodium(I) complex in methanol under hydrogen (50 atm), δ-amino alcohol hydrochloride (**6b**) was obtained in 88.4% ee, which was the best optical purity (entry 4). The ligand (*R*)(*S*)-BPPFOH (**7**), which has been successfully used for rhodium-catalyzed asymmetric hydrogenation of α-amino ketone,[3)] was ineffective for our present asym-

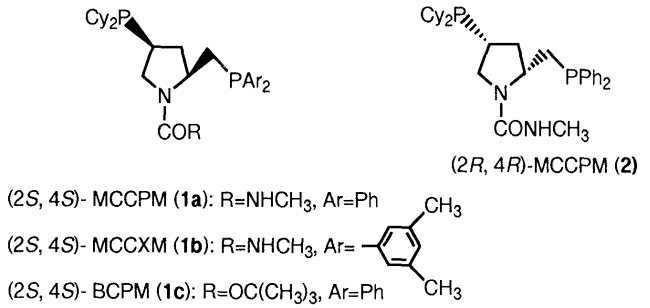
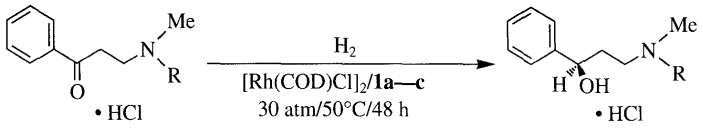


Fig. 1

Table 1. Asymmetric Hydrogenation of β-Amino Ketone Derivatives[a)]



3
3a: R = CH_2Ph
3b: R = H

(*R*)-**4**
4a: R = CH_2Ph
4b: R = H

Entry	Substrate	Ligand	Convn. (%)[b)]	S/C	ee(%)[c)]	Confign.
1	**3a**	**1a**	100	10^3	90.8	(*R*)
2	**3a**	**1b**	100	10^3	81.9	(*R*)
3	**3a**	**1c**	100	10^3	82.5	(*R*)
4	**3b**	**1a**	100	10^3	79.8	(*R*)
5	**3b**	**1b**	100	10^3	71.4	(*R*)
6	**3b**	**1c**	100	10^3	67.5	(*R*)

a) Reaction was carried out by using 0.1 mol% rhodium catalyst in methanol at 50 °C for 48 h under an initial hydrogen pressure of 30 atm. *b*) Determined by ^{1}H-NMR analysis. *c*) Entries 1, 2, 3: Determined by HPLC analysis of benzoate derivatives with a chiral column (Daicel Chiralcel OJ); entries 4, 5, 6: Determined by HPLC analysis of benzamide derivatives with a chiral column (Daicel Chiralcel OJ).

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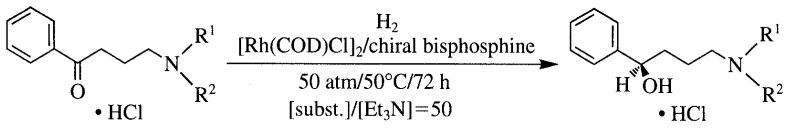
Table 2. Asymmetric Hydrogenation of γ-Amino Ketone Derivatives[a]

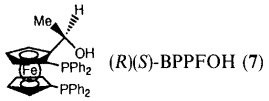


5
5a: $R^1=R^2=CH_3$
5b: $R^1=CH_3$, $R^2=CH_2Ph$
5c: $R^1=R^2=-(CH_2)_5-$

(*R*)-**6**
6a: $R^1=R^2=CH_3$
6b: $R^1=CH_3$, $R^2=CH_2Ph$
6c: $R^1=R^2=-(CH_2)_5-$

Entry	Substrate	Ligand	Convn. (%)[b]	S/C	ee(%)[c]	Confign.
1	**5a**	**1a**	100	250	81.7	(*R*)[e]
2	**5a**	**2**	100	250	80.5	(*S*)[e]
3	**5a**	**1c**	100	250	74.8	(*R*)[e]
4	**5b**	**1a**	100	250	88.4	(*R*)[f]
5	**5b**	**1c**	100	250	85.9	(*R*)[f]
6	**5c**	**1a**	100	250	77.5[d]	(*R*)[f]
7	**5c**	**1c**	100	250	69.1[d]	(*R*)[f]
8	**5a**	**7**	39.7	250	<17	(*S*)[e]

a) The reaction was carried out by using 0.4 mol% rhodium catalyst and 0.025 mmol of triethylamine in methanol at 50 °C for 72 h under an initial hydrogen pressure of 50 atm. The chemical yields were quantitative (entries 1—7). *b*) Determined by ^{1}H-NMR analysis. *c*) Determined by HPLC analysis of its free amine with a chiral column (Daicel Chiralcel OJ). *d*) Calculated on the basis of the maximum optical rotation of optically pure (*S*)-4-piperidino-1-phenyl-1-butanol hydrochloride $[\alpha]_D^{22}$ −20.4° (*c*=1.0, methanol) (see ref. 11); entry 6: +15.8° (*c*=0.7, methanol); entry 7: +14.1° (*c*=1.1, methanol). *e*) Determined from the sign of the rotation of its free amine (see ref. 13). *f*) Assignment based on the optical rotations of an authentic sample prepared from (*S*)-4-chloro-1-phenyl-1-butanol (see ref. 11).



