Catalytic C–H Amination for the Preparation of Substituted 1,2-Diamines

Supplementary Material
(*8 pages*)

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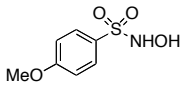
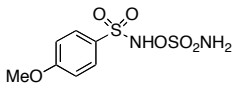
General. All reagents were obtained commercially unless otherwise noted. Reactions were performed using glassware that was flame-dried under vacuum (~1 Torr). Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated under reduced pressure (~15 Torr) by rotary evaporation. Solvents were purified by passage under 12 psi N_2 through activated alumina columns. Chlorosulfonyl isocyanate was purchased from Acros Chemicals, transferred via cannula to a Schlenk flask, and stored at –20 °C. Chromatography was performed on either Silicycle Silia-P Silica Gel (40-63 μm) or Fisher Davisil Grade 643 Type 150A silica gel (200-425 mesh). Compounds purified by chromatography were typically applied to the adsorbent bed using the indicated solvent conditions with a minimum amount of added chloroform as needed for solubility. High performance liquid chromatography (HPLC) was performed on a Varian Pro Star series instrument. Thin layer chromatography was performed on Whatman Partisil K6F Silica Gel 60 Å plates (250 μm). Visualization of the developed chromatogram was accomplished by fluorescence quenching or by staining with ninhydrin, aqueous potassium permanganate, or aqueous ceric ammonium molybdate (CAM).

Nuclear magnetic resonance (NMR) spectra were acquired on either a Varian Mercury-400 operating at 400 and 100 MHz or a Varian Inova-500 operating at 500 and 125 MHz for ^{1}H and ^{13}C, respectively, and are referenced internally according to residual solvent signals. Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; sext, sextet; m, multiplet), integration, coupling constant (Hz). Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). Infrared spectra were recorded on a Thermo-Nicolet IR300 spectrometer as thin films using NaCl salt plates or as KBr pellets and are reported in frequency of absorption. High-resolution mass spectra were obtained from the Vincent Coates Foundation Mass Spectrometry Laboratory at Stanford University.

General procedures and characterization data for all new compounds



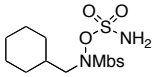
To a solution of hydroxylamine hydrochloride (6.73 g, 96.8 mmol, 2.0 equiv) and *N*,*N*-dimethylaminopyridine (0.59 g, 4.83 mmol, 0.10 equiv) in 50 mL of ice-cold pyridine was added portionwise solid 4-methoxybenzenesulfonyl chloride (10 g, 48.4 mmol). The reaction flask was removed from the ice bath and the resulting yellow solution was warmed to 25 °C and stirred for 15 min. The reaction mixture was transferred to a separatory funnel with 400 mL of EtOAc and washed with 3 x 250 mL of 1.0 M aqueous HCl. The aqueous washes were combined and extracted with 100 mL of EtOAc. The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The orange solid was redissolved in 20 mL of a 1:1 MeOH/toluene solution and concentrated under reduced pressure. This process was repeated two additional times and once with 20 mL of neat MeOH to afford the product as an orange solid (7.5 g, 76%). This material was used in the subsequent reaction without further purification. mp = 126–128 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93 (d, 2H, *J* = 9.2 Hz), 7.07 (d, 2H, *J* = 9.2 Hz), 6.64 (br d, 1H, *J* = 4.4 Hz), 5.92 (br d, 1H, *J* = 4.4 Hz), 3.93 (s, 3H) ppm; IR (thin film) ν 3438, 2104, 1643, 1495, 1457, 1326, 1253, 1092, 1013 cm^{-1}; HRMS (ES^+) calcd for $C_7H_9NO_4SNa^+$ 226.0150 found 226.0143 (MNa^+).



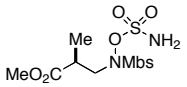
Formic acid (2.62 mL, 68.9 mmol, 2.0 equiv) was added dropwise to ice-cold chlorosulfonyl isocyanate (6.0 mL, 68.9 mmol, 2.0 equiv) with vigorous stirring. When gas evolution had ceased, 15 mL of CH_3CN was added and the mixture was stirred at 0 °C for 2 h and then at 25 °C for 6 h (*note:* solidification of the reaction mixture may occur prior to the addition of acetonitrile). The reaction flask was then placed in an ice bath and a solution of MbsNHOH (7.00 g, 34.5 mmol) in 55 mL of DMA was added dropwise. The orange solution was warmed to 25 °C and stirred for 12 h. The reaction was then quenched by the addition of 500 mL of H_2O, transferred to a separatory funnel, and extracted with 6 x 100 mL of EtOAc. The combined organic extracts were washed successively with 8 x 300 mL of H_2O and 2 x 200 mL of saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure to afford $MbsNHOSO_2NH_2$ as a pale orange solid (8.26 g, 85%). This material was used in the subsequent reaction

