A Copper-catalyzed Arylation of β -Amino Alcohols

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Supporting Information

General Considerations: Copper (I) iodide (98 %) and cesium carbonate were purchased from Strem Chemical Company. Potassium phosphate was manufactured by Riedel-de Haen and was purchased from Fluka (Note: We have found this finely granulated form to be best). All other reagents are available commercially and were used without further purification. All reagents were weighed and handled in air. Flash column chromatography was performed with Silicycle ultra pure silica gel (230-400 mesh). Melting points were recorded on a Mel-Temp II, Laboratory Devices, Inc. IR spectra were recorded on an ASI ReactIRTM 1000 and were obtained by placing samples directly on the DiComp probe. Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA. ¹H and ¹³C NMR were obtained on a Varian 300 or 500 MHz instrument with chemical shifts reported relative to tetramethyl silane using residual solvent signals or TMS as an internal standard. High resolution mass spectra were obtained on a Bruker ESP-300 EPR spectrometer. Gas chromatographic analyses were performed on a Hewlett Packard 5890 instrument with a FID detector and a Hewlett Packard 30 m x 0.25 mm i.d. HP-5 capillary column. Chiral HPLC analyses were performed on a Hewlett-Packard 1100 system with an HP 1100 Diode Array Detector (monitoring at 254 nm) using an analytical (*R,R*)-Whelk-O 1 column (25 cm x 4.6 mm i.d., 5 micron 100 Å spherical silica) purchased from Regis Technologies Inc., Morton Grove, IL. Samples were compared with their identically prepared racemates or were chromatographed in various ratios with their antipodes, likewise prepared identically. Control reactions without CuI were performed for all compounds; the amount of product observed by gas chromatography for the control reactions was 0-8%. Although satisfactory elemental analyses were obtained for all *N*-aryl products, the ¹H NMR of the products obtained as oils sometimes indicated the presence of trace amounts of chromatography solvent.

2-(2,6-Dimethyl-phenylamino)-1-phenyl-ethanol (Table 1, Entry 1). A screw-cap test tube was charged with CuI (5.0 mg, 0.025 mmol, 2.5 mol%), sodium hydroxide (80.0 mg, 2.0 mmol), 2-amino-1-phenyl ethanol (137 mg, 1.0 mmol), and 2,6-dimethyl-iodobenzene (169 μ L, 1.2 mmol). The test tube was fitted with a septum and purged with nitrogen before addition of DMSO (0.67 mL) and H₂O (0.33 mL). The test tube was then capped and stirred in an oil bath at 90 °C for 16.5 h. The resulting mixture was cooled to room temperature and diluted with water (4 mL) before extraction with methylene chloride (3 x 5 mL). The combined organic layers were washed with 0.1 M NaOH (1 x 5 mL), washed with brine (1 x 5 mL), dried over MgSO₄, and concentrated in vacuo. Flash chromatography of the crude product (CH₂Cl₂:Et₂O, 90:10) provided 206.4 mg (86 %) of the title compound as a pale yellow oil. ¹H NMR (300 MHz, CDCl₃): δ 2.20 (s, 3H), 3.04 (dd, *J* = 12.6, 8.5 Hz, 1H), 3.17 (dd, *J* = 12.9, 3.9 Hz, 1H), 3.41 (broad s, 2H), 4.69 (dd, *J* = 8.5, 3.6 Hz, 1H), 6.81 (app dd, *J* = 8.2, 6.2 Hz, 1H), 6.94 (app d, *J* = 8.1 Hz, 2H), 7.26 (m, 5H). ¹³C NMR (75 MHz, CDCl₃): δ 17.3, 51.3, 72.0, 110.2, 117.5, 122.6, 125.7, 127.0, 127.8, 128.4, 130.1, 142.0, 145.5. IR (CDCl₃, cm⁻¹): 3599, 3379, 3033, 2917, 1594, 1503, 1474, 1059. Anal. Calcd. for C₁₆H₁₉NO: C, 79.63; H, 7.94. Found: C, 79.64; H, 8.00.

