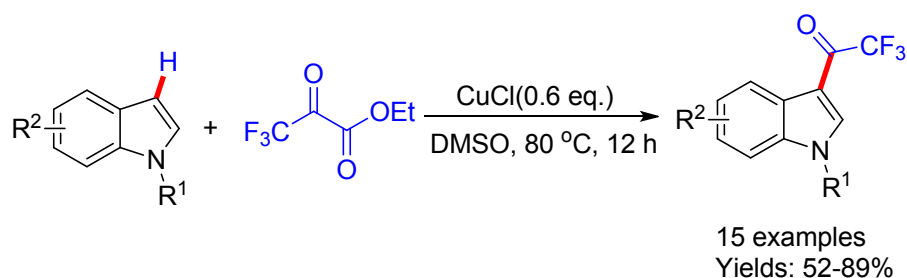


## Copper-Mediated Trifluoroacetylation of indoles with Ethyl Trifluoropyruvate

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**General** Indoles and ethyl trifluoropyruvate were purchased from Alfa Aesar and Shaoyuan Webstore. Chloroform-d was purchased from Cambridge Isotope Laboratories. All solvents were distilled prior to use. All reactions with air- and moisture-sensitive components were performed under a nitrogen atmosphere in a flame-dried reaction flask. For chromatography, 200-300 mesh silica gel (Qingdao, China) was employed. <sup>1</sup>H NMR (300 MHz) and <sup>13</sup>C NMR (75 MHz) spectra were measured on Bruker 300 M spectrometers. CDCl<sub>3</sub> was used as solvent with tetramethylsilane (TMS) as internal standard.

#### **General procedure for the preparation of *N*-methylindoles<sup>[1]</sup>**

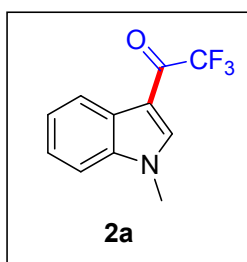
To a solution of an indole (2.0 mmol) in anhydrous dimethyl sulfoxide (DMSO) (2 mL), NaH (1.2 eq., 60%, dispersed in mineral oil) was added under inert gas at room temperature. After the reaction mixture was stirred for 2 h, the solution of iodomethane (1.5 eq.) in DMSO (1 mL) was added and stirred for 2 h, monitored by TLC. When the reaction was completed, the reaction was quenched with water and the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over MgSO<sub>4</sub> and evaporated to leave a residue, which was purified by column chromatography using the indicated eluent.

#### **Typical procedure for trifluoroacetylation of indoles with ethyl trifluoropyruvate**

Under air atmosphere, an indole (0.3 mmol), ethyl trifluoropyruvate (2.0 eq.), CuCl (0.6 eq.) and dimethyl sulfoxide (DMSO) (1.5 mL), were added to a screw-capped vial. The reaction vial was placed in a temperature-controlled aluminum-heating block set at 80 °C. The reaction progress was monitored by TLC. After the completion of the reaction, the vial was removed from the heating block and was left to cool to the ambient temperature. The reaction was quenched with water and the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over MgSO<sub>4</sub> and evaporated to leave a residue, which was purified by column chromatography using the indicated eluent.

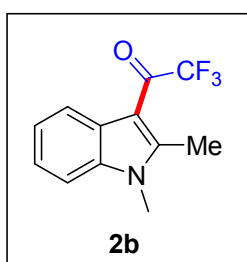
## Spectral data for the products

### 2,2,2-trifluoro-1-(1-methyl-1H-indol-3-yl)ethanone (2a) <sup>[2]</sup>



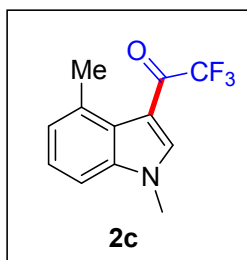
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ = 8.42-8.40 (m, 1H), 7.91 (s, 1H), 7.41 (s, 3H), 3.90 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ = 174.74(q, *J*<sub>CF</sub> = 34.58 Hz), 138.47(q, *J*<sub>CF</sub> = 4.95 Hz), 137.36, 126.93, 124.67, 124.01, 122.53, 117.15(q, *J*<sub>CF</sub> = 289.20 Hz), 110.24, 109.38, 34.05.

### 1-(1,2-dimethyl-1H-indol-3-yl)-2,2,2-trifluoroethanone (2b) <sup>[2]</sup>



<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ = 8.07 (s, 2H), 7.33-7.28 (m, 3H), 3.70 (s, 3H), 2.76 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ = 175.32(q, *J*<sub>CF</sub> = 35.55 Hz), 150.35, 136.90, 125.15, 123.30, 123.27, 120.90 (q, *J*<sub>CF</sub> = 4.43 Hz), 117.32(q, *J*<sub>CF</sub> = 288.0 Hz), 109.87, 107.88, 30.00, 13.19.