(*R*)(*S*)-BPPFOH (7)

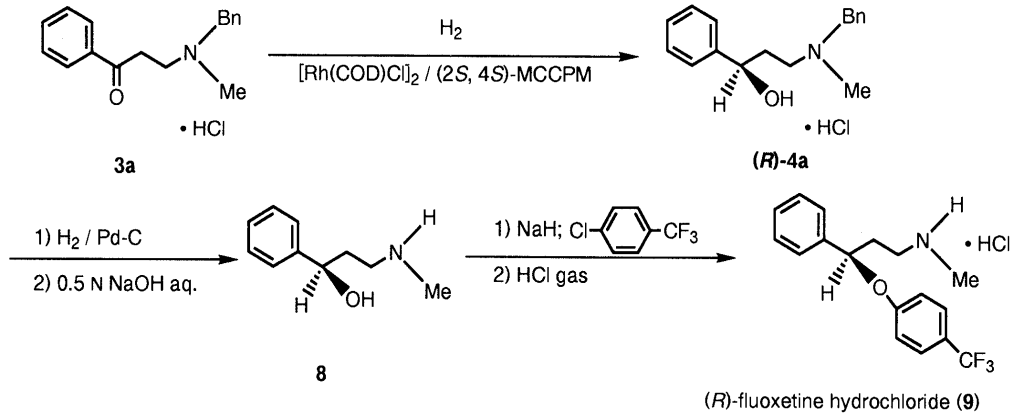
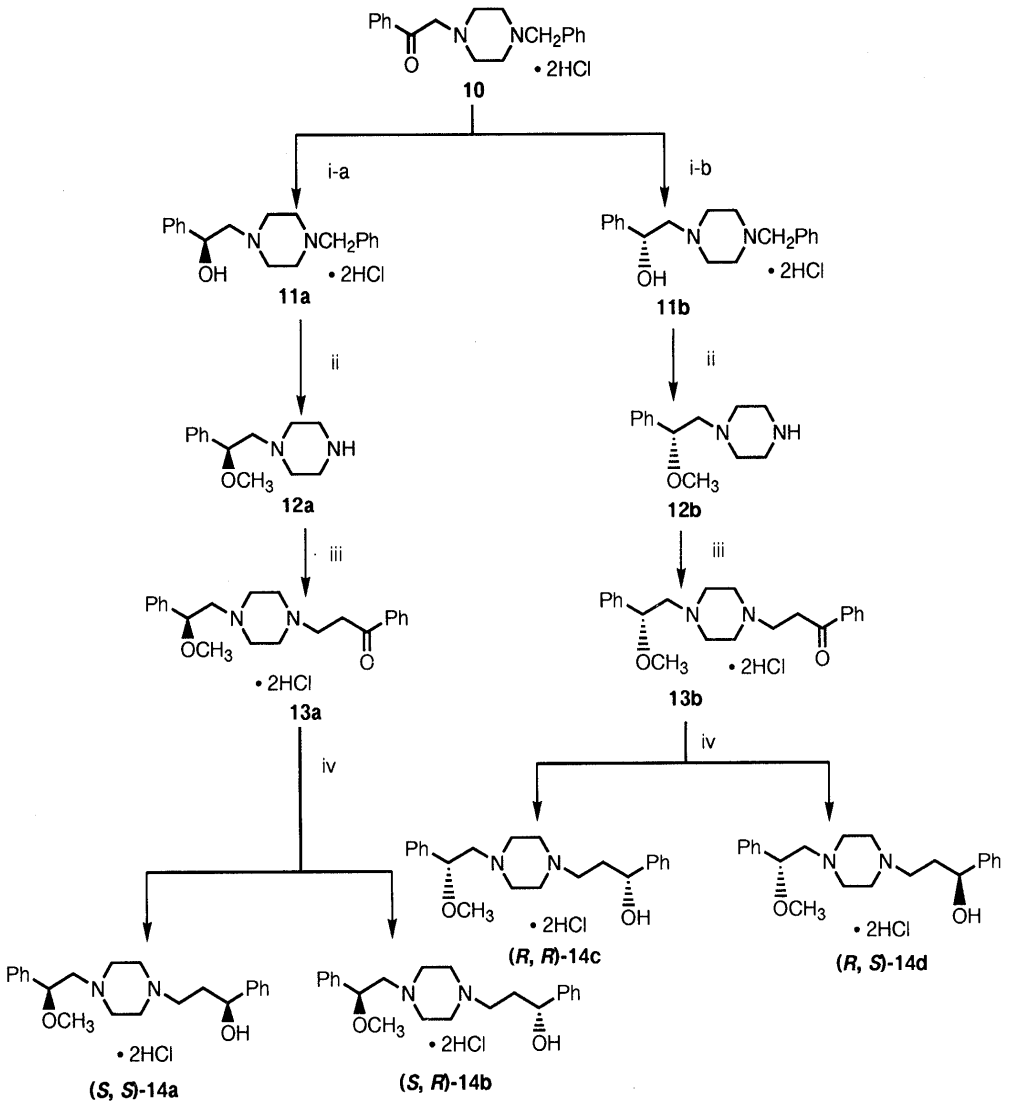


Chart 1

metric hydrogenation (entry 8).

