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A Simple Method of Synthesis of (±)-2,3-Diarylpiperazines and a Novel Method of Resolution of (±)-2,3-Diphenylpiperazine

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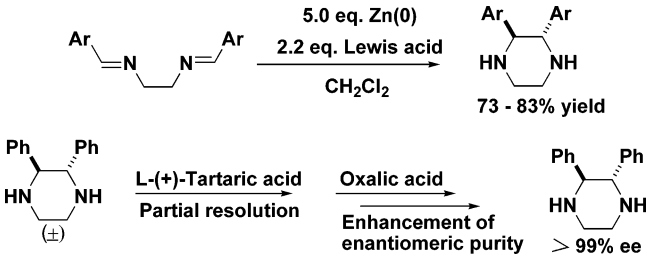
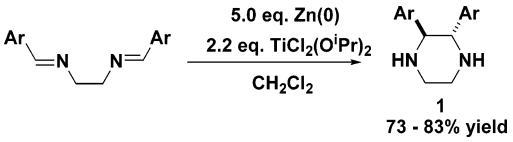


Intramolecular reductive coupling of diimines in the presence of Zn/Ti(O^{i}Pr)$_2$Cl$_2$ gives the corresponding (±)-2,3-diarylpiperazines in 73−83% yields with *dl*/*meso* ratio >99%:<1%. The (±)-2,3-diphenylpiperazine obtained in this way was readily resolved partially using L-(+)-tartaric acid, and the enantiomeric purity was enhanced to >99% ee via preparation of hydrogen-bonded salt aggregates using oxalic acid.

Piperazine moieties are found in a large number of biologically active compounds.[1] A recent molecular docking study of estrogenically active compounds with 1,2-diarylethane and 1,2-diarylethene pharmacophores reveals that the 2,3-diarylpiperazines are potentially active estrogen receptor modulators.[2] In addition, the piperazine derivatives were also used as chiral ligands in asymmetric catalysis.[3] Hence, a method of preparation of enantiomerically pure 2,3-diarylpiperazine derivatives is desirable. Though, the 2,5-disubstituted piperazines can be synthesized via the reduction of the corresponding diketopiperazines,[4] it is much more difficult to access the 2,3-disubstituted piperazines, which have been predicted to have interesting biological activity.[1f,2] Generally, intermolecular reductive dimerization of imines are carried out using Mn^0,[5] Mg^0,[6] alkali metal,[6] photolysis,[7] other metal reductants,[8−15] electrochemistry,[16] and low-valent titanium reagents.[17] However, very few methods give *dl* products in good yields.[5,16] Herein, we report a diastereoselective synthesis of (±)-*trans*-2,3-disubstituted piperazines **1** using the Ti(O^{i}Pr)$_2$Cl$_2$/Zn reagent system and resolution of (±)-2,3-diphenylpiperazine **1a** using L-(+)-tartaric acid following a novel method of enhancement of enantiomeric purity of partially resolved samples to obtain samples of >99% ee via preparation of hydrogen-bonded salt aggregates using oxalic acid.

SCHEME 1. Synthesis (±)-2,3-Diarylpiperazines 1



We have observed that the diastereomerically pure (±)-2,3-diarylpiperazines **1** are readily prepared in 73−83% yields by intramolecular reductive coupling of diimines in the presence of Zn/Ti(O^{i}Pr)$_2$Cl$_2$ (Scheme 1).

We have initially carried out the reductive coupling using reagent systems such as Zn/TiCl$_4$ [17] and ^{i}PrMgBr/TiCl$_4$. In these cases, the piperazine derivatives were obtained in 45−60% yield (Table 1, entries 2, 4, and 6). The yield was lower using the TiCl$_3$ prepared in the reaction of the TiCl$_4$/Et$_3$N reagent system, since the imine was cleaved to some extent into aldehyde under

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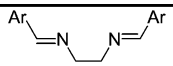
TABLE 1. Intramolecular Reductive Coupling of Diimines with $Zn/TiCl_2X_2$

