**Expanding the Substrate Scope for C-H Amination Reactions:
Oxidative Cyclization of Urea and Guanidine Derivatives**

Supplementary Material
(43 pages)

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General. All reagents were obtained commercially unless otherwise noted. Reactions were performed using oven-dried glassware under an atmosphere of dry nitrogen. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated under reduced pressure (ca. 15 mm Hg) by rotary evaporation. Solvents were purified by passage under 12 psi N₂ through activated alumina columns. Chlorobenzene was purchased from Fisher Scientific and used without purification. Chlorosulfonyl isocyanate was obtained from Acros Chemicals, transferred via cannula to a Schlenk flask, and stored at -20 °C. 2,2,2-Trichloroethanol was purchased from Acros Chemicals and used as received. Light magnesium oxide was flame-dried under reduced pressure (1 mm Hg) prior to use. The synthesis of 2,2,2-trichloroethylsulfamate was performed according to a previously published report.¹ This material is also available commercially from Aldrich Chemical Co. Chromatographic purification of products was accomplished using forced-flow chromatography on EM Science Geduran silica gel 60 (35–75 µm). Compounds purified by chromatography on silica gel were typically applied to the adsorbent bed using the indicated solvent conditions with a minimum amount of added dichloromethane as needed for solubility. Thin layer chromatography was performed on EM Science silica gel 60 F₂₅₄ plates (250 µm). Visualization of the developed chromatogram was accomplished by fluorescence quenching and by staining with ethanolic anisaldehyde, aqueous potassium permanganate, or aqueous ceric ammonium molybdate (CAM) solution.

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

Experimental Procedures and Characterization Data for Urea Substrates and Cyclic Products

N-(2,2,2-Trichloroethoxysulfonyl)urea (TcesNHC(O)NH₂)²

Chlorosulfonyl isocyanate (3.3 mL, 37.5 mmol) and 17 mL of C₆H₅Cl were combined in a 100 mL recovery flask equipped with a magnetic stir bar and a Liebig condenser. A solution of 2,2,2-trichloroethanol (3.6 mL, 37.5 mmol) in 25 mL of C₆H₅Cl was introduced dropwise via cannula over 5 min. The rubber septum and N₂ gas inlet atop the condenser were replaced with a drying tube containing Na₂CO₃ and the reaction was heated at reflux for 12 h. Following this period, the reaction was cooled to 23 °C and the condenser was replaced by a short path distillation head equipped with a 100 mL receiving flask. The C₆H₅Cl solvent was removed by distillation to give a light brown viscous residue. This material was dissolved in 40 mL of CH₂Cl₂ and the solution was cooled to 0 °C. Neat (Me₃Si)₂NH (7.9 mL, 37.5 mmol) was then added dropwise via syringe. The reaction mixture was stirred at 23 °C for 4 h. The solution was then concentrated under reduced pressure to give an off-white solid, which was subsequently dissolved in 40 mL of MeOH and 300 µL of AcOH. The resulting slurry was stirred vigorously for 5 h after which time all volatile materials were removed under reduced pressure and the oily product was dried azeotropically with 50 mL of toluene. The solid mass was recrystallized from ~300 mL of a 3:1 EtOAc/hexanes mixture to give the desired product as an amorphous white powder (6.98 g, 69%). ¹H NMR (CD₃CN, 400 MHz) δ 5.72 (br s, 2H), 4.87 (s, 2H) ppm; ¹³C NMR (CD₃CN, 100 MHz) δ 152.8, 94.2, 80.4 ppm; IR (thin film) ν 3472, 1717, 1374, 1179, 1007, 914, 873 cm⁻¹.

Preparation of *N*-Alkyl-*N*-(2,2,2-trichloroethoxysulfonyl)urea Substrates

To a mixture of alcohol (7 mmol), TcesNHC(O)NH₂ (2.53 g, 9.31 mmol, 1.33 equiv), and PPh₃ (2.39 g, 9.1 mmol, 1.3 equiv) in 23 mL of THF at 0 °C was added diethyl azodicarboxylate (1.43 mL, 9.1 mmol, 1.3 equiv) dropwise via syringe. The solution was warmed to 23 °C and stirred for 4–6 h until TLC showed complete consumption of the starting alcohol. After this time, all volatile materials were removed under reduced pressure. The resulting oily material was suspended in 30 mL of hexanes and concentrated again. This process was repeated twice. The isolated product was purified by chromatography on silica gel (conditions given below).

General Procedure for C–H Amination of Urea Substrates

To a solution of urea substrate (0.3 mmol) in 2.0 mL of toluene were added sequentially MgO (30 mg, 0.75 mmol, 2.5 equiv), PhI(OAc)₂ (145 mg, 0.45 mmol, 1.5 equiv) and Rh₂(esp)₂ (2.3 mg, 3 μmol, 0.01 equiv). The resulting green solution was stirred at 40 °C until TLC indicated no further progress in the reaction (~8 h). The yellowish green reaction mixture was cooled to 23 °C, diluted with 2 mL of CH₂Cl₂, and filtered through a pad of Celite (20 x 10 mm). The filter cake was rinsed with 2 x 3 mL of CH₂Cl₂ and the combined filtrates were evaporated under reduced pressure. Purification of the isolated material by chromatography on silica gel (conditions given below) afforded the desired product.

