A Scalable and Regioselective Synthesis of 2-Difluoromethyl Pyridines from Commodity Chemicals

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Supporting Information

Key to Abbreviated Terms:

$CDCl_3$ - Deuterated Chloroform
DCM – Dichloromethane
DFAA- Difluoroacetic Anhydride
DMSO- Dimethylsulfoxide
Et_2O - Diethyl Ether
EtOAc - Ethyl Acetate
Hex - Hexanes
MTBE – Methyl *t*-Butyl Ether
HCO_2NH_4 – Ammonium Formate
THF – Tetrahydrofuran
TFAA- Trifluoroacetic Anhydride

General Considerations:

General:
All chemical transformations requiring inert atmospheric conditions or vacuum distillation utilized Schlenk line techniques with a 5-port dual-bank manifold. Nitrogen was used to provide such an atmosphere. NMR Spectra (^{1}H, ^{13}C, ^{19}F) were performed at 298 K (unless otherwise specified) on either a Brüker Avance III Ultra Shield DPX-400 MHz NMR or Brüker Avance III Ultra Shield DRX 500 MHz NMR. ^{1}H-NMR Spectra obtained in $CDCl_3$ were referenced to residual non-deuterated chloroform (7.26 ppm) or DMSO (39.52 ppm) in the respective deuterated solvents. ^{13}C NMR Spectra obtained in $CDCl_3$ were referenced to chloroform (77.3 ppm). ^{19}F NMR spectra were referenced to fluorobenzene (-115.3 ppm).[1] Reactions were monitored using a Waters Acquity UPLC, ^{1}H NMR, and/or by TLC on silica gel plates (60Å porosity, 250 μm thickness). Low-resolution mass spectra were obtained using Waters Xevo TDQ attached to a Waters Acquity UPLC**.** High resolution mass spectral data were acquired using an Agilent LC/MSD TOF (time-of-flight) mass spectrometer in an electrospray positive ionization mode *via* flow injection. IR spectra were obtained using a Thermo Nicolet 3700 FT-IR. TLC analysis was performed using hexanes/MTBE as the eluent and visualized using UV light. Flash chromatography was accomplished using a Teledyne CombiFlash R_f (visualizing pyridines at 220 nm) with Silicycle SiliaSep Flash Cartridges (60Å porosity, 40-63 μm).

Chemicals:
Deuterated NMR solvents ($CDCl_3$) were purchased from Sigma Aldrich. Sodium sulfate, sodium carbonate, $SOCl_2$, CH_2Cl_2, methyl *t*-butyl ether, pyridine, ethyl acetate, trifluoroacetic anhydride and hexanes were purchased from Sigma-Aldrich. Difluoroacetic anhydride was purchased from Synquest Laboratories. Difluoroacetic acids were either purchased from Matrix Scientific or Oakwood Products. Butenones were prepared according to the protocols outlined below either starting from DFAA or the corresponding difluoroacetic acid derivatives. Representative syntheses of **1a** and **1c** are given. Preparation of **1b, 1d-1f**, **1h**, **1i**, and **1l** utilized the appropriate vinyl either or difluoroacetic acid derivative following these general protocols**.** The buteneone **1g** was prepared *via* the anhydride-based protocol using TFAA instead of DFAA as an acetylating reagent. The butanone **1k** was prepared using the protocol of Chopin. [2] The butanone **1j** was purchased from Synquest laboratories and distilled before use. Sodium enolates were prepared *via* a modification of the protocol outlined by American Cyanamid[3] or by treatment with sodium ethoxide followed by solvent removal. Both protocols are outlined below. Representative syntheses of **2a** and **2j** are given. Preparation of **2b-2i** and **2k** were prepared using the appropriate enolizable species or beta-keto ester.

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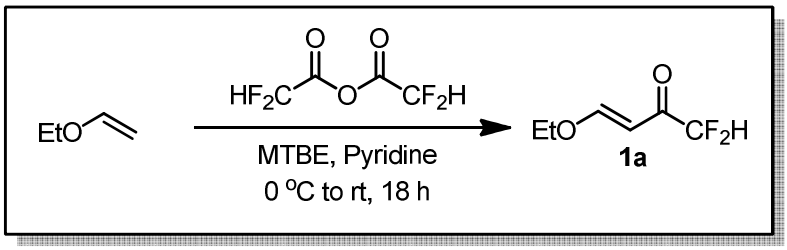
[1] (a) Furuya, T.; Kaiser, H. M.; Ritter, T. *Angew. Chem., Int. Ed.* **2008** , *47*, 5993. (b) Kelly, C. B; Mercadante, M. A.; Hamlin, T. A.; Fletcher, M. H.; Leadbeater, N. E. *J. Org. Chem.* **2012**, *77*, 8131.
[2] Chopin, N.; Decamps, S.; Gouger, A.; Médebille, M.; Picot, S.; Bienvenu, A.-L.; Pilet, G.; *J. Fluorine Chem.* **2011**, *132*, 850.
[3] Northey E. H. American Cyanamid US Patent 2394255, **1946**.

Synthesis of Butenones

General Procedure A: Butenones *via* Vinyl Ethers and DFAA



(E)-4-ethoxy-1,1-difluorobut-3-en-2-one, 1a

To a 2-neck 100 mL round bottom flask equipped with a stir bar and N_2 inlet adapter, was added MTBE (20 mL) followed by DFAA (14.26 g, 8.49 mL, 81.91 mmol, 1 equiv). The flask was sealed with a rubber septum and the reaction mixture was placed under nitrogen atmosphere. The flask was cooled to 0 °C in an ice-water bath for ten minutes. At this time, a solution of ethyl vinyl ether (7.09 g, 9.41 mL, 98.29 mmol, 1.2 equiv) in pyridine (6.80 g, 6.89 mL, 86 mmol, 1.05 equiv) was added to the solution dropwise *via* a syringe over 15 min. After this time the solution was allowed to slowly warm to room temperature will stirring overnight. Over time the solution became yellow and produced a white pyridinium precipitate. This precipitate was removed by filtration though a medium porosity fritted funnel, washing the solids with a minimum amount of MTBE (10-20 mL). The filtrate was poured into a stirring 10 % w/w solution of aqueous Na_2CO_3 to quench any remaining DFAA and was allowed to stir for 10 minutes. This biphasic mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with MTBE (2 X 25 mL) and the combine organic layers were washed with deionized water (75 mL). The organic layer was dried over Na_2SO_4 and the solvent was partially removed *in vacuo* by rotary evaporation (≥200 mbar, 20 °C, volatile) affording the crude butanone **1a** (37.75 g, 22.5 wt%,[4] 69.1% yield) in ≈ 3 volume equivalents of MTBE.[5,6,7]

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 1.38 (t, *J*=7.06 Hz, 3 H) 4.06 (q, *J*=6.90 Hz, 2 H) 5.75 (t, *J*=54.30 Hz, 1 H) 5.86 (dt, *J*=12.55, 1.10 Hz, 1 H) 7.83 (d, *J*=12.51 Hz, 1 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 14.22 (CH_3) 68.41 (CH_2) 98.89 (CH) 110.64 (t, $J_{C\text{-}F}$=252.40 Hz, CF_2H) 166.55

[4] Weight percent assays were performed via ^{1}H NMR using dimethyl fumarate as an internal standard

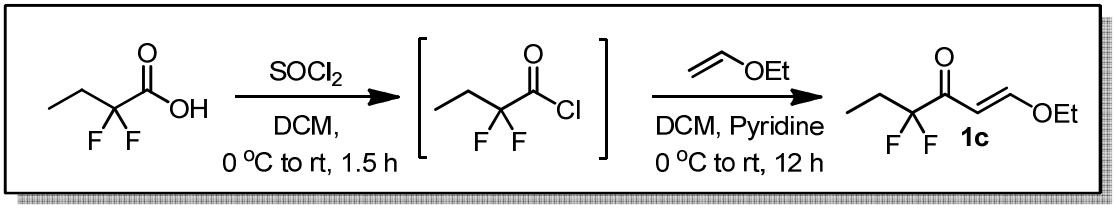
[5] The remainder of identifiable materials were MTBE (59.5 wt%), pyridine (5.6 wt%), and H_2O (2%). These impurities have no effect on pyridine synthesis.

[6] Butenones can be stored as crude solutions in MTBE with BHT as a stabilizer (See S22). Isolation of pure butanone is not necessary for pyridine synthesis

[7] If desired, butenones can be isolated following solvent removal and vacuum distillation (32–36 °C, 0.1–0.5 torr). This was done for **1a** for utilization in some pyridine syntheses (90-95wt% obtained), full characterization, and for butanone stability studies. As a cautionary note, distillation will often this will lead to substantially diminished yields due to polymerization of the butenones. It is recommended that butenones be used in solution for practical reasons.

(t, $J_{C\text{-}C\text{-}C\text{-}F}$ =1.83 Hz, CH) 187.71 (t, $J_{C\text{-}C\text{-}F}$=24.90 Hz, C) **^{19}F NMR** ($CDCl_3$, 377 MHz) δ ppm -127.98 (d, *J*=54.20 Hz) **LC-MS** (ESI+) calcd for $C_6H_8F_2O_2$ [M^+]: 150.1, found:150.9.

