Innate C–H Trifluoromethylation of Heterocycles

Yining Ji,[+] Tobias Brueckl,[+] Ryan D. Baxter, Yuta Fujiwara, Ian B. Seiple, Shun Su, Donna G. Blackmond and Phil S. Baran

Department of Chemistry, The Scripps Research Institute, 10550 N. Torrey Pines Rd, La Jolla, CA 92037

SUPPORTING INFORMATION – PROCEDURES

Table of Contents

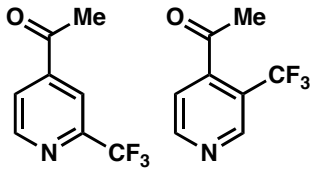
General Experimental. All reactions were carried out under an air atmosphere. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (^{1}H-NMR) homogeneous material, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica plates (60F-254), using UV light as the visualizing agent and $KMnO_4$ as a developing agent. Flash silica gel chromatography was performed using E. Merck silica gel (60, particle size 0.043–0.063 mm). Preparative HPLC was performed using a Phenomenex Gemini C18 110Å AXIA 5 μm column with dimension 30 or 50 x 100 mm, unless otherwise noted. NMR spectra were recorded on Bruker DRX-600, DRX-500, AMX-400, and Varian INOVA-399 instruments and were calibrated using residual undeuterated solvent as an internal reference ($CHCl_3$ @ 7.26 ppm ^{1}H-NMR, 77.16 ppm ^{13}C-NMR; CD_3OD @ 3.31 ppm ^{1}H-NMR, 49.0 ppm ^{13}C-NMR; CD_3CN 1.94 ppm ^{1}H-NMR, 1.32 ppm ^{13}C-NMR). The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Gas chromatograpy was performed on an Agilent Technologies 7890A instrument using a 30 meter DB-5 column with an internal diameter of 0.250 millimeters; reaction species were calibrated against tetradecane as an internal standard. *In situ* reaction calorimetry was performed using an Omnical Insight-CPR-220 calorimeter. High resolution mass spectra (HRMS) were recorded on an Agilent LC/MSD TOF mass spectrometer by electrospray ionization time of flight reflectron experiments. IR experiments were recorded

on a Perkin Elmer Spectrum BX FTIR spectrometer. Melting points were recorded on a Fisher-Johns 12-144 melting point apparatus and are uncorrected.

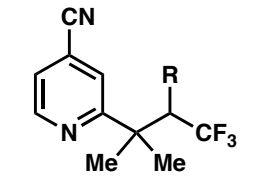
Trifluoromethylation of Heterocycles: Standard Procedure. To a solution of heterocycle (0.25 mmol, 1.0 equiv) and sodium trifluoromethylsulfinate (117 mg, 0.75 mmol, 3.0 equiv) in dichloromethane (1.0 mL) and water (0.4 mL) at 0 ºC was *slowly* added *tert*-butylhydroperoxide (70% solution in water, 0.17 mL, 1.25 mmol, 5.0 equiv) with vigorous stirring. The reaction was allowed to warm to room temperature and monitored by thin layer chromatography until completion. For substrates which do not go to completion in 24 h, a second addition of sodium trifluoromethylsulfinate (3.0 equiv) and *tert*-butylhydroperoxide (5.0 equiv) may be added to drive the reaction towards completion. Upon consumption of starting material, the reaction was partitioned between dichloromethane (2.0 mL) and saturated sodium bicarbonate (2.0 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 X 2.0 mL). The organic layers were dried with sodium sulfate, concentrated, and purified by column chromatography on silica gel.

NOTES: If a substrate fails to react or gives unfavorable selectivity, DMSO should be substituted for DCM as a cosolvent, as it causes substrate-dependent (and sometimes notable) changes in reactivity. For more polar substrates, EtOAc may be used in place of DCM for extractive workup. For water-soluble starting materials, a purely aqueous reaction may be run, usually with little to no impact on yield (simply run in 1.0 mL of water). In lieu of a workup, these reactions may be concentrated and purified directly. If the addition of *tert*-butylhydroperoxide is performed too rapidly, the resulting exotherm can result in reduced yield and selectivity. This is especially important on larger scales (see gram scale procedure below), where a syringe pump may be used to meter in *tert*-butylhydroperoxide.

Trifluoromethylation of Heterocycles: Gram Scale Procedure. To a solution of heterocycle (1.0 g) and sodium trifluoromethylsulfinate (3.0 equiv) in a mixture of dichloromethane/water (2.5:1, 0.18 M) at 0 ºC was added *tert*-butylhydroperoxide (70% solution in water, 5.0 equiv) using a syringe pump (0.1 mL/min). The reaction was allowed to warm to room temperature and monitored by thin layer chromatography until completion, and solvent was removed under reduced pressure. The resulting white solid was washed with EtOAc, and the filtrate was concentrated and purified by column chromatography on silica gel.

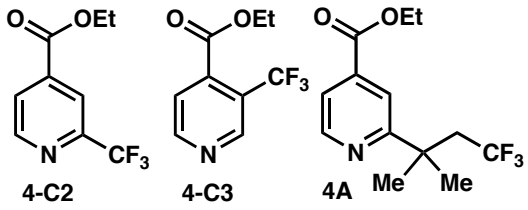


2-(Trifluoromethyl)-4-acetylpyridine (1-C2) and 3-(trifluoromethyl)-4-acetylpyridine (1-C3). The Standard Procedure was followed with a reaction time of 24 h (no second addition of reagents) to provide the products in 67 % yield (2.44 to 1). Data for **1-C2**: colorless oil; R_f = 0.34 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (d, J = 4.9 Hz, 1 H), 8.12 (s, 1 H), 7.94 (d, J = 4.7 Hz, 1 H), 2.69 (s, 3 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.7, 151.5, 149.8 (q, J = 35 Hz), 144.4, 124.6, 121.3 (q, J = 274 Hz), 118.3 (q, J = 3 Hz), 26.8 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -68.3 ppm; IR (neat) ν = 2920, 1701, 1362, 1328, 1236, 1180, 1135, 1112, 1085, 853, 735, 683 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_8H_7F_3NO$ [M + H$^+$]: 190.0474, found 190.0470. Data for **1-C3**: colorless oil; R_f = 0.20 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1 H), 8.90 (d, J = 5.0 Hz, 1 H), 7.33 (d, J = 4.9 Hz, 1 H), 2.59 (s, 3 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.0, 157.0, 151.2 (q, J = 5.2 Hz), 150.6, 126.3 (q, J = 274 Hz), 125.1 (q, J = 33 Hz), 123.5, 33.7 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -58.5 ppm; IR (neat) ν = 2924, 1716, 1558, 1330, 1288, 1253, 1140, 1105, 1033, 683 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_8H_7F_3NO$ [M + H$^+$]: 190.0474, found 190.0478.



3 (R = Me) + **5A** (R = H)

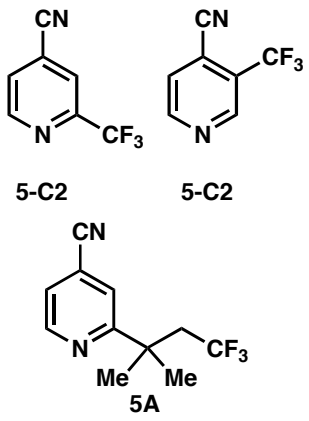
2-(4,4,4-Trifluoro-2,3-dimethylbutan-2-yl) isonicotinonitrile (3) and 2-(4,4,4-trifluoro-2-methylbutan-2-yl)isonicotinonitrile (5A). The Standard Procedure (0.5 mmol) was followed with a reaction time of 18 hours and with an addition of 2-methyl-but-2-ene (5.0 equiv) (no second addition of reagents) to provide the products in 17% yield (2:1 **3**:**5A**). Data for **3**: colorless oil; R_f = 0.77 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (dd, *J* = 4.9 and 1.0 Hz, 1 H), 7.54 (dd, *J* = 1.4 and 1.0 Hz, 1 H), 7.36 (dd, *J* = 4.9 and 1.4 Hz, 1 H), 3.37 – 3.24 (m, 1 H), 1.48 (q, *J* = 0.8 Hz, 3 H), 1.45 (q, *J* = 1.4 Hz, 3 H), 1.09 (dd, *J* = 7.2 and 0.5 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 150.6, 129.1 (q, *J* = 283 Hz), 123.4, 121.9, 117.7, 45.7 (q, *J* = 24 Hz), 42.7 (q, *J* = 1 Hz), 28.7 (q, *J* = 1 Hz), 23.6 (q, *J* = 2 Hz), 10.5 (q, *J* = 4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -65.6 ppm. Data for **3** and **5A**: IR (neat) ν = 2982, 1593, 1553, 1365, 1174, 1156, 1090, 1056, 842, 506 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{12}H_{14}F_3N_2$ [M + H$^+$]: 243.1104; found 243.1115, calc'd for $C_{11}H_{12}F_3N_2$ [M + H$^+$]: 229.0947; found 229.0953.



4-C2 **4-C3** **4A**

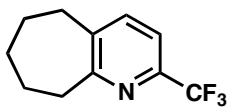
Ethyl 2-(trifluoromethyl)isonicotinate (4-C2) and ethyl 3-(trifluoromethyl)isonicotinate (4-C3), and ethyl 2-(4,4,4-trifluoro-2-methylbutan-2-yl)isonicotinate (4A). The Standard Procedure was followed with a reaction time of 40 hours (second addition of trifluoromethylsulfinate and *tert*-butylhydrogen peroxide after 16 h) to provide **4-C2** and **4-C3** (4.1:1 C2:C3) in 53% yield and the **4A** in 9% yield. Data for **4-C2**: colorless oil; R_f = 0.58 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (d, *J* = 4.9 Hz, 1 H), 8.23 (s, 1 H), 8.06 (d, *J* = 4.8 Hz, 1 H), 4.46 (q, *J* = 7.1 Hz, 2 H), 1.44 (t, *J* = 7.1 Hz, 3 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.00, 151.1, 149.4 (q,

J = 35 Hz), 139.6, 125.9, 121.4 (q, J = 274 Hz), 120.0 (q, J = 3 Hz), 62.6, 14.3 ppm; ^{19}F NMR (400 MHz, $CDCl_3$) δ -58.5 ppm; IR (neat) ν = 2983, 1731, 1329, 1253, 1239, 1179, 1139, 1101, 1082, 1017, 764, 696, 677 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_9H_9F_3NO_2$ [M + H$^+$] 220.0580, found: 220.0585. Data for **4-C3**: colorless oil; R_f = 0.45 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1 H), 8.91 (d, J = 4.9 Hz, 1 H), 7.64 (d, J = 4.9 Hz, 1 H), 4.44 (q, J = 7.1 Hz, 2 H), 1.40 (t, J = 7.1 Hz, 3 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.1, 153.8, 148.0 (q, J = 6 Hz), 139.0, 123.5 (d, J = 33 Hz), 123.2, 122.9 (q, J = 274 Hz), 63.0, 14.00 ppm; ^{19}F NMR (400 MHz, $CDCl_3$) δ -61.9 ppm; IR (neat) ν = 2982, 1739, 1328, 1303, 1270, 1206, 1141, 1085, 1031, 689 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_9H_9F_3NO_2$ [M + H$^+$] 220.0580, found: 220.0587. Data for **4A**: colorless oil; R_f = 0.65 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, J = 4.9 Hz, 1 H), 7.88 (s, 1 H), 7.69 (d, J = 4.9 Hz, 1 H), 4.42 (q, J = 7.1 Hz, 2 H), 2.74 (q, J = 11.5 Hz, 2 H), 1.50 (s, 6H), 1.42 (t, J = 7.1 Hz, 3 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.2, 165.6, 149.7, 138.3, 126.8 (q, J = 279 Hz), 120.6, 118.5, 61.9, 44.8 (q, J = 26 Hz), 38.7, 28.2, 14.4 ppm; ^{19}F NMR (400 MHz, $CDCl_3$) δ -60.3 ppm; IR (neat) ν = 2981, 1730, 1405, 1362, 1302, 1279, 1262, 1230, 1177, 1150, 1106, 1058, 1033, 1015, 764 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{13}H_{16}F_3NO_2$ [M + H$^+$] 276.1206, found 276.1199.

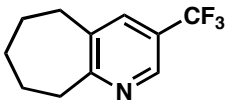


2-Trifluoromethyl-4-cyanopyridine (5-C2), 2-trifluoromethyl-4-cyanopyridine (5-C3) and 2-(4,4,4-trifluoro-2,3-dimethylbutan-2-yl)isonicotinonitrile (5A). The Standard Procedure was followed with a reaction time of 40 h (second addition of trifluoromethylsulfinate and *tert*-butylhydroperoxide after 16 h) to provide **5-C2** and **5-C3** in 48% yield (2.4:1 C2:C3) and **5A** in 10% yield. Data for **5-C2**: colorless oil; R_f = 0.53 (20% EtOAc/hexanes);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (d, J = 4.9 Hz, 1 H), 7.92 (s, 1 H), 7.76 (d, J = 4.8 Hz, 1 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.4, 149.9 (q, J = 36 Hz), 128.3, 122.4 (q, J = 3 Hz), 122.4, 120.7 (q, J = 275 Hz), 115.4 ppm; ^{19}F NMR (400 MHz, $CDCl_3$) δ -58.5 ppm; IR (neat) ν = 2922, 2852, 2244, 1603, 1560, 1420, 1325, 1184, 1141, 1111, 1086, 862, 743, 687 cm^{-1}; product did not ionize sufficiently on ESI-TOF HRMS to collect a high resolution mass spectrum. Data for **5-C3**: colorless oil; R_f = 0.31 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1 H), 9.03 (d, J = 5.0 Hz, 1 H), 7.74 (d, J = 4.9 Hz, 1 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.2, 147.9 (q, J = 5 Hz), 127.0, 126.8 (q, J = 33 Hz), 121.9 (q, J = 274 Hz), 118.6 (q, J = 2 Hz), 113.4 ppm; ^{19}F NMR (400 MHz, $CDCl_3$) δ -61.9 ppm; IR (neat) ν = 2923, 2244, 1603, 1560, 1420, 1325, 1184, 1143, 1111, 1086, 862, 742, 687 cm^{-1}; HRMS-ESI *m/z* calcd. for $C_8H_6F_3NO$: 172.0248, product did not ionize sufficiently on ESI-TOF HRMS to collect a high resolution mass spectrum. Data for **5A**: colorless oil; R_f = 0.61 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, J = 4.9 Hz, 1 H), 7.54 (s, 1 H), 7.37 (d, J = 4.9 Hz, 1 H), 2.73 (q, J = 11.4 Hz, 2 H), 1.48 (s, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.5, 150.7, 127.3 (q, J = 279 Hz), 123.6, 121.8, 121.7, 117.7, 45.3 (q, J = 27 Hz), 39.6, 28.7 ppm; ^{19}F NMR (400 MHz, $CDCl_3$) δ -68.7 ppm; IR (neat) ν = 2973, 2239, 1593, 1553, 1363, 1261, 1195, 1177, 1136, 1108, 1071, 1060, 1033, 1016, 841 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{11}H_{12}F_3N_2$ [M + H$^+$]: 229.0947, found 229.0971.