Characterization Data for Urea Substrates and Corresponding Amination Products

Purified by chromatography on silica gel (gradient elution: 6:1→4:1 hexanes/EtOAc); white solid (75%): TLC R_f = 0.4 (3:1 hexanes/EtOAc); ¹H NMR (CDCl₃, 400 MHz) δ 7.35–7.33 (m, 2H), 7.28–7.24 (m, 1H), 7.22–7.19 (m, 2H), 7.02 (br s, 1H), 5.49 (br s, 1H), 4.63 (s, 2H), 4.48 (t, 2H, *J* = 6.8 Hz), 3.00 (t, 2H, *J* = 7.2 Hz) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 160.4, 137.0, 129.1, 129.0, 127.2, 93.9, 78.7, 69.7, 35.0 ppm; IR (thin film) ν 3455, 3351, 1628, 1544, 1476, 1447, 1332, 1177, 1087, 1017, 853 cm⁻¹; HRMS (ES⁻) calcd for C₁₁H₁₃C₃N₂O₄S 373.9662 found 372.9569 (M–H⁺).

Purified by chromatography on silica gel (gradient elution: 5:1→2:1 hexanes/EtOAc); white solid (79%): TLC R_f = 0.25 (3:1 hexanes/EtOAc); ¹H NMR (CDCl₃, 400 MHz) δ 7.66 (br s, 1H), 7.47–7.41 (m, 3H), 7.33–7.31 (m, 2H), 5.21 (dd, 1H, *J* = 9.2, 7.2 Hz), 4.94 (t, 1H, *J* = 9.2 Hz), 4.73 (d, 1H, *J* = 10.8 Hz), 4.70 (d, 1H, *J* = 10.8 Hz), 4.42 (dd, 1H, *J* = 8.8, 6.8 Hz) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 163.0, 137.0, 130.0, 129.7, 126.3, 93.8, 78.7, 74.7, 58.9 ppm; IR (thin film) ν 3384, 1628, 1480, 1460, 1440, 1342, 1177, 1101, 1017, 879 cm⁻¹; HRMS (ES⁻) calcd for C₁₁H₁₁Cl₃N₂O₄S 371.9505 found 370.9411 (M–H⁺).

Purified by chromatography on silica gel (gradient elution: 6:1→3:1 hexanes/EtOAc); white solid (65%): TLC R_f = 0.3 (3:1 hexanes/EtOAc); ¹H NMR (CDCl₃, 400 MHz) δ 7.15–7.05 (m, 4H), 7.01 (br s, 1H), 5.56 (br s, 1H), 5.40 (tt, 1H, *J* = 6.0, 4.8 Hz), 4.67 (s, 2H), 3.12 (dd, 1H, *J* = 16.8, 4.8 Hz), 2.98–2.81 (m, 3H), 2.08 (td, 2H, *J* = 12.0, 6.0 Hz) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 159.8, 135.0, 132.5, 129.3, 128.6, 126.3, 126.1, 93.7, 78.4, 74.9, 34.2, 27.3, 25.7 ppm; IR (thin film) ν 3456, 3351, 1628, 1542, 1452, 1336, 1178, 1091, 1018, 857 cm⁻¹.

Purified by chromatography on silica gel (gradient elution: 8:1→4:1 hexanes/EtOAc); white solid (93%): TLC R_f = 0.4 (3:1 hexanes/EtOAc); ^1H NMR (CDCl_3 , 400 MHz) δ 7.43 (br s, 1H), 7.32–7.18 (m, 4H), 5.37 (td, 1H, J = 8.8, 3.4 Hz), 5.23 (d, 1H, J = 8.8 Hz), 4.61 (s, 2H), 2.85 (ddd, 1H, J = 16.0, 12.4, 3.6 Hz), 2.69 (dt, 1H, J = 16.0, 4.2 Hz), 2.42 (dq, 1H, J = 14.8, 3.4 Hz), 1.85 (ddt, 1H, J = 14.8, 12.0, 4.0 Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 162.3, 138.0, 130.9, 129.6, 129.4, 129.3, 127.9, 93.9, 79.3, 78.8, 56.0, 27.6, 23.8 ppm; IR (thin film) ν 3340, 1628, 1494, 1444, 1385, 1344, 1298, 1244, 1178, 1090, 1016, 853 cm^{-1} ; HRMS (ES^+) calcd for $\text{C}_{13}\text{H}_{13}\text{Cl}_3\text{N}_2\text{O}_4\text{S}$ 397.9662 found 398.9754 (MH^+).

Purified by chromatography on silica gel (gradient elution: 6:1→3:1 hexanes/EtOAc); white solid (65%): TLC R_f = 0.3 (3:1 hexanes/EtOAc); ^1H NMR (CDCl_3 , 400 MHz) δ 8.11 (br d, 1H, J = 7.2 Hz), 7.50 (ddd, 1H, J = 7.8, 1.2, 0.8 Hz), 7.42 (br s, 1H), 7.32 (ddd, 1H, J = 8.4, 7.6, 1.2 Hz), 7.24 (ddd, 1H, J = 8.4, 7.6, 1.2 Hz), 7.02 (br s, 1H), 5.47 (br s, 1H), 4.62 (s, 2H), 4.52 (t, 2H, J = 6.8 Hz), 3.08 (t, 2H, J = 6.8 Hz), 1.68 (s, 9H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 160.2, 149.6, 135.3, 130.1, 124.6, 123.5, 122.6, 118.6, 115.6, 115.4, 93.6, 83.8, 78.4, 68.2, 28.2, 24.3 ppm; IR (thin film) ν 3451, 3341, 1730, 1633, 1549, 1452, 1372, 1258, 1160, 1092, 1019, 853 cm^{-1} .

