# Chiral Piperazines as Catalysts for the Enantioselective Addition of Diethylzinc to Aldehydes

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**Enantioselective ethylation of benzaldehyde with diethylzinc in the presence of a catalytic amount of chiral piperazine derivatives was investigated. The chiral piperazine works as an asymmetric catalyst in the alkylation, yielding 1-phenylpropanol with a moderate enantioselectivity. The influence of structural variation of the piperazine ring upon the asymmetric induction and the mechanism involved are discussed.**

**Keywords** chiral piperazine; asymmetric alkylation; chiral catalyst; diethylzinc; enantioselective addition

Carbon–carbon bond formation is one of the most fundamental and important organic transformations. Realization of this process in enantioselective and catalytic fashion remains a challenging goal for the organic chemist. In 1984, Oguni and Omi found that aldehydes could be alkylated enantioselectively with dialkylzinc in the presence of a catalytic amount of chiral β-amino alcohols to give optically active alcohols.[1] Subsequently, a number of research groups have investigated the catalytic asymmetric alkylation of aldehydes[2] with dialkylzinc by employing various kinds of chiral ligands,[3] including chiral amino alcohols,[4,5] diols,[6] diamines,[7,8] α-amino acid amide,[9] some kinds of tridentate ligands[10] and the ligands complexed with titanium metal.[11] Effective catalytic systems are now available and the methodology has opened up a route for the efficient synthesis of secondary aliphatic and aromatic alcohols especially those carrying ethyl, methyl, vinyl and alkynyl groups, in high optical purity.[12] Furthermore, the catalyst system was successfully applied to the enantioselective catalytic conjugate addition to enones,[13] allowing the production of optically active β-alkylated carbonyl compounds, and also extended to asymmetric amplification with *N,N*-disubstituted tertiary β-amino alcohols possessing a bulky *tert*-butyl group on the carbon bonded to the hydroxyl.[14]

In the course of our studies to find an efficient chiral ligands for enantioselective organic transformations, we recently reported the stoichiometric asymmetric osmylation[15] of unactivated olefins by using novel polyamine ligands of bispiperazine structure as well as asymmetric protonation utilizing chiral piperazine hydrochlorides.[16] In this paper, we describe our results on catalytic asymmetric alkylation of aldehydes with dialkylzinc in the presence of a catalytic amount of chiral piperazine ligands of type **1** bearing two phenyl groups at C-2 and C-5 (Fig. 1), which were easily derived from the corresponding phenylglycine.

Aldehydes or ketones are generally inert to dialkylzinc of *sp*-hybridized linear geometry, but the presence of an effective ligand allows the addition to occur (ligand-accelerated reaction).[2] It is believed that chiral β-amino alcohols or 1,2-diamine ligands accelerate the reaction (nonlinear effect) and cause asymmetric induction through formation of a five-membered ring, which consists of an aldehyde and two molecules of dialkylzinc, in the transition state (two zinc species mechanism).[2,4g] In this context, a chiral piperazine derivative might be a promising candidate for a catalytic ligand in asymmetric alkylation, since the piperazine ring is cyclic and rigid, having an inherent 1,2-diamino functionality within a six-membered ring. To our knowledge, in spite of ready accessability of both enantiomeric forms, chiral piperazine derivatives have only recently been used as chiral auxiliaries in asymmetric alkylation.[17,18] (2*S*,5*S*)-Diisopropylpiperazine and its dilithium salt (**2**) were successfully used for the catalytic asymmetric alkylation of aldehydes with dialkylzinc by Soai *et al.*,[17] while Shono *et al.*[18] effectively synthesized chiral tri- and tetra-substituted piperazines from chiral 1,2-diamines through the electroreductive method and used them for the same reaction.

