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Hydrochloride of Chiral Piperazine as a Chiral Proton Source

Kaoru Fuji,* Kiyoshi Tanaka and Hisashi Miyamoto
Institute for Chemical Research, Kyoto University, Uji 611, Japan

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Abstract: Asymmetric protonation utilizing hydrochlorides of chiral piperazine derivatives has been investigated. Protonation of the lithium enolate derived from 1-acetoxy-2-benzylcyclohexene with (2*R*, 5*R*)-2,5-diphenylpiperazine monohydrochloride (**2**) resulted in a formation of (*S*)-2-benzylcyclohexanone in 70% ee. The enantioface-differentiating protonation with the salts of related chiral piperazine derivatives are also discussed.

Optically active carbonyl compounds bearing a stereogenic center α to the carbonyl group are important intermediates or synthons for the synthesis of optically active natural and unnatural compounds. Constructions of this kind of compound have been described in recent years and are still in progress. The diastereoselective α-alkylation[1] of the carbonyl compound carrying a chiral auxiliary group had been the principal to this kind of chiral derivatives, until the asymmetric deprotonation approach[2] appeared. Meanwhile, it turned out that when the metal enolate forms a complex with a chiral amine ligand, the resulting enolate complex exists in a chiral environment even if the original enolate is achiral. As a consequence, alkylation of the complex with an electrophile might make the reaction enantioselective. In this process, an optically active carbonyl compound carrying a hydrogen atom in the α position can be provided by quenching the enolate mixture with an achiral proton source[3] or internal proton return process.[4]

An alternative approach to these chiral carbonyl compounds involves asymmetric protonation,[5] which at first sight, is very close to, but essentially different from the asymmetric alkylation using a chiral base described above. The enantioface differentiating protonation of prochiral enol derivatives is a very simple and attractive route for the preparation of optically active carbonyl compounds and has been of increasing interest in recent years.[5-14] In this process, the prochiral face of the π-system of an intermediate enolate ion or enol can be discriminated by a chiral proton source consisting of an achiral proton and chiral nucleofugal group. The latter functions as a chiral auxiliary and is responsible for the asymmetric induction. If there is a significant difference in $\Delta G^{\neq}$ between the two diastereoisomeric transition state leading to the *R* and *S* configuration of the product, asymmetric induction might be feasible even though the proton transfer process is rapid. Taking the stereochemistry of the initial carbonyl compounds into account, the total process correlates to deracemization or kinetic epimerization and this approach constitutes a complementary method to

asymmetric alkylation. To exploit the general synthetic value of this procedure, the enantiodifferentiating protonation has been extensively studied by Duhamel's group[6] as well as other research groups[7-14] and high enantiomeric excesses have so far been reported only in some cases. Interestingly, only a catalytic amount of a chiral proton source is necessary in some special cases[10] and successful enantiodifferentiating protonation by catalytic antibodies[13] or the enzyme-mediated hydrolysis of α-substituted enol esters[14] have recently appeared in the literature. Most of the reagents employed as a chiral proton source are weakly acidic compounds allowing better transition state discrimination. These include acylated tartrates,[6,7] amino alcohols,[8,12] ureas,[12] diols,[7,12] α-ketols,[7] hydroxyesters[7,12] or lactols,[7,12] dilactams[9] and sugars.[7,11] One of the authors (K. F.) previously employed (*S*)-10-camphorsulfonic acid for enantiotopic group differentiation in the protonation of disodium hydroxylcarboxylate and applied it to kinetic resolution of racemic lactones.[15] In this context, it should be mentioned that natural alkaloids had been used as the chiral inducers in the asymmetric transformation, in which the protonated form served as a chiral proton source.[16] In contrast to the alkaloids, the hydrochloride of the chiral amine has rarely been used in the asymmetric protonation in spite of its ready accessibility. We report here the enantiodifferentiating protonation of the prochiral lithium enolate by utilizing the hydrochloride of chiral piperazine derivatives as a chiral proton source.

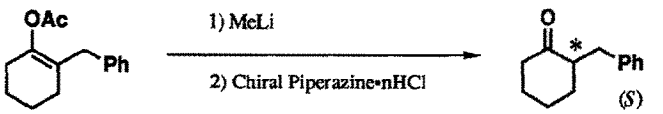
Generally, the proton source contains electron-rich groups with coordination or chelation ability which would enhance conformational rigidity in the transition state and the proton transferred should be located in proximity to the stereogenic center (asymmetric environment). Optimally, the chiral reagent should be readily accessible in both enantiomeric forms and be easily recovered. These criteria seem to be fulfilled with the hydrochlorides of piperazine derivatives, since both forms of chiral piperazine derivatives could be easily prepared from the corresponding α-amino acid and it was reported that some of the related compounds act as excellent catalytic ligands for the asymmetric ethylation of aldehydes with diethylzinc[17,18] as well as stoichiometric ligands in the asymmetric osmylation of unactivated olefins.[19] The existence of the two basic nitrogens in the molecule might allow to produce both the mono- and dihydrochloride by controlling the amount of hydrogen chloride added. It was also expected that the proximity of the hydrogen transferred and the nitrogen as a ligating site in the piperazine molecule would be beneficial for the asymmetric protonation of enolates.