Having demonstrated the utility of these ligands in asymmetric hydrogenations, we next turned our attention to the application of this methodology. Fluoxetine (*N*-methyl-γ-[4-(trifluoromethyl)phenoxy]benzenepropamine) (**9**)[8] is a potent and selective inhibitor of the neuronal serotonin-uptake carrier. Wong and co-workers reported that the enantiomers of fluoxetine had different biological activity and the (+)-isomer was slightly more potent than the (−)-isomer as a serotonin-uptake inhibitor in rat cortical synaptosomes.[9] A simple synthesis of (*R*)-fluoxetine hydrochloride based on our methodology is shown in Chart 1. (*R*)-3-(*N*-benzyl-*N*-methylamino)-1-phenylpropanol hydrochloride (**4a**) was readily available by the asymmetric hydrogenation of 3-(*N*-benzyl-*N*-methylamino)propiophenone hydrochloride (**3a**) using (2*S*,4*S*)-MCCPM–rhodium(I) complex, in 90.8% ee. After the debenzylation of **4a**, (*R*)-fluoxetine hydrochloride (**9**) was synthesized from **8** in 60.0% overall yield according to the reported method.[8]

Eprozinol[1-(2-methoxy-2-phenylethyl)-4-(3-hydroxy-3-phenylpropyl)piperazine] (**14**) was prepared as the racemate by three groups in the 1970s[10] and is used therapeutically as a bronchodilator. To our knowledge, asymmetric synthesis of **14** has not been reported. Eprozinol has two chiral atoms, so we prepared the four chiral forms of **14**.[14] Our approach is summarized in Chart 2. Asymmetric hydrogenation of α-amino ketone hydrochloride (**10**) proceeded smoothly in the presence of 0.4 mol% of (2*S*,4*S*)-MCCPM–rhodium(I) and triethylamine in methanol at 50 °C for 24 h under an initial hydrogen pressure of 30 atm. Usual work-up gave (*S*)-β-amino alcohol hydrochloride (**11a**) in 99% yield and 88.2% ee. Recrystallization of **11a** from methanol afforded enantiomerically pure **11a**. Optically pure **11b** was prepared by a similar procedure using (2*R*,4*R*)-MCCPM



reagents and conditions: (i-a) H_2 (30 atm), $[Rh(COD)Cl]_2$, (2*S*, 4*S*)-MCCPM, Et_3N, methanol, 50 °C, 24 h, > 99%; then recrystallization from methanol, 61% (*ca.* 100%ee); (i-b) H_2 (30 atm), $[Rh(COD)Cl]_2$, (2*R*, 4*R*)-MCCPM, Et_3N, methanol, 50 °C, 24 h, > 99% (91.7%ee); then recrystallization from methanol, 60.0% (*ca.* 100%ee); (ii) (1) NaOH aq. (2) NaH, iodomethane, *N*, *N*-dimethylacetamide, 0–r. t., overnight; (3) H_2, 5 % Pd-C, methanol, r. t., overnight; (iii) (1) 3-iodopropiophenone, ether, 0–r. t., 10 h; (2) HCl gas, ether; (iv) H_2 (30 atm), $[Rh(COD)Cl]_2$, (2*S*, 4*S*)- or (2*R*, 4*R*)-MCCPM, methanol, 50 °C, 72 h; then recrystallization from methanol-hexane.

Chart 2

Table 3. Asymmetric Hydrogenation of **13**

Substrate	Ligand	Conditions		Convn.[a] (%)	Product	
		atm/°C/h	S/C		(*S*,*S*)/(*S*,*R*)[b]	(*R*,*R*)/(*R*,*S*)[b]
13a	(2*S*,4*S*)-MCCPM (**1a**)	30/50/72	250	100	10.4/89.6	
13a	(2*R*,4*R*)-MCCPM (**2**)	30/50/72	250	100	89.7/10.3	
13b	(2*S*,4*S*)-MCCPM (**1a**)	30/50/72	250	100		90.9 / 9.1
13b	(2*R*,4*R*)-MCCPM (**2**)	30/50/72	250	100		8.6 /91.4

a) Determined by ^{1}H-NMR analysis. *b*) Determined by HPLC analysis of its free amine.

(**2**). Compound **11a** was converted to the β-amino ketone hydrochloride (**13a**) in the following way. The sodium alkoxide of **11a** free base was generated in *N*,*N*-dimethylacetamide using sodium hydride by reaction initially at 0 °C and then at 70 °C for 2 h. Iodomethane was added and the mixture was stirred at room temperature overnight. Extractive isolation afforded the (*S*)-*O*-methylated product, which was debenzylated with 5% Pd–C in methanol to yield **12a** (80.8%). Reaction of **12a** with 3-iodopropiophenone in ethyl ether produced the free base form of the β-amino ketone **13a** and treatment with hydrogen chloride gas in ethyl ether provided **13a** (56.6%). In a completely analogous manner we synthesized **13b**, starting with optically pure **11b**. Optically active eprozi-

nol dihydrochloride was obtained by the asymmetric hydrogenation of **13** in a quantitative yield. The results of the asymmetric hydrogenations of **13a** and **13b** with MCCPM–rhodium(I) complex are summarized in Table 3. Recrystallization of (*S*,*S*)- and (*S*,*R*)-eprozinol dihydrochloride (**14a** and **14b**) from hexane–methanol afforded optically pure **14a** and **14b**. Optically pure **14c** and **14d** were obtained similarly.

In conclusion, we found that the **1**– and **2**–rhodium(I) complexes were efficient catalysts for the asymmetric hydrogenation of β- and γ-amino ketones, and practical syntheses of optically active fluoxetine and eprozinol were achieved.