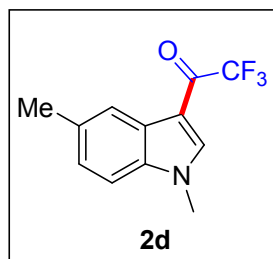
### 1-(1,4-dimethyl-1H-indol-3-yl)-2,2,2-trifluoroethanone (2c) <sup>[2]</sup>



<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ = 7.94 (s, 1H), 7.33-7.14 (m, 3H), 3.88 (s, 3H), 2.89 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ = 173.83(q, *J*<sub>CF</sub> = 33.45 Hz), 139.66 (q, *J*<sub>CF</sub> = 5.25

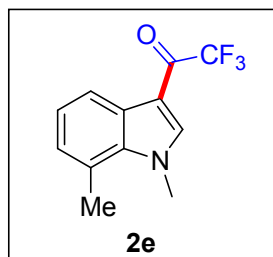
Hz), 138.28, 133.96, 125.96, 125.68, 124.79, 117.72(q,  $J_{CF} = 290.7$  Hz), 110.50, 107.73, 34.19, 23.16.

**1-(1,5-dimethyl-1H-indol-3-yl)-2,2,2-trifluoroethanone (2d)** <sup>[3]</sup>



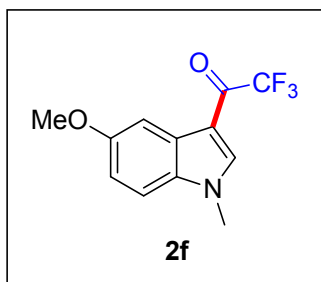
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta = 8.21$ (s, 1H), 7.87 (s, 1H), 7.30-7.21(m, 2H), 3.87 (s, 3H), 2.52 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta = 174.67$ (q,  $J_{CF} = 34.43$  Hz), 138.38 (q,  $J_{CF} = 5.25$  Hz), 135.73, 133.94, 127.21, 126.15, 122.31, 117.20(q,  $J_{CF} = 289.35$  Hz), 109.87, 109.01, 34.06, 21.60.

**1-(1,7-dimethyl-1H-indol-3-yl)-2,2,2-trifluoroethanone (2e)** <sup>[3]</sup>



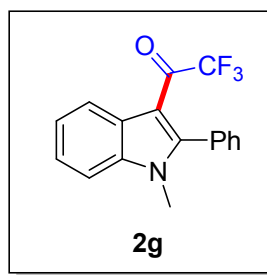
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta = 8.29$  (d,  $J = 8.1$  Hz, 1H), 7.79 (s, 1H), 7.28-7.22 (m, 1H), 7.09 (d,  $J = 6.9$  Hz, 1H), 4.13(s, 3H), 2.76 (s, 6H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta = 174.53$ (q,  $J_{CF} = 34.43$  Hz), 139.92 (q,  $J_{CF} = 5.25$  Hz), 136.06, 128.09, 127.46, 124.17, 122.18, 120.56, 117.16(q,  $J_{CF} = 289.43$  Hz), 108.86, 38.31, 19.49.

**2,2,2-trifluoro-1-(5-methoxy-1-methyl-1H-indol-3-yl)ethanone (2f)** <sup>[2]</sup>



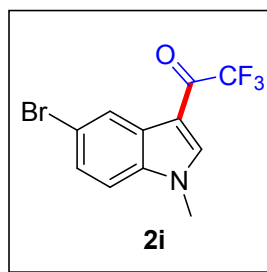
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.87-7.85 (m, 2H), 7.27 (d,  $J$  = 9.0 Hz, 1H), 7.03-6.99 (m, 1H), 3.91 (s, 3H), 3.87 (s, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 174.65(q,  $J_{\text{CF}}$  = 33.98 Hz), 157.48, 138.17 (q,  $J_{\text{CF}}$  = 4.50 Hz), 132.17, 128.02, 117.19(q,  $J_{\text{CF}}$  = 289.2 Hz), 114.84, 111.10, 109.09, 103.86, 55.83, 34.21

**2,2,2-trifluoro-1-(1-methyl-2-phenyl-1H-indol-3-yl)ethanone (2g)** <sup>[2]</sup>



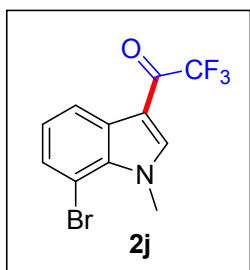
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 8.37-8.34 (m, 1H), 7.56 (d,  $J$  = 6.3 Hz, 3H), 7.45-7.40 (m, 5H), 3.57 (s, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 175.52 (q,  $J_{\text{CF}}$  = 36.08 Hz), 149.68, 136.97, 130.38(q,  $J_{\text{CF}}$  = 1.5 Hz), 129.89, 128.36, 126.48, 124.22, 123.93, 122.04, 122.01, 116.57(q,  $J_{\text{CF}}$  = 288.15 Hz), 110.32, 109.00, 31.31.