It should be pointed out that geometry of the enolate (E or Z) is largely responsible for asymmetric induction. In our study, the enol acetate of the cyclic ketone[12] was chosen as the precursor of prochiral enolate in order to secure the definite stereochemistry of the enolate. This system is free from the influence of the amine[20] usually employed as a base and it is already known that the enantiomeric excess of the cyclohexanone can be directly determined by HPLC.

Initial experiments focused on the determination of the effective structural elements of the inducer and experimental conditions. Thus, 1-acetoxy-2-benzylcyclohexene[21] was treated with 1.9 eq. of methyllithium[22] at -78 °C and then, the resulting lithium enolate was quenched by the addition of the hydrochloride of chiral piperazine derivatives.[23] After the usual work-up procedure the crude products containing 2-benzylcyclohexanone[24] were subjected to HPLC analysis on a chiral column to determine the %ee. From the mixture, the chiral piperazine can be easily retrieved with conservation of enantiomeric purity. The absolute stereochemistry of the product was deduced from the sign of the optical rotation reported.[24] These results are listed in Table I. Both the mono- and dihydrochlorides of chiral piperazines with or without *N*-substituents are

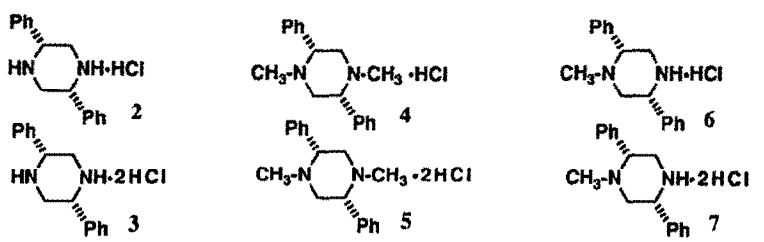
effective proton sources and the *N,N'*-disubstituted derivative is not (entries 10 and 11). At least one of the nitrogens of the piperazine ring should be unsubstituted. Diethyl ether with less ligating ability than THF is the solvent of choice (entries 4 and 13). Lowering the temperature during protonation strengthens the bimolecular interactions of a lithium enolate and a chiral proton source and therefore increases the enantioselectivity (entries 1, 5, 6, 7 and 8).

Table I. Asymmetric Protonation of 1-Acetoxy-2-benzylcyclohexene with Mono- or Dihydrochlorides of Chiral Piperazines, **2** - **7**.



Entry	Proton Source[a)]	Solvent	Temp. (°C)	Yield[b)] (%)	% Ee[c)]	Solubility[d)]
1	2	Et_2O	-78	86	63	susp.
2	2	Et_2O/CH_2Cl_2(1:1)	-78	89	63	soln.
3	2	CH_2Cl_2	-78	81	61	soln.
4	2	THF	-78	87	23	soln.
5	2	Et_2O/CH_2Cl_2(1:1)	-30	89	49	soln.
6	2	Et_2O/CH_2Cl_2(1:1)	0	82	41	soln.
7	2	Et_2O/CH_2Cl_2(1:1)	25	86	35	soln.
8	2	Et_2O/CH_2Cl_2(1:1)	-90	85	70	susp.
9	3	Et_2O	-78	89	50	susp.
10	4	Et_2O	-78	73	-0	susp.
11	5	Et_2O	-78	80	-0	susp.
12	6	Et_2O	-78	88	32	susp.
13	6	THF	-78	80	-0	susp.
14	7	Et_2O	-78	80	43	susp.
15	1	Et_2O/CH_2Cl_2(1:1)	-78	87	23	soln.

a) Hydrochlorides, **2** - **7** of (2*R*, 5*R*)-Diphenylpiperazine (**1**) and Related Compounds:



b) Isolated yield; c) Determined by HPLC on Chiralcel OJ column;
d) Solubility of the inducers: suspension (susp.) or solution (soln.)

Scheme 1. Preparation of Mono-*N*-alkylpiperazine Hydrochlorides **7** - **13** from **1**.

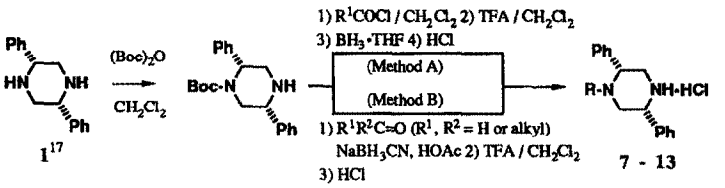
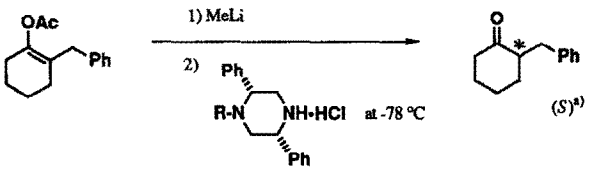
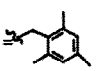
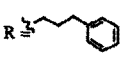
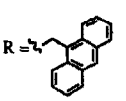


Table II. Asymmetric Protonation of 1-Acetoxy-2-benzylcyclohexene with Monohydrochloride of Mono-*N*-substituted Chiral Piperazines **7** - **13**.



