A Concise Asymmetric Synthesis of *cis*-2,6-Disubstituted *N*-Aryl Piperazines via Pd-Catalyzed Carboamination Reactions

Josephine S. Nakhla and John P. Wolfe*

Department of Chemistry, University of Michigan, 930 N. University Avenue, Ann Arbor, Michigan 48109-1055

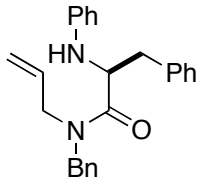
Supporting Information

Experimental procedures and characterization data for new compounds in Tables 1–2 and Schemes 2–3 (100 pages).

General: All reactions were carried out under an argon or nitrogen atmosphere in oven- or flame-dried glassware. All catalysts, reagents, and aryl bromides were obtained from commercial sources and were used without further purification. *N*-phenyl-L-phenylalanine and *N*-phenyl-L-valine were prepared according to published procedures.[1] DEPBT was prepared according to the procedure of Goodman and was purified by recrystallization from petroleum ether:ethyl acetate (1:1) followed by trituration with ethyl acetate to yield a white solid**.** Use of pure, colorless, reagent was essential to prevent degradation of enantiomeric purity during amide bond formation. Toluene, THF, ether, and dichloromethane were dried and purified using a GlassContour solvent purification system. Structural and stereochemical assignments were made on the basis of 2-D COSY, HSQC, and NOESY experiments. Ratios of diastereomers were determined by ^{1}H NMR and/or capillary GC analysis of crude reaction mixtures. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR, GC, and/or combustion analysis. The yields reported in the supporting information describe the result of a single experiment, whereas the yields reported in Tables 1-2 and Schemes 2–3 are average yields of two or more experiments. Thus, the yields reported in the supporting information may differ from those shown in Tables 1–2 and Schemes 2–3.

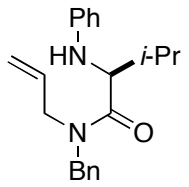
Synthesis of Substrates (Schemes 2–3)

General Procedure 1: Conversion of *N*-Phenyl Amino Acids (2) to *N*-Allyl-*N*-Benzyl-*N*'-Phenyl Amino Amides (3). A flame-dried round-bottomed flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with the *N*-phenyl amino acid substrate (1.0 equiv). THF was added to provide a 0.5 M solution, which was cooled to 0 °C and stirred. DEPBT[2] (1.2 equiv) was added, followed immediately by *N*-benzylallylamine (1 equiv), and the resulting reaction mixture was stirred at 0 °C until the starting amine had been consumed as judged by crude ^{1}H NMR analysis of an aliquot (ca. 3–4 h). Aqueous sodium bicarbonate was then added at 0 °C, and the resulting yellow reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated i*n vacuo*. The crude product was then purified via flash chromatography on silica gel.



4a

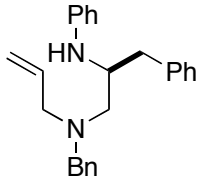
(*S*)-*N*-Allyl-*N*-benzyl-3-phenyl-2-phenylaminopropionamide (4a). General procedure 1 was employed for the coupling of (*S*)-3-phenyl-2-phenylaminopropionic acid[1] (3.63 g, 15.0 mmol) with *N*-benzylallylamine (2.21 g, 15.0 mmol). This procedure afforded 3.79 g (68%) of the title compound as a yellow oil. The enantiopurity was judged to be 98% ee by chiral hplc analysis (chiralcel OJ-H, 10% isopropanol/hexanes, 1 mL/min, RT = 11.14 min and 18.44 min). This molecule was observed as a 1.5:1 mixture of rotamers; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.17 (m, 9 H), 7.14–7.09 (m, 2 H), 6.92–6.91 (m, 1 H), 6.77–6.71 (m, 1 H), 6.66 (d, *J* = 8.0 Hz, 1 H), 6.54 (d, *J* = 7.5 Hz, 1 H), 5.73–5.66 (m, 0.4 H), 5.47–5.39 (m, 0.6 H), 5.15–4.97 (m, 2 H), 4.74 (d, *J* = 14.5 Hz, 0.6 H), 4.56–4.53 (m, 1.4 H), 4.49 (s, 0.5 H), 4.32 (d, *J* = 14.5 Hz, 0.6 H), 4.22–4.17 (m, 0.7 H), 4.03 (d, *J* = 17 Hz, 0.5 H), 3.65 (dd, *J* = 6.5, 15 Hz, 0.5 H), 3.53 (d, *J* = 5.5 Hz, 1.2 H), 3.13–3.02 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 172.8, 146.6, 146.5, 137.4, 137.3, 136.9, 136.2, 132.5, 132.4, 129.54, 129.50, 129.46, 129.43, 129.0, 128.7, 128.60, 128.56, 128.4, 127.7, 127.5, 126.9, 126.8, 126.5, 118.4, 118.1, 117.6, 114.3, 55.9, 55.6, 49.5, 48.7, 48.6, 46.4, 39.53, 39.49; IR (film) 3326, 3027, 1639 cm^{-1}. Anal. Calcd for $C_{25}H_{26}N_2O$: C, 81.05; H, 7.07; N, 7.56. Found: C, 80.90; H, 7.05; N, 7.50.



4b

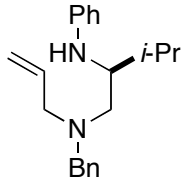
(*S*)-*N*-Allyl-*N*-benzyl-3-methyl-2-phenylaminobutyramide (4b). General procedure 1 was employed for the coupling of (*S*)-3-methyl-2-phenylaminobutyric acid[1] (1.27 g, 6.57 mmol) with *N*-benzylallylamine (967 mg, 6.57 mmol). This procedure afforded 1.37 g (65%) of the title compound as a tan solid, m.p. 48–55 °C. The enantiopurity was judged to be 99% ee by chiral hplc analysis (chiralcel OJ-H column, 10% isopropanol/hexanes, 1 mL/min, RT = 7.40 min and 10.00 min). This molecule was observed as a 1.5:1 mixture of rotamers; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.24 (m, 3 H), 7.16–7.14 (m, 2 H), 7.09–7.06 (m, 2 H), 6.73–6.66 (m, 2 H), 6.54 (d, 1 H), 5.76–5.66 (m, 1 H), 5.21–5.04 (m, 2 H), 4.88 (d, *J* = 14.5 Hz, 0.7 H), 4.70 (d, *J* = 17 Hz, 0.4 H), 4.46–4.28 (m, 2 H), 4.15 (s, 1 H), 3.97–3.93 (dd, *J* = 3.0, 17 Hz, 0.7 H), 3.84–3.79 (dd, *J* = 3.0, 17 Hz, 0.7 H), 3.60 (dd, *J* = 6.5, 15 Hz, 0.5 H), 2.09–2.08 (m, 1 H), 1.06–1.00 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 173.5, 148.25, 148.21, 137.2, 136.2, 132.7, 132.6, 129.2, 128.9, 128.6, 128.1, 127.7, 127.4, 126.6, 118.09, 118,07, 117.9, 117.7, 114.5, 114.4, 59.5, 59.2, 49.9, 48.8, 48.1, 48.0, 32.3, 32.2, 20.2, 20.1, 17.72, 17.68; IR (film) 3350, 2962, 1638 cm^{-1}. Anal. Calcd for $C_{21}H_{26}N_2O$: C, 78.22; H, 8.13; N, 8.69. Found: C, 77.96; H, 8.12; N, 8.68.