Purified by chromatography on silica gel (gradient elution: 3:1→1:1 hexanes/EtOAc); off-white solid (73%): TLC R_f = 0.2 (3:1 hexanes/EtOAc); ^1H NMR (CDCl_3 , 400 MHz) δ 8.17 (d, 1H, J = 4.2 Hz), 7.64 (s, 1H), 7.45 (ddd, 1H, J = 7.8, 1.2, 0.8 Hz), 7.37 (ddd, 1H, J = 8.4, 7.2, 1.2 Hz), 7.25 (td, 1H, J = 7.6, 1.2 Hz), 5.45 (dd, 1H, J = 9.6, 6.8 Hz), 4.93 (t, 1H, J = 9.2 Hz), 4.65 (s, 2H), 4.62 (dd, 1H, J = 9.2, 6.8 Hz), 1.65 (s, 9H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 162.6, 149.1, 136.1, 126.6, 125.5, 124.7, 123.4, 118.4, 115.96, 115.93, 93.6, 84.7, 78.6, 72.4, 52.2, 28.1 ppm; IR (thin film) ν 3349, 1736, 1634, 1453, 1371, 1257, 1178, 1098, 1020, 879 cm^{-1} ; HRMS (ES^+) calcd for $\text{C}_{18}\text{H}_{20}\text{Cl}_3\text{N}_3\text{O}_6\text{S}$ 511.0138 found 534.0032 (MNa^+).

Purified by chromatography on silica gel (gradient elution: 8:1→3:1 hexanes/EtOAc); white solid (75%): TLC R_f = 0.4 (3:1 hexanes/EtOAc); ^1H NMR (CDCl_3 , 400 MHz) δ 7.02 (br s, 1H), 5.61 (br s, 1H), 4.65 (s, 2H), 4.02 (d, 2H, J = 6.4 Hz), 2.03–1.93 (m, 1H), 0.94 (d, 6H, J = 6.4 Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 160.5, 93.7, 78.4, 75.2, 27.5, 18.8 ppm; IR (thin film) ν 3477, 3371, 1615, 1543, 1442, 1323, 1170, 1087, 1013, 874 cm^{-1} ; HRMS (ES^+) calcd for $\text{C}_7\text{H}_{13}\text{Cl}_3\text{N}_2\text{O}_4\text{S}$ 325.9662 found (M-H^+).

Purified by chromatography on silica gel (gradient elution: 6:1→3:1 hexanes/EtOAc); white solid (92%): mp 127–130 $^{\circ}\text{C}$; TLC R_f = 0.3 (3:1 hexanes/EtOAc); ^1H NMR (CDCl_3 , 400 MHz) δ 7.76 (br s, 1H), 4.64 (s, 2H), 4.26 (s, 2H), 1.46 (s, 6H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 161.6, 93.7, 79.2, 78.5, 59.1, 27.0 ppm; IR (thin film) ν

3341, 1631, 1443, 1343, 1171, 1090, 1020, 882 cm^{-1} ; HRMS (ES^+) calcd for $\text{C}_7\text{H}_{11}\text{Cl}_3\text{N}_2\text{O}_4\text{S}$ 323.9505 found 346.9390 (MNa^+).

Purified by chromatography on silica gel (gradient elution: 8:1→3:1 hexanes/EtOAc); white solid (70%): TLC R_f = 0.4 (3:1 hexanes/EtOAc); ^1H NMR (CDCl_3 , 400 MHz) δ 7.02 (br s, 1H), 5.48 (br s, 1H), 4.65 (s, 2H), 4.11 (dd, 1H, J = 10.4, 4.4 Hz), 4.03 (dd, 1H, J = 10.8, 4.6 Hz), 1.77-1.71 (m, 1H), 1.36-1.43 (m, 1H), 1.24-1.13 (m, 1H), 0.93-0.88 (m, 6H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 160.6, 93.7, 78.5, 73.9, 34.0, 25.7, 16.1, 11.1 ppm; IR (thin film) ν 3478, 3368, 1614, 1543, 1453, 1323, 1171, 1088, 1012, 877 cm^{-1} .

Purified by chromatography on silica gel (gradient elution: 6:1→3:1 hexanes/EtOAc); white solid (84%): TLC R_f = 0.3 (3:1 hexanes/EtOAc); ^1H NMR (CDCl_3 , 400 MHz) δ 7.50 (br s, 1H), 4.65 (s, 2H), 4.33 (d, 1H, J = 8.8 Hz), 4.20 (d, 1H, J = 8.8 Hz), 1.76-1.65 (m, 2H), 1.43 (s, 3H), 0.95 (t, 3H, J = 7.4 Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 162.0, 93.7, 78.5, 77.1, 62.1, 32.6, 25.1, 8.0 ppm; IR (thin film) ν 3477, 3371, 1615, 1543, 1455, 1323, 1170, 1087, 1013, 874 cm^{-1} ; HRMS (ES^+) calcd for $\text{C}_8\text{H}_{13}\text{Cl}_3\text{N}_2\text{O}_4\text{S}$ 337.9662 found 360.9718 (MNa^+).

Purified by chromatography on silica gel (gradient elution: 8:1→4:1 hexanes/EtOAc); white crystalline solid (60%): TLC R_f = 0.4 (3:1 hexanes/EtOAc); ^1H NMR (CDCl_3 , 400 MHz) δ 7.02 (br s, 1H), 5.74 (ddt, 1H, J = 17.2, 10.4, 6.8 Hz), 5.50 (br s, 1H), 5.15-5.08 (m, 2H), 4.65 (s, 2H), 4.29 (t, 2H, J = 6.6 Hz), 2.47-2.42 (m, 2H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 160.3, 133.0, 118.1, 93.6, 78.5, 68.2, 32.7 ppm; IR (thin film) ν 3479, 3372, 1616, 1544, 1460, 1324, 1171, 1014, 876 cm^{-1} .