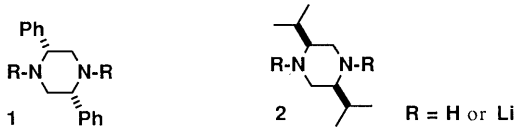



Fig. 1

## Results and Discussion

According to the procedure reported in the literature,[17] a basic piperazine compound possessing $C_2$ symmetry, (2*R*,5*R*)-diphenylpiperazine (**3**), was prepared from (*R*)-(−)-phenylglycine and used as a catalyst in the addition reaction of diethylzinc to benzaldehyde (Chart 1). The reaction was initiated at 0 °C for 1 h and the mixture was allowed to stand at ambient temperature for 19 h. The progress of the reaction was monitored by TLC analysis. Toluene was found to be essential as a solvent for the addition to benzaldehyde. The optical yield of 1-phenylpropanol was determined by comparison of the value and sign of the optical rotation with the reported values.[19] Although the main product was the desired 1-phenylpropanol, the recovery of the starting materials as well as the formation of benzyl alcohol and benzoic acid arising from disproportionation could not be avoided. These results are summarized in Table I. The chiral ligand employed as the catalyst could be recovered unchanged from the mixture. It was reported that the dilithium salt of a chiral piperazine derivative was a highly enantioselective catalyst for ethylation of benzaldehyde.[17] In our experiments, the addition of *n*-butyl lithium to the ligand slightly improved both the chemical and optical yields (entries 2 and 4). Subsequently, the mono-*N*-methyl derivative **4**[16] was examined and much better chemical and optical yields were observed with **4**. In sharp contrast to the above results, the

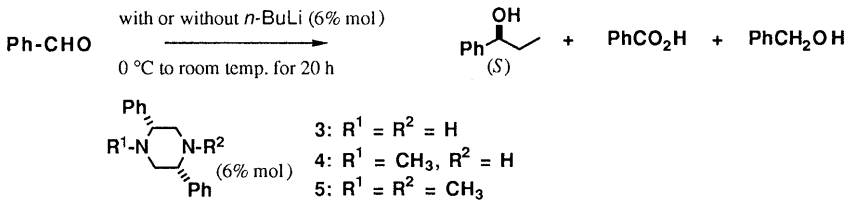



Chart 1

TABLE I. Enantioselective Ethylation of Benzaldehyde with Diethylzinc in the Presence of **3**, **4** or **5**

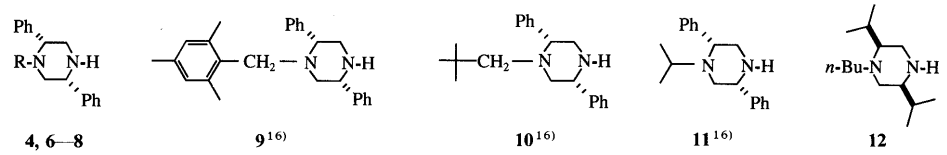
| Entry | Chiral catalyst | Additive | 1-Phenylpropanol | | | Benzyl alcohol (%)[c] | Benzoic acid (%)[c] | Benzaldehyde (%)[c] |
|---|---|---|---|---|---|---|---|---|
| | | | Chemical yield (%)[a] | %ee[b] | Config.[b] | | | |
| 1 | **3** | None | 22 | 16 | *S* | 18 | 12 | 12 |
| 2 | **3** | *n*-BuLi | 38 | 22 | *S* | 9.5 | 9.3 | 7.3 |
| 3 | **4** | None | 46 | 46 | *S* | 15 | 6.4 | 6.2 |
| 4 | **4** | *n*-BuLi | 59 | 41 | *S* | 14.5 | 9.4 | 9.4 |
| 5 | **5** | None | 32.5 | 1.6 | *S* | 17.7 | 20.5 | 10 |

*a*) Isolated yield. *b*) Based on the reported value[19] of $[\alpha]_D$ −45.45 ($c$=5.15, $CHCl_3$) for (*S*)-1-phenylpropanol. *c*) Determined by $^1$H-NMR analysis.

TABLE II. Asymmetric Addition of Diethylzinc to Benzaldehyde Catalyzed by Mono-*N*-alkylated Chiral Piperazines **4**, **6**—**12**

| Entry | Chiral catalyst[a] | Additive[a] | 1-Phenylpropanol | | | Benzyl alcohol (%)[e] | Benzoic acid (%)[e] | Benzaldehyde (%)[e] |
|---|---|---|---|---|---|---|---|---|
| | | | Chemical yield (%)[c] | %ee[d] | Config.[d] | | | |
| 1 | **4**: R=$CH_3$ | None | 46 | 46 | *S* | 15.0 | 6.4 | 6.2 |
| 2 | **4**: R=$CH_3$ | *n*-BuLi | 59 | 41 | *S* | 14.5 | 9.4 | 9.4 |
| 3 | **6**: R=$C_2H_5$ | *n*-BuLi | 37 | 9.3 | *R* | 17 | −0 | 8 |
| 4 | **7**: R=*n*-Bu | *n*-BuLi | 59 | 27 | *R* | 14 | 11.2 | 4.7 |
| 5 | **8**: R=$CH_2Ph$ | None | 15 | 5 | *R* | 15 | 15 | 15 |
| 6 | **8**: R=$CH_2Ph$ | *n*-BuLi | 45 | 27.4 | *R* | 18 | 18 | 9 |
| 7 | **9** | *n*-BuLi | 21 | 10.6 | *R* | 18 | 18 | 6.5 |
| 8 | **10** | *n*-BuLi | 30 | 6.7 | *R* | 19 | 30 | 5 |
| 9 | **11** | *n*-BuLi | 30 | 18.4 | *R* | — | — | — |
| 10 | **12** | *n*-BuLi | 31 | 48 | *R* | 19 | — | — |

