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Synthesis of Chiral 2,3-Disubstituted 1,4-Diazabicyclo[2.2.2]octane Derivatives

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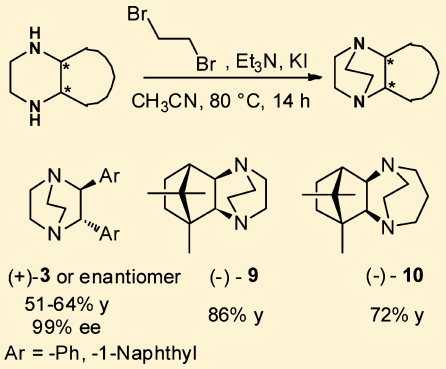
Supporting Information

ABSTRACT: Racemic 2,3-diaryl-1,4-diazabicyclo[2.2.2]octane (DABCO) derivatives are synthesized from the readily accessible piperazines in 50−64% yield by cyclization using ethylene bromide, triethylamine, and KI at 80 °C. The enantiomerically enriched 2,3-diphenylpiperazine and the 2,3-bis(1-naphthyl)-piperazine derivatives are prepared by a resolution method using commercially available optically active acids, yielding the corresponding DABCO derivatives in 51−64% yield with up to 99% ee. This mild cyclization can also be applied to enantiopure camphanyldiamine derivatives, and the products are obtained in 72−86% yields.



1,4-Diazabicyclo[2.2.2]octane (DABCO) is a cagelike unique structure with two nucleophilic and strongly basic nitrogens at the bridgehead positions. The DABCO skeleton has proven to have applications in the synthesis of multifunctional molecules,[1] and DABCO is widely used as a base catalyst in organic reactions.[2] Also, optically active DABCO derivatives have been employed as ligands and catalysts in asymmetric reactions.[3] For example, recently, an asymmetric electrophilic fluorocyclization method using optically active DABCO-based N-F reagents was reported.[4] Previously, the DABCO derivatives were prepared by cyclization of substituted stilbene diamines,[4−6] ethylene diamine,[7] and piperzines.[3,8−11] However, it was reported that the cyclization of meso 2,3-diphenylpiperazine using ethylene bromide and triethylamine gave the corresponding DABCO derivative in only 14% yield, and the reaction failed to give the cyclized DABCO product using the (*R*,*R*)-2,3-diphenylpiperazine.[11] Recently, methods for accessing enantiopure Troger base, a compound with bridgehead nitrogens, were reported by this laboratory.[12] Also, methods based on resolution and asymmetric synthesis of *trans*-2,3-diarylpiperazine derivatives have been reported.[13,14] Accordingly, we undertook studies aimed at the synthesis of enantiopure DABCO derivatives via development of a simple general method of cyclization of the corresponding piperazine derivatives. Herein, the results are described.

(±)-2,3-Diphenylpiperazine **2a** can be readily accessed via a method using Ti(IV) reagent developed in this laboratory.[13a] Initially, we have examined the reaction of this readily accessible (±)-2,3-diphenylpiperazine **2a** using ethylene bromide in the presence of 20 mol % KI and different bases and solvents at 80 °C (Scheme 1 and Table 1).

We have observed that racemic piperazine **2a** reacts with neat ethylene bromide to afford (±)-2,3-diphenyl-1,4-diazabicyclo[2.2.2]octane **3a** in 26% yield in the presence of K_2CO_3 (Table 1, entry 1). Whereas the reaction using ethylene bromide (1 equiv) in CH_3CN and THF solvents gave the (±)-2,3-diphenyl-1,4-diazabicyclo[2.2.2]octane **3a** product in only trace amounts using K_2CO_3 as a base (Table 1, entries 2 and 3). Fortunately, the reaction of piperazine (±)-**2a** with 2 and 4 equiv of ethylene bromide using triethylamine gave

