Chem, Volume *1*

Supplemental Information

Photochemical Perfluoroalkylation with Pyridine *N*-Oxides: Mechanistic Insights and Performance on a Kilogram Scale

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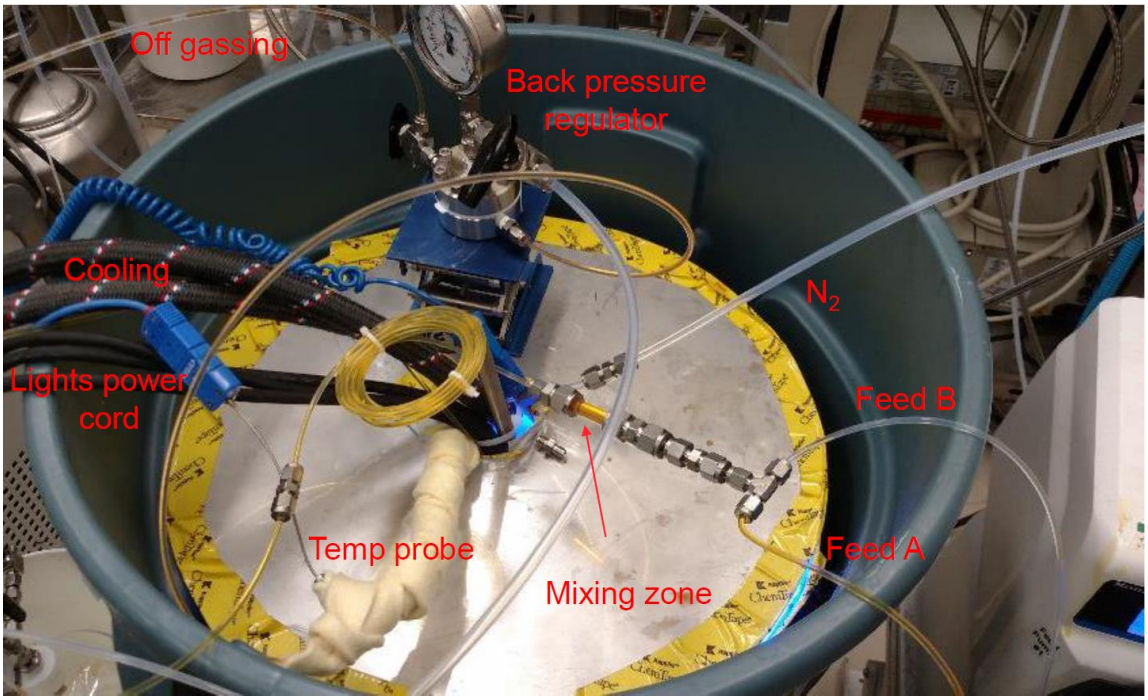

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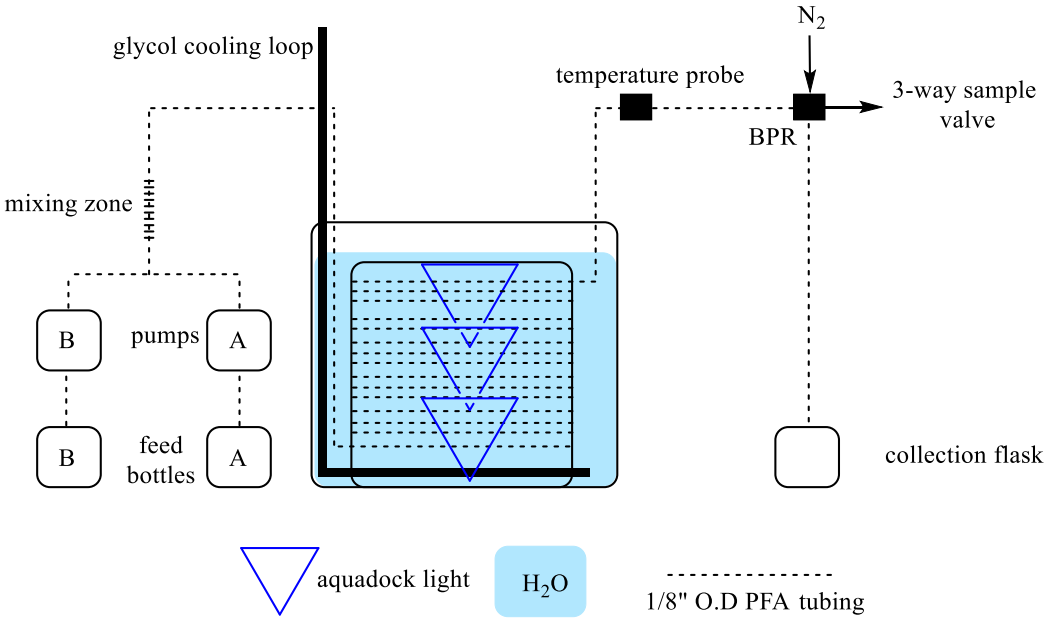
Figure S1. Pictures detailing reactor setup, Related to Figure 3.
(A) Glass reactor and tubing.
(B) Aquadock light source and holding stand.
(C) Assembly of reactor, lights, stainless steel housing, and outer secondary container.
(D) Detail of reactor construction from top down view.



* secondary container, nitrogen line, and internal temperature probe omitted for clarity

Figure S2. Schematic representation of the flow reactor, Related to Figure 3.

Supplemental Experimental Procedures

General Information: All chemicals were used as received. Reactions were monitored by TLC and visualized with a dual short wave/long wave UV lamp. Column flash chromatography was performed using 230-400 mesh silica gel or via automated column chromatography. Preparative TLC purifications were run on silica plates of 1000 µm thickness. NMR spectra were recorded on Varian MR400, Varian Inova 500, Varian Vnmrs 500, or Varian Vnmrs 700 spectrometers. Chemical shifts for ^{1}H NMR were reported as δ, parts per million, relative to the signal of $CHCl_3$ at 7.26 ppm. Chemical shifts for ^{13}C NMR were reported as δ, parts per million, relative to the center line signal of the $CDCl_3$ triplet at 77.0 ppm. Chemical shifts for ^{19}F NMR were reported as δ, parts per million, relative to the signal of a trifluorotoluene internal standard at -63.72 ppm. *N*-oxide screening experiments were quantitatively analyzed by ^{19}F NMR with a relaxation delay of 1s, while later optimization experiments (entries 13 through 23) and all other internal standard yields were quantified by ^{19}F NMR with a 5s relaxation delay. The abbreviations s, br. s, d, dd, br. d, ddd, t, q, br. q, qi, m, and br. m stand for the resonance multiplicity singlet, broad singlet, doublet, doublet of doublets, broad doublet, doublet of doublet of doublets, triplet, quartet, broad quartet, quintet, multiplet and broad multiplet, respectively. IR spectra were recorded on a Perkin-Elmer Spectrum BX FT-IR spectrometer fitted with an ATR accessory. Mass Spectra were recorded at the Mass Spectrometry Facility at the Department of Chemistry of the University of Michigan in Ann Arbor, MI on an Agilent Q-TOF HPCL-MS with ESI high resolution mass spectrometer. Fluorescence, actinometry, and quantum yield measurements were performed with a Fluoromax-2 fluorimeter equipped with a 150W Xe arc lamp. UV-VIS measurements were obtained on a Shimadzu UV-1601 UV-VIS Spectrometer. LED lights and the requisite power box and cables were purchased from Creative Lighting Solutions (http://www.creativelightings.com) with the following item codes: CL-FRS5050-12WP-12V (4.4W blue LED light strip), CL-PS94670-25W (25 W power supply), CL-PC6FT-PCW (power cord), CL-TERMBL-5P (terminal block).

Unless stated otherwise, all reactions were run on a 0.8mmol scale in a 2 dram vial equipped with stir bar and septum. The light apparatuses used to irradiate the reactions were constructed from test tube racks and wrapped with three 4W LED strips. Reactions were run only in slots marked by an X in the picture below so as to keep a moderate distance from the light source (~2.5 cm). At this distance the temperature of the reactions did not exceed 35 ˚C (**Figure S3**).

Figure S3: Experimental light array.

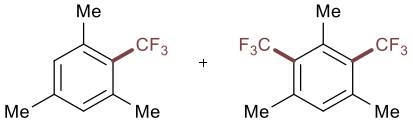
Optimization and Control Experiments: All optimization experiments were performed on a 0.8 mmol scale at 0.4 M concentration (2 ml of solvent) unless stated otherwise, with the equivalents or reagents used, atmosphere, catalyst loadings found in Table 1 of the manuscript.

Entries 1-16: To a 2 dram vial equipped with a stir bar was added the *N*-oxide derivative (0.4–1.6 mmol, 0.5–2.0 equiv.), $Ru(bpy)_3Cl_2•6H_2O$ (6.0 mg, 1.0 mol%), and substrate (0.80 mmol). The combined materials were then dissolved in dry MeCN (2.0 ml) and stirred briefly (~1 minute). Trifluoroacetic anhydride (120 µl, 190 mg, 0.88 mmol, 1.1 equiv.) was then added to the resulting solution. The vial was equipped with a screw-on cap. Three 4.4 W LED light strips were turned on and the reactions allowed to proceed for 12 hours before removal of the light source. Trifluorotoluene (98 µl, 0.80 mmol) was added as a stoichiometric internal standard. A sample of the reaction was removed and diluted with $CDCl_3$ for NMR analysis. The trifluorotoluene signal was referenced to δ -63.72. Product peaks in the crude ^{19}F NMR were integrated with 1,3,5-trimethyl-2-(trifluoromethyl)benzene observed at δ -54.70 (s, 3F) and 1,3,5-trimethyl-2,4-bis(trifluoromethyl)benzene observed at δ -53.89 (s, 6F).

Entries 17-23: Procedurally identical to entries 1-16, with key differences. For reactions with 0.1 mol% catalyst (**entries 19, 20, 23, 24**), 500 µl of a solution 1.2 mg/ml $Ru(bpy)_3Cl_2•6H_2O$ in dry MeCN (0.6 mg, 0.1 mol%) was added in lieu of 500 µl of solvent. Reactions were degassed (**entries 17-24**) upon dissolution of catalyst, *N*-oxide, and mesitylene in dry MeCN by sparging of the solution with nitrogen for 30 seconds, followed by the addition of TFAA (not degassed) under a stream of nitrogen. The reactions were quickly sealed with a rubber-lined screw on cap, and wrapped with parafilm. Light exclusion (**entry 23**) was achieved by wrapping the reaction in foil (before addition of TFAA) while placing the vessel in front of the light source so as to match the temperature profile of the other reactions. Before analysis of the light-exclusion experiment, methanol (500 µl) was added via syringe and the reaction was allowed to stir for 5 minutes before exposure to light during analysis.

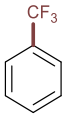
Preparation of Compounds 2a-20, 23: General Perfluoroalkylation Procedure: To a 2 dram vial equipped with a stir bar was added 4-phenylpyridine *N*-oxide (0.8–3.2 mmol, 1.0–4.0 equiv.) and substrate (0.80 mmol) followed by 500 ul of a 1.2 mg/ml solution of $Ru(bpy)_3Cl_2•6H_2O$ (0.6 mg, 0.1 mol%). The combined materials were then diluted with dry MeCN (1.5 ml, total volume 2 ml MeCN) and stirred briefly to form a heterogeneous solution, with the *N*-oxide only partially dissolved when used in higher equivalents. The reaction was sparged with nitrogen gas for 30 seconds with a glass pipette, followed by the addition of the fluorinated acylating reagent (0.88–3.28 mmol, 1.1–4.1 equiv.) under a stream of nitrogen before quickly sealing the vial with a rubber-lined screw-on cap. The trifluoroacetic anhydride solubilizes any remaining solid *N*-oxide within seconds to minutes. Three 4.4 W LED light strips were turned on and the reactions were allowed to proceed for 3–12 hours before removal of the light source (see Supplemental Information for geometry of LED setup). Upon reaction completion, trifluorotoluene (98 µl, 0.80 mmol) was added as a stoichiometric internal standard. A sample of the reaction was removed and diluted with $CDCl_3$ for NMR analysis, with the trifluorotoluene signal referenced to δ -63.72. Workup conditions were substrate-dependent.

1,3,5-trimethyl-2-(trifluoromethyl)benzene[1] (2a) and 1,3,5-trimethyl-2,4-bis(trifluoromethyl)benzene[2] (2b)



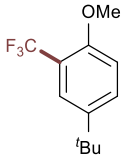
Following the general procedure, using 4-phenylpyridine *N*-oxide (273.9 mg, 1.6 mmol, 2.0 equiv.) and TFAA (237 µl, 1.68 mmol, 2.1 equiv.), the reaction was run for 12 hours. ^{19}F NMR analysis of the crude reaction mixture vs. the injected trifluorotoluene standard revealed the volatile title compounds 1,3,5-trimethyl-2-(trifluoromethyl)benzene [^{19}F NMR (470 MHz, $CDCl_3$) δ = -54.70 (s, 3F, 65% yield)] and 1,3,5-trimethyl-2,4-bis(trifluoromethyl)benzene [^{19}F NMR (470 MHz, $CDCl_3$) δ = -53.89 (s, 6F, 14% yield)] in a 4.6:1 ratio.
Yield: 0.632 mmol (79%, 4.6:1 2a:2b); ^{19}F NMR (470 MHz, $CDCl_3$) δ = -54.70 (s, 3F, 2a 65% yield), -53.89 (s, 3F, 2b 14% yield). The isolation and characterization of these compounds has previously been reported.[3]

(trifluoromethyl)benzene (3a)



Following the general procedure, using 4-phenylpyridine *N*-oxide (137.0 mg, 0.8 mmol, 1.0 equiv.) as the limiting reagent, TFAA (124 µl, 0.88 mmol, 1.1 equiv.), and benzene (713 µl, 8.0 mmol, 10.0 equiv.), the reaction was run for 12 hours. Upon completion, the reaction was quenched with methanol (500 µl) and removed from the light source. Trifluoroethanol (58 µl, 0.8 mmol) was added as internal standard. Due to the wide availability and volatility of the product, no purification was attempted on this reaction mixture.
Yield: 0.632 mmol (79%); ^{19}F NMR (500 MHz, $CDCl_3$) δ = -63.72 (s, 3F). The proton and fluorine signals of the product were identical to those of a commercial sample.

4-(tert-butyl)-1-methoxy-2-(trifluoromethyl)benzene[4] (4a)



Following the general procedure, using 4-phenylpyridine *N*-oxide (273.9 mg, 1.6 mmol, 2.0 equiv.) and TFAA (237 µl, 1.68 mmol, 2.1 equiv.), the reaction was run for 5 hours. ^{19}F NMR analysis of the crude reaction mixture vs. the injected trifluorotoluene standard revealed the volatile title compound in 59% yield. The reaction was partitioned with 1N HCl and diluted with dichloromethane. The organic phase was separated, washed with sat. $NaHCO_3$, brine, and dried over sodium sulfate before filtering and concentrating. The crude reaction mixture was purified by prep TLC (100% hexanes run up x2) to yield to title compound as a volatile, clear oil (R_f = 0.32, hexanes).
Yield: 0.472 mmol (59%) ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56 (d, J = 2.4 Hz, 1H), 7.50 (dd, J = 8.8, 2.4 Hz, 1H), 6.94 (d, J = 8.8 Hz, 1H), 3.88 (s, 3H), 1.31 (s, 9H); ^{19}F NMR (470 MHz, $CDCl_3$) δ = -63.13 (s, 3F); ^{13}C NMR (175 MHz, $CDCl_3$) δ = 155.2 (q, JC-F = 1.4 Hz), 142.9, 129.9, 123.9 (q, JC-F = 272.5 Hz), 123.89 (q, JC-F = 4.8 Hz), 118.0 (q, JC-F = 30.7 Hz), 111.7, 55.9, 34.2, 31.3; HRMS (EI+) m/z: $[M + H]^+$ calculated 232.1075, found 232.1077. IR (neat): ν = 2965, 1620, 1589, 1509, 1325, 1280, 1253, 1119, 1057.

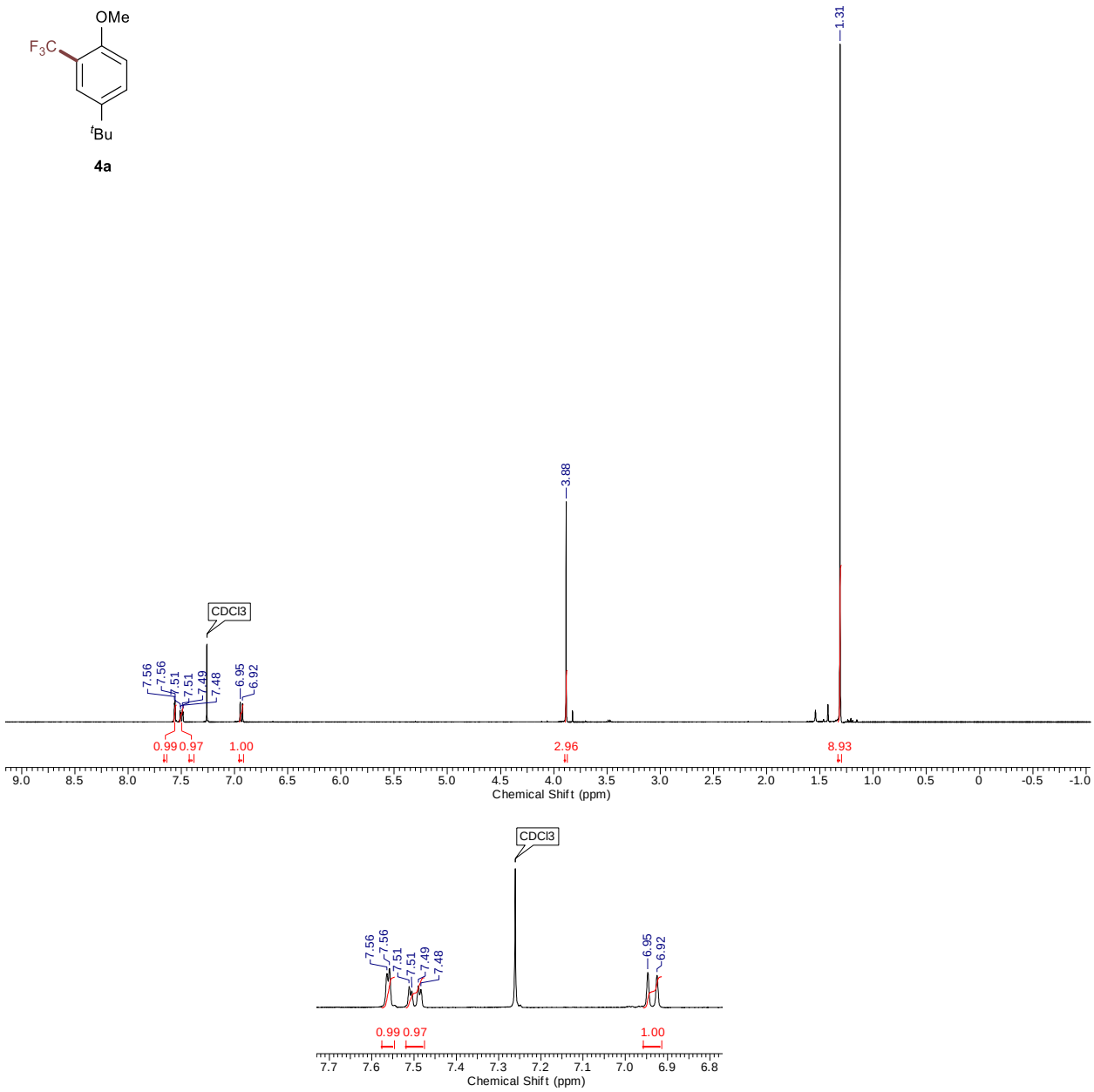


Figure S4. ^{1}H NMR spectrum (700 MHz, $CDCl_3$) of **4a**.

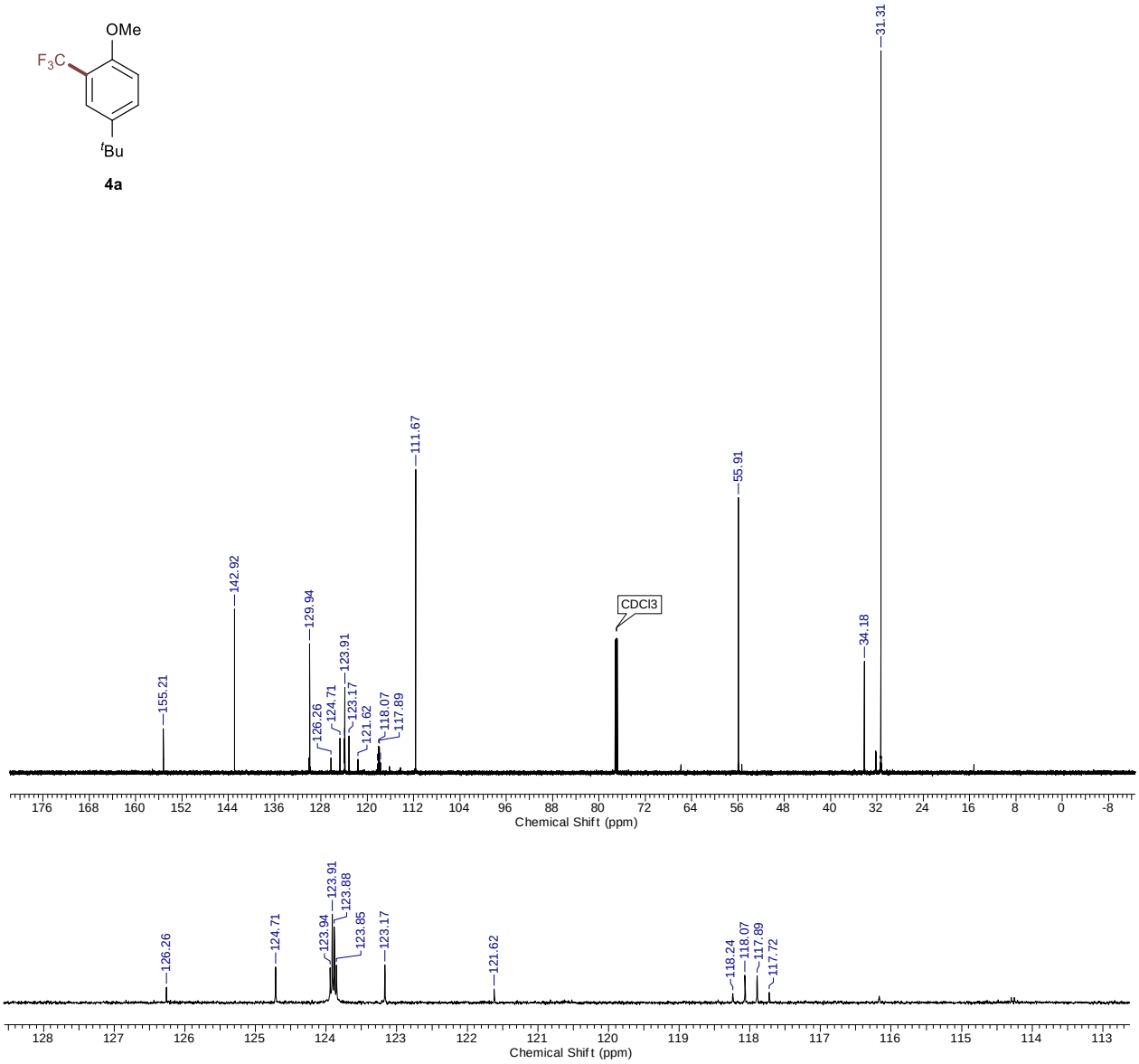
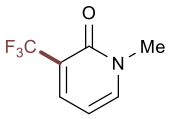


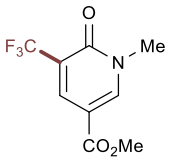
Figure S5. ^{13}C NMR spectrum (175 MHz, $CDCl_3$) of **4a**.