***trans*-2-Phenylamino-cyclohexanol (Table 1, Entry 2).** A screw-cap test tube was charged with CuI (5.0 mg, 0.025 mmol, 2.5 mol%), sodium hydroxide (120.0 mg, 3.0 mmol), *trans*-2-amino-1-cyclohexanol hydrochloride (152 mg, 1.0 mmol), and iodobenzene (134 μ L, 1.2 mmol). The test tube was fitted with a septum and purged with nitrogen before addition of DMSO (0.67 mL) and H₂O (0.33 mL). The test tube was then capped and stirred in an oil bath at 90 °C for 15 h. The resulting mixture was cooled to room temperature and diluted with water (4 mL) before extraction with methylene chloride (3 x 5 mL). The combined organic layers were washed with 3 M HCl (3 x 5 mL). The acid extracts were cooled on ice and a saturated NaOH solution was added until the mixture became cloudy (pH~12). The solution was then washed with methylene chloride (3 x 10 mL). The combined organic layers were washed with brine (1 x 10 mL), dried over MgSO₄ and concentrated in vacuo to yield 165.8 mg (87 %) of the title compound as an off-white solid. ¹H NMR (500 MHz, CDCl₃): δ 0.96 (m, 1H), 1.29 (m, 3H), 1.68 (m, 2H), 2.05 (m, 2H), 3.06 (ddd, J = 13.1, 9.2, 4.0 Hz, 1H), 3.12 (broad s, 1H), 3.27 (ddd, J = 10.1, 9.2, 4.3 Hz, 1H), 3.42 (broad s, 1H), 6.66 (app dd, J = 8.6, 1.2 Hz, 2H), 6.71 (app tt, J = 7.3, 0.9 Hz, 1H), 7.14 (app dt, J = 7.8, 1.2 Hz, 2H). ¹³C NMR (125 MHz, CDCl₃): δ 24.1, 24.7, 31.3, 33.1, 59.7, 74.0, 114.0, 117.9, 129.1, 147.7. IR (CDCl₃, cm⁻¹): 3525, 3390, 2937, 2860, 1602, 1501, 1065, 1040. Melting point: 57-58 °C. Anal. Calcd. for C₁₂H₁₇NO: C, 75.35; H, 8.96. Found: C, 75.25; H, 8.90.

(*S*)-2-(3,5-Dimethyl-phenylamino)-3-methyl-butan-1-ol (Table 1, Entry 3). A screw-cap test tube was charged with CuI (5.0 mg, 0.025 mmol, 2.5 mol%), sodium hydroxide (80.0 mg, 2.0 mmol), (*S*)-valinol (111 μ L, 1.0 mmol), and 3,5-dimethyl-iodobenzene (173 μ L, 1.2 mmol). The test tube was fitted with a septum and purged with nitrogen before adding DMSO (0.67 mL) and H₂O (0.33 mL). The test tube was then capped and stirred in an oil bath at 90 °C for 16.5 h. The resulting mixture was cooled to room temperature and diluted with water (4 mL) before extraction with methylene chloride (3 x 5 mL). The combined organic layers were washed with 0.1 M NaOH (1 x 5 mL), washed with brine (1 x 5 mL), dried over MgSO₄, and concentrated in vacuo. Flash chromatography of the crude product (CH₂Cl₂:EtOAc, 90:10) provided 183.1 mg (88 %) of the title compound as a pale yellow oil that solidified into an off-white solid under high vacuum. ¹H NMR (500 MHz, CDCl₃): δ 0.91 (d, J = 6.9 Hz, 3H), 0.94 (d, J = 6.9 Hz, 3H), 1.83 (dsept, J = 6.8, 6.7 Hz, 1H), 2.22 (s, 6H), 2.55 (broad s, 1H), 3.23 (dd, J = 6.5, 6.4 Hz, 1H), 3.44 (broad s, 1H), 3.46 (dd, J = 11.0, 7.0 Hz, 1H), 3.69 (d, J = 10.1 Hz, 1H), 6.28 (s, 2H), 6.36 (s, 1H). ¹³C NMR (125 MHz, CDCl₃): δ 18.9, 19.0, 21.3, 30.0, 60.7, 62.4, 111.5, 119.5, 138.8, 148.4. IR (CDCl₃, cm⁻¹): 3614, 3415, 3025, 2962, 1600, 1468, 1337, 1185. Melting point: 44-45 °C. Anal. Calcd. for C₁₃H₂₁NO: C, 75.32; H, 10.21. Found: C, 75.19; H, 10.31. Chiral chromatography: Ambient temperature, mobile phase = hexanes:iPrOH (98.5:1.5), flow rate = 1.75 mL/min, t₁(*S*) = 13.3 min, t₂(*R*) = 25.8 min. [α]_D²⁰ -33.5 (CHCl₃, c = 0.23).

(*R*)-2-(2-Bromo-phenylamino)-2-phenyl-ethanol (Table 1, Entry 4). A screw-cap test tube was charged with CuI (5.0 mg, 0.025 mmol, 2.5 mol%), sodium hydroxide (80.0 mg, 2.0 mmol), (*R*)-phenylglycinol (137 mg, 1.0 mmol), and 2-bromo-iodobenzene (154 μ L, 1.2 mmol). The test tube was fitted with a septum and purged with nitrogen before adding isopropanol (1.0 mL). The test tube was then capped and stirred in an oil bath at 90 °C for 16.5 h. The resulting mixture was cooled to room temperature and diluted with water (4 mL) before extraction with methylene chloride (3 x 5 mL). The combined organic layers were washed with 0.1 M NaOH (1 x 5 mL), washed with brine (1 x 5 mL), dried over MgSO₄, and concentrated in vacuo. Flash chromatography of the crude product (CH₂Cl₂) provided 246.9 mg (84 %) of the title compound as a yellow oil. For reaction 4b, the conditions above were modified as follows: (*R*)-