Experimental

General Procedures All melting points were determined with a micro-melting point apparatus (Yazawa) 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-EX 270 spectrometers using tetramethylsilane (TMS) as an internal standard, and the chemical shifts are given in δ values. The abbreviations of signal patterns are as follows: s, singlet; br s, broad singlet; d, doublet; br d, broad doublet; t, triplet; br t, broad triplet; m, multiplet. Column chromatography was carried out on Silica gel 60 (70—230 mesh, Merck).

3-(*N*-Benzyl-*N*-methylamino)propiophenone Hydrochloride (3a) Concentrated HCl (12.8 g) was added to a mixture of acetophenone (30.0 g, 0.25 mol), *N*-benzyl-*N*-methylamine (40.0 g, 0.33 mol) and paraformaldehyde (9.9 g) in ethanol (40 ml) under ice cooling, then the mixture was refluxed for 4 h. After cooling to room temperature, the precipitate was separated by filtration and washed with acetone. The crystalline residue was recrystallized from methanol to afford **3a** as white crystals (35.9 g, 50%). mp 188—190 °C. IR (KBr): 1670 (CO) cm^{-1}. ^{1}H-NMR δ (CD_3OD): 2.87 (3H, s, NCH_3), 3.5—3.7 (4H, m, $PhCCH_2CH_2N$), 4.44 (2H, br s, NCH_2Ph), 7.50—7.68, 8.02—8.06 (10H, m, Ar-H). *Anal.* Calcd for $C_{17}H_{20}ClNO$: C, 70.46; H, 7.00; N, 4.83. Found: C, 70.45; H, 7.09; N, 4.80.

3-(*N*-Methylamino)propiophenone Hydrochloride (3b) A mixture of 3-(*N*-benzyl-*N*-methylamino)propiophenone (13.0 g, 51 mmol), ethyleneglycol (6.8 g, 0.11 mol) and *p*-toluenesulfonic acid monohydrate (13.6 g, 71 mmol) in benzene (50 ml) was refluxed with azeotropic removal of water in a Dean-Stark trap for 4 h. After cooling to room temperature, the reaction mixture was made alkaline with 33% NaOH under ice cooling. The organic layer was separated and further extraction of the aqueous layer with ether was carried out. The combined organic layer was dried over anhydrous $MgSO_4$ and then evaporated. The residue was dissolved in methanol (100 ml), then 5% Pd–C (7.0 g) was added. The mixture was stirred for 20 h at room temperature under a hydrogen atmosphere (1 atm), then filtered. The filtrate was evaporated and the residue was dissolved in benzene (10 ml). Then 30% HCl (50 ml) was added and the whole was stirred at room temperature for 2 h. The mixture was made alkaline with 33% NaOH under ice cooling. The organic layer was separated and further extraction of the aqueous layer with ether was carried out. The combined organic layer was dried over anhydrous $MgSO_4$ and evaporated. The residue was dissolved in ether (120 ml) and acidified with hydrogen chloride gas under ice cooling. The precipitate was separated by decantation and purified by column chromatography on silica gel with CH_2Cl_2–methanol (20 : 1) as the eluent to give **3b** (3.0 g, 30%). mp 125—128 °C. IR (KBr): 1680 (CO) cm^{-1}. ^{1}H-NMR δ ($CDCl_3$): 2.78 (3H, s, NCH_3), 3.42 (2H, t, CH_2CH_2N), 3.57 (2H, t, CH_2CH_2N), 7.49—7.67, 8.02—8.05 (5H, m, Ar-H). *Anal.* Calcd for $C_{10}H_{14}ClNO$: C, 60.15; H, 7.01; N, 7.01. Found: C, 58.69; H, 7.14; N, 6.36.

Asymmetric Hydrogenation of β-Amino Ketone Hydrochloride (3) (General Procedure) A mixture of $[Rh(COD)Cl]_2$ (chloro(1,5-cyclooctadiene)rhodium(I) dimer, 1.2 mg, 2.5×10^{-3} mmol), chiral bisphosphine (6.0×10^{-3} mmol) and degassed methanol (5 ml) was stirred at room temperature under an argon atmosphere for 5 min. This catalytic solution (1.25 ml) was added to a solution of β-amino ketone hydrochloride (**3**) (1.25 mmol) in degassed methanol (total 15 ml). The mixture was placed in an autoclave, pressurized with hydrogen to 30 atm and stirred for 48 h at 50 °C. The reaction mixture was brought to ambient temperature, and active carbon powder (250 mg) was added. The mixture was stirred for 30 min and filtered. The filtrate was evaporated to give the γ-amino alcohol hydrochloride (**4**) quantitatively. Conversion was measured by ^{1}H-NMR analysis. The enantiomeric purity of **4a** and **4b** was determined by HPLC analysis of the benzoate of **4a** and the benzamide of **4b**, respectively (**4a**: Daicel Chiralcel OJ, *n*-hexane : 2-propanol = 9 : 1; **4b**: Daicel Chiralcel OD, *n*-hexane : 2-propanol = 4 : 1). **4a** and **4b** were led to 3-(*N*-methylamino)-1-phenyl-1-propanol (**8**), and the absolute configurations of **4a** and **4b** were determined to be *R* by measuring the optical rotation (optically pure (*S*)-(−)-(**8**) $[\alpha]_D^{22}$ −37.37° (c = 1.0, $CHCl_3$) (ref. 8*d*)).