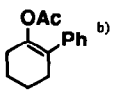
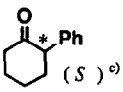
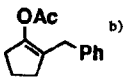
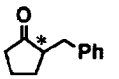
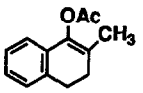
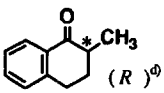
Entry	Proton Source (R =)	Solvent for inductor	Chemical Yield (%)[b]	% Ee[c]	Solubility
1	**7**; R = -Me	diethyl ether	88	32	susp.
2	**8**; R = 	diethyl ether	73	65	soln.
3	**9**; R = 	diethyl ether	75	32	soln.
4	**10**; R = 	diethyl ether	91	69	soln.
5	**10**; R = 	toluene	91	50	soln.
6	**11**; R = 	diethyl ether	91	46	susp.
7	**12**; R = 	diethyl ether / methlene chloride (4 / 1)	89	64	soln.
8	**13**; R = 	diethyl ether	87	36	susp.

a) Ref. 24, b) Isolated yield, c) Determined by HPLC

Subsequently, several monohydrochlorides of chiral *N*-monosubstituted piperazine derivatives, **8** - **13**, were prepared from (2*R*,5*R*)-diphenylpiperazine (**1**)[17] according to the procedure described in Scheme 1 (method A or B) and the asymmetric protonation was investigated with them (Table II). As can be seen from the table, the enantiomeric excess is not significantly affected by the bulk or nature of the substituents on the nitrogen atom. In other words, the relatively small variation in %ee might be attributable to the solubility of the inducers, since the solubility of the piperazine hydrochloride is limited at low temperature in nonpolar solvents such as diethyl ether. For example, the highest selectivity for (*S*)-2-benzylcyclohexanone was observed with the soluble **10**, whereas the insoluble **13** gave a poor result (entries 4 and 8).

Other types of cyclic enolacetates as prochiral precursors were also examined with the chiral proton source **2** or **10** and showed moderate asymmetric inductions (Table III).

Table III. Asymmetric Protonation of the Enol Acetate with **2** or **10**.

Enol Acetate	Product (Configuration)	Chiral Proton Source	Chemical Yield (%)[a]	% Ee
 [b]	 (*S*)[c]	**2**	84	34[e]
		10	85	53[e]
 [b]		**2**	86	32[e]
		10	84	26[e]
	 (*R*)[d]	**2**	88	40[f]
		10	90	24[f]

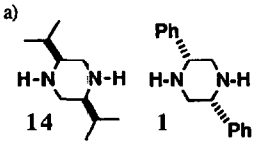
a) Isolated yield; b) Ref. 21; c) Ref. 26; d) Ref. 24 and 25; e) Determined by HPLC on Chiralcel OJ; f) Determined by HPLC on Chiralpak AS;

A change in the substituents on piperazine ring at the C(2) and C(5) positions from the phenyl to the isopropyl group showed no favorable effect (Table IV), in contrast to its remarkable ability as an asymmetric catalyst[17] in ethylation of aldehyde with diethylzinc. As expected, the enantiomeric excess for the ketone reverses by using hydrochlorides of **14** in place of those of **1**. Table IV also describes the influence of the counter ion upon the selectivity. These results suggest the asymmetric induction is not very sensitive to the nature of counter ions and the resulting lithium salt does not significantly participate in the reaction. The chiral piperazine salts of both forms of MTPA afforded the same configuration of the product (entries 7 and 8), indicating that the piperazine moiety is responsible for the asymmetric induction.

Table IV. Asymmetric Protonation of 1-Acetoxy-2-benzylcyclohexene with Hydrochlorides of **14** and Various Salts of **1**.

Entry	Proton Source[a]	Chemical Yield (%)[b]	% Ee	Configuration of Product
1	**14** • HCl[c]	85	12.3	*R*
2	**14** • 2HCl	92	17.6	*R*
3	**1** • HCl (**2**)	86	63.0	*S*
4	**1** • $HClO_4$ (**15**)	86	51.4	*S*
5	**1** • HOAc (**16**)	87	40.2	*S*
6	**1** • HBr (**17**)	87	58.4	*S*
7	**1** • (*S*)-MTPA (**18**)[d]	84	33.2	*S*
8	**1** • (*R*)-MTPA (**19**)[d]	85	58.4	*S*

a)



b) Isolated yield

c) **14**•HCl was prepared in a similar manner to that of **2** from each uniequivalent of **14**•2HCl and the corresponding free amine.

d) α-Methoxy-α-(trifluoromethyl)phenylacetic acid

It is well documented that kinetic protonation of enolates or enols proceeds in a highly stereocontrolled manner with a perpendicular approach to the sp^2-hybridized plane from the less hindered site, when both overlap and steric controls are involved.[27] Although piperazine is cyclic and rigid in structure and conformational analysis of the some piperazine derivatives has been available in the literature,[28] the chiral piperazine hydrochlorides in the transition state of the asymmetric protonation is still ambiguous, where aggregated enolates[29] and complex and subtle proton transfer steps seem to be involved. The results in our study do not yet allow us to draw definite mechanistic conclusion on the transition state and we can not provide any reasonable explanation for the observed sterreochemistry in the products. In order to obtain the mechanistic insight associated with an elucidation of the conformation of the inductor, further investigations are in progress.

