

Generation of 1-(trifluoromethyl)isoquinolines via a copper-catalyzed reaction of isoquinoline-N-oxide with Togni reagent

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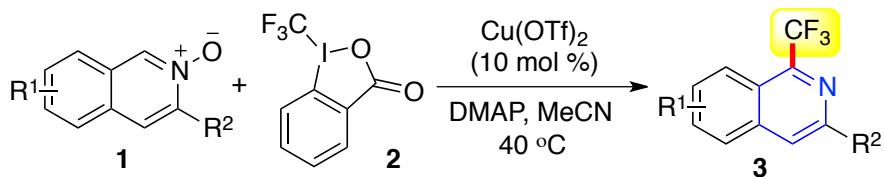
Supporting Information

1. General experimental methods (S2).
2. General experimental procedure and characterization data (S2-S7).
3. ¹H and ¹³C NMR spectra of compound 3 (S8-S49).

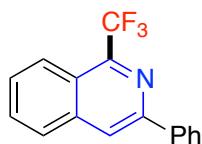
General experimental methods:

Unless otherwise stated, all commercial reagents were used as received. All solvents were dried and distilled according to standard procedures. Flash column chromatography was performed using silica gel (60-Å pore size, 32–63 μ m, standard grade). Analytical thin-layer chromatography was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated on rotary evaporators at ~20 Torr at 25–35°C. Nuclear magnetic resonance (NMR) spectra are recorded in parts per million from internal tetramethylsilane on the δ scale. ^1H and ^{13}C NMR spectra were recorded in CDCl_3 on a Bruker DRX-400 spectrometer operating at 400 MHz and 100 MHz, respectively. All chemical shift values are quoted in ppm and coupling constants quoted in Hz. High resolution mass spectrometry (HRMS) spectra were obtained on a micrOTOF II Instrument.

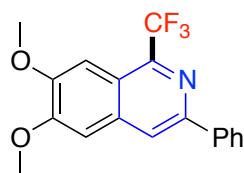
General experimental procedure for the synthesis of 1-(trifluoromethyl)isoquinolines via a copper-catalyzed reaction of isoquinoline-N-oxide with Togni reagent



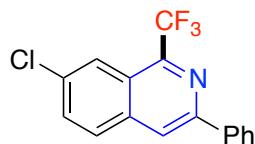
Isoquinoline *N*-oxide **1** (0.2 mmol) was added to a solution of 1-trifluoromethyl-1,2-benziodoxol-3(1*H*)-one (Togni Reagent) (0.24 mmol), DMAP (0.6 mmol), and $\text{Cu}(\text{OTf})_2$ (0.02 mmol) in CH_3CN (2.0 mL) under N_2 atmosphere. The mixture was stirred at 40°C for 8 - 12 hours. After completion of reaction as indicated by TLC, the solvent was evaporated and the residue was purified by column chromatography on silica gel to provide the product **3**.



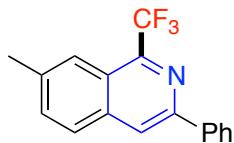
3-Phenyl-1-(trifluoromethyl)isoquinoline **3a.** ^1H NMR (400 MHz, CDCl_3) δ 8.31 (d, $J = 8.8$ Hz, 1H), 7.92 (s, 1H), 7.82 (d, $J = 8.0$ Hz, 1H), 7.75 (dd, $J = 6.4, 2.8$ Hz, 2H), 7.72 - 7.65 (m, 1H), 7.60 (t, $J = 7.5$ Hz, 1H), 7.53 - 7.44 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 152.9, 148.0, 131.7, 130.5, 129.9, 129.8, 128.6, 128.4, 128.2, 127.9, 127.5, 125.8 (q, $^1J_{\text{CF}} = 286.1$ Hz), 122.2; ^{19}F NMR (378 MHz, CDCl_3) δ -62.05; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{11}\text{F}_3\text{N}$: 274.0838 ($\text{M} + \text{H}^+$), found: 274.0832.