phenylglycinol (165 mg, 1.2 mmol), and 2-bromo-iodobenzene (128 μ L, 1.0 mmol). ^1H NMR (300 MHz, CDCl_3): δ 2.21 (broad s, 1H), 3.72 (dd, J = 11.3, 7.0 Hz, 1H), 3.88 (dd, J = 11.3, 4.3 Hz, 1H), 4.47 (ddd, J = 6.4, 5.8, 4.3 Hz, 1H), 5.15 (d, J = 5.8 Hz, 1H), 6.37 (app dd, J = 7.9, 1.2 Hz, 1H), 6.50 (app dt, J = 7.5, 1.2 Hz, 1H), 6.94 (app dt, J = 7.7, 1.5 Hz, 1H), 7.26 (m, 5H), 6.94 (app dd, J = 7.9, 1.5 Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3): δ 59.6, 67.1, 110.2, 112.9, 118.2, 126.5, 127.6, 128.2, 128.8, 132.2, 139.3, 143.8. IR (CDCl_3 , cm^{-1}): 3575, 3400, 3029, 2879, 1596, 1503, 1453, 1322, 1021. Anal. Calcd. for $\text{C}_{14}\text{H}_{14}\text{NOBr}$: C, 57.55; H, 4.83. Found: C, 57.60; H, 4.90. Chiral chromatography: Temperature = 0 $^\circ\text{C}$, mobile phase = hexanes:iPrOH (98.5:1.5), flow rate = 1.75 mL/min, $t_1(\text{R})$ = 17.6 min, $t_2(\text{S})$ = 20.4 min. $[\alpha]_{\text{D}}^{20}$ -22.9 (CHCl_3 , c = 1.97).

(1*S*,2*R*)-2-(3-Methoxy-phenylamino)-1-phenyl-propan-1-ol (Table 1, Entry 5). A screw-cap test tube was charged with CuI (5.0 mg, 0.025 mmol, 2.5 mol%), sodium hydroxide (80.0 mg, 2.0 mmol), (1*S*,2*R*)-norephedrine (151 mg, 1.0 mmol), and 3-iodo-anisole (143 μ L, 1.2 mmol). The test tube was fitted with a septum and purged with nitrogen before adding isopropanol (1.0 mL). The test tube was then capped and stirred in an oil bath at 90 $^\circ\text{C}$ for 16 h. The resulting mixture was cooled to room temperature and diluted with water (4 mL) before extraction with methylene chloride (3 x 5 mL). The combined organic layers were washed with 0.1 M NaOH (1 x 5 mL), washed with brine (1 x 5 mL), dried over MgSO_4 , and concentrated in vacuo. Flash chromatography of the crude product (CH_2Cl_2 :EtOAc, 95:5) provided 216.1 mg (84 %) of the title compound as a yellow oil. For reaction 5b, the conditions above were modified as follows: (1*S*,2*R*)-norephedrine hydrochloride (188 mg, 1.0 mmol) and sodium hydroxide (120 mg, 3.0 mmol). ^1H NMR (300 MHz, CDCl_3): δ 0.95 (d, J = 6.6 Hz, 3H), 2.80 (broad s, 1 H), 3.67 (m, 1H), 3.70 (s, 3H), 3.82 (broad s, 1H), 4.88 (d, J = 2.5 Hz, 1H), 6.18 (app t, J = 2.2 Hz, 1H), 6.25 (app ddd, J = 7.8, 5.4, 2.2 Hz, 2H), 7.04 (t, J = 8.3 Hz, 1H), 7.26 (m, 5H). ^{13}C NMR (75 MHz, CDCl_3): δ 13.9, 54.3, 55.1, 74.2, 99.8, 102.8, 106.7, 125.7, 127.2, 128.1, 130.0, 141.2, 148.2, 160.6. IR (CDCl_3 , cm^{-1}): 3612, 3413, 2975, 1615, 1600, 1509, 1212, 1164. Anal. Calcd. for $\text{C}_{16}\text{H}_{19}\text{NO}_2$: C, 74.68; H, 7.44. Found: C, 74.48; H, 7.41. $[\alpha]_{\text{D}}^{20}$ -74.4 (CHCl_3 , c = 1.53).

2-[Ethyl-(2-methoxyphenyl)-amino]-ethanol (Table 1, Entry 6). A screw-cap test tube was charged with CuI (5.0 mg, 0.025 mmol, 2.5 mol%), sodium hydroxide (80.0 mg, 2.0 mmol), 2-(aminoethyl)ethanol (294 μ L, 3.0 mmol), and 2-iodo-anisole (130 μ L, 1.0 mmol). The test tube was fitted with a septum and purged with nitrogen before adding isopropanol (0.8 mL). The test tube was then capped and stirred in an oil bath at 90 $^\circ\text{C}$ for 17 h. The resulting mixture was cooled to room temperature and diluted with water (4 mL) before extraction with methylene chloride (3 x 5 mL). The combined organic layers were washed with 0.1 M NaOH (1 x 5 mL), washed with brine (1 x 5 mL), dried over MgSO_4 , and concentrated in vacuo. Flash chromatography of the crude product (CH_2Cl_2 :EtOAc, 80:20) provided 151.2 mg (77 %) of the title compound as a pale yellow oil. For the reaction in 6b, the solvent was neat amino alcohol (1.0 mL, 10.2 mmol). ^1H NMR (300 MHz, CDCl_3): δ 0.99 (t, J = 7.0 Hz, 1H), 3.12 (q, J = 7.0 Hz, 2H), 3.14 (t, J = 5.5 Hz, 3H), 3.37 (broad s, 1H), 3.56 (t, J = 5.2 Hz, 2H), 3.82 (s, 3H), 6.87 (app dd, J = 7.9, 1.2 Hz, 1H), 6.90 (app dt, J = 7.6, 1.2 Hz, 1H), 7.05 (app dt, J = 7.7, 1.8 Hz, 1H), 7.07 (app dd, J = 7.6, 1.5 Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3): δ 12.5, 47.0, 55.2, 55.6, 59.1, 111.4, 120.6, 123.4, 124.3, 138.6, 154.7. IR (CDCl_3 , cm^{-1}): 3429, 2968, 2836, 1594, 1499, 1235, 1027. Anal. Calcd. for $\text{C}_{11}\text{H}_{17}\text{NO}_2$: C, 67.66; H, 8.78. Found: C, 67.47; H, 8.96.