General Procedure B: Butenones *via* Vinyl Ethers and Acid Chlorides



(E)-1-ethoxy-4,4-difluorohex-1-en-3-one, 1a

To a 2-neck 50 mL round bottom flask equipped with a stir bar and N_2 inlet adapter, was added DCM (11.1 mL) followed by 2,2-difluorobutanoic acid (1.24 g, 10 mmol, 1 equiv). The flask was sealed with a rubber septum and the reaction mixture was placed under nitrogen atmosphere. The flask was cooled to 0 °C in an ice-water bath for ten minutes. At this time, $SOCl_2$ (1.19 g, 0.73 mL, 10 mmol, 1 equiv) was added to the solution dropwise *via* a syringe over 5 min. After this addition, the solution was allowed to stir at 0 °C for 10 minutes. The ice-water bath was then removed and the solution was allowed to warm to room temperature.

After 1.5 h the reaction was judged complete[8] and was cooled to 0 °C *via* an ice-water bath. Once cooled (≈ 10 minutes), pyridine (0.87g, 0.89 mL, 11 mmol, 1.1 equiv) was added to the reaction mixture dropwise *via* a syringe over 5 minutes. A white pyridinium precipitate formed and the solution was stirred at 0 °C for 10 minutes after addition. At this time, a solution of ethyl vinyl ether (0.901 g, 1.20 mL, 12.5 mmol, 1.25 equiv) in pyridine (0.79 g, 0.81 mL, 10 mmol, 1 equiv) was added to the solution dropwise *via* a syringe over 15 min. After this time the solution was allowed to slowly warm to room temperature will stirring overnight. Over time the solution became bright yellow. At this time, the solution was slowly poured into a stirring 10 % w./w. solution of aqueous Na_2CO_3 to quench any residual acid or $SOCl_2$ and was allowed to stir for 10 minutes. This biphasic mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with DCM (2 X 25 mL) and the combine organic layers were washed with deionized water (75 mL). The organic layer was dried over Na_2SO_4. The solvent was partially removed *in vacuo* by rotary evaporation affording the crude butanone **1c** (13.24 g, 8.5 wt%[9], 63% yield) in ≈ 7 volume equivalents of DCM.

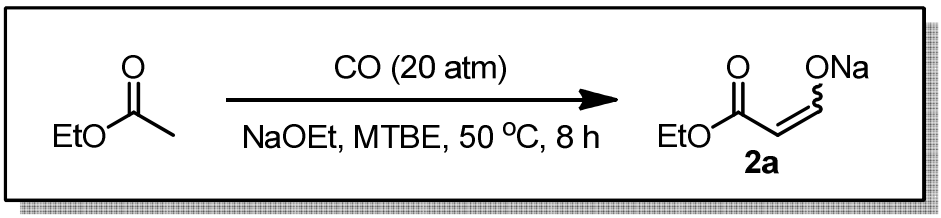
[8] Reaction Progress was determined by quenching an small aliquot (≈ 0.1 mL) of the reaction mixture with a small aliquot (>0.05 mL) of morpholine in DCM and analyzing the conversion by ^{1}H NMR spectroscopy

[9] Weight percent assays were performed via ^{1}H NMR using dimethyl fumarate as an internal standard. Note that for all butenones synthesized from acid chlorides were stored and used as crude solutions in DCM. Again the impurities were solvent, pyridine, and residual water.

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 1.02 (t, *J*=7.50 Hz, 3 H) 1.38 (t, *J*=7.10 Hz, 3 H) 2.03 (tq, *J*=17.30, 7.60 Hz, 2 H) 4.05 (q, *J*=7.00 Hz, 2 H) 5.95 (dt, *J*=12.42, 1.30 Hz, 1 H) 7.81 (d, *J*=12.33 Hz, 1 H)

Synthesis of Enolates

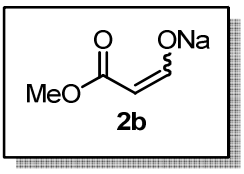
General Procedure A: *Via* α-Carbonylation of Enolizable Species



A stainless steel autoclave (HEL Autolab High Pressure Reactor) was charged with ethyl acetate (6.6mL, 67.4 mmol, 1.35 equiv.) and MTBE (22 mL). NaOEt (3.4g, 49.9 mmol, 1.0 equiv.) was added all at once and the autoclave was sealed. The autoclave was pressurized with nitrogen and then evacuated twice. The autoclave was then pressurized with CO and then evacuated twice (**CAUTION!** Carbon monoxide is highly toxic and should be handled in a well-ventilated hood equipped with a CO detector). The autoclave was pressurized with 20 atm (290 psi) of CO. The heterogeneous mixture was stirred for about 10-15 minutes. After this time, the autoclave was heated to 50 °C for 10 h. After this time the autoclave was cooled down to room temperature, evacuated and the contents were filtered through a paper filter with a Büchner funnel. The crude off-white solid was rinsed with MTBE (10 mL) followed by hexanes (20 mL). The solid was transferred to a flask an allowed to dry overnight under vacuum to give the desired enolate[10] (6.3 g, 92 wt%,[11] 82% yield) as a pale yellow powdery solid.

^{1}H NMR (D_2O, 500 MHz) 1.17 (t, *J*=7.10 Hz, 3 H) 4.01 (q, *J*=6.87 Hz, 2 H) 8.56 (s, 1 H) **^{13}C NMR** (D_2O, 100 MHz) δ ppm 13.81 (CH_3) 59.69 (CH_2) 89.55 (t, $J_{C\text{-}D}$=24.20 Hz, CD) 174.97 (s, C) 179.17 (s, CH)

Enolate Product Data[12]



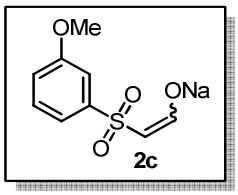
Sodium 3-methoxy-3-oxoprop-1-en-1-olate, 2b (9.0 g, 73 wt% 86%) was prepared *via* General Procedure A for the preparation of enolates from methyl acetate (6.6 mL, 83.6 mmol, 1.35 equiv.) ***with the following modifications:*** NaOMe (3.34 g, 61.9 mmol, 1 equiv.) was used instead of NaOEt. **2b** was obtained as a off-white powdery solid. **^{1}H NMR** (D_2O, 500

[10] Note that while enolates are stable to atmospheric conditions, they are somewhat hygroscopic and are recommended to be stored in a sealed container to minimize water absorption

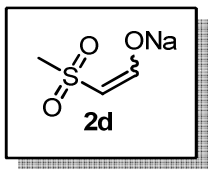
[11] Weight percent assays were performed in D_2O via ^{1}H NMR using triethanolamine as an internal standard

[12] Note that the olefinic proton between the EWG and the sodium enolate under goes rapid exchange in D_2O and is not observed in ^{1}H NMR spectra. C-D coupling is observed in some of the ^{13}C, confirming this observation.

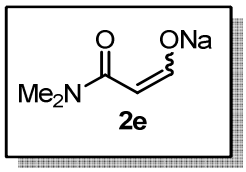
MHz) δ ppm 3.66 (s, 3 H) 8.39 (s, 1 H) **^{13}C NMR** (D_2O, 100 MHz) 67.17 (CH_3) 88.15 (br. CD) 180.21 (C) 184.15 (CH)



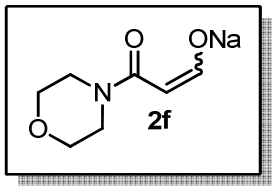
Sodium 2-((3-methoxyphenyl)sulfonyl)ethenolate, 2c (6.5 g, 73 wt%, 61%) was prepared *via* General Procedure A for the preparation of enolates from 3-methoxyphenylmethyl sulfone (8.3 g, 44.6 mmol, 1.35 equiv.) and sodium ethoxide (2.2 g, 33.0 mmol, 1.0 equiv.) **2c** was obtained as a light yellow powdery solid. **^{1}H NMR** (D_2O, 500 MHz) δ ppm 3.72 (s, 3 H) 6.98 (dt, *J*=7.44, 2.00 Hz, 1 H) 7.23 (s, 1 H) 7.28 - 7.37 (m, 2 H) 8.28 (s, 1 H) **^{13}C NMR** (D_2O, 100 MHz) 55.61 (CH_3) 92.69 (br., CD) 110.24 (CH) 117.64 (CH) 118.06 (CH) 130.61 (CH) 141.35 (C) 159.55 (br., C) 175.66 (CH)



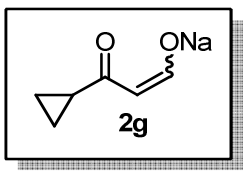
Sodium 2-(methylsulfonyl)ethenolate, 2d (4.98 g, 52 wt%, 36%) was prepared *via* General Procedure A for the preparation of enolates from dimethylsulfone (4.7 g, 50 mmol, 1 equiv.) and sodium ethoxide (3.74 g, 55 mmol, 1.1 equiv.) ***with the following modifications:*** The reaction was performed in toluene at 70 °C for 18h with an excess of sodium ethoxide. **2d** was obtained as an orange-brown powdery solid.[13] **^{1}H NMR** (D_2O, 400 MHz) δ ppm 3.02 (s, 3 H) 8.15 (s, 1 H) **^{13}C NMR** (D_2O, 100 MHz) 45.98 (CH_3) 129.16 (br. CD) 192.89 (CH)