Entry		X	Product[a]	Yield (%)
1	Ar = phenyl	O^{i}Pr	**1a**	83
2	Ar = phenyl	Cl	**1a**	60
3	Ar = 2-methoxyphenyl	O^{i}Pr	**1b**	73
4	Ar = 2-methoxyphenyl	Cl	**1b**	58
5	Ar = 4-methoxyphenyl	O^{i}Pr	**1c**	75
6	Ar = 4-methoxyphenyl	Cl	**1c**	45
7	Ar = 4-chlorophenyl	O^{i}Pr	**1d**	80
8	Ar = 4-methylphenyl	O^{i}Pr	**1e**	76

[a] The products were identified using physical constants and spectroscopic data (IR, ^{1}H and ^{13}C NMR, and mass spectral data) and comparison with reported data.[3]

TABLE 2. Resolution of (±)-2,3-Diphenylpiperazine 1a Using Chiral L-(+)-Tartaric Acid

			piperazine **1a** obtained from			
			precipitate fraction		filtrate fraction	
entry	solvent (mL)[a]	L-(+)-tartaric acid (mmol)	% ee[b]/ config	yield[c] (%)	% ee[b]/ config	yield[c] (%)
1	THF (50)	5	16 (*S*,*S*)	56	8 (*R*,*R*)	39
2	THF (100)	5	20 (*S*,*S*)	62	25 (*R*,*R*)	38
3	THF (100)	2.5	20 (*S*,*S*)	38	12 (*R*,*R*)	52
4	THF (250)	5	31 (*S*,*S*)	38	16 (*R*,*R*)	54
5	THF (500)	5	48 (*S*,*S*)	42	22 (*R*,*R*)	57
6	acetone (50)	5	15 (*S*,*S*)	43	12 (*R*,*R*)	51
7	CH_2Cl_2 (200)	5	45 (*S*,*S*)	32	27 (*R*,*R*)	67
8	CH_2Cl_2 (250)	10	61 (*S*,*S*)	33	15 (*R*,*R*)	63

[a] All experiments were carried out using 10 mmol of (±)-2,3-diphenylpiperazine **1a**. [b] All ee values reported here are based on HPLC analysis and the maximum $[\alpha]^{25}_D = -104.6$ (*c* 1.0, $CHCl_3$) for (*S*,*S*)-**1a**. [c] The yields are of the isolated products.

the reaction conditions. The $Ti(O^iPr)_2Cl_2/Zn$ system gave better yields (Table 1, entries 1, 3, 5, 7, and 8). Optimum yields were obtained by using 5 equiv of zinc powder, and yields were low when 2 equiv of zinc powder was used.

The configuration of the product was confirmed to be *trans* by single-crystal X-ray analysis of the trifluoroacetamide derivative **2a** of the product (±)-**1a**,[18] and the *dl*/*meso* ratio was determined to be >99:<1 by HPLC analysis.

Resolution methods are widely used, especially when both the isomers are required. Surprisingly, methods were not reported for the resolution of (±)-2,3-diarylpiperazines **1**. We have examined the resolution of the (±)-2,3-diphenylpiperazine **1a.** We have carried out the resolution of (±)-2,3-diphenylpiperazine **1a** in various solvents using L-(+)-tartaric acid (Table 2). Partial resolution could be easily realized under these conditions, and the partially resolved **1a** could be readily enriched to obtain samples of >99% ee by repeating the operation (Table 2 and Scheme 2).

SCHEME 2. Resolution of (±)-2,3-Diphenylpiperazine 1a

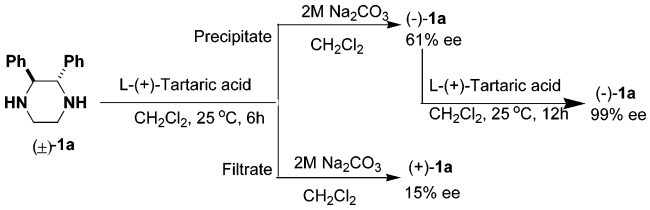


TABLE 3. Purification of Nonracemic 2,3-Diphenylpiperazine 1a Using Oxalic Acid[a]