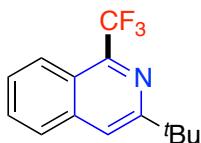
6,7-Dimethoxy-3-phenyl-1-(trifluoromethyl)isoquinoline **3b.** ^1H NMR (400 MHz, CDCl_3) δ 7.60 (d, $J = 7.3$ Hz, 2H), 7.33 (t, $J = 7.4$ Hz, 2H), 7.29 - 7.24 (m, 1H), 6.74 (d, $J = 10.9$ Hz, 2H), 6.41 (s, 1H), 3.91 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 154.2, 152.4, 149.5, 148.3, 143.3, 130.9, 128.8, 128.1, 127.4, 127.0, 125.3 (q, $^1J_{\text{CF}} = 283.8$ Hz), 124.1, 119.0, 110.6, 107.7, 56.4, 55.8; ^{19}F NMR (378 MHz, CDCl_3) δ -63.95; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{15}\text{F}_3\text{NO}_2$: 334.1049 ($\text{M} + \text{H}^+$), found: 334.1066.



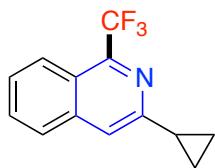
7-Chloro-3-phenyl-1-(trifluoromethyl)isoquinoline **3c.** ^1H NMR (400 MHz, CDCl_3) δ 8.29 (s, 1H), 7.89 (s, 1H), 7.76 (d, $J = 8.8$ Hz, 1H), 7.73 (dd, $J = 6.5, 2.9$ Hz, 2H), 7.55 (d, $J = 8.7$ Hz, 1H), 7.52 - 7.46 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 153.0, 149.3, 137.1, 131.3, 130.5, 130.0, 129.8, 129.3, 129.2, 128.7, 128.3, 127.6, 125.3 (q, $^1J_{\text{CF}} = 283.3$ Hz), 125.7, 121.2; ^{19}F NMR (378 MHz, CDCl_3) δ -62.32; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{10}\text{ClF}_3\text{N}$: 308.0448 ($\text{M} + \text{H}^+$), found: 308.0432.



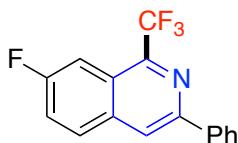
7-Methyl-3-phenyl-1-(trifluoromethyl)isoquinoline **3d.** ^1H NMR (400 MHz, CDCl_3) δ 8.08 (s, 1H), 7.87 (s, 1H), 7.78 - 7.68 (m, 3H), 7.46 (m, 4H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 151.5, 147.2, 141.1, 131.9, 130.5, 129.9, 129.6, 128.2, 127.7, 127.1, 126.7, 125.2 (q, $^1J_{\text{CF}} = 284.8$ Hz), 121.2, 22.6; ^{19}F NMR (378 MHz, CDCl_3) δ -61.77; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{13}\text{F}_3\text{N}$: 288.0995 ($\text{M} + \text{H}^+$), found: 288.1004.



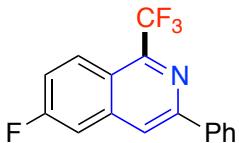
3-(tert-Butyl)-1-(trifluoromethyl)isoquinoline **3e.** ^1H NMR (400 MHz, CDCl_3) δ 8.21 (t, $J = 10.4$ Hz, 1H), 7.82 - 7.72 (m, 2H), 7.62 - 7.56 (m, 1H), 7.52 (t, $J = 7.3$ Hz, 1H), 1.58 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.1, 151.6, 133.4, 129.9, 127.8, 126.6, 126.4, 125.4 (q, $^1J_{\text{CF}} = 286.1$ Hz), 124.1, 121.5, 30.2, 27.8; ^{19}F NMR (378 MHz, CDCl_3) δ -62.28; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{15}\text{F}_3\text{N}$: 254.1151 ($\text{M} + \text{H}^+$), found: 254.1124.



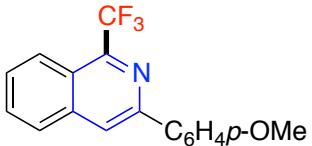
3-Cyclopropyl-1-(trifluoromethyl)isoquinoline **3f.** ^1H NMR (400 MHz, CDCl_3) δ 8.25 (d, $J = 8.7$ Hz, 1H), 7.71 (d, $J = 7.9$ Hz, 1H), 7.64 - 7.58 (m, 1H), 7.55 (d, $J = 14.7$ Hz, 1H), 7.45 (s, 1H), 2.63 - 2.69 (m, 1H), 1.17 - 1.28 (m, 2H), 0.79 - 0.87 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 151.7, 150.3, 132.7, 129.8, 128.4, 128.0, 127.3, 127.2, 125.3 (q, $^1J_{\text{CF}} = 282.3$ Hz) 122.1, 15.4, 7.8; ^{19}F NMR (378 MHz, CDCl_3) δ -62.13; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{11}\text{F}_3\text{N}$: 238.0838 ($\text{M} + \text{H}^+$), found: 238.0837.