Scheme 1

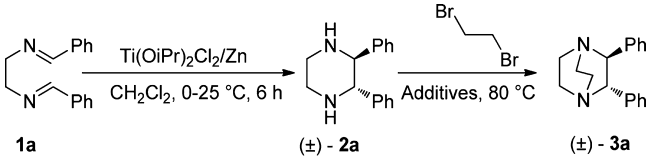


Table 1. Optimization of the Reaction Condition[a]

entry	base	solvent	$Br(CH_2)_2Br$ (equiv)	yield (%)[b]
1	K_2CO_3	–	8 mL	26
2	K_2CO_3	CH_3CN	1	trace
3	K_2CO_3	THF	1	trace
4	NaH	CH_3CN	1	22
5	Et_3N	CH_3CN	1	28
6	Et_3N	CH_3CN	2	39
7	Et_3N	CH_3CN	4	64
8	Et_3N	CH_3CN	6	65

[a]The reactions were conducted with (±)-2,3-diphenylpiperazine **2a** (5 mmol), KI (20 mol %), and base (10 mmol) at 80 °C for 14 h. [b]Isolated yield of **3a**.

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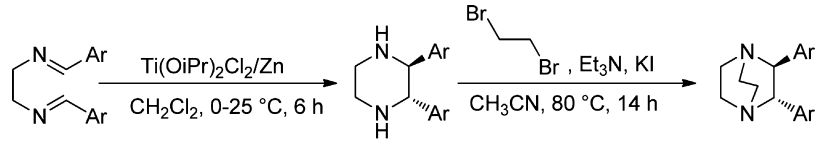
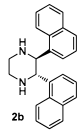
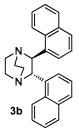
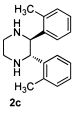
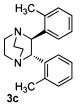
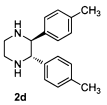
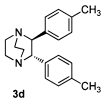
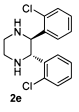
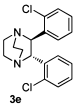
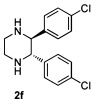
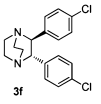
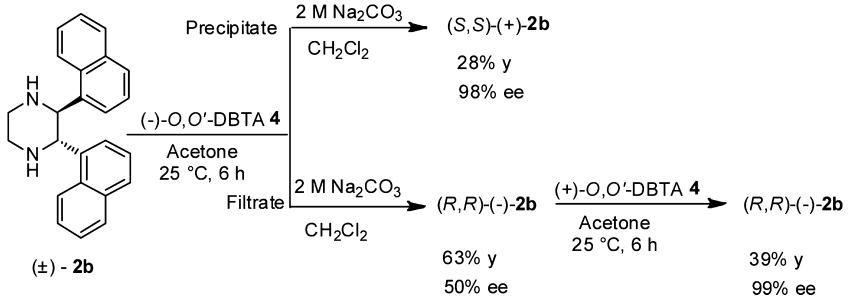
Table 2. Synthesis of (±)-2,3-Diarylpiperazine Derivatives 2 and Reaction with Ethylene Bromide



Entry	Product **2**	Yield (%)[b]	Product **3**[a]	Yield (%)[b]
1		72		52
2		75		59
3		76		50
4		73		55
5		80		53

[a]The reactions were conducted using (±)-2,3-diarylpiperazine derivatives (5 mmol), KI (20 mol %), and Et_3N (10 mmol) at 80 °C for 14 h. [b]The yields are for isolated products.

Scheme 2



product (±)-**3a** in 39 and 64% yields, respectively (Table 1, entries 6 and 7). The product **3a** was characterized by X-ray single-crystal structural analysis.[15] We have also examined the reaction using 6 equiv of ethylene bromide, but there was no significant change in the yields of product (±)-**3a** (Table 1, entry 8).