General Procedure 2: Reduction of *N*-Allyl-*N*-Benzyl-*N'*-Phenyl Amino Amides (4) to *N*-Allyl-*N*-Benzyl-*N'*-Phenyl-1,2-Diamines (1). A flame-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with the *N*-allyl-*N*-benzyl-*N'*-phenyl amino amide substrate (1.0 equiv). Diethyl ether was added to provide a 0.5 M solution, which was cooled to 0 °C with stirring. A solution of lithium aluminum hydride in diethyl ether (1 M, 2 equiv) was added dropwise, and the resulting mixture was stirred at 0 °C until the starting amide was completely consumed as judged by TLC analysis (ca. 2 h). Water (2 mL) was added dropwise, followed by 10 M aqueous NaOH (5 mL), and additional water (2 mL). The resulting suspension was stirred at rt for 5–10 minutes, then decanted, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel.



1a

(*S*)-*N*^{1}-Allyl-*N*^{1}-benzyl-3,*N*^{2}-diphenyl-propane-1,2-diamine (1a). General procedure 2 was conducted using (*S*)-*N*-allyl-*N*-benzyl-3-phenyl-2-phenylaminopropionamide **4a** (3.79 g, 10.22 mmol) as substrate. This procedure afforded 3.13 g (86%) of the title compound as a yellow oil that was judged to be 98% ee by chiral hplc analysis (chiralcel OD-H, 0.5% isopropanol/hexanes, 1 mL/min, RT = 11.15 min and 12.72 min), $[\alpha]^{23}_{D}$ –43.08° (*c* 0.26, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.23 (m, 8 H), 7.21–7.14 (m, 5 H), 6.68 (t, *J* = 7.6 Hz, 1 H), 6.60 (d, *J* = 8.4 Hz, 1 H), 5.89–5.79 (m, 1 H), 5.14–5.11 (m, 2 H), 3.93 (s, 1 H), 3.72–3.65 (m, 1 H), 3.62 (d, *J* = 13.6 Hz, 1 H), 3.51 (d, *J* = 13.6 Hz, 1 H), 3.14–3.01 (m, 2 H), 2.92 (dd, *J* = 5.2, 14.0 Hz, 1 H), 2.80 (dd, *J* = 7.2, 14.4 Hz, 1 H), 2.57–2.47 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 139.3, 138.7, 135.5, 129.6, 129.4, 129.2, 128.4, 127.2, 126.3, 118.0, 117.3, 113.4, 58.7, 57.4, 56.9, 52.3, 39.2 (one aromatic carbon signal is absent due to incidental equivalence); IR (film) 3400, 2957, 1600 cm^{-1}. Anal. Calcd for $C_{25}H_{28}N_2$: C, 84.23; H, 7.92; N, 7.86. Found: C, 84.23; H, 7.98; N, 7.87.



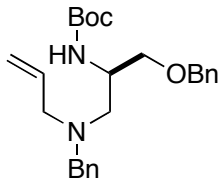
1b

(*S*)-*N*^{1}-Allyl-*N*^{1}–benzyl-3-methyl-*N*^{2}-phenyl-butane-1,2-diamine (1b) General procedure 2 was conducted using (*S*)-*N*-allyl-*N*-benzyl-3-methyl-2-phenylaminobutyramide **4b** (1.34 g, 4.16 mmol) as substrate. This procedure afforded 1.13 g (88%) of the title compound as a yellow oil that was judged to be 99% ee by chiral hplc analysis (chiralcel OD-H, 0.1% isopropanol/hexanes, 0.2 mL/min, RT = 31.65 min and 35.18 min), $[\alpha]^{23}_{D}$ –59.5° (*c* 0.98, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.23 (m, 5 H), 7.22–7.12 (m, 2 H), 6.65 (t, *J* = 7.5, 1 H), 6.56 (d, *J* = 8.5 Hz, 2 H), 5.88 (ddt, *J* = 6.0, 10.5, 16.5 Hz, 1 H), 5.18–5.13 (m, 2 H), 3.72 (s, 1 H), 3.63 (d, *J* = 13.5 Hz, 1 H), 3.50 (d, *J* = 13.5 Hz, 1 H), 3.37–3.33 (m, 1 H), 3.11 (dd, *J* = 6.0, 14.5 Hz, 1 H), 3.04 (dd, *J* = 7.0, 13.5 Hz, 1 H), 2.52–2.44 (m, 2 H), 2.13–2.06 (m, 1 H), 0.87 (dd, *J* = 4.5, 7.0 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 139.7, 136.0, 129.4, 129.2, 128.4, 127.1, 117.8, 116.8, 113.2, 58.9, 57.5, 55.9, 54.3, 29.5, 18.6, 17.5; IR (film)

3400, 3025, 1601 cm^{-1}. Anal. Calcd for $C_{21}H_{28}N_2$: C, 81.77; H, 9.15; N, 9.08. Found: C, 81.73; H, 9.21; N, 9.09.

General Procedure 3: Conversion of *N*-Boc Amino Acids (5) to *N*-Boc-*N'*-Allyl-1,2-Diamines (7). A flame-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with the *N*-boc amino acid (1.0 equiv), DCC (2.0 equiv) and a sufficient volume of dichloromethane to provide a solution with a 0.5 M amine concentration. The solution was stirred for 30 min at rt then the appropriate allylamine derivative (1.0 equiv) was added. The resulting mixture was stirred at room temperature for 12 h then filtered to remove the dicyclohexylurea byproduct. The resulting solution was washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude *N*-boc-*N'*-allyl amino amide product was purified by flash chromatography on silica gel. In some cases the purified product was contaminated with small amounts of dicyclohexyl urea. This material was carried on without further purification.

A flame-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with the *N*-boc-*N'*-allyl amino amide (1.0 equiv). Diethyl ether was added to provide a 0.5 M solution, which was cooled to 0 °C. A solution of lithium aluminum hydride in diethyl ether (1 M, 2.0 equiv) was added dropwise and the reaction was stirred at 0 °C until the starting amide was consumed as judged by TLC analysis (ca. 3 h). Water (2 mL) was added dropwise, followed by 10 M aqueous NaOH (5 mL), and additional water (2 mL). The resulting suspension was stirred at rt for 5–10 minutes, then decanted, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel.

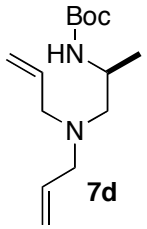


7c

(*R*)-*tert*-Butyl 1-[allyl(benzyl)amino]-3-(benzyloxy)propan-2-ylcarbamate (7c). General procedure 3 was used for the coupling of (*S*)-3-(benzyloxy)-2-(*tert*-butoxycarbonylamino)propanoic acid (5.99 g, 20.28 mmol) with *N*-benzylallylamine (2.98 g, 20.28 mmol). This procedure afforded 7.67 g (89%) of (*S*)-*tert*-butyl 1-[allyl(benzyl)amino]-3-(benzyloxy)-1-oxopropan-2-ylcarbamate as a white solid, which was contaminated with ca. 15% dicyclohexylurea. This material was carried on without further purification. The enantiopurity was judged to be 98% ee by chiral hplc analysis (chiralcel OD column,

5% isopropanol/hexanes, 1 mL/min, RT = 7.19 min and 9.13 min). This molecule was isolated as a 4.6:1 mixture of rotamers; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (m, 6 H), 7.20–7.17 (m, 4 H), 5.82–5.69 (m, 1 H), 5.43 (m, 0.8 H), 5.26–5.07 (m, 2 H), 4.99–4.97 (m, 0.2 H), 4.71–4.53 (m, 3.8 H), 4.44–4.40 (m, 0.2 H), 4.17–4.07 (m, 0.2 H), 4.02–3.96 (m, 1.8 H), 3.86–3.79 (m, 2.8 H), 3.71–3.66 (m, 0.2 H), 1.43 (m, 9 H).