1-methyl-3-(trifluoromethyl)pyridine-2(1H)-one[3,5] (5a)



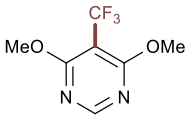
Following the general procedure using 4-phenylpyridine *N*-oxide (137.0 mg, 0.8 mmol, 1.0 equiv.) and TFAA (124 µl, 0.88 mmol, 1.1 equiv.), the reaction was run for 15 hours. ^{19}F NMR analysis of the crude reaction mixture vs. the injected trifluorotoluene standard revealed the title compound in 50% yield. The reaction was partitioned with 1N HCl and diluted with ethyl acetate. The organic phase was separated and washed with sat. $NaHCO_3$, brine, and dried over sodium sulfate before filtering and concentrating. Re-extraction of the combined and basified aqueous phase (basified further with sat. $NaHCO_3$) led to full material recovery, while the initial acidic workup conditions result in a significant loss of material. The crude reaction mixture was purified on silica gel with 0-50% EtOAc in hexanes to yield the title compound as a tan solid.
Yield: 71.8 mg (51%) The characterization of this compound has previously been reported.[3]

methyl 1-methyl-6-oxo-5-(trifluoromethyl)-1,6-dihydropyridine-3-carboxylate[3] (6a)



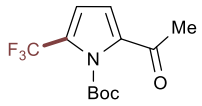
Following the general procedure using 4-phenylpyridine *N*-oxide (273.9 mg, 1.6 mmol, 2.0 equiv.) and TFAA (237 µl, 1.68 mmol, 2.1 equiv.), the reaction was run for 15 hours. ^{19}F NMR analysis of the crude reaction mixture vs. the injected trifluorotoluene standard revealed the title compound in **49% yield**. The reaction mixture was diluted with ethyl acetate and washed with sat. $NaHCO_3$. The aqueous layer was washed twice with ethyl acetate, and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated. The crude reaction mixture was purified by prep TLC (20% CH_2Cl_2 in EtOAc) to yield the title compound as a tan solid.
Yield: 93.0 mg (49%) The characterization of this compound has been previously reported.[3]

4,6-dimethoxy-5-(trifluoromethyl)pyrimidine (7a)



Following the general procedure using 4-phenylpyridine *N*-oxide (237.9 mg, 1.6 mmol, 2.0 equiv.) and TFAA (451 µl, 3.2 mmol, 4.0 equiv.), the reaction was run for 12 hours. ^{19}F NMR analysis of the crude reaction mixture vs. the injected trifluorotoluene standard revealed the title compound in **39% yield**. The reaction mixture was diluted with ethyl acetate and was partitioned with 1N HCl. The organic phase was separated, washed with sat. $NaHCO_3$, brine, and dried over sodium sulfate before filtering and concentrating. The crude reaction mixture was purified by prep TLC (30% EtOAc in hexanes) to yield the title compound as a clear crystalline solid.
Yield: 53.0 mg (32%) The characterization of this compound has previously been reported.[3]

tert-butyl 2-acetyl-5-(trifluoromethyl)-1H-pyrrole-1-carboxylate (8a)



Following the general procedure, using 4-phenylpyridine *N*-oxide (273.9 mg, 1.6 mmol, 2.0 equiv.) and TFAA (237 µl, 1.68 mmol, 2.1 equiv.), the reaction was run for 5 hours. ^{19}F NMR analysis of the crude reaction mixture vs. the injected trifluorotoluene standard revealed the title compound in **70% yield**. The reaction was partitioned with 1N HCl and diluted with dichloromethane. The organic phase was separated, washed with sat. $NaHCO_3$, brine, and dried over sodium sulfate before filtering and concentrating. The crude reaction mixture was purified on silica gel with 50% dichloromethane in hexanes to yield the title compound as a clear oil (R_f = 0.3, 70% dichloromethane in hexanes).
Yield: 157.2 mg (71%); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.80 (d, J = 3.6 Hz, 1H), 6.61 (d, J = 3.6 Hz, 1H), 2.48 (s, 3H), 1.61 (s, 9H); ^{19}F NMR (470 MHz, $CDCl_3$) δ = -59.82; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 187.8, 147.8, 135.1 (q, JC-F = 1.8 Hz), 126.5 (q, JC-F = 40.1 Hz), 119.9 (q, JC-F = 268.6 Hz), 116.1, 112.2 (q, JC-F = 3.4 Hz), 86.8, 27.0, 26.7; HRMS (ESI+) m/z: $[M - Boc + H]^+$ calculated 177.0401, found 177.0404. IR (neat): v = 2988, 1775, 1679, 1550, 1372, 1248, 1125;

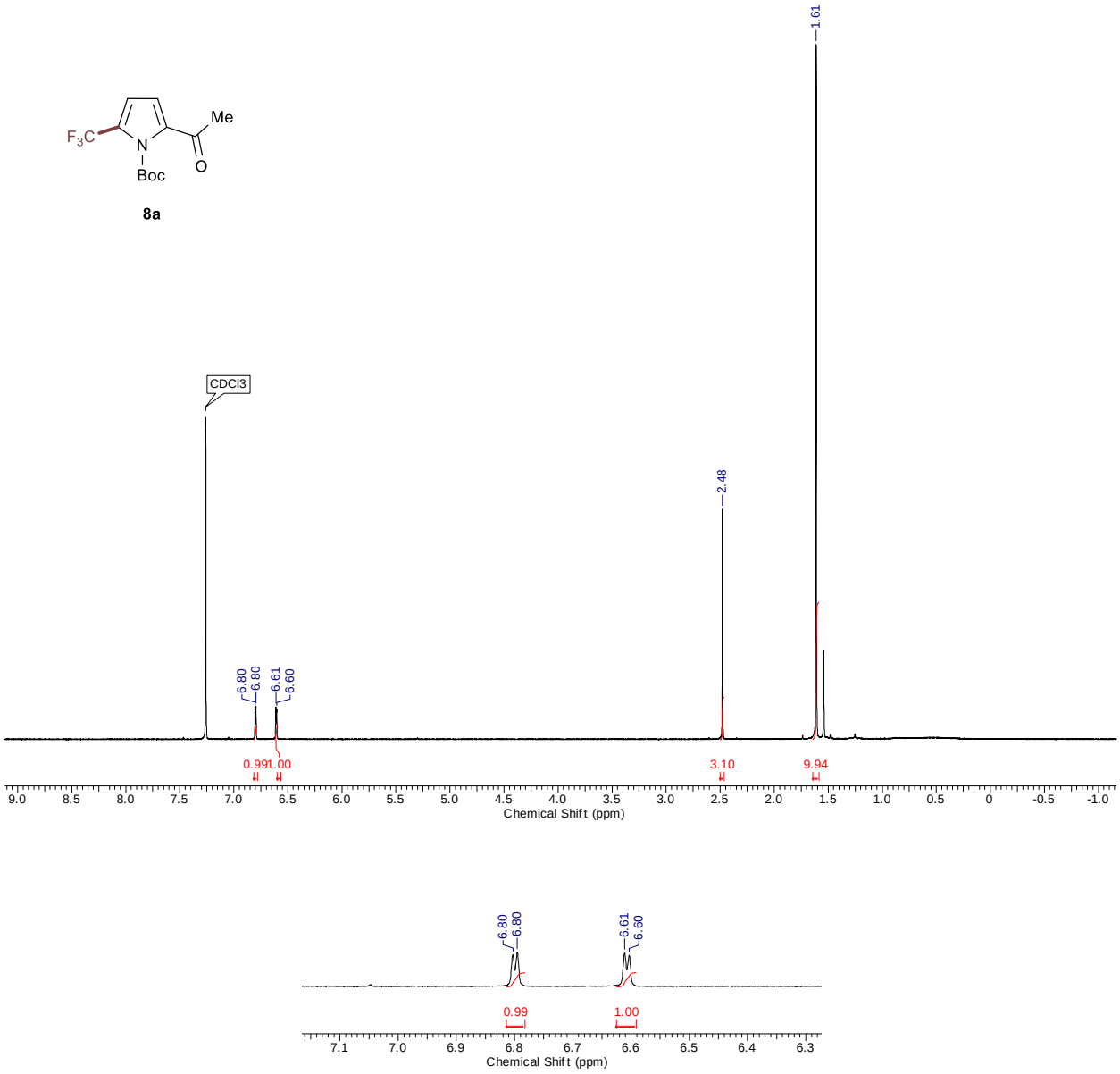


Figure S6 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **8a**.

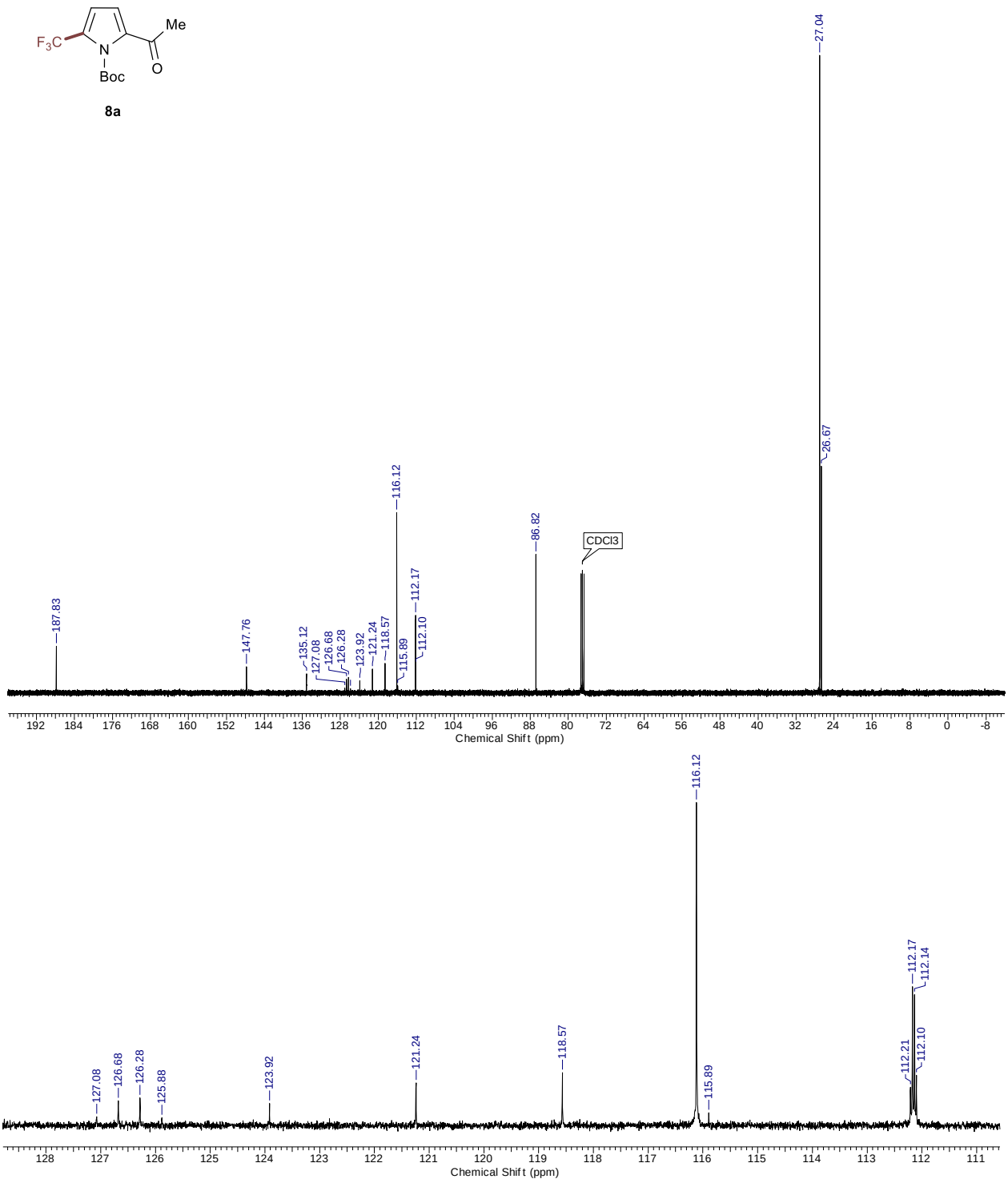
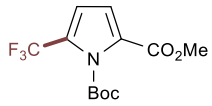


Figure S7. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **8a**.

1-(tert-butyl) 2-methyl 5-(trifluoromethyl)-1H-pyrrole-1,2-dicarboxylate (9a)



Following the general procedure, using 4-phenylpyridine *N*-oxide (273.9 mg, 1.6 mmol, 2.0 equiv.) and TFAA (237 µl, 1.68 mmol, 2.1 equiv.), the reaction was run for 3 hours. ^{19}F NMR analysis of the crude reaction mixture vs. the injected trifluorotoluene standard revealed the title compound in 63% yield. The reaction was partitioned with 1N HCl and diluted with dichloromethane. The organic phase was separated, washed with sat. $NaHCO_3$, brine, and dried over sodium sulfate before filtering and concentrating. The crude reaction mixture was purified on silica gel with 10%–30% dichloromethane in hexanes to yield the title compound as a clear oil (R_f = 0.14, 40% dichloromethane in hexanes).
Yield: 140.1 mg (60%); ^{1}H NMR (700 MHz, $CDCl_3$) δ = 6.80 (d, J = 3.8 Hz, 1H), 6.61 (d, J = 3.8 Hz, 1H), 3.87 (s, 3H), 1.61 (s, 9H); ^{19}F NMR (470 MHz, $CDCl_3$) δ = -59.66; ^{13}C NMR (175 MHz, $CDCl_3$) δ = 160.2, 147.2, 127.8, 125.6 (q, JC-F = 125.6 Hz), 119.9 (q, JC-F = 267 Hz), 116.1, 112.8 (q, JC-F = 3.6 Hz), 86.9, 52.1, 27.1; HRMS (EI+) m/z: $[M - Boc + H]^+$ calculated 193.0351, found 193.0351. IR (neat): v = 2989, 1777, 1728, 1558, 1373, 1247, 1123.

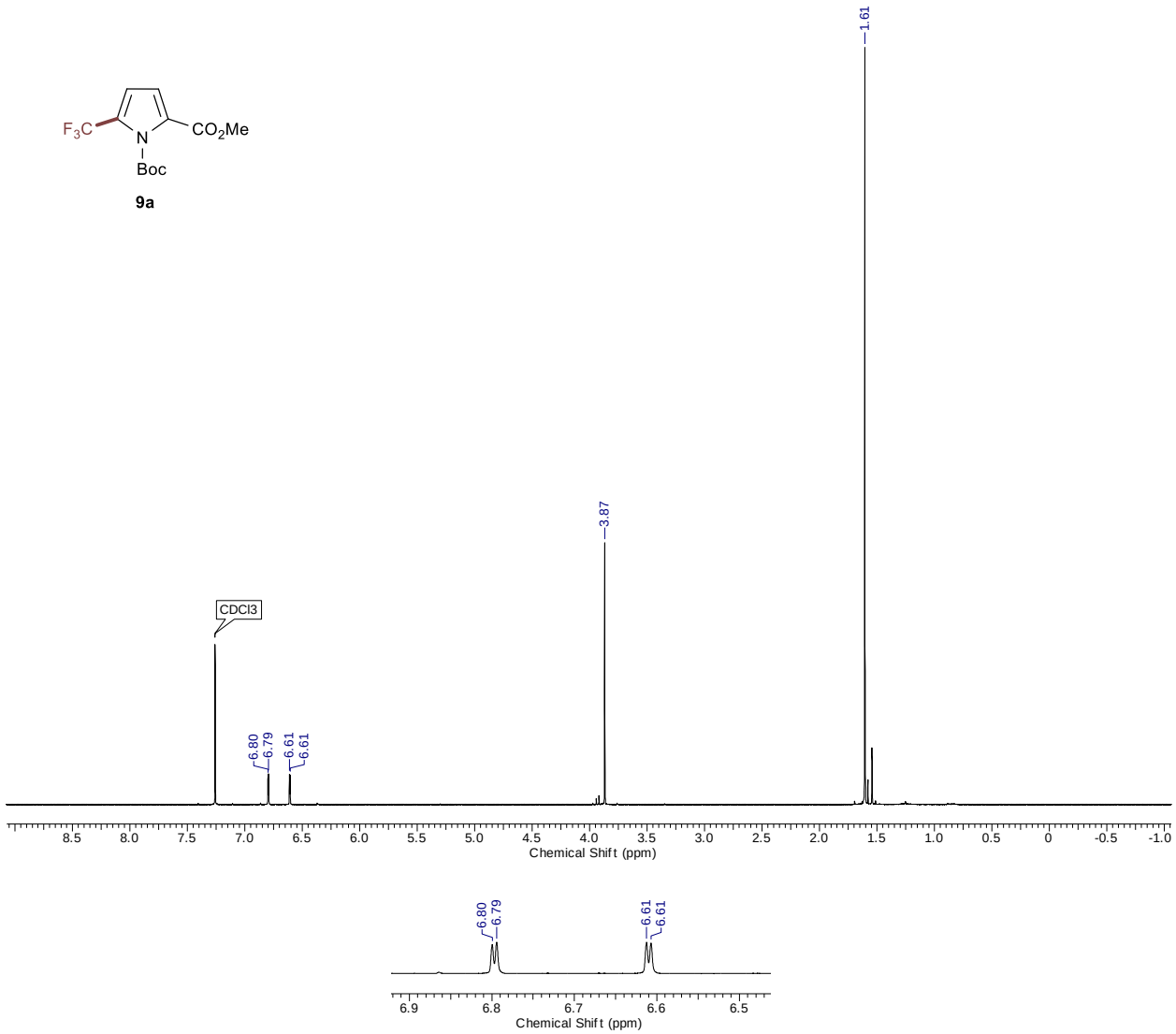


Figure S8. ^{1}H NMR spectrum (700 MHz, $CDCl_3$) of **9a**.

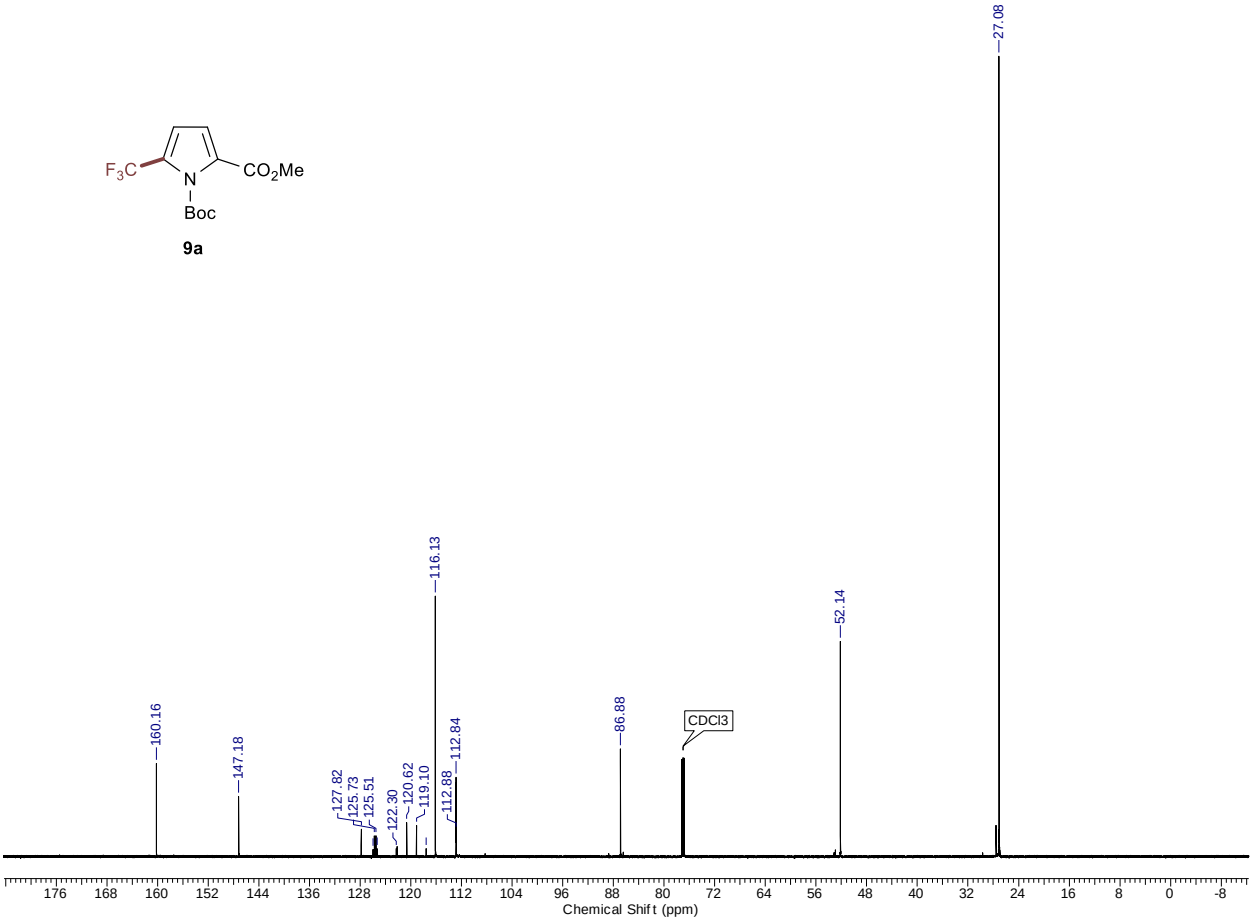
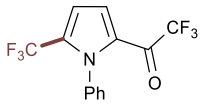


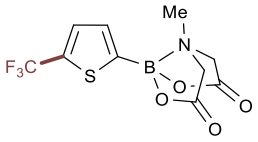
Figure S9. ^{13}C NMR spectrum (175 MHz, $CDCl_3$) of **9a.**

2,2,2-trifluoro-1-(1-phenyl-5-(trifluoromethyl)-1H-pyrrol-2-yl)ethan-1-one (10a)