Sodium 3-methoxy-3-oxoprop-1-en-1-olate, 2e (7.75 g, 91 wt%, 81%) was prepared *via* General Procedure A for the preparation of enolates from dimethylacetamide (7.9 mL, 87.12 mmol, 1.35 equiv.) and sodium ethoxide (4.27g, 62 mmol, 1 equiv.). **2e** was obtained as a pale yellow powdery solid. **^{1}H NMR** (D_2O, 500 MHz) δ ppm 2.84 (s, 6 H) 8.28 (s, 1 H) **^{13}C NMR** (D_2O, 100 MHz) 34.35 (CH_3) 38.09 (CH_3) 90.79 (t, $J_{C\text{-}D}$ =23.50 Hz, CD) 172.81 (C) 174.75 (CH)

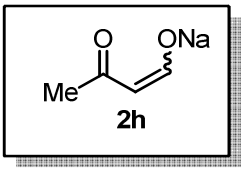


Sodium 3-morpholino-3-oxoprop-1-en-1-olate, 2f (0.6 g, 77 wt% 61%) was prepared *via* General Procedure A for the preparation of enolates from morpholinoacetamide (0.72 g, 5.6 mmol, 1.35 equiv.) and sodium ethoxide (0.28 g, 4.1 mmol, 1 equiv.) **2f** was obtained as a pale yellow powdery solid. **^{1}H NMR** (D_2O, 500 MHz) δ ppm 3.45 (t, *J*=4.60 Hz, 4 H) 3.64 (t, *J*=4.10 Hz, 4 H) 8.41 (s, 1 H) **^{13}C NMR** (D_2O, 100 MHz) 43.76 (br. CH_2) 66.49 (CH_2) 89.90 (t, $J_{C\text{-}D}$=23.10 Hz, CD) 172.85 (C) 176.45 (CH)

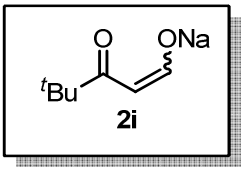


Sodium 3-cyclopropyl-3-oxoprop-1-en-1-olate, 2g (7.46 g, 83 wt%, 84%) was prepared *via* General Procedure A for the preparation of enolates from cyclopropylmethylketone (6.9 mL, 73.6 mmol, 1.35 equiv.) and sodium ethoxide (3.7 g, 54.5 mmol, 1 equiv.). **2g** was obtained as a pale yellow powdery solid. **^{1}H NMR** (D_2O, 500 MHz) δ ppm 0.68 - 0.88 (m, 4 H) 1.69 - 2.36 (br. m, 1 H) 8.95 (br. s., 1 H) **^{13}C NMR** (D_2O, 100 MHz) 8.35 (CH_2) 16.02 (CH) 105.30 (br., CD) 182.95 (br., CH) 202.01 (C)

[13] This enolate is especially hygroscopic so care should be taken when filtering during workup



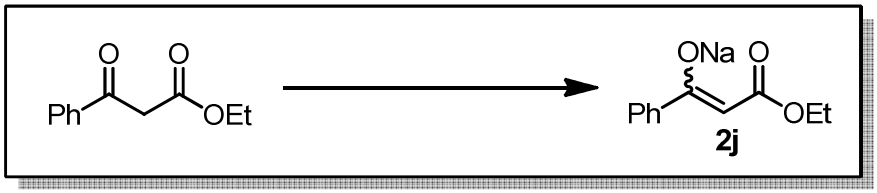
Sodium 3-oxobut-1-en-1-olate, 2h (35 g, 97 wt%, 76%) was prepared *via* General Procedure A for the preparation of enolates from acetone (37.5 mL, 511 mmol, 1.25 equiv.) ***with the following modifications:*** **2h** was obtained as a powdery light yellow powdery solid. **^{1}H NMR** (D_2O, 500 MHz) δ ppm 2.08 (br. s., 3 H) 8.89 (br. s, 1 H) **^{13}C NMR** (D_2O, 100 MHz) 22.31 (br., CH_3) 186.15 (br., CH) 104.28 (br, CD) 199.94 (br., C)



Sodium 4,4-dimethyl-3-oxopent-1-en-1-olate, 2i (6.09 g, 87 wt% 61%) was prepared *via* General Procedure A for the preparation of enolates from pinacolone (9.76 mL, 78.1 mmol, 1.35 equiv.) and sodium ethoxide (3.93 g, 57.8 mmol, 1 equiv.) **2i** was obtained as a pale yellow powdery solid. **^{1}H NMR** (D_2O, 500 MHz) δ ppm 1.03 (s, 9 H) 8.86 (s, 1 H) **^{13}C NMR** (D_2O, 100 MHz) 27.18 (CH_3) 40.66 (C) 99.70 (t, + =23.80 Hz, CD) 183.92 (CH) 209.19 (C)

Synthesis of Enolates

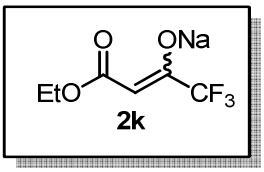
General Procedure B: *Via* Deprotonation of keto-esters



Sodium 3-ethoxy-3-oxo-1-phenylprop-1-en-1-olate, 2j

To a two-neck 250 mL round bottom flask equipped with a stir bar, rubber septum, and an N_2 inlet adapter was added the sodium ethoxide (1.7g, 24.7 mmol, 1 equiv) and MTBE (25 mL). The mixture was allowed to stir at room temperature for approximately five minutes and then ethyl benzoyl acetate (4.2 mL, 26.03 mmol, 1.05 equiv) was charged over 30 min. The mixture was allowed to stir at room temperature for 2 h, then hexanes (25 mL) were charged. The resulting heterogeneous mixture was stirred for another 2 h, then it was filtered through a paper filter with a Büchner funnel. The crude off-white solid was rinsed with hexanes (20 mL). The solid was transferred to a flask an allowed to dry overnight under vacuum to give the desired enolate **2j** (3.75 g, 74 wt%, 50% yield) as a white powdery solid.

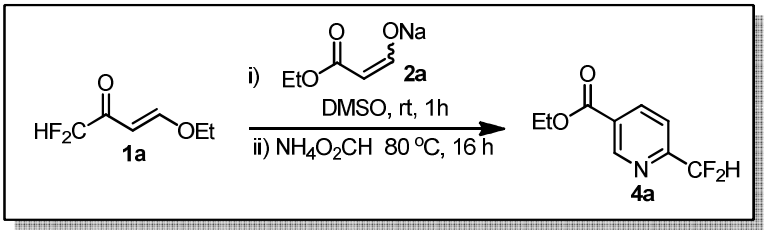
^{1}H NMR (D_2O, 500 MHz) 1.20 (t, *J*=6.18 Hz, 3 H) 4.04 (q, *J*=6.90 Hz, 2 H) 7.35 (br. s., 3 H) 7.58 (br. s., 2 H) **^{13}C NMR** (D_2O, 100 MHz) δ ppm 16.80 (CH_3) 57.41 (CH_2) 81.34 (br, CD) 128.63 (CC) 128.86 (CH) 131.20 (C) 134.14 (CH) 175.18 (C) 199.65 (CH)



Sodium 4-ethoxy-1,1,1-trifluoro-4-oxobut-2-en-2-olate, 2k (2.2 g, 96.3 wt% 38%) was prepared *via* General Procedure B for the preparation of enolates from sodium ethoxide (1.7 g, 25.8 mmol, 1.0 equiv.) and Ethyl 4,4,4-trifluoroacetoacetate (5 g, 27.1 mmol, 1.05 equiv.) ***with the following modifications:*** MTBE was replaced by hexanes (25 mL) and the filtration was performed after cooling the reaction mixture at 0 °C. **2k** was obtained as a powdery white solid.

^{1}H NMR (D_2O, 500 MHz) 1.20 (t, *J*=7.30 Hz, 3 H) 4.06 (q, *J*=6.87 Hz, 2 H) δ ppm **^{13}C NMR** (D_2O, 100 MHz) 16.76 (CH_3) 57.39 (CH_2) 82.09 (t, $J_{C\text{-}D}$ =24.20 Hz, CD) 123.30 (q, $J_{C\text{-}F}$ =285.98 Hz, CF_3) 160.32 (C) 167.42 (q, $J_{C\text{-}C\text{-}F}$= 30.10 Hz, C) **^{19}F NMR** (D_2O, 377 MHz) δ ppm -86.61 (s)