(*R*)-3-(*N*-Methylamino)-1-phenyl-1-propanol (8) The catalyst 5% Pd–C (80 mg) was added to a solution of **4a** (360 mg, 1.2 mmol, 90.8% ee) in ethanol (20 ml), then the mixture was stirred for 20 h at room temperature under a hydrogen atmosphere (1 atm). The reaction mixture was filtered and the filtrate was evaporated. Ether (10 ml) was added to the residue and the mixture was made alkaline with 0.5 N NaOH under ice cooling. The organic layer was separated and further extraction of the aqueous layer with ether was carried out. The combined organic layer was washed with saturated aqueous NaCl, and dried over anhydrous $MgSO_4$. Concentration *in vacuo* gave **8** as a colorless oil, which was used without further purification (173 mg, 87%). ^{1}H-NMR δ ($CDCl_3$): 1.72—1.92 (2H, m, $PhCCH_2CH_2N$), 2.44 (3H, s, NCH_3), 2.79—2.93 (2H, m, $PhCCH_2CH_2N$), 4.94 (1H, dd, J = 3.3, 8.6 Hz, PhCH(OH)), 7.21—7.39 (5H, m, Ar-H).

(*R*)-Fluoxetine Hydrochloride (9) (*R*)-Fluoxetine was prepared from **8** according to the literature (ref. 8). Under an argon atmosphere, a solution of **8** (173 mg, 1.0 mmol) in *N*,*N*-dimethyacetamide (5 ml) was added to a suspension of sodium hydride (50 mg of a 60% dispersion in oil, 1.25 mmol; oil removed with *n*-hexane) in *N*,*N*-dimethylacetamide (10 ml) under ice cooling, and the mixture was stirred at 0 °C for 5 min. The mixture was heated at 70 °C for 30 min, affording an orange solution. To this solution was added a solution of *p*-chlorobenzotrifluoride (226 mg, 1.3 mmol) in *N*,*N*-dimethylacetamide (1 ml), and the mixture was heated at 100 °C for 3 h. After cooling, the reaction mixture was poured into cold water and extracted with ether. The combined extracts were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and evaporated. The residue was dissolved in ether and acidified with hydrogen chloride gas to give an acidic ethereal solution. The solution was concentrated to give a yellow oil, which was purified by preparative TLC on silica gel with CH_2Cl_2–methanol (10 : 1) as the eluent to give a slightly yellow oil. A solution of this oil in ether (5 ml) was left to stand at room temperature for 2 h, and the precipitate was collected to provide **9** as a white crystals (210 mg, 60%). mp 133—135 °C. $[\alpha]_D^{22}$ −1.5° (c = 0.88, methanol) [lit. $[\alpha]_D^{23}$ +1.60° (c = 1, methanol) for (*S*)-isomer (ref. 8*d*); $[\alpha]_D^{23}$ −2.16° (c = 1.62, methanol) (ref. 8*a*); $[\alpha]_D^{22}$ −3.01° (c = 5.3, methanol) (ref. 8*c*)]. ^{1}H-NMR δ ($CDCl_3$): 2.17—2.5 (2H, m, $PhCCH_2CN$), 2.6 (3H, s, NCH_3), 2.83—3.30 (2H, m, $PhCCCH_2N$), 5.20—5.58 (1H, dd, PhCH(OH)), 6.67—6.97 (2H, d, Ar-H *ortho* to O), 7.25—7.38 (5H, m, C_6H_5), 7.26—7.49 (2H, d, Ar-H *ortho* to CF_3). *Anal.* Calcd for $C_{17}H_{19}ClF_3NO$: C, 59.05; H, 5.54; N, 4.05. Found: C, 58.95; H 5.51; N; 3.97.

4-(*N*-Dimethylamino)butyrophenone Hydrochloride (5a) 4-(*N*-Dimethylamino)butyrophenone (**15**) was prepared according to the procedure in ref. 13. Compound **15** (5.7 g, 30 mmol) was dissolved in ether (100 ml) and the solution was acidified with hydrogen chloride gas at 0 °C. The precipitate was collected and recrystallized from 2-propanol to give **5a** (3.9 g, 57%). mp 157—160 °C. IR (KBr): 1681 (CO) cm^{-1}. ^{1}H-NMR δ (CD_3OD): 2.15 (2H, m, $PhC(O)CCH_2CN$), 2.93 (6H, s, $N(CH_3)_2$), 3.21—3.24 (4H, m, $PhC(O)CH_2CCH_2N$), 7.49—7.63 (3H, m, *p*- and *m*-Ar-H), 8.01 (2H, m, *o*-Ar-H). *Anal.* Calcd for $C_{12}H_{18}ClNO \cdot 1/2H_2O$: C, 60.88; H, 8.09; N, 5.92. Found: C, 60.95; H, 8.20; N, 5.85.