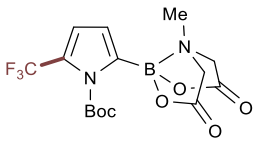
Following the general procedure, using 4-phenylpyridine *N*-oxide (273.9 mg, 1.6 mmol, 2.0 equiv.) and TFAA (237 µl, 1.68 mmol, 2.1 equiv.), the reaction was run for 7 hours. ^{19}F NMR analysis of the crude reaction mixture vs. the injected trifluorotoluene standard revealed the title compound in **59% yield** with 22% remaining starting material. The use of more equivalents of reagent did not result in higher yields of product, but further consumed the starting material. The reaction was partitioned with 1N HCl and diluted with dichloromethane. The organic phase was separated, washed with sat. $NaHCO_3$, brine, and dried over sodium sulfate before filtering and concentrating. The crude reaction mixture was purified by prep TLC (10% ethyl acetate in hexanes) to yield the title compound as a clear oil (R_f = 0.53, 25% dichloromethane in hexanes).
Yield: 143.0 mg (53%). The isolation and characterization of this compound has previously been reported.[3]

(5-(trifluoromethyl)thiophen-2-yl)boronic acid MIDA ester (11a)



Following the general procedure, using 4-phenylpyridine *N*-oxide (547.8 mg, 3.2 mmol, 4.0 equiv.) and TFAA (463 µl, 3.28 mmol, 4.1 equiv.) with 4 ml total of dry MeCN (0.2M) the reaction was run for 12 hours. ^{19}F NMR analysis of the crude reaction mixture vs. the injected trifluorotoluene standard revealed the title compound in 73% yield. The use of fewer equivalents of reagent at shorter reaction times provided comparable yields of product, but incompletely consumed the starting material, which was inseparable from the product. The reaction was partitioned with 1N HCl and diluted with dichloromethane. The organic phase was separated, washed with brine, and dried over sodium sulfate before filtering and concentrating. The crude reaction mixture was purified on silica gel. Pyridine derivatives were flushed off the column with ~750 ml of 2% methanol in diethyl ether[6] before the product was eluted with 10% MeCN in CH_2Cl_2 as an amorphous, off-white solid (R_f = 0.44, 100% THF).
Yield: 179.7 mg (73%). The isolation and characterization of this compound has previously been reported.[3]

(1-(tert-butoxycarbonyl)-5-(trifluoromethyl)-1H-pyrrol-2-yl)boronic acid MIDA ester (12a)



Following the general procedure, using 4-phenylpyridine *N*-oxide (410.9 mg, 2.4 mmol, 3.0 equiv.) and TFAA (350 µl, 2.48 mmol, 3.1 equiv.) with 4 ml total of dry MeCN (0.2M) the reaction was run for 12 hours. It should be noted that for this substrate the reaction mixture gets very dark upon exposure to light, which limits conversion at higher concentrations (0.4M). ^{19}F NMR analysis of the crude reaction mixture vs. the injected trifluorotoluene standard revealed the title compound in 75% yield. The reaction was filtered through silica gel with 50% MeCN in CH_2Cl_2 and concentrated. The crude reaction mixture was purified on silica gel. Pyridine derivatives were flushed off the column with ~750 ml of 2% methanol in diethyl ether before the product was eluted with 10% MeCN in CH_2Cl_2 as an off-white solid (R_f = 0.43, 25% MeCN in CH_2Cl_2). This material was further purified by preparative TLC (25% MeCN in CH_2Cl_2) to yield the title compound as a white solid.
Yield: 190.6 mg (62%); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.72 (d, J = 3.6 Hz, 1H), 6.68 (d, J = 3.6 Hz, 1H), 4.18 (d, J = 16.8 Hz, 2H), 3.95 (d, J = 16.8 Hz, 2H), 3.00 (s, 3H), 1.57 (s, 9H); ^{19}F NMR (470 MHz, $CDCl_3$) δ = –58.01; ^{13}C NMR (175 MHz, $CDCl_3$) δ = 169.7, 150.8, 125.5 (q, JC-F = 38.8 Hz), 121.9 (q, JC-F = 265.7 Hz), 121.7, 117.4 (q, JC-F = 4.1 Hz), 87.8, 65.9, 50.5, 27.6; HRMS (EI+) m/z: $[M - Boc + H]^+$ calculated 290.0686, found 290.0687; IR (neat): v = 2999, 1741, 1564, 1454, 1334, 1220, 1126, 1032.

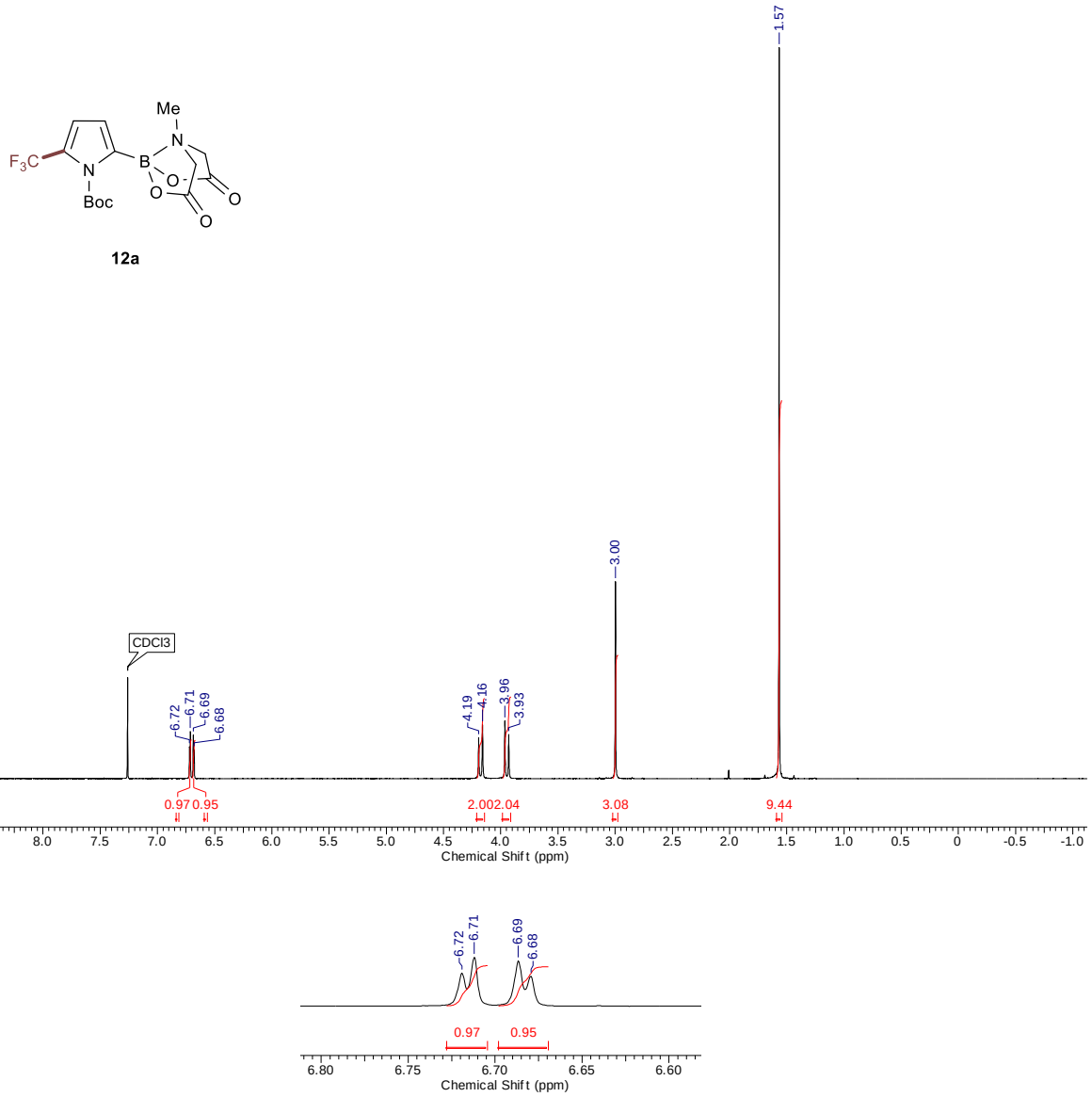


Figure S10. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **12a**.

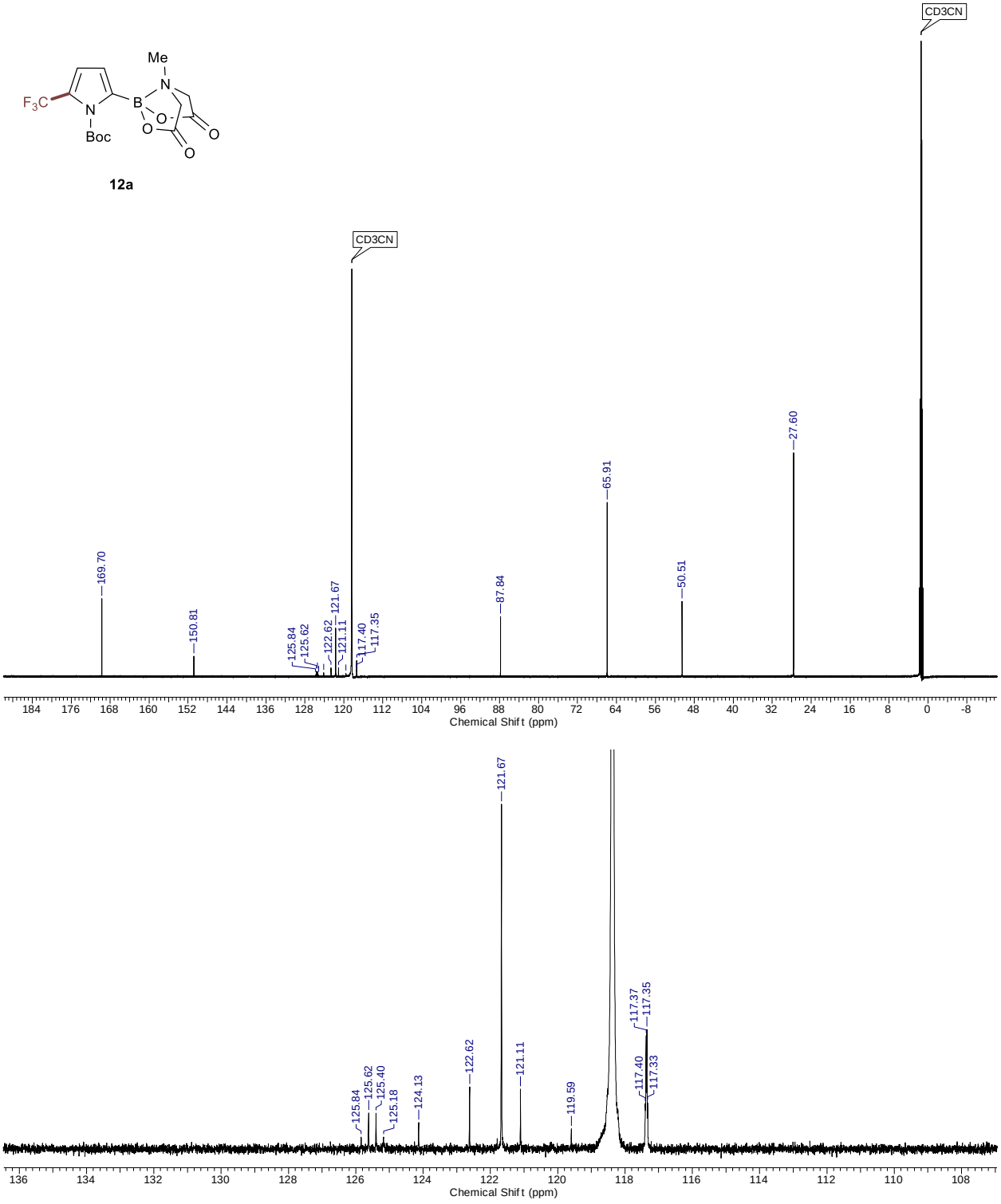
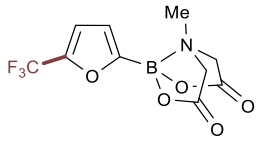


Figure S11. ^{13}C NMR spectrum (175 MHz, CD_3CN) of **12a**.

(5-(trifluoromethyl)furan-2-yl)boronic acid MIDA ester (13a)



Following the general procedure, using 4-phenylpyridine *N*-oxide (273.9 mg, 1.6 mmol, 2.0 equiv.) and TFAA (237 µl, 1.68 mmol, 2.1 equiv.), the reaction was run for 6 hours. ^{19}F NMR analysis of the crude reaction mixture vs. the injected trifluorotoluene standard revealed the title compound in 60% yield. The reaction was filtered through silica gel with 50% MeCN in CH_2Cl_2 and concentrated. The crude reaction mixture was purified on silica gel. Pyridine derivatives were flushed off the column with ~750 ml of 2% methanol in diethyl ether[6] before the product was eluted with 10% MeCN in CH_2Cl_2 as an amorphous, off-white solid (R_f = 0.46, 20% MeCN/CH_2Cl_2).
Yield: 137.8 mg (59%); ^{1}HNMR (700 MHz, MeCN-*d3*) δ = 6.99 (d, J = 3.2 Hz, 1H), 6.85 (d, J = 3.2 Hz, 1H), 4.12 (d, J = 17.3 Hz, 2H), 3.96 (d, J = 17.3 Hz, 2H), 2.70 (s, 3H); ^{19}F NMR (470 MHz, $CDCl_3$) δ = -64.95; ^{13}C NMR (175 MHz, MeCN-*d3*) δ = 169.3, 145.4 (q, JC-F = 41.8 Hz), 120.9 (q, JC-F = 267.7 Hz), 120.5, 113.8 (q, JC-F = 2.7 Hz), 63.1, 48.6; HRMS (ESI+) m/z: $[M + NH_4]^+$ calculated 309.0864, found 309.0866; IR (neat): v = 2953, 1757, 1605, 1462, 1309, 1279, 1218, 1173, 1125, 1102, 1050, 1009, 936.

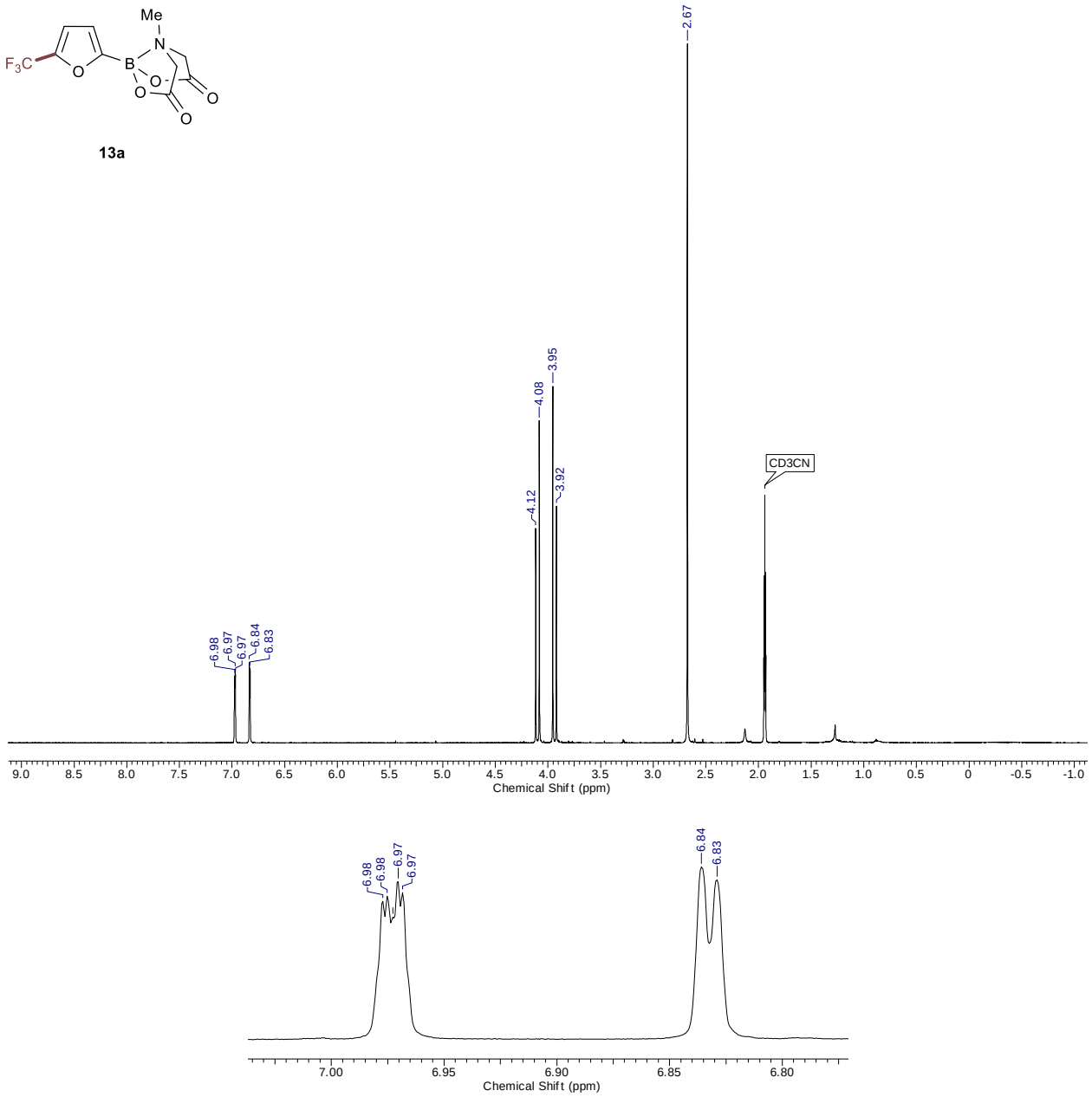


Figure S12. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **13a**.

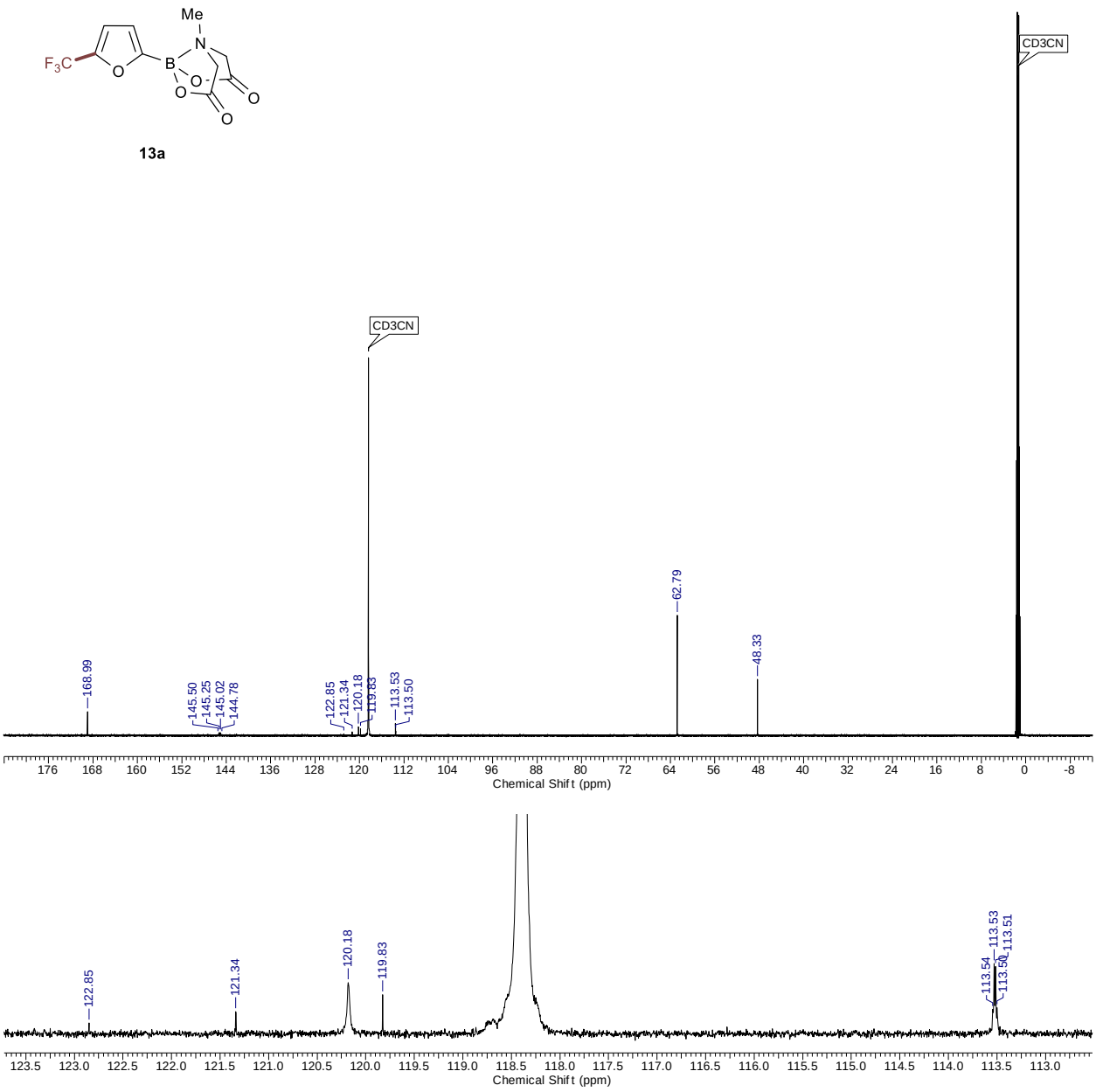
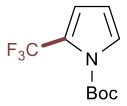


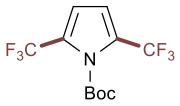
Figure S13. ^{13}C NMR spectrum (175 MHz, CD_3CN) **13a**.

tert-butyl 2-(trifluoromethyl)-1H-pyrrole-1-carboxylate (14a)



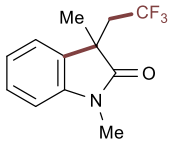
Following the general procedure using 4-phenylpyridine *N*-oxide (137.0 mg, 0.8 mmol, 1.0 equiv.) and TFAA (124 µl, 0.88 mmol, 1.1 equiv.), the reaction was run for 15 hours. ^{19}F NMR analysis of the crude reaction mixture vs. the injected trifluorotoluene standard revealed the volatile title compound tert-butyl 2-(trifluoromethyl)-1H-pyrrole-1-carboxylate [^{19}F NMR (470 MHz, $CDCl_3$) δ = -59.29 (s, 3F, 56% yield)] and tert-butyl 2,5-bis(trifluoromethyl)-1H-pyrrole-1-carboxylate [^{19}F NMR (470 MHz, $CDCl_3$) δ = -59.36 (s, 6F, 9% yield)] in a 6:1ratio.
Yield: 0.520 mmol (65%, 6:1 14a:14b); ^{19}F NMR (470 MHz, $CDCl_3$) δ = -59.29 (s, 3F, 14a 56% yield), -59.36 (s, 6F, 14b 9%). The isolation and characterization of this compound has been previously reported.[3]

tert-butyl 2,5-bis(trifluoromethyl)-1H-pyrrole-1-carboxylate (15a)



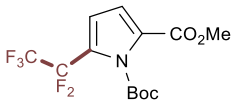
Following the general procedure using 4-phenylpyridine *N*-oxide (410.9 mg, 2.4 mmol, 3.0 equiv.) and TFAA (350 µl, 2.48 mmol, 3.1 equiv.), the reaction was run for 15 hours. ^{19}F NMR analysis of the crude reaction mixture vs. the injected trifluorotoluene standard revealed the volatile title compound tert-butyl 2-(trifluoromethyl)-1H-pyrrole-1-carboxylate [^{19}F NMR (470 MHz, $CDCl_3$) δ = -59.29 (s, 3F, 7% yield)] and tert-butyl 2,5-bis(trifluoromethyl)-1H-pyrrole-1-carboxylate [^{19}F NMR (470 MHz, $CDCl_3$) δ = -59.36 (s, 6F, 56% yield)] in a 8:1ratio.
Yield: 0.504 mmol (63%, 1:8 14a:14b); ^{19}F NMR (470 MHz, $CDCl_3$) δ = -59.29 (s, 3F, 14a 7% yield), -59.36 (s, 6F, 14b 56%). The isolation and characterization of this compound has been previously reported.[3]

1,3-dimethyl-3-(2,2,2-trifluoroethyl)indolin-2-one (16a)



Following the general procedure using 4-phenylpyridine *N*-oxide (273.9 mg, 1.6 mmol, 2.0 equiv.) and TFAA (451 µl, 3.2 mmol, 4.0 equiv.), the reaction was run for 12 hours. ^{19}F NMR analysis of the reaction mixture cannot be accurately accomplished due to peak overlap of theproduct with a minor impurity. The reaction was partitioned with 1N HCl and diluted with ethyl acetate. The organic phase was separated, washed with sat. $NaHCO_3$, brine, and dried over sodium sulfate before filtering and concentrating. The crude reaction mixture was purified by column chromatography (0% to 50% ethyl acetate in hexanes) to yield the title compound.
Yield: 89.5 mg (46%). The isolation and characterization of this compound has been previously reported.[3]

1-(tert-butyl) 2-methyl 5-(perfluoroethyl)-1H-pyrrole-1,2-dicarboxylate (18)



Following the general procedure, using 4-phenylpyridine *N*-oxide (137.0 mg, 0.8 mmol, 1.0 equiv.) and pentafluoropropionic anhydride (174 µl, 0.88 mmol, 1.1 equiv.), the reaction was run for 6 hours. ^{19}F NMR analysis of the crude reaction mixture vs. the injected trifluorotoluene standard revealed the title compound in 80% yield. The reaction was partitioned with 1N HCl and diluted with dichloromethane. The organic phase was separated, washed with sat. $NaHCO_3$, brine, and dried over sodium sulfate before filtering and concentrating. The crude reaction mixture was purified by column chromatography (30% dichloromethane in hexanes) to yield the title compound as a clear oil (R_f = 0.1, 25% dichloromethane in hexanes).