General Procedure for the Preparation of Difluoromethyl Pyridines



Ethyl 6-(difluoromethyl)nicotinate, **4a**

To a two-neck 50 mL round bottom flask equipped with stir bar, rubber septum, and an N_2 inlet adapter was added the sodium enolate, **2a** (0.86 g, 91 wt%, 5.9 mmol, 1.15 equiv) and DMSO (4.7 mL). The mixture was allowed to stir at room temperature for approximately five minutes until complete dissolution of the enolate, giving a clear yellow-orange solution. At this time, the butenone, **1a** (0.79g, 4.9 mmol, 92 wt%, 1 equiv) dissolved in DMSO (1 mL) was added dropwise over 10 minutes to the flask *via* a syringe. The reaction mixture was stirred at room temperature for 1 h and gradually turned red-orange. Once complete conversion to the intermediate was attained,[14] HCO_2NH_4 (0.62g, 13.8 mmol, 2 equiv.) was added to the flask all at once and the solution was allowed to stir at room temperature for 1 h. After this time, the reaction temperature was ramped to 80 °C over 1 h and was incubated at that temperature for overnight (12–16h). Once the reaction was judged complete,[15] the contents of the flask were transferred to a separatory funnel and diluted with 10-20 mL of MTBE. The flask was rinsed thoroughly with deionized water (10-20 mL) and back extracted with MTBE (10-20 mL) and the rinses were added to the separatory funnel. The combine MTBE layers were dried with Na_2SO_4. The solvent removed *in vacuo* by rotary evaporation to afford a crude red liquid. Further purification was accomplished by flash column chromatography (0 to 20% MTBE in hexanes)[16] to afford **4a** as a clear yellow oil (0.87g, 91%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 1.42 (t, *J*=7.15 Hz, 3 H) 4.44 (q, *J*=7.14 Hz, 2 H) 6.67 (t, *J*=55.20 Hz, 1 H) 7.72 (d, *J*=8.10 Hz, 1 H) 8.44 (d, *J*=8.19 Hz, 1 H) 9.23 (s, 1 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 14.22 (CH_3) 61.87 (CH_2) 113.55 (t, $J_{C\text{-}F}$=241.00 Hz, CF_2H) 119.81 (CH) 127.99 (C) 138.53 (CH) 150.62 (CH) 156.12 (t, $J_{C\text{-}C\text{-}F}$ =26.00 Hz, C) 164.47 (C) **^{19}F NMR** ($CDCl_3$, 377 MHz) δ ppm -118.75 (d, *J*=55.21 Hz) **FT-IR** (cm^{-1}, neat, ATR) 2986 (vw, br.) 1723 (s) 1370 (m) 1280 (s, br.) 1113 (m) 1087 (m) 1044 (s) 1025 (vs) 838 (m) 737 (m) **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_9H_9F_2NO_2$: 202.0674, found: 202.0670.

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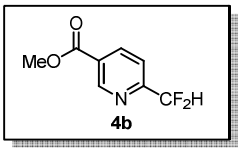
[14] Note that, it is possible that intermediate enolate formation is completed much sooner (<1 hr) due to the rapid appearance a red coloration after addition of the butenone. However, it is recommended that the reaction is monitored by LC-MS to determine reaction progress. If no conversion is observed, heating the reaction to 50 °C for 1 h may be required.

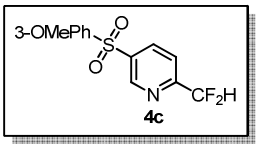
[15] Determined by UPLC and/or LC-MS analysis. In most cases, the reaction was complete after only 12 h but in some cases (indicated below) additional heating or higher temperatures were needed.

[16] MTBE was selected as an eluent as it does not absorb at the same wavelength as the pyridines synthesized in this study (220 nm)

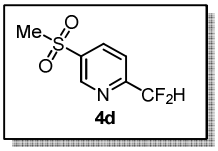
Pyridine Product Data



Methyl 6-(difluoromethyl)nicotinate[17]**, 4b** (0.6 g, 87%) was prepared according to the representative procedure from enolate **2b** (0.72 g, 73 wt%, 4.3 mmol, 1.15 equiv.). **4b** was obtained as a powdery white solid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm 3.98 (s, 3 H) 6.67 (t, *J*=55.20 Hz, 1 H) 7.73 (d, *J*=8.01 Hz, 1 H) 8.44 (d, *J*=8.01 Hz, 1 H) 9.23 (s, 1 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 52.92 (CH_3) 113.61 (t, $J_{C\text{-}F}$=241.40 Hz, CF_2H) 120.05 (t, $J_{C\text{-}C\text{-}C\text{-}F}$ =2.93 Hz, CH) 127.81 (C) 138.76 (CH) 150.81 (CH) 156.38 (t, $J_{C\text{-}C\text{-}F}$=26.00 Hz, C) 165.15 (C) **^{19}F NMR** ($CDCl_3$, 377 MHz) -118.81 (d, *J*=55.21 Hz) **FT-IR** (cm^{-1}, neat, ATR) 3073 (vw, br.) 1722 (s) 1602 (m) 1444 (m) 1280 (s, br.) 1118 (s) 1079 (s) 1017 (vs) 866 (s) **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_8H_7F_2NO_2$: 188.0518, found: 188.0512.

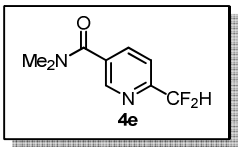


2-(Difluoromethyl)-5-((3-methoxyphenyl)sulfonyl)pyridine, 4c (1.1 g, 98%) was prepared according to the representative procedure from enolate **2c** (1.38 g, 73 wt%, 4.3 mmol, 1.15 equiv.) ***with the following modifications:*** Ethyl acetate in hexane (50:50) was used to perform the purification by flash chromatography. **4c** was obtained as a powdery light brown solid. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm 3.86 (s, 3 H) 6.48 - 6.81 (m, 1 H) 7.14 (ddd, *J*=8.47, 2.52, 0.92 Hz, 1 H) 7.43 - 7.48 (m, 2 H) 7.54 (*apparent doublet of quartets*, *J*=7.80, 0.90 Hz, 1 H) 7.77 (d, *J*=8.24 Hz, 1 H) 8.35 (dd, *J*=8.24, 2.29 Hz, 1 H) 9.15 (d, *J*=1.90 Hz, 1 H) **^{13}C NMR** ($CDCl_3$, 125 MHz) 56.00 (CH_3) 113.12 (t, $J_{C\text{-}F}$=241.00 Hz, CF_2H) 112.76 (CH) 120.29 (CH) 120.63 (CH) 120.78 (t, $J_{C\text{-}C\text{-}C\text{-}F}$=2.98 Hz, CH) 131.11 (CH) 137.07 (CH) 140.19 (t, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$ =1.67 Hz, CH) 141.45 (C) 148.62 (CH) 156.67 (t, $J_{C\text{-}C\text{-}F}$ =26.20 Hz, C) 160.59 (C) δ ppm **^{19}F NMR** ($CDCl_3$, 377 MHz) -118.98 (d, *J*=55.21 Hz) **FT-IR** (cm^{-1}, neat, ATR) 3067 (vw, br.) 1597 (m) 1585 (m) 1483 (m) 1313 (s) 1257 (s) 1159 (s) 1092 (s) 1043 (s) 1029 (s) 879 (m)) **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{13}H_{11}F_2NO_3S$: 300.0500, found: 300.0492.

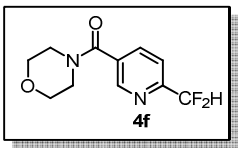


2-(Difluoromethyl)-5-(methylsulfonyl)pyridine, 4d (1.38 g, 83%) was prepared according to the representative procedure from **1a** (1.33 g, 90.7 wt%, 8 mmol, 1 equiv) and **2d** (2.63 g, 52.63 wt%, 9.6 mmol, 1.2 equiv) ***with the following modifications:*** 1) After solvent removal post-workup, a dark brown solid was obtained. This solid was washed thoroughly with hexanes and was dried under vacuum to give **4d** as a grannular light brown solid. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm 3.15 (s, 3 H) 6.71 (t, *J*=54.90 Hz, 1 H) 7.87 (d, *J*=8.24 Hz, 1 H) 8.40 (dd, *J*=8.24, 2.20 Hz, 1 H) 9.19 (d, *J*=1.37 Hz, 1 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 44.96 (CH_3) 113.04 (t, $J_{C\text{-}F}$=241.70 Hz, CF_2H) 120.85 (t, $J_{C\text{-}C\text{-}C\text{-}F}$=2.90 Hz, CH) 137.19 (CH) 138.75 (t, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$=1.50 Hz, C) 148.61 (CH) 157.39 (t, $J_{C\text{-}C\text{-}F}$=26.40 Hz, C) **^{19}F NMR** ($CDCl_3$, 377 MHz) δ ppm -118.99 (d, *J*=54.71 Hz) **FT-IR** (cm^{-1}, neat, ATR) 3033 (vw) 2933 (vw) 1587 (vw) 1372 (m) 1284 (m) 1149 (m) 1101 (s) 936 (m) 786 (m) 532 (vs) **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_7H_7F_2NO_2S$: 208.0238, found: 208.0239.

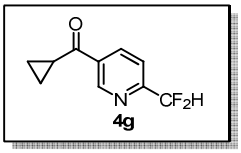
[17] Fujiwara, Y.; Dixon, J. A.; Rodriguez, R. A.; Baxter, R. D.; Dixon, D. D.; Collins, M. R.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 1494



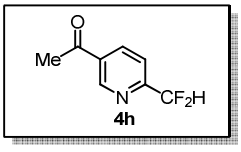
6-(Difluoromethyl)-N,N-dimethylnicotinamide, 4e (0.55 g, 74%) was prepared according to the representative procedure from enolate **2e** (0.64 g, 91wt%, 4.3 mmol, 1.15 equiv.) ***with the following modifications:*** Ethyl acetate in hexane (50:50) was used to perform the purification by flash chromatography. **4e** was obtained as a thick, clear yellow oil. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm 3.02 (br. s, 3 H) 3.15 (br. s, 3 H) 6.66 (t, *J*=55.40 Hz, 1 H) 7.70 (d, *J*=7.78 Hz, 1 H) 7.92 (dd, *J*=8.01, 2.06 Hz, 1 H) 8.71 (d, *J*=1.37 Hz, 1 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 35.39 (CH_3) 39.40 (CH_3) 113.48 (t, $J_{C\text{-}F}$=240.60 Hz, CF_2H) 119.95 (t, $J_{C\text{-}C\text{-}C\text{-}F}$ =3.30 Hz, CH) 133.94 (t, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$=1.65 Hz, C) 136.27 (CH) 147.74 (CH) 153.37 (t, $J_{C\text{-}C\text{-}F}$ =25.90 Hz, C) 168.03 (C) **^{19}F NMR** ($CDCl_3$, 377 MHz) δ ppm -118.41 (d, *J*=55.20 Hz) **FT-IR** (cm^{-1}, neat, ATR) 2937 (vw, b.) 1628 (vs) 1400 (m) 1374 (m) 1087 (s) 1023 (vs) 847 (m) **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_9H_{10}F_2N_2O$: 201.0834, found: 201.0842.