Purified by chromatography on silica gel (gradient elution: 6:1→3:1 hexanes/EtOAc); white solid (41%): TLC R_f = 0.35 (3:1 hexanes/EtOAc); ^1H NMR (CDCl_3 , 400 MHz) δ 7.42 (br s, 1H), 5.81 (ddd, 1H, J = 17.2, 10.0, 7.2 Hz), 5.42 (d, 1H, J = 16.8 Hz), 5.38 (d, 1H, J = 10.4 Hz), 4.72 (t, 1H, J = 8.8 Hz), 4.67-4.61 (m, 1H), 4.67 (s, 2H), 4.26 (dd, 1H, J = 8.6, 7.6 Hz), ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 162.6, 133.2, 120.9, 93.6, 78.6, 72.1, 57.7 ppm; IR (thin film) ν 3350, 1629, 1444, 1344, 1179, 1019, 881 cm^{-1} ; HRMS (ES^+) calcd for $\text{C}_7\text{H}_9\text{Cl}_3\text{N}_3\text{O}_4\text{S}$ 321.9349 found 344.9237 (MNa^+).

Purified by chromatography on silica gel (gradient elution: 8:1→4:1 hexanes/EtOAc); white, crystalline solid (70%): TLC R_f = 0.3 (3:1 hexanes/EtOAc); ^1H NMR (CDCl_3 , 400 MHz) δ 7.01 (br s, 1H), 5.46 (br s, 1H), 4.65 (s, 2H), 4.23 (t, 2H, J = 6.6 Hz), 1.68-1.61 (m, 2H), 1.42-1.33 (m, 2H), 0.92 (t, 3H, J = 7.4 Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 160.4, 93.7, 78.5, 69.3, 30.3, 18.8, 13.6 ppm; IR (thin film) ν 3474, 3366, 1616, 1543, 1322, 1171, 1013, 876 cm^{-1} .

Purified by chromatography on silica gel (gradient elution: 4:1→2:1 hexanes/EtOAc); white solid (31%): TLC R_f = 0.2 (3:1 hexanes/EtOAc); ^1H NMR (CDCl_3 , 400 MHz) δ 7.54 (br s, 1H), 4.65 (t, 1H, J = 8.8 Hz), 4.65 (s, 2H), 4.23 (dd, 1H, J = 8.8, 6.4 Hz), 4.16–4.10 (m, 1H), 1.77–1.62 (m, 2H), 0.96 (t, 3H, J = 7.4 Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 162.7, 93.7, 78.5, 72.1, 56.4, 27.3, 9.0 ppm; IR (thin film) ν 3356, 1633, 1445, 1346, 1179, 1089, 1020, 883 cm^{-1} ; HRMS (ES^+) calcd for $\text{C}_7\text{H}_{11}\text{Cl}_3\text{N}_3\text{O}_4\text{S}$ 321.9349 found 346.9398 (MNa^+).

Experimental Procedures and Characterization Data for Guanidine Substrates and Cyclic Products

Preparation of *S,S*-Dimethyl-*N*-(2,2,2-trichloroethoxysulfonyl)carbonimidodithionate ($\text{TcesN}=\text{C}(\text{SMe})_2$)

To a stirred solution of 2,2,2-trichloroethylsulfamate (6.85 g, 30.0 mmol) in 23.0 mL of DMF at 0 °C were added sequentially 20 M aqueous NaOH (2.10 mL, 42.0 mmol, 1.4 equiv) and CS_2 (1.07 mL, 17.8 mmol, 0.6 equiv). Two additional portions of 20 M aqueous NaOH (1.05 mL, 21.0 mmol, 0.7 equiv) and CS_2 (0.54 mL, 9.0 mmol, 0.3 equiv) were added at 15 min intervals. The contents were stirred at 0 °C for 20 min and then warmed to 23 °C. After 2 h the reddish-orange solution was cooled to 0 °C and Me_2SO_4 (5.97 mL, 63 mmol, 2.1 equiv) was added dropwise over 10 min. The resulting yellow solution was warmed to 23 °C and stirred for 3 h after which time 40 mL of H_2O was added slowly. The mixture was cooled once again to 0 °C and stirred vigorously. A yellow-orange solid slowly precipitated (~1 h), which was collected upon filtration through a fritted funnel. Recrystallization of this material from ~75 mL of MeOH (2 crops) afforded the desired product as white needles (5.50 g, 55%): TLC R_f = 0.45 (2:1 hexanes/EtOAc); mp 61–62 °C; ^1H NMR (CDCl_3 , 400 MHz) δ 4.71 (s, 2H), 2.60 (s, 6H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 190.0, 93.3, 79.3, 16.7 ppm; IR (thin film) ν 3024, 2958, 1425, 1357, 1267, 1171, 1090, 1012, 840 cm^{-1} .

Preparation of *S*-Methyl-*N*-(2,2,2-trichloroethoxysulfonyl)isothioureia ($\text{TcesN}=\text{C}(\text{SMe})\text{NH}_2$)

To a suspension of *S,S*-dimethyl-*N*-(2,2,2-trichloroethoxysulfonyl)carbonimidodithionate (3.26 g, 9.79 mmol) in 10 mL of MeOH was added 2 M methanolic NH_3 (5.38 mL, 10.8 mmol, 1.1 equiv). The reaction mixture was heated to 50 °C and stirred for 1 h. The solution was cooled to 23 °C and concentrated under reduced pressure. Purification of the oily residue by chromatography on silica gel (gradient elution: 4:1→2:1 hexanes/EtOAc) afforded the desired product as a white solid (2.48 g, 84%): TLC R_f = 0.33 (2:1 hexanes/EtOAc); mp 64–65 °C; ^1H NMR (CDCl_3 , 400 MHz) δ 4.66 (s, 2H), 2.45 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 171.9, 93.6, 78.8, 14.3 ppm; IR (KBr pellet) ν 3451, 3343, 1608, 1512, 1360, 1158, 1010, 883, 829, 785 cm^{-1} .