To further examine the scope of this reaction, we have synthesized several diastereomerically pure (±)-2,3-diarylpiperazines **2b–f** in 72–80% yields by the reductive coupling of diimines **1** using the Zn/Ti(O^iPr)$_2Cl_2$ reagent system.[13a] Racemic piperazine derivatives **2b–f** were then reacted with ethylene bromide and triethylamine in the presence of KI under the optimized experimental conditions (Table 1, entry 7). The results are summarized in Table 2. The reaction of (±)-2,3-bis(1-naphthyl)piperazine **2b** gave the corresponding (±)-2,3-bis(1-naphthyl)-1,4-diazabicyclo[2.2.2]octane **3b** in 52% yield (Table 2, entry 1). The *ortho* methyl- and *ortho* chloro-substituted (±)-2,3-diphenylpiperazine derivatives **2c** and **2e** afforded the (±)-2,3-di-*o*-tolyl-1,4-diazabicyclo[2.2.2]octane **3c** and (±)-2,3-bis(2-chlorophenyl)-1,4-diazabicyclo[2.2.2]octane **3e** in 59 and 55% yield, respectively (Table 2, entries 2 and 4). Also, *para* methyl- and *para* chloro-substituted (±)-2,3-

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diphenyl-1,4-diazabicyclo[2.2.2]octane **3d** and **3f** were obtained in 50 and 53% yield, respectively (Table 2, entries 3 and 5).

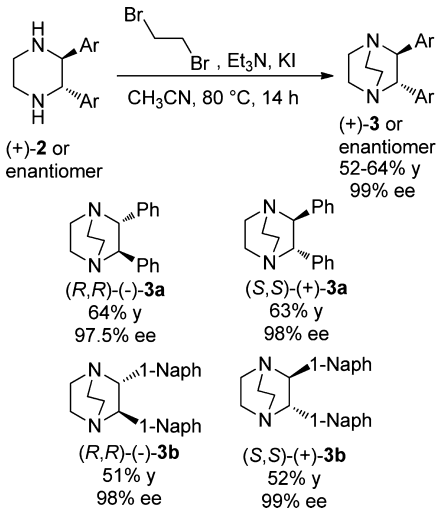
Enantiomerically enriched 2,3-diphenylpiperazine compound **2a** was previously synthesized by resolution methods using L-(+)-tartaric acid and 1*S*-(+)-10-camphorsufonic acid (CSA) developed in this laboratory.[13a,b] We have found that these resolution methods using L-(+)-tartaric acid or (+)-CSA are not effective in the case of racemic 2,3-bis(1-naphthyl)piperazine **2b**. Fortunately, the resolution of racemic 2,3-bis(1-naphthyl)-piperazine **2b** using the (−)-dibenzoyl-L-tartaric acid **4** in acetone solvent was successful, and (+)-**2b** compound was obtained in 28% yield with 98% ee (Scheme 2).[12a,b]

The (*S*,*S*)-isomer of 2,3-bis(1-naphthyl)piperazine **2b** was obtained in 98% ee from the precipitate fraction, while the (*R*,*R*)-isomer of 2,3-bis(1-naphthyl)piperazine **2b** was obtained in 50% ee from the filtrate fraction. The (*R*,*R*)-isomer was easily enriched up to 99% ee by repeating the experiment using the (+)-dibenzoyl-D-tartaric acid **4**.

Diastereomeric complex **5a** [(+)-**2b**·(−)-**4**)][15] was crystallized to obtain crystals suitable for single-crystal X-ray analysis. The configuration of enantiomer (+)-**2b** was assigned as (*S*,*S*) relative to the chiral acid (*R*,*R*)-(−)-**4** used, and the enantiomeric ratio was determined by HPLC analysis.

We have also examined the cyclization reactions using the enantiomerically enriched piperazines **2a** and **2b** following the same reaction conditions followed for entry 7 of Table 1 (Scheme 3). The (*R*,*R*) and (*S*,*S*) enantiomers of 2,3-diphenyl-

Scheme 3



1,4-diazabicyclo[2.2.2]octane **3a** were obtained in 64 and 63% yield and 97.5 and 98% ee, respectively. Also, the reaction of (*R*,*R*) and (*S*,*S*) enantiomers of the 2,3-bis(1-naphthyl)-piperazine **2b** furnished corresponding DABCO derivatives **3b** in 51 and 52% yield with up to 99% ee. Product (*S*,*S*)-(+)-**3b** was also characterized by single-crystal X-ray structural analysis.[15]

The enantioselective 2,3-diarylpiperazines can be also accessed following asymmetric coupling of the corresponding diimines using a chiral Ti(IV) complex followed by enhancement of enantiomeric purity via preparation of homochiral or heterochiral aggregates using carboxylic acids like oxalic or fumaric acids reported from this laboratory.[13c] Accordingly, the synthetic method developed here (Scheme 3) to access enantiopure DABCO derivatives **3a** and **3b** should be widely applicable for the synthesis of several such aryl-substituted enantiomerically pure 2,3-diaryl DABCO derivatives.