			piperazine **1a** obtained from			
			precipitate fraction		filtrate fraction	
entry	substrate % ee[b]/(mmol)/ config	oxalic acid (mmol)	% ee[b]/ config	yield[c] (%)	% ee[b]/ config	yield[c] (%)
1	39 (2.00) (*S*,*S*)	0.60	71 (*S*,*S*)	30	22 (*S*,*S*)	65
2	45 (2.00) (*S*,*S*)	0.75	73 (*S*,*S*)	51	18 (*S*,*S*)	37
3	73 (2.00) (*S*,*S*)	1.30	99 (*S*,*S*)	62	21 (*S*,*S*)	33
4	53 (5.00) (*S*,*S*)	1.00	84 (*S*,*S*)	21	28 (*S*,*S*)	77
5	84 (0.75) (*S*,*S*)	0.55	99 (*S*,*S*)	67	20 (*S*,*S*)	28
6	48 (2.00) (*R*,*R*)	0.80	77 (*R*,*R*)	36	19 (*R*,*R*)	60

[a] All of the reactions were carried out using nonracemic piperazine **1a** and oxalic acid in THF. [b] All ee values reported here are based on HPLC analysis and the maximum $[\alpha]^{25}_D = -104.6$ (*c* 1.0, $CHCl_3$) for (*S*,*S*)-**1a**. [c] The yields are of the isolated products.

The configuration of the enantiomer (−)-**1a** was assigned as (*S*,*S*) by single-crystal X-ray analysis of the corresponding tartrate salt **3a**,[19] and the enantiomeric ratio was determined by HPLC analysis.

We have also examined the effect of amount of THF and the amount of resolving agent on the resolution process (Table 2). Reasonable results were realized when the (±)-2,3-diphenylpiperazine **1a** and L-(+)-tartaric acid were used in a 1:0.5 molar ratio (Table 2, entries 1, 2, 4−7). Use of **1a** and L-(+)-tartaric acid in a 1:0.25 molar ratio gave samples with only 20% ee in the precipitate fraction and samples with 12% ee in the filtrate fraction (Table 2, entry 3). Results are better when 50 mL of THF was used per 1 mmol of amine (Table 2, entry 5). There was no appreciable change in ee when acetone was used as solvent instead of THF (Table 2, entries 1 and 6). When the (±)-2,3-diphenylpiperazine **1a** and L-(+)-tartaric acid were used in a 1:1 molar ratio in THF, precipitation occurred but there was no resolution. However, appreciable resolution was realized by using the (±)-2,3-diphenylpiperazine **1a** and L-(+)-tartaric acid in a 1:1 mole ratio in CH_2Cl_2 (Table 2, entry 8).

Recently, a simple method of purification of certain nonracemic samples of amino alcohols via preparation of the corresponding hydrogen-bonded aggregates using achiral dicarboxylic acids was developed in this laboratory.[20] We have followed this methodology to enhance the optical purity of the partially resolved piperazine **1a**. Enantiomerically enriched samples with 99% ee can be readily obtained following this method (Table 3).

(18) **Crystal Data.** For compound **2a**: molecular formula $C_{20}H_{16}F_6N_2O_2$, MW = 430.35, monoclinic, space group *P*2(1)/*c*, a = 22.3786(10) Å, b = 16.5405(7) Å, c = 11.1443(5) Å, β = 103.3050(10)°, V = 4014.4(3) Å^3, Z = 8, ρ_c = 1.424 mg M^{-3}, μ = 0.130 mm^{-1}, T = 273(2) K. Of the 45980 reflections collected, 9632 were unique (R_{int} = 0.0378). Refinement on all data converged at R_1 = 0.0799, wR_2 = 0.2291.

(19) **Crystal Data.** For compound **3a**: molecular formula $C_{20}H_{28}N_2O_8$, MW = 424.44, orthorhombic, space group *P*2(1)2(1)2, a = 9.2088(10) Å, b = 35.387(4) Å, c = 6.2519(7) Å, V = 2037.3(4) Å^3, Z = 4, ρ_c = 1.384 mg M^{-3}, μ = 0.107 mm^{-1}, T = 273(2) K. Of the 23736 reflections collected, 4860 were unique (R_{int} = 0.0451). Refinement on all data converged at R_1 = 0.0483, wR_2 = 0.1071.