Preparation of (2,2,2-Trichloroethoxysulfonyl)carbonchloroimidothioic acid methyl ester ($\text{TcesN}=\text{C}(\text{SMe})\text{Cl}$)

Sulfuryl chloride (903 μL , 11.2 mmol, 2.5 equiv) was added dropwise to a stirred solution of *S,S*-dimethyl-*N*-(2,2,2-trichloroethoxysulfonyl)carbonimidodithionate (1.5 g, 4.51 mmol) in 4.5 mL of CH_2Cl_2 . After 6 h the reaction was concentrated in vacuo (~1 torr) to a slightly yellow solid. Purification by chromatography on silica gel (gradient elution: 9:1→5:1 hexanes/EtOAc) afforded the desired compound as a white solid (1.36 g, 94%): mp 61–64 °C; ^1H NMR (CDCl_3 , 500 MHz) δ 4.76 (s, 2H), 2.54 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 166.5, 92.8, 79.6, 18.4 ppm; IR (thin film) ν 1561, 1372, 1181, 1086, 1003, 951, 872, 835 cm^{-1} .

Preparation of *N*-Alkyl-*N*-(2,2,2-trichloroethoxysulfonyl)guanidines (Tces guanidine)

Method A

A 15 mL thick-walled tube was charged with *S*-methyl-*N*-(2,2,2-trichloroethoxysulfonyl)isothiourea (754 mg, 2.5 mmol), 1° amine (2.5 mmol), 2.5 mL of H₂O, and a magnetic stir bar. The vessel was sealed with a teflon screw-cap and the contents heated at 100 °C for 4 h. The reaction mixture was cooled to 23 °C and 5 mL of CH₂Cl₂ was added. The biphasic solution was transferred to a separatory funnel, partitioned between 10 mL CH₂Cl₂ and 10 mL H₂O, and extracted with 3 x 10 mL of CH₂Cl₂. The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. Purification of the isolated material by chromatography on silica gel (conditions given below) afforded the desired guanidine substrate.

Method B

A solution of (2,2,2-trichloroethoxysulfonyl)carbonylchloroimidodithioic acid methyl ester (353 mg, 1.1 mmol, 1.1 equiv) in 5 mL of CH₂Cl₂ was cooled to 0 °C and neat 1° amine (1 mmol) was added dropwise. To the resulting slightly turbid mixture was added triethylamine (182 µL, 1.2 mmol, 1.2 equiv). The reaction was warmed to 23 °C and stirred for 4 h. The pale yellow solution was then concentrated in vacuo. Purification by chromatography on silica gel (conditions given below) furnished the isothiourea product.

To a solution of isothiourea (0.5 mmol) in 5 mL of MeCN was added successively (Me₃Si)₂NH (265 µL, 1.25 mmol, 2.5 equiv) and HgCl₂ (149 mg, 0.55 mmol, 1.1 equiv). After 1 h the milky white suspension was filtered through Celite and the filtrate was concentrated under reduced pressure. Purification of the oily residue by chromatography on silica gel (conditions given below) gave the desired *N*-Tces guanidine.

General Procedure for C–H Amination of Guanidine Substrates

A flame-dried 25 mL Schlenk flask was charged with Tces guanidine (0.2 mmol), Rh₂(esp)₂ (3 mg, 4 µmol, 0.02 equiv), PhI(OAc)₂ (106 mg, 0.33 mmol, 1.65 equiv), and MgO (20 mg, 0.5 mmol, 2.5 equiv). The reaction vessel was stoppered with a rubber septum, the contents placed briefly under vacuum (~5 torr), and the flask then back-filled with N₂. This process was repeated two additional times prior to the addition of 2 mL of deoxygenated toluene. The resulting deep green suspension was heated to 40 °C and stirred for 12 h. After this time, the mixture was cooled to 23 °C, applied directly to a column of silica gel, and the product eluted using the conditions given below.

Characterization Data for Guanidine Substrates and Corresponding Amination Products

Prepared according to **method A**. Purified by chromatography on silica gel (gradient elution: 3:1→1:1 hexanes/EtOAc); white solid (80%): mp 96–97 °C; TLC *R_f* = 0.22 (1:1 toluene/Et₂O); ¹H NMR (CD₃CN, 400 MHz, 60 °C) δ 6.11 (br s, 3H), 4.59 (s, 2H), 3.02 (t, 2H, *J* = 6.2 Hz), 1.83 (sept, 1H, *J* = 6.8 Hz), 0.92 (d, 6H, *J* = 6.8 Hz) ppm; ¹³C NMR (CD₃CN, 125 MHz, 45 °C) δ 158.6, 95.5, 78.8, 49.5, 28.9, 20.2 ppm; IR (thin film) ν 3367, 2964, 1594, 1404, 1317, 1190, 1089, 1021, 845, 749 cm⁻¹.

Purified by chromatography on silica gel (gradient elution: 1:0→2:1 toluene/Et₂O); white solid (74%): mp 195 °C; TLC *R_f* = 0.30 (1:1 toluene/Et₂O); ¹H NMR (CD₃CN, 400 MHz) δ 6.50 (br s, 1H), 6.36 (br s, 1H), 4.57 (s, 2H), 3.36

(s, 2H), 1.31 (s, 6H) ppm; ^{13}C NMR (CD_3CN , 125 MHz) δ 160.4, 95.3, 78.5, 58.6, 55.7, 27.5 ppm; IR (thin film) ν 3393, 3217, 2974, 1598, 1535, 1271, 1159, 1082, 1018, 842, 753, 722, 592 cm^{-1} ; HRMS (ES^+) calcd for $\text{C}_7\text{H}_{12}\text{Cl}_3\text{N}_3\text{O}_3\text{S}$ 322.9665 found 345.9549 (MNa^+).