Yield: 198.9 mg (72%); ^{1}H NMR (700 MHz, $CDCl_3$) δ = 6.87 (d, J = 3.8 Hz, 1H), 6.58 (d, J = 3.8 Hz, 1H), 3.87 (s, 3H), 1.61 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$) δ = -84.23 (3F), -107.82 (2F); ^{13}C NMR (175 MHz, $CDCl_3$) δ = 159.8, 147.7, 127.3, 123.1 (t, JC-F = 27.2 Hz), 118.5 (qt, JC-F = 287.1, 38.1 Hz), 116.1, 113.6 (app. tq, JC-F = 5.7, 1.9 Hz), 110.3 (tq, JC-F = 252.7, 40.1 Hz), 87.1, 52.1, 27.0; HRMS (EI+) m/z: $[M - Boc + H]^+$ calculated 243.0319, found 243.0314; IR (neat): v = 2991, 1782, 1726, 1546, 1373, 1250, 1207, 1133, 1096, 1034.

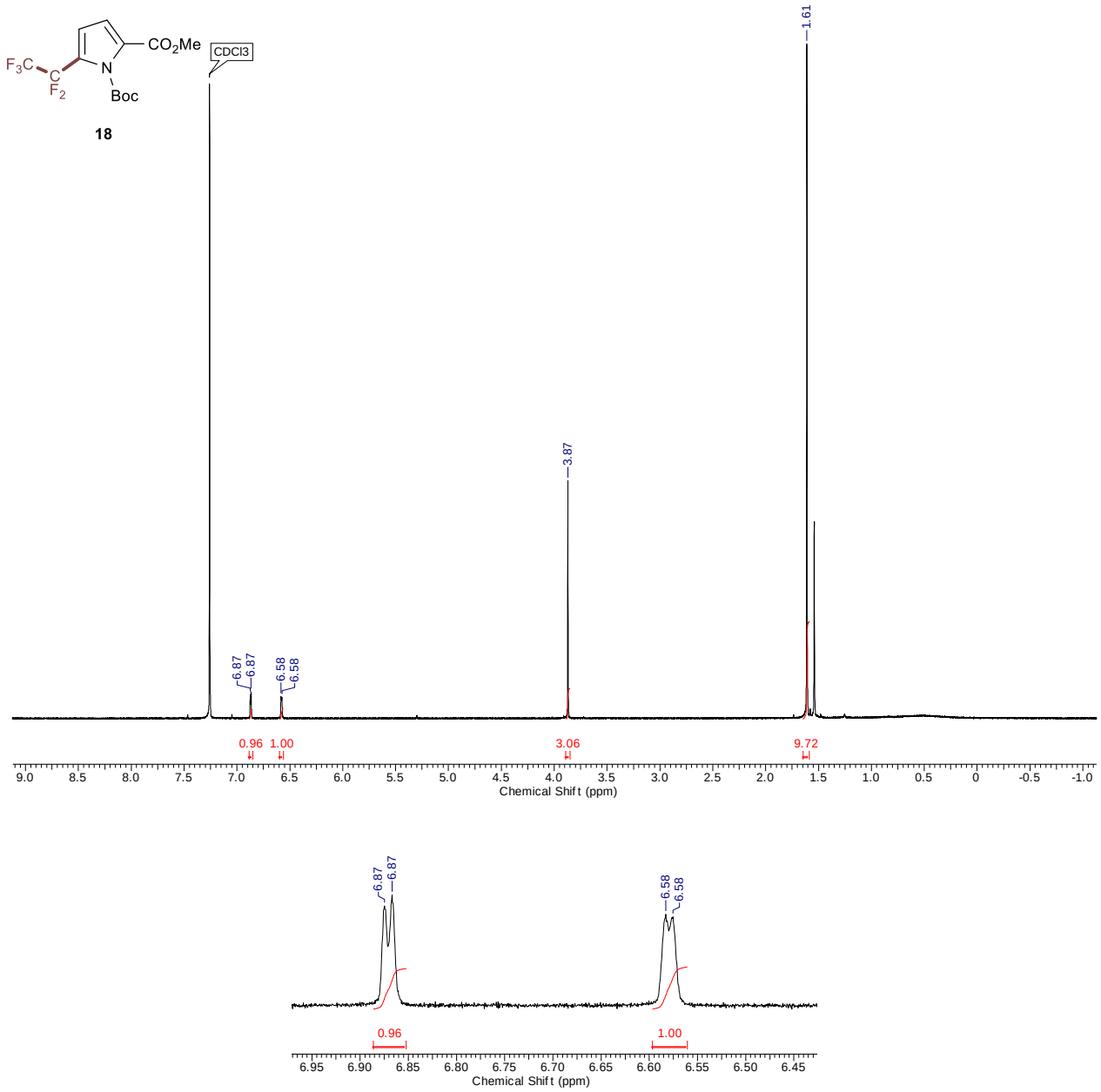


Figure S14. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **18**.

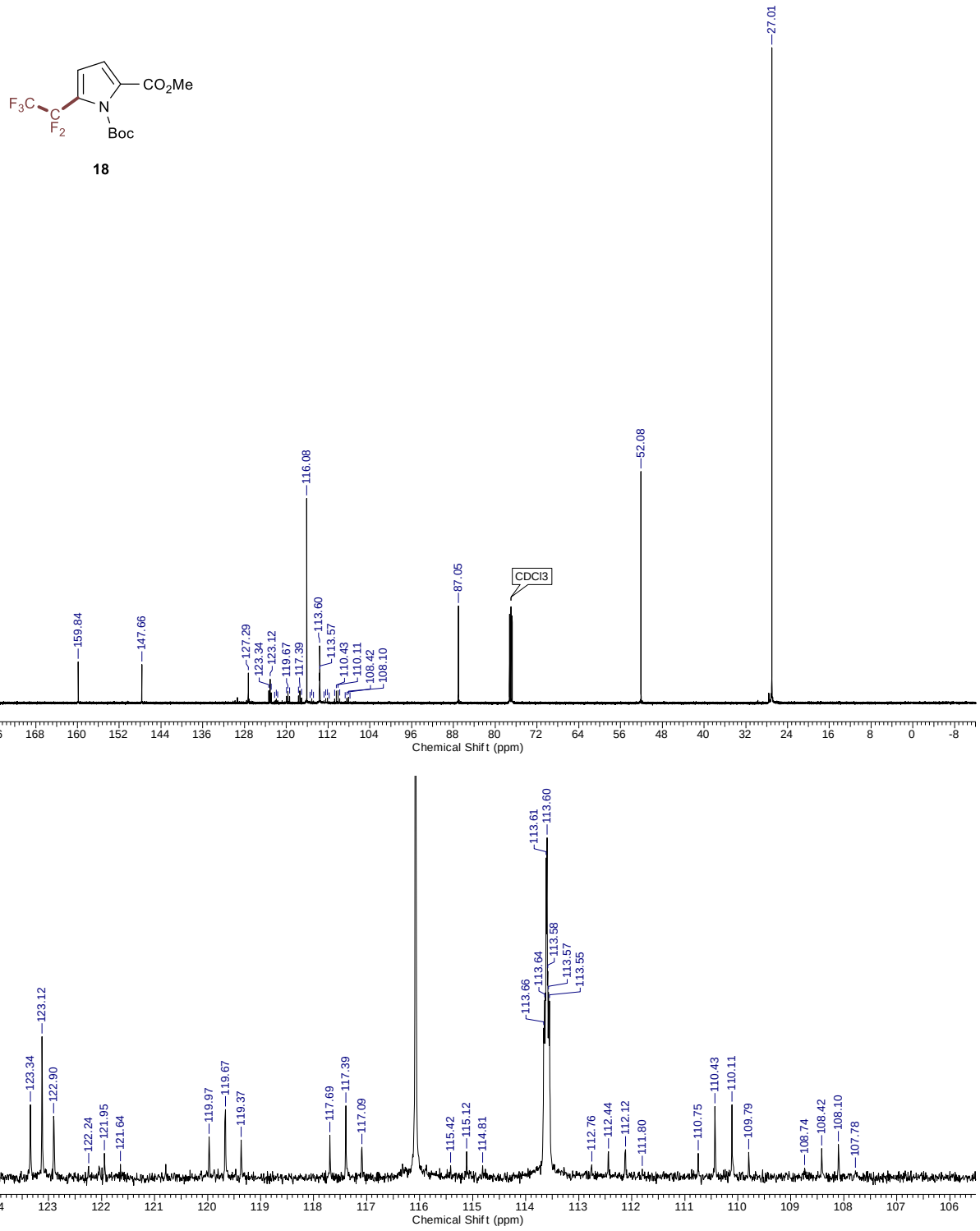
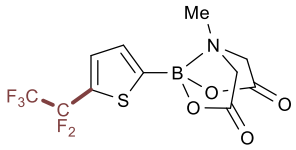


Figure S15. ^{13}C NMR spectrum (175 MHz, $CDCl_3$) of **18**.

(5-(perfluoroethyl)thiophen-2-yl)boronic acid MIDA ester (19)



Following the general procedure, using 4-phenylpyridine *N*-oxide (410.9 mg, 2.4 mmol, 3.0 equiv.) and pentafluoropropionic anhydride (517 µl, 2.48 mmol, 3.1 equiv.) with 4 ml total of dry MeCN (0.2M) the reaction was run for 12 hours. ^{19}F NMR analysis of the crude reaction mixture vs. the injected trifluorotoluene standard revealed the title compound in 95% yield. The reaction was partitioned with 1N HCl and diluted with dichloromethane. The organic phase was separated, washed with brine, and dried over sodium sulfate before filtering and concentrating. The crude reaction mixture was purified on silica gel. Pyridine derivatives were flushed off the column with ~750 ml of 2% methanol in diethyl ether[6] before the product was eluted with 10% MeCN in CH_2Cl_2 as an amorphous, off-white solid (R_f = 0.33, 20% MeCN in CH_2Cl_2).

Yield: 260.0 mg (91%); ^{1}H NMR (700 MHz, MeCN-*d3*) δ = 7.62 (d, J = 3.5 Hz, 1H), 7.36 (dt, J = 3.5 Hz, JH-F = 1.9 Hz, 1H), 4.12 (d, J = 17.2 Hz, 2H), 3.96 (d, J = 17.2 Hz, 2H), 2.65 (s, 3H); ^{19}F NMR (376 MHz, MeCN-*d3*) δ = -86.08 (br. s, 3F), -105.14 (s, 2F); ^{13}C NMR (175 MHz, MeCN-*d3*) δ = 168.9, 134.9, 133.0 (t, JC-F = 29.7 Hz), 132.9 (t, JC-F = 5.4 Hz), 119.9 (qt, JC-F = 285.4, 40.9 Hz), 113.7 (tq, JC-F = 251.4, 39.5 Hz), 62.8, 48.7; HRMS (ESI+) m/z: $[M + H]^+$ calculated 358.0338, found 358.0344, $[M + Na]^+$ calculated 380.0159, found 380.0159; IR (neat): ν = 3011, 1760, 1535, 1459, 1337, 1285, 1258, 1196, 1165, 1030, 980.

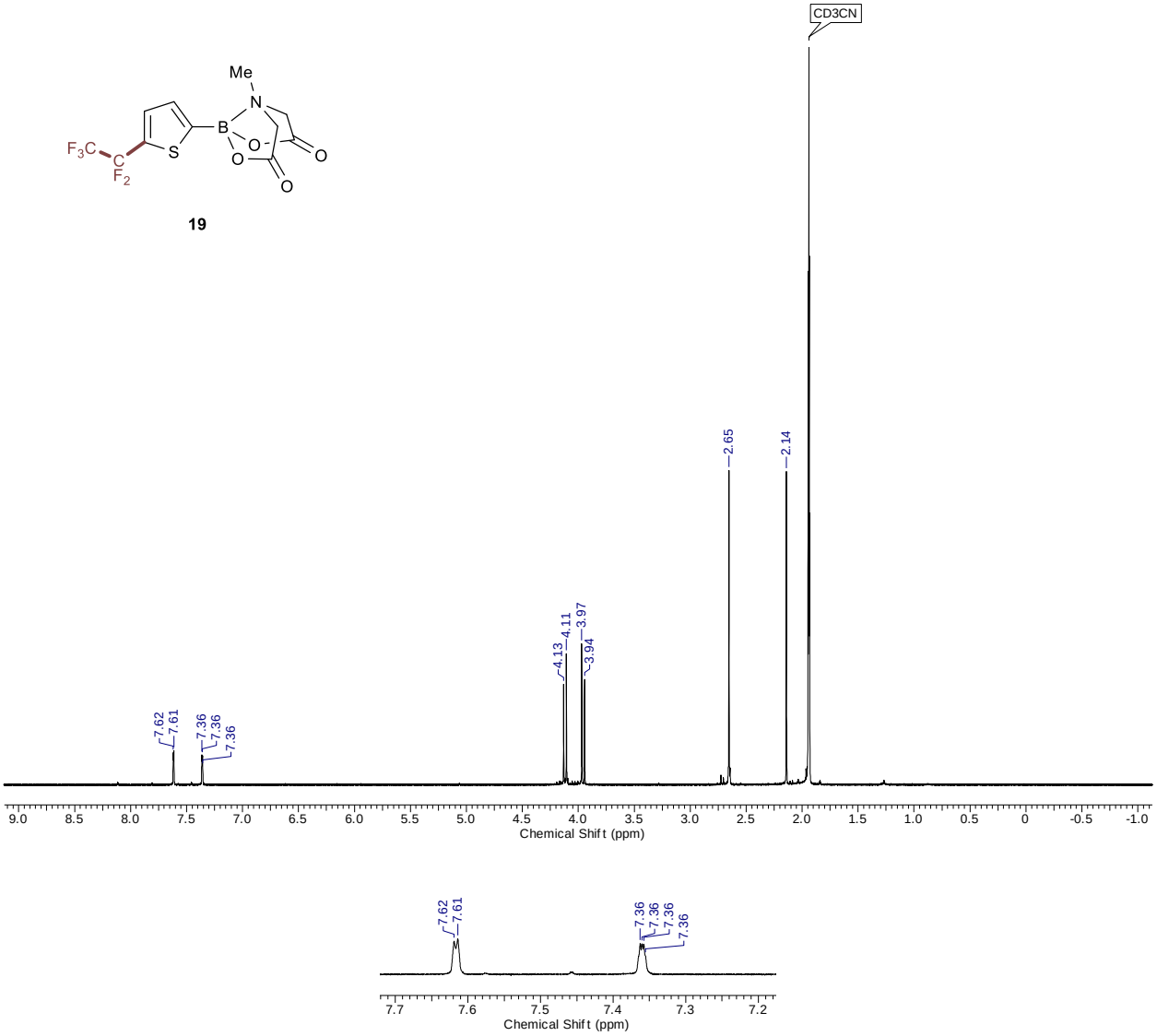


Figure S16. ^{1}H NMR spectrum (700 MHz, CD_3CN) of **19**.

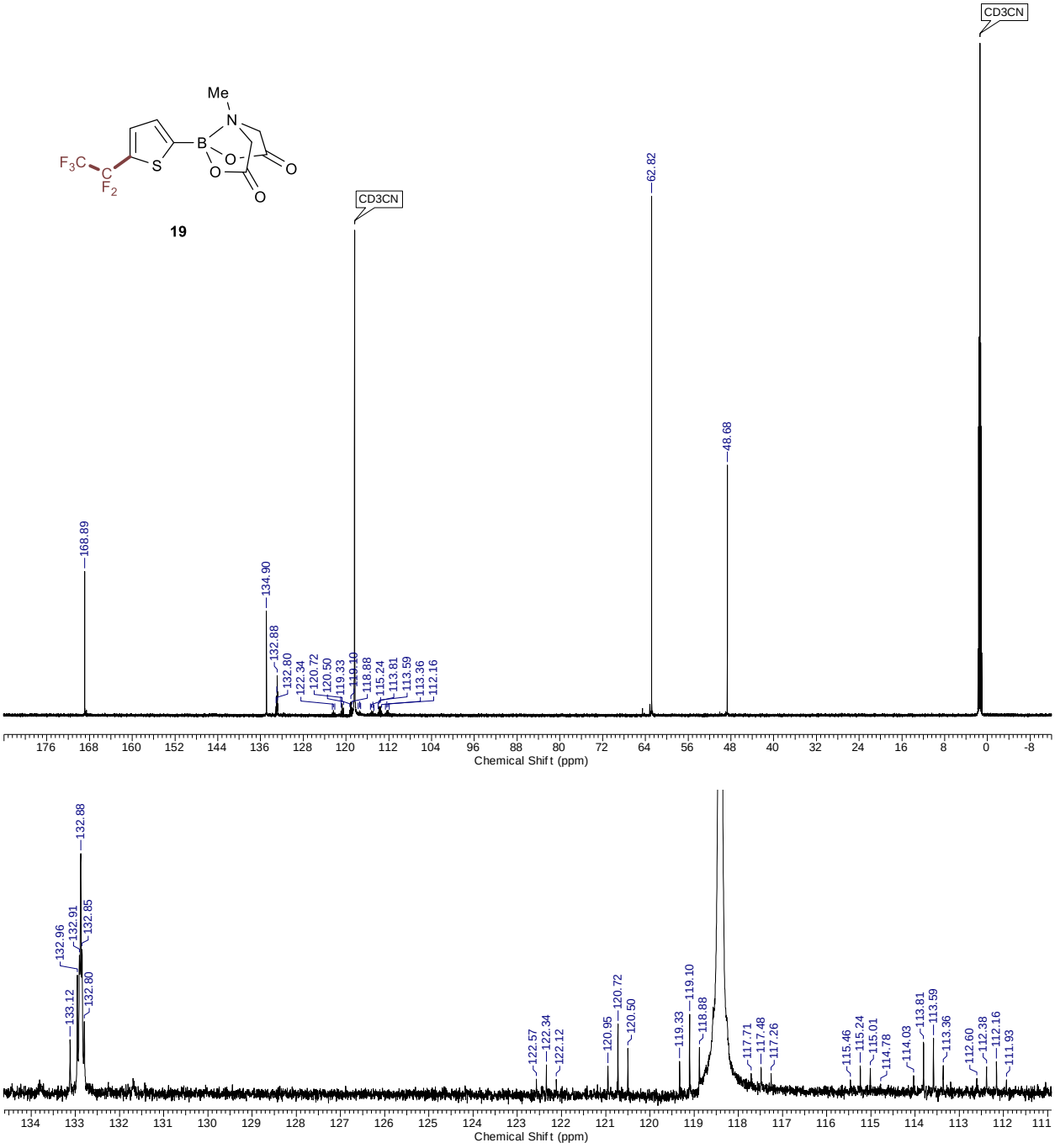
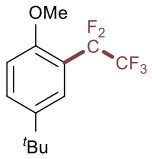


Figure S17. ^{13}C NMR spectrum (175 MHz, CD_3CN) of **19**.

4-(tert-butyl)-1-methoxy-2-(perfluoroethyl)benzene (20)



Following the general procedure, using 4-phenylpyridine *N*-oxide (410.9 mg, 2.4 mmol, 3.0 equiv.) and pentafluoropropionic anhydride (489 µl, 2.48 mmol, 3.1 equiv.), the reaction was run for 8 hours. ^{19}F NMR analysis of the crude reaction mixture vs. the injected trifluorotoluene standard revealed the title compound in 81% yield. The reaction was partitioned with 1N HCl and diluted with dichloromethane. The organic phase was separated, washed with sat. $NaHCO_3$, brine, and dried over sodium sulfate before filtering and concentrating. The crude reaction mixture was purified by prep TLC (100% hexanes run up x2) to yield the slightly volatile title compound as a clear oil (R_f = 0.57, 10% dichloromethane in hexanes). Yield: 0.648 mmol (81%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.53-7.49 (m, overlap, 2H), 6.95 (d, J = 8.4 Hz, 1H), 3.85 (s, 3H), 1.31 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$) δ = -84.89 (3F), -112.60 (2F); ^{13}C NMR (175 MHz, $CDCl_3$) δ = 156.0 (t, JC-F = 2.7 Hz), 143.2, 130.2, 125.6 (t, JC-F = 8.5 Hz), 119.5 (qt, JC-F = 287.5, 39.5 Hz), 115.9 (t, JC-F = 115.9 Hz), 113.9 (tq, JC-F = 254.8, 41.6 Hz), 112.2, 56.0, 34.2, 31.3; HRMS (EI+) m/z: $[M]^+$ 282.1043, found 282.1042; IR (neat): v = 2961, 1617, 1510, 1464, 1268, 1194, 1074, 1030, 991.