**1-(5-bromo-1-methyl-1H-indol-3-yl)-2,2,2-trifluoroethanone (2i)** <sup>[2]</sup>



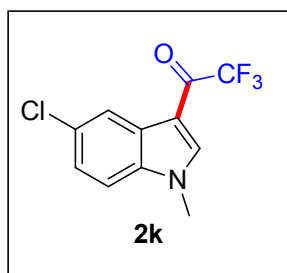
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 8.48 (s, 1H), 7.87 (s, 1H), 7.43 (d,  $J$  = 7.2 Hz, 1H), 7.23 (d,  $J$  = 7.8 Hz, 1H), 2.08 (s, 6H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 174.60(q,  $J_{\text{CF}}$  = 35.03 Hz), 138.88(q,  $J_{\text{CF}}$  = 4.50 Hz), 136.00, 128.35, 127.64, 125.03, 116.92(q,  $J_{\text{CF}}$  = 289.20 Hz), 117.72, 111.65, 108.82, 34.26.

**1-(7-bromo-1-methyl-1H-indol-3-yl)-2,2,2-trifluoroethanone (2j)** <sup>[3]</sup>



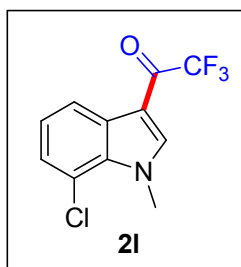
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 8.40 (d,  $J$  = 8.1 Hz, 2H), 7.88 (s, 1H), 7.53 (d,  $J$  = 7.8 Hz, 1H), 7.20 (t,  $J$  = 7.8 Hz, 1H), 4.28 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  = 174.62 (q,  $J_{CF}$  = 35.43 Hz), 140.88, 133.99, 129.96, 129.78, 125.11, 121.93, 116.93 (q,  $J_{CF}$  = 289.35 Hz), 108.79, 104.62, 38.68.

**1-(5-chloro-1-methyl-1H-indol-3-yl)-2,2,2-trifluoroethanone (2k)** <sup>[3]</sup>



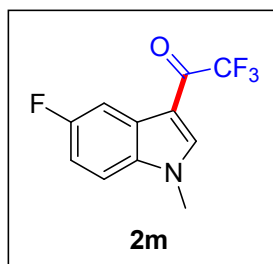
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 8.35 (s, 1H), 7.91 (s, 1H), 7.32-7.28 (m, 2H), 3.92 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  = 174.61 (q,  $J_{CF}$  = 34.73 Hz), 139.04, 135.72, 130.10, 127.91, 125.07, 122.11, 116.94 (q,  $J_{CF}$  = 289.05 Hz), 111.26, 108.96, 34.29.

**N-(2,4,6-trimethylphenyl)-4-nitrobenzenesulfonamide (2l)** <sup>[3]</sup>



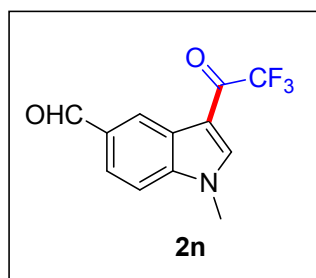
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 8.33 (d,  $J$  = 7.8 Hz, 1H), 7.85 (s, 2H), 6.87 (s, 1H), 7.33-7.24 (m, 2H), 4.25 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  = 174.59 (q,  $J_{CF}$  = 34.88 Hz), 140.56 (q,  $J_{CF}$  = 5.25 Hz), 132.82, 129.91, 126.23, 124.78, 121.30, 117.88, 116.95 (q,  $J_{CF}$  = 289.20 Hz), 109.02, 38.46.