without further purification. mp = ~140 °C (decomp); ^{1}H NMR (CD_3CN, 400 MHz) δ 9.16 (s, 1H), 7.86 (d, 2H, J = 8.7 Hz), 7.14 (d, 2H, J = 8.7 Hz), 6.19 (s, 2H), 3.90 (s, 3H) ppm; ^{13}C NMR (CD_3CN, 100 MHz) δ 165.6, 131.9, 127.9, 115.6, 56.7 ppm; IR (KBr pellet) ν 3340, 3299, 3188, 2983, 2954, 2849, 2825, 1597, 1498, 1388, 1354, 1268, 1195, 1161, 733 cm^{-1}; HRMS (ES$^+$) calcd for $C_7H_{10}N_2O_6S_2Na^+$ 304.9878 found 304.9888 (MNa^+).

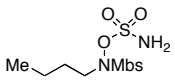
General procedure for substrate preparation. Neat diethyl azodicarboxylate (0.10 mL, 0.65 mmol, 1.3 equiv) was added dropwise to an ice-cold solution of alcohol (0.5 mmol), $MbsNHOSO_2NH_2$ (0.18 g, 0.65 mmol, 1.3 equiv), and PPh_3 (0.17 g, 0.65 mmol, 1.3 equiv) in 2.5 mL of THF. The yellow solution was warmed to 25 °C and stirred until the alcohol was completely consumed, as determined by TLC (10–15 h). All volatile materials were then removed under reduced pressure. The oily residue was redissolved in 2.0 mL of a 1:1 hexanes/EtOAc solution and concentrated. The desired product was isolated following purification by chromatography on silica gel (conditions given below).



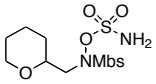
Purified by chromatography on silica gel (4:1 hexanes/EtOAc); white solid (97%): TLC R_f = 0.63 (1:1 hexanes/EtOAc); mp = 132–134 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, 50 °C) δ 7.82 (d, 2H, J = 9.0 Hz), 7.07 (d, 2H, J = 9.0 Hz), 5.29 (br s, 2H), 3.91 (s, 3H), 2.86 (br s, 2H), 1.95-1.84 (m, 1H), 1.74-1.62 (m, 4H), 1.34-1.10 (m, 4H), 0.97-0.85 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.9, 132.2, 122.8, 114.8, 62.1, 56.0, 34.9, 31.2, 26.5, 25.6 ppm: IR (thin film) ν 3400, 2928, 1643, 1597, 1498, 1403, 1360, 1266, 1198, 1165, 1092 cm^{-1}; HRMS (ES$^+$) calcd for $C_{14}H_{22}N_2O_6S_2Na^+$ 401.0817 found 401.0829 (MNa^+).



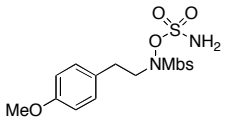
Purified by chromatography on silica gel (4:1 hexanes/EtOAc); off-white foam (57%): TLC R_f = 0.45 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz, 50 °C) δ 7.84 (d, 2H, J = 9.0 Hz), 7.07 (d, 2H, J = 9.0 Hz), 5.50 (br s, 2H), 3.91 (s, 3H), 3.69 (s, 3H), 3.49-3.04 (br d, 2H), 3.09 (m, 1H), 1.25 (d, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.9, 165.0, 132.2, 122.7, 114.9, 57.5, 56.0, 52.2, 37.5, 15.6 ppm; IR (thin film) ν 3629, 3367, 3274, 3104, 2954, 2846, 1727, 1595, 1498, 1401, 1366, 1200, 1167, 1092, 735 cm^{-1}.