*a*) The following ligands, **4** (6% mol), **6**—**12** (8% mol each), were used for the reaction.




**4**, **6**—**8** **9**[16] **10**[16] **11**[16] **12**

*b*) *n*-BuLi (8%mol) was used. *c*) Isolated yield. *d*) Based on the reported value[19] of $[\alpha]_D$ −45.45 ($c$=5.15, $CHCl_3$) for (*S*)-1-phenylpropanol. *e*) Determined by $^1$H-NMR.

*N*,*N*′-dimethyl derivative **5**[16] afforded a poor enantioselectivity. Judging from the amount of the by-product due to disproportion reaction, the *N*,*N*′-disubstituted piperazine may not sufficiently activate the addition reaction of diethylzinc (entry 5), whereas mono-*N*-substituted piperazine derivatives are effective catalysts.

Subsequently, several mono-*N*-alkylated compounds were prepared and the effect of the *N*-substituent of the catalyst on asymmetric induction was investigated. The synthesis of the chiral ligands involved reductive alkylation of the monosubstituted derivatives with a *tert*-butoxycarbonyl group. Seven chiral *N*-monoalkylated piperazine derivatives having *N*-substituents of different size and nature were examined and the results are summarized in Table II. Unfortunately, this type of chiral ligand did not give a significant improvement in ee and reactivity, in fact, these ligands **6**—**11** exert a topologically reversed bias, resulting in preferential formation of (*R*)-1-phenylpropanol. This implies that introduction of substituents bigger than an ethyl group on one of the nitrogen atoms can alter the steric course of the addition reaction without changing the absolute configuration of the substituent on the parent piperazine ring. For comparison, the piperazine derivative **12** bearing different substituents from those of compounds **5**—**11** at C-2 and C-5 was examined, because a closely related compound **2**, substituted with isopropyl groups, was reported as an excellent catalyst by Soai and coworkers.[17] Compared with **7**, a better optical yield was obtained with **12** (entries 4 and 10). It is clear that the nature of the substituent on the piperazine ring exerts a significant in-

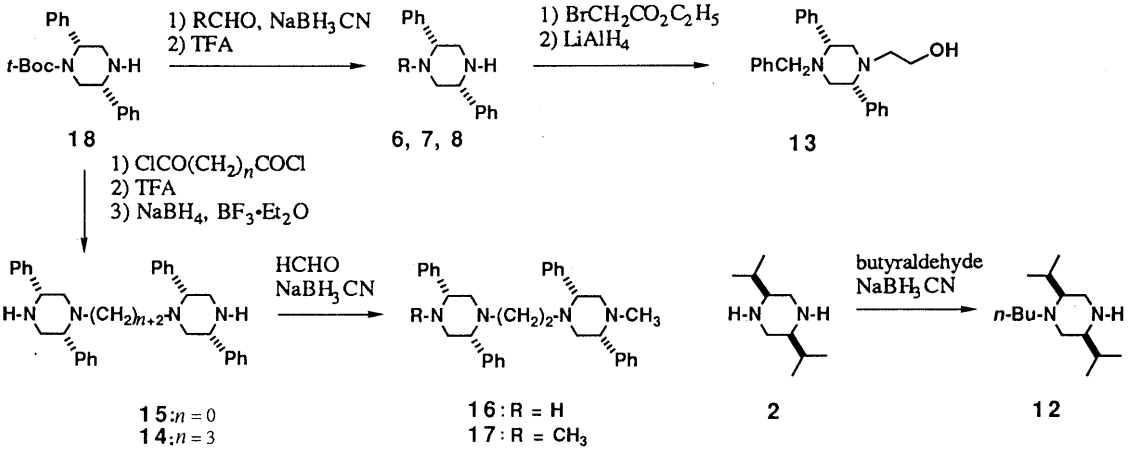


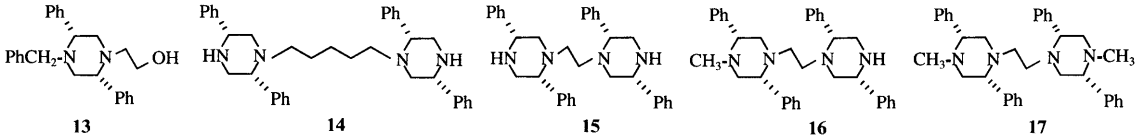

Chart 2

TABLE III. Addition[a] of Diethylzinc to Benzaldehyde Catalyzed by the Flexible Piperazine Ligands **13**—**17**