2-(2-Amino-phenylamino)-1-phenyl-ethanol (Table 1, Entry 7). A screw-cap test tube was charged with CuI (5.0 mg, 0.025 mmol, 2.5 mol%), sodium hydroxide (80.0 mg, 2.0 mmol), 2-

amino-1-phenylethanol (137 mg, 1.0 mmol), and 2-iodoaniline (263 mg, 1.2 mmol). The test tube was fitted with a septum and purged with nitrogen before adding isopropanol (1.0 mL). The test tube was then capped and stirred in an oil bath at 90 °C for 14.5 h. The resulting mixture was cooled to room temperature and diluted with EtOAc (10 mL). This mixture was washed with water (2 x 5 mL), dried over MgSO₄, and concentrated in vacuo. Flash chromatography of the crude product (CH₂Cl₂:EtOAc, 75:25) provided a dark yellow solid that was recrystallized from hexanes/EtOAc to yield 143.7 mg (63 %) of the title compound as fibrous, light brown crystals. ¹H NMR (300 MHz, CDCl₃): δ 3.19 (broad s, 4H), 3.30 (dd, J = 12.9, 8.8 Hz, 1H), 3.41 (dd, J = 12.4, 3.3 Hz, 1H), 4.95 (dd, J = 8.8, 3.6 Hz, 1H), 6.71 (m, 3H), 6.79 (m, 1H), 7.36 (m, 5H). ¹³C NMR (125 MHz, CDCl₃): δ 52.0, 72.3, 112.6, 116.7, 119.4, 120.6, 125.8, 127.9, 128.6, 134.7, 136.9, 142.0. IR (CDCl₃, cm⁻¹): 3415, 3053, 1625, 1598, 1509, 1455, 1059. Anal. Calcd. for C₁₄H₁₆N₂O: C, 73.66; H, 7.06. Found: C, 73.55; H, 6.93.

2-(3-Nitro-phenylamino)-1-phenyl-ethanol (Table 2, Entry 1). A screw-cap test tube was charged with CuI (5.0 mg, 0.025 mmol, 2.5 mol%), potassium phosphate (425.0 mg, 2.0 mmol), 2-amino-1-phenylethanol (165 mg, 1.2 mmol), ethylene glycol (56 µL, 1.0 mmol), and 3-nitro-1-iodobenzene (249 mg, 1.0 mmol). The test tube was fitted with a septum and purged with nitrogen before adding isopropanol (1.1 mL). Next, the test tube was capped and stirred in an oil bath at 75 °C for 16 h. The resulting mixture was cooled to room temperature and diluted with H₂O (10 mL). The reaction mixture was then extracted with methylene chloride (3 x 10 mL). The organic layers were washed with brine (1 x 10 mL), dried over MgSO₄, and concentrated in vacuo. Flash chromatography of the crude product (CH₂Cl₂:EtOAc, 95:5) provided 188.1 mg (73 %) of the title compound as an orange oil. For reaction 1b, the conditions above were modified as follows: 2-amino-1-phenylethanol (137 mg, 1.0 mmol) and 3-nitro-1-iodobenzene (299 mg, 1.2 mmol). ¹H NMR (300 MHz, CDCl₃): δ 2.95 (broad s, 1H), 3.28 (ddd, J = 13.1, 8.5, 4.9 Hz, 1H), 3.38 (ddd, J = 12.8, 7.0, 4.0 Hz, 1H), 4.52 (dd, J = 6.6, 4.9 Hz, 1H), 4.88 (dd, J = 8.6, 4.0 Hz), 6.85 (app ddd, J = 8.0, 2.2, 0.5 Hz, 1H), 7.22 (app t, J = 8.0 Hz, 1H), 7.31 (m, 1H), 7.34 (m, 1H), 7.36 (m, 4H), 7.47 (app ddd, J = 8.0, 2.2, 0.8 Hz, 1H). ¹³C NMR (125 MHz, CDCl₃): δ 52.0, 72.3, 112.6, 116.7, 119.4, 120.6, 125.8, 127.9, 128.6, 134.7, 136.9, 142.0. IR (CDCl₃, cm⁻¹): 3415, 3053, 1625, 1598, 1509, 1455, 1059. Anal. Calcd. for C₁₄H₁₄N₂O₃: C, 73.66; H, 7.06. Found: C, 73.55; H, 6.93.