In conclusion, the present study revealed that easily accessible chiral *N*-unsubstituted or monosubstituted piperazine mono- and dihydrochlorides serve as effective chiral proton sources in enantiofacedifferentiating protonations of prochiral enolates. It implies that chirality transfer from the leaving group of the chiral proton source to the product is realized. The simplicity of this approach might allow the asymmetric protonation with chiral piperazine hydrochloride to enter into one of the useful preparative methods of α-substituted optically active carbonyl compounds.

Experimental Section

General. Melting points were determined with a Yanagimoto melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on a JASCO A-202 spectrophotometer in chloroform. Proton nuclear magnetic resonance (^{1}H NMR) spectra were taken with a Varian Gemini 200 (200 MHz) or Bruker AC-200 (200 MHz) with chemical shift being reported as δ ppm from tetramethylsilane as an internal standard and couplings are expressed in hertz. Optical rotations were recorded on a Horiba SEPA-200 polarimeter. High performance liquid chromatography was undertaken with Shimadzu LC-10A apparatus on the chiral column of Chiralcel OJ or Chiralpak AS (Daicel Chemical Industries, Ltd.) with 2-propanol in *n*-hexane as an eluent, detecting at 254 nm. Flash columun chromatography was conducted on Silica gel 60 and Silica gel GF254 plates (E. M. Merck) were used for preparative TLC. All reactions employing dry solvent were run under argon or nitrogen. THF and diethyl ether were distilled from sodium metal-benzophenone ketyl and methylene chloride was from calcium hydride. Organic extracts were dried over magnesium sulfate and filtered before removal of the solvent under reduced pressure.

(2*R*,5*R*)-1-*tert*-Butoxycarbonyl-2,5-Diphenylpiperazine. A solution of di-*tert*-butyl dicarbonate (2.6g, 12mmol) in methylene chloride (52ml) was added dropwise to a stirred solution of **1**[17] (2.4g, 10mmol) in methylene chloride (50ml) for 1 h at room temperature, and the mixture was stirred for 1 h at room temperature, then evaporated. The residue was acidified with dil. HCl and extracted with diethyl ether. The separated aqueous layer was made alkaline with 10% aqueous potassium carbonate solution and extracted with methylene chloride. The crystalline residue was recrystallized from *n*-hexane-diethyl ether to give (2*R*,5*R*)-1-*tert*-butoxycarbonyl-2,5-diphenylpiperazine (1.8g, 53%) as colorless needles, mp 77-78 °C. $[\alpha]_D^{25}$ -107.7 (c 0.58, $CHCl_3$). IR (KBr) 1690, 1405, 1110, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ; 1.48 (9H, s), 1.74 (1H,, bs), 2.74-2.95 (1H, m), 3.35 (1H, dd, *J* = 12.4, 4.4 Hz), 3.60-4.22 (3H, m), 5.15-5.45 (1H, m), 7.20-7.62 (10H, m). *Anal.* Calcd for $C_{21}H_{26}N_2O_2$: C, 74.57; H, 7.86; N, 8.15. Found: C, 74.53; H, 7.74; N, 8.23.

(2*R*,5*R*)-2,5-Diphenylpiperazine Monohydrochloride (2). A mixture of **1** (0.24g, 1.0mmol) and **3** (0.31g, 1.0mmol) was dissolved in ethanol (10ml) by warming and the resulting solution was evaporated. To the residue was added methylene chloride (8ml) and then filtered. The filtrate was evaporated and diethyl ether was added to the residue resulting in precipitates, which were collected by filtration to give **2** as white powder, mp 171-3°C. $[\alpha]_D^{25}$ +4.4 (c 0.82, $CHCl_3$). IR (KBr) 3400, 3050-2550, 1595, 1495, 1455, 1130, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ; 3.35 (2H, dd, *J* = 12.4, 6.2 Hz), 3.54 (2H, dd, *J* = 12.4, 3.3 Hz), 4.55 (2H, dd, *J* = 6.2, 3.3 Hz), 7.27-7.45 (6H, m), 7.71 (4H, d, *J* = 6.5 Hz). *Anal.* Calcd for $C_{16}H_{18}N_2$•HCl•1/2H_2O: C, 67.96; H, 7.13; N, 9.91. Found: C, 67.77; H, 7.36; N, 9.84.