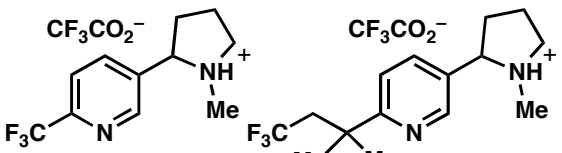
6-C2



6-C3

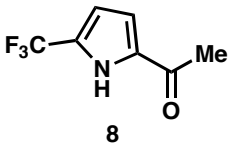
2-(trifluoromethyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine (6-C2) and 3-(trifluoromethyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine (6-C3). The Standard Procedure was followed with a reaction time of 40 hours (56% of conversion, second addition of trifluoromethylsulfinate and *tert*-butylhydroperoxide after 16 h) to provide the

products in 43% yield (1.1:1, C2:C3). Data for **6-C2**: colorless oil; R_f = 0.62 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 7.7 Hz, 1 H), 7.39 (d, J = 7.7 Hz, 1 H), 3.23 – 3.00 (m, 2 H), 2.92 – 2.70 (m, 2 H), 2.13 – 1.81 (m, 2 H), 1.75 – 1.67 (m, 4 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.1, 145.5 (q, J = 34 Hz), 142.5, 138.0, 122.7 (q, J = 274 Hz), 118.8 (q, J = 3 Hz), 40.0, 36.0, 33.2, 28.5, 27.1 ppm; ^{19}F NMR (400 MHz, $CDCl_3$) δ -68.7 ppm; IR (neat) ν = 2922, 2846, 1054, 1033, 1013 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{11}H_{13}F_3N$ [M + H^+]: 216.0995, found: 216.0995. Data for **6-C3**: colorless oil; R_f = 0.38 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 5.1 Hz, 1 H), 7.32 (d, J = 5.2 Hz, 1 H), 3.23 – 3.11 (m, 2 H), 2.95 (m, 2 H), 1.88 (m, 2 H), 1.79 – 1.61 (m, 4 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.9, 147.3, 136.8, 136.4 (q, J = 30 Hz), 124.4 (q, J = 275 Hz), 118.1 (q, J = 5 Hz), 39.8, 32.7, 29.9, 27.7, 26.9 ppm; ^{19}F NMR (400 MHz, $CDCl_3$) δ -58.5 ppm; IR (neat) ν = 2925, 1316, 1159, 1134, 1054, 1033, 1013 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{11}H_{13}F_3N$ [M + H^+] 216.0995, found: 216.0996.



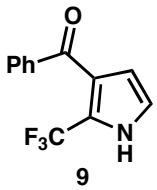
Nicotine-CF_3•TFA (7•TFA) and 1-methyl-2-(6-(4,4,4-trifluoro-2-methylbutan-2-yl)pyridin-3-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate (7A•TFA). The Standard Procedure was followed (1.0 equiv of TFA added before initial addition of reagents) with a reaction time of 21 h (no second addition of reagents) to provide the products **7•TFA** and **7A•TFA** in 44% and 7% yield respectively. Purification was accomplished by preparative HPLC (10% to 45% MeCN in water, 0.1% TFA, 25 minute ramp; R_T for **7•TFA** = 9.0 min, R_T for **7A•TFA** = 15.3 min). Data for **7•TFA**: colorless oil; ^{1}H NMR (400 MHz, CD_3OD) δ 8.85 (d, J = 1.8 Hz, 1 H), 8.24 (d, J = 8.1 Hz, 1 H), 7.92 (d, J = 8.2 Hz, 1 H), 4.54 (br, 1 H), 3.89 (br, 1 H), 3.33 (br, 1 H), 2.80 (s, 3 H), 2.59 (m, 1 H), 2.38 (br, 1 H), 2.32 – 2.27 (m, 2

H) ppm; ^{13}C NMR (150 MHz, CD_3OD) δ 162.0 (q, *J* = 33 Hz), 151.8, 150.4 (q, *J* = 35 Hz), 139.6, 133.7, 122.7 (q, *J* = 274 Hz), 122.4, 117.6 (q, *J* = 289 Hz), 70.8, 57.5, 39.3, 32.2, 22.8 ppm; ^{19}F NMR (400 MHz, $CDCl_3$) δ -68.8, -77.4 ppm; IR (neat) ν = 3342, 2981, 1662, 1462, 1424, 1337, 1176, 1124, 1087, 835, 799, 721 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{11}H_{13}F_3N_2$ [M + H$^+$]: 231.1104, found 231.1109. Data for **7A•TFA**: corlorless oil, ^{1}H NMR (400 MHz, CD_3OD) δ 8.66 (d, *J* = 2.1 Hz, 1 H), 7.95 (dd, *J* = 8.3 and 2.0 Hz, 1 H), 7.61 (d, *J* = 8.3 Hz, 1 H), 4.43 (dd, *J* = 10.4 and 7.7 Hz, 1 H), 3.89 – 3.82 (m, 1 H), 2.37 – 2.30 (m, 1 H), 2.79 (q, *J* = 11.6 Hz, 2 H), 2.78 (s, 3 H), 2.61 – 2.52 (m, 1 H), 2.42 – 2.33 (m, 1 H), 2.33 – 2.23 (m, 2 H), 1.47 (s, 6 H) ppm; ^{13}C NMR (150 MHz, CD_3OD) δ 169.5, 161.6 (q, *J* = 37 Hz), 150.2, 138.1, 128.3 (q, *J* = 251 Hz), 127.3, 121.5, 117.5 (q, *J* = 290 Hz), 71.2, 57.2, 45.3 (q, *J* = 26 Hz), 39.6, 39.1, 31.8, 28.4, 22.7 ppm; ^{19}F NMR (400 MHz, $CDCl_3$) δ -61.7, -77.5 ppm; IR (neat) ν = 3347, 1672, 1432, 1202, 1138, 1015 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{15}H_{22}F_3N_2$ [M + H$^+$]: 287.1730, found: 287.1731.



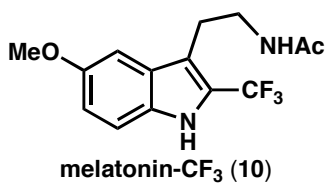
8

1-(5-(trifluoromethyl)-1H-pyrrol-2-yl)ethanone (8). The Standard Procedure was followed with a reaction time of 24 h (no second addition of reagents) to provide the product in 57% yield: white solid; R_f = 0.45 (20% EtOAc/hexanes); m.p.: 65-67 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (brs, 1 H), 6.89 (brs, 1 H), 6.64 (brs, 1 H), 2.51 (s, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.0, 133.6, 125.9 (q, *J* = 40 Hz), 120.5 (q, *J* = 268 Hz), 115.9, 111.1 (q, *J* = 3 Hz), 25.81 ppm; ^{19}F NMR (400 MHz, $CDCl_3$) δ -61.0 ppm; IR (neat) ν = 3254, 2923, 1671, 1561, 1333, 1292, 1164, 1115, 1096, 1049, 1033, 795, 738 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_7H_6F_3NO$ [M - H$^+$]: 176.0329, found 176.0332.



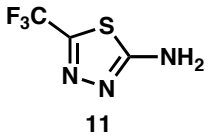
9

Phenyl(2-(trifluoromethyl)-1H-pyrrol-3-yl)methanone (9). The Standard Procedure was followed with a reaction time of 24 h (73% conversion) to provide the product in 68% yield: white solid; m.p.: 117-120 ºC; R_f = 0.24 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (s, 1 H), 8.01 – 7.78 (m, 2 H), 7.67 – 7.55 (m, 1 H), 7.53 – 7.48 (m, 2 H), 6.92 (q, J = 2.8 Hz, 1 H), 6.59 – 6.54 (m, 1 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 190.3, 138.5, 132.7, 129.8, 128.4, 124.0 (q, J = 2 Hz), 122.5 (q, J = 39 Hz), 120.6 (q, J = 268 Hz), 118.8, 113.9 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -59.0 ppm; IR (neat) ν = 3265, 2981, 1645, 1421, 1300, 1169, 1099, 1047, 1033, 885, 731 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{12}H_9F_3NO$ [M + H$^+$] 240.0631, found 240.0627.



melatonin-CF_3 (10)

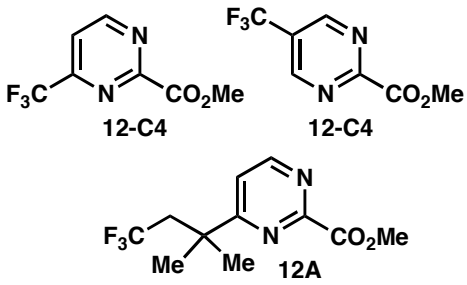
2-Trifluoromethyl-melatonin (10). The Standard Procedure was followed with a reaction time of 18 hours (no second addition of reagents). Purification was accomplished by preparative HPLC (5% to 60% MeCN in H_2O, 0.1% TFA, 25 minute ramp; R_T = 17.3 min) to provide the product in 51% yield : colorless solid; m.p.: 68 - 72 ºC; R_f = 0.68 (EtOAc); ^{1}H NMR (600 MHz, CD_3OD) δ 7.30 (d, J = 9.0 Hz, 1 H), 7.15 (d, J = 2.4 Hz, 1 H), 6.92 (dd, J = 9.0 and 2.4 Hz, 1 H), 3.84 (s, 3 H), 3.41 (t, J = 7.1 Hz, 2 H), 3.05 (t, J = 7.1 Hz, 2 H), 1.88 (s, 3 H); ^{13}C NMR (150 MHz, CD_3OD) δ 173.4, 155.9, 132.6, 128.9, 123.8 (q, J = 267 Hz), 123.6 (q, J = 34 Hz), 116.6, 115.0 (q, J = 3 Hz), 101.4, 101.4, 56.1, 41.3, 24.9, 22.6; ^{19}F NMR (376 MHz, CD_3OD) δ -59.5; IR (neat) ν = 1605, 1565, 1483, 1367, 1195, 1220, 1158, 1103, 1075, 1026, 973, 801, 523, 430 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{14}H_{16}F_3N_2O_2$ [M + H$^+$]: 301.1158; found 301.1164.



11

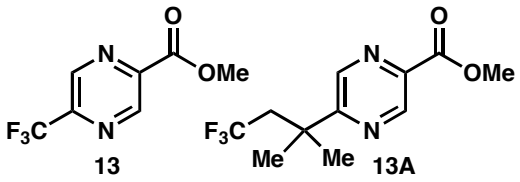
5-Trifluoromethyl-1,3,4-thiadiazol-2-amine (11). The Standard Procedure was followed with a reaction time of 48 hours (second addition of

trifluoromethylsulfinate and *tert*-butylhydroperoxide after 24 h) to provide the product in 33% yield: colorless solid; m.p.: 129 - 132 ºC; R_f = 0.72 (EtOAc); ^{13}C NMR (150 MHz, CD_3OD) δ 173.8, 146.6 (q, J = 40 Hz), 121.1 (q, J = 274 Hz); ^{19}F NMR (376 MHz, CD_3OD) δ -61.7; IR (neat) ν = 2487, 2361, 2230, 1525, 1494, 1329, 1189, 1141, 1112, 1033, 743, 637, 620, 438, 409 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_3H_3F_3N_3S$ [M + H$^+$]: 169.9994; found 169.9996.