(1*R*,2*S*)-2-(3-Hydroxymethyl-phenylamino)-1-phenyl-propan-1-ol (Table 2, Entry 2). A screw-cap test tube was charged with CuI (5.0 mg, 0.025 mmol, 2.5 mol%), potassium phosphate (425.0 mg, 2.0 mmol), (1*R*, 2*S*)-norephedrine (151 mg, 1.0 mmol), ethylene glycol (56 µL, 1.0 mmol), and 3-iodobenzyl alcohol (152 µL, 1.2 mmol). The test tube was fitted with a septum and purged with nitrogen before adding isopropanol (1.1 mL). Next, the test tube was capped and stirred in an oil bath at 80 °C for 16.5 h. The resulting mixture was cooled to room temperature and diluted with H₂O (10 mL). The reaction mixture was then extracted with methylene chloride (3 x 10 mL). The organic layers were washed with brine (1 x 10 mL), dried over MgSO₄, and concentrated in vacuo. Flash chromatography of the crude product (CH₂Cl₂:EtOAc, 60:40) provided 195.6 mg (76 %) of the title compound as a clear oil. ¹H NMR (300 MHz, CDCl₃): δ 0.98 (d, J = 6.6 Hz, 3H), 3.20 (broad s, 1H), 3.50 (broad s, 2H), 3.74 (dq, J = 6.6, 3.0 Hz, 1H), 4.55 (s, 2H), 4.94 (d, J = 2.8 Hz, 1H), 6.56 (app ddd, J = 8.0, 2.4, 0.8 Hz, 1H), 6.64 (m, 2H), 7.14 (app t, J = 8.0 Hz, 1H), 7.28 (m, 5H). ¹³C NMR (75 MHz, CDCl₃): δ 13.6, 55.1, 65.2, 73.9, 113.2, 113.6, 117.2, 125.7, 127.2, 128.1, 129.4, 141.1, 142.2, 146.1. IR (CDCl₃, cm⁻¹): 3589, 3396, 3054, 2979, 2877, 1607, 1488, 1266. Anal. Calcd. for C₁₆H₁₉NO₂: C, 74.68; H, 7.44. Found: C, 74.80; H, 7.29. [α]_D²⁰ +69.2 (CHCl₃, c = 1.15).

(S)-1-[3-(1-Hydroxymethyl-2-methyl-propylamino)-phenyl]-ethanone (Table 2, Entry 3). A screw-cap test tube was charged with CuI (5.0 mg, 0.025 mmol, 2.5 mol%), potassium phosphate (425.0 mg, 2.0 mmol), (*S*)-valinol (134 μ L, 1.2 mmol), ethylene glycol (56 μ L, 1.0 mmol), and 3-iodobenzophenone (246 mg, 1.0 mmol). The test tube was fitted with a septum and purged with nitrogen before adding isopropanol (1.1 mL). Next, the test tube was capped and stirred in an oil bath at 75 °C for 16.5 h. The resulting mixture was cooled to room temperature and diluted with H₂O (2 mL) and methylene chloride (5 mL). The organic layer was washed with brine (1 x 5 mL), dried over MgSO₄, and concentrated in vacuo. Flash chromatography of the crude product (CH₂Cl₂:EtOAc, 80:20) provided 165.0 mg (75 %) of the title compound as a yellow oil. ¹H NMR (300 MHz, CDCl₃): δ 0.96 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 1.83 (dsept, *J* = 6.9, 6.8 Hz, 1H), 2.39 (dd, *J* = 6.9, 4.5 Hz, 1H), 2.50 (s, 3H), 3.22 (m, 1H), 3.57 (ddd, *J* = 10.1, 6.3, 3.9 Hz, 1H), 3.74 (ddd, *J* = 11.0, 6.9, 4.1 Hz, 1H), 3.89 (d, *J* = 6.6 Hz, 1H), 6.83 (m, 1H), 7.21 (m, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 19.1, 19.3, 26.8, 30.1, 60.6, 62.5, 112.0, 117.7, 118.0, 129.3, 137.9, 148.5, 198.6. IR (CDCl₃, cm⁻¹): 3427, 2964, 2877, 1677, 1602, 1358. Anal. Calcd. for C₁₃H₂₁NO: C, 70.56; H, 8.65. Found: C, 70.28; H, 8.50. Chiral chromatography: Ambient temperature, mobile phase = hexanes:iPrOH (98.5:1.5), flow rate = 1.75 mL/min, *t*₁(*S*) = 18.7 min, *t*₂(*R*) = 25.7 min. [α]_D²⁰ -44.7 (CHCl₃, *c* = 1.48).