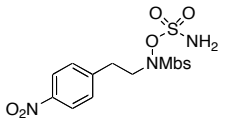
Purified by chromatography on silica gel (4:1 hexanes/EtOAc); white solid (97%): TLC R_f = 0.60 (1:1 hexanes/EtOAc); mp = 91–93 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, 50 °C) δ 7.87 (d, 2H, J = 9.0 Hz), 7.10 (d, 2H, J = 9.0 Hz), 5.34 (br s, 2H), 3.95 (s, 3H), 3.15 (br s, 2H), 1.78-1.68 (m, 2H), 1.45-1.34 (m, 2H), 0.94 (t, 3H, J = 7.3 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.9, 132.2, 122.9, 114.8, 56.0, 55.5, 28.9, 20.1, 13.7 ppm; IR (thin film) ν 3385, 2963, 2875, 1638, 1596, 1399, 1359, 1266, 1198, 1165, 1091 cm^{-1}.



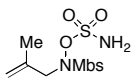
Purified by chromatography on silica gel (4:1 hexanes/EtOAc); off-white foam (98%): TLC R_f = 0.61 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz, 50 °C) δ 7.88 (d, 2H, J = 9.2 Hz), 7.09 (d, 2H, J = 9.2 Hz), 5.47 (br s, 2H), 3.98 (dt, 1H, J = 11.3, 2.1 Hz), 3.94 (s, 3H), 3.82-3.74 (m, 1H), 3.48 (td, 1H, J = 11.3, 2.9 Hz), 3.33-3.22 (br m, 1H), 3.09-2.97 (br m, 1H), 1.91-1.82 (m, 1H), 1.74-1.66 (m, 1H), 1.60-1.51 (m, 3H), 1.33-1.22 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.0, 132.3, 123.0, 114.8, 77.4, 68.4, 59.8, 56.0, 29.8, 25.8, 23.0 ppm: IR (thin film) ν 3390, 2942, 2859, 1638, 1595, 1497, 1399, 1364, 1266, 1199, 1166, 1090, 731 cm^{-1}.



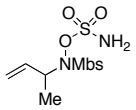
Purified by chromatography on Davisil silica gel (4:1 hexanes/EtOAc); off-white foam (99%): TLC R_f = 0.52 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz, 50 °C) δ 7.84 (d, 2H, *J* = 9.2 Hz), 7.09 (d, 2H, *J* = 8.7 Hz), 7.05 (d, 2H, *J* = 9.2 Hz), 6.82 (d, 2H, *J* = 8.7 Hz), 5.21 (br s, 2H), 3.90 (s, 3H), 3.78 (s, 3H), 3.34 (br s, 2H), 2.99 (t, 2H, *J* = 8.1 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.0, 158.4, 132.1, 129.9, 129.6, 122.8, 114.8, 114.1, 56.8, 55.9, 55.3, 32.8 ppm; IR (thin film) ν 3372, 3279, 2943, 2841, 1595, 1513, 1400, 1267, 1249, 1198, 1165, 721 cm^{-1}.



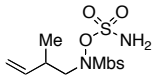
Purified by chromatography on silica gel (gradient elution: CH_2Cl_2→9:1 CH_2Cl_2/EtOAc); white solid (94%): TLC R_f = 0.43 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz, 50 °C) δ 8.16 (d, 2H, *J* = 8.7 Hz), 7.84 (d, 2H, *J* = 9.2 Hz), 7.37 (d, 2H, *J* = 8.7 Hz), 7.07 (d, 2H, *J* = 9.2 Hz), 5.20 (br s, 2H), 3.92 (s, 3H), 3.39 (br s, 2H), 3.17 (t, 2H, *J* = 7.8 Hz) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.2, 145.4, 132.2, 130.5, 129.9, 124.0, 122.5, 115.0, 56.1, 55.8, 33.4 ppm; IR (thin film) ν 3372, 3277, 1595, 1518, 1399, 1346, 1198, 1164, 722 cm^{-1}.



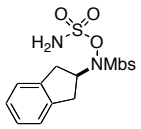
Purified by chromatography on silica gel (4:1 hexanes/EtOAc); off-white foam (100%): TLC R_f = 0.51 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz, 50 °C) δ 7.84 (d, 2H, *J* = 9.0 Hz), 7.08 (d, 2H, *J* = 9.0 Hz), 5.22 (br s, 2H), 4.99-4.97 (m, 1H), 4.88-4.86 (m, 1H), 3.92 (s, 3H), 3.64 (s, 2H), 1.89-1.87 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.0, 138.3, 132.3, 122.8, 117.5, 114.9, 62.5, 56.0, 20.5 ppm; IR (thin film) ν 3381, 3285, 3084, 2980, 1595, 1402, 1365, 1267, 1199, 1165 cm^{-1}.