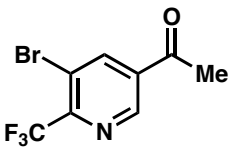


Methyl 4-(trifluoromethyl)pyrimidine-2-carboxylate (12-C4), methyl 5- (trifluoromethyl)pyrimidine-2-carboxylate (12-C5) and methyl 4-(4,4,4-trifluoro-2-methylbutan-2-yl)pyrimidine-2-carboxylate (12A). The Standard Procedure was followed with a reaction time of 40 hours (second addition of trifluoromethylsulfinate and *tert*-butylhydroperoxide after 16 h) to provide **12-C4** and **12-C5** in 37% yield (1:1 C4:C5) and **12A** in 10 % yield. Data for **12-C4**: white solid; m.p.: 88-90 ºC; R_f = 0.40 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (d, J = 5.0 Hz, 1 H), 7.84 (d, J = 5.0 Hz, 1 H), 4.10 (s, 3 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.6, 161.2, 158.0, 157.7 (q, J = 38 Hz), 120.8 (q, J = 276 Hz), 119.7 (q, J = 3 Hz), 54.8 ppm; ^{19}F NMR (400 MHz, $CDCl_3$) δ -58.5 ppm; IR (neat) ν = 2927, 1740, 1563, 1392, 1326, 1143, 1023, 738, 738, 708 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_7H_6F_3N_2O_2$ [M + H$^+$]: 207.0376, found: 207.0382. Data for **12-C5**: white solid; m.p.: 129-131 ºC; R_f = 0.62 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (s, 2 H), 4.11 (s, 3 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.5, 159.5, 156.2 (q, J = 4 Hz), 127.3 (q, J = 35 Hz), 122.9 (q, J = 273 Hz), 54.9 ppm; ^{19}F NMR (400 MHz, $CDCl_3$) δ -62.7 ppm; IR (neat) ν = 3074, 1742, 1581, 1446, 1395, 1340, 1308, 1221, 1148, 1125, 1099, 964, 881, 715, 666 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_7H_6F_3N_2O_2$ [M + H$^+$]: 207.0376, found 207.0378. Data for **12A**: colorless oil; R_f = 0.33 (30% EtOAc/hexanes);

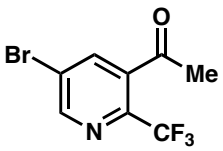
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, J = 5.3 Hz, 1 H), 7.47 (d, J = 5.3 Hz, 1 H), 4.05 (s, 3 H), 2.80 (q, J = 11.3 Hz, 2 H), 1.50 (s, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.2, 164.2, 158.3, 156.2, 126.5 (q, J = 279 Hz), 118.7, 53.5, 44.2 (q, J = 27 Hz), 38.8, 27.6 ppm; ^{19}F NMR (400 MHz, $CDCl_3$) δ -61.9 ppm; IR (neat) ν = 2957, 1743, 1576, 1434, 1364, 1310, 1260, 1225, 1161, 1101, 1073, 984, 763 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{11}H_{14}F_3N_2O_2$ [M + H$^+$]: 263.1002, found: 263.1008.



Methyl 5-(trifluoromethyl)pyrazine-2-carboxylate (13) and methyl 5-(4,4,4-trifluoro-2-methylbutan-2-yl)pyrazine-2-carboxylate (13A). The Standard Procedure was followed with a reaction time of 40 hours (second addition of trifluoromethylsulfinate and *tert*-butylhydroperoxide after 16 h) to provide **13** and **13A** in 50% and 19% yield respectively. Data for **13**: white solid; m.p. 71-73 ºC; R_f = 0.37 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1 H), 9.08 (s, 1 H), 4.10 (s, 3 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.02, 147 (q, J = 36 Hz), 146.5, 146.4, 142.1 (q, J = 3 Hz), 121.5 (q, J = 275 Hz), 54.5 ppm; ^{19}F NMR (400 MHz, $CDCl_3$) δ -58.5 ppm; IR (neat) ν = 2965, 1720, 1440, 1364, 1306, 1180, 1162, 1139, 1024, 739 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_7H_6F_3N_2O_2$ [M + H$^+$]: 207.0376, found: 207.0385. Data for **13A**: white solid; m.p.: 76-78 ºC; R_f = 0.27 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1 H), 8.74 (s, 1 H), 4.04 (s, 3 H), 2.75 (q, J = 11.3 Hz, 2 H), 1.55 (s, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.7, 164.6, 144.9, 140.9, 140.9, 126.4 (q, J = 279 Hz), 53.2, 44.6 (q, J = 27 Hz), 38.1, 27.8 ppm; ^{19}F NMR (400 MHz, $CDCl_3$) δ -61.9 ppm; IR (neat) ν = 2958, 1726, 1437, 1363, 1282, 1258, 1146, 1100, 1069, 1029, 971, 914, 767, 740, 676 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{11}H_{14}F_3N_2O_2$ [M + H$^+$] 263.1002, found: 263.1004.

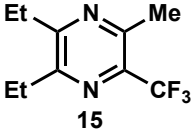


14-C2 [X-RAY]



14-C6

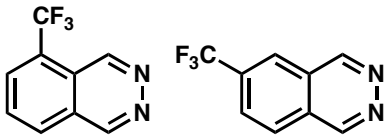
2-Trifluoromethyl-3-bromo-5-acetylpyridine (14-C2) and 6-trifluoromethyl-3-bromo-5-acetylpyridine (14-C3). The Standard Procedure was followed with a reaction time of 48 hours (second addition of trifluoromethylsulfinate and *tert*-butylhydroperoxide after 24 h) to provide the products in 65% yield (1:1.5, C2:C6). Data for **14-C2**: white solid; m.p.: 91-93 ºC; R_f = 0.45 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (s, 1 H), 8.55 (s, 1 H), 2.68 (s, 3 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.1, 149.8 (q, J = 34 Hz), 147.5, 143.3, 135.7, 121.5 (q, J = 277 Hz), 119.5, 27.9 ppm; ^{19}F NMR (400 MHz, $CDCl_3$) δ -66.6 ppm; IR (neat) ν = 1711, 1360, 1288, 1223, 1142, 1086, 1050, 896, 803, 768, 684, 623, 607 cm^{-1}; product did not ionize sufficiently on ESI-TOF HRMS to collect a high resolution mass spectrum. Data for **14-C6:** colorless oil; R_f = 0.37 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.50 (s, 1H), 2.57 (q, J = 1.0 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.7, 156.0, 146.6, 138.0 (q, J = 2 Hz), 134.1 (q, J = 33 Hz), 122.5 (q, J = 276 Hz), 119.0, 32.6 (q, J = 2 Hz) ppm; ^{19}F NMR (400 MHz, $CDCl_3$) δ -58.7 ppm; IR (neat) ν = 3063, 1692, 1379, 1318, 1283, 1247, 1213, 1170, 1136, 1111, 1031, 938, 836, 768, 741, 660 cm^{-1}; product did not ionize sufficiently on ESI-TOF HRMS to collect a high resolution mass spectrum.



15

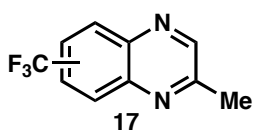
2,3-Diethyl-5-methyl-6-(trifluoromethyl)pyrazine (15). The Standard Procedure was followed with a reaction time of 40 hours (84% conversion, second addition of trifluoromethylsulfinate and *tert*-butylhydroperoxide after 16 h) to provide the product in 57% yield: colorless oil; R_f = 0.49 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.92 – 2.81 (m, 4 H), 2.66 (br, 3 H), 1.31 (t, J = 7.5 Hz, 3 H), 1.30 (t,

J = 7.5 Hz, 3 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.3, 153.3, 149.2, 139.2 (q, J = 34 Hz), 123.2 (q, J = 274 Hz), 28.4, 27.7, 21.8 (d, J = 2 Hz), 13.6, 13.5 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -65.3 ppm; IR (neat) ν = 2975, 1417, 1298, 1186, 1125, 1032, 733 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{10}H_{14}F_3N_2$ [M + H$^+$] 219.1104, found 219.1101.



16-C4 16-C5

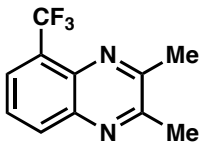
4-Trifluoromethyl-phthalazine (16-C4), 5-Trifluoromethyl-phthalazine (16-C5). The Standard Procedure was followed with a reaction time of 1 hour (no second addition of reagents) to provide the products in 70% yield (2.3:1, C4:C5). The products could not readily be separated by silica gel chromatography or preparative TLC, so they were characterized as a mixture. Data for **16-C4** and **16-C5**: yellow solid; m.p.: 49 – 53 ºC; R_f = 0.18 (Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (s, 1 H), 9.65 (s, 1 H), 9.62 (s, 1 H), 8.29 (s, 0.4 H), 8.24 (d, J = 7.6 Hz, 1 H), 8.18 (d, J = 8.4 Hz, 1 H), 8.15 – 8.10 (m, 1 H), 8.01 (m, 1 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.2, 151.0, 151.6, 147.4, 131.6, 130.9, 130.6 (q, J = 5 Hz), 128.7 (q, J = 3 Hz), 127.8, 127.6, 126.9, 126.1 (q, J = 33 Hz), 125.9, 124.3 (q, J = 4 Hz), 123.4 (q, J = 275 Hz), 122.7, C-CF3 of the minor product resulted in an insufficient signal to noise ratio; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.3, -59.0 ppm; IR (neat) ν = 3042, 1594, 1470, 1448, 1379, 1333, 1296, 1264, 1206, 1165, 1125, 1065, 999, 933, 877, 824, 770, 741, 676 cm^{-1}; HRMS (ESI-TOF) calc'd $C_9H_6F_3N_2$ for [M + H$^+$]: 199.0478; found 199.0484.



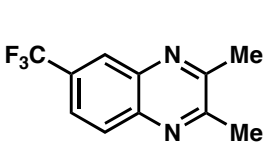
17
(4 products)

2-Methylquinoxaline-CF_3 (17). The Standard Procedure was followed with a reaction time of 16 hours to provide the products in 54% yield. The products could not be separated by silica gel chromatography or preparative TLC, so they were characterized as a mixture. Data for **17**: orange solid; m.p.: 37 –

40 ºC; R_f = 0.51 (25% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1 H), 8.84 (s, 0.3 H), 8.83 (s, 0.1 H), 8.80 (0.3 H), 8.39 – 8.17 (m, 2 H), 8.15 – 8.03 (m, 2 H), 7.93 – 7.87 (m, 0.5 H), 7.81 – 7.70 (m, 1.8 H), 2.82 (s, 1 H), 2.82 (s, 1 H), 2.81 (s, 3 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.3, 155.6, 155.0, 155.0, 148.1, 147.5, 146.8, 146.7, 143.3, 142.2, 142.1, 141.3, 140.9, 140.1, 139.4, 137.9, 133.7, 133.4, 131.8 (q, J = 33 Hz), 130.8 (q, J = 33 Hz), 130.6, 130.1, 128.7, 128.2 (q, J = 5 Hz), 127.9 (q, J = 30 Hz), 127.6 (q, J = 30 Hz), 127.5, 127.4, 127.3 (q, J = 5 Hz), 126.9 (q, J = 4 Hz), 125.8 (q, J = 3 Hz), 124.8 (q, J = 3 Hz), 123.8 (q, J = 273 Hz), 123.8 (q, J = 273 Hz), 123.7 (q, J = 272 Hz), 23.1, 22.9, 22.8, 22.7 ppm; CF3 of the minor product resulted in an insufficient signal to noise ratio; ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.0, -60.1, -62.8, -62.9 ppm; IR (neat) ν = 2936, 1574, 1495, 1350, 1325, 1308, 1258, 1187, 1135, 1062, 1021, 981, 928, 838, 772, 740, 706 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{10}H_8F_3N_2$ [M + H$^+$]: 213.0634; found 213.0627.



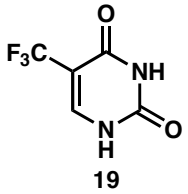
18-C5



18-C6

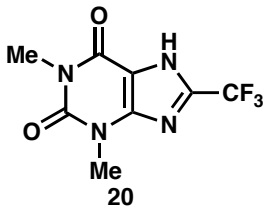
2,3-Dimethyl-5-(trifluoromethyl)quinoxaline (18-C5), 2,3-dimethyl-6-(trifluoromethyl)quinoxaline (18-C6). The Standard Procedure was followed with a reaction time of 19 hours (no second addition of reagents) to provide the products in 64% yield (2:1, C5:C6). Data for **18-C5**: yellow crystalline solid; m.p.: 54 – 57 ºC; R_f = 0.42 (50% DCM/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (d, J = 7.8 Hz, 1 H), 8.00 (d, J = 7.8 Hz, 1 H), 7.68 (dd, J = 7.8 and 7.8 Hz, 1 H), 2.78 (s, 3 H), 2.74 (s, 3 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.7, 154.6, 141.1, 138.3, 132.9, 127.5, 127.3, 127.0 (q, J = 5.5 Hz), 123.1 (q, J = 272.1 Hz), 23.7, 23.3 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -59.9 ppm; IR (neat) ν = 1585, 1486, 1402, 1350, 1319, 1297, 1215, 1135, 1057, 997, 947, 858, 835, 770, 734, 714, 697, 677 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{11}H_{10}F_3N_2$ [M + H$^+$]: 227.0791; found 227.0799. Data for **18-C6**:

yellow crystalline solid; m.p.: 56 – 58 ºC; R_f = 0.24 (50% DCM/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1 H), 8.08 (d, J = 8.6 Hz, 1 H), 7.84 (d, J = 8.6 Hz, 1 H), 2.77 (s, 3 H), 2.76 (s, 3 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.0, 155.4, 142.4, 140.2, 130.7, 129.7, 126.5 (q, J = 4 Hz), 124.7 (q, J = 3 Hz), 124.0 (q, J = 273 Hz), 23.5, 23.4 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.7 ppm; IR (neat) ν = 1434, 1153, 1111, 846, 694 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{11}H_{10}F_3N_2$ [M + H$^+$]: 227.0791; found 227.0798.



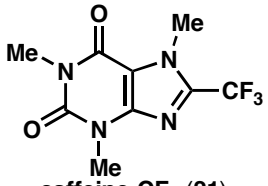
19

Uracil-CF_3 (19). The Standard Procedure was followed with a reaction time of 16 h (no second addition of reagents) to provide the product in 87 % yield: white solid; m.p.: 243-245 ºC; R_f = 0.67 (EtOAc); ^{1}H NMR (400 MHz, CD_3OD) δ 7.94 (s, 1 H) ppm; ^{13}C NMR (150 MHz, CD_3OD) δ 162.1, 152.5, 144.8 (q, J = 6 Hz), 124.0 (q, J = 268 Hz), 104.8 (q, J = 33 Hz) ppm; ^{19}F NMR (376 MHz, CD_3OD) δ -65.1 ppm; IR (neat) ν = 3214, 2925, 1687, 1436, 1336, 1257, 1190, 1132, 1053, 1033, 794 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_5H_2F_3N_2O_2$ [M - H$^+$]: 179.0074; found 179.0071.