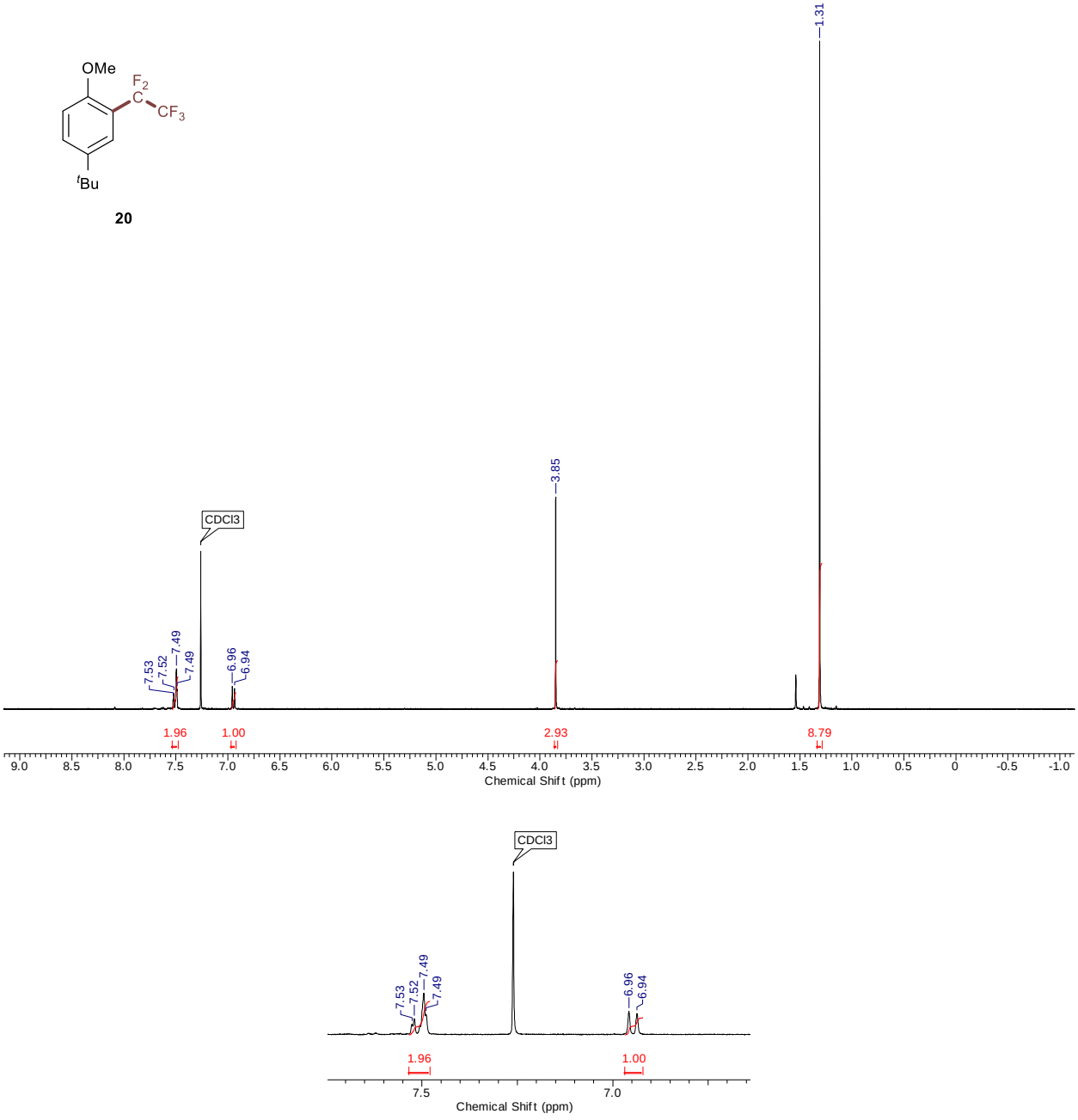
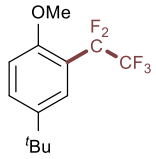


Figure S18. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **20**.



20

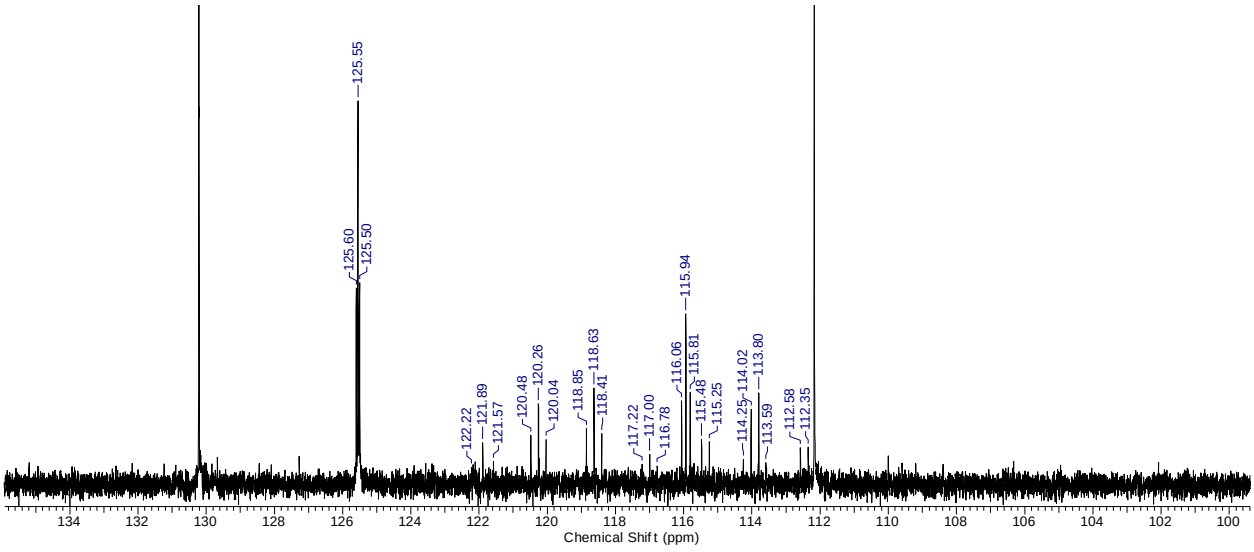
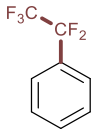


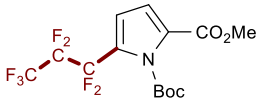
Figure S19. ^{13}C NMR spectrum (175 MHz, $CDCl_3$) of **20**.

(perfluoroethyl)benzene (21)



Following the general procedure, using 4-phenylpyridine *N*-oxide (137.0 mg, 0.8 mmol, 1.0 equiv.) as the limiting reagent, pentafluoropropionic anhydride (174 µl, 0.88 mmol, 1.1 equiv.), and benzene (713 µl, 8.0 mmol, 10.0 equiv.), the reaction was run for 12 hours. Upon completion, the reaction was quenched with methanol (500 µl) and removed from the light source. ^{19}F NMR analysis of the crude reaction mixture vs. the injected trifluorotoluene standard revealed the title compound in 76% yield. Due to the volatility of the product, no purification was attempted on this reaction mixture. The fluorine signals of the product were consistent to those reported in the literature: in one report,[7] values are listed vs. trifluorotoluene (referenced to δ 0.0) with positive values to high field, and are reproduced here with trifluorotoluene referenced to δ -63.72: ^{19}F NMR (no solvent reported, 60 MHz): δ -119.3 (m, 2F), -88.9 (t, J_{FF} = 1.7 Hz, 3F); Another report[8] reports the shifts in toluene-*d8* (δ -84, -113), while yet another[9] reports the shifts in benzene-*d6* (δ -84.86, -114.75).
Yield: 0.608 mmol (76%); ^{19}F NMR ($CDCl_3$, 470 MHz): δ -85.78 (s, 3F), -115.95 (s, 2F).

1-(tert-butyl) 2-methyl 5-(perfluoropropyl)-1H-pyrrole-1,2-dicarboxylate (24)



With heptafluorobutyric anhydride: Following the general procedure, using 4-phenylpyridine *N*-oxide (273.9 mg, 1.6 mmol, 2.0 equiv.) and heptafluorobutyric anhydride (412 µl, 1.68 mmol, 2.1 equiv.), the reaction was run for 4 hours. ^{19}FNMR analysis of the crude reaction mixture vs. the injected trifluorotoluene standard revealed the title compound in 78% yield. The reaction was partitioned with 1N HCl and diluted with dichloromethane. The organic phase was separated, washed with sat. $NaHCO_3$, brine, and dried over sodium sulfate before filtering and concentrating. The crude reaction mixture was purified by column chromatography (10-30% dichloromethane in hexanes) to yield the title compound as a clear oil (R_f = 0.31, 50% CH_2Cl_2 in hexanes).
Yield: 225.9 mg (72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.89 (dt, J = 4.0, 1.2 Hz, 1H), 6.59 (d, J = 4.0 Hz, 1H), 3.87 (s, 3H), 1.60 (s, 9H); ^{19}F NMR (376 Hz, $CDCl_3$) δ = -81.01 (t, J_{FF} = 9.5 Hz, 3F), -105.91 (ap. sxt, tq, J_{FF} = 9.5, 8.9 Hz, 2F), -125.84 (t, J_{FF} = 8.9 Hz, 2F); ^{13}C NMR (175 MHz, $CDCl_3$) δ = 159.9, 147.7, 127.2, 123.1 (t, JC-F = 29.3 Hz), 117.9 (qt, JC-F = 287.5, 34.7), 116.1, 114.1 (t, JC-F = 5.4 Hz), 112.5 (tt, JC-F = 254.8, 32.7 Hz). 108.4 (ttq, JC-F = 265.0, 38.1, 38.1 Hz), 87.1, 52.1, 27.0 Hz; HRMS (EI+) m/z: $[M - Boc + H]^+$ calculated 293.0287, found 293.0291; IR (neat): v = 2984, 1784, 1727, 1546, 1437, 1373, 1248, 1202, 1154, 111, 1088, 838, 741.

With heptafluorobutyryl chloride: Following the general procedure, using 4-phenylpyridine *N*-oxide (273.9 mg, 1.6 mmol, 2.0 equiv.) and heptafluorobutyryl chloride (251 µl, 1.68 mmol, 2.1 equiv.), the reaction was run for 4 hours. ^{19}FNMR analysis of the crude reaction mixture vs. the injected trifluorotoluene standard revealed the title compound in 67% yield. The reaction was partitioned with 1N HCl and diluted with dichloromethane. The organic phase was separated, washed with sat. $NaHCO_3$, brine, and dried over sodium sulfate before filtering and concentrating. The crude reaction mixture was purified by column chromatography (10-30% dichloromethane in hexanes) to yield the title compound as a clear oil.
Yield: 193.2 mg (61%); Full characterization is above.

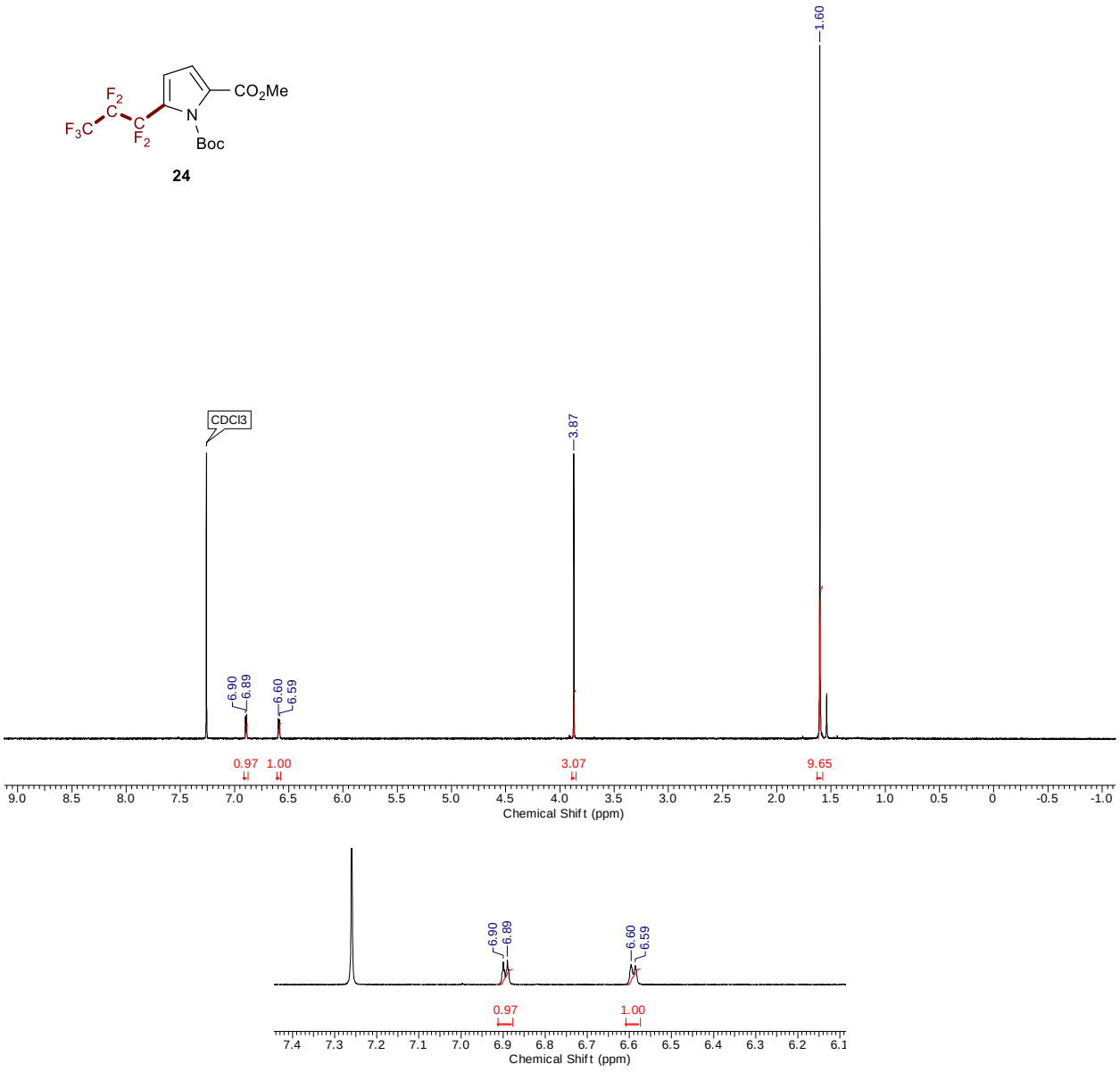


Figure S20. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **24**.

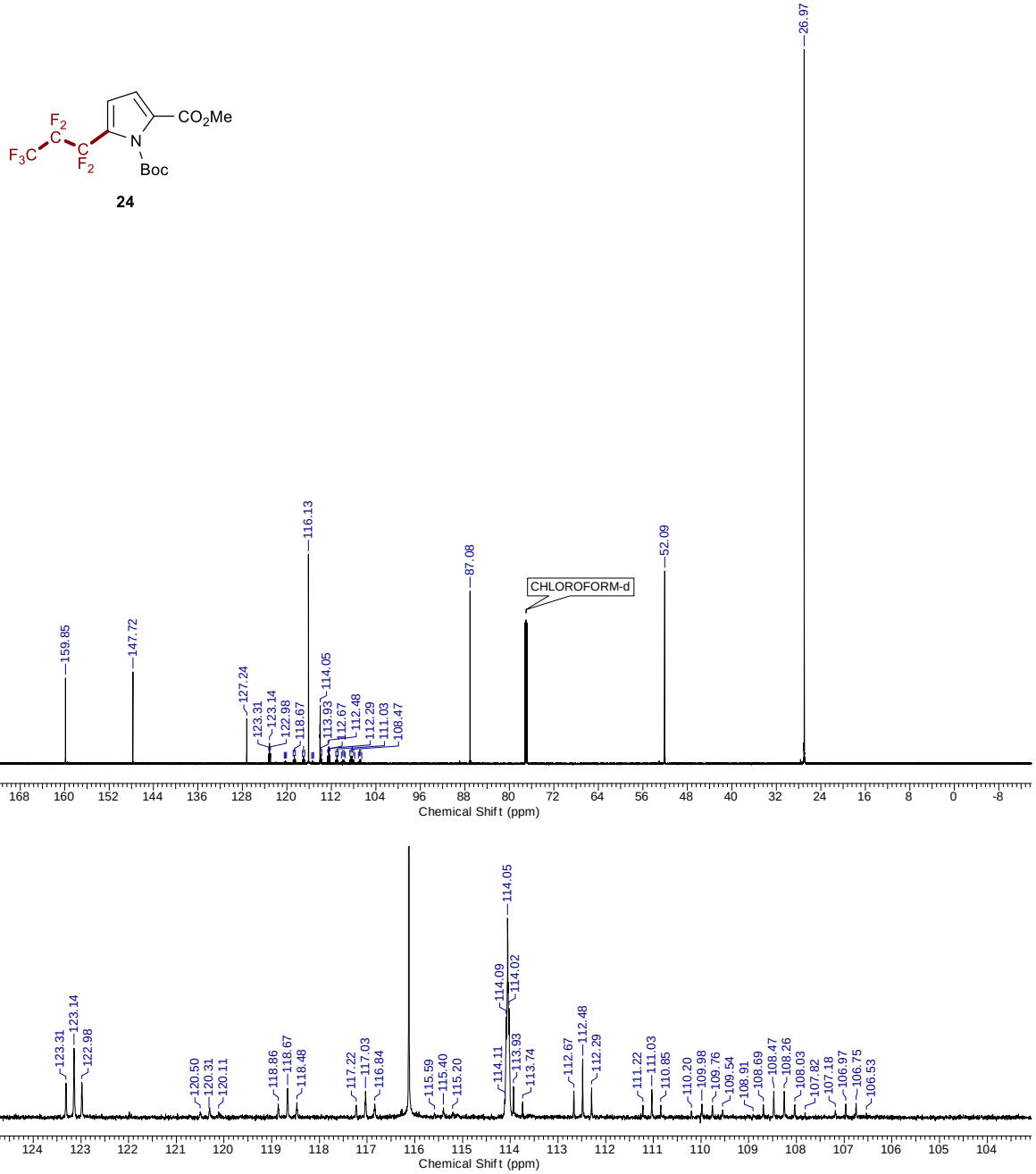
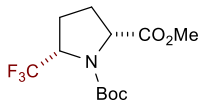


Figure S21. ^{13}C NMR spectrum (175 MHz, $CDCl_3$) of **24**.

***cis*-1-(tert-butyl) 2-methyl 5-(trifluoromethyl)pyrrolidine-1,2-dicarboxylate (17)**



To a 10mL RBF equipped with a stir bar was added palladium on activated carbon (17 mg, 10 wt %, 0.016 mmol, 0.10 equiv). The flask was evacuated and backfilled with N_2 three times. Methanol (3 mL) was then added to the flask followed by pyrrole **9a** (46 mg, 0.16 mmol, 1 equiv). The heterogeneous mixture was stirred for 10 min under a H_2 atmosphere (gas balloon), filtered over silica, and concentrated under reduced pressure to give pure pyrrolidine **17** as white solid (R_f = 0.15, 10% ethyl acetate in hexanes). The solid could be re-crystallized in a minimum (1 mL) 1:1 pentane/Et_2O mixture to give colorless crystals.

Yield: 45.2 mg (97%); ^{1}H NMR (400 MHz, DMSO at 60 °C) δ = 4.61 (p, J = 8.2 Hz, 1H), 4.44 (t, J = 8.7 Hz, 1H), 3.78 (s, 3H), 2.45 (dd, J = 11.4, 8.2 Hz, 1H), 2.32 (dt, J = 12.5, 8.4 Hz, 1H), 2.13 (dd, J = 7.6, 5.6 Hz, 1H), 2.08 (m, 1H), 1.51 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$) δ = -74.73 (3F); ^{13}C NMR (175 MHz, $CDCl_3$) δ = 172.0, 153.8, 125.3 (q, JC-F = 283.9 Hz), 81.4, 60.4 (d, JC-F = 96.0), 58.4 (m), 52.0, 28.3 (d, JC-F = 109.2), 27.9, 25.8 (d, JC-F = 111.6); HRMS (EI+) m/z: $[M - Boc + H]^+$ calculated 198.0736, found 198.0737; IR (neat): v = 2978, 1760, 1708, 1438, 1364, 1284, 1156, 1118, 1053.

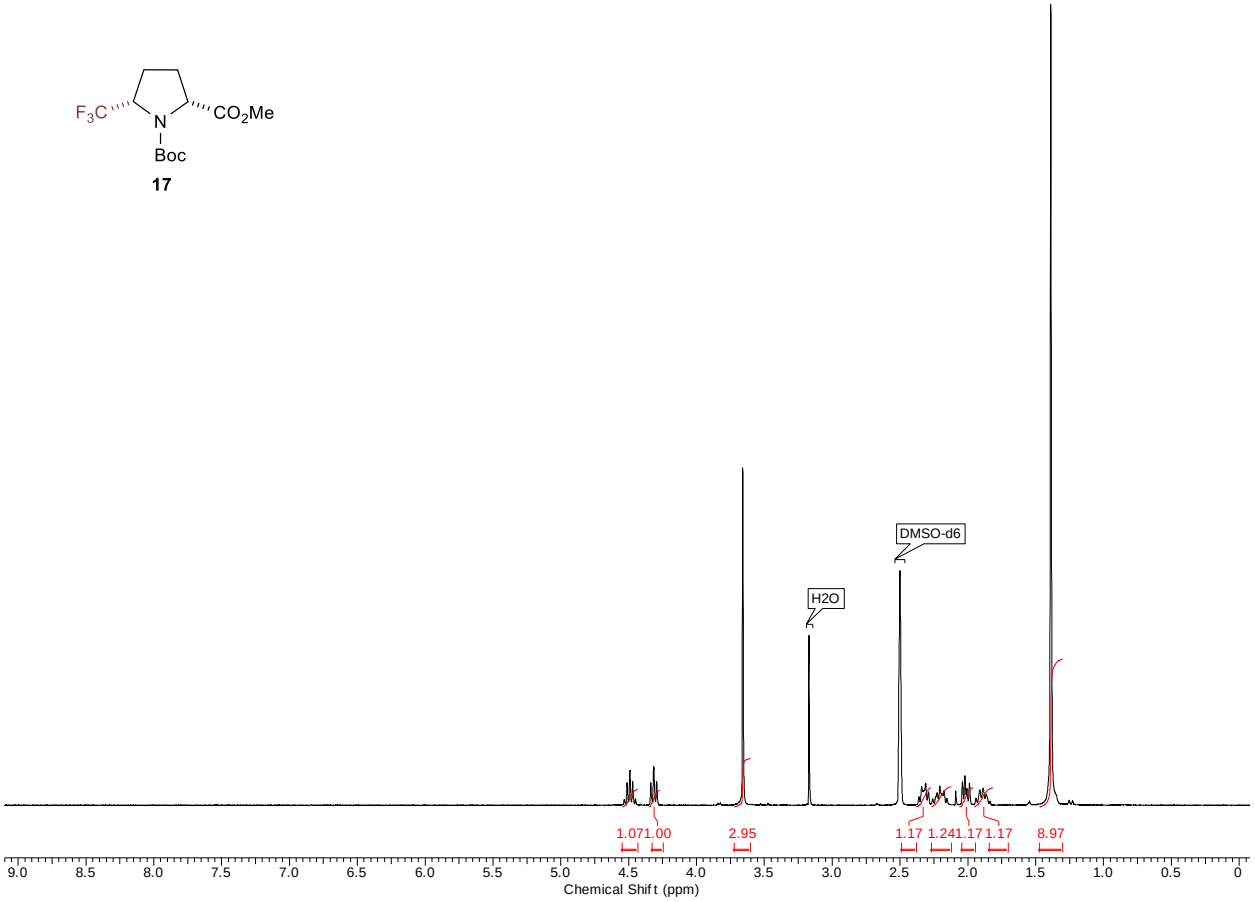


Figure S22. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **17**.