(1*S*,2*R*)-Methyl-(1-methyl-2-phenoxy-2-phenyl-ethyl)-amine (Table 3, Entry 1). A screw-cap test tube was charged with CuI (10.0 mg, 0.05 mmol, 5 mol%), cesium carbonate (652.0 mg, 2.0 mmol), (*1R*, 2*S*)-ephedrine (165 mg, 1.0 mmol), and iodobenzene (168 μ L, 1.5 mmol). The test tube was fitted with a septum and purged with nitrogen before adding butyronitrile (1.0 mL). Next, the test tube was capped and stirred in an oil bath at 125 °C for 25 h. The reaction mixture was cooled to room temperature and filtered, washing well with EtOAc. The filtrate was concentrated to yield a yellow oil that was taken up in a few drops of Et₂O and added to 5 mL of 0.24 M HCl contained in a fritted glass Buchner funnel. A solid immediately precipitated and the aqueous solution was removed by vacuum filtration. The filter cake was washed with water (5 mL) and then hexanes. The title compound was obtained as a white solid (206.1 mg, 74 %). The ¹³C NMR spectrum was obtained using the free base. ¹H NMR (300 MHz, d₆ DMSO): δ 1.16 (d, *J* = 6.7 Hz, 3H), 2.63 (s, 3H), 3.58 (m, 1H), 5.91 (d, *J* = 2.2 Hz, 1H), 6.91 (m, 3H), 7.23 (m, 2H), 7.34 (m, 5H), 9.27 (broad s, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 14.8, 34.0, 60.3, 81.3, 115.6, 120.6, 126.4, 127.4, 128.3, 129.1, 139.2, 158.0. IR (solid HCl salt, cm⁻¹): 2983, 2836, 2765, 2721, 1596, 1495, 1241, 1179, 1005, 747, 704. Melting point > 260 °C. Anal. Calcd. for C₁₆H₂₀NO₂Cl: C, 69.18; H, 7.26. Found: C, 68.99; H, 7.34. [α]_D²⁰ +21.4 (DMSO, *c* = 0.35).

(1*R*,2*S*)-1-[3-(2-Methylamino-1-phenyl-propoxy)-phenyl]-ethanone (Table 3, Entry 2). A screw-cap test tube was charged with CuI (10.0 mg, 0.05 mmol, 5 mol%), cesium carbonate (652.0 mg, 2.0 mmol), (*1R*, 2*S*)-ephedrine (165 mg, 1.0 mmol), and 3-iodoacetophenone (295 mg, 1.2 mmol). The test tube was fitted with a septum and purged with nitrogen before adding butyronitrile (1.0 mL). Next, the test tube was capped and stirred in an oil bath at 125 °C for 21 h. The reaction mixture was cooled to room temperature and filtered, washing well with ethyl acetate. The filtrate (25 mL) was washed with 3 M HCl (3 x 10 mL) and the acid extracts were washed with CH₂Cl₂ (4 x 10 mL). The organic layers were dried over MgSO₄, filtered, and concentrated to provide a yellow solid that was triturated in Et₂O. The yellow solid was collected by vacuum filtration and the filter cake was washed with ethyl acetate (1 x 3 mL) and Et₂O to provide 167.7 mg (52 %) of the title compound as an off-white solid. NMR spectra were

taken using the HCl salt. ^1H NMR (300 MHz, CDCl_3): δ 1.33 (d, J = 6.8 Hz, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.41 (m, 1H), 5.92 (d, J = 2.4 Hz, 1H), 7.09 (app ddd, J = 8.2, 2.5, 1.0 Hz, 2H), 7.18 (app t, J = 8.1 Hz, 1H), 7.32 (m, 5H), 7.43 (app dt, J = 7.5, 1.2 Hz, 1H), 7.58 (app t, J = 2.1 Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3): δ 9.5, 26.9, 30.1, 31.0, 59.4, 116.2, 120.2, 121.3, 126.0, 128.5, 128.9, 129.5, 135.4, 138.1, 156.5, 197.5. IR (solid HCl salt, cm^{-1}): 2964, 2715, 1679, 1578, 1445, 1270, 1208, 1007, 745, 702. Melting point: 178-179 $^\circ\text{C}$. Anal. Calcd for $\text{C}_{18}\text{H}_{22}\text{NO}_2\text{Cl}$: C, 67.60, H, 6.93. Found: C, 67.36, H, 6.78. $[\alpha]_D^{20} +58.1$ (CHCl_3 , c = 0.43).