(2*R*,5*R*)-1,4-Dimethyl-2,5-Diphenylpiperazine Monohydrochloride (4) and Dihydrochloride (5). Acetic acid (1.7ml, 30mmol) was added to a mixture of **1** (1.1g, 4.6mmol), 37% formaline solution (2.1 ml, 30mmol), $NaBH_3CN$ (1.7g, 27mmol) and methanol (40ml) at 0°C. The mixture was stirred for 2 h at room temperature and then evaporated. The residue was made alkaline with 10%

aqueous potassium carbonate and extracted with ethyl acetate. The residue was dissolved in ethanol (10ml), and then conc. HCl (2ml) was added. The resulting precipitates were collected by filtration and recrystallized from ethanol-water to give **5** (1.3g, 83%) as colorless prisms, mp 203-205°C. $[\alpha]_D^{25}$ -64.0 (c 0.30, H_2O). IR (KBr) 3020, 2700-2400, 1495, 1420, 1150, 730 cm^{-1}. ^1H NMR as free amine ($CDCl_3$) δ; 2.13 (6H, dd, J = 12.0, 3.8 Hz), 2.94 (2H, dd, J = 12.0, 6.2 Hz), 3.57 (2H, dd, J = 6.2, 3.8 Hz), 7.24-7.50 (6H, m), 7.64-7.77 (2H, d, J = 6.3 Hz). *Anal.* Calcd for $C_{18}H_{22}N_2 \cdot 2HCl \cdot 1/4H_2O$: C, 62.88; H, 7.18; N, 8.15. Found: C, 63.08; H, 7.08; N, 8.24.

The monohydrochloride **4** was obtained by the same procedure as described for the preparation of **2**. Mp 193-195 °C. $[\alpha]_D^{25}$ -109.8 (c 1.0, $CHCl_3$). IR (KBr) 3300, 2700, 2400-2150, 1500, 1190, 730 cm^{-1}. *Anal.* Calcd for $C_{18}H_{22}N_2 \cdot HCl$: C, 71.39; H, 7.65; N, 9.25. Found: C, 71.29; H, 7.90; N, 9.18.

(2*R*,5*R*)-2,5-Diphenyl-1-Methylpiperazine Monohydrochloride (6) and Dihydrochloride (7). To a stirred solution of (2*R*,5*R*)-1-*tert*-butoxycarbonyl-2,5-diphenylpiperazine (0.79g, 2.3mmol), 37% formaline solution (0.9ml, 12mmol) and $NaBH_3CN$ (0.7g, 11mmol) in methanol (20ml) was added dropwise acetic acid (0.7ml, 12mmol). The mixture was stirred for 2 h at room temperature and evaporated. The residue was basified with 10% aqueous potassium carbonate and then extracted with ethyl acetate to afford the residue, which was treated with trifluoroacetic acid (1.6ml) and methylene chloride (3ml) for 1 h at room temperature. The reaction mixture was evaporated, made alkaline with 10% aqueous potassium carbonate and extracted with ethyl acetate to furnish a colorless oil. Addition of conc. HCl (2ml) to the solution of the oil in ethanol (5ml) provided the precipitates. Filtration and recrystallization from ethanol-water gave **7** (0.58g, 77%) as colorless prisms, mp 204-206 °C. $[\alpha]_D^{25}$ -6.7 (c 0.30, H_2O). IR (KBr) 2700-2400, 1490, 1420, 1150, 730 cm^{-1}. ^1H NMR as free amine ($CDCl_3$) δ; 1.85 (1H, bs), 2.09 (3H, s), 2.67 (1H, dd, J = 12.0, 4.0 Hz), 2.81 (1H, dd, J = 12.0, 4.0 Hz), 2.92 (1H, dd, J = 12.0, 8.1 Hz), 3.19 (1H, dd, J = 8.1, 4.0 Hz), 3.26 (1H, dd, J = 12.0, 4.0 Hz), 7.21-7.45 (8H, m), 7.74 (2H, d, J = 6.7 Hz). *Anal.* Calcd for $C_{17}H_{20}N_2 \cdot 2HCl \cdot 1/4H_2O$: C, 61.91; H, 6.88; N, 8.49. Found: C, 61.64; H, 6.79; N, 8.40.

The monohydrochloride **6** was obtained by the same procedure as described for **2**. Mp 219-221 °C. $[\alpha]_D^{25}$ -25.2 (c 1.0, $CHCl_3$). IR (KBr) 3000-2400, 1540, 1500, 1190, 1135, 735 cm^{-1}. *Anal.* Calcd for $C_{17}H_{20}N_2 \cdot HCl$: C, 70.70; H, 7.33; N, 9.70. Found: C, 70.29; H, 7.44; N, 9.86.

(2*R*,5*R*)-2,5-Diphenyl-1-(2,4,6-Trimethylbenzyl)piperazine Monohydrochloride (8). Starting from (2*R*,5*R*)-1-*tert*-butoxycarbonyl-2,5-diphenylpiperazine (0.51g, 1.5mmol) and mesitaldehyde (0.67g, 4.5mmol), the monohydrochloride **8** (0.45g, 73%) was obtained by the same procedure as described for the preparation of **7**. Mp 146-148 °C. $[\alpha]_D^{25}$ -17.0 (c 1.0, $CHCl_3$). IR (KBr) 3000-2500, 1580, 1450, 700 cm^{-1}. ^1H NMR as free amine ($CDCl_3$) δ; 2.22 (3H, s), 2.27 (6H, s), 2.38 (1H, bs), 2.59 (1H, dd, J = 11.9, 3.7 Hz), 2.91 (1H, dd, J = 12.4, 3.7 Hz), 3.05 (1H, dd, J = 12.4, 8.1 Hz), 3.16 (1H, dd, J = 11.9, 3.7 Hz), 3.20 (1H, d, J = 12.4 Hz), 3.43 (1H, dd, J = 8.1, 3.7 Hz), 3.46 (1H, d, J = 12.4 Hz), 4.03 (1H, t, J = 3.7 Hz), 6.79 (2H, s), 7.20-7.53 (10H, m). *Anal.* Calcd for $C_{26}H_{30}N_2 \cdot HCl \cdot 1/4H_2O$: C, 75.89; H, 7.72; N, 6.81. Found: C, 75.94; H, 7.69; N, 6.67.