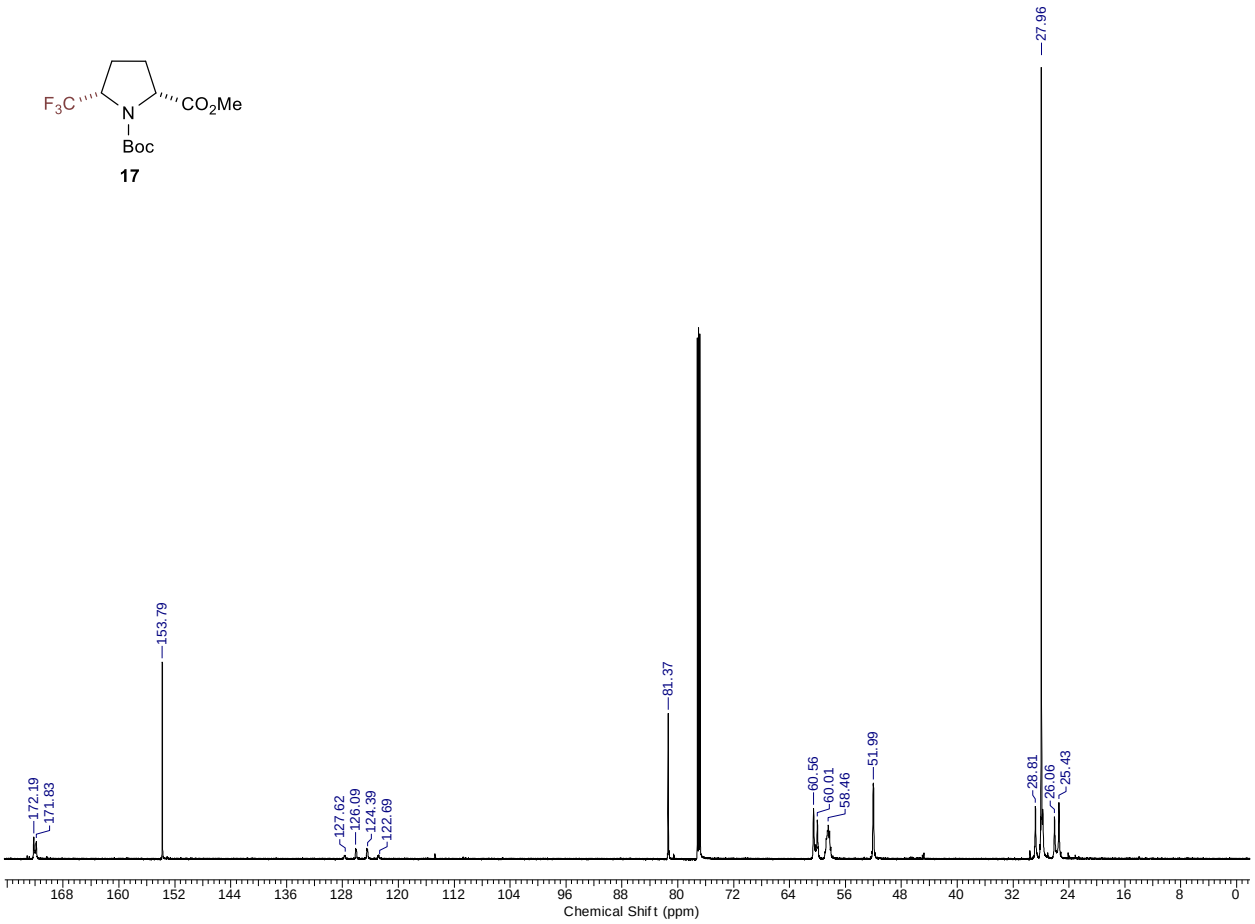


Figure S23. ^{13}C NMR spectrum (175 MHz, $CDCl_3$) of **17**.

Crystallographic data for *cis*-1-(tert-butyl) 2-methyl 5-(trifluoromethyl)pyrrolidine-1,2-dicarboxylate (17)

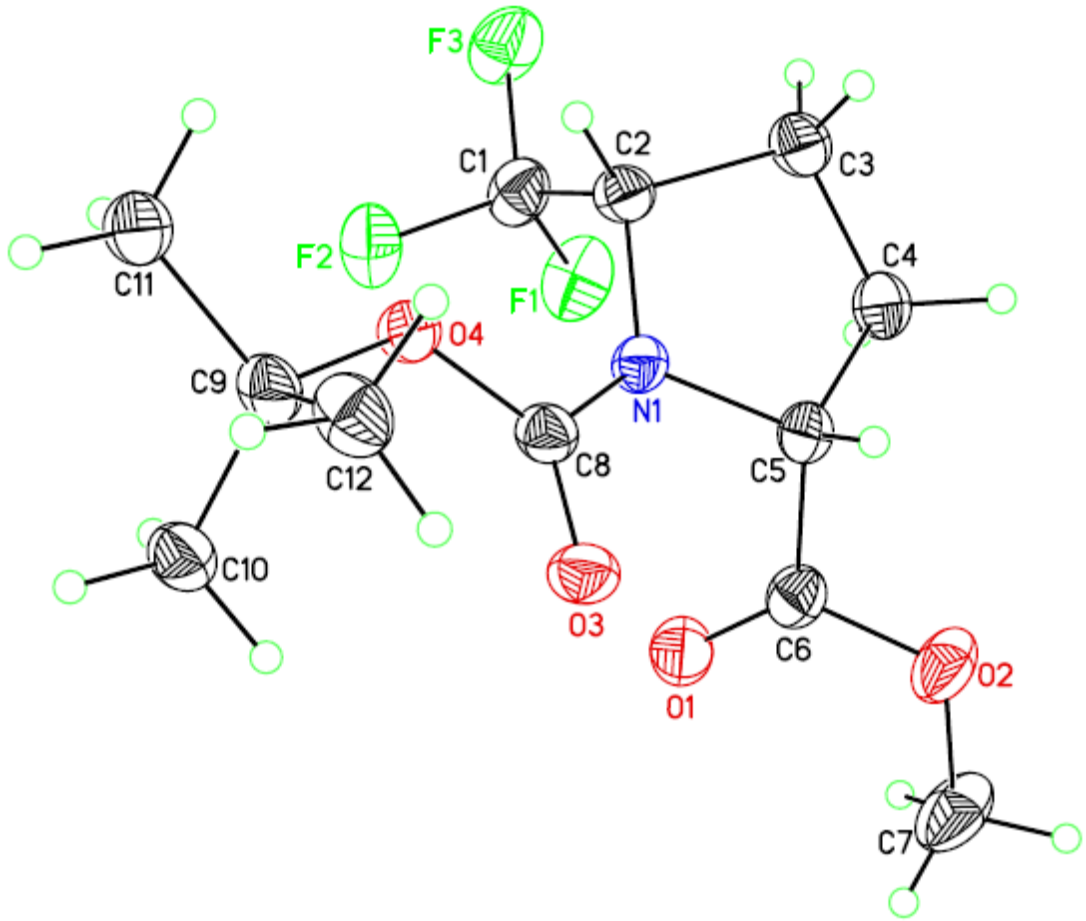


Figure S24. Structural figure of compound **17**, with 50% probability ellipsoids.

Structure Determination

Colorless plates of **17** were grown from a diethyl ether/pentane solution of the compound at 22 deg. C. A crystal of dimensions 0.10 x 0.07 x 0.02 mm was mounted on a Rigaku AFC10K Saturn 944+ CCD-based X-ray diffractometer equipped with a low temperature device and Micromax-007HF Cu-target micro-focus rotating anode (λ = 1.54187 A) operated at 1.2 kW power (40 kV, 30 mA). The X-ray intensities were measured at 85(1) K with the detector placed at a distance 42.00 mm from the crystal. A total of 2028 images were collected with an oscillation width of 1.0˚ in ω. The exposure times were 1 sec. for the low angle images, 8 sec. for high angle. Rigaku d*trek images were exported to CrysAlisPro for processing and corrected for absorption. The integration of the data yielded a total of 21112 reflections to a maximum 2θ value of 139.34˚ of which 2668 were independent and 2483 were greater than 2σ(I). The final cell constants (Table 1) were based on the xyz centroids 10158 reflections above 10σ(I). Analysis of the data showed negligible decay during data collection. The structure was solved and refined with the Bruker SHELXTL (version 2014/6) software package, using the space group P2(1)/c with Z = 4 for the formula $C_{12}H_{18}NO_4F_3$. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in idealized positions. Full matrix least-squares refinement based on F^2 converged at R1 = 0.0395

and wR2 = 0.1035 [based on I > 2σ(I)], R1 = 0.0420 and wR2 = 0.1070 for all data. Acknowledgement is made for funding from NSF grant CHE-0840456 for X-ray instrumentation.

Sheldrick, G.M. SHELXTL, v. 2014/6; Bruker Analytical X-ray, Madison, WI, 2014.

CrystalClear Expert 2.0 r16, Rigaku Americas and Rigaku Corporation (2014), Rigaku Americas, 9009, TX, USA 77381-5209, Rigaku Tokyo, 196-8666, Japan.

CrysAlisPro 1.171.38.41 (Rigaku Oxford Diffraction, 2015).

Background EDA Reaction Controls:

For each substrate type, control reactions without catalyst were performed to determine the degree of contribution of the EDA mechanism to the overall transformation. These were specifically designed to probe substrate-specific effects, and consequently a ratio of 2:1 TFAA:4-Ph-pyridine *N*-oxide was employed for these reactions, despite the fact that optimized conditions in the manuscript utilize a 1.1:1 ratio. This is to eliminate the contribution of the putative complexation between acylated and non-acylated *N*-oxide, which also results in productive chemistry. The reactions below were performed on 0.2 mmol scale (0.4 M in MeCN, 0.5 ml MeCN), with 2 equivalents of 4-Ph-PNO and 4 equivalents of TFAA.

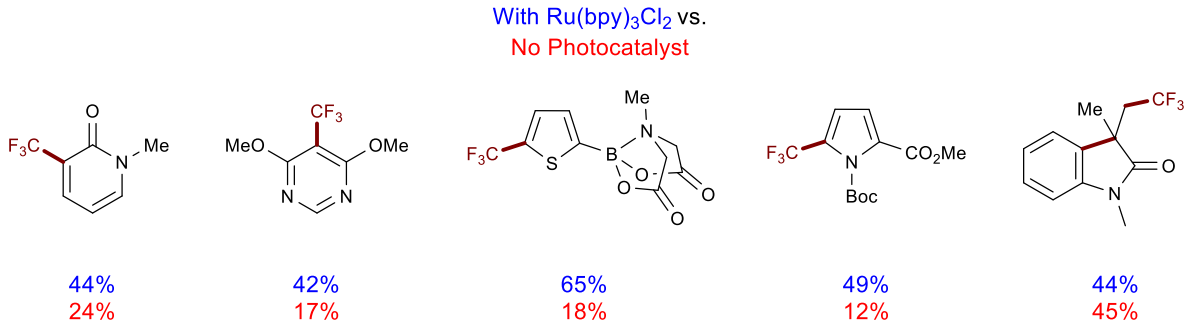


Figure S25. Control reactions with and without photocatalyst.

Flow reactor design

Reactor: The main reactor is 250 ft of 1/8" O.D 0.0625" I.D PFA (theoretical volume 150.8 mL) tubing *(Sain-Gobain vendor catalog # TSFE14-0125-031/250FT Catalog number NC0942238 purchased from Cole Palmer)* wrapped around a glass beaker (12" O.D 18" high). The ends are fixed with transparent duct tape and the total height of the coiled tubing is 11 " orientated 3.5 " from the bottom and 3.5" from the top (Figure S1A).
Inside the Pyrex beaker is a clamp stand with 3 AquaDock Blue MegaWatt LED lights *(http://aquadocklights.com/buy/)* facing downwards inserted onto the clamp stand pole. There are spacing weights between the lights to match the height of the lights to that of the tubing and to counter the buoyancy of the lights. They are further fixed together with cable ties (Figure S1B). The AquaDock lights are designed to be operated fully submerged in water and should not be illuminated unless so.

Reactor housing:
The glass beaker is placed inside a stainless steel housing tube with a 16" O.D and a 20" height (Figure S1C). The housing is constructed from regular stainless steel and has only a moderate level of

reflectiveness. Preliminary unreported results indicate that the use of a steel housing with increased reflectance may lead to higher photon flux within the reactor and allow shorter residence times. There is a coil of 10 ft, ¼" O.D stainless steel tubing in the bottom of the reactor housing around the pyrex beaker that is connected to glycol cooling fluid outlet −7 °C, metered via a peristaltic pump. Both the internal pyrex reactor and cavity between the reactor and stainless steel housing is filled with deionized water above the height of the pyrex reactor. A nitrogen feed line is placed into the bottom of the cavity between the pyrex glass reactor and the stainless steel housing to provide fluid turbulence. There was no appreciable temperature difference between the top and bottom of the water once the water had reached a constant temperature (after approximately 3 h). Cooling was required to maintain a water temperature of 45 °C ± 3 °C as the lights were calculated to contribute 0.84 kW/h of heat. A stainless steel lid 20" in diameter with a 2" diameter hole is placed on the top of the reactor housing. Through the hole is placed the reactor tubing inlet and outlet, the power cables for the lights, the cooling fluid and return hose, the nitrogen feed line, and a temperature probe to monitor the water temperature inside the pyrex reactor (Figure S1D). The stainless steel reactor housing is placed within a secondary container (purchased from home depot Model # FG863292GRAY) placed upon a moving dolly (purchased from home depot Model # FG264020BLA)

Feed streams:

The reaction components are separated into two feed streams A and B. Feeds were prepared in batches containing 300 g of pyrrole **9** due to the limitation in volume of the 2.0 L feed bottles.

Both feed streams are pumped from individual pressure bottles fitted with stainless Swagelok fittings comprising a pressure gauge and a check valve, a nitrogen inlet and an outflow. The feed bottles are placed on balances. The outflow is connected to a Masterflex® peristaltic pump (Item# HV-07522-20) fitted with an easy load head (Item# HV-77200-60) with a L/S 16 Gore Sta-Pure tube (Cole-Palmer Part # 96212-16). Two ft of 1/8" PFA tubing connects the outlet of the pump to a stainless steel Swagelok T piece uniting the two individual feed streams. The outlet of the T piece is connected to 1" of 3/8" PFA tubing that acts as a mixing zone for the two feeds. This 3/8" PFA tubing ids connected to the inlet of the reactor by 12 ft of 1/8" PFA tubing. The inlet for the liquid flow begins at the bottom of the reactor and flows upwards around the pyrex beaker to the outlet (Fig S1D details of reactor from top down view). The outlet of the reactor is connected via a stainless steel Swagelok union to 2 feet of 1/8" PFA tubing that terminates at a stainless steel Swagelok T piece. One entry to the T piece contains a thermocouple heat probe connected to monitor the outlet temperature of the reaction solution. The outlet of the T piece is connected via 2 feet of 1/8" PFA tubing to a Equilibar® diaphragm back pressure regulator (BPR) (Serial number EB1U1F1-HC276) set to 20 psi. Significant off gassing is observed downstream of the BPR (Fig S1D details of reactor from top down view). At the outlet of the BPR is placed a Swagelok 3-way valve to allow sampling of the reaction solution. 3 ft of 1/8" PFA tubing connects one outlet of the 3-way valve to a 4L collection bottle (headspace swept with nitrogen) placed on a balance. A schematic of the setup is depicted in Figure S2.

Large scale reaction:

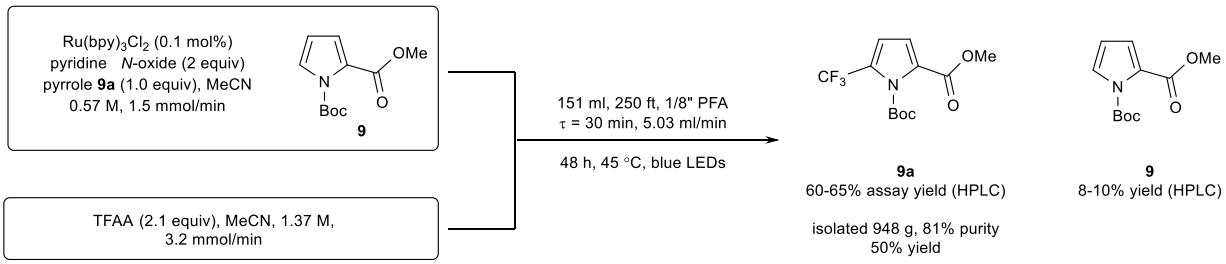


Figure S26. Kilogram scale trifluoromethylation in flow.

Synthesis of methyl-1-boc-pyrrole-2-carboxylate (9):
To a 3 Neck 3L RBF with an overhead stirrer, temp probe and a pressure equalized dropping funnel with a nitrogen inlet was added; methyl 1H-pyrrole-2-carboxylate (100 g, 1.00 equiv, 775 mmol), 4-dimethylaminopyridine (4.83 g, 0.05 equiv, 39.5 mmol), ethyl acetate (775 mL), and triethylamine (120 mL, 1.11 equiv, 861 mmol, 87.1 g) and the homogenous solution was stirred as the temperature decreased to about 13 °C upon dissolution. A solution of di-tert-butyl-dicarbonate (186 g, 1.10 equiv, 853 mmol) in ethyl acetate (775 mL) was added over 1.25 h with a temperature rise to 20 °C. The homogenous solution was stirred for 1 h before the addition of 1 N HCl (400 mL) and further stirring for 5 minutes. The biphasic solution was transferred to a 4 L separatory funnel, the lower layer removed and the remaining orangic layer washed with 1 N HCl (400 mL) followed by sat NaCl (400 mL). The organic solution was concentrated under reduced pressure to give methyl-1-boc-pyrrole-2-carboxylate **9** as a colorless oil with data consistent with that reported in the literature.[10]
Yield: 176 g, (98%, 98% purity by NMR)

Feed preparation:
Feed stream A: To a solution of $Ru(bpy)_3Cl_2.6H_20$ (0.98 g, 1.31 mmol, 0.001 equiv) dissolved in deoxygenated MeCN (2000 mL) (*note: a small quantity of black solid remained insoluble in the MeCN*), was added methyl-1-boc-pyrrole-2-carboxylate **9** (300 g, 1.31 mol, 1.0 equiv). Pyridine-*N*-oxide (248 g, 2.61 mol, 2.0 equiv) was dissolved separately in in deoxygenated MeCN (200 mL) (note: there is a significant endotherm upon pyridine-*N*-oxide dissolution, a water bath was used to hasten full dissolution). The pyridine–*N*-oxide solution was added to the solution of $Ru(bpy)_3Cl_2$ and pyrrole **9**, and the combined solution sparged with nitrogen with 2 minutes.
Total volume 2300 mL, density 0.855 g/ml, 0.568 M wrt to pyrrole X. Pump set to 2.67 mL/min providing 1.53 mmol/min.

Feed stream B: Trifluoroactic anhydride (576 g, 2.74 mol, 2.1 equiv) was dissolved in deoxygenated MeCN (1640 mL) (*note: it takes significant agitation to reach a homogenous solution)* and the combined solution was sparged with nitrogen for 2 minutes.
Total volume 2000 mL, density 0.917 g/ml, 1.37 M wrt to trifluoroacetic anhydride. Pump set to 2.34 mL/min providing 3.21 mmol/min.

Reaction and isolation

2 L of feed stream A was transferred to a 2 L pressure bottle and used with feed stream B (prepared directly in a 2 L pressure bottle). The reaction was started with the reactor filled with MeCN and the total contents of the reaction collected. The contents of the feed stream pressure bottles were refilled as required during the run at which point the pumps were temporarily stopped. Samples were taken at 1 h intervals until the 4.5 h mark, then sampling was conducted every 2 h. The *in situ* HPLC assay yield remained 60-66% over the course of the run with 4-11% starting material remaining. A representative HPLC trace of the crude reaction is below. *Feed streams were prepared as above a total of 4 times during a 48 h run giving the total quantities of reactants as:* Methyl-1-boc-pyrrole-2-carboxylate **9** (1.20 Kg, 5.22 mol, 1.0 equiv), pyridine-*N*-oxide (992 g, 10.4 mol, 2.0 equiv), $Ru(bpy)_3Cl_2.6H_20$ (3.92 g, 5.22 mmol, 0.001 equiv), trifluoroactic anhydride (1.73 Kg, 11.0 mol, 2.1 equiv) and MeCN (15.4 L). Once the

4L collection bottle approached capacity it was switched and the contents concentrated to approximately 1 L under reduced pressure to give a viscous black solution. This solution was transferred to a 5 L vessel to conduct the work up. To the black solution was added heptane (1.0 L, 1 vol) and 1 N HCl (1.0 L, 1 vol) and the contents stirred vigorously for 5 min before separation. The aqueous phase was extracted a further 2 times with heptane (2 × 1.0 L), the organic heptane portion combined and washed with saturated Na_2CO_3 (1.0 L) upon which the heptane changed from a light yellow to light pink in color. The heptane was then washed with saturated NaCl (1.0 L). This solution was retained under an atmosphere of nitrogen prior to the combination of all solutions after work up and concentration in a rotary evaporator at reduced pressure. Concentration of the combined heptane solutions in a rotary evaporator at reduced pressure following work up gave a 1-(tert-butyl) 2-methyl 5-(trifluoromethyl)-1H-pyrrole-1,2-dicarboxylate **9a** as dark red/black oil (948 g, 81% strength by HPLC, 50% yield *adjusted for purity*) with data in accordance with that reported. The major impurities present were identified as unreacted starting material **9** 7%, 1-tert-butyl 2-methyl 3-(trifluoromethyl)-1H-pyrrole-1,2-dicarboxylate 1%, 1-tert-butyl 2-methyl 3,5-bis(trifluoromethyl)-1H-pyrrole-1,2-dicarboxylate 0.8%.

The pumps were calibrated prior to the reaction using MeCN. Catch and weigh samples reported 105-110% observed mass flow rate vs the predicted during the course of the reaction. For more accurate flow rates pumps should be calibrated with the reaction solutions which in our case had densities that deviated from that of the calibration solvent.

The overall mass balance for the entire run was calculated at 95.2% = (total recorded mass input/total recorded mass output) = (15139 g/14416 g) = 95.2%. Reaction HPLC traces before and after workup are shown below, as well as ^{1}H NMR and ^{19}F NMR spectra of the crude reaction following workup to demonstrate purity.