The chiral camphanyl piperazine (+)-**7** and the analogous chiral diamine (+)-**8** are also readily accessible following a method reported by this laboratory.[16] Accordingly, it was also of interest to us to examine the efficacy of the method of cyclization developed for the reaction of 2,3-diarylpiperazines for cyclizations using the camphanyl piperazine (+)-**7** and the analogous diamine (+)-**8**. Indeed, the camphanyl piperazine (+)-**7** reacts with ethylene bromide in the presence of triethylamine to give the enantiopure DABCO derivative (−)-**9** in 86% yield. Similarly, the camphanyl diazepine (+)-**8** was readily converted to the corresponding enantiopure diazepine derivative (−)-**10** in 72% yield (Scheme 4).

In summary, we have devised a simple, convenient method for the synthesis of racemic and enantiomerically enriched 2,3-diaryl-1,4-diazabicyclo[2.2.2]octane derivatives from the corresponding piperazines using ethylene bromide for cyclization. The cyclization method is also useful for accessing the camphanyl DABCO **9** and camphanyl diazepine **10** derivatives via reaction of the corresponding bicyclic camphanyldiamine derivatives **7** and **8**. Because the starting 2,3-diarylpiperazines and the camphanyldiamines can be readily accessed from simple starting materials and reagents, the synthetic methods described here have good potential for applications in organic synthesis.

EXPERIMENTAL SECTION

General Procedure for the Preparation of 2,3-Diaryl-1,4-diazabicyclo[2.2.2]octane Derivatives (3a−f). To a reaction flask cooled under N_2 were added 2,3-diarylpiperazine **2a−f** (5 mmol) and KI (0.166 g, 20 mol %) in acetonitrile (40 mL). Then triethylamine (1.01 g, 1.3 mL, 10 mmol) and ethylene bromide (3.76 g, 1.7 mL, 20 mmol) were added at 25 °C, and the reaction mixture was refluxed for 14 h. It was then cooled to 25 °C; the solvent was removed and the reaction quenched with a 2 M NaOH solution. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL), and the combined organic extract was successively washed with water and brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was subjected to chromatography on silica gel using 2−5% methanol in ethyl acetate to elute the desired 2,3-diaryl-1,4-diazabicyclo[2.2.2]-octane **3a−f** derivatives.

2,3-Diphenyl-1,4-diazabicyclo[2.2.2]octane ***3a***. Yield: 0.85 g (64%). Pale yellow solid. Mp: 73−75 °C (lit.[4a] mp 74−76 °C). IR (KBr): 3090, 3052, 3024, 2926, 2854, 1495, 1441, 1369, 1326, 1238, 1189, 1090, 1046, 980, 920, 816, 750, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.48−7.46 (m, 4H), 7.38−7.34 (m, 4H), 7.30−7.27 (m, 2H), 4.17 (s, 2H), 3.03−2.98 (m, 4H), 2.83−2.75 (m, 2H), 2.65−2.58 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.2, 128.4, 127.7, 127.1, 62.4, 49.5, 41.1. HRMS (ESI-TOF): $[M + H]^+$ calcd for $C_{18}H_{20}N_2$ *m*/*z* 265.1705, found *m*/*z* 265.1706.