The (*S*)-*tert*-butyl 1-[allyl(benzyl)amino]-3-(benzyloxy)-1-oxopropan-2-ylcarbamate product of the DCC coupling reaction (7.65 g, 18.0 mmol) was reduced following general procedure 3. This procedure afforded 4.83 g (65%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.17 (m, 10 H), 5.80 (dt, *J* = 6.8, 10.4 Hz, 1 H), 5.15–5.08 (m, 2 H), 4.81 (s, 1 H), 4.42–4.35 (m, 2 H), 3.80 (s, 1 H), 3.65–3.58 (m, 2 H), 3.51–3.44 (m, 2 H), 3.11 (dd, *J* = 8.0, 14.4 Hz, 1 H), 3.01 (dd, *J* = 6.4, 14.4 Hz, 1 H), 2.64 (dd, *J* = 7.6, 12.8 Hz, 1 H), 2.47 (dd, *J* = 6.0, 12.4 Hz, 1 H), 1.41 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 139.7, 138.5, 136.0, 129.1, 128.5, 128.4, 127.80, 127.77, 127.1, 117.7, 79.3, 73.4, 70.2, 58.6, 57.3, 54.5, 48.9, 28.6; IR (film) 3436, 2976, 1713 cm^{-1}; MS (ESI) 411.2637 (411.2648 calcd for $C_{25}H_{34}N_2O_3$, M + H^+).

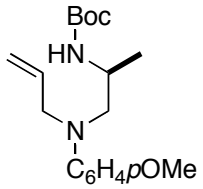


7d

(*S*)-*tert*-Butyl 1-(diallylamino)propan-2-ylcarbamate (7d). General procedure 3 was used for the coupling of (*S*)-2-*tert*-butoxycarbonylaminopropionic acid (1.16 g, 6.13 mmol), with diallylamine (595 mg, 754 μL, 6.13 mmol). This procedure afforded 1.64 g (100%) of (*S*)-*tert*-butyl 1-(diallylamino)-1-oxopropan-2-ylcarbamate as a white solid, which was contaminated with 5% dicyclohexylurea. This material was carried on without further purification. This molecule was observed as a 5:1 mixture of rotamers. Data are for the mixture ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83–5.70 (m, 2 H), 5.39 (d, *J* = 7.5 Hz, 0.8 H), 5.25–5.11 (m, 4 H), 4.99–4.96 (m, 0.2 H), 4.59–4.57 (m, 0.8 H), 4.43–4.41 (m, 0.2 H), 4.18–4.10 (m, 0.2 H), 4.06–3.88 (m, 3.6 H), 3.70–3.60 (m, 0.2 H), 1.43 (s, 9 H), 1.31 (d, *J* = 6.5 Hz, 3 H).

The (*S*)-*tert*-butyl 1-(diallylamino)-1-oxopropan-2-ylcarbamate product of the DCC coupling reaction (1.64 g, 6.16 mmol) was reduced with lithium aluminium hydride following general procedure 3. This procedure afforded 1.13 g (72%) of the title compound as a white solid, m.p. 45–47 °C. ^{1}H

NMR (500 MHz, $CDCl_3$) δ 5.85–5.77 (m, 2 H), 5.18–5.11 (m, 4 H), 4.68 (s, 1 H), 3.67–3.63 (m, 1 H), 3.12 (dd, *J* = 6.0, 14 Hz, 2 H), 3.04 (dd, *J* = 6.5, 14 Hz, 2 H), 2.40–2.30 (m, 2 H), 1.44 (s, 9 H), 1.12 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 135.9, 117.7, 79.1, 58.7, 57.3, 44.8, 28.7, 19.7; IR (film) 3326, 2930, 1690 cm^{-1}; MS (EI) 254.2003 (254.1994 calcd for $C_{14}H_{26}N_2O_2$, M + H^+).



7e

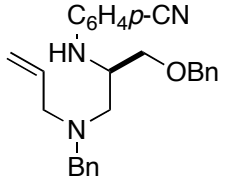
(*S*)-*tert*-Butyl 1-[allyl(4-methoxyphenyl)amino]propan-2-ylcarbamate (7e). General procedure 3 was used for the coupling of (*S*)-2-*tert*-butoxycarbonylaminopropionic acid (828 mg, 4.38 mmol) and *N*-*p*-methoxyphenylallylamine[1,3] (710 mg, 4.38 mmol). This procedure afforded 1.28 g (88%) of (*S*)-*tert*-butyl 1-[allyl(4-methoxyphenyl)amino]-1-oxopropan-2-ylcarbamate as a white solid, which was contaminated with ca. 15% of dicyclohexylurea. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.5 Hz, 2 H), 6.92 (d, *J* = 9.5 Hz, 2 H), 5.82 (ddt, *J* = 6.0, 11.0, 17 Hz, 1 H), 5.28 (d, *J* = 8.0 Hz, 1 H), 5.12 (dd, *J* = 1.5, 11 Hz, 1 H), 5.07 (dd, *J* = 1.5, 17 Hz, 1 H), 4.34–4.27 (m, 2 H), 4.18–4.11 (m, 1 H), 3.82 (s, 3 H), 1.41 (s, 9 H), 1.11 (d, *J* = 6.5 Hz, 3 H).

The (*S*)-*tert*-butyl 1-[allyl(4-methoxyphenyl)amino-1-oxopropan-2-ylcarbamate coupling product of the DCC reaction (1.28 g, 3.83 mmol) was reduced with lithium aluminum hydride following general procedure 3. This procedure afforded 4.83 g (65%) of the title compound as a white solid, m.p. 99–102 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84–6.75 (m, 4 H), 5.85–5.76 (m, 1 H), 5.14–5.10 (m, 2 H), 4.46 (s, br, 1 H), 3.95–3.76 (m, 3 H), 3.74 (s, 3 H), 3.36 (dd, *J* = 6.0, 14.4 Hz, 1 H), 3.05 (dd, *J* = 5.6, 14.4 Hz, 1 H), 1.43 (s, 9 H), 1.16 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 152.0, 143.5, 134.5, 116.7, 115.2, 114.9, 57.3, 55.9, 55.3, 45.7, 29.9, 28.6, 19.2; IR (film) 3357, 1676 cm^{-1}; MS (EI) 320.2095 (320.2100 calcd for $C_{18}H_{28}N_2O_3$).

General Procedure 4: Conversion of *N*-Boc-*N'*-Allyl-1,2-diamines (7) to *N*-aryl-*N'*-Allyl-1,2-diamines (1). A flask equipped with magnetic stirbar was charged with the appropriate *N*-boc-*N'*-allyl-1,2-diamine (1.0 equiv) and a sufficient volume of dioxane to provide a 0.1 M solution. A solution of 4 M aqueous HCl (33 equiv) was added and the reaction mixture was heated to 50 °C for 2 h. The reaction mixture was cooled to room temperature and NH_4OH was added dropwise until the solution

pH was >11. The resulting mixture was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo to afford the corresponding primary amine product. The crude product was immediately carried on without further purification.

A flame dried Schlenk tube equipped with a magnetic stirbar was charged with $Pd_2(dba)_3$ (1 mol % complex, 2 mol % Pd), (±)-BINAP (2 mol %), sodium *tert*-butoxide (1.2 equiv), the appropriate aryl bromide (1.0 equiv), and a 0.5 M solution of the primary amine (1.0 equiv) in toluene. The reaction mixture was heated to 80 °C with stirring until the starting material had been consumed as judged by TLC analysis (ca. 6 h). The mixture was cooled to rt and a solution of aqueous ammonium chloride was added (4 mL). The resulting mixture was extracted with ethyl acetate and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel.