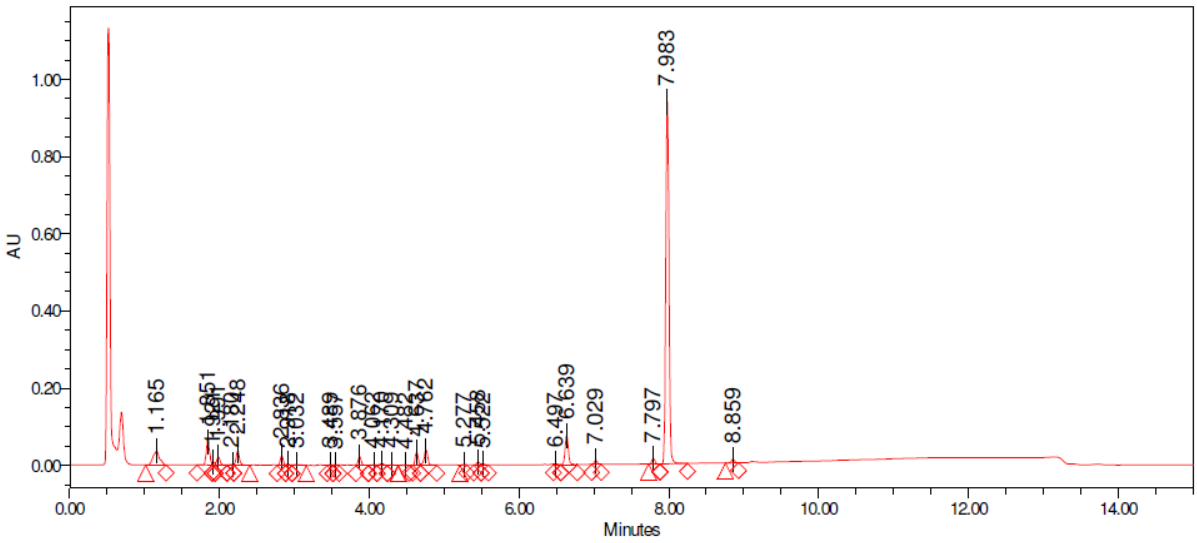
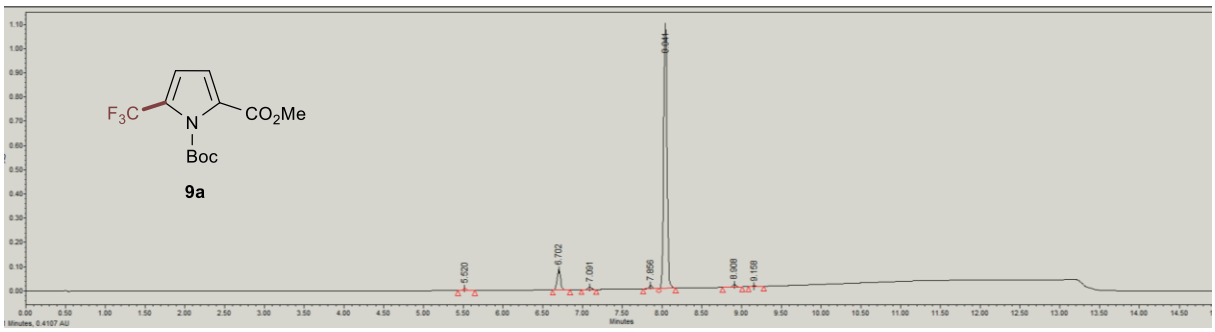


Figure S27. HPLC chromatogram showing representative reaction sample at steady state.



Retention Time (min)	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Dissolved Amount	Dissolved Percent	Peak Type	Peak Codes	ActivityFactor	ActivityResult	AdjArea	AdjAreaPct
5.520	26978	0.76	9358	bb					Unknown	C06			26978	0.760995
6.702	247181	6.97	83142	bb					Unknown	C06			247181	6.972350
7.091	30036	0.85	10358	bb					Unknown	C06			30036	0.847228
7.856	40453	1.14	13937	bv					Unknown	C06			40453	1.141088
8.041	3160760	89.16	1083712	vb					Unknown	C06			3160760	89.157059
8.908	29748	0.84	10330	bb					Unknown	C06			29748	0.839117
9.158	10003	0.28	2390	bb					Unknown	C06			10003	0.282162

Figure S28. HPLC chromatogram showing the crude material following work up.

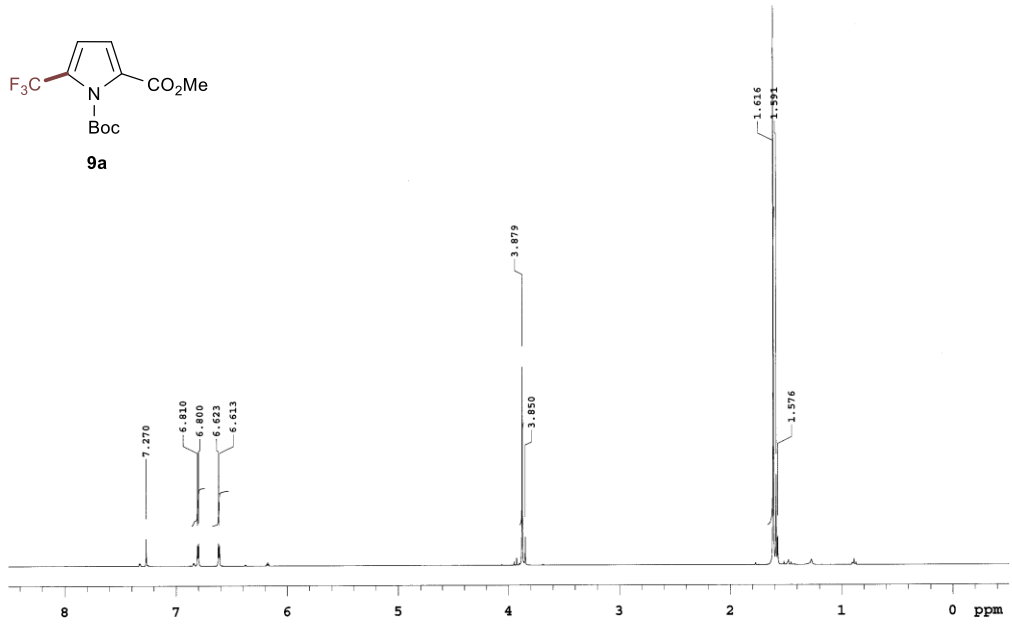


Figure S29. ^{1}H NMR showing the crude material **9a** following workup.

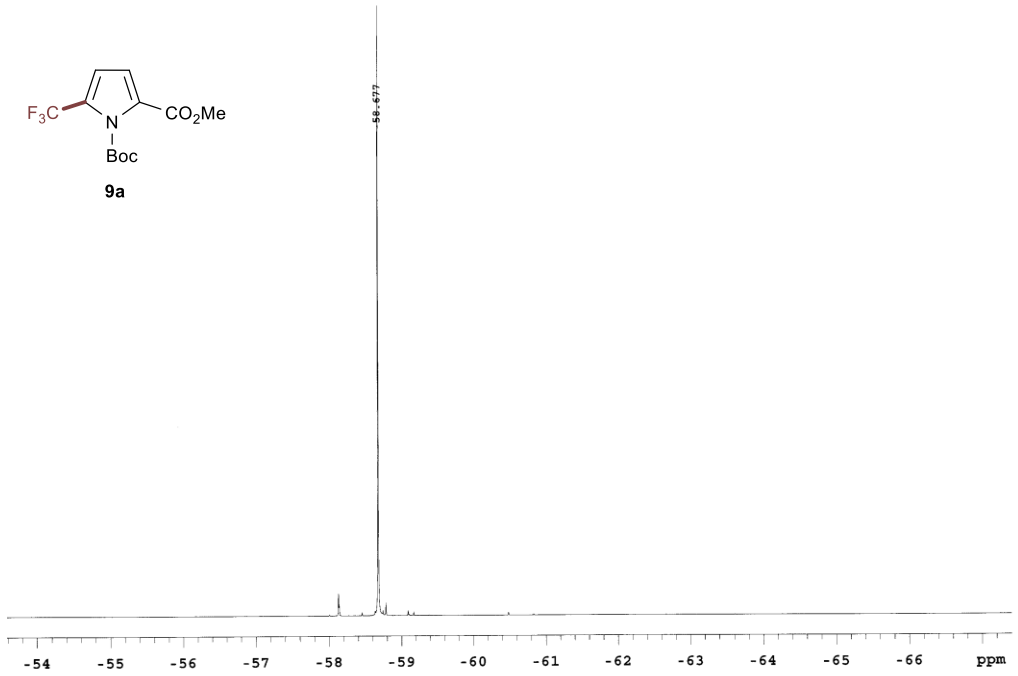
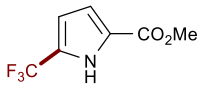


Figure S30. ^{19}F NMR showing the crude material **9a** following workup

Boc de-protection: Synthesis of methyl 5-(trifluoromethyl)-1H-pyrrole-2-carboxylate (26):



This is an un-optimized process. To a one neck 200 mL flask under an atmosphere of nitrogen was added crude 1-(tert-butyl) 2-methyl 5-(trifluoromethyl)-1H-pyrrole-1,2-dicarboxylate (52.8 g, 140 mmol, 1.0 equiv, 81% purity) and heptane (50 mL) to give a bright red solution. Trifluoroacetic acid (16.0 mL, 24.13 g, 212 mmol, 1.51 equiv) was added and the solution stirred for 14 h. Trifluoroacetic acid (16.0 mL, 24.13 g, 212 mmol, 1.51 equiv) was added and the solution stirred for a further 6 h before concentration under reduced pressure. The light pink solid was redissolved in 25 mL of heptane at 60 °C and slowly cooled to rt over 4 h and stirred for a further 10 h. The slurry was filtered, the filtrate cooled to 0 °C to induce further precipitation then filtered. The combine solids were dried in a vacuum oven at 40 C for 2 to give methyl 5-(trifluoromethyl)-1H-pyrrole-2-carboxylate **26** as a light pink solid.
Yield: 20.9 g (77%, 99% purity); ^{1}H NMR (400 MHz, CD_3CN) δ = 10.04 (s, 1H), 6.14–6.15 (m, 1H), 5.95–5.96 (m, 1H), 3.13 (s, 1H); ^{19}F NMR (376 MHz, CD_3CN) δ = -60.6 (s). This data is in accordance with that previously reported.[11]

HPLC chromatogram of 26

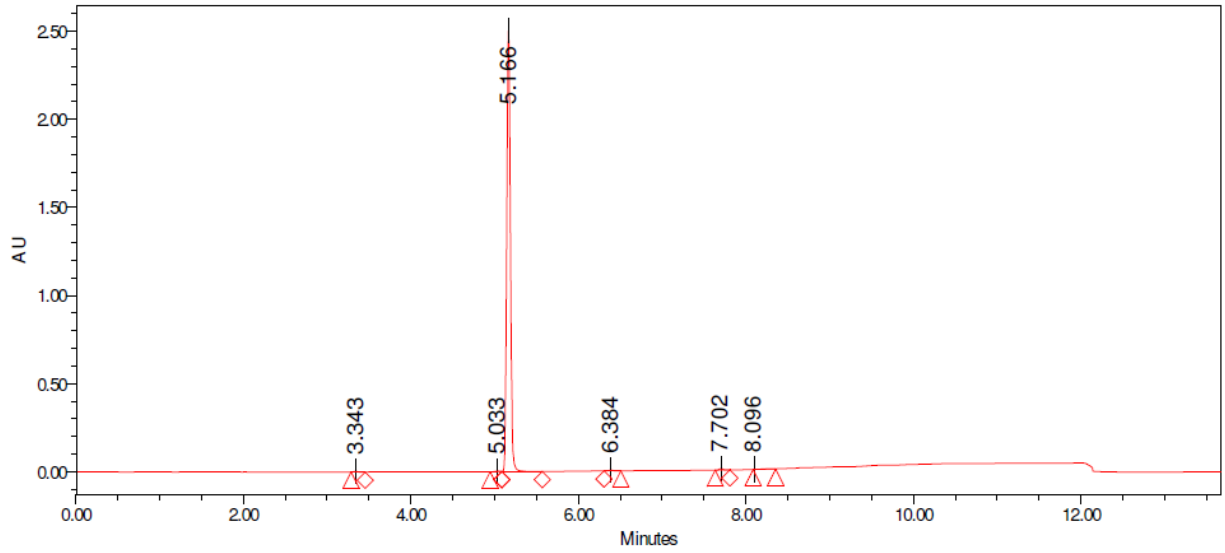


Figure S31. HPLC chromatogram of **26**.

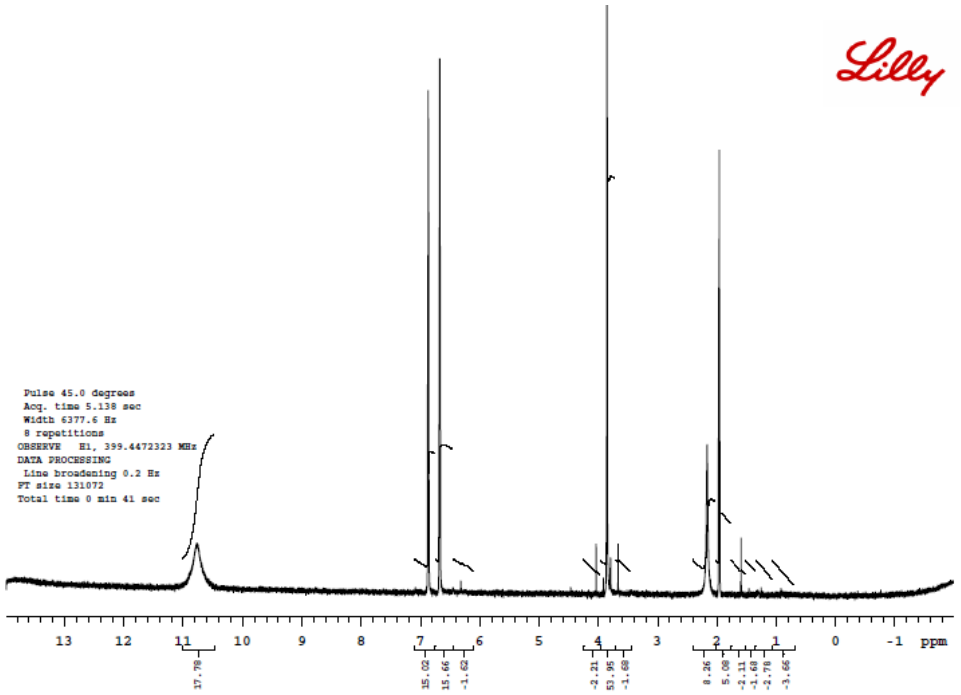


Figure S32. ^{1}H NMR of **26**.

UV-Vis Studies:
All UV-VIS measurements were performed on a Shimadzu UV-1601 UV-VIS Spectrometer. Samples were prepared using dry MeCN as the solvent. Measurements were taken in 1cm path length quartz cuvettes at room temperature and were not degassed. Evaluation of the various component contributions to the EDA absorbance at 0.4M is performed in the manuscript; these effects were seen at lower concentrations as well (orange curve, below), however, there is a threshold at which the EDA shoulder peak is unobservable. Optical absorbance spectra of a mixture of 4-phenylpyridine *N*-oxide, mesitylene, and TFAA in relevant stoichiometry (1.0 : 1.0 : 1.1) over a range of concentrations in dry MeCN.

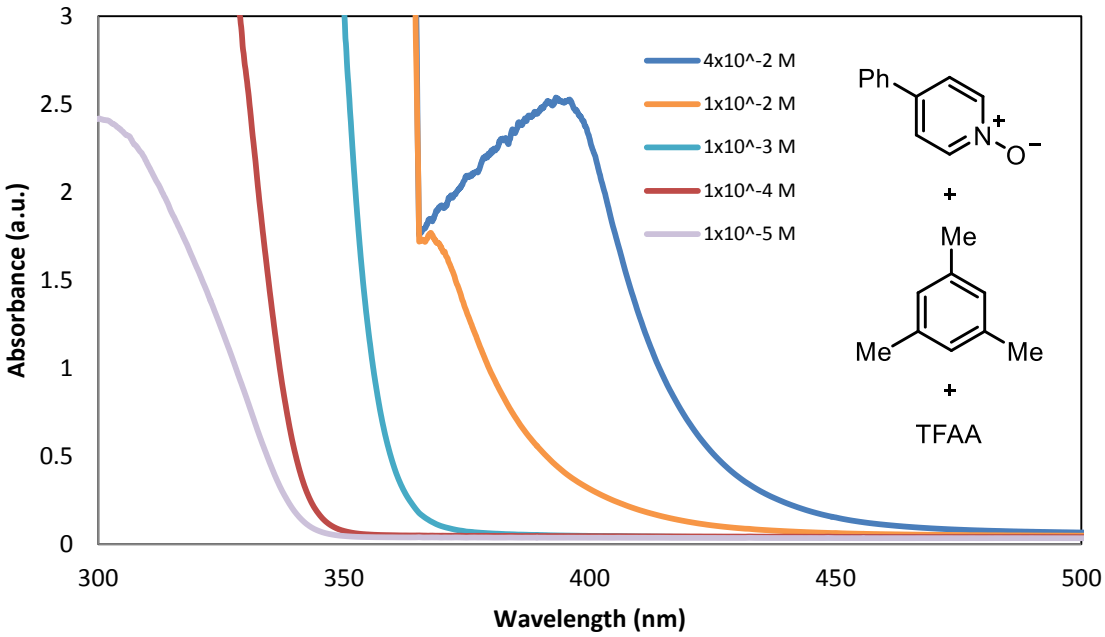


Figure S33. Optical absorbance spectra of the reaction solution at varied concentrations.

Electrochemical Measurements
The measurement of reduction potentials for the acylonium salts reported in this manuscript cannot be accurately performed through cyclic voltammetry analysis. The observed signal using cyclic voltammetry has variations in shape and peak potential from run to run, and the peak shape in particular is dependent upon sweep rate. Literature precedent in this area for alkylated pyridine *N*-oxides suggests that these molecules can undergo extremely fast ("barrierless") fragmentation upon single-electron reduction (k_{obs} on the order of 1.8×10^{12} s^{-1} for 1-methoxy-4-phenylpyridinium and 4.1×10^{12} s^{-1} for 1-methoxypyridinium).[12] Furthermore, another paper concerning similar structures reports that "[r]eduction potentials of *N*-methoxypyridinium salts are not readily accessible through conventional electrochemical techniques because of the relatively fast reductive cleavage of these compounds."[13]

Differential pulse voltammetry (DPV) was performed to obtain the reduction potentials of the various pyridine *N*-oxide/anhydride combinations, and reproducible potentials were obtained through these methods. Measurements were performed with a model CHI660C multi-potentiostat from CH Instruments. Measurements were performed with a glassy carbon working electrode, Pt auxiliary electrode, Ag/AgCl reference electrode, Bu_4NPF_6 electrolyte (0.1 M in MeCN), and analyte (pyridine-N-oxide:TFAA, 1:1, 0.01 M) with the following settings: Incr E (V) = 0.001, Amplitude (V) = 0.005, Pulse Width (sec) = 0.05, Sampling Width (sec) = 0.01, Pulse Period (sec) = 0.5.

All voltammograms are reported/displayed *after* conversion to voltage vs. SCE, where:

$$\mathbf{V_{SCE} = V_{AgCl} - 0.05\ V}$$

Onset potentials are estimated based on the intersection of the baseline and onset slope (shown).

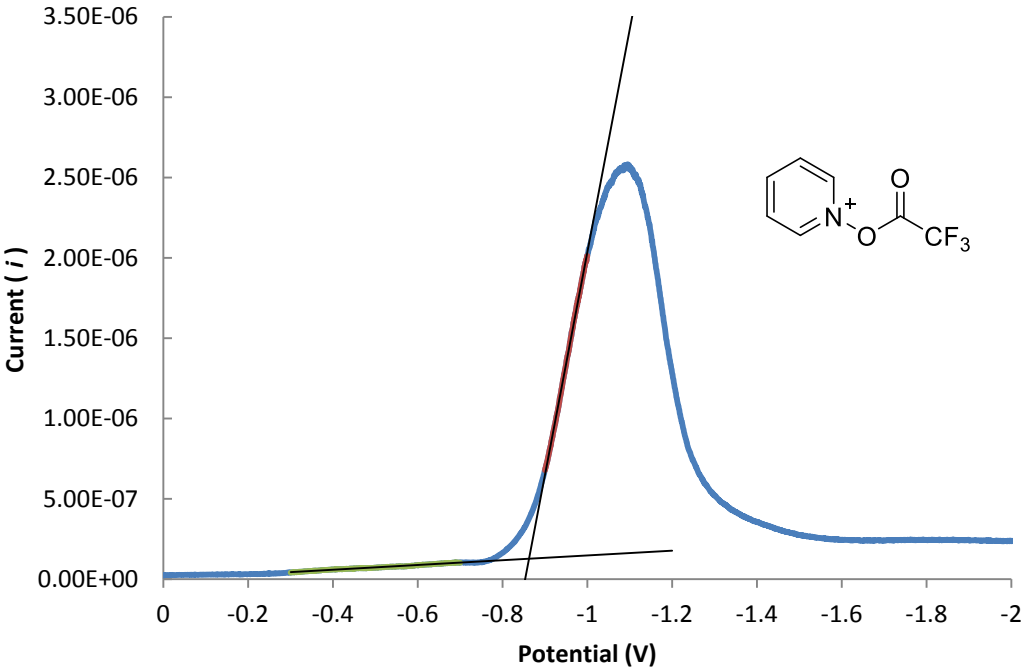


Figure S34. DPV of the pyridine *N*-oxide/TFAA adduct. Onset reduction is observed at –0.86 V vs. SCE. Peak reduction is observed at –1.10 V vs. SCE.

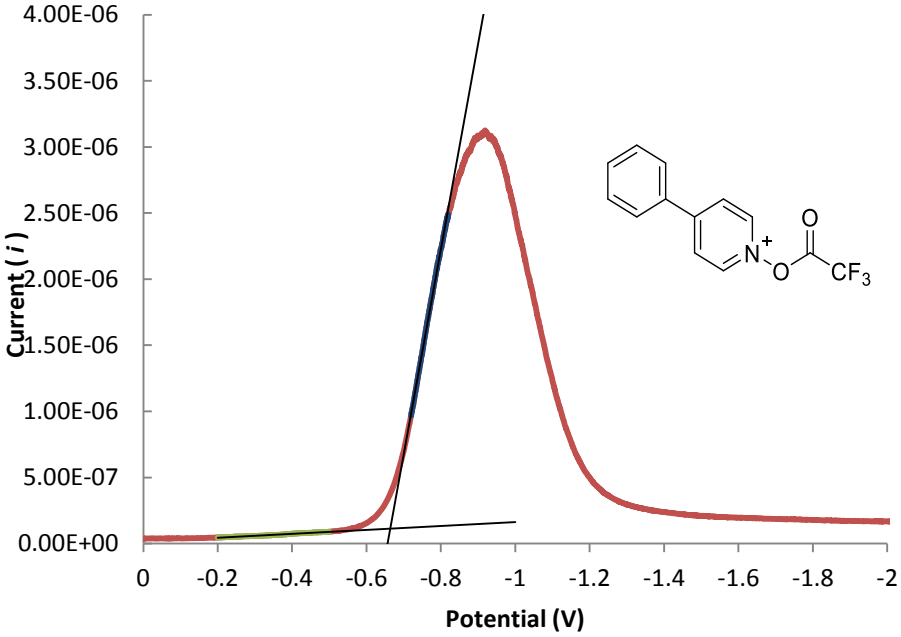


Figure S35. DPV of the 4-phenylpyridine *N*-oxide/TFAA adduct. Onset reduction is observed at –0.65 V vs. SCE. Peak reduction is observed at –0.91 V vs. SCE.