| Entry | Chiral ligand[b] | 1-Phenylpropanol | | |
|---|---|---|---|---|
| | | Chemical yield (%) | %ee[c] | Configuration[c] |
| 1 | **13** | 26.4 | 13.0 | *S* |
| 2 | **14** | 54 | 26 | *R* |
| 3 | **15** | 52 | 28 | *S* |
| 4 | **16** | 32 | −0 | — |
| 5 | **17** | 34 | 6 | *S* |

*a*) Reaction was carried out in toluene at room temperature for 20 h in the presence of 8 % mol each of the ligand and *n*-BuLi.

*b*)



**13** **14** **15** **16** **17**

*c*) Based on the reported value[19] of $[\alpha]_D$ −45.45 ($c$=5.15, $CHCl_3$) for (*S*)-1-phenylpropanol.

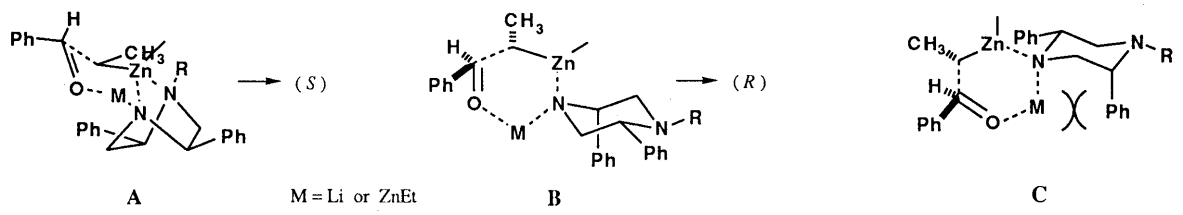



Fig. 2. Possible Transition State Models for Preferential Formation of (*S*) or (*R*)-1-Phenylpropanol

fluence upon asymmetric induction on 1-phenylpropanol.

The chiral piperazine catalysts so far used are cyclic and rigid compounds. Next, we examined chiral piperazine ligands having a slightly flexible and tri- or tetradentate character. The ligands, **13**—**17**, were prepared from **18** (Chart 2) and used for asymmetric alkylation under the same reaction conditions. The first one **13** has an ethanolamine structural unit and the remaining derivatives **14**—**17** are of bispiperazine structure with two piperazine rings connected through a linker arm of five or two carbons. A derivative closely related to the latter type of compounds serves as an excellent stoichiometric ligand in asymmetric osmylation of olefins.[15] The results obtained with small amounts of these ligands are shown in Table III. As can be seen from the table, the expected high asymmetric induction was not realized.

The stereochemical outcome of asymmetric alkylation has been generally interpreted by consideration of a cyclic transition state assembly. The mechanism in the presence of chiral amino alcohols was well investigated in connection with crystallographic analysis of the complexes by Noyori and coworkers.[2,4g] Namely, the reaction proceeds *via* the dinuclear zinc complex and the chirality of the 5/4-fused bicyclic intermediates determines the chirality of the alcoholic products.

For our piperazine-promoted asymmetric induction, we postulate the transition state model shown in Fig. 2, based on a six-center mechanism[20] rather than the mechanism through the 5/4-fused bicyclic intermediate. Thus, diethylzinc may be chelated with two nitrogens of the piperazine ring in a boat conformation with two phenyl substituents in the *pseudo*-equatorial conformation. Benzaldehyde approaches from the less hindered face so as to avoid interaction with the phenyl group of the piperazine ring,

resulting in a six-membered transition state A (six-center mechanism). Thus, the *S*-alcohol is produced from this complex. On the other hand, when the ligand has a bulkier *N*-alkyl substituent than the ethyl group, increasing steric repulsion between the *N*-substituent and the methyl group in the chair-form six-membered ring including the zinc metal and the aldehyde, prohibits a transition state like A, leading to another transition state B, in which the piperazine ring can adopt either chair or boat conformation. The zinc chelation should occur at the unsubstituted nitrogen vicinal to the axially oriented phenyl group, because of the severe 1,3-diaxial interaction in the alternative model C. The degree of asymmetric induction is not susceptible to the bulkiness and nature of the *N*-substituents, if the reaction proceeds *via* transition state B. These considerations are consistent with the obtained results and lead to the observed absolute stereochemistry for 1-phenylpropanol, except for that with ligand **12**. Recently, a similar transition state model was proposed by Soai and coworkers.[17]