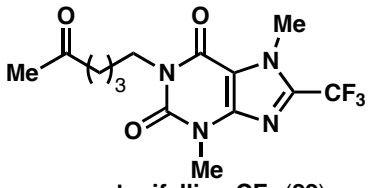


20

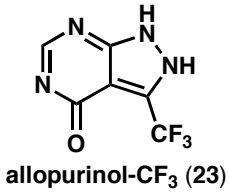
Theophyline-CF_3 (20). The Standard Procedure was followed with a reaction time of 17 h (no second addition of reagents) to provide the product in 96% yield as a white solid; m.p.: 234-237 ºC; R_f = 0.36 (EtOAc); ^{1}H NMR (400 MHz, CD_3OD) δ 3.55 (s, 3 H), 3.37 (s, 3 H) ppm; ^{13}C NMR (150 MHz, CD_3OD) δ 159.5, 153.8, 150.2, 145.4 (q, J = 38 Hz), 121.6 (q, J = 269 Hz), 116.0, 30.8, 28.4 ppm; ^{19}F NMR (376 MHz, CD_3OD) δ -64.7 ppm; IR (neat) ν = 3484, 2965, 1695, 1640, 1272, 1160, 1114, 1061, 1033, 751 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_8H_8F_3N_4O_2$ [M + H$^+$]: 249.0594, found 249.0592.


caffeine-CF_3 (**21**)
[X-RAY]

Caffeine-CF_3 (21). The Standard Procedure was followed with a reaction time of 40 hours (no second addition of reagents) to provide the product in 80% yield: white solid; R_f = 0.23 (25% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (s, 3 H), 3.55 (s, 3 H), 3.38 (s, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 151.4, 146.6, 139.0 (q, J = 40 Hz), 118.3 (q, J = 270 Hz), 109.7, 33.3 (q, J = 2 Hz), 30.0, 28.3 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.7 ppm; IR (neat) ν = 3378, 2958, 1710, 1661, 1611, 1553, 1511, 1459, 1404, 1367, 1346, 1252, 1210, 1181, 1145, 1127, 1100, 1022, 978, 821, 761, 745, 732, 710, 683 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_9H_{10}F_3N_4O_2$ [M + H$^+$]: 263.0750; found 263.0753.

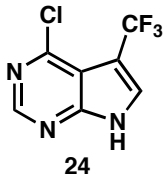

pentoxifylline-CF_3 (**22**)

2-Trifluoromethyl-pentoxifylline (22). The Standard Procedure was followed with a reaction time of 48 hours (second addition of trifluoromethylsulfinate and *tert*-butylhydroperoxide after 24 h) to provide the product in 47% yield: colorless solid; m.p.: 67 - 69 ºC; R_f = 0.16 (33% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.14 (s, 3 H), 4.01 (t, J = 7.1 Hz, 2 H), 3.57 (s, 3 H), 2.49 (t, J = 7.1 Hz, 2 H), 2.13 (s, 3 H), 1.69 – 1.60 (m, 4 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.7, 155.4, 151.2, 146.7, 139.1 (q, J = 40 Hz), 118.3 (q, J = 272 Hz), 109.8, 43.2, 41.3, 33.3 (q, J = 2 Hz), 30.1, 30.0, 27.4, 21.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.6; IR (neat) ν = 1712, 1652, 1608, 1545, 1459, 13796, 1245, 1203, 1129, 1099, 748, 600, 474 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{14}H_{18}F_3N_4O_3$ [M + H$^+$]: 347.1326; found 347.1330.


allopurinol-CF_3 (**23**)

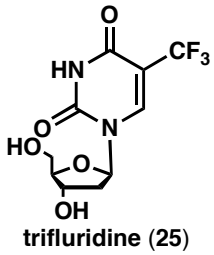
Allopurinol-CF_3 (23). The Standard Procedure was followed with a reaction time of 40 hours (second addition of trifluoromethylsulfinate and *tert*-butylhydroperoxide after 16 h) to provide the product in 76%: white

solid; m.p.: 300-303 ºC; R_f = 0.51 (EtOAc); ^{1}H NMR (400 MHz, CD_3OD) δ 8.08 (s, 1 H) ppm; ^{13}C NMR (150 MHz, CD_3OD) δ 158.0, 156.5, 150.1, 138.9 (d, J = 40 Hz), 121.9 (q, J = 268 Hz), 103.9 ppm; ^{19}F NMR (376 MHz, CD_3OD) δ -64.0 ppm; IR (neat) ν = 2982, 1736, 1373, 1253, 1044, 1033, 1017, 847 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_6H_4F_3N_4O$ [M + H^+]: 205.0332; found 205.0338.



24

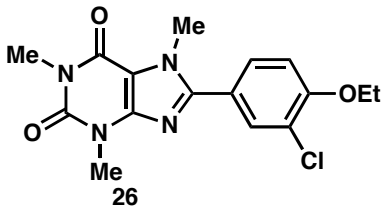
4-Chloro-5-(trifluoromethyl)-7H-pyrrolo[2,3-d]pyrimidine (24). The Standard Procedure was followed with a reaction time of 61 hours to provide the product in 43% yield: colorless solid; m.p.: 52 – 56 ºC; R_f = 0.75 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.24 (br s, 1 H), 8.83 (s, 1 H), 7.10 (s, 1 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.7, 152.4, 151.6, 128.5 (q, J = 41 Hz), 120.5 (q, J = 268 Hz), 117.5, 101.7 (q, J = 3 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.8 ppm; IR (neat) ν = 1572, 1313, 1222, 1191, 1126, 987, 872 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_7H_4ClF_3N_3$ [M + H^+] 222.0040; found 222.0049.



trifluridine (25)

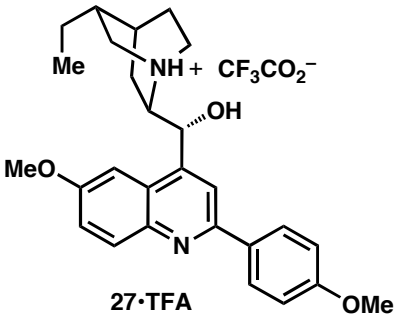
Trifluridine (25). The Standard Procedure (with 1 ml water and without organic solvent) was followed with a reaction time of 6 hours (no second addition of reagents) to provide the product in 57% yield: colorless solid; m.p.: 181 ºC (decomposition); R_f = 0.45 (EtOAc); ^{1}H NMR (600 MHz, CD_3CN) δ 9.28 (s, 1 H), 8.65 (s, 1 H), 6.11 (t, J = 6.0 Hz, 1 H), 4.37 – 4.33 (m, 1 H), 3.90 (m, 1 H), 3.78 (ddd, J = 11.9, 4.6, and 2.9 Hz, 1 H), 3.70 (ddd, J = 11.9, 4.6, and 2.9 Hz, 1 H), 3.38 (d, J = 4.5 Hz, 1 H), 3.29 (t, J = 4.6 Hz, 1 H), 2.29 (ddd, J = 13.7, 6.0, and 5.0 Hz, 1 H), 2.24 – 2.19 (m, 1 H); ^{13}C NMR (150 MHz, CD_3CN) δ 159.9, 150.5, 143.4 (q, J = 6 Hz), 123.8 (q, J = 269 Hz), 104.4 (q, J = 32 Hz), 88.6, 87.0, 70.7, 61.5, 41.7; ^{19}F NMR (376 MHz, CD_3CN) δ -63.8

ppm; IR (neat) ν = 3391, 3062, 1727, 1670, 1479, 1273, 1121, 1097, 1038, 874, 626, 597, 565, 535, 439 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{10}H_{12}F_3N_2O_5$ [M + H^+]: 297.0693; found 297.0694.



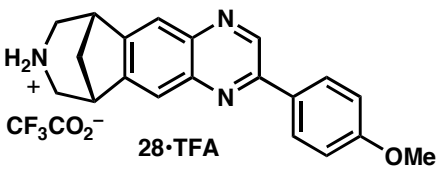
26

(3-Chloro-4-ethoxyphenyl)-caffeine (26). To a solution of caffeine (0.25 mmol, 1.0 equiv) in DCM (1.25 mL) was added trifluoroacetic acid (19 μL, 0.25 mmol, 1.0 equiv) followed by 3-chloro-4-ethoxyphenylboronic acid (0.38 mmol, 1.5 equiv). Water (0.75 mL) was then added, followed by silver (I) nitrate (8.5 mg, 0.05 mmol, 0.2 equiv) in water (0.50 mL). Potassium persulfate (202 mg, 0.75 mmol, 3.0 equiv) was then added and the solution was stirred vigorously at room temperature and monitored by thin-layer chromatography of the organic layer. After 3 hours, a second addition of solid silver(I)nitrate (8.5 mg, 0.05 mmol, 0.2 equiv) and potassium persulfate (202 mg, 0.75 mmol, 3.0 equiv) was performed. After 19 hours, the reaction was diluted with DCM (3 mL) and washed with 5% sodium bicarbonate. The layers were separated, and the aqueous layer was extracted with DCM (3 x 4 mL), dried over sodium sulfate, and evaporated *in vacuo*. Purification was performed by silica gel chromatography to provide the product in 63% yield: colorless solid; R_f = 0.44 (50% EtOAc/hexanes); m.p.: 205 – 209 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J = 2.2 Hz, 1 H), 7.54 (dd, J = 8.7 and 2.2 Hz, 1 H), 7.02 (d, J = 8.7 Hz, 1 H), 4.18 (q, J = 7.0 Hz, 2 H), 4.05 (s, 3 H), 3.61 (s, 3 H), 3.42 (s, 3 H), 1.50 (t, J = 7.0 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 155.6, 151.8, 150.9, 148.4, 131.1, 128.8, 123.7, 121.4, 113.1, 108.9, 65.1, 34.1, 29.9, 28.1, 14.7 ppm; IR (neat) ν = 1697, 1656, 1456, 747 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{16}H_{18}ClN_4O_3$ [M + H^+] 349.1062; found 349.1074.



27•TFA

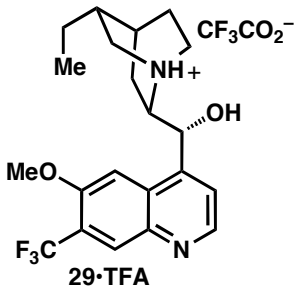
2-(4-Methoxyphenyl)-dihydroquinine (27). To a solution of dihydroquinine (41 mg, 0.125 mmol, 1.0 equiv) in dicloromethane/water (0.6/0.4 mL) was added trifluoroacetic acid (19 μL, 0.25 mmol, 2.0 equiv) followed by 4-methoxyphenylboronic acid (38 mg, 0.19 mmol, 1.5 equiv), silver(I)nitrate (4.3 mg, 0.025 mmol, 0.2 equiv) and ammoniumum persulfate (87 mg, 0.38 mmol, 3.0 equiv). The solution was stirred vigorously at room temperature for 3h (89% conv.), and the solvent was removed under reduced pressure. Purification was accomplished by preparative HPLC (10% to 45% MeCN in water, 0.1% TFA, 25 minute ramp; R_T for **27•TFA** = 17.7 min) to afford the product in 48% yield. The product was free-based for characterization (due to broadened signals in the salt form): white solid; m.p.: 98-100 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 8.01 (m, 3 H), 7.91 (s, 1 H), 7.33 (ddd, J = 9.2, 2.5 and 1.0 Hz, 1 H), 7.13 (s, 1 H), 7.00 (d, J = 7.9 Hz, 2 H), 5.64 (s, 1 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 3.70 – 3.54 (m, 1 H), 3.21 – 3.06 (m, 2 H), 2.81 – 2.66 (m, 1 H), 2.50 – 2.40 (m, 1 H), 1.82 (br, 3 H), 1.56 – 1.39 (m, 3 H), 1.32 – 1.14 (m, 3 H), 0.81 (t, J = 7.4 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 157.6, 154.3, 147.6, 144.4, 132.4, 131.7, 128.7, 125.1, 121.8, 115.9, 114.2, 101.1, 71.6, 59.9, 58.5, 55.9, 55.5, 43.6, 37.4, 27.9, 27.7, 25.5, 20.8, 12.1 ppm; IR (neat) ν = 3345, 1654, 1431, 1181, 1126, 722 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{27}H_{33}N_2O_3$ [M + H$^+$]: 433.2486, found 433.2491.



28•TFA

(4-methoxyphenyl)-varenicline•TFA (28•TFA). To a solution of varenicline (0.25 mmol, 1.0 equiv) in DCM (1.25 mL) was added trifluoroacetic acid (57 μL, 0.75 mmol, 3.0 equiv) followed by 4-methoxyphenylboronic acid (0.38 mmol, 1.5 equiv). Water (0.75 mL) was then added, followed by silver (I) nitrate (17 mg, 0.1 mmol, 0.4 equiv) in water (1.00 mL).