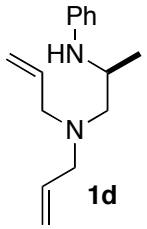


1c

(*R*)-4-{1-[Allyl(benzyl)amino]-3-(benzyloxy)propan-2-ylamino}benzonitrile (1c). General procedure 4 was used for the deprotection of (*R*)-*tert*-butyl 1-[allyl(benzyl)amino]-3-(benzyloxy)propan-2-ylcarbamate **7c** (3.9 g, 9.51 mmol). This procedure afforded 3.1 g (100%) of (*S*)-N^1-allyl-N^1-benzyl-3-benzyloxypropane-1,2-diamine as a yellow oil. The crude product was immediately subjected to the subsequent reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.21 (m, 10 H), 5.86 (dt, *J* = 6, 11 Hz, 1 H), 5.17–5.12 (m, 2 H), 4.50 (s, 2 H), 3.67 (d, *J* = 13.5 Hz, 1 H), 3.51– 3.48 (m, 2 H), 3.30–3.26 (m, 1 H), 3.20–3.12 (m, 2 H), 3.00 (dd, *J* = 5.4, 7.5 Hz, 1 H), 2.46–2.38 (m, 2 H), 1.60 (s, 2 H); MS (ESI) 311.2116 (311.2123 calcd for $C_{20}H_{26}N_2O$, M + H^+).

General procedure 4 was used for the *N*-arylation of (*S*)- N^1-allyl-N^1-benzyl-3-benzyloxypropane-1,2-diamine (900 mg, 2.89 mmol) with 4-bromobenzonitrile (527 mg, 2.89 mmol). This procedure afforded 864 mg (73%) of the title compound as an orange oil. The enantiopurity was judged to be 98% ee by chiral hplc analysis (chiralcel AD column, 0.7% isopropanol/hexanes, 1 mL/min, RT = 24.75 min and 28.10 min), $[\alpha]^{23}_D$ –25.59° (*c* 0.79, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.28

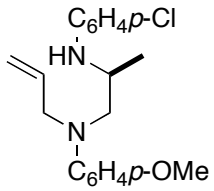
(m, 12 H), 6.40 (d, *J* = 8.5 Hz, 2 H), 5.85 (dt, *J* = 6.5, 10.5 Hz, 1 H), 5.22–5.16 (m, 2 H), 4.54 (d, *J* = 6.5 Hz, 1 H), 4.49–4.44 (m, 2 H), 3.67 (dd, *J* = 3.0, 9.0 Hz, 1 H), 3.65–3.56 (m, 2 H), 3.53–3.46 (m, 2 H), 3.17–3.10 (m, 2 H), 2.74 (dd, *J* = 7.5, 13.5 Hz, 1 H), 2.60 (dd, *J* = 6.5, 13.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 139.5, 138.0, 135.6, 133.8, 129.1, 128.6, 128.5, 127.99, 127.90, 127.4, 120.7, 118.1, 112.7, 98.6, 73.5, 69.9, 59.3, 58.3, 54.3, 51.4; IR (film) 3365, 2211, 1606 cm^{-1}; MS (ESI) 412.2383 (412.2389 calcd for $C_{27}H_{29}N_3O$, M + H$^+$).



1d

(*S*)-*N*^{1},*N*^{1}-Diallyl-*N*^{2}-phenylpropane-1,2-diamine (1d). General procedure 4 was used for the deprotection of 1.08 g (4.24 mmol) of (*S*)-*tert*-butyl 1-(diallylamino)propan-2-ylcarbamate **7d** (1.08 g, 4.24 mmol). This procedure afforded 654 mg (85%) of (*S*)-*N*^{1},*N*^{1}-diallylpropane-1,2-diamine as a yellow oil. The crude product was immediately subjected to the subsequent reaction without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95–5.87 (m, 2 H), 5.19–5.15 (m, 4 H), 3.70 (s, br, 2 H), 3.36–3.30 (m, 1 H), 3.24–3.20 (m, 2 H), 3.13–3.10 (m, 2 H), 2.66 (dd, *J* = 10.5, 15 Hz, 1 H), 2.53 (dd, *J* = 4.5, 14 Hz, 1 H). 1.40 (d, *J* = 6.5 Hz, 3 H).

General procedure 4 was used for the *N*-arylation of (*S*)-*N*^{1},*N*^{1}-diallylpropane-1,2-diamine (379 mg, 2.46 mmol) with bromobenzene (386 mg, 2.46 mmol). This procedure afforded 390 mg (69%) of the title compound as a yellow oil. The enantiopurity was judged to be 99% ee by chiral hplc analysis (chiralcel OJ-H column, 1% IPA/hexanes, 0.2 mL/min, RT = 38.71 min and 43.68 min), $[\alpha]^{23}_D$ –4.61° (*c* 0.23, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18–7.15 (m, 2 H), 6.69 (t, *J* = 7.5 Hz, 1 H), 6.64 (d, *J* = 8.5 Hz, 2 H), 5.83 (ddt, *J* = 6.5, 7.0, 10 Hz, 2 H), 5.18–5.12 (m, 4 H), 4.20 (s, 1 H), 3.50–3.43 (m, 1 H), 3.17 (dd, *J* = 6.0, 14 Hz, 2 H), 3.04 (dd, *J* = 7.0, 14.5 Hz, 2 H), 2.54 (dd, *J* = 8.5, 13 Hz, 1 H), 2.42 (dd, *J* = 6.0, 13 Hz, 1 H), 1.19 (d, *J* = 6.0 Hz, 3 H); ^{13}C (100 MHz, $CDCl_3$) δ 148.4, 135.7, 129.3, 117.7, 117.3, 113.7, 59.0, 57.2, 46.6, 19.9; IR (film) 3350, 2924, 1602 cm^{-1}; MS (EI) 230.1787 (230.1783 calcd for $C_{15}H_{22}N_2$).



1e

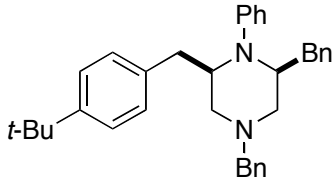
(*S*)-*N*^{1}-Allyl-*N*^{2}-(4-chlorophenyl)-*N*^{1}-(4-methoxyphenyl)propane-1,2-diamine (1e) General procedure 4 was used for the deprotection of (*S*)-*tert*-butyl 1-[allyl(4-methoxyphenyl)amino]propan-2-ylcarbamate **7e** (513 mg, 1.60 mmol). This procedure afforded 318 mg (91%) of (*S*)-*N*^{1}-allyl-*N*^{1}-(4-methoxyphenyl)propane-1,2-diamine as a yellow oil. The crude product was immediately subjected to the subsequent reaction without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (d, *J* = 9.0 Hz, 2 H), 6.75 (d, *J* = 9.0 Hz, 2 H), 5.86–5.79 (m, 1 H), 5.14–5.11 (m, 2 H), 3.90 (dd, *J* = 1.5, 5.0 Hz, 2 H), 3.75 (s, 3 H), 3.26–3.21 (m, 1 H), 3.20 (d, *J* = 4.5 Hz, 1 H), 3.00–2.96 (m, 1 H), 1.60 (s, br, 2 H), 1.09 (d, *J* = 6.0 Hz, 3 H).