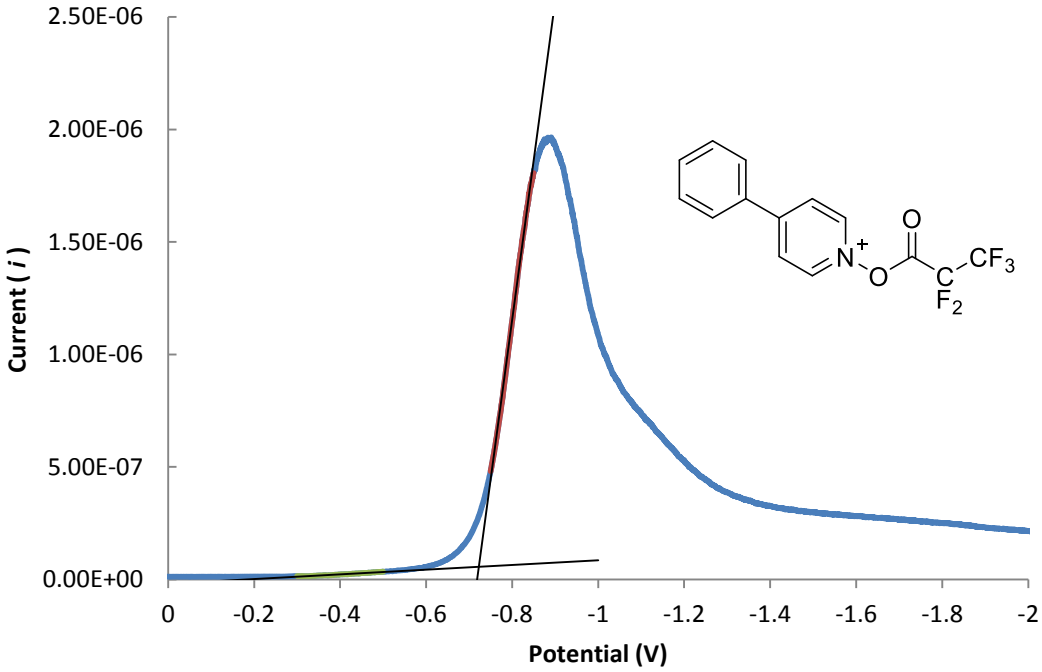


Figure S36. DPV of the 4-phenylpyridine *N*-oxide/pentafluoropropionic anhydrude adduct. Onset reduction is observed at –0.72 V vs. SCE. Peak reduction is observed at –0.88 V vs. SCE.

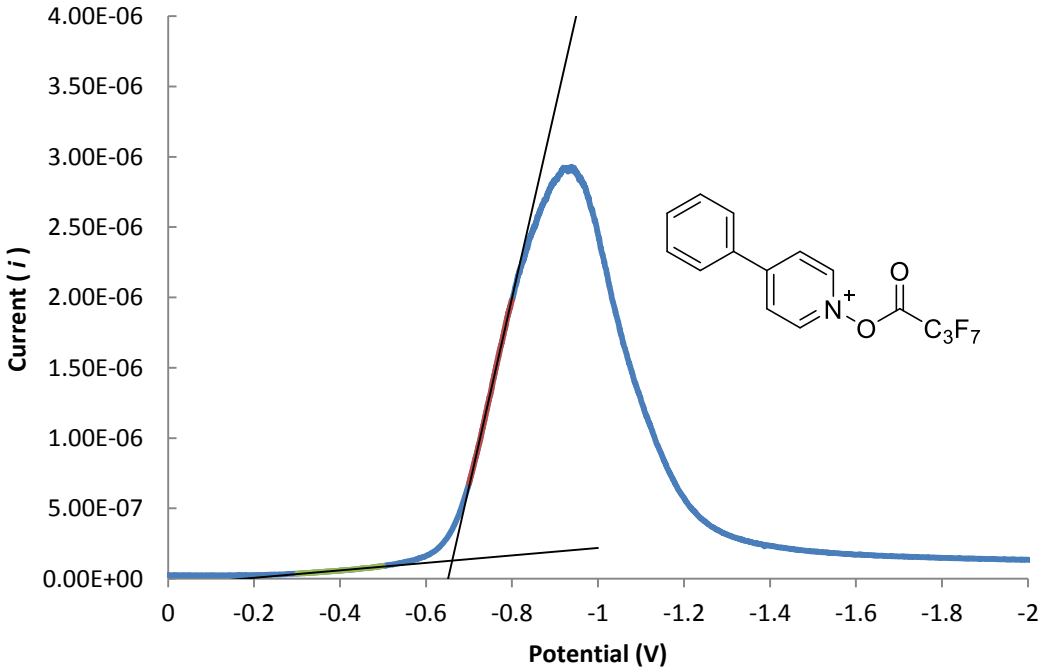


Figure S37. DPV of the 4-phenylpyridine *N*-oxide/heptafluorobutyric anhydrude adduct. Onset reduction is observed at –0.66 V vs. SCE. Peak reduction is observed at –0.93 V vs. SCE.

Fluorescence Quenching Studies:

Quenching data was obtained using a Fluoromax-2 Fluorimeter. All quenching data was recorded using a quartz cuvette with a stir bar at between 24.5 and 25.5 ˚C with $Ru(bpy)_3Cl_2$ (9.97 $x10^{-6}$ M) in dry, degassed MeCN (sparged for 5 minutes). Excitation was performed at 452 nm with emission measured at 615 nm. All values are the average of three measurements.

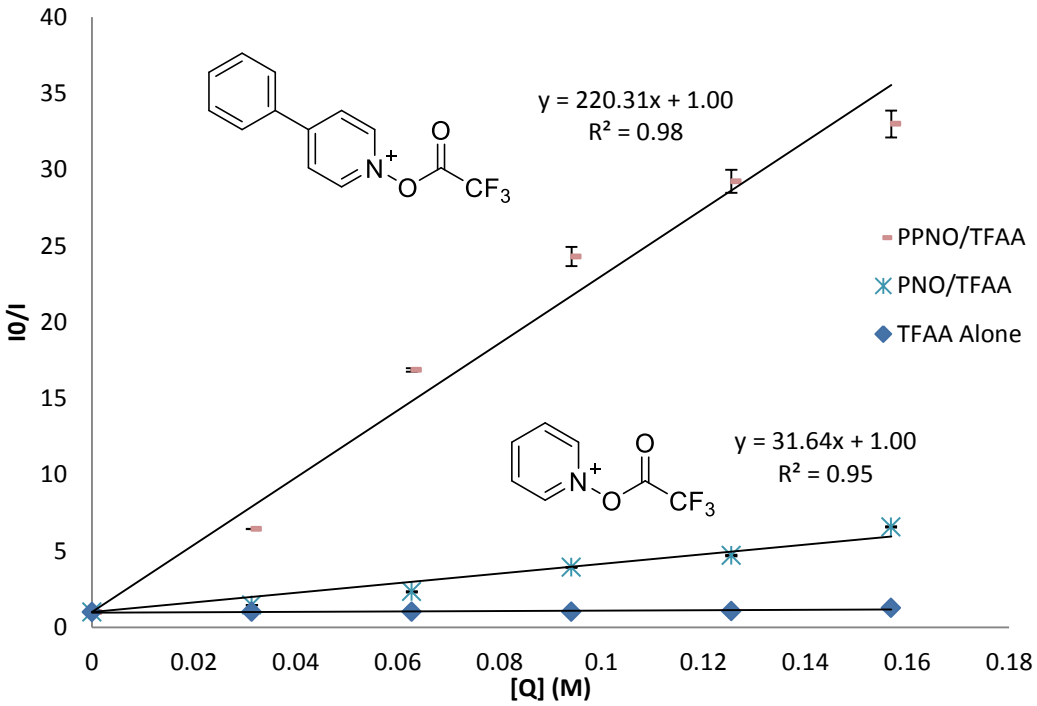


Figure S38. Stern-Volmer Quenching of $Ru(bpy)_3Cl_2$ with 4-phenylpyridine *N*-oxide (PPNO)/TFAA or with pyridine *N*-oxide (PNO)/TFAA. For each measurement the concentration of quencher refers to the concentration of the *N*-oxide, which is the limiting reagent in a ratio of 1.0:1.1 in relation to TFAA. Error bars refer to a single standard deviation, with the measurement performed in triplicate.

From the data above, quenching rates (k_q) may be extracted based on the following equation:

$$\frac{I_0}{I} = k_q \tau_0 [Q] + 1$$

Where τ_0 represents the catalyst excited state lifetime[14] at 25 ˚C in MeCN, for which we used a value of 0.87 µs.[15]

	k_q (M^{-1} s^{-1})
pyridine *N*-oxide/TFAA	$3.6x10^7$
4-Ph-pyridine *N*-oxide/TFAA	$2.5x10^8$

These rates are *not quantitatively useful*, as the quenching behavior of the PPNO/TFAA adduct does not appear to be entirely linear. Although the equilibrium constant of this reaction is not known, the increase in quencher concentration will likely shift this equilibrium towards the acylated side of the equilibrium, thus potentially explaining the non-linear trend observed above.

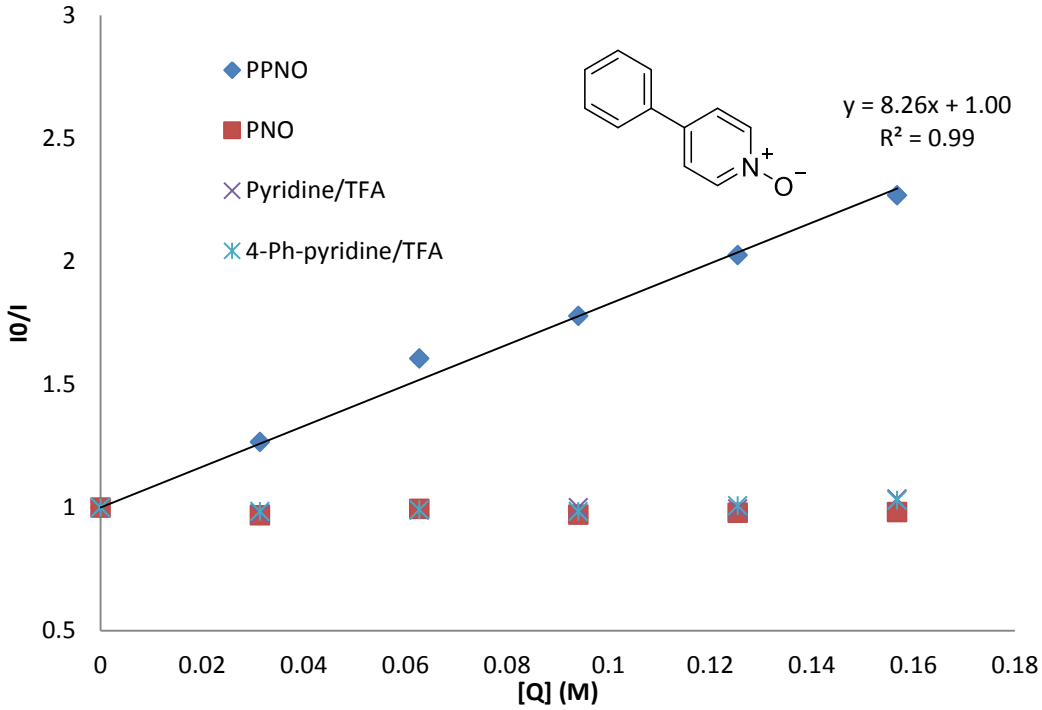


Figure S39. Stern-Volmer Quenching of $Ru(bpy)_3Cl_2$, component controls. Of the individual components of the reaction, only 4-phenylpyridine *N*-oxide (PPNO) quenched the photocatalyst, while PNO, TFAA, 4-phenylpyridinum trifluoroacetate, and pyridinium trifluoroacetate did not quench the catalyst.

Quantum Yield Measurements

Quantum yield experimental design was based on the procedure by Cismesia and Yoon.[16] Experiments were performed using a Fluoromax-2 Fluorimeter equipped with a 150 W Xenon Arc lamp. Actinometry was performed with potassium ferrioxalate trihydrate. The procedure for determining photon flux, as described by Cismesia and Yoon, is reproduced below:

> *"The photon flux of the spectrophotometer was determined by standard ferrioxalate actinometry. A 0.15 M solution of ferrioxalate was prepared by dissolving 2.21 g of potassium ferrioxalate hydrate in 30 mL of 0.05 M H_2SO_4. A buffered solution of phenanthroline was prepared by dissolving 50 mg of phenanthroline and 11.25 g of sodium acetate in 50 mL of 0.5 M H_2SO_4. Both solutions were stored in the dark. To determine the photon flux of the spectrophotometer, 2.0 mL of the ferrioxalate solution was placed in a cuvette and irradiated for 90.0 seconds at λ = 436 nm with an emission slit width at 10.0 nm. After irradiation, 0.35 mL of the phenanthroline solution was added to the cuvette. The solution was then allowed to rest for 1 h to allow the ferrous ions to completely coordinate to the phenanthroline."*

At this point, our protocol differed slightly from the published protocol. Our absorbance measurements in the 1 cm quartz cuvette at 510 nm for the Fe^{2+} phenanthroline complex were above 2.0 absorbance units, and were deemed too high for accurate quantification. Instead, we obtained the absorbance of the solutions at 510 nm after transferring some of the solution to a 1 mm (0.1 cm) path length cuvette, which provided absorbance units an order of magnitude lower. An additional sample was prepared exactly as above, was not irradiated, and upon development with the phenanthroline solution for 1 hour its absorbance was measured at 510 nm in the 1 mm path cuvette. The amount of Fe^{2+} was quantified according to the equation below.

> *"Where V is the total volume (0.00235 L) of the solution after addition of phenanthroline, ΔA is the difference in absorbance at 510 nm between the irradiated and non-irradiated solutions, l is the path length… [0.100 cm], and ε is the molar absorptivity at 510 nm (11,100 L mol^{-1} cm^{-1})."*

$$\text{mol Fe}^{2+} = \frac{\text{V} \cdot \Delta\text{A}}{\text{l} \cdot \varepsilon} = \frac{0.00235\ \text{L} \cdot 0.234009}{0.100\ \text{cm} \cdot 11{,}100\ \text{L mol}^{-1}\text{cm}^{-1}} = 4.95 \text{ x } 10^{-7}\ \text{mol Fe}^{2+}$$

Photon flux was then determined as follows:

$$\text{photon flux} = \frac{\text{mol Fe}^{2+}}{\Phi \cdot \text{t} \cdot \text{f}} = \frac{4.95 \text{ x } 10^{-7}\ \text{mol}}{1.01 \cdot 90\ \text{s} \cdot 0.99907} = 5.46 \text{ x } 10^{-9} \text{einstein s}^{-1}$$

Φ = the quantum yield of ferrioxalate at 0.15 M and λ=436 nm

f = fraction of light absorbed at λ=436 nm, which can be determined from the equation $\text{f} = 1 - 10^{-\text{A}}$. The absorbance spectrum of the non-irradiated 0.15 M ferrioxalate solution was taken and is shown on the next page. The absorbance at 436 nm was found to be 3.03186, which results in a value of 0.99907 for f.

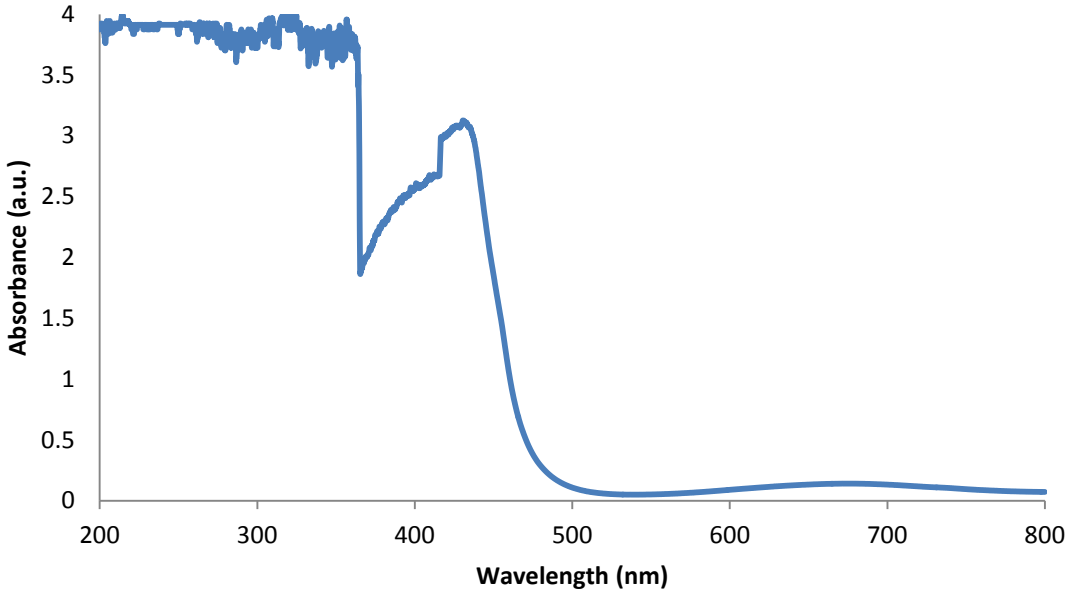
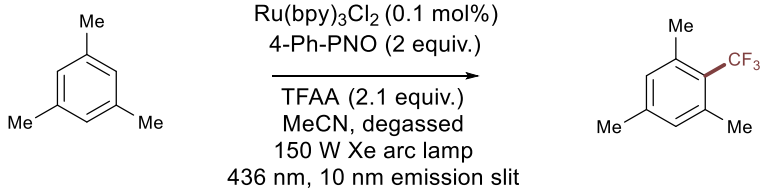


Figure S40. Optical absorbance spectrum for $K_3Fe(C_2O_4)_3$, 0.15 M in 0.05M H_2SO_4. The absorbance of the sample at 436 nm is 3.03186, which means that >99.9% of incident light is absorbed at this wavelength.

Quantum yield for the trifluoromethylation of mesitylene under standard conditions was determined as follows:



In a dark room, 4-phenylpyridine *N*-oxide (273.9 mg, 1.6 mmol, 2.0 equiv.), and mesitylene (111 µL, 96.2 mg, 0.80 mmol, 1.0 equiv.) were combined in a 1 cm path length cuvette equipped with stir bar. 500 µl of a solution 1.2 mg/ml $Ru(bpy)_3Cl_2$•$6H_2O$ in dry MeCN (0.6 mg, 0.1 mol%) was added to the cuvette, followed by 1.5 ml of dry MeCN. The solution was sparged for 30 seconds, followed by the addition of TFAA (237 µl, 353 mg, 2.1 equiv., not degassed) under a stream of nitrogen. The reaction was quickly sealed with a screw on cap, and wrapped with parafilm. Light exclusion was achieved by wrapping the reaction in foil until the reaction was placed in the fluorimeter. The sample-holder was pre-equilibrated to 35 ˚C, and the reaction sample was allowed to equilibrate to this temperature over 10 minutes. The sample was stirred and irradiated at 436 nm with a 10 nm slit width for 28,800 s (8 h). After irradiation, 0.5 ml of methanol was added to the reaction solution. After stirring for an additional 2 minutes, trifluorotoluene (98 µl, 0.8 mmol, 1.0 equiv.) was added as an internal standard, and the reaction was analyzed by ^{19}F NMR. The reaction yielded 17% (0.136 mmol) of 1,3,5-trimethyl-2-(trifluoromethyl)benzene.

The quantum yield was calculated as follows:

$$\Phi = \frac{\text{mol product}}{\text{flux}\cdot t\cdot f} = \frac{1.36\,\text{x}10^{-4}\text{mol}}{5.46\,\text{x}10^{-9}\text{einstein s}^{-1}\cdot 28800\text{ s}\cdot 1.00} = 0.87$$

Where f is the fraction of light absorbed at λ=436 nm, which can be determined from the equation $f = 1 - 10^{-A}$. The absorbance spectrum of the non-irradiated 0.15 M ferrioxalate solution was taken and is shown below. The absorbance at 436 nm was found to be 3.389282, which results in a value > 0.999 for f.

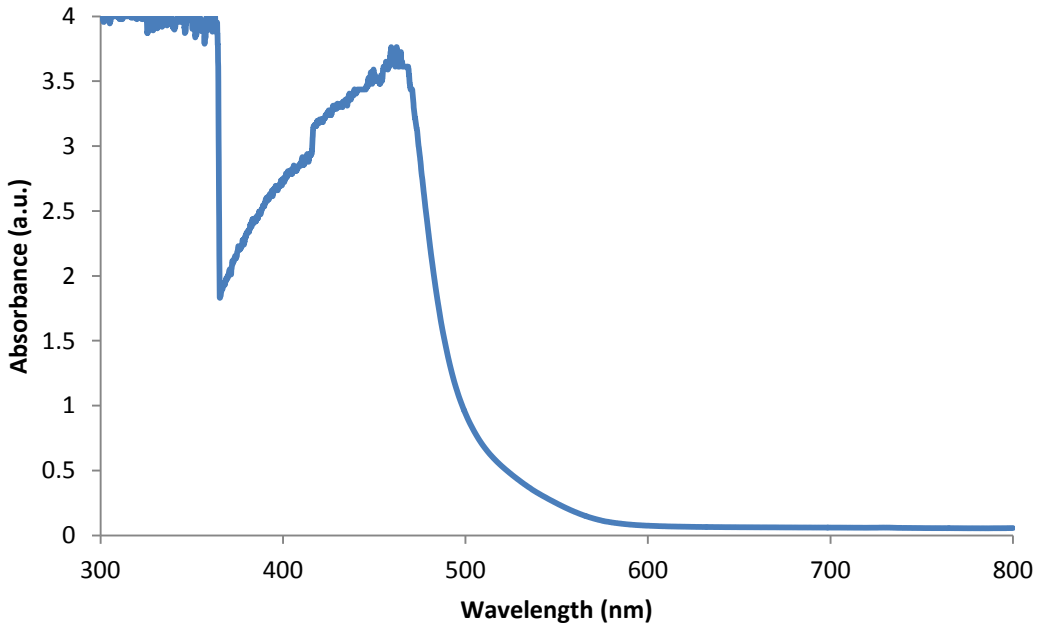


Figure S41. Optical absorbance spectrum for the full reaction mixture (0.4 M in MeCN). Reactant stoichiometry is 1.0 : 2.0 : 2.1 for mesitylene, 4-phenylpyridine *N*-oxide, and TFAA, respectively, with 0.1 mol% $Ru(bpy)_3Cl_2$. The absorbance of the sample at 436 nm is 3.389282, which means that >99.9% of incident light is absorbed at this wavelength.

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