2,3-Bis(1-naphthyl)-1,4-diazabicyclo[2.2.2]octane ***3b***. Yield: 0.95 g (52%). Pale yellow solid. Mp: 165−167 °C. IR (KBr): 3084, 3035, 2964, 2931, 2909, 2849, 1594, 1501, 1457, 1095, 1041, 827, 778 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, *J* = 8.40 Hz, 2H), 7.87 (d, *J* = 7.92 Hz, 2H), 7.75 (d, *J* = 8.08 Hz, 2H), 7.67 (t, *J* = 7.2 Hz, 2H), 7.55−7.51 (m, 2H), 7.47 (d, *J* = 7.0 Hz, 2H), 7.30−7.28 (m, 2H), 5.35 (s, 2H), 3.53−3.50 (m, 2H), 3.08−2.91 (m, 4H), 2.73−2.68 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.5, 134.1, 133.3, 128.9, 128.7, 126.6, 125.7, 124.7, 124.6, 123.2, 55.6, 49.2, 41.3. HRMS (ESI-TOF): $[M + H]^+$ calcd for $C_{26}H_{24}N_2$ *m*/*z* 365.2018, found *m*/*z* 365.2017.

2,3-Di-o-tolyl-1,4-diazabicyclo[2.2.2]octane ***3c***. Yield: 0.86 g (59%). Yellow liquid. IR (neat): 3013, 2958, 2936, 2920, 2860, 1490, 1463, 1375, 1260, 1068, 1035, 980, 816, 745 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.36−7.34 (m, 2H), 7.24−7.23 (m, 2H), 7.18−7.13 (m, 4H), 4.60 (s, 2H), 3.26−3.18 (m, 4H), 2.97−2.83 (m, 4H),

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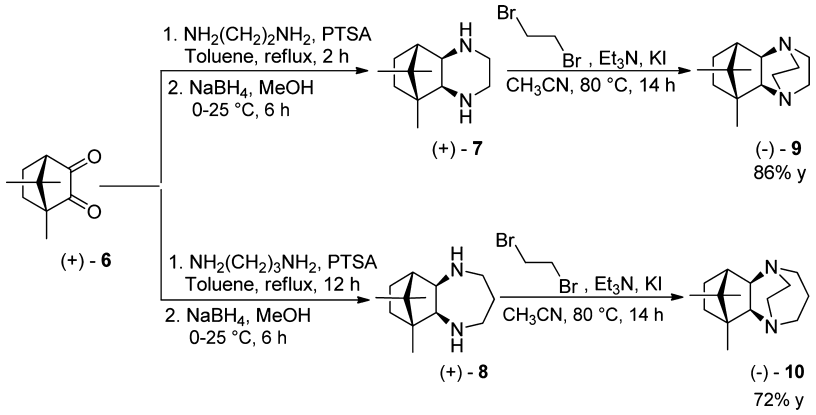
Scheme 4



2.57 (s, 6H), 2.57−2.50 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.2, 137.0, 131.4, 127.4, 125.4, 125.1, 56.1, 49.7, 40.6, 20.0. HRMS (ESI-TOF): $[M + H]^+$ calcd for $C_{20}H_{24}N_2$ m/z 293.2018, found m/z 293.2017.

2,3-Di-p-tolyl-1,4-diazabicyclo[2.2.2]octane ***3d***. Yield: 0.73 g (50%). Yellow liquid. IR (neat): 3024, 2958, 2926, 2871, 1512, 1457, 1375, 1079, 1052, 1024, 860, 805, 756 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, J = 7.36 Hz, 4H), 7.17 (d, J = 7.48 Hz, 4H), 4.12 (s, 2H), 3.01−2.97 (m, 4H), 2.83−2.75 (m, 2H), 2.64−2.57 (m, 2H), 2.36 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.1, 136.7, 129.1, 127.7, 62.2, 49.5, 41.0, 21.0. HRMS (ESI-TOF): $[M + H]^+$ calcd for $C_{20}H_{24}N_2$ m/z 293.2018, found m/z 293.2022.

2,3-Bis(2-chlorophenyl)-1,4-diazabicyclo[2.2.2]octane ***3e***. Yield: 0.91 g (55%). Pale yellow solid. Mp: 182−184 °C. IR (KBr): 3068, 2947, 2920, 2865, 1463, 1441, 1205, 1123, 1073, 1035, 750 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51−7.45 (m, 4H), 7.26−7.19 (m, 4H), 4.88 (s, 2H), 3.37−3.31 (m, 2H), 2.99−2.83 (m, 4H), 2.67−2.60 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.9, 135.9, 130.7, 128.9, 127.0, 126.5, 56.1, 49.6, 40.4. HRMS (ESI-TOF): $[M + H]^+$ calcd for $C_{18}H_{18}N_2Cl_2$ m/z 333.0926, found m/z 333.0920.