## Conclusion

In summary, the present study revealed that chiral piperazines of type **1**, both enantiomeric forms of which can be easily derived from commercially available phenylglycine, served as catalysts in the enantioselective addition of diethylzinc to benzaldehyde. Beside the absolute configuration of the substituents on the piperazine ring, the existence of the *N*-substituent has a decisive effect in controlling the enantioselectivity of the reaction. These observations can be explained in terms of a transition state model based on a six-center mechanism.

### Experimental

Melting points were determined with Yanagimoto melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on a JASCO A-202 spectrophotometer. Proton nuclear magnetic resonance ($^1$H-NMR) spectra were taken with a Varian Gemini 200 or Bruker AC-200 (200 MHz) in chloroform-*d* with chemical shifts being reported as $\delta$ ppm from tetramethylsilane as an internal standard; couplings are expressed in hertz. Optical rotations were recorded on a Horiba SEPA-200 polarimeter. Flash column chromatography was conducted on Silica gel 60 and Silica gel GF254 plates (E. Merck) were used for preparative TLC. All reactions employing dry solvents were run under argon or nitrogen. Toluene 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-Benzyl-2,5-diphenylpiperazine (8) and Its Dihydrochloride** Acetic acid (0.26 ml, 4.5 mmol) was added to a stirred mixture of **18**[15] (0.51 g, 1.5 mmol), benzaldehyde (0.48 g, 4.5 mmol), $NaBH_3CN$ (0.28 g, 4.5 mmol) and methanol (15 ml) at 0 °C. The mixture was stirred for 2 h at room temperature and then evaporated. The residue was basified with aqueous 10% $K_2CO_3$ solution and extracted with ethyl acetate. The organic layer was dried and evaporated to give the residue, which was treated with trifluoroacetic acid (2 ml) and $CH_2Cl_2$ (2 ml) for 1 h at room temperature and then concentrated. The resulting residue was made alkaline and extracted with ethyl acetate in the same manner as above to afford crude **8**. Ethanol (5 ml) and concentrated HCl (1 ml) were added to the crude **8** and evaporated. Diethyl ether was added to the residue and the resulting precipitates were collected by filtration. Recrystallization from a mixture of ethanol and water gave **8**·2HCl (0.44 g, 73% yield) as a white powder of mp 149—151 °C. IR (KBr) *v*: 3100—2300, 1460, 695 cm$^{-1}$. *Anal.* Calcd for $C_{23}H_{24}N_2 \cdot 2HCl \cdot 1/4H_2O$: C, 68.06; H, 6.59; N, 6.90. Found: C, 68.08; H, 6.53; N, 6.90. **8**: $[\alpha]_D^{21}$ +67.4 ($c$=0.67, $CHCl_3$). $^1$H-NMR $\delta$: 2.26 (1H, br s), 2.57 (1H, dd, $J$=12.1, 4.0 Hz), 2.83—3.03 (3H, m), 3.26 (1H, dd, $J$=12.1, 3.7 Hz), 3.47 (1H, dd, $J$=12.4, 4.1 Hz), 3.76 (1H, d, $J$=13.2 Hz), 4.10 (1H, t, $J$=3.7 Hz), 7.15—7.42 (11H, m), 7.53 (2H, d, $J$=12.1 Hz), 7.60 (2H, d, $J$=12.1 Hz).