Purified by chromatography on silica gel (4:1 hexanes/EtOAc); off-white foam (91%): TLC R_f = 0.55 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz, 50 °C) δ 7.84 (d, 2H, *J* = 9.0 Hz), 7.04 (d, 2H, *J* = 9.0 Hz), 5.70 (br s, 1H), 5.29 (br s, 2H), 4.99 (br s, 2H), 4.30 (br m, 1H), 3.91 (s, 3H), 1.09 (br s, 3H) ppm; IR (thin film) ν 3371, 3280, 3103, 2987, 2945, 1595, 1498, 1400, 1362, 1266, 1199, 1164, 768, 672 cm^{-1}.

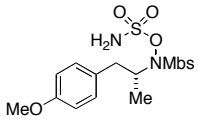


Purified by chromatography on silica gel (4:1 hexanes/EtOAc); off-white foam (77%): TLC R_f = 0.60 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz, 48 °C) δ 7.83 (d, 2H, *J* = 9.0 Hz), 7.07 (d, 2H, *J* = 9.0 Hz), 5.78-5.68 (m, 1H), 5.29 (br s, 2H), 5.14-5.03 (m, 2H), 3.92 (s, 3H), 2.95 (br s, 2H), 2.81 (m, 1H), 1.08 (d, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.0, 140.7, 132.2, 122.8, 115.4, 114.9, 61.1, 56.0, 35.2, 17.9 ppm; IR (thin film) ν 3380, 3284, 3082, 2974, 1595, 1498, 1401, 1360, 1267, 1199, 1165, 1092, 738 cm^{-1}.



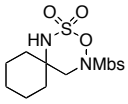
Purified by chromatography on silica gel (4:1 hexanes/EtOAc); off-white foam (97%): TLC R_f = 0.52 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.88 (d, 2H, *J* = 8.9 Hz), 7.12 (br m, 4H), 7.08 (d, 2H, *J* = 8.9 Hz),

5.17 (br s, 2H), 4.18 (quint, 1H, J = 8.5 Hz), 3.93 (s, 3H), 3.47 (br s, 1H), 3.26 (br s, 1H), 3.08 (br s, 1H), 2.55 (br s, 1H) ppm; IR (thin film) ν 3371, 3281, 2946, 2845, 1595, 1497, 1401, 1365, 1266, 1197, 1164, 1091, 737 cm^{-1}.

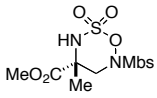


Purified by chromatography on silica gel (4:1 hexanes/EtOAc); off-white foam (68%): TLC R_f = 0.39 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.85 (br d, 2H, J = 6.7 Hz), 7.13 (br s, 2H), 7.02 (br d, 2H, J = 8.8 Hz), 6.82 (br s, 2H), 5.39 (br s, 2H), 4.04 (br m, 1H), 3.88 (s, 3H), 3.78 (s, 3H), 3.26-2.48 (br m, 2H), 0.85-0.44 (br s, 3H) ppm; IR (thin film) ν 3370, 3277, 3103, 2942, 2841, 1595, 1513, 1400, 1266, 1249, 1198, 1164 cm^{-1}.

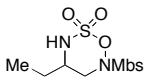
General procedure for C–H insertion reaction. Solid MgO (14 mg, 0.35 mmol, 2.3 equiv), $Rh_2(oct)_4$ (2 mg, 3.00 μmol, 0.02 equiv), and $PhI(OAc)_2$ (53 mg, 0.17 mmol, 1.1 equiv) were added sequentially to a solution of substrate (0.15 mmol) in 1.5 mL of benzene. The green suspension was stirred at 25 °C for 4 h, diluted with 1–2 mL of CH_2Cl_2, and filtered through a small pad of Celite. The flask and filter cake were rinsed with CH_2Cl_2 and the combined filtrates concentrated under reduced pressure to a blue-green residue. The desired product was isolated following purification by chromatography on silica gel (conditions given below).