Prepared according to **method A**. Purified by chromatography on silica gel (gradient elution: 3:1 $\rightarrow$ 3:2 hexanes/ EtOAc); white solid (89%): mp 61–64 $^\circ\text{C}$; TLC R_f = 0.27 (1:1 toluene/ Et_2O); ^1H NMR (CDCl_3 , 500 MHz, 58 $^\circ\text{C}$) δ 7.39–7.33 (m, 2H), 7.31–7.26 (m, 1H), 7.25–7.21 (m, 2H), 5.89 (br s, 3H), 4.60 (s, 2H), 3.53 (q, 2H, J = 6.5 Hz), 2.92 (t, 2H, J = 6.5 Hz) ppm; ^{13}C NMR (CDCl_3 , 125 MHz, 58 $^\circ\text{C}$) δ 157.3, 137.7, 129.1, 128.8, 127.2, 94.4, 78.4, 43.3, 35.4 ppm; IR (thin film) ν 3461, 3355, 2945, 1550, 1497, 1454, 1406, 1310, 1181, 1132, 1087, 1021, 851 cm^{-1} .

Purified by chromatography on silica gel (gradient elution: 1:0 $\rightarrow$ 2:1 toluene/ Et_2O); white solid (57%): mp 168 $^\circ\text{C}$; TLC R_f = 0.45 (1:1 toluene/ Et_2O); ^1H NMR (CD_3CN , 400 MHz) δ 7.42–7.32 (m, 5H), 6.82 (br s, 1H), 6.51 (br s, 1H), 5.04 (dd, 1H, J = 9.2, 7.6 Hz), 4.63 (s, 2H), 4.03 (t, 1H, J = 9.6 Hz), 3.42 (dd, 1H, J = 9.6, 7.6 Hz) ppm; ^{13}C NMR (CD_3CN , 125 MHz, 50 $^\circ\text{C}$) δ 162.2, 141.9, 130.0, 129.4, 127.3, 95.6, 79.0, 58.7, 51.6 ppm; IR (thin film) ν 3408, 3171, 1623, 1542, 1177, 1116, 1020, 840 cm^{-1} ; HRMS (ES^+) calcd for $\text{C}_{11}\text{H}_{12}\text{Cl}_3\text{N}_3\text{O}_3\text{S}$ 370.9665 found 393.9572 (MNa^+).

Prepared according to **method A**. Purified by chromatography on silica gel (gradient elution: 3:1 $\rightarrow$ 1:1 hexanes/ EtOAc); white solid (85%): mp 127–128 $^\circ\text{C}$; TLC R_f = 0.30 (1:1 toluene/ Et_2O); ^1H NMR (CD_3CN , 400 MHz, 60 $^\circ\text{C}$) δ 6.10 (br s, 3H), 4.59 (s, 2H), 3.04 (br t, 2H, J = 5.8 Hz), 1.76–1.69 (m, 4H), 1.69–1.63 (m, 1H), 1.59–1.48 (m, 1H), 1.33–1.13 (m, 3H), 1.03–0.92 (m, 2H) ppm; ^{13}C NMR (CD_3CN , 125 MHz, 65 $^\circ\text{C}$) δ 159.0, 95.8, 79.1, 48.7, 38.6, 31.6, 27.4, 26.7 ppm; IR (thin film) ν 3465, 3376, 3267, 2928, 1643, 1597, 1326, 1191, 1140, 833 cm^{-1} .

Purified by chromatography on silica gel (gradient elution: 1:0 $\rightarrow$ 2:1 toluene/ Et_2O); white solid (80%): mp 212–214 $^\circ\text{C}$; TLC R_f = 0.44 (1:1 toluene/ Et_2O); ^1H NMR (CD_3CN , 400 MHz) δ 6.53 (br s, 1H), 6.43 (br s, 1H), 4.57 (s, 2H), 3.40 (s, 2H), 1.70–1.54 (m, 6H), 1.49–1.25 (m, 4H) ppm; ^{13}C NMR (CDCl_3 , 125 MHz, 50 $^\circ\text{C}$) δ 159.6, 94.5, 78.3, 61.2, 52.9, 37.1, 24.7, 22.8 ppm; IR (thin film) ν 3400, 3225, 2931, 1609, 1537, 1327, 1169, 1027, 848 cm^{-1} ; HRMS (ES^+) calcd for $\text{C}_{10}\text{H}_{16}\text{Cl}_3\text{N}_3\text{O}_3\text{S}$ 362.9978 found 385.9863 (MNa^+).

Prepared according to **method B**. Purified by chromatography on silica gel (gradient elution: 6:1 $\rightarrow$ 3:1 hexanes/ EtOAc); white solid (92%): mp 83–85 $^\circ\text{C}$; TLC R_f = 0.26 (1:1 toluene/ Et_2O); ^1H NMR (CD_3CN , 400 MHz, 65 $^\circ\text{C}$) δ 6.10 (br s, 3H), 4.59 (s, 2H), 3.62 (br s, 1H), 1.81–1.69 (m, 1H), 1.10 (d, 3H, J = 6.4 Hz), 0.92 (d, 3H, J = 6.8 Hz), 0.91 (d, 3H, J = 6.8 Hz) ppm; ^{13}C NMR (CD_3CN , 125 MHz, 60 $^\circ\text{C}$) δ 158.3, 95.7, 79.0, 54.0, 34.0, 18.9, 17.81, 17.76 ppm; IR (thin film) ν 3462, 3356, 2967, 1630, 1548, 1406, 1309, 1184, 1089, 1022, 852 cm^{-1} .