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In conclusion, the simple, convenient method of synthesis of (±)-2,3-diarylpiperazines by the intramolecular reductive coupling of diimines in the presence of $Zn/Ti(O^iPr)_2Cl_2$ and the partial resolution of the (±)-2,3-diphenylpiperazine **1a** using L-(+)-tartaric acid and enhancement of the enantiomeric purity using oxalic acid have good synthetic potential, in view of the potential biological activity predicted for 2,3-disubstituted piperazines.[2]

Experimental Section

Representative Procedure for the Intramolecular Coupling of Diimines Using Zn and $Ti(O^iPr)_2Cl_2$. In a 100 mL, two-necked round-bottom (RB) flask, containing a magnetic stirring bar equipped with a dropping funnel and an air condenser protected by mercury trap, were placed CH_2Cl_2 (40 mL), $TiCl_4$ (1.043 g, 5.5 mmol), and $Ti(O^iPr)_4$ (1.563 g, 5.5 mmol) under nitrogen, and the mixture was stirred for 10−15 min. To this was added activated zinc powder (1.634 g, 25.0 mmol) in three portions, and the stirring was continued for another 1 h. Then, diimine (5.0 mmol) dissolved in CH_2Cl_2 (10 mL) was added in drops through a dropping funnel at 0 °C. After the addition was completed, the reaction mixture was stirred at 25 °C for 5−6 h. The reaction mixture was poured into saturated aqueous K_2CO_3 solution at 0 °C and filtered. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extract was washed with water and brine solution and dried using anhydrous K_2CO_3. The solvent was evaporated, and the product was purified by column chromatography (Basic alumina, hexane/$CHCl_3$ = 9/1 and then $CHCl_3$).

Spectral data for products **1a**−**e**:

1a: yield 83% (0.99 g); mp 94−96 °C (lit.[3] mp 96−98 °C); IR (KBr) 3318, 3280, 3030, 2949, 2820, 1603, 1491 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.00 (br s, 2 H, NH), 3.15 (s, 4 H), 3.72 (s, 2 H), 7.07−7.12 (m, 10 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 47.0, 68.1, 127.3, 127.8, 128.0, 141.2; MS (EI) m/z = 238 [M^+].

1b: yield 73% (1.08 g); mp 106−108 °C; IR (KBr) 3314, 3032, 3006, 2955, 1605, 1585 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.96 (br s, 2 H, NH), 3.10 (s, 4 H), 3.56 (s, 6 H), 4.30 (s, 2 H), 6.61 (d, 2 H, J = 8.8 Hz), 6.76 (t, 2 H, J = 6.8 Hz), 7.04 (t, 2 H, J = 6.8 Hz), 7.28 (d, 2 H, J = 8.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 46.9, 55.1, 59.9, 110.2, 120.1, 127.9, 128.9, 129.2, 157.0; MS (EI) m/z = 298 [M^+].

1c: yield 75% (1.12 g); mp 96−98 °C (lit.[3] mp 100−101 °C); IR (KBr) 3271, 3040, 3003, 2957, 1612, 1584 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.27 (br s, 2 H, NH), 3.10 (s, 4 H), 3.63 (s, 2 H), 3.70 (s, 6 H), 6.65 (d, 4 H, J = 8.0 Hz), 7.00 (d, 4 H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 47.0, 55.1, 67.4, 113.2, 129.0, 133.6, 158.6; MS (EI) m/z = 298 [M^+].

1d: yield 80% (1.23 g); mp 119−120 °C; IR (KBr) 3317, 3047, 3003, 2947, 2893, 1593, 1485 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.91 (br s, 2 H, NH), 3.11 (s, 4 H), 3.60 (s, 2 H), 6.99 (d, 4 H, J = 8.4 Hz), 7.10 (d, 4 H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.9, 67.7, 128.1, 129.3, 133.0, 139.7; MS (EI) m/z = 306 [M^+].