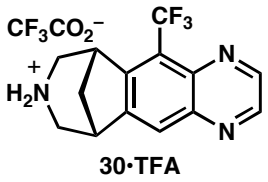
Potassium persulfate (202 mg, 0.75 mmol, 3.0 equiv) was then added and the solution was stirred vigorously at room temperature and monitored by thin-layer chromatography of the organic layer. After 16 hours, the reaction was diluted with a solution of 20% MeOH in DCM (3 mL) and washed with 5% sodium bicarbonate. The layers were separated, and the aqueous layer was extracted with a solution of 20% MeOH in DCM (3 mL), dried over sodium sulfate, and evaporated *in vacuo*. Purification was accomplished by preparative HPLC (5% to 50% MeCN in H_2O, 0.1% TFA, 30 minute ramp; R_T = 17.3 min) to provide the product in 45% yield: yellow solid; m.p.: 229 - 234 ºC; R_f = 0.47 (10% MeOH/DCM); ^{1}H NMR (600 MHz, D_2O) δ 8.73 (s, 1 H), 7.72 (s, 1 H), 7.69 (s, 1 H), 7.65 (d, *J* = 8.6 Hz, 2 H), 6.86 (d, *J* = 8.6 Hz, 2 H), 3.78 (s, 3 H), 3.58 (br, 1 H), 3.53 (br, 1 H), 3.49 (d, *J* = 12.2 Hz, 1 H), 3.48 (d, *J* = 12.6 Hz, 1 H), 3.31 (d, *J* = 12.6 Hz, 1 H), 3.27 (d, *J* = 12.2 Hz, 1 H), 2.33 (m, 1 H), 2.18 (d, *J* = 11.6 Hz, 1 H) ppm; ^{13}C NMR (150 MHz, D_2O) δ 163.4 (q, *J* = 36 Hz), 162.4, 150.6, 148.5, 147.1, 142.3, 140.7, 139.2, 130.1, 126.4, 122.5, 122.3, 116.9 (q, *J* = 290 Hz), 115.4, 56.1, 48.0, 40.7, 39.2, 39.1, 30.9 ppm; IR (neat) ν = 3387, 2924, 2473, 1673, 1609, 1456, 1205, 1055,1033, 670, 571, 542, 537, 526, 524 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{20}H_{20}N_3O$ [M + H$^+$]: 318.1601; found 318.1609.



29•TFA

Dihydroquinine-CF_3•TFA (29•TFA). The Standard Procedure was followed with a reaction time of 16h (1 equiv. of TFA added; 89% conversion; no second addition of reagents). The solvent was removed under reduced pressure and purification was accomplished by preparative HPLC (10% to 45% MeCN in water, 0.1% TFA, 25 minute ramp; R_T for **7•TFA** = 22.3 min) . to provide **29•TFA** in 50% yield: colorless oil; ^{1}H NMR (400 MHz, CD_3OD) δ 8.93 (d, *J* = 4.8 Hz, 1 H), 8.37 (s, 1 H), 8.02 (d, *J* = 4.8 Hz, 1 H), 7.62 (s, 1 H), 6.02 (s, 1 H), 4.29 – 4.17 (m, 1 H), 4.13 (s, 3 H), 3.73 – 3.65 (m, 1 H), 3.61 (dd, *J* = 12.7 and

10.6 Hz, 1 H), 3.03 (ddd, *J* = 12.7, 5.9 and 2.7 Hz, 1 H), 2.32 – 2.17 (m, 2 H), 2.13 – 2.08 (m, 1 H), 2.04 – 1.84 (m, 3 H), 1.67 – 1.57 (m, 1 H), 1.44 – 1.28 (m, 2 H), 0.86 (t, *J* = 7.4 Hz, 3 H) ppm; ^{13}C NMR (150 MHz, CD_3OD) δ 160.5 (q, *J* = 38 Hz), 156.5, 148.8, 148.3, 140.7, 129.2, 128.3, 124.7 (q, *J* = 32 Hz), 123.6 (q, *J* = 273 Hz), 122.2, 116.6 (d, *J* = 286 Hz), 103.5, 68.0, 60.6, 57.0, 56.9, 44.8, 36.0, 26.8, 25.3, 25.1, 18.5, 11.2 ppm; IR (neat) ν = 3345, 2981, 1654, 1431, 1181, 1126, 839, 799, 722 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{21}H_{26}F_3N_2O_2$ [M + H$^+$]: 433.2486, found 433.2491.



30·TFA

5-Trifluoromethyl-varenicrine (30-C5) and 2-Trifluoromethyl-varenicrine (30-C2). The tartrate salt of varenicrine was used in this reaction as obtained from Pfizer. The Standard Procedure was followed with a reaction time of 18 hours (no second addition of reagents) to provide the product in 50% yield (4:1 C5:C2). Purification was accomplished by preparative HPLC (4% to 50% MeCN in H_2O, 0.1% TFA, 25 minute ramp; R_T for **30-C5** = 21.3 min; R_T for **30-C2** = 24.7). Data for **30-C5**: colorless solid; m.p.: 176 ºC (decomposition); R_f = 0.58 (10% Et_3N/EtOAc); ^{1}H NMR (600 MHz, D_2O) δ 8.83 (d, *J* = 2.0 Hz, 1 H), 8.80 (d, *J* = 2.0 Hz, 1 H), 8.12 (s, 1 H), 4.04 (s, 1 H), 3.65 (s, 1 H), 3.49 (dd, *J* = 12.7 and 1.4 Hz, 1 H), 3.46 (dd, *J* = 12.6 and 1.3 Hz, 1 H), 3.38 – 3.34 (m, 1 H), 3.31 – 3.27 (m, 1 H), 2.39 – 2.34 (m, 1 H), 2.16 (d, *J* = 12.1 Hz, 1 H); ^{13}C NMR (150 MHz, D_2O) δ 163.7 (q, *J* = 37 Hz), 147.1, 146.4, 145.9, 145.9, 143.0, 140.4, 128.2, 124.8 (q, *J* = 272 Hz), 123.2 (q, *J* = 30 Hz), 117.1 (q, *J* = 291 Hz), 47.94, 47.60, 40.00, 39.6 (q, *J* = 4 Hz), 38.69; ^{19}F NMR (376 MHz, D_2O) δ -55.5, -75.8 ppm; IR (neat) ν = 2970, 1672, 1458, 1340, 1229, 1179, 1129, 1086, 961, 939, 797, 752, 719, 444 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{14}H_{13}F_3N_3$ [M + H$^+$]: 280.1056; found 280.1060. Data for **30-C2**: colorless solid; m.p.: 194 ºC (decomposition); R_f = 0.60 (10% Et_3N/EtOAc); ^{1}H NMR (600 MHz, D_2O) δ 9.14 (s, 1 H), 8.05

(s, 1 H), 8.02 (s, 1 H), 3.66 (br, 2 H), 3.48 – 3.44 (m, 2 H), 3.33 – 3.29 (m, 2 H), 2.45 – 2.39 (m, 1 H), 2.15 (d, J = 11.9 Hz, 1 H); ^{13}C NMR (150 MHz, D_2O) δ 163.8 (q, J = 36 Hz), 149.7, 148.7, 144.5 (q, J = 1 Hz), 142.8 (q, J = 36 Hz), 141.9, 141.6 (q, J = 3 Hz), 124.3, 124.1, 121.7 (q, J = 275 Hz), 48.2, 48.2, 40.7, 39.3, 39.2; ^{19}F NMR (376 MHz, D_2O) δ -67.2, -75.8 ppm; IR (neat) ν = 2973, 1672, 1476, 1322, 1209, 1149, 1111, 1030, 984, 835, 719, 457 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{14}H_{13}F_3N_3$ [M + H^+]: 280.1056; found 280.1060.

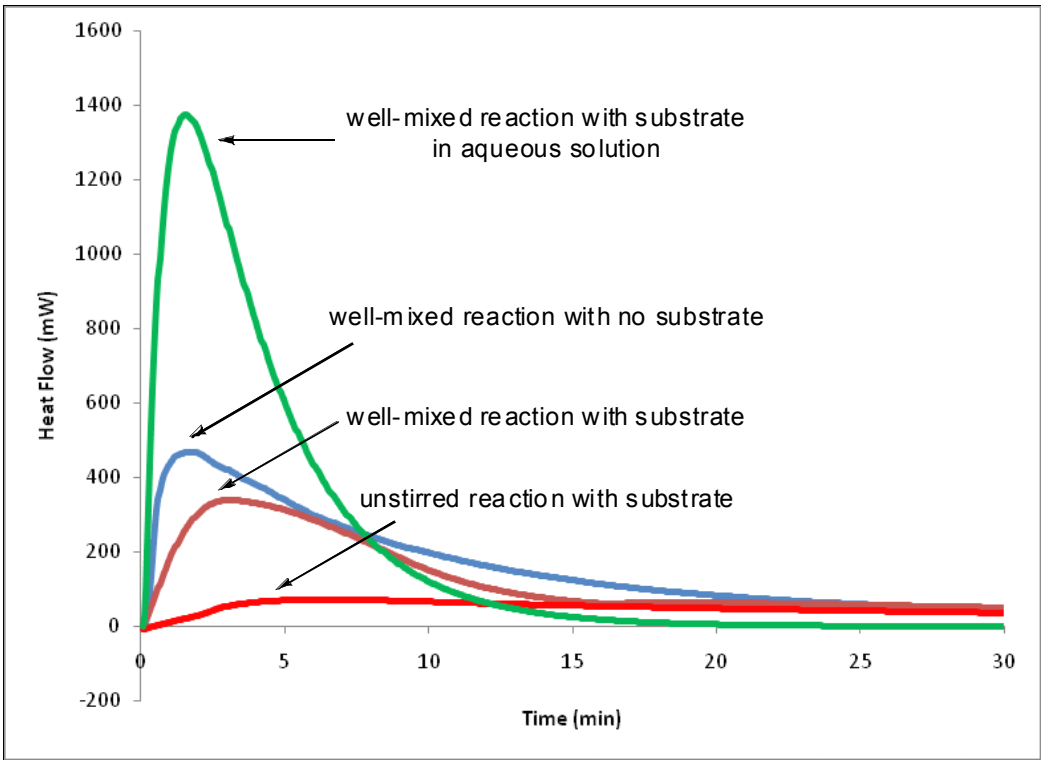
***In Situ* Reaction Calorimetric Monitoring.** Measurements were performed in an Omnical Insight-CPR-220 reaction calorimeter which allows for continuous monitoring of the instantaneous heat absorbed or released by a chemical reaction taking place within the reaction vessel. Reaction vessels were septum-capped vials equipped with stirbars (in cases of stirring).

Aqueous Reaction: 4-acetylpyridine (0.25 mmol, 1.0 equiv) and sodium trifluoromethylsulfinate (0.75 mmol, 3.0 equiv) were combined in 1.4 mL of H_2O at room temperature and stirred at 600 rpm. *Tert*-butylhydrogenperoxide (70% solution in water, 1.25 mmol, 5.0 equiv) was added to the stirred mixture via syringe.

Well-Mixed No Substrate: Sodium trifluoromethylsulfinate (0.75 mmol, 3.0 equiv) was dissolved in a mixture of dichloromethane/water (1.0 mL/0.4 mL) at room temperature and stirred at 600 rpm. *Tert*-butylhydrogenperoxide (70% solution in water, 1.25 mmol, 5.0 equiv) was added to the stirred mixture via syringe.

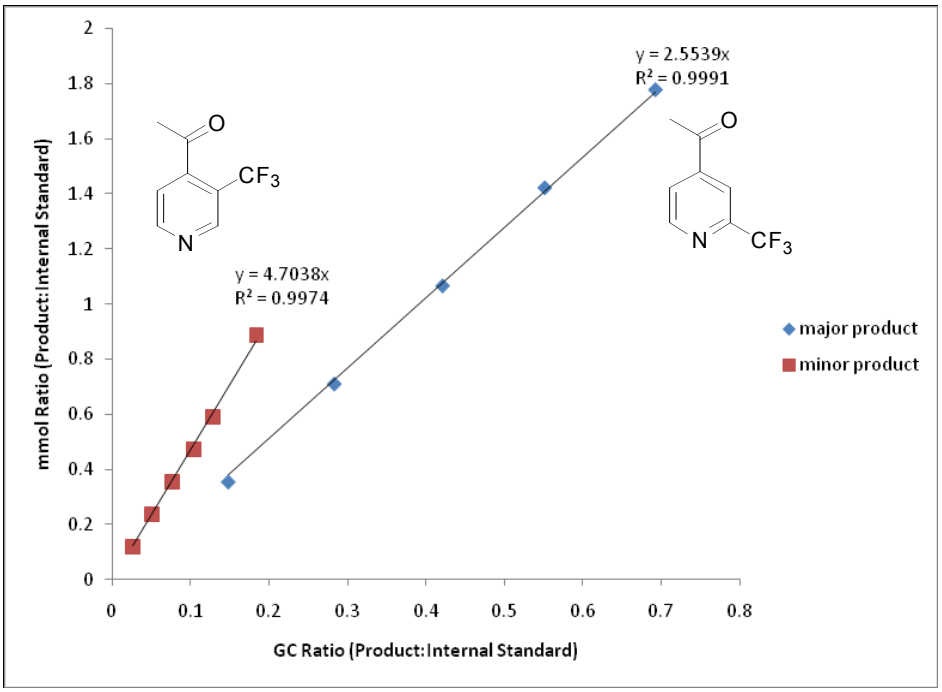
Well-Mixed Substrate: 4-acetylpyridine (0.25 mmol, 1.0 equiv) and sodium trifluoromethylsulfinate (0.75 mmol, 3.0 equiv) were combined in mixture of dichloromethane/water (1.0 mL/0.4 mL) at room temperature and stirred at 600 rpm. *Tert*-butylhydrogenperoxide (70% solution in water, 1.25 mmol, 5.0 equiv) was added to the stirred mixture via syringe.

Unstirred Substrate: 4-acetylpyridine (0.25 mmol, 1.0 equiv) and *tert*-butylhydrogenperoxide (70% solution in water, 1.25 mmol, 5.0 equiv). Sodium trifluoromethylsulfinate (0.75 mmol, 3.0 equiv) was dissolved in 0.4 mL of water and carefully layered on top of the dichloromethane solution of arene and peroxide. The mixture was allowed to react undisturbed in the reaction calorimeter.