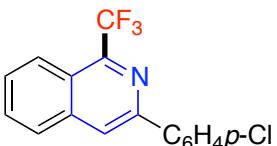
7-Fluoro-3-phenyl-1-(trifluoromethyl)isoquinoline **3g**. ^1H NMR (400 MHz, CDCl_3) δ 7.93 (dd, $J = 10.6, 8.7$ Hz, 2H), 7.83 (dd, $J = 8.9, 5.8$ Hz, 1H), 7.72 (dd, $J = 6.6, 3.0$ Hz, 2H), 7.53 - 7.45 (m, 3H), 7.41 - 7.34 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.3 (d, $^1J_{\text{CF}} = 250.4$ Hz), 152.5, 148.8, 131.4, 130.6, 130.5, 129.9, 129.8, 128.3, 127.2, 125.2 (q, $^1J_{\text{CF}} = 278.3$ Hz), 118.7, 107.2; ^{19}F NMR (378 MHz, CDCl_3) δ -62.54, -105.61; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{10}\text{F}_4\text{N}$: 292.0744 ($\text{M} + \text{H}^+$), found: 292.0748.



6-Fluoro-3-phenyl-1-(trifluoromethyl)isoquinoline **3h**. ^1H NMR (400 MHz, CDCl_3) δ 8.33 (dd, $J = 10.3, 5.0$ Hz, 1H), 7.86 (s, 1H), 7.78 - 7.70 (m, 2H), 7.53 - 7.42 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3) δ 161.5 (d, $^1J_{\text{CF}} = 252.3$ Hz), 151.2, 149.1, 131.3, 130.1, 129.9, 128.3, 126.6, 126.5, 124.8 (q, $^1J_{\text{CF}} = 273.3$ Hz), 120.9, 111.8; ^{19}F NMR (378 MHz, CDCl_3) δ -62.08, -109.13; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{10}\text{F}_4\text{N}$: 292.0744 ($\text{M} + \text{H}^+$), found: 292.0752.

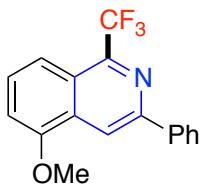


3-(4-Methoxyphenyl)-1-(trifluoromethyl)isoquinoline **3i**. ^1H NMR (400 MHz, CDCl_3) δ 9.31 (s, 1H), 8.08 (d, $J = 8.7$ Hz, 2H), 8.02 - 7.94 (d, $J = 8.2$ Hz, 2H), 7.68 (t, $J = 7.3$ Hz, 1H), 7.58 - 7.53 (m, 1H), 7.04 (d, $J = 8.7$ Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 152.3, 148.4, 131.4, 130.4, 128.2, 127.6, 127.5, 126.8, 126.7, 124.4 (q, $^1J_{\text{CF}} = 275.4$ Hz), 115.4, 114.2, 55.4; ^{19}F NMR (378 MHz, CDCl_3) δ -62.07; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{13}\text{F}_3\text{NO}$: 304.0944 ($\text{M} + \text{H}^+$), found: 304.0941.

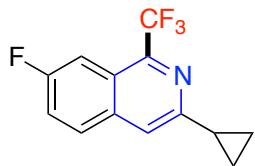


3-(4-Chlorophenyl)-1-(trifluoromethyl)isoquinoline **3j**. ^1H NMR (400 MHz, CDCl_3) δ 8.31 (d, $J = 8.8$ Hz, 1H), 7.91 (s, 1H), 7.83 (d, $J = 8.0$ Hz, 1H), 7.75 - 7.66 (m, 3H), 7.62 (t, $J = 7.4$ Hz, 1H), 7.46 (d, $J = 8.5$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 151.1, 146.9, 136.0, 131.2, 130.7, 130.1, 130.0, 128.8, 128.5, 127.9, 127.4, 127.1, 125.3

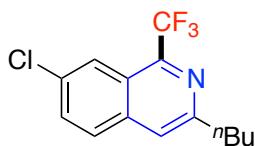
(q, $^1J_{CF} = 288.3$ Hz), 122.3; ^{19}F NMR (378 MHz, CDCl₃) δ -62.08; HRMS (ESI) calcd for C₁₆H₁₀ClF₃N: 308.0448 (M + H⁺), found: 308.0456.