(6-(Difluoromethyl)pyridin-3-yl)(morpholino)methanone, 4f (0.4 g, 98%) was prepared according to the representative procedure from **2f** (0.48 g, 72wt%, 1.9 mmol, 1.15 equiv.). **4f** was obtained as a tan powdery solid. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm 3.31 - 3.96 (br. m, 8 H) 6.66 (t, *J*=55.40 Hz, 1 H) 7.72 (d, *J*=7.78 Hz, 1 H) 7.91 (dd, *J*=8.01, 2.06 Hz, 1 H) 8.70 (d, *J*=1.37 Hz, 1 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 42.77 (CH_2) 48.29 (CH_2) 66.82 (CH_2) 113.52 (t, $J_{C\text{-}F}$=240.80 Hz, CF_2H) 120.22 (t, $J_{C\text{-}C\text{-}C\text{-}F}$=3.12 Hz, CH) 133.06 (t, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$=1.65 Hz, C) 136.54 (CH) 147.84 (CH) 153.92 (t, $J_{C\text{-}C\text{-}F}$=25.90 Hz, C) 166.95 (C) **^{19}F NMR** ($CDCl_3$, 377 MHz) δ ppm -118.47 (d, *J*=55.21 Hz) **FT-IR** (cm^{-1}, neat, ATR) 2992 (vw) 2866 (vw, br.) 1625 (vs) 1600 (m) 1467 (m) 1442 (m) 1363 (m) 1286 (m) 1109 (s) 1034 (vs) 1003 (s) 848 (s) **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{11}H_{12}F_2N_2O_2$: 243.0940, found: 243.0938.

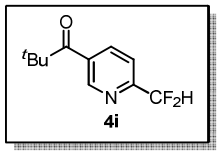


Cyclopropyl(6-(difluoromethyl)pyridin-3-yl)methanone, 4g (0.69 g, 94%) was prepared according to the representative procedure from enolate **2g** (0.69 g, 82 wt%, 4.3 mmol, 1.15 equiv.). **4g** was obtained as a clear, pale yellow oil. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm 1.16 (dq, *J*=7.67, 3.70 Hz, 2 H) 1.33 (quin, *J*=3.89 Hz, 2 H) 2.65 (tt, *J*=7.78, 4.58 Hz, 1 H) 6.69 (t, *J*=55.40 Hz, 1 H) 7.76 (d, *J*=8.24 Hz, 1 H) 8.39 (dd, *J*=8.24, 1.83 Hz, 1 H) 9.25 (d, *J*=1.37 Hz, 1 H) **^{13}C NMR** ($CDCl_3$, 125 MHz) δ ppm 12.61 (CH_2) 17.98 (CH) 113.56 (t, $J_{C\text{-}F}$=241.00 Hz, CF_2H) 120.17 (CH) 134.50 (C) 136.89 (CH) 149.27 (CH) 155.84 (t, $J_{C\text{-}C\text{-}F}$=25.30 Hz, C) 198.85 (C) **^{19}F NMR** ($CDCl_3$, 377 MHz) δ ppm 118.74 (d, *J*=55.20 Hz) **FT-IR** (cm^{-1}, near, ATR) 3012(vw, br.) 1674 (s) 1595 (m) 1371 (s) 1236 (s) 1087 (s) 1038 (vs) 959 (vs) 840 (m) 743 (m) **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{10}H_9F_2NO$: 198.0725, found: 198.0.723.

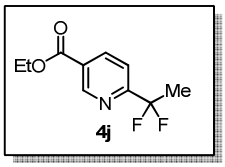


1-(6-(Difluoromethyl)pyridin-3-yl)ethanone, 4h (0.18 g, 79%) was prepared according to the representative procedure from enolate **2h** (0.15 g, 97 wt%, 1.3 mmol, 1.05 equiv.) ***with the following modifications:*** 1) Portion-wise addition of HCO_2NH_4 was performed (1.2-1.5 equiv). 2) After addition of HCO_2NH_4, the reaction mixture was heated to 40 °C for 12h. **4h** was obtained as a clear pale brown oil. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm 2.66 (d, *J*=1.37 Hz, 3 H) 6.66 (t, *J*=55.10 Hz, 1 H) 7.75 (d, *J*=8.24 Hz, 1 H) 8.36 (d, *J*=8.24 Hz, 1 H) 9.16 (s, 1 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 26.77 (CH_3) 113.39 (t, $J_{C\text{-}F}$=241.00 Hz, CF_2H) 120.11 (t, $J_{C\text{-}C\text{-}C\text{-}F}$ =3.30 Hz, CH) 133.46 (t, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$ =1.50 Hz, C) 137.00 (CH) 149.52 (CH) 155.96 (t, $J_{C\text{-}C\text{-}F}$

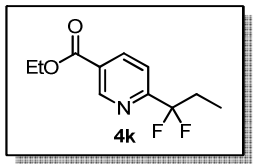
=25.90 Hz, C) 196.01 (C) **^{19}F NMR** ($CDCl_3$, 377 MHz) δ ppm -118.85 (d, *J*=55.20 Hz) **FT-IR** (cm^{-1}, neat, ATR) 1691 (vs) 1597 (m) 1373 (s) 1092 (vs) 1039 (vs) 1021 (vs) 840 (s) 713 (m, br.) **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_8H_7F_2NO$: 172.0568, found: 172.0575.



1-(6-(Difluoromethyl)pyridin-3-yl)-2,2-dimethylpropan-1-one, 4i (0.47 g, 59%) was prepared according to the representative procedure from **2i** (0.74 g, 87 wt%, 4.3 mmol) ***with the following modifications:*** Further purification was accomplished by flash column chromatography (Gradient: Hex to 95:5 to 9:1 Hex:MTBE). **4i** was obtained as a clear, colorless oil. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm 1.36 (s, 9 H) 6.66 (t, *J*=55.40 Hz, 1 H) 7.70 (d, *J*=8.24 Hz, 1 H) 8.11 (dd, *J*=8.24, 1.83 Hz, 1 H) 8.95 (d, *J*=1.37 Hz, 1 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 27.67 (CH_3) 44.78 (C) 113.66 (t, $J_{C\text{-}F}$ =240.60 Hz, CF_2H) 119.89 (t, $J_{C\text{-}C\text{-}C\text{-}F}$=2.93 Hz, CH) 135.89 (t, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$=1.80 Hz, C) 136.98 (CH) 148.56 (CH) 154.42 ($J_{C\text{-}C\text{-}F}$, *J*=26.40 Hz, C) 207.05 (C) **^{19}F NMR** ($CDCl_3$, 377 MHz) -118.69 (d, *J*=56.21 Hz) **FT-IR** (cm^{-1}, neat, ATR) 2974 (w, br) 1682 (m) 1374 (m) 1088 (s) 1040 (vs) 960 (s) 871 (m) **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{11}H_{13}F_2NO$: 214.1038, found: 214.1043.

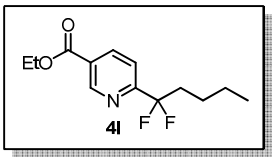


Ethyl 6-(1,1-difluoroethyl)nicotinate, 4j (0.455 g, 83%) was prepared according to the representative procedure from butanone **1b** (1.5 g, 28 wt%, 2.6 mmol, 1.0 equiv.) ***with the following modifications:*** 1) The round bottom flask was equipped with a Dean-Stark trap and reflux condenser when heating was initiated. This allowed for removal of the DCM that **1c** was dissolved in prior to its addition into the reaction mixture. Further purification was accomplished by flash column chromatography (Gradient: Hex to 9:1 Hex:MTBE). **4j** was obtained as a clear, colorless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm 1.42 (t, *J*=7.11 Hz, 3 H) 2.03 (t, *J*=18.67 Hz, 3 H) 4.44 (q, *J*=7.02 Hz, 2 H) 7.73 (d, *J*=8.19 Hz, 1 H) 8.40 (d, *J*=8.28 Hz, 1 H) 9.23 (s, 1 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 14.25 (CH_3) 23.16 (t, *J*=27.50 Hz, CH_3) 61.76 (CH_2) 120.72 (t, $J_{C\text{-}F}$=239.20 Hz, CF_2H) 119.11 (t, $J_{C\text{-}C\text{-}C\text{-}F}$ =4.20 Hz, CH) 127.33 (t, $J_{C\text{-}C\text{-}C\text{-}F}$=1.50 Hz, C) 138.38 (CH) 150.44 (CH) 158.74 ($J_{C\text{-}C\text{-}F}$, *J*=29.70 Hz, C) 164.60 (C) **^{19}F NMR** ($CDCl_3$, 377 MHz) δ ppm -93.48 (q, *J*=18.91 Hz) **FT-IR** (cm^{-1}, neat, ATR) 2986 (vw, br.) 1722 (s) 1600 (w) 1394 (w) 1275 (s) 1182 (m) 1115 (vs) 1026 (m) 918 (m) 856 (w) 790 (m) 736 (m) 635 (w) **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{10}H_{11}F_2NO_2$: 216.0831, found: 216.0834.