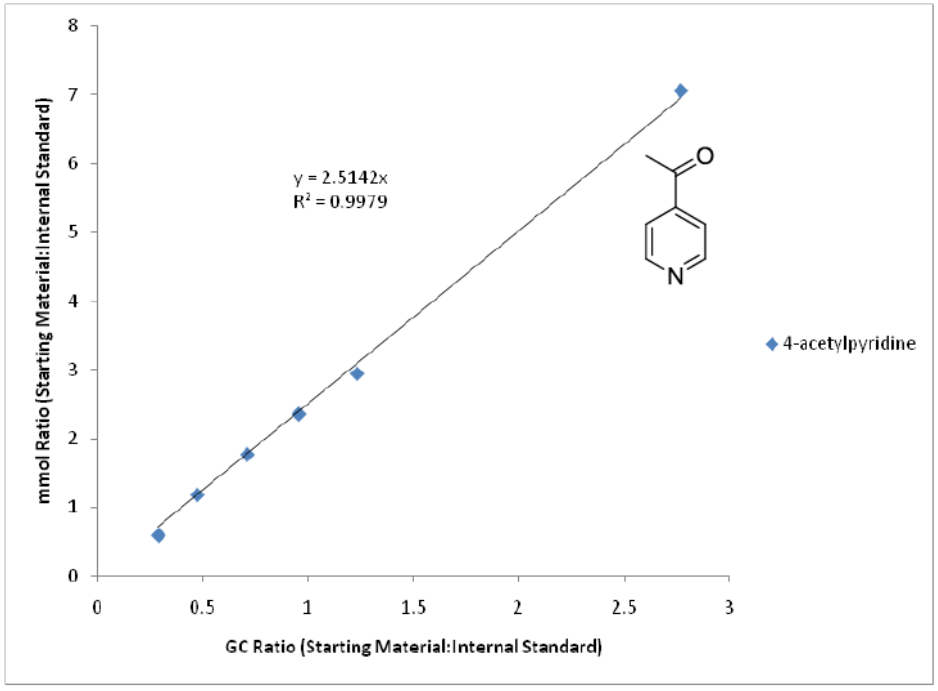


GC Analysis of Reaction Progression and Conversion. The trifluoromethylation of 4-acetylpyridine was examined under various conditions. To simplify the analysis of reaction progressions, the following procedure was utilized: 4-acetylpyridine (0.25 mmol, 1.0 equiv) was combined with *tert*-butylhydrogenperoxide (70% solution in water, 1.25 mmol, 5.0 equiv) and tetradecane (10 uL, 0.04 mmol) in 1.0 mL of dichloromethane. A solution of trifluoromethylsulfinate (0.75 mmol, 3.0 equiv) in 0.4 mL of water was then added dropwise to the dichloromethane solution (stirred between 0-600 rpm). Small aliquots (~20 uL) were removed from the organic layer at timed intervals, quenched in 1 mL of $NaHCO_3$ (sat.) and extracted with 2 mL of dichloromethane for GC analysis.

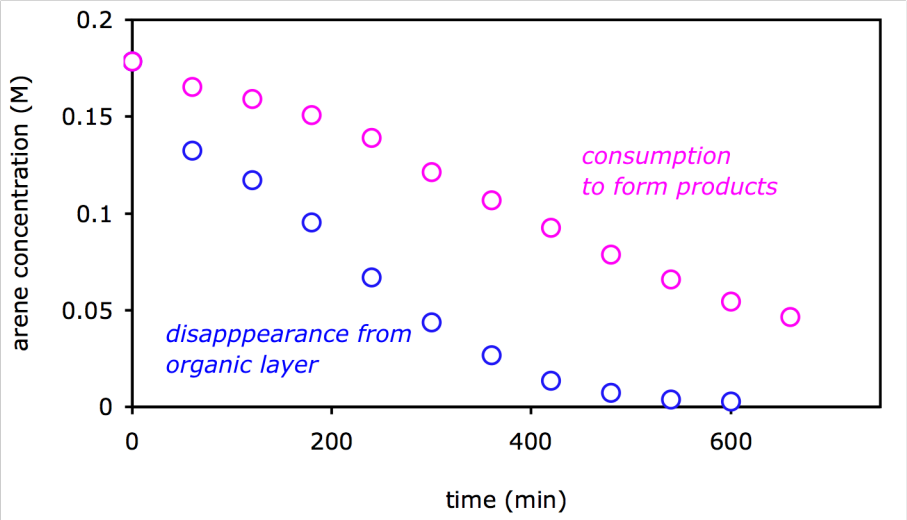
Product Calibration



Starting Material Calibration

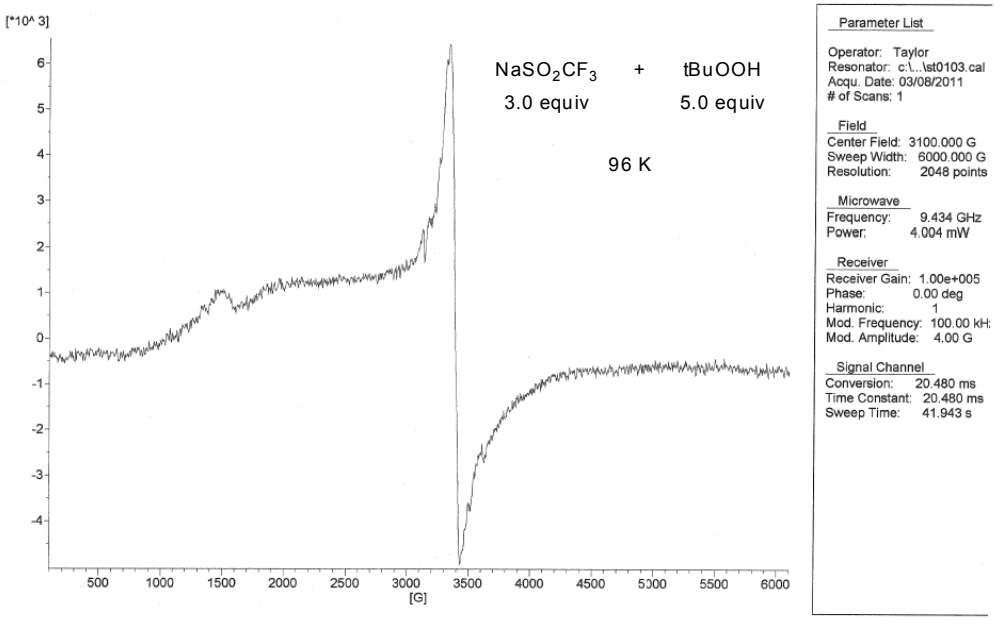


NMR Analysis of Arene Phase Partitioning. Because the trifluoromethylation likely occurs at the interface of the biphasic mixture, the improved conversion obtained when the reaction is not well-mixed may be attributed to the suppression of degradation pathways available to the sulfinate and peroxide when combined directly in the aqueous phase. NMR spectroscopy shows that the trifluoromethylated products do not enter the aqueous phase, although the peroxide and the arene pass from the organic into the aqueous layer. The disappearance of arene from the organic phase is thus due to both phase partitioning and consumption to product, as shown below.

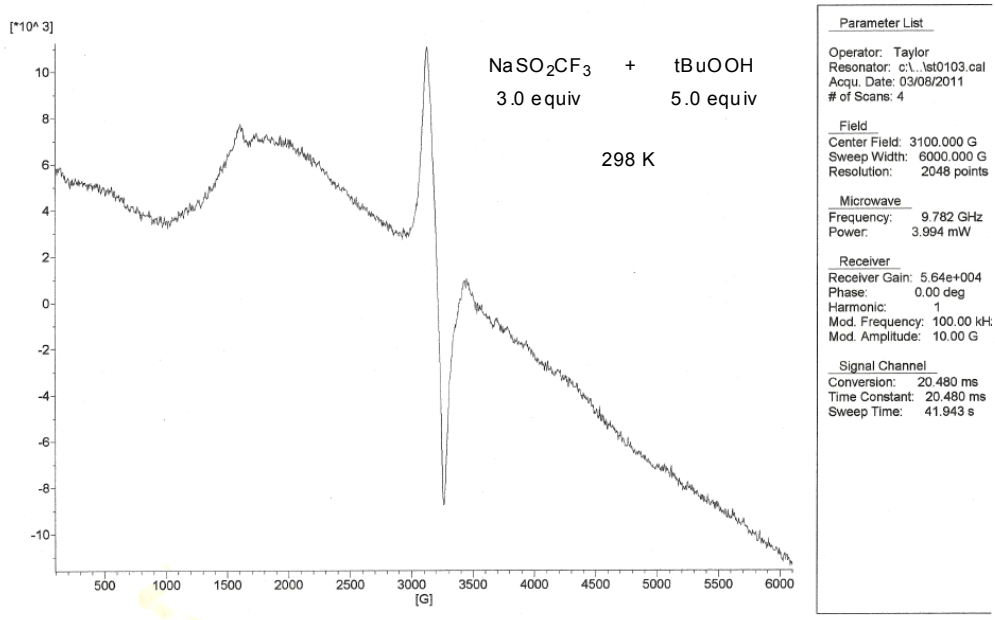


Arene concentration in the organic phase in the unstirred two-phase reaction shown in Table 1 using 0.18 M arene, 5.0 equiv. ^{t}BuOOH, 3.0 equiv. CF_3SO_2Na in (DCM:H_2O 2.5:1).

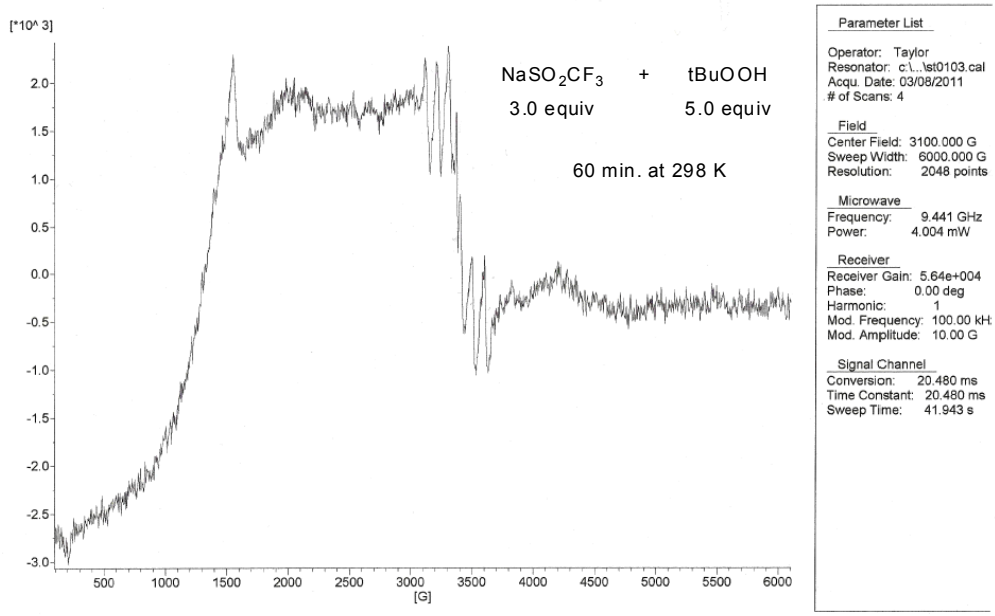
EPR Evidence for Free Radical Generation: EPR spectra were acquired on a Bruker EMX X-band (9 GHz) instrument and visualized using WinEPR software. Due to expected solvent interference in aqueous solution, spectra were initially acquired at 96 K. Shown below is an initial spectrum acquired from a sample which was frozen shortly after combining trifluoromethylsulfinate and *tert*-butylhydroperoxide in aqeuous solution.

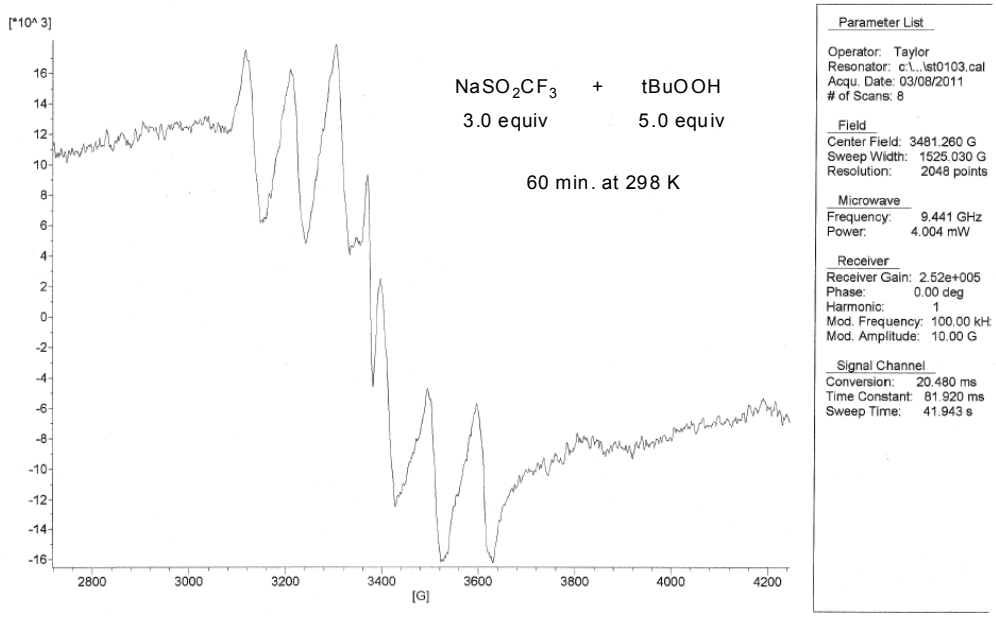


Due to the high signal to noise ratio observed, subsequent spectra were acquired at approximately 298 K in a narrow melting point capillary placed inside an EPR tube.