5-Methoxy-3-phenyl-1-(trifluoromethyl)isoquinoline 3k. 1H NMR (400 MHz, CDCl₃) δ 7.65 (d, $J = 7.1$ Hz, 2H), 7.33 (t, $J = 7.7$ Hz, 2H), 7.23 - 7.28 (m, 1H), 7.19 (t, $J = 7.9$ Hz, 1H), 6.84 (t, $J = 7.6$ Hz, 2H), 6.78 (s, 1H), 4.93 (t, $J = 8.4$ Hz, 1H), 3.87 (s, 3H), 1.00 (s, 9H); ^{13}C NMR (100 MHz, CDCl₃) δ 155.2, 148.6, 138.1, 133.0, 131.1, 128.9, 128.8, 128.5, 127.0, 125.8 (q, $^1J_{CF} = 287.5$ Hz), 125.6, 116.4, 114.1, 55.8; ^{19}F NMR (378 MHz, CDCl₃) δ -63.55; HRMS (ESI) calcd for C₁₇H₁₃F₃NO: 304.0944 (M + H⁺), found: 304.0938.

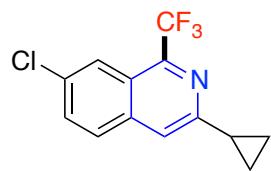


3-Cyclopropyl-7-fluoro-1-(trifluoromethyl)isoquinoline 3l. 1H NMR (400 MHz, CDCl₃) δ 8.84 (s, 1H), 8.02 (d, $J = 7.8$ Hz, 1H), 7.82 (d, $J = 7.9$ Hz, 1H), 7.60 (s, 1H), 2.04 (m, 1H), 1.23 - 1.27 (m, 2H), 0.83 - 0.88 (m, 2H); ^{13}C NMR (100 MHz, CDCl₃) δ 162.1 (d, $^1J_{CF} = 252.6$ Hz), 152.7, 148.5, 133.0, 130.9, 128.9, 128.0, 126.0, 125.1 (q, $^1J_{CF} = 276.7$ Hz), 106.9, 14.2, 8.9; ^{19}F NMR (378 MHz, CDCl₃) δ -62.17, -107.01; HRMS (ESI) calcd for C₁₃H₁₀F₄N: 256.0744 (M + H⁺), found: 256.0739.



3-Butyl-7-chloro-1-(trifluoromethyl)isoquinoline 3m. 1H NMR (400 MHz, CDCl₃) δ 7.89 (d, $J = 11.6$ Hz, 1H), 7.77 (dd, $J = 8.9, 5.9$ Hz, 1H), 7.71 (s, 1H), 7.34 (t, $J = 8.3$ Hz, 1H), 3.03 - 2.94 (m, 2H), 1.75 (dt, $J = 15.4, 7.6$ Hz, 2H), 1.49 (dt, $J = 14.5, 7.3$ Hz, 2H), 0.99 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl₃) δ 151.1, 150.4, 133.0, 129.9, 129.8, 127.3, 127.2, 125.3, 125.2 (q, $^1J_{CF} = 286.9$ Hz), 124.8, 36.8, 28.5, 22.5,

13.8; ^{19}F NMR (378 MHz, CDCl_3) δ -62.64; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{14}\text{ClF}_3\text{N}$: 288.0761 ($\text{M} + \text{H}^+$), found: 288.0772.



7-Chloro-3-cyclopropyl-1-(trifluoromethyl)isoquinoline **3n**. ^1H NMR (400 MHz, CDCl_3) δ 7.26 - 7.04 (m, 4H), 2.04 (s, 1H), 1.19 - 1.29 (m, 2H), 1.00 - 0.90 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 150.4, 150.2, 133.8, 132.8, 128.9, 125.2, 125.1, 125.0 (q, $^1J_{\text{CF}} = 280.6$ Hz), 124.7, 28.5, 19.1, 8.1; ^{19}F NMR (378 MHz, CDCl_3) δ -62.09; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{10}\text{ClF}_3\text{N}$: 272.0448 ($\text{M} + \text{H}^+$), found: 272.0469.