(2*R*,5*R*)-1-(2,2-Dimethylpropyl)-2,5-Diphenylpiperazine Monohydrochloride (9).

Pivaloyl chloride (0.5ml, 4mmol) was added dropwise to a solution of (2*R*,5*R*)-1-*tert*-butoxycarbonyl-2,5-diphenylpiperazine (0.51g, 1.5mmol) and triethylamine (0.6ml, 4mmol) in methylene chloride (10ml) at room temperature. The mixture was stirred for 30 min and washed successively with 10% aqueous potassium carbonate and potassium bisulfate solution and then concentrated. To the residue in methylene chloride (2ml) was added trifluoriacetic acid (1.5ml) and the mixture was stirred for 1 h at room temperature. The mixture was concentrated, basified with 10% aqueous potassium carbonate and extracted with methylene chloride. Borontrifluoride etherate (1.1ml, 8.9mmol) was added to the residue in THF (12ml) and the mixture was refluxed for 12 h. After cooling, water (5ml) was added and then concentrated. Aqueous HCl (18%, 10ml) was added to the residue and the mixture was refluxed for 1 h and then evaporated to leave the residue. The residue was made alkaline with 28% ammonia and extracted with methylene chloride. The residue was dissolved in a mixture of ethanol (5ml) and conc. HCl (1ml) and concentrated to give a crystalline residue. Recrystallization of the residue from ethanol-water gave the dihydrochloride (0.49g, 86%), mp 164-166 °C. *Anal.* Calcd for $C_{21}H_{28}N_2 \cdot 2HCl \cdot 1/4H_2O$: C, 65.63; H, 7.97; N, 7.26. Found: C, 65.67; H, 7.83; N, 7.36.

The monohydrochloride **9** was obtained by the same procedure as described for the preparation of **2**. Mp 156-158 °C. $[\alpha]_D^{25}$ -43.9 (c 0.46, $CHCl_3$). IR (KBr) 3300, 2950-2420, 1640, 1510, 730 cm^{-1}. ^1H NMR as free amine ($CDCl_3$) δ; 0.88 (9H, s), 1.73 (1H, bs), 2.25 (1H, d, *J* = 14.0 Hz), 2.36 (1H, d, *J* = 14.0 Hz), 2.66 (1H, dd, *J* = 12.3, 3.5 Hz), 3.23 (1H, dd, *J* = 12.3, 3.5 Hz), 3.31 (2H, d, *J* = 3.9 Hz), 3.64 (1H, t, *J* = 3.9 Hz), 4.05 (1H, dd, *J* = 8.6, 3.5 Hz), 7.20-7.66 (10H, m). *Anal.* Calcd for $C_{21}H_{28}N_2 \cdot HCl \cdot 1/4H_2O$: C, 72.18; H, 8.22; N, 8.02. Found: C, 72.56; H, 8.15; N, 8.20.

(2*R*,5*R*)-1-(3,3-Dimethylbutyl)-2,5-Diphenylpiperazine Monohydrochloride (10).

Starting from (2*R*,5*R*)-1-*tert*-butoxycarbonyl-2,5-diphenylpiperazine (0.51g, 1.5mmol) and *tert*-butylacetyl chloride (0.3g, 2.2mmol), the monohydrochloride **10** (0.37g, 67%) was obtained by the same procedure as described for the preparation of **9**. Mp 184-186 °C. $[\alpha]_D^{25}$ -34.8 (c 0.65, $CHCl_3$). IR (KBr) 3000-2350, 1640, 1550, 1510, 730 cm^{-1}. ^1H NMR as free amine ($CDCl_3$) δ; 0.76 (9H, s), 1.32 (1H, dt, *J* = 11.9, 5.0 Hz), 1.51 (1H, dt, *J* = 11.9, 5.0 Hz), 2.07 (1H, dt, *J* = 11.9, 5.0 Hz), 2.46 (1H, dt, *J* = 11.9, 5.0 Hz), 2.67 (1H, dd, *J* = 11.9, 4.0 Hz), 2.85-3.00 (2H, m), 3.33 (1H, dd, *J* = 11.9, 4.0 Hz), 3.46 (1H, dd, *J* = 6.7, 4.6 Hz), 4.13 (1H, t, *J* = 4.0 Hz), 7.20-7.55 (8H, m), 7.74 (2H, d, *J* = 6.9 Hz). *Anal.* Calcd for $C_{22}H_{30}N_2 \cdot HCl \cdot 1/4H_2O$: C, 72.70; H, 8.74; N, 7.71. Found: C, 72.73; H, 8.77; N, 7.66.