[2-(2,6-Dimethylphenoxy)-ethyl]-ethylamine (Table 3, Entry 3). A screw-cap test tube was charged with CuI (10.0 mg, 0.05 mmol, 5 mol%), cesium carbonate (652.0 mg, 2.0 mmol), 2-(ethylamino)ethanol (195 μL , 2.0 mmol), and 2,6-dimethyl-1-iodobenzene (140 μL , 1.0 mmol). The test tube was fitted with a septum and purged with nitrogen before adding butyronitrile (1.0 mL). Next, the test tube was capped and stirred in an oil bath at 125 $^\circ\text{C}$ for 30 h. The reaction mixture was cooled to room temperature, transferred to a separatory funnel, and diluted with ethyl acetate to a volume of approximately 25 mL. The mixture was washed with water (2 x 5 mL), dried over MgSO_4 , filtered, and concentrated. The oil obtained was taken up in 8 mL Et_2O and 1 mL of HCl in Et_2O (1.0 M) was added. The resulting precipitate was collected by filtration, washed with 16 mL Et_2O , washed with 3 mL acetone, and washed again with 16 mL Et_2O . Approximately 15 mL of Et_2O were then added to the mother liquor and a second crop of white precipitate formed upon standing. The two crops were combined to provide 163.6 mg (72 %) of the title compound as a white solid. NMR spectra were taken using the free base. ^1H NMR (300 MHz, CDCl_3): δ 1.18, (t, J = 7.2 Hz, 3H), 1.85 (broad s, 1H), 2.28 (s, 3H), 2.76 (q, J = 7.2 Hz, 2H), 3.01 (t, J = 5.2 Hz, 2H), 3.89 (t, J = 5.2 Hz, 2H), 6.89 (app dd, J = 8.3, 6.3 Hz, 1H), 6.98 (app d, J = 7.1 Hz, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 15.4, 16.3, 44.2, 49.8, 71.1, 123.8, 128.6, 130.7, 155.4. IR (solid HCl salt, cm^{-1}): 2943, 2786, 2750, 2726, 2472, 1457, 1262, 1204, 1030, 760. Melting point: 170-171 $^\circ\text{C}$. Anal. Calcd for $\text{C}_{12}\text{H}_{20}\text{NOCl}$: C, 62.73, H, 8.77. Found: C, 62.73, H, 9.01.

Ethyl-[2-(3-nitrophenoxy)-ethyl]-amine (Table 3, Entry 4). A screw-cap test tube was charged with CuI (10.0 mg, 0.05 mmol, 5 mol%), cesium carbonate (652.0 mg, 2.0 mmol), 2-(ethylamino)ethanol (195 μL , 2.0 mmol), and 3-nitro-1-iodobenzene (249 mg, 1.0 mmol). The test tube was fitted with a septum and purged with nitrogen before adding butyronitrile (1.0 mL). Next, the test tube was capped and stirred in an oil bath at 125 $^\circ\text{C}$ for 21 h. The reaction mixture was cooled to room temperature, filtered, and concentrated. The concentrate was taken up in 10 mL of methylene chloride and washed with water (2 x 5 mL). The organic layers were dried over MgSO_4 , filtered, and concentrated to yield dark oil. The oil was taken up in acetone and 1 mL of HCl in Et_2O (1.0 M) was added. The resulting precipitate was collected by filtration and washed well with Et_2O , EtOAc (5 mL), and Et_2O again. The title compound was obtained as a brown solid (132.7 mg, 54 %). NMR spectra were taken using the HCl salt. ^1H NMR (300 MHz, CDCl_3): δ 1.45 (t, J = 7.2 Hz, 3H), 3.15 (q, J = 5.5 Hz, 2H), 3.38 (t, J = 5.1 Hz, 2H), 4.46 (t, J = 5.1 Hz, 2H), 7.34 (app ddd, J = 8.4, 2.2, 1.1 Hz, 1H), 7.41 (app t, J = 8.0 Hz, 1H), 7.72 (app t, J = 2.2 Hz, 1H), 7.82 (app ddd, J = 8.0, 1.9, 1.0 Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3): δ 11.3, 43.3, 45.6, 63.5, 108.9, 116.7, 121.8, 130.1, 148.8, 157.7. IR (solid HCl salt, cm^{-1}): 2954, 2794, 2738, 2686, 2503, 1526, 1355, 1258, 1038, 799, 735, 675. Melting point: 155-156 $^\circ\text{C}$. Anal. Calcd. for $\text{C}_{10}\text{H}_{15}\text{N}_2\text{O}_3\text{Cl}$: C, 48.69, H, 6.13. Found: C, 48.45, H, 6.09.

(1*S*,2*R*)-1-Methyl-2-phenoxy-2-phenyl-ethylamine (Table 3, Entry 5). A screw-cap test tube was charged with CuI (10.0 mg, 0.05 mmol, 5 mol%), cesium carbonate (652.0 mg, 2.0 mmol),

(*1R, 2S*)-norephedrine (151 mg, 1.0 mmol), and iodobenzene (134 μ L, 1.2 mmol). The test tube was fitted with a septum and purged with nitrogen before adding butyronitrile (1.0 mL). Next, the test tube was capped and stirred in an oil bath at 125 °C for 14 h. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated and the resulting oil was taken up in 10 mL of methylene chloride. A solution of HCl in Et₂O (1.0 M, 1 mL) was added and the resulting precipitate was collected by filtration to yield 140.1 mg (53 %) of the title compound as a white solid. NMR spectra were taken using the HCl salt. ¹H NMR (300 MHz, d₆-DMSO): δ 1.14 (d, *J* = 6.7 Hz, 3H), 3.61 (broad s, 1H), 5.73 (d, *J* = 3.1 Hz, 1H), 6.91 (app t, *J* = 8.2 Hz, 1H), 6.91 (app dd, *J* = 8.4 Hz, 2H), 7.22 (app dd, *J* = 8.4, 7.3 Hz, 2H), 7.34 (m, 5H), 8.50 (broad s, 3H). ¹³C NMR (75 MHz, d₆-DMSO): δ 12.0, 51.1, 78.1, 116.1, 121.4, 126.4, 128.2, 128.7, 136.6, 157.0. IR (solid HCl salt, cm⁻¹): 3033, 2939, 2827, 1598, 1492, 1237, 1036, 980, 745, 700, 691. Melting point: 248-250 °C. High resolution mass spectrum: 227.1309 (M⁺), 183.0807, 134.0966, 115.0543. $[\alpha]_D^{20}$ -34.4 (H₂O, *c* = 0.47).