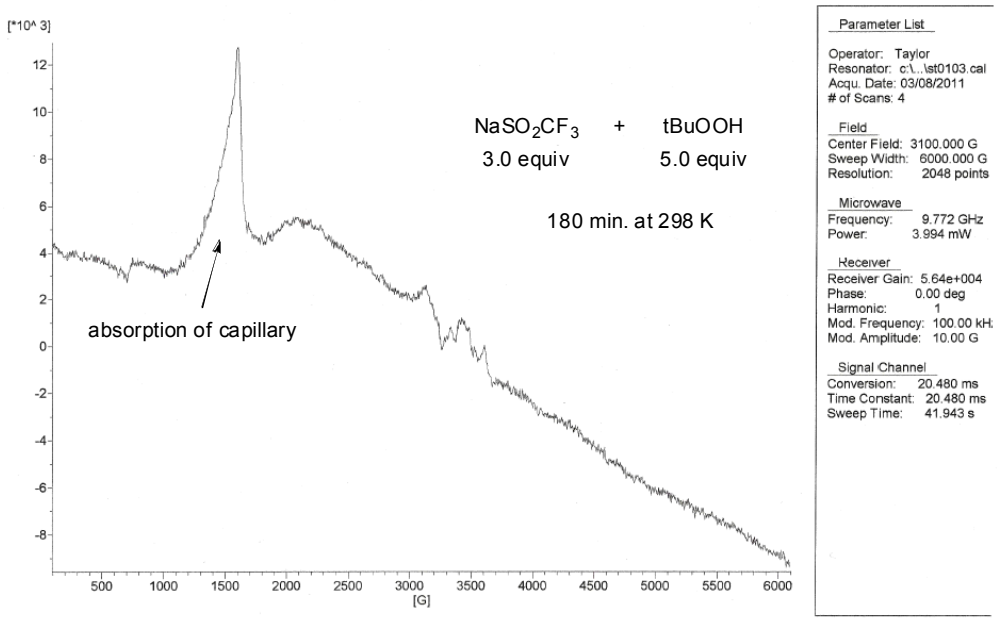


Allowing this solution to stand for approximately one hour at room temperature reveals the presence of more complex signals arising from species containing unpaired electrons.

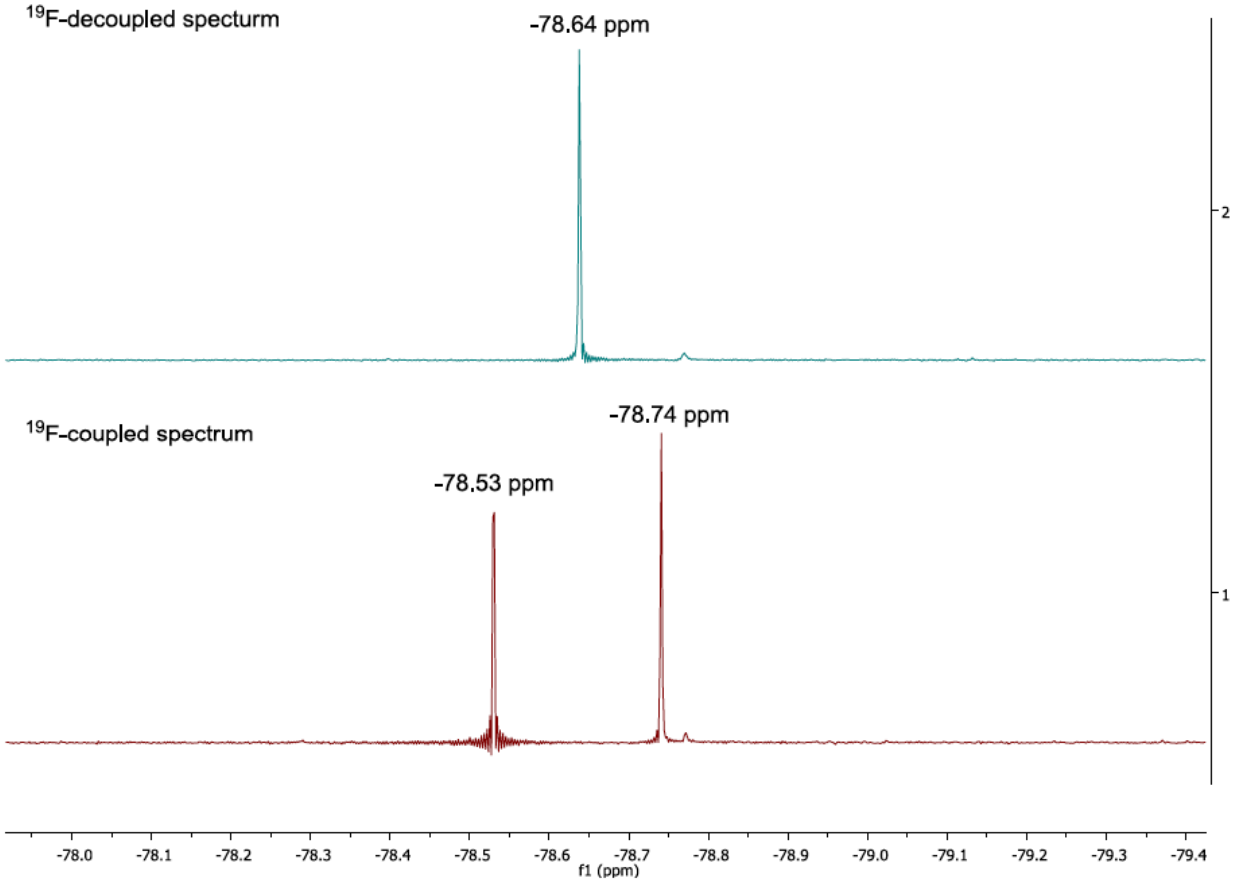




In the absence of a coupling partner, nearly all radical species have disappeared over the course of three hours.


[*10^ 3]
12
10
8
6
4
2
0
-2
-4
-6
-8
500
1000
1500
2000
2500
3000
3500
4000
4500
5000
5500
6000
[G]
absorption of capillary
NaSO2CF3 + tBuOOH
3.0 equiv 5.0 equiv
180 min. at 298 K
Parameter List
Operator: Taylor
Resonator: c:\...\st0103.cal
Acqu. Date: 03/08/2011
# of Scans: 4
Field
Center Field: 3100.000 G
Sweep Width: 6000.000 G
Resolution: 2048 points
Microwave
Frequency: 9.772 GHz
Power: 3.994 mW
Receiver
Receiver Gain: 5.64e+004
Phase: 0.00 deg
Harmonic: 1
Mod. Frequency: 100.00 kH
Mod. Amplitude: 10.00 G
Signal Channel
Conversion: 20.480 ms
Time Constant: 20.480 ms
Sweep Time: 41.943 s

Observation of CF_3H via ^{19}F-NMR. Trifluoromethylsulfinate (117 mg, 0.75 mmol) was dissolved in a combination of CD_2CL_2 and D_2O (1 mL each) and placed into an NMR tube. *Tert*-butylhydrogenperoxide (70% solution in water, 0.17 mL, 1.25 mmol) was added dropwise to the mixture and gas was allowed to evolve (exothermic). The tube was then sealed, inverted, and ^{19}F-NMR spectra were collected once the biphasic mixture had settled into distinct layers. A fluorinated-alkyl species was observed at -78.64 ppm (referenced to $CFCl_3$) in the ^{19}F-^{1}H decoupled spectrum. A subsequent ^{19}F-^{1}H coupled spectrum was immediately acquired which yielded a clear doublet centered around the original peak at -78.64 ppm, indicative of the CF_3 fluorines being split by a single hydrogen.



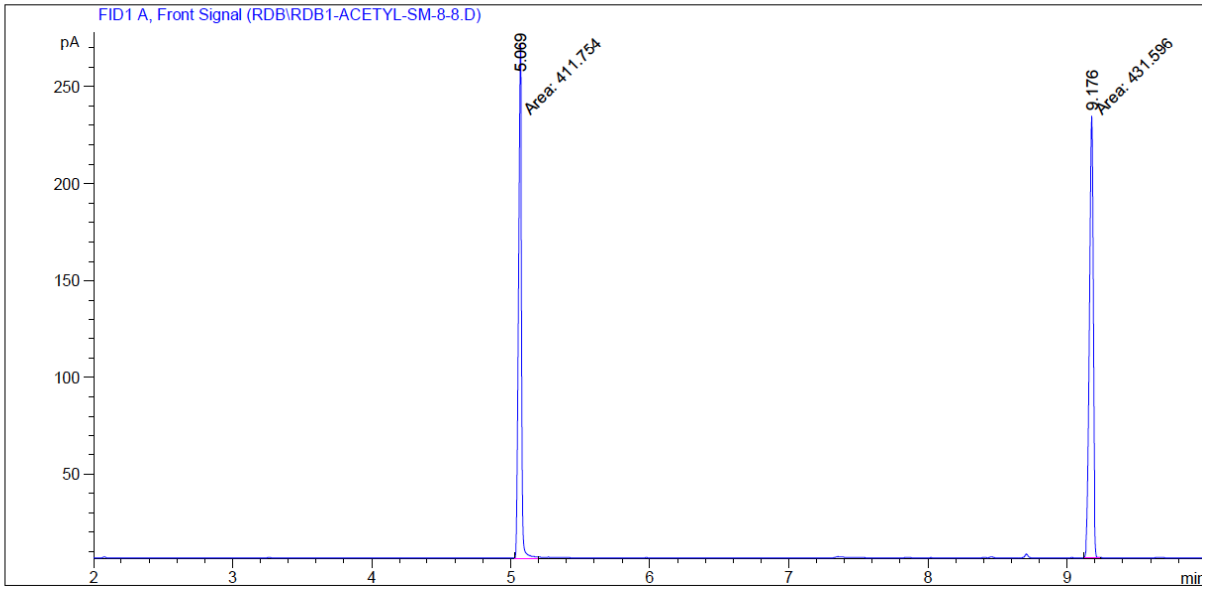
Trace Elemental Analysis of *tert*-butylhydroperoxide ("Liquid Sample") CF_3SO_2Na ("Solid Sample"):

Analyze samples for metals via ICP-MS. Samples reported as parts per billion (ppb)
ND=element was not detectable in sample.

	Liquid Sample ppb	Solid Sample ppb		Liquid Sample ppb	Solid Sample ppb
Li	17.73	28.13	Nb	ND	28.98
Be	ND	ND	Mo	ND	1746.29
B	6791.00	7023.22	Ru	ND	ND
Al	24.50	567.78	Rh	ND	ND
Sc	112.28	484.01	Cd	ND	ND
V	ND	357.04	Sn	ND	28.68
Cr	1864.85	24599.62	Sb	ND	31.12
Mn	4.92	1456.86	Ba	ND	ND
Co	ND	431.89	La	ND	ND
Ni	24.02	6634.85	Hf	ND	ND
Cu	14.73	4707.94	W	ND	11.61
Zn	24.02	6634.85	Re	ND	ND
Ga	ND	ND	Ir	ND	ND
Ge	ND	12.43	Tl	ND	ND
As	ND	62.54	Pb	ND	ND
Rb	ND	4.81	Bi	127.49	367.79
Sr	ND	5.50	Ca	8.13	968.11
Y	ND	ND	Fe	17.11	30006.10
Zr	ND	ND			

GC Trace from Figure 7 – 4-acetylpyridine with tetradecane standard

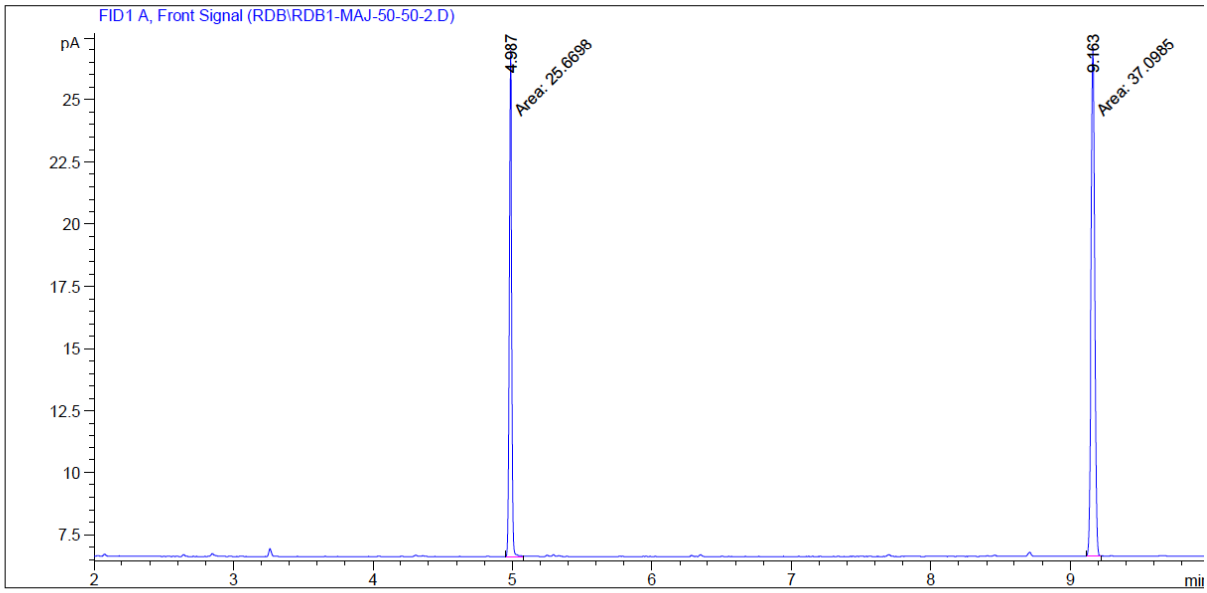
```
Data File C:\CHEM32\1\DATA\RDB\RDB1-ACETYL-SM-8-8.D
Sample Name: rdb1-acetyl-sm-8-8

    ======================================================================
    Acq. Operator   : Ryan                          Seq. Line :   8
    Acq. Instrument : GC-FID                        Location : Vial 8
    Injection Date  : 3/28/2011 12:30:24 PM             Inj :   1
                                                   Inj Volume : 1 µl
    Acq. Method     : C:\CHEM32\1\METHODS\DB-5-GENERAL-SHORT.M
    Last changed    : 3/23/2011 11:30:50 AM by Ryan
    Analysis Method : C:\CHEM32\1\METHODS\BETADEX-1B.M
    Last changed    : 4/16/2011 12:13:31 PM by Ryan
                      (modified after loading)
```




```
    ======================================================================
                           Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier:                   :      1.0000
    Dilution:                     :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: FID1 A, Front Signal

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [pA*s]      [pA]        %
    ----|-------|----|-------|----------|----------|--------|
       1   0.401 BV    0.0570 6.70501e-2 1.79374e-2  0.00014
       2   1.314 BV    0.0151 7.85758e-2 7.60041e-2  0.00017
       3   1.347 VV    0.0192 8.01223e-2 6.14528e-2  0.00017
       4   1.380 VV    0.0133 6.91922e-2 7.85648e-2  0.00015
       5   1.409 VV    0.0115    1.40246    1.93218  0.00300

GC-FID 5/5/2011 3:51:24 PM Ryan                          Page   1 of 2
```