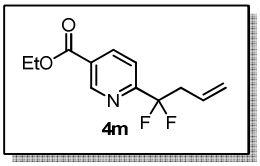


Ethyl 6-(1,1-difluoropropyl)nicotinate, 4k (1.16 g, 81%) was prepared according to the representative procedure from **1c** (13.16 g, 8.5 wt%, 6.28 mmol, 1 equiv) and **2a** (1.18 g, 88 wt%, 7.53 mmol, 1.2 equiv) ***with the following modifications:*** 1) The round bottom flask was equipped with a Dean-Stark trap and reflux condenser when heating was initiated. This allowed for removal of the DCM that **1c** was dissolved in prior to its addition into the reaction mixture. Further purification was accomplished by flash column chromatography (Gradient: Hex to 9:1 Hex:MTBE) **4k** was obtained as a clear, light yellow oil. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm 0.99 (t, *J*=7.55 Hz, 3 H) 1.41 (t, *J*=7.32 Hz, 3 H) 2.34 (tq, *J*=16.90, 7.30 Hz, 2 H) 4.43 (q, *J*=7.02 Hz, 2 H) 7.70 (d, *J*=8.24 Hz, 1 H) 8.39 (dd, *J*=8.24, 1.83 Hz, 1 H) 9.23 (s, 1 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 6.44 (t, $J_{C\text{-}C\text{-}C\text{-}F}$=5.14 Hz, CH_3) 14.33 (CH_3) 29.67 (t, $J_{C\text{-}C\text{-}F}$=25.90 Hz, CH_2) 61.82 (CH_2) 121.88 (t, $J_{C\text{-}F}$=242.10 Hz, CF_2H) 119.81 (t, $J_{C\text{-}C\text{-}C\text{-}F}$=4.70 Hz,

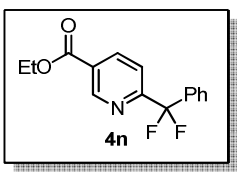
CH) 127.24 (t, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$=1.50 Hz, C) 138.31 (CH) 150.65 (CH) 158.38 (t, $J_{C\text{-}C\text{-}F}$=29.70 Hz, C) 164.72 (C) **^{19}F NMR** ($CDCl_3$, 377 MHz) δ ppm -103.57 (t, *J*=16.56 Hz) **FT-IR** (cm^{-1}, neat, ATR) 2985 (w) 2946 (vw, br.) 1723 (s) 1600 (w) 1277 (vs) 1174 (m) 1109 (s) 1026 (s) 984 (s) 945 (m) 856 (m) 785 (m) 736 (m) **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{11}H_{13}F_2NO_2$: 230.0987, found: 230.0990.



Ethyl 6-(1,1-difluoropentyl)nicotinate, 4l (1.31 g, 88%) was prepared according to the representative procedure from **1d** (12.36 g, 9.56 wt%, 5.78 mmol, 1 equiv) and **2a** (1.09 g, 88 wt%, 6.94 mmol, 1.2 equiv) ***with the following modifications:*** 1) The round bottom flask was equipped with a Dean-Stark trap and reflux condenser when heating was initiated. This allowed for removal of the DCM that **1d** was dissolved in prior to its addition into the reaction mixture. Further purification was accomplished by flash column chromatography (Gradient: Hex to 95:5 Hex:MTBE). **4l** was obtained as a clear, pale yellow-orange oil. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm 0.89 (t, *J*=7.10 Hz, 3 H) 1.24 - 1.47 (m, 7 H) 2.12 - 2.44 (m, 2 H) 4.44 (q, *J*=7.32 Hz, 2 H) 7.70 (d, *J*=8.70 Hz, 1 H) 8.40 (dd, *J*=8.24, 1.83 Hz, 1 H) 9.24 (s, 1 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 13.97 (CH_3) 14.41 (CH_3) 22.57 (CH_2) 24.33 (t, $J_{C\text{-}C\text{-}C\text{-}F}$=4.00 Hz, CH_2) 36.15 (t, $J_{C\text{-}C\text{-}F}$ =24.90 Hz, CH_2) 61.88 (CH_2) 121.75 (t, $J_{C\text{-}F}$=242.10 Hz, CF_2H) 119.75 (t, $J_{C\text{-}C\text{-}C\text{-}F}$ =4.70 Hz, CH) 127.26 (t, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$=1.47 Hz, C) 138.38 (CH) 150.73 (CH) 158.69 (t, $J_{C\text{-}C\text{-}F}$=29.70 Hz, C) 164.80 (C) **^{19}F NMR** ($CDCl_3$, 377 MHz) δ ppm -101.60 (t, *J*=16.81 Hz) **FT-IR** (cm^{-1}, neat, ATR) 2962 (w) 2936 (w) 2875 (vw) 1724 (s) 1600 (w) 1275 (vs) 1173 (m) 1112 (s) 1007 (s) 857 (m) 791 (m) 773 (m) **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{13}H_{17}F_2NO_2$: 258.1300 found: 258.1302.

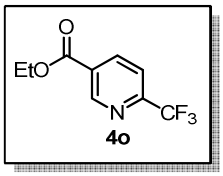


Ethyl 6-(1,1-difluorobut-3-en-1-yl)nicotinate, 4m (0.94 g, 70%) was prepared according to the representative procedure from **1e** (8.15 g, 13 wt%, 5.57 mmol, 1 equiv) and **2a** (1.05 g, 88 wt%, 6.69 mmol, 1.2 equiv) ***with the following modifications:*** 1) The round bottom flask was equipped with a Dean-Stark trap and reflux condenser when heating was initiated. This allowed for removal of the DCM that **1e** was dissolved in prior to its addition into the reaction mixture. Further purification was accomplished by flash column chromatography (Gradient: Hex to 9:1 Hex:MTBE). **4m** was obtained as a clear, yellow oil. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm 1.42 (t, *J*=7.32 Hz, 3 H) 3.12 (td, *J*=16.37, 7.10 Hz, 2 H) 4.44 (q, *J*=7.32 Hz, 2 H) 5.12 - 5.22 (m, 2 H) 5.73 (ddt, *J*=17.22, 10.24, 7.10, 7.10 Hz, 1 H) 7.69 (d, *J*=8.24 Hz, 1 H) 8.39 (dd, *J*=8.24, 1.83 Hz, 1 H) 9.25 (s, 1 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 14.31 (CH_3) 40.87 (t, *J*=25.70 Hz, CH_2) 61.82 (CH_2) 120.39 (t, $J_{C\text{-}F}$=243.20 Hz, CF_2H) 119.86 (t, $J_{C\text{-}C\text{-}C\text{-}F}$=4.40 Hz, CH) 121.05 ($CH_2$) 127.32 (t, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$=1.60 Hz, C) 128.59 (t, $J_{C\text{-}C\text{-}C\text{-}F}$=5.20 Hz, CH) 138.30 (CH) 150.60 (CH) 157.97 (t, $J_{C\text{-}C\text{-}F}$=29.30 Hz, C) 164.65 (C) **^{19}F NMR** ($CDCl_3$, 377 MHz) δ ppm -101.16 (t, *J*=16.56 Hz) **FT-IR** (cm^{-1}, neat, ATR) 3084 (vw) 2986 (vw, br.) 1723 (s) 1278 (vs) 1172 (m) 1111 (s) 1016 (s) 887 (m) 792 (m) 738 (m) **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{12}H_{13}F_2NO_2$: 242.0987, found: 242.0988.



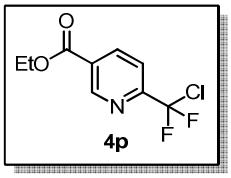
Ethyl 6-(difluoro(phenyl)methyl)nicotinate, 4n (1.68 g, 82%) was prepared according to the representative procedure from **1f** (8.21 g, 20.42 wt%, 7.41 mmol, 1 equiv) and **2a** (1.40 g, 88 wt%, 8.89 mmol, 1.2 equiv) ***with the following modifications:*** 1) The round bottom flask was equipped

with a Dean-Stark trap and reflux condenser when heating was initiated. This allowed for removal of the DCM that **1f** was dissolved in prior to its addition into the reaction mixture. Further purification was accomplished by flash column chromatography (Gradient: Hex to 9:1 Hex:MTBE). **4n** was obtained as a clear, light yellow oil. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm 1.40 (t, *J*=7.10 Hz, 3 H) 4.42 (q, *J*=7.32 Hz, 2 H) 7.36 - 7.48 (m, 3 H) 7.51 - 7.65 (m, 2 H) 7.82 (d, *J*=8.24 Hz, 1 H) 8.41 (dd, *J*=8.24, 1.37 Hz, 1 H) 9.23 (s, 1 H) **^{13}C NMR** ($CDCl_3$, 125 MHz) δ ppm 14.29 (CH_3) 61.80 (CH_2) 118.56 (t, J_{C-F}=244.10 Hz, CF_2H) 119.83 (t, $J_{C-C-C-F}$ =4.30 Hz, CH) 125.88 ($J_{C-C-C-F}$, *J*=6.00 Hz, CH) 127.10 (t, $J_{C-C-C-C-F}$, *J*=1.40 Hz, C) 128.56 (CH) 130.31 (t, $J_{C-C-C-C-F}$, *J*=1.67 Hz, CH) 136.15 (t, J_{C-C-F}, *J*=27.20 Hz, CH) 138.45 (C) 150.85 (CH) 158.95 (t, J_{C-C-F} =31.00 Hz, C) 164.57 (C) **^{19}F NMR** ($CDCl_3$, 377 MHz) δ ppm -98.03 (s) **FT-IR** (cm^{-1}, neat, ATR) 2983 (vw, br.) 1722 (s) 1273 (s, br.) 1112 (s) 1059 (s) 1025 (s) 962 (s) 855 (w, br.) 792 (m) 760 (m) 696 (vs) **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{15}H_{13}F_2NO_2$: 278.0987, found: 278.0975.