2,3-Bis(4-chlorophenyl)-1,4-diazabicyclo[2.2.2]octane ***3f***. Yield: 0.88 g (53%). Yellow liquid. IR (neat): 3052, 2958, 2926, 2865, 1490, 1457, 1397, 1369, 1315, 1265, 1084, 1052, 1008, 904, 849, 800 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.30 (m, 8H), 4.02 (s, 2H), 2.98−2.94 (m, 4H), 2.72−2.58 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.4, 133.1, 129.0, 128.6, 61.9, 49.3, 41.0. HRMS (ESI-TOF): $[M + H]^+$ calcd for $C_{20}H_{24}N_2$ m/z 333.0926, found m/z 333.0924.

General Procedure for the Preparation of (±)-2,3-Diarylpiperazine Derivatives (2a−f) Using Zn and Ti(O^{i}Pr)$_2$Cl$_2$.[13a] To a reaction flask cooled under N_2 were added $TiCl_4$ (1.04 g, 0.6 mL, 5.5 mmol) and Ti(O^{i}Pr)$_4$ (1.56 g, 1.62 mL, 5.5 mmol) in CH_2Cl_2 (40 mL). After the mixture had been stirred for 10−15 min, activated zinc powder (1.65 g, 25 mmol) was added in three portions and continued for an additional 1 h. The diimine (5 mmol) dissolved in CH_2Cl_2 (10 mL) was added dropwise through a dropping funnel at 0 °C for 20 min. Then the reaction mixture was stirred at 25 °C for 5−6 h. The reaction was quenched with a 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 successively washed with water and brine and dried over anhydrous K_2CO_3. After removal of the solvent, the residue was subjected to chromatography on silica gel using 5−10% methanol in ethyl acetate to elute the desired (±)-2,3-diarylpiperazine **2a−f** derivatives.

2,3-Bis(1-naphthyl)piperazine ***2b***. Yield: 1.21 g (72%). Yellow solid. Mp: 106−108 °C (lit.[17] mp 100−101 °C). IR (KBr): 3326, 3276, 3057, 2953, 2909, 2849, 1600, 1506, 1402, 1326, 1117, 1084, 958, 778, 717 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96−7.26 (m, 14H), 5.01 (s, 2H), 3.34−3.24 (m, 4H), 2.33 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.1, 133.5, 131.4, 128.5, 127.7, 125.5, 125.1, 124.9, 122.5, 60.3, 47.6. HRMS (ESI-TOF): $[M + H]^+$ calcd for $C_{24}H_{22}N_2$ m/z 339.1862, found m/z 339.1862.

2,3-Di-o-tolylpiperazine ***2c***. Yield: 1.0 g (75%). Yellow solid. Mp: 116−118 °C. IR (KBr): 3271, 3150, 3063, 3019, 2926, 2843, 1583, 1484, 1457, 1315, 1117, 909, 756 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 6.96 Hz, 2H), 7.13−7.09 (m, 2H), 7.04−7.00 (m, 2H), 6.85 (d, J = 7.44 Hz, 2H), 4.19 (s, 2H), 3.14 (s, 4H), 1.91 (s, 2H), 1.87 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5, 136.2, 129.9, 127.9, 127.2, 125.6, 61.6, 46.3, 19.3. HRMS (ESI-TOF): $[M + H]^+$ calcd for $C_{18}H_{22}N_2$ m/z 267.1862, found m/z 267.1863.

2,3-Bis(2-chlorophenyl)piperazine ***2e***. Yield: 1.2 g (73%). Yellow solid. Mp: 94−96 °C. IR (KBr): 3287, 3227, 3063, 2926, 2849, 1581, 1479, 1441, 1358, 1320, 1112, 1041, 865, 821, 756 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (s, 2H), 7.15−7.09 (m, 4H), 7.04−7.00 (m, 2H), 4.51 (s, 2H), 3.14−3.08 (m, 4H), 2.05 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 133.5, 129.8, 129.1, 128.5, 126.7, 61.2, 47.2. HRMS (ESI-TOF): $[M + H]^+$ calcd for $C_{16}H_{16}Cl_2N_2$ m/z 307.077, found m/z 307.0772.