Purified by chromatography on silica gel (gradient elution: 9:1→5:1 hexanes/EtOAc); clear oil (96%): TLC R_f = 0.55 (3:1 hexanes/EtOAc); ^1H NMR (CDCl_3 , 400 MHz) δ 7.84 (br d, 1H, J = 9.2 Hz), 4.63 (s, 2H), 3.60–3.51 (m, 1H), 2.44 (s, 3H), 1.84–1.76 (m, 1H), 1.19 (d, 3H, J = 6.4 Hz), 0.95 (d, 3H, J = 6.8 Hz), 0.93 (d, 3H, J = 6.4 Hz) ppm; IR (thin film) ν 3296, 2966, 1572, 1429, 1344, 1140, 1088, 1021, 870, 751 cm^{-1} .

Purified by chromatography on silica gel (gradient elution: 1:0→2:1 toluene/ Et_2O); white solid (54%): mp 201–202 °C; TLC R_f = 0.39 (1:1 toluene/ Et_2O); ^1H NMR (CDCl_3 , 500 MHz, 50 °C) δ 6.69 (br s, 1H), 6.60 (br s, 1H), 4.57 (s, 2H), 3.67 (q, 1H, J = 6.5 Hz), 1.35 (s, 3H), 1.23–1.19 (m, 6H) ppm; ^{13}C NMR (CDCl_3 , 125 MHz, 50 °C) δ 159.2, 94.4, 78.3, 60.7, 60.0, 27.8, 22.1, 15.0 ppm; IR (thin film) ν 3383, 3234, 1637, 1513, 1318, 1171, 1088, 1024, 862 cm^{-1} ; HRMS (ES^+) calcd for $\text{C}_8\text{H}_{14}\text{Cl}_3\text{N}_3\text{O}_3\text{S}$ 336.9821 found 359.9709 (MNa^+).

Prepared according to **method B**. Purified by chromatography on silica gel (gradient elution: 6:1→3:1 hexanes/EtOAc); white solid (89%): mp 148–150 °C; TLC R_f = 0.48 (1:1 toluene/ Et_2O); ^1H NMR (CD_3CN , 500 MHz, 65 °C) δ 6.25 (br s, 2H), 6.08 (br s, 1H), 4.58 (s, 2H), 4.23 (br s, 1H), 1.91–1.83 (m, 1H), 1.54–1.45 (m, 1H), 1.47 (s, 9H), 1.30–1.20 (m, 1H), 0.97–0.92 (m, 6H) ppm; ^{13}C NMR (CD_3CN , 125 MHz, 65 °C) δ 171.2, 158.6, 95.7, 83.3, 79.2, 60.2, 38.8, 28.6, 26.5, 16.1, 12.1 ppm; IR (thin film) ν 3473, 3372, 2980, 2361, 1699, 1617, 1580, 1534, 1339, 1186, 1088, 1031, 853 cm^{-1} .

Purified by chromatography on silica gel (gradient elution: 9:1→5:1 hexanes/EtOAc); clear oil (97%): TLC R_f = 0.52 (3:1 hexanes/EtOAc); ^1H NMR (CDCl_3 , 400 MHz) δ 8.42 (br d, 1H, J = 8.8 Hz), 4.65 (s, 2H), 4.10 (dd, 1H, J = 8.6, 4.6 Hz), 2.45 (s, 3H), 1.96–1.92 (m, 1H), 1.54–1.47 (m, 1H), 1.47 (s, 9H), 1.32–1.24 (m, 1H), 0.96–0.93 (m, 6H) ppm; IR (thin film) ν 3296, 2970, 1735, 1571, 1431, 1343, 1158, 1088, 1021, 876 cm^{-1} .

Purified by chromatography on silica gel (gradient elution: 1:0→4:1 toluene/ Et_2O); white solid (91%): mp 139–140 °C; TLC R_f = 0.58 (1:1 toluene/ Et_2O); ^1H NMR (CDCl_3 , 400 MHz) δ 6.60 (br s, 1H), 6.49 (br s, 1H), 4.63 (d, 1H, J = 11.2 Hz), 4.57 (d, 1H, J = 11.2 Hz), 4.10 (s, 1H), 1.76 (q, 2H, J = 7.6 Hz), 1.48 (s, 9H), 1.29 (s, 3H), 0.98 (t, 3H, J = 7.4 Hz) ppm; ^{13}C NMR (CDCl_3 , 500 MHz) δ 167.6, 159.1, 94.1, 83.5, 78.2, 64.2, 63.5, 34.3, 28.0, 22.1, 8.0 ppm; IR (thin film) ν 3365, 3168, 2978, 1744, 1623, 1521, 1315, 1231, 1158, 1019, 914, 845 cm^{-1} ; HRMS (ES^+) calcd for $\text{C}_{13}\text{H}_{22}\text{Cl}_3\text{N}_3\text{O}_5\text{S}$ 437.0346 found 460.0253 (MNa^+).