**2,2,2-trifluoro-1-(5-fluoro-1-methyl-1H-indol-3-yl)ethanone (2m)**



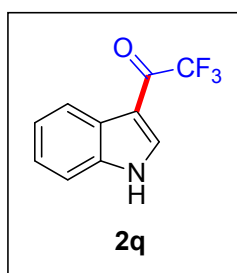
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 8.03(d,  $J$  = 9.0 Hz, 1H), 7.92(s, 1H), 7.35-7.28 (m, 1H), 7.12 (t,  $J$  = 7.8 Hz, 1H), 3.92 (s, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 174.65(q,  $J_{\text{CF}}$  = 35.03 Hz), 160.47(d,  $J_{\text{CF}}$  = 238.95 Hz), 139.27(q,  $J_{\text{CF}}$  = 5.25 Hz), 133.84, 127.80(d,  $J_{\text{CF}}$  = 11.48 Hz), 117.00(q,  $J_{\text{CF}}$  = 288.90 Hz), 113.06(d,  $J_{\text{CF}}$  = 26.33 Hz), 111.17, 109.32(d,  $J_{\text{CF}}$  = 4.43 Hz), 108.13(d,  $J_{\text{CF}}$  = 25.2 Hz), 34.37; HRMS calcd for  $\text{C}_{11}\text{H}_7\text{F}_4\text{NO}$   $[\text{M} + \text{Na}]^+$ : 268.0360, found: 268.0362.

**1-methyl-3-(2,2,2-trifluoroacetyl)-1H-indole-5-carbaldehyde (2n)**



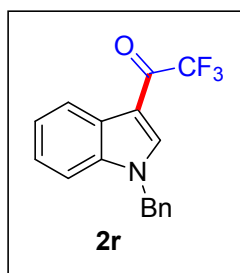
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 10.13(s, 1H), 8.87(s, 1H), 8.04-7.97(m, 2H), 7.53(d,  $J$  = 8.7 Hz, 1H), 4.00(s, 3H),  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 192.26, 174.96(q,  $J_{\text{CF}}$  = 35.33 Hz), 140.45, 139.77(q,  $J_{\text{CF}}$  = 5.25 Hz), 132.81, 127.97, 126.79, 124.00, 116.84(q,  $J_{\text{CF}}$  = 289.05 Hz), 111.07, 110.48, 34.40; HRMS calcd for  $\text{C}_{12}\text{H}_8\text{F}_3\text{NO}_2$   $[\text{M} + \text{Na}]^+$ : 278.0403, found: 278.0405.

**2,2,2-trifluoro-1-(1H-indol-3-yl)ethanone (2q) <sup>[2]</sup>**



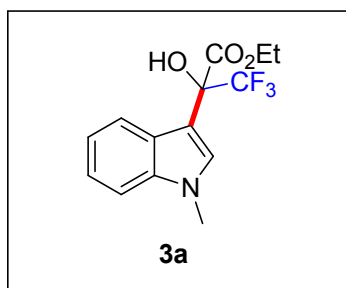
$^1\text{H}$  NMR (300 MHz, DMSO  $d_6$ )  $\delta$  = 12.74(s, 1H), 8.50(s, 1H), 8.20 (d,  $J$  = 5.4 Hz, 1H), 7.60-7.59(m, 1H) 7.35-7.32(t,  $J$  = 3.6 Hz, 2H),  $^{13}\text{C}$  NMR (75 MHz, DMSO  $d_6$ )  $\delta$  = 174.39 (q,  $J_{\text{CF}}$  = 33.75 Hz), 138.10(q,  $J_{\text{CF}}$  = 5.25 Hz), 137.16, 126.26, 124.83, 123.92, 121.61, 117.40 (q,  $J_{\text{CF}}$  = 289.8 Hz), 113.51, 109.36.

#### 1-(1-benzyl-1H-indol-3-yl)-2,2,2-trifluoroethanone (2r) <sup>[4]</sup>



$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 8.46 (d,  $J$  = 7.2 Hz, 1H), 8.02 (s, 1H), 7.38-7.37 (m, 6H), 7.22-7.20 (m, 2H), 5.42(s, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 174.98 (q,  $J_{\text{CF}}$  = 34.73 Hz), 137.80 (q,  $J_{\text{CF}}$  = 5.25 Hz), 136.91, 135.03, 134.85, 129.99, 129.28, 129.12, 128.63, 127.21, 124.82, 124.13, 122.75, 117.10(q,  $J_{\text{CF}}$  = 289.28 Hz), 110.88, 109.94, 51.42.

#### ethyl 3,3,3-trifluoro-2-hydroxy-2-(1-methyl-1H-indol-3-yl)propanoate (3a) <sup>[5]</sup>



$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.94 (d,  $J$  = 7.8 Hz, 1H), 7.38-7.31 (m, 3H), 7.23-7.21 (m, 1H), 4.50-4.39 (m, 3H), 1.39 (t,  $J$  = 6.9 Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 168.27(q,  $J_{\text{CF}}$  = 194.0 Hz), 137.31, 129.36, 128.96(d,  $J_{\text{CF}}$  = 1.73 Hz), 125.67(d,  $J_{\text{CF}}$  = 14.1 Hz), 122.30, 121.78, 121.34(d,  $J_{\text{CF}}$  = 1.35 Hz), 121.33, 120.20, 117.99, 109.64, 106.87, 64.65, 33.08, 14.01.

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