General Procedure for the Preparation of Camphanyldiamine Derivatives 9 and 10. To a reaction flask cooled under N_2 were added camphanylamines **7** and **8** (5 mmol) and KI (0.166 g, 20 mol %) in acetonitrile (40 mL). Then triethylamine (1.01 g, 1.3 mL, 10 mmol) and ethylene bromide (3.76 g, 1.7 mL, 20 mmol) were added at 25 °C, and the reaction mixture was refluxed for 14 h. It was then cooled to 25 °C; the solvent was removed and the reaction quenched with a 2 M NaOH solution. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL), and the combined organic extracts were successively washed with water and brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was subjected to chromatography on silica gel using 40% ethyl acetate in hexane to elute desired compounds **9** and **10**.

(5R,8S)-5,9,9-Trimethyloctahydro-1,4-ethano-5,8-methanoquinoxaline ***9***. Yield: 0.946 g (86%). White solid. Mp: 120−122 °C. $[\alpha]_D^{25}$ −22.3 (c 0.57, $CHCl_3$). IR (KBr): 3065, 2961, 2893, 2698, 1651, 1560, 1483, 1452, 1415, 1396, 1284, 1153, 1111, 1074, 1051, 902, 661, 613 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.82−3.78 (m, 1H), 3.40−3.35 (m, 2H), 3.21−3.14 (m, 2H), 3.12−3.04 (m, 2H), 2.70 (s, 1H), 2.61 (d, J = 8.0 Hz, 1H), 2.42−2.35 (m, 1H), 2.05 (d, J = 4.0 Hz, 1H), 1.84−1.78 (m, 1H), 1.66−1.59 (m, 1H), 1.48 (s, 3H), 1.25 (s, 4H), 1.12−1.05 (m, 1H), 0.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 68.6, 64.0, 55.3, 49.0, 47.5, 46.4, 45.4, 39.7, 35.1, 27.9, 26.1, 21.8, 21.3, 12.3. HRMS (ESI-TOF): $[M + H]^+$ calcd for $C_{14}H_{24}N_2$ m/z 221.2018, found m/z 221.2021.

(6R,9S)-6,10,10-Trimethyloctahydro-2H-1,5-ethano-6,9-methanobenzo[b][1,4]diazepine ***10***. Yield: 0.846 g 72%. White solid. Mp: 126−128 °C. $[\alpha]_D^{25}$ −32.2 (c 0.36, $CHCl_3$). IR (KBr): 2951, 2824, 1730, 1668, 1604, 1454, 1386, 1309, 1257, 1213, 1174, 1130, 1111, 1010, 935, 896 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.41−3.33 (m, 2H), 3.26−3.20 (m, 1H), 3.13−3.06 (m, 1H), 3.02−2.95 (m, 2H), 2.56 (s, 2H), 2.37−2.32 (m, 2H), 1.90 (d, J = 4.76 Hz, 1H), 1.70−1.67 (m, 2H), 1.51−1.47 (m, 2H), 1.10 (s, 4H), 1.04−0.97 (m, 1H), 0.86 (s, 3H), 0.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 74.6, 74.3,

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58.3, 57.1, 50.7, 49.0, 47.8, 46.7, 36.4, 32.2, 28.6, 27.2, 21.7, 20.5, 13.1. HRMS (ESI-TOF): $[M + H]^+$ calcd for $C_{15}H_{26}N_2$ m/z 235.2175, found m/z 235.2174.