(*R*)-2-(3,5-dimethyl-phenoxy)-1-phenyl-ethylamine (Table 3, Entry 6). A screw-cap test tube was charged with CuI (10.0 mg, 0.05 mmol, 5 mol%), cesium carbonate (652.0 mg, 2.0 mmol), (*R*)-phenylglycinol (137 mg, 1.0 mmol), and 3,5-dimethyl-1-iodobenzene (173 μ L, 1.2 mmol). The test tube was fitted with a septum and purged with nitrogen before adding butyronitrile (1.0 mL). Next, the test tube was capped and stirred in an oil bath at 125 °C for 14 h. The reaction mixture was cooled and filtered. The filtrate was concentrated in vacuo and the oil obtained was taken up in ethyl acetate (8 mL). To this solution was added 1 mL of HCl in Et₂O (1.0 M). The white precipitate that formed was collected by filtration and the filter cake was washed with hexanes. A volume of hexanes (15 mL) was added to the mother liquor and the solution was allowed to stand overnight. A second crop of white precipitate formed and was added to the first crop. The title compound was obtained as a white solid (130.0 mg, 47 %). NMR spectra were taken using the HCl salt. ¹H NMR (500 MHz, CDCl₃): δ 2.22 (s, 3H), 4.06 (dd, *J* = 9.8, 4.1 Hz, 1H), 4.15 (broad s, 1H), 4.38 (t, *J* = 8.9 Hz, 1H), 6.62 (s, 1H), 6.68 (s, 2H), 7.19 (app t, *J* = 7.0 Hz, 2H), 7.26 (app t, *J* = 7.6, 1H), 7.36 (app d, *J* = 7.3 Hz, 2H). ¹³C NMR (125 MHz, CDCl₃): δ 21.4, 55.0, 68.0, 112.5, 123.2, 127.5, 129.0, 129.1, 133.0, 139.3, 157.8. IR (solid HCl salt, cm⁻¹): 3033, 2941, 2838, 1598, 1492, 1237, 1036, 980, 745, 700, 691. Melting point: 229-230 °C. High resolution mass spectrum: 241.1462 (M⁺), 120.0808, 106.0648. $[\alpha]_D^{20}$ -42.0 (H₂O, *c* = 0.49).

Synthesis of the acetyl derivative of 2-(3,5-dimethyl-phenoxy)-1-phenyl-ethylamine. A round bottom flask was charged with the hydrochloride salt of 2-(3,5-dimethyl-phenoxy)-1-phenyl-ethylamine and dissolved in methylene chloride. Excess triethylamine and acetic anhydride were added and the reaction was stirred at room temperature overnight. The reaction was quenched by addition of a solution of saturated bicarbonate equal to the reaction volume. After stirring for a half hour the contents of the flask were transferred to a separatory funnel and the organic layer was washed with equal volumes of a saturated sodium bicarbonate solution (2x) and then with equal volumes of water (2x). The organic layer was dried over MgSO₄, filtered, and concentrated to yield a white solid that was recrystallized from hexanes and ethyl acetate. ¹H NMR (500 MHz, CDCl₃): δ 2.03 (s, 3H), 2.26 (s, 6H), 4.18 (dd, *J* = 9.5, 4.3 Hz, 1H), 4.22 (dd, *J* = 9.6, 4.6 Hz, 1H), 5.37 (dt, *J* = 7.9, 3.9 Hz, 1H), 6.25 (d, *J* = 7.9 Hz, 1H), 6.51 (s, 2H), 6.60 (s, 1H), 7.27 (app tt, *J* = 7.2, 1.4 Hz, 1H), 7.33 (app t, *J* = 7.2 Hz, 2H), 7.38 (app d, *J* = 7.3 Hz, 2H). ¹³C NMR (125 MHz, CDCl₃): δ 21.4, 23.4, 52.3, 69.7, 112.2, 123.0, 127.0, 127.7, 128.1, 139.3, 139.4, 158.3, 169.5. IR (solid, cm⁻¹): 3284, 3068, 2923, 1632, 1542, 1297, 1169, 1075, 832, 695. Melting point: 120-122 °C. Anal. Calcd. for C₁₈H₂₁NO₂: C, 76.30; H, 7.47. Found: C,

76.34; H, 7.44. Chiral chromatography: Ambient temperature, mobile phase = hexanes:EtOAc (75:25), flow rate = 1.75 mL/min, $t_1(R) = 8.75$ min, $t_2(S) = 17.4$ min. $[\alpha]_D^{20} +29.0$ (CHCl₃, c = 0.42).