General procedure 4 was used for the *N*-arylation of (*S*)-*N*^{1}-allyl-*N*^{1}-(4-methoxyphenyl)propane-1,2-diamine (64 mg, 0.29 mmol) with 4-chlorobromobenzene (55 mg, 0.29 mmol). This procedure afforded 65 mg (69%) of the title compound as a yellow oil. The enantiopurity was judged to be 98% ee by chiral hplc analysis (chiralcel OD column, 1% isopropanol/hexanes, 0.2 mL/min, RT = 59.14 min and 63.37 min), $[\alpha]^{23}_{D}$ +21.46° (*c* 0.11, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.8 Hz, 2 H), 6.83 (d, *J* = 9.2 Hz, 2 H), 6.75 (d, *J* = 9.2 Hz, 2 H), 6.48 (d, *J* = 8.8 Hz, 2 H), 5.86–5.77 (m, 1 H), 5.16–5.11 (m, 2 H), 3.95–3.79 (m, 2 H), 3.77 (s, 3 H), 3.74–3.63 (m, 2 H), 3.32–3.22 (m, 2 H), 1.22 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 146.4, 143.6, 134.6, 129.2, 121.9, 116.9, 116.2, 114.9, 114.6, 57.8, 55.9, 55.7, 48.0, 19.5; IR (film) 3391, 2929, 1598 cm^{-1}; MS (EI) 330.1490 (330.1500 calcd for $C_{19}H_{23}ClN_2$).

Synthesis of Piperazines via Coupling with Aryl Bromides (Tables 1–2)

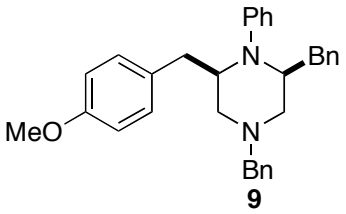
General Procedure for Pd-Catalyzed Synthesis of Piperazines. A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with $Pd_2(dba)_3$ (1 mol % complex, 2 mol % Pd), P(2-furyl)$_3$ (8 mol %), sodium *t*-butoxide (1.2 equiv), and the aryl bromide (1.2 equiv). The Schlenk tube was purged with nitrogen and the amine was added as a solution in toluene (2.5 mL/0.5 mmol substrate). The Schlenk tube was then heated to 105 °C with stirring until

the starting material has been consumed as judged by ^{1}H NMR analysis of an aliquot taken from the reaction mixture. The reaction mixture was then cooled to room temperature, saturated aqueous ammonium chloride (2–3 mL) was added, and the resulting mixture was extracted with ethyl acetate (3 x 8 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.



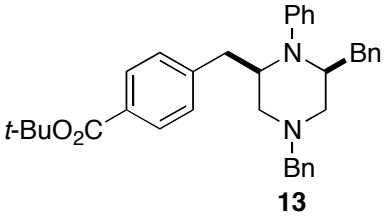
12

(2*S*,6*R*)-2,4-Dibenzyl-6-(4-*tert*-butylbenzyl)-1-phenylpiperazine (12). The reaction of 150 mg (0.42 mmol) of N^1-allyl-N^1-benzyl-3,N^2-diphenylpropane-1,2-diamine (**1a**) with 108 mg (0.51 mmol) of 4-bromo-tert-butylbenzene was conducted for 10 h according to the general procedure. The product was formed with >20:1 dr as judged by ^{1}H NMR analysis of a sample taken from the crude reaction mixture. Upon purification, 132 mg (64%) of the title compound was obtained as a white solid, m.p. 74–77 °C. This material was judged to be of >20:1 dr by ^{1}H NMR analysis. The enantiopurity was judged to be 99% ee by chiral hplc analysis (chiralcel OJ-H column, 2 % isopropanol/hexanes, 0.1 mL/min, RT = 55.13 min and 101.14 min), $[\alpha]^{23}_D$ + 5.48° (*c* 0.27, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.38 (m, 7 H), 7.24–7.17 (m, 5 H), 7.07–6.99 (m, 6 H), 6.83 (t, *J* = 7.2 Hz, 1 H), 3.80 (d, *J* = 6.4 Hz, 2 H), 3.54-3.44 (m, 2 H), 3.07 (t, *J* = 12.8 Hz, 2 H), 2.94–2.87 (m, 2 H), 2.79 (t, *J* = 11.2 Hz, 2 H), 2.15–2.07 (m, 2 H), 1.31 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 147.1, 140.4, 139.0, 137.3, 130.1, 129.9, 129.5, 129.1, 128.7, 128.6, 127.5, 126.2, 125.6, 117.4, 113.5, 63.2, 55.6, 55.5, 54.5, 54.1, 37.5, 36.9, 34.6, 31.6; IR (film) 2960, 1597 cm^{-1}; MS (ESI) 489.3272 (489.3270 calcd for $C_{35}H_{40}N_2$, M + H$^+$).



9

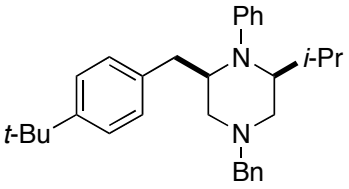
(2*S*,6*R*)-2,4-Dibenzyl-6-(4-methoxybenzyl)-1-phenylpiperazine (9). The reaction of 150 mg (0.42 mmol) of N^1-allyl-N^1-benzyl-3,N^2-diphenylpropane-1,2-diamine (**1a**) with 95 mg (0.51 mmol) of 4-bromoanisole was conducted for 10 h according to the general procedure. The product was formed with >20:1 dr as judged by ^{1}H NMR analysis of a sample taken from the crude reaction mixture. Upon purification, 120 mg (62%) of the title compound was obtained as a white solid, m.p. 119–122 °C. This material was judged to be of >20:1 dr by ^{1}H NMR analysis. The enantiopurity was judged to be 99% ee by chiral hplc analysis (chiralcel OJ-H column, 10 % isopropanol/hexanes, 0.5 mL/min, RT = 15.12 min and 30.50 min), $[\alpha]^{23}_{D}$ +13.51° (*c* 0.48, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.38 (m, 7 H), 7.26–7.18 (m, 3 H), 7.06 (d, *J* = 8.0 Hz, 4 H), 6.95 (d, *J* = 8.4 Hz, 3 H), 6.84 (t, *J* = 6.0 Hz, 1 H), 6.77 (d, *J* = 8.4 Hz, 1 H), 3.83–3.74 (m, 5 H), 3.52–3.45 (m, 2 H), 3.11–2.99 (m, 2 H), 2.89 (d, *J* = 11.6 Hz, 2 H), 2.83-2.73 (m, 2 H), 2.13–2.10 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 147.0, 140.3, 138.9, 132.4, 130.4, 130.1, 129.9, 129.5, 128.7, 128.6, 127.4, 126.2, 117.4, 114.1, 113.5, 63.2, 55.8, 55.6, 55.4, 54.3, 54.1, 37.5, 36.5; IR (film) 3026, 2812, 1597 cm^{-1}; MS (ESI) 463.2744 (463.2749 calcd for $C_{32}H_{34}N_2O$, M + H^+).