1e: yield 76% (1.01 g); mp 128−130 °C (lit.[3] mp 122−125 °C); IR (KBr) 3321, 3024, 2953, 2814, 1658, 1512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.88 (br s, 2 H, NH), 2.23 (s, 6 H), 3.13 (s, 4 H), 3.68 (s, 2 H), 6.93 (d, 4 H, J = 7.6 Hz), 6.98 (d, 4 H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 47.3, 67.8, 128.0, 128.5, 136.6, 138.7; MS (EI) m/z = 266 [M^+].

Resolution of (±)-2,3-Diphenylpiperazine 1a Using L-(+)-Tartaric Acid. The L-(+)-tartaric acid (1.50 g, 10.0 mmol) and (±)-2,3-diphenylpiperazine **1a** (2.40 g, 10.0 mmol) were taken in CH_2Cl_2 (250 mL), and the contents were stirred at 25 °C for 6 h and filtered. The precipitate was suspended in a mixture of CH_2Cl_2 and aq Na_2CO_3 (2 M) and stirred until dissolution occurred. The organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to obtain the (*S*,*S*)-**1a** enantiomer (61% ee, 33% yield). The filtrate was treated as outlined above to obtain **1a** enriched in the (*R*,*R*)-enantiomer (15% ee, 63% yield).

Resolution of Nonracemic 2,3-Diphenylpiperazine 1a Using L-(+)-Tartaric Acid. To a solution of nonracemic 2,3-diphenylpiperazine (*S*,*S*)-**1a** (61% ee, 0.60 g, 2.5 mmol) in CH_2Cl_2 (60 mL) was added L-(+)-tartaric acid (0.38 g, 2.5 mmol), and the contents were stirred at room temperature for 12 h and filtered. The precipitate was suspended in a mixture of CH_2Cl_2 and aq Na_2CO_3 (2 M) and stirred until dissolution occurred. The organic extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness to obtain the (*S*,*S*)-**1a** isomer (>99% ee, 35% yield). The filtrate was concentrated, and the residue was treated as outlined above to obtain **1a** enriched in the (*S*,*S*)-enantiomer (38% ee, 61% yield).

Enrichment of Enantiomeric Purity of Nonracemic 2,3-Diphenylpiperazine 1a Using Oxalic Acid. To a solution of nonracemic 2,3-diphenylpiperazine (*S*,*S*)-**1a** (73.0% ee, 2.0 mmol) in THF (30 mL) was added oxalic acid (0.165 g, 1.30 mmol), and the contents were stirred at room temperature for 2 h and filtered. The precipitate was suspended in a mixture of CH_2Cl_2 and aq Na_2CO_3 (2 M) and stirred until dissolution occurred. The organic extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness to obtain the (*S*,*S*)-**1a** isomer (>99% ee, 62% yield). The filtrate was concentrated, and the residue was treated as outlined above to obtain **1a** enriched in the (*S*,*S*)-enantiomer (21% ee, 33% yield).

HPLC Analysis of the Trifluoroacetamide Derivatives of 2,3-Diarylpiperazines. The diamine (**1a**−**e**) (0.5 mmol) in CH_2Cl_2 (ca. 25 mL) was stirred overnight with excess trifluoroacetic anhydride (TFAA). The solution was concentrated under reduced pressure to remove the solvent, and excess TFAA and the residue were recrystallized from hexane/CH_2Cl_2 (99:1) mixture. The trifluoroacetamide derivatives were dissolved in 2-propanol (~10 mg/mL), and HPLC analyses were performed using a Chiralcel OD-H column supplied by Daicel Chemical Industries, Ltd., with an isochratic method using hexane/2-propanol (98:2) with a flow rate 0.5 mL/min. Retention times for the trifluoroacetamide derivatives (**2a**) of 2,3-diphenylpiperazine are 10.5 min for the (*R*,*R*) and 12.3 min for the (*S*,*S*).

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Supporting Information Available: ^{13}C NMR spectra of compounds **1a**−**e**. Crystallographic diagrams and CIF for compounds **2a** and **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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