4-(*N*-Benzyl-*N*-methylamino)butyrophenone Hydrochloride (5b) A solution of 4-iodobutyrophenone (9.0 g, 33 mmol) in ether (50 ml) was added dropwise to a solution of *N*-benzyl-*N*-methylamine (36.3 g, 0.3 mol) in ether (100 ml) under ice cooling. After standing at room temperature for a day, the precipitate was filtered off and then the filtrate was concentrated to give a yellow oil. H_2O (50 ml) was added, the mixture was acidified with 36% HCl under ice cooling, and the aqueous layer was washed with ether. The acid layer was made alkaline with 2 N NaOH, then extracted with ether. The extract was washed with water, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified

by column chromatography on silica gel with *n*-hexane–2-propanol (9 : 1) as the eluent to give an oil. This oil was dissolved in ether and acidified with hydrogen chloride gas at 0 °C. The precipitate was collected and recrystallized from methanol to give **5b** (4.0 g, 40%). mp 179—181 °C. IR (KBr): 1689 (CO) cm^{-1}. ^{1}H-NMR δ (CD_3OD): 2.19 (2H, m, $PhC(O)CCH_2CN$), 2.84 (3H, s, NCH_3), 3.20—3.25 (4H, m, $PhC(O)CH_2CH_2N$), 4.38 (2H, s, NCH_2Ph), 7.49—7.63 (8H, m, $NCH_2C_6H_5$, *p*- and *m*-Ar-H of $C_6H_5C(O)$), 8.0 (2H, m, *o*-Ar-H of $C_6H_5C(O)$). *Anal.* Calcd for $C_{18}H_{21}ClNO \cdot 1/8H_2O$: C, 70.63; H, 7.33; N, 4.58. Found: C, 70.55; H, 7.43; N, 4.51.

4-Piperidinobutyrophenone Hydrochloride (5c) Compound **5c** was prepared by means of a similar procedure to that for the preparation of **5b** using piperidine (25.5 g, 0.3 mol) and 4-iodobutyrophenone (9.0 g, 33 mmol). Yield 40%. mp 199—201 °C. IR (KBr): 1683 (CO) cm^{-1}. ^{1}H-NMR δ (CD_3OD): 1.52—1.97 (6H, m, $N-CH_2(CH_2)_3CH_2-$), 2.16 (2H, m, $PhC(O)CCH_2CN$), 2.97—3.60 (8H, m, $PhC(O)CH_2CCH_2N$, $N-CH_2(CH_2)_3CH_2-$), 7.49—7.62 (3H, m, *m*- and *p*-Ar-H), 8.00—8.02 (2H, m, *o*-Ar-H). *Anal.* Calcd for $C_{15}H_{22}ClNO$: C, 67.28; H, 8.28; N, 5.23. Found: C, 66.90; H, 8.42; N, 5.04.

Asymmetric Hydrogenation of γ-Aminoketone Hydrochlorides (5) (General Procedure) A mixture of $[Rh(COD)Cl]_2$ (1.2 mg, 2.5×10^{-3} mmol), chiral bisphosphine (6.0×10^{-3} mmol) and degassed methanol (2 ml) was stirred at room temperature under an argon atmosphere for 5 min. This catalytic solution was added to a solution of a γ-amino ketone hydrochloride (**5**) (1.25 mmol) and triethylamine (2.5 mg, 2.5×10^{-2} mmol) in degassed methanol (total 12 ml). The mixture was placed in an autoclave, pressurized with hydrogen to 50 atm and stirred for 72 h at 50 °C. The reaction mixture was brought to ambient temperature, and active carbon powder (250 mg) was added. The mixture was stirred for 30 min and filtered. The filtrate was evaporated to give the corresponding δ-amino alcohol hydrochloride (**6**) quantitatively. Conversion was measured by ^{1}H-NMR analysis. Part of the **6a** or **6b** was led to the free base form, and optical purity was determined by HPLC analysis using a column packed with Chiralcel OD (Daicel; eluent; *n*-hexane : ethanol = 1 : 4). The enantiomeric purity of **6c** was calculated on the basis of the maximum optical rotation of optically pure **6c** (ref. 11).

α-(4-Benzylpiperazinyl)acetophenone Dihydrochloride (10) A solution of α-bromoacetophenone (1.0 g, 5.0 mmol) in 2-propanol (5 ml) was added dropwise to a solution of 1-benzylpiperazine (1.0 g, 5.7 mmol) in 2-propanol (10 ml) at 0 °C. The mixture was stirred at 50 °C for 12 h, then concentrated *in vacuo*. The residue was treated with 2 N NaOH (20 ml) and extracted with ether. The combined extracts were washed with H_2O, dried over anhydrous $MgSO_4$ and then evaporated. The residue was dissolved in ether and acidified with hydrogen chloride gas at 0 °C. The precipitate was separated by filtration and recrystallized from methanol, affording **10** (944 mg, 51%). mp 197—200 °C. IR (KBr): 1703 (CO) cm^{-1}. ^{1}H-NMR δ (CD_3OD): 3.61—3.79 (8H, m, $NCH_2CH_2N \times 2$), 4.52 (2H, s, NCH_2Ph), 5.11 (2H, s, $PhC(O)CH_2N$), 7.51—7.76 (8H, m, $NCH_2C_6H_5$, *m*- and *p*-Ar-H of $C_6H_5C(O)$), 7.99—8.07 (2H, m, *o*-Ar-H of $C_6H_5C(O)$). FAB-MS: $(M+H)^+$ 295. *Anal.* Calcd for $C_{19}H_{24}Cl_2N_2O \cdot 3/4H_2O$: C, 59.92; H, 6.75; N, 7.35. Found: C, 60.05; H, 6.68; N, 7.37.