13

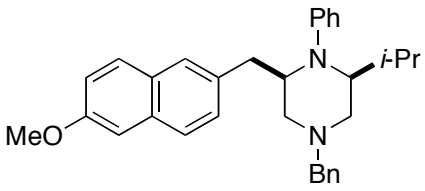
(2*R*,6*S*)-*tert*-butyl 4-[(4,6-dibenzyl-1-phenylpiperazin-2-yl)methyl]benzoate (13). The reaction of 150 mg (0.42 mmol) of N^1-allyl-N^1-benzyl-3,N^2-diphenylpropane-1,2-diamine with 130 mg (0.51 mmol) of 4-bromo-*tert*-butylbenzoate was conducted for 10 h according to the general procedure. The product was formed with >20:1 dr as judged by ^{1}H NMR analysis of a sample taken from the crude reaction mixture. Upon purification, 132 mg (59%) of the title compound was obtained as a white solid, m.p. 75–77 °C. This material was judged to be of >20:1 dr by ^{1}H NMR analysis. The enantiopurity was judged to be 99% ee by chiral hplc analysis (chiralcel OD-H column, 5 % isopropanol/hexanes, 2 mL/min, RT = 1.40 min and 1.94 min), $[\alpha]^{23}_{D}$ + 35.1° (*c* 0.30, CH_2Cl_2). ^{1}H

NMR (500 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 1.5, 6.5 Hz, 2 H), 7.47–7.40 (m, 7 H), 7.27–7.25 (m, 2 H), 7.24–7.18 (m, 1 H), 7.08–7.06 (m, 6 H), 6.87 (t, *J* = 7.0 Hz, 1 H), 3.82 (t, *J* = 11 Hz, 2 H), 3.49 (m, 2 H), 3.16–3.06 (m, 2 H), 2.91–2.81 (m, 4 H), 2.18–2.11 (m, 2 H), 1.61 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 146.9, 145.2, 140.2, 138.7, 130.10, 130.06, 129.96, 129.86, 129.4, 129.3, 128.7, 128.6, 127.6, 126.3, 117.8, 113.7, 81.0, 63.1, 55.7, 55.5, 54.3, 54.1, 37.6, 37.4, 28.4; IR (film) 2975, 1711, 1598 cm^{-1}; MS (ESI) 533.3166 (533.3168 calcd for $C_{36}H_{40}N_2O_2$,M + H^+).



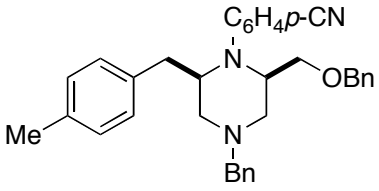
14

(2*S*,6*R*)-4-Benzyl-2-(4-*tert*-butylbenzyl)-6-isopropyl-1-phenylpiperazine (14). The reaction of 150 mg (0.49 mmol) of N^1-allyl-N^1-benzyl-3-methyl-N^2-phenylbutane-1,2-diamine (**1b**) with 145 mg (0.68 mmol) of 4-bromo-*tert*-butylbenzene was conducted for 10 h according to the general procedure using 2 mol % $Pd_2(dba)_3$ and 16 mol % P(2-furyl)$_3$. The product was formed with >20:1 dr as judged by ^{1}H NMR analysis of a sample taken from the crude reaction mixture. Upon purification, 110 mg (51%) of the title compound was obtained as a white solid, m.p. 83–86 °C. This material was judged to be of >20:1 dr by ^{1}H NMR analysis. The enantiopurity was judged to be 99% ee by chiral hplc analysis (chiralcel OD-H column, 100% hexanes, 1 mL/min, RT = 6.29 min and 7.06 min), $[\alpha]^{23}_D$ + 3.13° (*c* 0.17, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.29 (m, 7 H), 7.24–7.18 (m, 4 H), 7.01 (t, *J* = 7.2 Hz, 1 H), 6.95 (d, *J* = 8.0 Hz, 2 H), 3.57 (d, *J* = 13.2 Hz, 1 H), 3.49–3.47 (m, 1 H), 3.44 (d, *J* = 16 Hz, 1 H), 3.30–3.27 (m, 1 H), 2.74–2.62 (m, 2 H), 2.57–2.54 (m, 1 H), 2.49–2.45 (m, 2 H), 2.37–2.32 (m, 1 H), 1.94–1.89 (m, 1 H), 1.32 (9 H), 0.90 (d, *J* = 6.8 Hz, 3 H), 0.81 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 148.8, 138.5, 136.8, 129.4, 129.3, 129.0, 128.3, 127.1, 125.2, 121.8, 63.4, 63.0, 60.7, 57.2, 53.7, 38.3, 34.5, 31.6, 29.8, 20.8, 18.2 (one aromatic carbon signal is absent due to incidental equivalence); IR (film) 2915, 1604 cm^{-1}. MS (ESI) 441.3269 (441.3270 calcd for $C_{31}H_{40}N_2$, M + H^+).



15

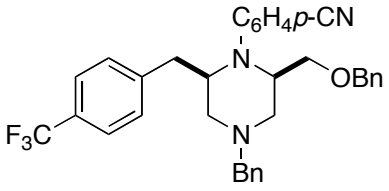
(2*S*,6*R*)-4-Benzyl-2-isopropyl-6-(6-methoxynaphthalen-2-ylmethyl)-1-phenylpiperazine (15). The reaction of 100 mg (0.32 mmol) of N^1-allyl-N^1-benzyl-3-methyl-N^2-phenylbutane-1,2-diamine with 108 mg (0.45 mmol) of 2-bromo-6-methoxynapthalene was conducted for 10 h according to the general procedure. The product was formed with >20:1 dr as judged by ^{1}H NMR analysis of a sample taken from the crude reaction mixture. Upon purification, 77 mg (51%) of the title compound was obtained as a white solid, m.p. 114–119 °C. This material was judged to be of >20:1 dr by ^{1}H NMR analysis. The enantiopurity was judged to be 99% ee by chiral hplc analysis (chiralcel AD column, 5% isopropanol/hexanes, 0.9 mL/min, RT = 4.22 min and 5.78 min), $[\alpha]^{23}_{D}$ + 33.5° (*c* 0.34, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 6.4, 8.8 Hz, 2 H), 7.36–7.26 (m, 7 H), 7.21–7.19 (m, 3 H), 7.13–7.07 (m, 3 H), 7.01 (t, *J* = 7.2 Hz, 1 H), 3.91 (s, 3 H), 3.56 (d, *J* = 12.8 Hz, 1 H), 3.54–3.49 (m, 1 H), 3.35 (d, *J* = 13.2 Hz, 1 H), 3.29–3.25 (m, 1 H), 2.86–2.73 (m, 2 H), 2.55 (dd, *J* = 3.2, 10.8 Hz, 1 H), 2.47–2.41 (m, 2 H), 2.35 (dd, *J* = 6.4, 10.8 Hz, 1 H), 1.93–1.87 (m, 1 H), 0.89 (d, *J* = 6.8 Hz, 3 H), 0.79 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 150.4, 138.5, 135.1, 133.2, 129.44, 129.36, 129.17, 129.16, 128.5, 128.4, 127.6, 127.2, 126.8, 122.0, 118.8, 105.8, 63.5, 63.2, 60.8, 57.3, 55.5, 53.7, 39.0, 29.8, 20.8, 18.2 (one aromatic carbon signal is absent due to incidental equivalence); IR (film) 2956, 1604 cm^{-1}; MS (ESI) 465.2899 (465.2906 calcd for $C_{32}H_{36}N_2O$, M + H^+).