Prepared according to **method A**. Purified by chromatography on silica gel (gradient elution: 3:1→2:1 hexanes/EtOAc); white solid (71%): mp 84–85 °C; TLC R_f = 0.26 (1:1 toluene/Et₂O); ¹H NMR (CD₃CN, 400 MHz, 70 °C) δ 6.13 (br s, 3H), 4.59 (s, 2H), 3.18 (dt, 2H, J = 6.8, 5.6 Hz), 1.58–1.50 (m, 2H), 1.38–1.30 (m, 4H), 0.91 (t, 3H, J = 6.8 Hz) ppm; ¹³C NMR (CD₃CN, 125 MHz, 60 °C) δ 158.8, 95.8, 79.0, 42.5, 29.7, 29.6, 23.1, 14.4 ppm; IR (thin film) ν 3461, 3355, 2934, 2871, 1554, 1406, 1307, 1186, 1021, 861 cm⁻¹.

Purified by chromatography on silica gel (gradient elution: 1:0→2:1 toluene/Et₂O); white solid (30%): mp 98–99 °C; TLC R_f = 0.47 (1:1 toluene/Et₂O); ¹H NMR (CDCl₃, 500 MHz) δ 6.60 (br s, 1H), 5.98 (br s, 1H), 4.58 (d, 1H, J = 11.0 Hz), 4.56 (d, 1H, J = 11.0 Hz), 4.02–3.96 (m, 1H), 3.78 (t, 1H, J = 9.5 Hz), 3.33 (dd, 1H, J = 9.3, 7.3 Hz), 1.68–1.60 (m, 1H), 1.58–1.50 (m, 1H), 1.39–1.28 (m, 2H), 0.94 (t, 3H, J = 7.5 Hz) ppm; ¹³C NMR (CDCl₃, 125 MHz) δ 160.6, 94.2, 78.1, 54.9, 47.8, 37.3, 18.5, 13.9 ppm; IR (thin film) ν 3393, 3243, 2962, 1613, 1533, 1327, 1265, 1175, 1087, 1026, 915, 849 cm⁻¹; HRMS (ES⁺) calcd for C₈H₁₄Cl₃N₃O₃S 336.9821 found 359.9712 (MNa⁺).

Experimental Procedure for Tces Guanidine Deprotection

To a suspension of powdered Zn (44 mg, 0.67 mmol, 5.0 equiv) in 1.3 mL of a 1:1 MeOH/AcOH solution was added 2-trichloroethoxysulfonylamino-4-phenylimidazole (50 mg, 0.13 mmol). The mixture was stirred vigorously at 40 °C for 16 h. The reaction was then cooled to 23 °C and diluted with 1 mL of MeOH, and the contents filtered through a small pad of Celite. The flask and filter cake were rinsed with an additional 5 mL of MeOH. The combined filtrates were concentrated under reduced pressure to give a solid white residue. Purification of the product was performed by reverse phase HPLC on a Varian ProStar 210 Instrument with an Alltima C18 10 μm column (22 x 250 mm). A product retention time of 8.46 min was recorded using a 19:1→1:9 H₂O/MeCN buffered with 0.1% CF₃CO₂H gradient elution over 14.60 min (white solid, 34 mg, 91%): ¹H NMR (CD₃OD, 400 MHz) δ 7.43–7.33 (m, 5H), 5.11 (dd, 1H, J = 9.6, 7.2 Hz), 4.09 (t, 1H, J = 9.8 Hz), 3.47 (dd, 1H, J = 9.6, 7.2 Hz) ppm; ¹⁹F NMR (CD₃OD, 376 MHz, referenced to α,α,α-trifluorotoluene) δ –77.4 ppm; IR (KBr pellet) ν 3367, 1680, 1584, 1493, 1458, 1376, 1122, 881 cm⁻¹; HRMS (ES⁺) calcd for C₉H₁₁N₃ 161.0953 found 162.1028 (MH⁺).

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^1H NMR
(CD_3CN , 400 MHz)

¹H NMR
(CDCl₃, 400 MHz)

^1H NMR
(CDCl_3 , 400 MHz)

^1H NMR
(CDCl_3 , 400 MHz)

^1H NMR
(CDCl_3 , 400 MHz)

^1H NMR
(CDCl_3 , 400 MHz)

^1H NMR
(CDCl_3 , 400 MHz)

¹H NMR
(CDCl₃, 400 MHz)

^1H NMR
(CDCl_3 , 400 MHz)

¹H NMR
(CDCl₃, 400 MHz)

$^1\text{H NMR}$
(CDCl_3 , 400 MHz)

¹H NMR
(CDCl₃, 400 MHz)

^1H NMR
(CDCl_3 , 400 MHz)

^1H NMR
(CDCl_3 , 400 MHz)

^1H NMR
(CDCl_3 , 400 MHz)

^1H NMR
(CDCl_3 , 400 MHz)

¹H NMR
(CDCl₃, 400 MHz)

^1H NMR
(CDCl_3 , 500 MHz)

^1H NMR
(CD_3CN , 400 MHz)

^1H NMR
(CD_3CN , 400 MHz)

^1H NMR
(CDCl_3 , 500 MHz)

^1H NMR
(CD_3CN , 400 MHz)

^1H NMR
(CD_3CN , 400 MHz, 60 $^\circ\text{C}$)

^1H NMR
(CD_3CN , 400 MHz)

^1H NMR
(CD_3CN , 400 MHz, 65 °C)

^1H NMR
(CDCl_3 , 400 MHz)

^1H NMR
(CDCl_3 , 500 MHz, 50 $^\circ\text{C}$)

^1H NMR
(CD_3CN , 500 MHz, 65 °C)

¹H NMR
(CDCl₃, 400 MHz)

¹H NMR
(CDCl₃, 400 MHz)

^1H NMR
(CD_3CN , 400 MHz, 70 $^\circ\text{C}$)

^1H NMR
(CDCl_3 , 500 MHz)

^1H NMR
(CD_3OD , 400 MHz)