**(2*R*,5*R*)-2,5-Diphenyl-1-ethylpiperazine (6) and Its Dihydrochloride** Starting from **18** (0.38 g, 1.1 mmol) and acetaldehyde (0.30 ml, 5.4 mmol), **6**·2HCl (0.26 g) was obtained by the same procedure as described for the preparation of **8**·2HCl in 68% yield. mp 170—172 °C. IR (KBr) *v*: 3000—2350, 1460, 695 cm$^{-1}$. *Anal.* Calcd for $C_{28}H_{22}N_2 \cdot 2HCl \cdot 1/4H_2O$: C, 62.88; H, 7.18; N, 8.15. Found: C, 63.08; H, 7.04; N, 8.19. **6**: $[\alpha]_D^{21}$ −31.2 ($c$=2.68, $CHCl_3$). $^1$H-NMR $\delta$: 1.03 (3H, t, $J$=7.2 Hz), 1.90 (1H, br s), 2.03—2.22 (1H, m), 2.40—2.61 (1H, m), 2.66 (1H, dd, $J$=11.9, 3.9 Hz), 2.81—2.99 (2H, m), 3.30—3.51 (2H, m), 4.15 (1H, t, $J$=3.9 Hz), 7.20—7.53 (8H, m), 7.77 (2H, d, $J$=8.7 Hz).

**(2*R*,5*R*)-1-Butyl-2,5-diphenylpiperazine (7) and Its Dihydrochloride** Starting from **18** (0.45 g, 1.3 mmol) and butyraldehyde (0.4 ml, 4.4 mmol), **7**·2HCl (0.36 g) was obtained by the same procedure as described for the preparation of **8**·2HCl in 73% yield. mp 133—135 °C. IR (KBr) *v*: 3000—2400, 1460, 690 cm$^{-1}$. *Anal.* Calcd for $C_{23}H_{24}N_2 \cdot 2HCl \cdot 1/4H_2O$: C, 64.60; H, 7.72; N, 7.53. Found: C, 64.49; H, 7.68; N, 7.51. **7**: $[\alpha]_D^{21}$ −39.7 ($c$=1.93, $CHCl_3$). $^1$H-NMR $\delta$: 0.82 (3H, t, $J$=7.1 Hz) 1.05—1.60 (4H, m), 1.75—2.50 (2H, m), 2.35—2.52 (1H, m), 2.62 (1H, dd, $J$=11.9, 3.9 Hz), 2.80—2.98 (2H, m), 3.25—3.50 (2H, m), 4.14 (1H, t, $J$=3.9 Hz), 7.20—7.52 (8H, m), 7.74 (2H, d, $J$=7.0 Hz).

**(2*R*,5*R*)-1-Benzyl-2,5-diphenyl-4-(2-hydroxyethyl)piperazine (13)** Ethyl bromoacetate (57 $\mu$l, 0.51 mmol) was added to a stirred solution of **8** (0.14 g, 0.43 mmol) and triethylamine (69 $\mu$l, 0.51 mmol) in benzene (3 ml) at 80 °C and the resulting mixture was refluxed for 6 h with stirring. After cooling, the reaction mixture was poured into ice-water and extracted with ethyl acetate. The ethyl acetate solution was dried and evaporated to give the residue, which was mixed with diethyl ether (3 ml) and lithium aluminum hydride (87 mg, 2.3 mmol). The mixture was refluxed with stirring for 2 h and then cooled to 0 °C. The excess reagent was decomposed with water (0.4 ml) and 15% aqueous NaOH (0.3 ml), the resulting precipitate was filtered off. The washings and filtrate were combined and concentrated to dryness. The residue was purified by preparative TLC with ethyl acetate–*n*-hexane (1 : 1) to furnish **13** (0.12 g, 76% yield) as a white powder, mp 90—91 °C. $[\alpha]_D^{27}$ +45.0 ($c$=0.8, $CHCl_3$). IR (KBr) *v*: 3420, 2800, 1500, 710 cm$^{-1}$. $^1$H-NMR $\delta$: 2.35—2.73 (5H, m), 2.97 (1H, dd, $J$=12.3, 8.6 Hz), 3.03 (1H, dd, $J$=12.0, 8.6 Hz), 3.11 (1H, dd, $J$=12.0, 3.9 Hz), 3.44—3.85 (5H, m), 7.10—7.52 (11H, m), 7.55—7.80 (4H, m). *Anal.* Calcd for $C_{25}H_{28}N_2O$: C, 80.61; H, 7.58; N, 7.52. Found: C, 80.76; H, 7.72; N, 7.43.