16

(2*R*,6*R*)-4-[4-Benzyl-2-benzyloxymethyl-6-(4-methylbenzyl)piperazin-1-yl]benzonitrile (16). The reaction of 150 mg (0.37 mmol) of (*R*)-4-{1-[allyl(benzyl)amino]-3-(benzyloxy)propan-2-ylamino}benzonitrile (**1c**) with 75 mg (0.48 mmol) of 4-bromotoluene was conducted for 10 h according to the general procedure. The product was formed with 14:1 dr as judged by ^{1}H NMR analysis of a sample taken from the crude reaction mixture. Upon purification, 128 mg (70%) of the title compound was obtained as a white solid, m.p. 125–133 °C. This material was determined to

contain a 14:1 mixture of diastereomers as judged by ^{1}H NMR analysis. The enantiopurity of the major diastereomer was judged to be 97% ee by chiral hplc analysis (chiralcel AD column, 10 % isopropanol/hexanes, 1 mL/min, RT = 5.32 min and 7.41 min), $[\alpha]^{23}_D$ +168.99° (*c* 0.17, CH_2Cl_2). Data are for the major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 9.0 Hz, 2 H), 7.40–7.33 (m, 7 H), 7.32–7.28 (m, 3 H), 6.96 (d, *J* = 8.0 Hz, 2 H), 6.84 (d, *J* = 9.0 Hz, 2 H), 6.69 (d, *J* = 8.0 Hz, 2 H), 4.55–4.48 (m, 2 H), 3.95–3.89 (m, 2 H), 3.72–3.70 (m, 1 H), 3.61 (d, *J* = 12 Hz, 1 H), 3.39–3.35 (m, 2 H), 3.26 (dd, *J* = 1.5, 11 Hz, 1 H), 2.83 (d, *J* = 11.5 Hz, 1 H), 2.75 (t, *J* = 12 Hz, 1 H), 2.44 (d, *J* = 12.5 Hz, 1 H), 2.31–2.28 (M, 1 H), 2.28 (s, 3 H), 1.96 (dd, *J* = 3.0, 11 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.2, 138.6, 138.2, 136.2, 135.8, 134.1, 129.8, 129.5, 129.2, 128.7, 128.6, 128.13, 128.06, 127.6, 120.6, 112.1, 99.6, 73.7, 68.5, 62.8, 55.0, 54.4, 53.1, 52.6, 37.0, 21.2; IR (film) 2919, 1603 cm^{-1}; MS (ESI) 524.2679 (524.2678 calcd for $C_{34}H_{35}N_3O$, M + Na^+).



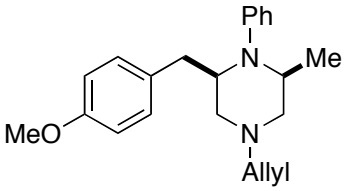
17

(2*R*,6*R*)-4-[4-Benzyl-2-benzyloxymethyl-6-(4-trifluoromethylbenzyl)piperazin-1-yl]benzonitrile (17). The reaction of 150 mg (0.37 mmol) of (*R*)-4-{1-[allyl(benzyl)amino]-3-(benzyloxy)propan-2-ylamino}benzonitrile (**1c**) with 98 mg (0.44 mmol) of 4-bromobenzotrifluoride was conducted for 10 h according to the general procedure. The product was formed with 14:1 dr as judged by ^{1}H NMR analysis of a sample taken from the crude reaction mixture. Upon purification, 131 mg (65%) of the title compound was obtained as a white solid, m.p. 154–157 °C. This material was determined to contain a 14:1 mixture of diastereomers as judged by ^{1}H NMR analysis. The enantiopurity of the major diastereomer was judged to be 99% ee by chiral hplc analysis (chiralcel AD column, 10 % isopropanol/hexanes, 1 mL/min, RT = 5.99 min and 8.68 min), $[\alpha]^{23}_D$ + 155.58° (*c* 0.13, CH_2Cl_2). The diastereomers were subsequently separated by careful flash chromatography on silica gel.

Major (*cis*) diastereomer (**17**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.0 Hz, 2 H), 7.41–7.31(m, 12 H), 6.82 (t, *J* = 8.8 Hz, 4 H), 4.59–4.51 (m, 2 H), 3.97–3.89 (m, 2 H), 3.74–3.71 (m, 1 H), 3.66 (d, *J* = 12.4 Hz, 1 H), 3.38 (d, *J* = 6.8 Hz, 1 H), 3.32–3.27 (m, 2 H), 2.80 (t, *J* = 12.4 Hz, 1 H), 2.71 (d, *J* = 11.6, 1 H), 2.51 (d, *J* = 12.4 Hz, 1 H), 2.37 (dd, *J* = 2.4, 11.6 Hz, 1 H), 1.95 (dd, *J* = 3.2, 12 Hz, 1 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 150.0, 142.8, 138.4, 138.1, 134.1, 130.0, 129.6, 129.0, 128.74, 128.69,

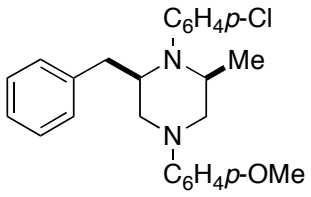
128.2, 128.1, 127.7, 125.6 (q, J = 14.5 Hz), 124.3 (q, J = 270.5 Hz), 120.4, 112.1, 99.1, 73.6, 68.4, 62.8, 54.7, 54.5, 53.2, 52.1, 37.3; IR (film) 2817, 1603 cm^{-1}; MS (ESI) 578.2402 (578.2395 calcd for $C_{34}H_{32}F_3N_3O$, M + Na^+).

Minor (*trans*) diastereomer (**17b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.4 Hz, 2 H), 7.37–7.26 (m, 11 H), 7.19–7.17 (m, 2 H), 7.10 (d, J = 8.4 Hz, 2 H), 6.79 (d, J = 8.0 Hz, 2 H), 4.38 (s, 2 H), 3.80–3.76 (m, 1 H), 3.68–3.62 (m, 2 H), 3.49 (dd, J = 2.4, 9.6 Hz, 1 H), 3.34–3.31 (m, 2 H), 3.19 (dd, J = 2.4, 11.2 Hz, 1 H), 3.03–2.97 (m, 1 H), 2.53–2.49 (m, 2 H), 2.46–2.41 (m, 1 H), 2.30 (dd, J = 3.2, 11.2 Hz, 1 H).



18

(2*R*,6*S*)-4-Allyl-2-(4-methoxybenzyl)-6-methyl-1-phenylpiperazine (18). The reaction of 124 mg (0.54 mmol) of (*S*)-N^1,N^1-diallyl-N^2-phenylpropane-1,2-diamine (**1d**) with 121 mg (0.65 mmol) of 4-bromoanisole was conducted for 10 h according to the general procedure. The product was formed with >20:1 dr as judged by ^{1}H NMR analysis of a sample taken from the crude reaction mixture. Upon purification, 91 mg (50%) of the title compound was obtained as a yellow oil. This material was judged to be of >20:1 dr by ^{1}H NMR analysis. The enantiopurity was judged to be 99% ee by chiral hplc analysis (OD-H column, 100% hexanes, 1 mL/min, RT = 19.75 min and 22.39 min), $[\alpha]^{23}_D$ + 112.18 (*c* 0.26, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (t, J = 8.5 Hz, 2 H), 7.17 (d, J = 8.0 Hz, 2 H), 7.07 (t, J = 7.5 Hz, 1 H), 6.98 (d, J = 9.0 Hz, 2 H), 6.79–6.76 (m, 2 H), 5.90–5.82 (m, 1 H), 5.20–5.12 (m, 2 H), 3.77 (s, 3 H), 3.45–3.40 (m, 1 H), 3.38–3.35 (m, 1 H), 3.06–3.01 (m, 1 H), 2.92–2.88 (m, 1 H), 2.71 (dd, J = 2.0, 11 Hz, 1 H), 2.57 (dd, J = 3.5, 13.5 Hz, 1 H), 2.51 (d, J = 10 Hz, 1 H), 2.44–2.40 (m, 1 H), 2.26–2.18 (m, 2 H), 0.94 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 149.2, 135.2, 131.8, 130.2, 129.4, 123.2, 118.1, 113.8, 61.9, 60.5, 60.4, 57.4, 55.4, 54.2, 37.9, 18.8 (one carbon signal is absent due to incidental equivalence); IR (film) 3400, 2929, 1597 cm^{-1}; MS (ESI) 337.2263 (337.2280 calcd for $C_{22}H_{28}N_2O$, M + H^+).