4-Benzyl-1-[(*S*)-2-hydroxy-2-phenylethyl]piperazine Dihydrochloride (11a) A mixture of $[Rh(COD)Cl]_2$ (1.2 mg, 2.5×10^{-3} mmol), (2*S*,4*S*)-MCCPM (3.1 mg, 6.0×10^{-3} mmol) and degassed methanol (5 ml) was stirred at room temperature under an argon atmosphere for 5 min. This catalytic solution (2.5 ml) was added to a solution of **10** (230 mg, 0.63 mmol) and triethylamine (1.3 mg, 25×10^{-3} mmol) in degassed methanol (total 15 ml). The mixture was placed in an autoclave, pressurized with hydrogen to 30 atm and stirred for 24 h at 50 °C. The reaction mixture was brought to ambient temperature, and active carbon powder (250 mg) was added. The mixture was stirred for 30 min and filtered. The filtrate was evaporated and the residue was recrystallized from methanol, affording optically pure **11a** (142 mg, 61%). The enantiomeric purity was measured by reaction with benzoyl chloride, followed by HPLC analysis (Daicel, Chiralcel OJ, *n*-hexane : 2-propanol = 4 : 1) of the resulting benzoate. mp 223 °C (dec.) $[\alpha]_D^{22}$ +34.6° (c = 1.0, methanol). ^{1}H-NMR δ (CD_3OD): 3.44 (2H, m, $PhCH(OH)CH_2N$), 3.69—3.87 (8H, m, $NCH_2CH_2N \times 2$), 4.50 (2H, s, NCH_2Ph), 5.20 (1H, dd, J = 10.4, 3.4 Hz, $PhCH(OH)CH_2N$), 7.31—7.94 (10H, m, Ar-H). FAB-MS: $(M+H)^+$ 297. *Anal.* Calcd for $C_{19}H_{26}ClN_2O$: C, 61.79; H, 7.10, N, 7.59. Found: C, 61.39; H, 6.82; N, 7.26.

4-Benzyl-1-[(*R*)-2-hydroxy-2-phenylethyl]piperazine Dihydrochloride (11b) This β-amino alcohol hydrochloride was prepared by means of the same procedure as for the preparation of the (*S*)-isomer (**11a**) using (2*R*,4*R*)-MCCPM–Rh(I) as a catalyst. mp 226 °C (dec.) $[\alpha]_D^{22}$ −34.3° (c = 1.0, methanol).

1-[(*S*)-2-Methoxy-2-phenylethyl]piperazine (12a) A 2 N NaOH solution (10 ml) was added to a solution of **11a** (1.3 g, 3.5 mmol) in ether (10 ml) at 0 °C, then the mixture was stirred for 10 min at 0 °C. The organic layer was separated and further extraction of the aqueous layer with ether was carried out. The combined organic layer was washed with water, dried over anhydrous $MgSO_4$ and then evaporated to give the free base form of **11a** (1.0 g, 96.4%). Under an argon atmosphere, a solution of this compound (1.0 g, 3.4 mmol) in *N*,*N*-dimethylacetamide (15 ml) was added to a suspension of sodium hydride (1.36 g of a 60% dispersion in oil, 34 mmol; oil removed with *n*-hexane) in *N*,*N*-dimethylacetamide (100 ml) at 0 °C and the mixture was heated at 70 °C for 2 h. After cooling of this reaction mixture, a solution of iodomethane (2.4 g, 17 mmol) in *N*,*N*-dimethylacetamide (10 ml) was added to it at 0 °C, and the whole was stirred at room temperature for 18 h, then poured into cold water and extracted with ether. The organic layer was washed with H_2O, dried over anhydrous $MgSO_4$ and evaporated. The residue was dissolved in methanol (20 ml), then 5% Pd–C (440 mg) was added. The mixture was stirred for 20 h at room temperature under a hydrogen atmosphere (1 atm), then the reaction mixture was filtered. The filtrate was evaporated and the residue was purified by column chromatography on silica gel with CH_2Cl_2–methanol (10 : 1) as the eluent to give **12a** as an oil (623 mg, 81%). ^{1}H-NMR δ ($CDCl_3$): 2.51—2.95 (8H, m, $NCH_2CH_2N \times 2$), 2.39 (1H, dd, J = 13.4, 3.4 Hz, H_a of $PhCCH_2N$), 2.77 (1H, dd, J = 13.4, 9.2 Hz, H_b of $PhCCH_2N$), 3.22 (3H, s, OCH_3), 4.38 (1H, dd, J = 3.4, 9.2 Hz, $PhCH(OCH_3)$), 7.20—7.36 (5H, m, Ar-H). FAB-MS: $(M+H)^+$ 221.

1-[(*R*)-2-Methoxy-2-phenylethyl]piperazine (**12b**): **12b** was prepared according to the above procedure with **11b** as the starting material.