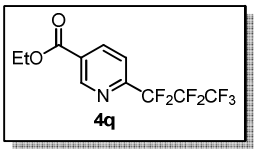
4o

Ethyl 6-(trifluoromethyl)nicotinate, 4o (2.26 g, 95%) was prepared according to the representative procedure from **1g** (6.89 g, 26.49 wt%, 10.85 mmol, 1 equiv) and **2a** (2.01 g, 89.5 wt%, 13.02 mmol, 1.2 equiv) ***with the following modifications:*** 1) The round bottom flask was equipped with a Dean-Stark trap and reflux condenser when heating was initiated. This allowed for removal of the MTBE that **1g** was dissolved in prior to its addition into the reaction mixture. Further purification was accomplished by flash column chromatography (Gradient: Hex to 95:5 Hex:MTBE). **4o** was obtained as a clear, colorless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm 1.43 (t, *J*=7.11 Hz, 3 H) 4.46 (q, *J*=7.11 Hz, 2 H) 7.78 (d, *J*=8.10 Hz, 1 H) 8.48 (d, *J*=8.37 Hz, 1 H) 9.30 (s, 1 H) **^{13}C NMR** ($CDCl_3$, 125 MHz) δ ppm 14.29 (CH_3) 62.21 (CH_2) 121.32 (q, J_{C-F}=274.50 Hz, CF_3) 120.27 (CH) 129.03 (C) 138.86 (CH) 151.31 (q, J_{C-C-F}=35.80 Hz, C) 151.14 (CH) 164.15 (C) **^{19}F NMR** ($CDCl_3$, 377 MHz) -70.44 (s) **FT-IR** (cm^{-1}, neat, ATR) 2987 (vw, br.) 1724 (s) 1332 (m) 1280 (s) 1176 (m) 1135 (s) 1112 (vs) 1083 (vs) 1025 (s) 859 (m, br.) 790 (m) 736 (w) **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_9H_8F_3NO_2$: 220.0580, found: 220.0587.



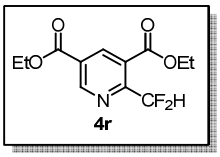
4p

Ethyl 6-(chlorodifluoromethyl)nicotinate, 4p (1.37 g, 83 %) was prepared according to the representative procedure from **1h** (10.91 g, 11.84 wt%, 7 mmol, 1 equiv) and **2a** (1.26 g, 92 wt%, 8.4 mmol, 1.2 equiv) ***with the following modifications:*** 1) The round bottom flask was equipped with a Dean-Stark trap and reflux condenser when heating was initiated. This allowed for removal of the DCM that **1h** was dissolved in prior to its addition into the reaction mixture. Further purification was accomplished by flash column chromatography (Gradient: Hex to 9:1 Hex:MTBE).**4p** was obtained as a clear, light yellow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm 1.43 (t, *J*=7.15 Hz, 3 H) 4.45 (q, *J*=7.14 Hz, 2 H) 7.75 (dd, *J*=8.23, 0.67 Hz, 1 H) 8.46 (dd, *J*=8.14, 2.02 Hz, 1 H) 9.29 (d, *J*=1.26 Hz, 1 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 14.26 (CH_3) 62.09 (CH_2) 118.99 (t, $J_{C-C-C-F}$=3.48 Hz, CH) 124.28 (t, J_{C-F}=291.40 Hz, CF_2Cl) 128.49 (C) 138.93 (CH) 150.95 (CH) 155.55 (t, J_{C-C-F}=29.00 Hz, C) 164.06 (C) **^{19}F NMR** ($CDCl_3$, 377 MHz) δ ppm -58.25 (s) **FT-IR** (cm^{-1}, neat, ATR) 2986 (vw, br) 1724 (m) 1276 (vs) 1111 (s) 1074 (s) 1025 (m) 924 (vs) 851 (m) 782 (m) 738 (m) 634 (w) **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_9H_8ClF_2NO_2$: 236.0284, found: 236.0295.



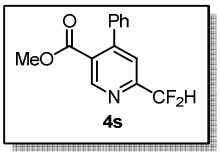
4q

Ethyl 6-(perfluoropropyl)nicotinate, 4q (1.63 g, 85%) was prepared according to the representative procedure from **1i** (13.53 g, 11.89 wt%, 6 mmol, 1 equiv) and **2a**(1.08 g, 92 wt%, 7.2 mmol, 1.2 equiv) ***with the following modifications:*** 1) The round bottom flask was equipped with a Dean-Stark trap and reflux condenser when heating was initiated. This allowed for removal of the DCM that **1i** was dissolved in prior to its addition into the reaction mixture. Further purification was accomplished by flash column chromatography (Gradient: Hex to 95:5 Hex:MTBE). **4q** was obtained as a clear pale yellow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm 1.43 (t, *J*=7.10 Hz, 3 H) 4.46 (q, *J*=7.32 Hz, 2 H) 7.78 (d, *J*=8.24 Hz, 1 H) 8.50 (dd, *J*=8.24, 2.29 Hz, 1 H) 9.34 (d, *J*=1.83 Hz, 1 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 14.24 (CH_3) 62.27 (CH_2) 109.08 (tq, $J_{C\text{-}F}$=266.30, $J_{C\text{-}C\text{-}F}$=38.10 Hz, CF_2) 112.89 (tt, $J_{C\text{-}F}$=255.30, $J_{C\text{-}C\text{-}F}$=30.40 Hz, CF_2) 118.05 (qt, $J_{C\text{-}F}$ =287.20, $J_{C\text{-}C\text{-}F}$=34.10 Hz, CF_3) 122.22 (t, $J_{C\text{-}C\text{-}C\text{-}F}$=4.40 Hz, CH) 129.03 (t, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$ =1.47 Hz, C) 138.63 (CH) 151.12 (t, $J_{C\text{-}C\text{-}F}$=25.30 Hz, C) 151.07 (CH) 164.25 C) **^{19}F NMR** ($CDCl_3$, 377 MHz) δ ppm -128.49 (s, 2 F) -117.29 (q, *J*=9.04 Hz, 2 F) -82.40 (t, *J*=9.29 Hz, 3 F) **FT-IR** (cm^{-1}, neat, ATR) 2989 (vw, b) 1728 (m) 1281 (m) 1204 (s) 1115 (vs) 1025 (m) 902 (m) 738 (m) **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{11}H_8F_7NO_2$: 320.0516, Found: 320.0511.



4r

Diethyl 2-(difluoromethyl)pyridine-3,5-dicarboxylate, 4r (0.724 g, 53%) was prepared according to the representative procedure from **1j**[18] (1.11 g, 5 mmol, 1 equiv) and **2a** (0.902 g, 88 wt%, 5.75 mmol, 1.2 equiv) ***with the following modifications:*** 1) The reaction was performed in a screw top reaction tube in a Mettler Toledo EasyMax^{TM} synthesis workstation. 2) Portion-wise addition of HCO_2NH_4 was performed (1.5 equiv, followed by 0.5 equiv after 3 h). Further purification was accomplished by flash column chromatography (Gradient: Hex to 7:3 Hex:MTBE). **4r** was obtained as a pale yellow powdery solid. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm 1.45 (t, *J*=7.32 Hz, 6 H) 4.47 (*apparent quartet of doublets*, *J*=7.17, 3.20 Hz, 4 H) 7.45 (t, *J*=54.00 Hz, 1 H) 8.86 (s, 1 H) 9.39 (d, *J*=1.83 Hz, 1 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 14.34 (CH_3) 14.48 (CH_3) 62.50 (CH_2) 62.91 (CH_2) 110.53 (t, $J_{C\text{-}F}$=241.40 Hz, CF_2H) 126.25 (t, $J_{C\text{-}C\text{-}C\text{-}F}$ =3.30 Hz, C) 127.94 (t, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$ =1.80 Hz, C) 140.18 (CH) 153.08 (CH) 155.01 (t, $J_{C\text{-}C\text{-}F}$ =22.40 Hz, C) 163.94 (C) 164.36 (C) **^{19}F NMR** ($CDCl_3$, 377 MHz) δ ppm -120.85 (d, *J*=54.71 Hz) **FT-IR** (cm^{-1}, neat, ATR) 3000 (w, br.) 1719 (vs) 1599 (w) 1241 (s, br.) 1194 (m) 1049 (vs) 1016 (s) 856 (m) **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{12}H_{13}F_2NO_4$: 274.0885, found: 274.0891.