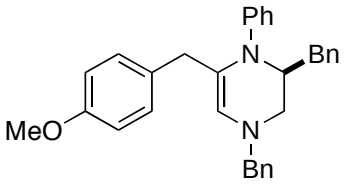


19

(2*R*,6*S*)-2-Benzyl-1-(4-chlorophenyl)-4-(4-methoxyphenyl)-6-methylpiperazine (19). The reaction of 47 mg (0.14 mmol) of N^1-allyl-N^2-(4-chlorophenyl)-N^1-(4-methoxyphenyl)propane-1,2-diamine (**1e**) with 22 mg (0.17 mmol) of bromobenzene was conducted for 10 h according to the general procedure. The product was formed with >20:1 dr as judged by ^{1}H NMR analysis of a sample taken from the crude reaction mixture. Upon purification, 29 mg (51%) of the title compound was obtained as a yellow oil. This material was judged to be of >20:1 dr by ^{1}H NMR analysis. The enantiopurity was judged to be 99% ee by chiral hplc analysis (chiralcel OD-H column, 1% isopropanol/hexanes, 0.5 mL/min, RT = 9.27 min and 10.30 min), $[\alpha]^{23}_{D}$ + 58.87° (*c* 0.55, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.27 (m, 4 H), 7.21–7.18 (m, 1 H), 7.12–7.09 (m, 4 H), 6.86–6.81 (m, 4 H), 3.76 (s, 3 H), 3.59–3.55 (m, 1 H), 3.52–3.49 (m, 1 H), 3.25 (dd, *J* = 3.5, 12 Hz, 1 H), 3.07 (dd, *J* = 3.0, 12 Hz, 1 H), 2.92–2.88 (m, 2 H), 2.68 (dd, *J* = 3.5, 13.5 Hz, 1 H), 2.58 (dd, *J* = 10.5, 13.5 Hz, 1 H), 1.05 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.2, 147.5, 146.0, 139.4, 129.5, 129.3, 128.7, 128.0, 126.5, 123.6, 118.9, 114.7, 60.2, 58.3, 55.8, 54.7, 53.8, 38.6, 18.5; IR (film) 2930, 1510 cm^{-1}; MS (ESI) 407.1895 (407.1890 calcd for $C_{25}H_{27}ClN_2O$, M + H^+).

Isolation and Characterization of Side Products 10 and 11

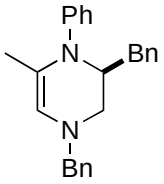
Side products **10** and **11** were isolated by careful chromatography of the crude mixture of products obtained from the $Pd_2(dba)_3$/P(*o*-tol)$_3$-catalyzed reaction of **1a** with 4-bromoanisole. These compounds were characterized by ^{1}H NMR and 2-D COSY analysis. Data are as follows:



10

(*S*)-4-allyl-6-(4-methoxybenzyl)-2-methyl-1-phenyl-1,2,3,4-tetrahydropyrazine (10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.31 (m, 4 H), 7.20–7.12 (m, 5 H), 6.99–6.97 (m, 2 H), 6.89–6.85 (m, 1 H),

6.80–6.77 (m, 2 H), 6.75–6.73 (m, 2 H), 6.69 (d, *J* = 8.0 Hz, 1 H), 6.60 (dd, *J* = 1.0, 8.5 Hz, 2 H), 5.82 (s, 1 H), 4.08–3.98 (m, 2 H), 3.79 (s, 3 H), 3.56–3.52 (m, 1 H), 3.36 (d, *J* = 10.5, 15.5 Hz, 1 H), 3.14 (d, *J* = 15 Hz, 1 H), 2.74–2.66 (m, 2 H), 2.61–2.59 (m, 1 H), 2.49 (dd, *J* = 5.0, 13 Hz, 1 H).



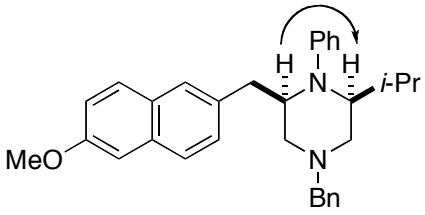
11

(*S*)-4-allyl-2,6-dimethyl-1-phenyl-1,2,3,4-tetrahydropyrazine (11). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.19 (m, 10 H), 7.13–7.10 (m, 2 H), 6.82 (dt, *J* = 1.0, 7.0 Hz, 1 H), 6.56 (d, *J* = 8.0 Hz, 2 H), 5.68 (s, 1 H), 4.04–3.95 (m, 2 H), 3.67–3.64 (m, 1 H), 3.07 (dd, *J* = 4.0, 13 Hz, 1 H), 2.73–2.68 (m, 2 H), 2.62 (dd, *J* = 2.5, 10.5 Hz, 1 H), 1.73 (s, 3 H).

Assignment of Stereochemistry

2-Isopropylpiperazines 14 and 15

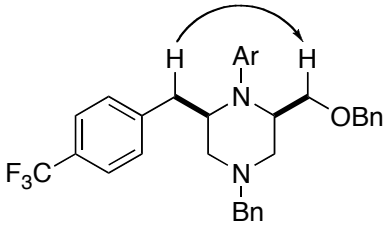
The stereochemistry of 2-isopropylpiperazine **15** was assigned on the basis of 2D NOESY experiments. The key nOe signals are shown below. The stereochemistry of piperazine **14** was assigned based on analogy to **15**.



15

2-Benzyloxymethylpiperazines 16 and 17

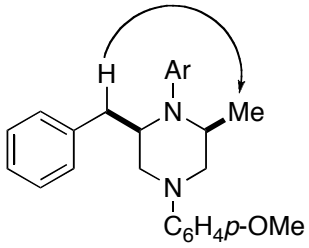
The stereochemistry of 2-benzyloxymethylpiperazine **17** was assigned on the basis of 2D NOESY experiments. The key nOe signals are shown below. The stereochemistry of piperazine **16** was assigned based on analogy to **17**.



17
(Ar = *p*-C_6H_4CN)

2-Methylpiperazine 19

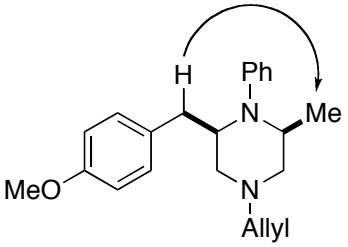
The stereochemistry of 2-methylpiperazine **19** was assigned on the basis of 2D NOESY experiments. The key nOe signals are shown below.



19
(Ar = C_6H_4Cl)

2-Methylpiperazine 18 and 2-Benzylpiperazines 9, 12, and 13

The stereochemistry of 2-methylpiperazine **18** was assigned on the basis of 2D NOESY experiments. The key nOe signals are shown below. The stereochemistry of 2-benzylpiperazines **9**, **12**, and **13** was assigned based on analogy to **17**.



18

References

(1) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, 120, 12459–12467.

(2) Li, H.; Jiang, X.; Ye, Y.-h.; Fan, C.; Romoff, T.; Goodman, M. *Org. Lett.* **1999,** 1, 91–94.

(3) Cai,Q.; Zhu, W.; Zhang, H.; Zhang, Y.; Ma, D. *Synthesis* **2005**, 496–499.