3-[1-[(*S*)-2-Methoxy-2-phenylethyl]-4-piperazinyl]propiophenone Dihydrochloride (13a) A solution of 3-iodopropiophenone (572 mg, 2.2 mmol) in ether (5 ml) was added dropwise to a solution of **12a** (490 mg, 2.2 mmol) in ether (10 ml) at 0 °C. After standing at room temperature for a day, the reaction mixture was acidified with 2 N HCl at 0 °C and the organic layer was separated. The acid layer was made alkaline with 2 N NaOH and extracted with ether. The organic layer was dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by preparative TLC on silica gel with CH_2Cl_2–methanol (20 : 1) as the eluent to give a slightly yellow oil. This oil was dissolved in ether (15 ml) and acidified with hydrogen chloride gas at 0 °C. The precipitate was collected to give **13a** (530 mg, 57%). mp 153—155 °C. $[\alpha]_D^{22}$ +37.3° (c = 1.5, methanol). IR (KBr): 1685 (CO) cm^{-1}. ^{1}H-NMR δ (CD_3OD): 3.26—3.73 (6H, m, $PhCCH_2N$, NCH_2CH_2CPh), 3.29 (3H, s, OCH_3), 3.70—4.35 (8H, m, $NCH_2CH_2N \times 2$), 5.02 (1H, br d, PhCHCN), 7.30—7.65 (8H, m, C_6H_5CCN, *m*- and *p*-Ar-H of $C(O)C_6H_5$), 8.01 (2H, m, *o*-Ar-H of $C(O)C_6H_5$). *Anal.* Calcd for $C_{22}H_{30}Cl_2N_2O_2 \cdot 5/4H_2O$: C, 58.99; H, 7.31; N, 6.25. Found: C, 59.08; H, 7.00; N, 6.17. FAB-MS: $(M+H)^+$ 353.

3-[1-[(*R*)-2-Methoxy-2-phenylethyl]-4-piperazinyl]propiophenone Dihydrochloride (**13b**): **13b** was prepared according to the above procedure with **12b** as the starting material. mp 151—153 °C. $[\alpha]_D^{22}$ −38.9° (c = 1.0, methanol).

1-(2-(*S*)-Methoxy-2-phenylethyl)-4-(3-(*S*)-hydroxy-3-phenylpropyl)-piperazine Dihydrochloride; (*S*,*S*)-Eprozinol Dihydrochloride (14a) A mixture of $[Rh(COD)Cl]_2$ (1.4 mg, 2.8×10^{-3} mmol), (2*R*,4*R*)-MCCPM (3.6 mg, 6.8×10^{-3} mmol) and degassed methanol (5 ml) was stirred at room temperature under an argon atmosphere for 5 min. This catalytic solution (1 ml) was added to a solution of **13a** (120 mg, 0.28 mmol) in degassed methanol (total 10 ml). The mixture was placed in an autoclave, pressurized with hydrogen to 30 atm and stirred for 72 h at 50 °C. The reaction mixture was brought to ambient temperature, and active carbon powder (150 mg) was added. The mixture was stirred for 30 min and filtered. The filtrate was evaporated and the residue was recrystallized from *n*-hexane–methanol, affording optically pure **14a** (77 mg, 64%). Part of the product **14a** was led to the free base form, and the diastereomeric purity was determined by HPLC analysis using a column packed with Chiralcel OJ (Daicel; eluent; *n*-hexane : ethanol = 1 : 4). mp 197—200 °C. $[\alpha]_D^{22}$ +19.2° (c = 0.7, methanol). FAB-MS: $(M+H)^+$ 355. ^{1}H-NMR was analyzed for the free base form of **14a**. ^{1}H-NMR δ ($CDCl_3$): 1.84 (2H, m, $NCCH_2CPh$), 2.41 (1H, dd, J = 13.4, 3.1 Hz, H_a of $PhCCH_2N$), 2.55—2.72 (10H, m, $NCH_2CH_2N \times 2$, NCH_2CCPh), 2.79 (1H, dd, J = 13.4, 8.9 Hz, H_b of $PhCCH_2N$), 3.22 (3H, s, OCH_3), 4.36

(1H, dd, J=3.1, 8.9 Hz, PhCH(OMe)CN), 4.93 (1H, br t, NCCCH(OH)-Ph), 7.22—7.37 (10H, m, Ar-H).

(*R*,*R*)-Eprozinol Dihydrochloride (**14c**): **14c** was prepared according to the above procedure with **13b** as the starting material and (2*S*,4*S*)-MCCPM–Rh(I) complex as a catalyst.

(*S*,*R*)-Eprozinol Dihydrochloride (14b) This compound was prepared by means of the same procedure as for the preparation of the (*S*,*S*)-isomer (**14a**) using (2*S*,4*S*)-MCCPM–Rh(I) as a catalyst. Recrystallization of the product **14b** from *n*-hexane–methanol gave optically pure **14b** (50%). mp 190—193 °C, $[\alpha]_D^{22}$ +58.6° (c=0.6, methanol). FAB-MS: $(M+H)^+$ 355. ^{1}H-NMR was analyzed as the free base form of **14b**. ^{1}H-NMR δ ($CDCl_3$): 1.85 (2H, m, $NCCH_2CPh$), 2.42 (1H, dd, J=13.4, 3.1 Hz, H_a of $PhCCH_2N$), 2.55—2.71 (10H, m, $NCH_2CH_2N\times 2$, NCH_2CCPh), 2.80 (1H, dd, J=13.4, 9.2 Hz, H_b of $PhCCH_2N$), 3.22 (3H, s, OCH_3), 4.36 (1H, dd, J=3.1, 9.2 Hz, PhCH(OMe)CN), 4.92 (1H, br t, NCCCH(OH)-Ph), 7.22—7.37 (10H, m, Ar-H).

(*R*,*S*)-Eprozinol Dihydrochloride (**14d**): **14d** was prepared according to the above procedure with **13b** as the starting material and (2*R*,4*R*)-MCCPM–Rh(I) complex as a catalyst.

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