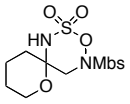
Purified by chromatography on silica gel (4:1 hexanes/EtOAc); off-white foam (99%): TLC R_f = 0.27 (2:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (d, 2H, J = 9.0 Hz), 7.05 (d, 2H, J = 9.0 Hz), 4.08 (s, 1H), 3.91 (s, 3H), 3.23 (s, 2H), 2.06-1.97 (m, 2H), 1.67-1.50 (m, 7H), 1.43-1.31 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.9, 132.1, 123.8, 114.8, 60.1, 56.0, 55.9, 34.4, 25.5, 21.0 ppm; IR (thin film) ν 3264, 2938, 2862, 1595, 1374, 1267, 1200, 1166, 1092, 726 cm^{-1}; HRMS (ES^+) calcd for $C_{14}H_{20}N_2O_6S_2Na^+$ 399.0661 found 399.0662 (MNa^+).



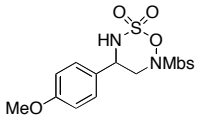
Purified by chromatography on silica gel (2:1 hexanes/EtOAc); off-white foam (82%): TLC R_f = 0.09 (2:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87, (d, 2H, J = 9.2 Hz), 7.06 (d, 2H, J = 9.2 Hz), 5.33 (s, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.77 (d, 1H, J = 12.8 Hz), 3.13 (d, 1H, J = 12.8 Hz), 1.84 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.2, 164.8, 131.8, 122.9, 114.6, 62.2, 55.7, 54.0, 53.0, 21.1 ppm; IR (thin film) ν 3256, 2956, 2847, 1744, 1595, 1440, 1376, 1268, 1191, 1167, 1092, 735 cm^{-1}; HRMS (ES^+) calcd for $C_{12}H_{16}N_2O_8S_2Na^+$ 403.0246 found 403.0247 (MNa^+).



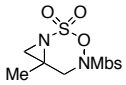
Purified by chromatography on silica gel (3:1 hexanes/EtOAc); white solid (26%): TLC R_f = 0.31 (2:1 hexanes/EtOAc); mp = 100–102 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (d, 2H, J = 9.2 Hz), 7.05 (d, 2H, J = 9.2 Hz), 3.99 (d, 1H, J = 10.8 Hz), 3.91 (s, 3H), 3.89-3.83 (m, 2H), 2.71 (dd, 1H, J = 13.3, 10.8 Hz), 1.69-1.56 (m, 2H), 1.05 (t, 3H, J = 7.3 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.0, 132.2, 123.5, 114.8, 57.4, 56.0, 51.5, 25.6, 10.0 ppm; IR (thin film) ν 3258, 2926, 1595, 1373, 1267, 1203, 1166, 727 cm^{-1}; HRMS (ES^+) calcd for $C_{11}H_{16}N_2O_6S_2Na^+$ 359.0348 found 359.0343 (MNa^+).



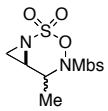
Purified by chromatography on silica gel (1:1 hexanes/EtOAc); white solid (71–97%, product is somewhat unstable to silica gel): TLC R_f = 0.57 (1:2 hexanes/EtOAc); mp = ~112 °C (decomp); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (d, 2H, *J* = 9.0 Hz), 7.05 (d, 2H, *J* = 9.0 Hz), 4.35 (s, 1H), 3.91 (s, 3H), 3.83 (m, 1H), 3.48 (d, 1H, *J* = 12.5 Hz), 3.22 (d, 1H, *J* = 12.5 Hz), 2.26 (m, 1H), 1.84-1.59 (m, 6H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.0, 132.2, 123.5, 114.9, 87.9, 62.9, 57.2, 56.0, 32.3, 24.6, 18.0 ppm; IR (thin film) ν 3278, 2949, 1594, 1369, 1267, 1209, 1187, 1165, 1050, 726 cm^{-1}; HRMS (ES$^+$) calcd for $C_{13}H_{18}N_2O_7S_2Na^+$ 401.0453 found 401.0457 (MNa^+).