(2*R*,5*R*)-2,5-Diphenyl-1-Isopropylpiperazine Monohydrochloride (11).

Starting from (2*R*,5*R*)-1-*tert*-butoxycarbonyl-2,5-diphenylpiperazine (0.51g, 1.5mmol) and acetone (0.87g, 15 mmol), the monohydrochloride **11** (0.33g, 71%) was obtained by the same procedure as described for the preparation of **7**. Mp 118-120 °C. $[\alpha]_D^{25}$ -12.6 (c 1.0, $CHCl_3$). IR (KBr) 3350, 2950-2500, 1630, 1510, 1230, 730 cm^{-1}. ^1H NMR as free amine ($CDCl_3$) δ; 0.87 (3H, d, *J* = 6.8 Hz), 1.05 (3H, d, *J* = 6.8 Hz), 1.85 (1H, bs), 2.73 (1H, dd, *J* = 12.1, 3.6 Hz), 2.80-2.95 (3H, s), 3.34 (1H, dd, *J* = 11.8, 3.4 Hz), 3.66 (1H, dd, *J* = 8.8, 3.6 Hz), 4.15 (1H, t, *J* = 3.4 Hz), 7.15-7.45 (8H, m), 7.79 (2H, d, *J* = 7.0

Hz). *Anal.* Calcd for $C_{19}H_{24}N_2$•HCl•1/2H_2O: C, 70.03; H, 8.04; N, 8.60. Found: C, 69.94; H, 8.13; N, 8.70.

(2*R*,5*R*)-2,5-Diphenyl-1-(3-Phenylpropyl)piperazine Monohydrochloride (12). Starting from (2*R*,5*R*)-1-*tert*-butoxycarbonyl-2,5-diphenylpiperazine (0.33g, 1.0mmol) and hydrocinnamaldehyde (0.2g, 1.5mmol), the monohydrochloride **12** (0.24g, 62%) was obtained by the same procudure as described for the preparation of **7**. Amorphous. $[\alpha]_D^{25}$ -6.1 (c 0.66, $CHCl_3$). IR (KBr) 3000-2350, 1640, 1550, 1510, 730 cm^{-1}. ^1H NMR as free amine ($CDCl_3$) δ; 1.68-1.90 (1H, m), 1.96 (1H, m), 2.00-2.21 (1H, m), 2.35-2.72 (4H, m), 2.81-3.05 (2H, m), 3.35-3.50 (2H, m), 4.16 (1H, t, *J* = 3.9 Hz), 7.05-7.55 (13H, m), 7.75 (2H, d, *J* = 7.2 Hz). *Anal.* Calcd for $C_{25}H_{28}N_2$•HCl•1/4H_2O: C, 75.55; H, 7.36; N, 7.05. Found: C, 75.44; H, 7.42; N, 7.07.

(2*R*,5*R*)-2,5-Diphenyl-1-(9-Phenanthrenylmethyl)piperazine Monohydrochloride (13). Starting from (2*R*,5*R*)-1-*tert*-butoxycarbonyl-2,5-diphenylpiperazine (0.51g, 1.5mmol) and phenanthrene-9-carboxaldehyde (0.61g, 3.0 mmol), the monohydrochloride **13** was obtained by the same procedure as described for the preparation of **7**. Mp 160-162 °C. $[\alpha]_D^{25}$ -37.5 (c 0.4, $CHCl_3$). IR (KBr) 2950-2350, 1640, 1510, 730 cm^{-1}. ^1H NMR as free amine ($CDCl_3$) δ; 1.88 (1H, bs), 2.67 (1H, dd, *J* = 12.0, 3.9 Hz), 3.01 (1H, dd, *J* = 12.4, 3.7 Hz), 3.17 (1H, dd, *J* = 12.4, 8.2 Hz), 3.27 (1H, dd, *J* = 12.0, 3.9 Hz), 3.52 (1H, d, *J* = 13.3 Hz), 3.59 (1H, dd, *J* = 8.2, 3.7 Hz), 4.08 (1H, t, *J* = 3.9 Hz), 4.19 (1H, d, *J* = 13.3 Hz), 7.15-7.90 (16H, m), 8.28-8.52 (1H, m), 8.60-8.78 (2H, m). *Anal.* Calcd for $C_{31}H_{28}N_2$•HCl•1/2H_2O: C, 78.55; H, 6.38; N, 5.91. Found: C, 78.54; H, 6.26; N, 5.77.

1-Acetoxy-2-Methyl-3,4-Dihydronaphthalene. An aqueous solution of $HClO_4$ (70%, 0.12g, 0.8 mmol) was added to a solution of 2-methyltetralone (0.35g, 2.2 mmol) and acetic anhydride (1.0ml, 11mmol) in carbon tetrachloride (5.5 ml) at 0 °C, and the mixture was stirred for 2 h at room temperature. The reaction mixture was poured into ice-water, and extracted with diethyl ether. The residue was purified by silica gel flash column chromatography (eluent, *n*-hexane: diethyl ether = 20 : 1) to give pure 1-acetoxy-2-methyl-3,4-dihydronaphthalene (0.22g, 50%), mp 49-50 °C. IR (KBr) 2850, 1790, 1720, 1530, 1470, 1410, 1250, 1180, 1120, 800 cm^{-1}. ^1H NMR ($CDCl_3$) δ; 1.76 (3H, s), 2.32 (3H, s), 2.40 (2H, t, *J* = 8.2 Hz), 2.86 (2H, t, *J* = 8.2 Hz), 6.90-7.20 (5H, m). *Anal.* Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 7.01. Found: C, 77.06; H, 7.01.