GC Trace from Figure 7 – 2-trifluoromethyl-4-acetylpyridine (1-C2) with tetradecane standard

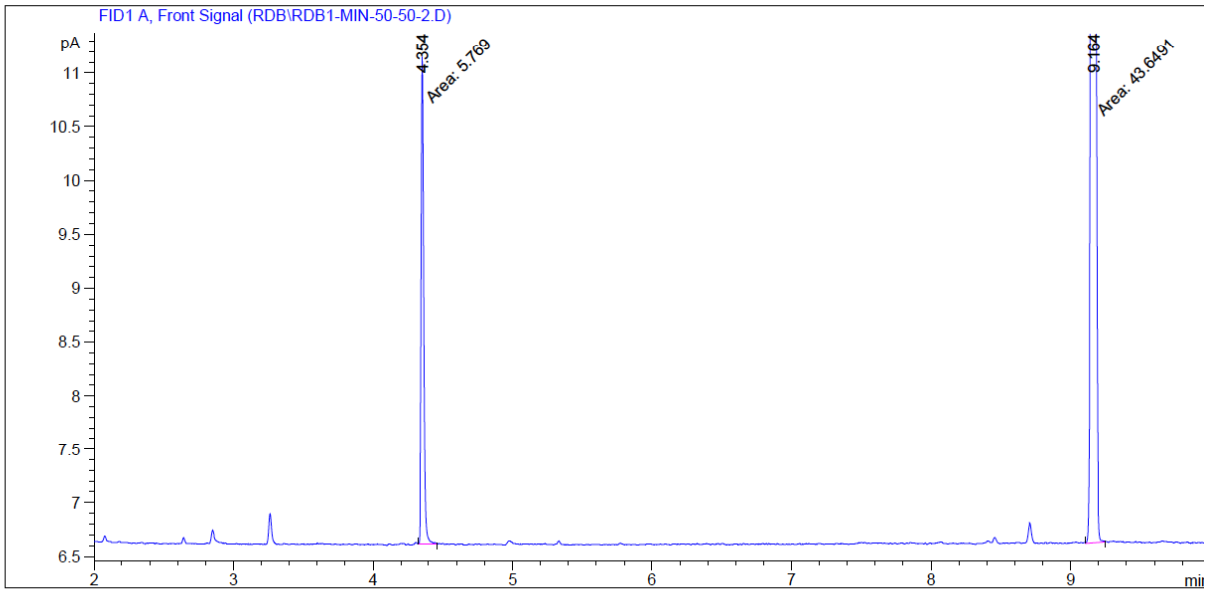
```
Data File C:\CHEM32\1\DATA\RDB\RDB1-MAJ-50-50-2.D
Sample Name: rdb1-maj-50-50-2

==========================================================================
Acq. Operator   : Ryan                              Seq. Line :  20
Acq. Instrument : GC-FID                            Location : Vial 25
Injection Date  : 3/29/2011 9:22:17 PM                   Inj :  1
                                                  Inj Volume : 1 µl
Acq. Method     : C:\CHEM32\1\METHODS\DB-5-GENERAL-SHORT.M
Last changed    : 3/23/2011 11:30:50 AM by Ryan
Analysis Method : C:\CHEM32\1\METHODS\BETADEX-1B.M
Last changed    : 4/16/2011 12:13:31 PM by Ryan
                  (modified after loading)
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A, Front Signal

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1   1.348 VV    0.0169 6.41681e-2 5.79595e-2  0.00013
   2   1.380 VV    0.0124 5.20701e-2 6.48676e-2  0.00011
   3   1.431 VB S  0.0204 4.88915e4  3.27260e4  99.81003
   4   1.532 BB X  0.0166 3.09201e-1 3.09655e-1  0.00063
   5   1.605 BV X  0.0150 8.10648e-2 8.62715e-2  0.00017
```

GC Trace from Figure 7 – 3-trifluoromethyl-4-acetylpyridine (1-C3) with tetradecane standard

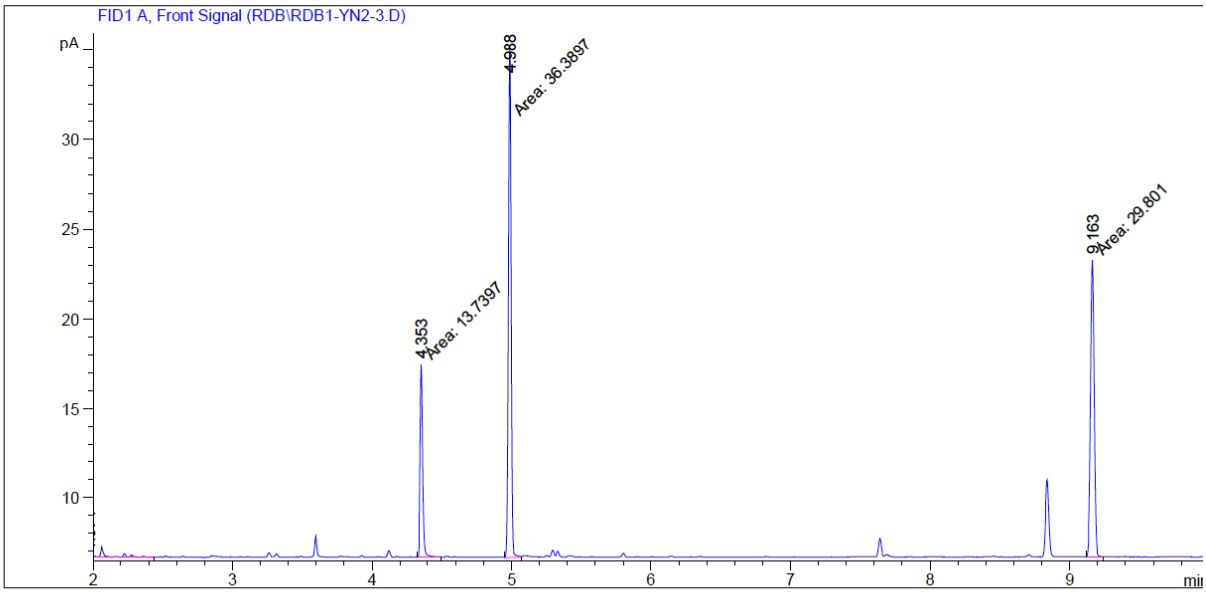
```
Data File C:\CHEM32\1\DATA\RDB\RDB1-MIN-50-50-2.D
Sample Name: rdb1-min-50-50-2

======================================================================
Acq. Operator    : Ryan                              Seq. Line :  21
Acq. Instrument : GC-FID                              Location : Vial 35
Injection Date  : 3/29/2011 9:34:24 PM                    Inj :   1
                                                    Inj Volume : 1 µl
Acq. Method     : C:\CHEM32\1\METHODS\DB-5-GENERAL-SHORT.M
Last changed    : 3/23/2011 11:30:50 AM by Ryan
Analysis Method : C:\CHEM32\1\METHODS\BETADEX-1B.M
Last changed    : 4/16/2011 12:13:31 PM by Ryan
                  (modified after loading)
```




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A, Front Signal

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1   1.314 BV    0.0150 4.54913e-2 4.83437e-2 9.336e-5
   2   1.347 VV    0.0164 7.72374e-2 7.26970e-2  0.00016
   3   1.381 VV    0.0135 6.40000e-2 7.84168e-2  0.00013
   4   1.431 VB S  0.0204 4.86479e4  3.26120e4  99.84193
   5   1.747 BB X  0.0172   27.41441   26.14367  0.05626

GC-FID 5/5/2011 3:48:05 PM Ryan                          Page   1 of 2
```

GC Trace from Figure 7 – Standard solvent system reaction (2.5:1 DCM:H_2O) after 24 h.

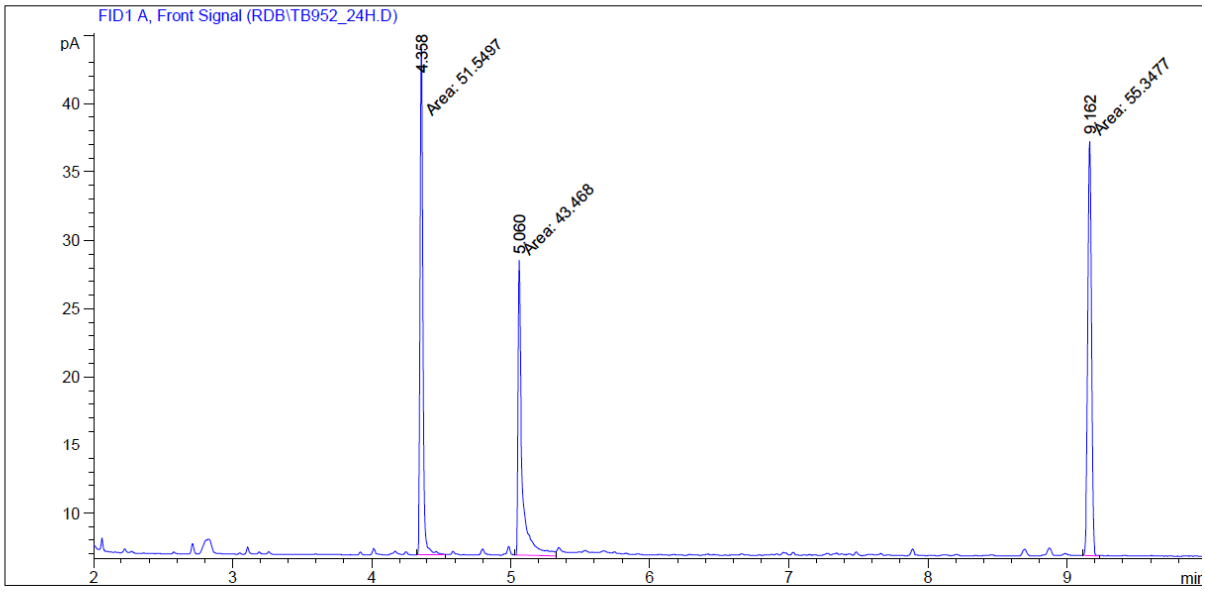
```
Data File C:\CHEM32\1\DATA\RDB\RDB1-YN2-3.D
Sample Name: rdb1-YN2-3

==========================================================================
Acq. Operator    : Ryan                              Seq. Line :  23
Acq. Instrument : GC-FID                              Location : Vial 73
Injection Date  : 4/2/2011 7:06:28 PM                     Inj :   1
                                                   Inj Volume : 1 µl
Acq. Method     : C:\CHEM32\1\METHODS\DB-5-GENERAL-SHORT.M
Last changed    : 3/23/2011 11:30:50 AM by Ryan
Analysis Method : C:\CHEM32\1\METHODS\BETADEX-1B.M
Last changed    : 4/16/2011 12:13:31 PM by Ryan
                  (modified after loading)
```




```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A, Front Signal

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1   1.315 BV    0.0159 3.09993e-1 3.03168e-1  0.00068
   2   1.360 VV    0.0163 5.15667e-1 4.51734e-1  0.00113
   3   1.387 VV    0.0129 7.84142e-1 9.64555e-1  0.00172
   4   1.410 VV   9.68e-3    2.15038    3.50760  0.00471
   5   1.431 VB S  0.0203 4.55489e4  3.06509e4  99.75052

GC-FID 5/5/2011 3:54:36 PM Ryan                          Page   1 of 2
```

GC Trace from Figure 7 – Trifluorotoluene:Acetone (1:1) after 24 h (~50% yield with SM left).

```
Data File C:\CHEM32\1\DATA\RDB\TB952_24H.D
Sample Name: TB952_24h

==========================================================================
Acq. Operator    : Ryan                          Seq. Line :   1
Acq. Instrument : GC-FID                          Location : Vial 25
Injection Date  : 4/30/2011 9:22:34 AM                Inj :   1
                                                 Inj Volume : 1 µl
Acq. Method     : C:\CHEM32\1\METHODS\DB-5-GENERAL-SHORT.M
Last changed    : 4/27/2011 11:04:44 AM by Ryan
Analysis Method : C:\CHEM32\1\METHODS\BETADEX-1B.M
Last changed    : 4/16/2011 12:13:31 PM by Ryan
                  (modified after loading)
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A, Front Signal

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1   4.358 MM    0.0225   51.54967   38.11177 34.28292
   2   5.060 MM    0.0333   43.46805   21.75716 28.90827
   3   9.162 MM    0.0302   55.34772   30.55031 36.80880

Totals :                   150.36543   90.41924
```