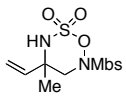
Purified by chromatography on Davisil silica gel (gradient elution: 2:1→1:1 hexanes/EtOAc); white solid (64–82%, product is somewhat unstable to silica gel): TLC R_f = 0.23 (2:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.88 (d, 2H, *J* = 9.0 Hz), 7.21 (d, 2H, *J* = 8.7 Hz), 7.06 (d, 2H, *J* = 9.0 Hz), 6.93 (d, 2H, *J* = 8.7 Hz), 5.02 (td , 1H, *J* = 10.6, 3.2 Hz), 4.41 (d, 1H, *J* = 10.6 Hz), 4.10 (dd, 1H, *J* = 12.7, 3.2 Hz), 3.92 (s, 3H), 3.82 (s, 3H), 3.10 (dd, 1H, *J* = 12.7, 11.0 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.1, 160.6, 132.2, 128.0, 126.2, 123.4, 115.0, 114.9, 58.5, 56.0, 55.6, 51.8 ppm; IR (KBr pellet) ν 3262, 2970, 2843, 1596, 1518, 1423, 1371, 1268, 1251, 1201, 1188, 1163, 1093, 1023, 830, 797, 775, 707 cm^{-1}; HRMS (ES$^+$) calcd for $C_{16}H_{18}N_2O_7S_2Na^+$ 437.0453 found 437.0454 (MNa^+).



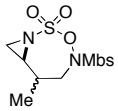
Purified by chromatography on silica gel (1:1 hexanes/EtOAc); white solid (90%): TLC R_f = 0.10 (2:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (d, 2H, *J* = 9.2 Hz), 7.07 (d, 2H, *J* = 9.2 Hz), 4.16 (d, 1H, *J* = 13.3 Hz), 3.92 (s, 3H), 3.35 (s, 1H), 3.15 (d, 1H, *J* = 13.3 Hz), 2.58 (s, 1H), 1.50 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.3, 132.3, 122.7, 115.0, 56.0, 51.6, 49.3, 41.0, 21.1 ppm; IR (KBr pellet) ν 3103, 2986, 2946, 2845, 1596, 1497, 1382, 1368, 1270, 1202, 1169, 1090, 835, 801, 768, 668 cm^{-1}; HRMS (ES$^+$) calcd for $C_{11}H_{14}N_2O_6S_2Na^+$ 357.0191 found 357.0176 (MNa^+).



Purified by chromatography on silica gel (2:1 hexanes/EtOAc); white solid (98%, 4:1 mixture of diastereomers, stereochemistry not assigned): TLC R_f = 0.12 (2:1 hexanes/EtOAc); *major diastereomer* ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.85 (d, 2H, *J* = 9.2 Hz), 7.02 (d, 2H, *J* = 9.2 Hz), 4.73 (q, 1H, *J* = 6.7 Hz), 3.90 (s, 3H), 3.13 (t, 1H, *J* = 4.9 Hz), 3.00 (d, 1H, *J* = 4.9 Hz), 2.66 (dd, 1H, *J* = 4.9, 0.8 Hz), 1.62 (d, 3H, *J* = 6.7 Hz) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.2, 132.0, 125.6, 114.9, 56.1, 50.0, 49.8, 34.9, 15.3 ppm; IR (thin film) ν 2947, 1595, 1391, 1267, 1251, 1196, 1165, 785, 671, 621 cm^{-1}; HRMS (ES$^+$) calcd for $C_{11}H_{14}N_2O_6S_2Na^+$ 357.0191 found 357.0175 (MNa^+).

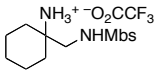


Purified by chromatography on silica gel (gradient elution: 2:1 hexanes/EtOAc→1:1 hexanes/EtOAc); white solid (39%): TLC R_f = 0.26 (2:1 hexanes/EtOAc); mp = ~118 °C (decomp); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (d, 2H, *J* = 9.0 Hz), 7.06 (d, 2H, *J* = 9.0 Hz), 5.97-5.88 (m, 1H), 5.39-5.32 (m, 2H), 4.31 (s, 1H), 3.91 (s, 3H), 3.41 (d, 1H, *J* = 12.8 Hz), 3.33 (d, 1H, *J* = 12.8 Hz), 1.59 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.0, 138.1, 132.1, 123.6, 116.8, 114.8, 60.7, 56.0, 54.9, 24.5 ppm; IR (thin film) ν 3267, 2946, 2845, 1595, 1498, 1372, 1268, 1206, 1166, 1092, 731 cm^{-1}; HRMS (ES$^+$) calcd for $C_{12}H_{16}N_2O_6S_2Na^+$ 371.0348 found 371.0360 (MNa^+).