**1,1′-Ethylenebis[(2*R*,5*R*)-2,5-diphenylpiperazine] (15)** Oxalyl chloride (0.8 ml, 9.2 mmol) was added dropwise to a suspension of **18** (5.2 g, 15 mmol) and $K_2CO_3$ (3.2 g, 23 mmol) at 0 °C and the mixture was stirred for 30 min at room temperature. The mixture was made acidic with 5% HCl and extracted with $CH_2Cl_2$. The $CH_2Cl_2$ extract was dried and evaporated. To the residue were added $CH_2Cl_2$ (20 ml) and trifluoroacetic acid (20 ml), and the mixture was stirred for 1 h at room temperature. The mixture was then concentrated, made alkaline with 10% aqueous $K_2CO_3$ solution and extracted with ethyl acetate. The extract was dried and evaporated to afford the residue, which was dissolved in tetrahydrofuran (THF) (160 ml). Boron trifluoride etherate (25 ml, 0.2 mol) and $NaBH_4$ (5.7 g, 0.15 mol) were added to the solution at 0 °C and the whole solution was refluxed for 12 h. After cooling, the mixture was poured into water (50 ml) and concentrated. The residue was mixed with 18% HCl (50 ml), refluxed for 1 h, and then evaporated to give the residue, which was basified with 28% ammonium hydroxide and extracted with $CH_2Cl_2$. The $CH_2Cl_2$ layer was dried and evaporated, and the resulting residue was dissolved in a mixture of ethanol (50 ml) and concentrated HCl (5 ml). Concentration of the mixture gave a crystalline residue, which was recrystallized from water to yield the pure hydrochloride of **15**. The crystals were suspended in water, made alkaline with 10% aqueous $K_2CO_3$ solution and then extracted with ethyl acetate. The ethyl acetate solution was dried and evaporated to give **15** (3.1 g) in 86% yield as a colorless amorphous solid. $[\alpha]_D^{21}$ −27.6 ($c$=1.6, $CHCl_3$). IR (KBr) *v*: 2800, 1500, 1455, 700 cm$^{-1}$. $^1$H-NMR $\delta$: 1.84 (2H, br s), 2.05—2.22 (2H, m), 2.48—2.70 (4H, m), 2.81—3.00 (4H, m), 3.22 (2H, dd, $J$=11.8, 4.2 Hz), 3.35 (2H, dd, $J$=6.8, 4.2 Hz), 4.07 (2H, t, $J$=4.2 Hz), 7.10—7.45 (16H, m), 7.73 (4H, d, $J$=6.6 Hz). *Anal.* Calcd for $C_{34}H_{38}N_4 \cdot 1/4H_2O$: C, 80.51; H, 7.65; N, 11.05. Found: C, 80.37; H, 7.69; N, 11.00.

**1,1′-Pentamethylenebis[(2*R*,5*R*)-2,5-diphenylpiperazine] (14)** Starting from **18** (0.71 g, 2.1 mmol) and glutaryl dichloride (0.2 g, 1.2 mmol), **14** (0.45 g) was obtained in 79% yield as a colorless amorphous solid by the same procedure as described for the preparation of **15**. $[\alpha]_D^{21}$ −45.0 ($c$=2.7, $CHCl_3$). IR (KBr) *v*: 3000—2200, 1460, 710 cm$^{-1}$. $^1$H-NMR $\delta$: 1.05—1.52 (6H, m), 1.85—2.05 (4H, m), 2.28—2.46 (2H, m), 2.56 (2H, dd, $J$=11.8, 4.0 Hz), 2.77—2.95 (4H, m), 3.27—3.39 (4H, m), 4.11 (2H, t, $J$=4.0 Hz),

7.15—7.50 (16H, m), 7.67—7.77 (4H, m). **14**·4HCl: *Anal.* Calcd for $C_{37}H_{44}N_4 \cdot 4HCl \cdot 1/2H_2O$: C, 63.52; H, 7.06; N, 8.01. Found: C, 63.17; H, 6.83; N, 8.08.

**(2*R*,5*R*)-1-[2-[(2*R*,5*R*)-2,5-Diphenylpiperazinyl]]ethyl-4-methyl-2,5-diphenylpiperazine (16) and 1,1′-Ethylenebis[(2*R*,5*R*)-4-methyl-2,5-diphenylpiperazine] (17)** Acetic acid (67 μl, 1.2 mmol) was added to a stirred mixture of **15** (0.36 g, 0.72 mmol), 37% formalin (76 μl, 1.0 mmol), $NaBH_3CN$ (67 mg, 1.1 mmol) and methanol (5 ml) at 0 °C. The mixture was stirred for 1 h at room temperature and evaporated. The residue was basified with 10% aqueous $K_2CO_3$ solution and extracted with ethyl acetate. The organic layer was dried and evaporated. The residue was purified by preparative TLC with ethyl acetate–methanol (10 : 1) to afford **16** (160 mg) and **17** (83 mg) as colorless amorphous solids in 43% and 22% yield, respectively.