The salts of the piperazine **1**, **15** - **19**, were obtained by the same procedure as described for the preparation of **2**.

(2*R*,5*R*)-2,5-Diphenylpiperazine Monoperchlorate (15). Mp 162-163 °C. $[\alpha]_D^{26}$ +6.8 (c 0.56, $CHCl_3$). ^1H NMR ($CDCl_3$) δ; 3.44 (2H, dd, *J* = 12.9, 6.2 Hz), 3.60 (2H, dd, *J* = 12.9, 3.5 Hz), 4.62 (2H, dd, *J* = 6.2, 3.5 Hz), 7.30-7.50 (6H, m), 7.65-7.82 (4H, m). *Anal.* Calcd for $C_{16}H_{18}N_2$•$HClO_4$: C, 56.72; H, 5.65; N, 8.27. Found: C, 56.97; H, 5.68; N, 8.23.

(2*R*,5*R*)-2,5-Diphenylpiperazine Monoacetate (16). Mp 101-103 °C. $[\alpha]_D^{25}$ -8.4 (c 0.76, $CHCl_3$). ^1H NMR ($CDCl_3$) δ; 2.06 (3H, s), 3.27 (4H, d, *J* = 4.8 Hz), 7.21-7.45 (6H, m), 7.61 (4H, d, *J* = 6.5 Hz). *Anal.* Calcd for $C_{16}H_{18}N_2 \cdot CH_3CO_2H$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.13; H, 7.53; N, 9.23.

(2*R*,5*R*)-2,5-Diphenylpiperazine Monohydrobromide (17). Mp 176-178 °C. $[\alpha]_D^{26}$ +4.7 (c 0.24, H_2O). ^1H NMR ($CDCl_3$) δ; 3.36 (2H, dd, *J* = 12.7, 6.4 Hz), 3.65 (2H, dd, *J* = 12.7, 3.2 Hz), 4.69 (2H, dd, *J* = 6.4, 3.2 Hz), 5.13 (3H, bs), 7.26-7.50 (6H, m), 7.73 (4H, d, *J* = 6.2 Hz). *Anal.* Calcd for $C_{16}H_{18}N_2 \cdot HBr \cdot 1/4H_2O$: C, 59.36; H, 6.07; N, 8.65. Found: C, 59.55; H, 5.93; N, 8.71.

(2*R*,5*R*)-2,5-Diphenylpiperazine (*S*)-(-)-Methoxytrifluoromethylphenyl Monoacetate (18). Amorphous. $[\alpha]_D^{25}$ -53.3 (c 1.4, $CHCl_3$). ^1H NMR ($CDCl_3$) δ; 3.05-3.33 (4H, m), 3.49 (3H, s), 4.31 (2H, t, *J* = 3.9 Hz), 5.45 (3H, bs), 7.10-7.80 (15H, m). *Anal.* Calcd for $C_{16}H_{18}N_2 \cdot C_{10}H_9O_3F_3$: C, 66.09; H, 5.76; N, 5.93. Found: C, 65.94; H, 5.81; N, 5.87.

(2*R*,5*R*)-2,5-Diphenylpiperazine (*R*)-(+)-Methoxytrifluoromethylphenyl Monoacetate (19). Amorphous. $[\alpha]_D^{25}$ +12.3 (c 1.2, $CHCl_3$). ^1H NMR ($CDCl_3$) δ; 3.10-3.35 (4H, m), 3.53 (3H, s), 4.32 (2H, t, *J* = 3.7 Hz), 5.31 (3H, bs), 7.10-7.75 (15H, m). *Anal.* Calcd for $C_{16}H_{18}N_2 \cdot C_{10}H_9O_3F_3$: C, 66.09; H, 5.76; N, 5.93. Found: C, 66.36; H, 5.92; N, 6.17.

General Procudure for Asymmetric Protonation. Methyl lithium (1.0ml in *n*-hexane, 1.0mmol) was added to a stirred solution of 1-acetoxy-2-benzylcyclohexene (121mg, 0.53 mmol) in diethyl ether (6ml) at 0 °C and the mixture was stirred for 30 min at room temperature. The lithium enolate solution (1.5ml) thus obtained was added slowly to a solution of 2 (92mg, 0.34 mmol) in diethyl ether (2ml) and methylene chloride (2ml) at -78 °C. The mixture was stirred for 1 h at the same temperature and then gradually warmed to room temperature. The reaction mixture was quenched with the phosphate buffer (pH = 6.8) and extracted with diethyl ether. The residue obtained was purified by preparative TLC to give 2 (18.6mg, 89%).

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