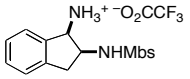


Purified by chromatography on silica gel (gradient elution: 2:1 hexanes/EtOAc→1:1 hexanes/EtOAc); off-white foam (56%, 1.3:1 mixture of diastereomers, stereochemistry not assigned): TLC R_f = 0.09 *minor diastereomer*, 0.07 *major diastereomer* (2:1 hexanes/EtOAc); *major diastereomer* ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.88, (d, 2H, *J* = 9.0 Hz), 7.04 (d, 2H, *J* = 9.0 Hz), 3.91 (s, 3H), 3.73 (dd, 1H, *J* = 14.3, 5.0 Hz), 3.23 (d, 1H, *J* = 14.3 Hz), 2.90 (q, 1H, *J* = 5.0 Hz), 2.77-2.70 (m, 1H), 2.70 (dd, 1H, *J* = 5.5, 1.1 Hz), 2.54 (dd, 1H, *J* = 5.5, 0.8 Hz), 1.52 (d, 3H, *J* = 7.2 Hz) ppm; *minor diastereomer* ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87, (d, 2H, *J* = 9.0 Hz), 7.04 (d, 2H, *J* = 9.0 Hz), 3.91 (s, 3H), 3.87 (dd, 1H, *J* = 14.6, 3.7 Hz), 3.12 (m, 1H), 2.97 (td, 1H, *J* = 5.5, 2.7 Hz), 2.75 (dd, 1H, *J* = 14.6, 11.3 Hz), 2.69 (d, 1H, *J* = 5.5 Hz), 2.48 (d, 1H, *J* = 5.5 Hz), 1.21 (d, 3H, *J* = 7.2 Hz) ppm; *diastereomeric mixture* ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.9, 164.8, 132.1, 132.0, 124.2, 123.9, 114.72, 114.70, 55.9, 53.2, 52.9, 47.4, 46.3, 33.6, 33.1, 29.0, 17.4, 17.3 ppm; HRMS (ES^+) calcd for $C_{12}H_{16}N_2O_6S_2Na^+$ 371.0348 found 371.0346 (MNa^+).

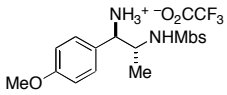
Procedures for Reductive Ring Opening Reactions



To a solution of the purified oxathiadiazinane (100 mg, 0.27 mmol) in 4.0 mL of ice-cold 1:1 MeOH/AcOH was added Zn(Cu) couple (87 mg, 1.35 mmol, 5.0 equiv). The black suspension was stirred at 0 °C for 1.5 h, warmed to 25 °C, and filtered through a small pad of Celite. The flask and filter cake were rinsed with MeOH and the combined filtrates were concentrated under reduced pressure. The isolated residue was redissolved in 10 mL of 1.0 M methanolic HCl and the solution was stirred for 12 h. Following this time, the mixture was concentrated under reduced pressure and the material was purified by reverse-phase HPLC (Alltima C_{18} 22 x 250 mm column, 10 μm, flow rate = 20 mL/min, gradient elution: 5→70% CH_3CN/H_2O with 0.1% CF_3CO_2H, R_t = 11.9 min) to furnish the desired product as a white solid (98 mg, 90%). ^{1}H NMR (DMSO, 400 MHz) δ 7.94 (t, 1H, *J* = 7.0 Hz), 7.87 (br s, 3H), 7.77 (d, 2H, *J* = 9.0 Hz), 7.15 (d, 2H, *J* = 9.0 Hz), 3.84 (s, 3H), 2.85 (d, 2H, *J* = 7.0 Hz), 1.68-1.19 (m, 10H) ppm; IR (thin film) ν 3158, 2944, 1673, 1598, 1499, 1328, 1264, 1203, 1153, 1095 cm^{-1}; HRMS (ES^+) calcd for $C_{14}H_{23}N_2O_3S^+$ 299.1429 found 299.1424 (M^+).