**16**: $[\alpha]_D^{27}$ −46.8 ($c$=1.1, $CHCl_3$). IR (KBr) $\nu$: 2950, 2800, 1460, 710 $cm^{-1}$. $^1$H-NMR $\delta$: 1.96 (1H, br s), 2.09 (3H, s), 2.05—2.30 (2H, m), 2.45—2.95 (9H, m), 3.36—3.52 (3H, m), 3.61 (1H, t, $J$=4.1 Hz), 4.10 (1H, t, $J$=3.9 Hz), 7.10—7.45 (14H, m), 7.46—7.65 (4H, m), 7.78 (2H, d, $J$=6.9 Hz). *Anal.* Calcd for $C_{35}H_{40}N_4 \cdot 1/2H_2O$: C, 79.96; H, 7.86; N, 10.66. Found: C, 79.84; H, 7.61; N, 10.38.

**17**: $[\alpha]_D^{20}$ −63.5 ($c$=1.0, $CHCl_3$). IR (KBr) $\nu$: 2800, 1490, 1450, 700 $cm^{-1}$. $^1$H-NMR $\delta$: 2.08 (6H, s), 2.15—2.28 (2H, m), 2.46—2.68 (6H, m), 2.83 (2H, dd, $J$=11.8, 6.6 Hz), 2.97 (2H, dd, $J$=11.8, 5.9 Hz), 3.46—3.63 (4H, m), 7.10—7.78 (20H, m). *Anal.* Calcd for $C_{36}H_{42}N_4 \cdot 1/4H_2O$: C, 80.78; H, 8.00; N, 10.47. Found: C, 80.87; H, 8.06; N, 10.51.

**(2*S*,5*S*)-1-Butyl-2,5-diisopropylpiperazine (12) and Its Dihydrochloride** Acetic acid (36 μl, 0.63 mmol) was added to a mixture of (2*S*,5*S*)-2,5-diisopropylpiperazine dihydrochloride (0.10 g, 0.41 mmol), butyraldehyde (39 mg, 0.54 mmol), $NaBH_3CN$ (36 mg, 0.57 mmol) and methanol (2 ml) at 0 °C. The mixture was stirred for 1 h at room temperature, then concentrated, made alkaline with 10% aqueous $K_2CO_3$ solution and extracted with $CH_2Cl_2$. The $CH_2Cl_2$ extract was dried and evaporated. The residue was mixed with ethanol (2 ml) and concentrated HCl (0.2 ml) and evaporated to leave the crystalline residue, which was recrystallized from ethanol–diethyl ether to furnish **12**·2HCl (52 mg) as colorless prisms in 42% yield, mp 175—177 °C. $[\alpha]_D^{21}$ −5.8 ($c$=0.45, methanol). IR (KBr) $\nu$: 3000—2400, 1595, 1470 $cm^{-1}$. *Anal.* Calcd for $C_{14}H_{30}N_2 \cdot 2HCl \cdot 1/2H_2O$: C, 54.54; H, 10.79; N, 9.09. Found: C, 54.18; H, 10.41; N, 8.95. **12**: $^1$H-NMR $\delta$: 0.80—1.10 (15H, m), 1.20—1.50 (4H, m), 1.58—1.80 (2H, m), 1.91—1.99 (1H, m), 2.08—2.30 (1H, m), 2.35—2.58 (3H, m), 2.63—2.95 (4H, m).

**General Procedure for Addition of Diethylzinc to Benzaldehyde** A solution of *n*-butyllithium (58 μl, in 1.52 M *n*-hexane solution, 88 μmol) was added to a solution of **7** (22 mg, 87 μmol) in toluene (6 ml) at 0 °C and the mixture was stirred for 10 min at the same temperature. A solution of diethylzinc in *n*-hexane (3.1 ml of 1 M solution, 3.1 mmol) was added to the mixture and the whole was stirred for 30 min at room temperature. After the mixture was cooled to 0 °C, benzaldehyde (0.15 ml, 1.5 mmol) was added and the resulting mixture was stirred for 20 h at room temperature. The mixture was cooled and the reaction was quenched by addition of 10% HCl (5 ml), then the whole was extracted with $CH_2Cl_2$. The organic extract was dried and evaporated. The resulting residue was purified by preparative TLC with $CH_2Cl_2$ to give 1-phenylpropanol (116 mg) in 59% yield. The optical yield of 1-phenylpropanol was determined by comparison of the value and sign of the specific rotation with the reported data.[19]

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