Resolution of 2,3-Bis(1-naphthyl)piperazine 2b Using (−)-Dibenzoyl-L-tartaric acid 4. The (−)-dibenzoyl-L-tartaric acid **4** (10.75 g, 30 mmol) and (±)-2,3-bis(1-naphthyl)piperazine **2b** (3.4 g, 10 mmol) were taken in acetone (150 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 a 2 M Na_2CO_3 solution and stirred until dissolution occurred. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extract was washed with brine and dried over anhydrous K_2CO_3, and the solvent was evaporated to obtain the enriched (*S*,*S*)-**2b** enantiomer (0.95 g, 28% yield, 98% ee). $[\alpha]_D^{25}$ = +260.8 (*c* 1.08, $CHCl_3$). The filtrate was concentrated, and the residue was treated as outlined above to produce the (*R*,*R*)-**2b** enantiomer (2.13 g, 63% yield, 50% ee). The (*R*,*R*)-**2b** enantiomer with 50% ee was further enriched by repeating the experiment using the (+)-dibenzoyl-D-tartaric acid **4** to produce the sample of 99% ee (1.31 g, 39% yield). $[\alpha]_D^{25}$ = −261.9 (*c* 1.0, $CHCl_3$). The enatiomeric purity was estimated by chiral HPLC analysis on a chiralcel OJ-H column: 97:3 hexanes/2-propanol, flow rate of 1.5 mL/min, 254 nm, retention times of 14.4 min (*R*,*R*) and 21.4 min (*S*,*S*).

The enantiomerically enriched compounds **3a** and **3b** were prepared from samples of **2a** and **2b**, respectively, using ethylene bromide according to the following general procedure.

A sample of (*R*,*R*)-**2a** with 98% ee[13b] was utilized for the preparation of (*R*,*R*)-**3a**. Yield: 0.85 g (64%). 97.5% ee. $[\alpha]_D^{25}$ = −93.3 (*c* 0.5, MeOH) [lit.[4a] $[\alpha]_D^{22}$ = −93.9 (*c* 0.5, MeOH)].

A sample of (*S*,*S*)-**2a** with 99% ee[13a] was utilized for the preparation of (*S*,*S*)-**3a**. Yield: 0.83 g (63%). 98% ee. $[\alpha]_D^{25}$ = +93.4 (*c* 0.5, MeOH) [lit.[6] $[\alpha]_D^{25}$ = +93.1 (*c* 4.34, MeOH)].

HPLC analyses were conducted using a chiral column: chiralcel OD-H, 99:1 hexanes/i-PrOH, flow rate of 1.0 mL/min, 254 nm, retention times of 7.8 min (*R*,*R*) and 10.5 min (*S*,*S*).

A sample of (*S*,*S*)-**2b** with 98% ee was utilized for the preparation of (*S*,*S*)-**3b**. Yield: 0.95 g (52%). 98% ee. $[\alpha]_D^{25}$ = +373.4 (*c* 0.7, $CHCl_3$).

A sample of (*R*,*R*)-**2b** with 98% ee was utilized for the preparation of (*R*,*R*)-**3b**. Yield: 0.93 g (51%). 99% ee. $[\alpha]_D^{25}$ = −374.9 (*c* 0.7, $CHCl_3$).

HPLC analyses were conducted using a chiral chiralcel OD-H column [99.5:0.5 hexanes/i-PrOH, flow rate of 1.5 mL/min, 254 nm, retention times of 24.6 min (*S*,*S*) and 35.1 min (*R*,*R*)] and also using a chiral chiralcel cellulose-1 column [95:5 hexanes/i-PrOH, flow rate of 0.5 mL/min, 220 nm, retention times of 21.8 min (*S*,*S*) and 25.5 min (*R*,*R*)]. The enatiomeric purities of samples (*S*,*S*)-**3b** and (*R*,*R*)-**3b** were determined on the basis of HPLC analyses using a chiralcel cellulose-1 column that gave better resolution.

X-ray Crystallography. X-ray reflections were collected on a CCD X-ray diffractometer equipped with a Cu Kα X-radiation (λ = 1.54184 Å) source and Mo Kα X-radiation (λ = 0.71073 Å) at 298 K. CCDC-1027412 (for **3a**), CCDC-1027414 (for **5a**), and CCDC-1027413 (for **3b**) contain the crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of the ^1H and ^{13}C NMR spectra of the products, HPLC analysis profiles, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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