Solid MgO (14 mg, 0.35 mmol, 2.3 equiv), $Rh_2(oct)_4$ (2 mg, 3.0 μmol, 0.02 equiv), and $PhI(OAc)_2$ (53 mg, 0.17 mmol, 1.1 equiv) were added sequentially to a solution of substrate (60 mg, 0.15 mmol) in 1.5 mL of benzene. The green suspension was stirred at 25 °C for 4 h, diluted with 1–2 mL of CH_2Cl_2, and filtered through a small pad of Celite. The flask and filter cake were rinsed with CH_2Cl_2, and the combined filtrates were concentrated under reduced pressure to an oily residue. This material was redissolved in 1.2 mL of an ice-cold 1:1 MeOH/AcOH solution to which Zn(Cu) couple (49 mg, 0.75 mmol, 5 equiv) was then added. The suspension was stirred at 0 °C for 2 h, warmed to 25 °C, and filtered through a small pad of Celite. The flask and filter cake were rinsed with MeOH and the combined filtrates were concentrated under reduced pressure. The isolated product was dissolved in 10 mL of 1.0 M methanolic HCl and this solution was stirred for 12 h. Following this time, the mixture was concentrated under reduced pressure and the material was purified by reverse-phase HPLC (Alltima C_{18} 22 x 250 mm column, 10 μm, flow rate = 20 mL/min, gradient elution: 5→70% CH_3CN/H_2O with 0.1% CF_3CO_2H, R_t = 14.3 min) to yield the desired product as a white solid (55 mg, 85% for two steps). ^{1}H NMR (DMSO, 400 MHz) δ 8.30 (d, 1H, *J* = 4.7 Hz), 8.24 (br s, 3H), 7.85 (d, 2H, *J* = 9.0 Hz), 7.50 (d, 1H, *J* = 7.0 Hz), 7.36-7.22 (m, 3H), 7.15 (d, 2H, *J* = 9.0 Hz), 4.59 (m, 1H), 3.85 (s, 3H), 3.80 (m, 1H), 2.92 (dd, 1H, *J* = 16.0, 8.5 Hz), 2.75 (dd, 1H, *J* = 16.0, 7.8 Hz) ppm; IR (thin film) ν 3079, 1671, 1597, 1500, 1264, 1202, 1154, 1093 cm^{-1}; HRMS (ES^+) calcd for $C_{16}H_{19}N_2O_3S^+$ 319.1116 found 319.1112 (M^+).



Solid MgO (11 mg, 0.28 mmol, 2.3 equiv), $Rh_2(esp)_2$ (1 mg, 2.4 μmol, 0.02 equiv), and $PhI(OAc)_2$ (41 mg, 0.13 mmol, 1.1 equiv) were added sequentially to a solution of substrate (50 mg, 0.12 mmol) in 1.2 mL of isopropyl acetate. The green suspension was stirred at 25 °C for 4 h, diluted with 1–2 mL of CH_2Cl_2, and filtered through a small pad of Celite. The flask and filter cake were rinsed with CH_2Cl_2, and the combined filtrates were concentrated under reduced pressure to an oily residue. This material was redissolved in 1.8 mL of an ice-cold 1:1 MeOH/AcOH solution to which Zn(Cu) couple (38 mg, 0.60 mmol, 5.0 equiv) was then added. The suspension was stirred at 0 °C for 1.5 h, warmed to 25 °C, and filtered through a small pad of Celite. The flask and filter cake were rinsed with MeOH and the combined filtrates were concentrated under reduced pressure. The isolated product was dissolved in 10 mL of 1.0 M methanolic HCl and this solution was stirred for 12 h. Following this time, the mixture was concentrated under reduced pressure and the material was purified by reverse-phase HPLC (Alltima C_{18} 22 x 250 mm column, 10 μm, flow rate = 20 mL/min, gradient elution: 5→70% CH_3CN/H_2O with 0.1% CF_3CO_2H, R_t = 15.7 min) to yield the desired product as a white solid (23 mg, 43% for two steps). The product stereochemistry and the 6:1 diastereomeric ratio was assigned based on ^1H NMR and coupling constant analysis of the intermediate oxathiadiazinane). ^1H NMR (DMSO, 400 MHz) δ 8.37 (br s, 3H), 7.79 (d, 1H, J = 8.6 Hz), 7.77 (d, 2H, J = 9.0 Hz), 7.34 (d, 2H, J = 8.9 Hz), 7.13 (d, 2H, J = 9.0 Hz), 6.98 (d, 2H, J = 8.9 Hz), 4.00 (m, 1H), 3.83 (s, 3H), 3.75 (s, 3H), 3.46 (m, 1H), 0.50 (d, 3H, J = 6.7 Hz) ppm; IR (thin film) ν 3159, 2943, 1684, 1614, 1597, 1519, 1500, 1262, 1202, 1184, 1156, 1092, 835 cm^{-1}; HRMS (ES^+) calcd for $C_{17}H_{23}N_2O_4S^+$ 351.1379 found 351.1380 (M^+).