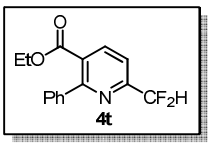


4s

Methyl 6-(difluoromethyl)-4-phenylnicotinate, 4s (1.001 g, 76%) was prepared according to the representative procedure from **1k** (1.06 g, 5 mmol, 1 equiv) and **2b** (1.02 g, 73.2 wt%, 6 mmol, 1.2 equiv) ***with the following modifications:*** 1) The reaction was performed in a screw top reaction tube in a Mettler Toledo EasyMax^{TM} synthesis workstation. 2) Conversion to intermediate **3s** required heating to 50 ^{o}C for 24 h. 3) Conversion from intermediate **3s** to the desired pyridine only required 2 h post addition of HCO_2NH_4. Further purification was accomplished by flash column chromatography (Gradient: Hex to 8:2 Hex:MTBE). **4s** was obtained as a bright yellow powdery solid. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm 3.72 (s, 3 H) 6.69 (t, *J*=55.10 Hz, 1 H) 7.28 - 7.39 (m, 2 H) 7.41 - 7.50 (m, 3 H) 7.66 (s, 1 H) 9.02 (d, *J*=0.92 Hz, 1 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 52.68 (CH_3) 113.61 (t, $J_{C\text{-}F}$=241.70 Hz, CF_2H)

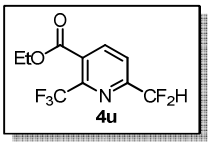
[18] Purchased commercially from Synquest Laboratories, freshly distilled before use.

121.59 (t, $J_{C\text{-}C\text{-}C\text{-}F}$=3.12 Hz, CH) 128.18 (CH) 128.28 (t, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$=1.90 Hz, C) 128.75 (CH) 129.23 (CH) 137.92 (C) 150.75 (CH) 151.80 (C) 154.94 (t, $J_{C\text{-}C\text{-}F}$ =25.70 Hz, C) 166.84 (C) **^{19}F NMR** ($CDCl_3$, 377 MHz) δ ppm -118.75 (d, *J*=55.21 Hz) **FT-IR** (cm^{-1}, neat, ATR) 3042 (vw) 2999 (vw) 2958 (vw) 1753 (s) 1385 (m) 1275 (s) 1224 (m) 1083 (s) 1036 (vs) 1026 (s) 895 (m) 756 (s) 691 (m) 623 (m) **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{14}H_{11}F_2NO_2$: 264.0831 found: 264.0839.



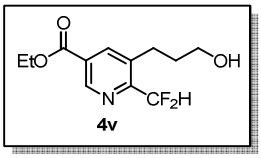
4t

Ethyl 6-(difluoromethyl)-2-phenylnicotinate, 4t (0.63 g, 61%) was prepared according to the representative procedure from enolate **2j** (1.19 g, 74 wt%, 4.1 mmol) ***with the following modifications:*** 1) The reaction was performed in a screw top reaction tube in a Mettler Toledo EasyMax^{TM} synthesis workstation. 2) Conversion to intermediate **3t** required heating to 50 °C for 12 h. 3) Conversion from intermediate **3t** to the desired pyridine required 4 equiv. of HCO_2NH_4. Further purification was accomplished by flash column chromatography (Gradient: 0 to 10% EtOAc in Hex). **4t** was obtained as a clear light yellow oil. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm 1.06 (t, *J*=7.10 Hz, 3 H) 4.17 (q, *J*=7.02 Hz, 2 H) 6.70 (t, *J*=55.40 Hz, 1 H) 7.42 - 7.47 (m, 3 H) 7.52 - 7.57 (m, 2 H) 7.68 (d, *J*=8.24 Hz, 1 H) 8.23 (d, *J*=7.78 Hz, 1 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 13.72 (CH_3) 61.94 (CH_2) 113.78 (t, $J_{C\text{-}F}$ =241.00 Hz, CF_2H) 118.06 (t, $J_{C\text{-}C\text{-}C\text{-}F}$=2.93 Hz, CH) 128.39 (CH) 128.78 (CH) 129.22 (CH) 129.26 (C) 139.34 (C) 139.38 (CH) 154.19 (t, $J_{C\text{-}C\text{-}F}$ =26.60 Hz, C) 158.70 (C) 167.64 (C) **^{19}F NMR** ($CDCl_3$, 377 MHz) δ ppm -118.23 (d, *J*=55.40 Hz) **FT-IR** (cm^{-1}, neat, ATR) 2985, (vw, br.) 1719 (s) 1407 (m) 1278 (s), 1115 (s) 1084 (m) 1048 (vs) 840 (m) 762 (m) 698 (vs) **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{15}H_{13}F_2NO_2$: 278.0987, found: 278.0994.



4u

Ethyl 6-(difluoromethyl)-2-(trifluoromethyl)nicotinate, 4u (0.44 g, 44%) was prepared according to the representative procedure from enolate **2k** (# g, # mmol) ***with the following modifications:*** 1) The reaction was performed in a screw top reaction tube in a Mettler Toledo EasyMax^{TM} synthesis workstation. 2) Conversion to intermediate **3u** required heating to 80 °C for 12 h. 3) Conversion from intermediate **3u** to the desired pyridine required 3 equiv. of HCO_2NH_4. Further purification was accomplished by flash column chromatography (Gradient: 0 to 20% EtOAc in Hex). **4u** was obtained as a clear colorless oil. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm 1.41 (t, *J*=7.10 Hz, 3 H) 4.45 (q, *J*=7.32 Hz, 2 H) 6.70 (t, *J*=54.90 Hz, 1 H) 7.92 (d, *J*=8.24 Hz, 1 H) 8.26 (d, *J*=8.24 Hz, 1 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 14.04 (CH_3) 63.23 (CH_2) 113.00 (t, $J_{C\text{-}F}$ =241.70 Hz, CF_2H) 120.93 (q, $J_{C\text{-}F}$ =275.20 Hz, CF_3) 122.89 (t, $J_{C\text{-}C\text{-}C\text{-}F}$=2.57 Hz, CH) 130.04 (C) 140.26 (CH) 145.64 (q, $J_{C\text{-}C\text{-}F}$=34.10 Hz, C) 154.21 (t, $J_{C\text{-}C\text{-}F}$=27.50 Hz, C) 165.02 (C) **^{19}F NMR** ($CDCl_3$, 377 MHz) δ ppm -118.48 (d, *J*=54.90 Hz, 2 F) -66.60 (s, 3 F) **FT-IR** (cm^{-1}, neat, ATR) 2991 (vw, br.) 1736 (s) 1309 (s) 1288 (s) 1190 (s) 1098 (vs) 1057 (vs) 843 (m) 777 (w) **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{10}H_8F_5NO_2$: 270.0548, found: 270,0546.

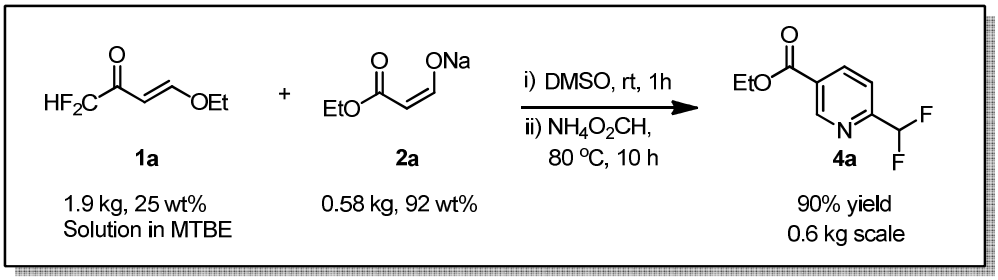


4v

Ethyl 6-(difluoromethyl)-5-(3-hydroxypropyl)nicotinate, 4v (1.34 g, 48%) was prepared according to the representative procedure from **1l** (11.60 g, 15.16 wt%, 10.85 mmol, 1 equiv) and **2a** (1.95 g, 92 wt%, 13.02 mmol, 1.2 equiv) ***with the following modifications:*** 1) The round bottom flask was equipped with a Dean-Stark trap and reflux condenser when heating was initiated. This allowed for removal of the DCM that **1i** was dissolved in prior to its

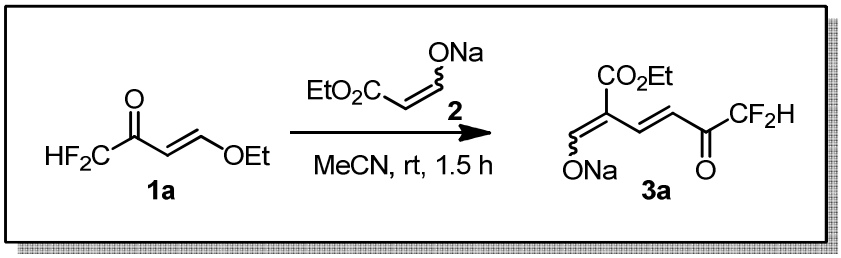
addition into the reaction mixture. Further purification was accomplished by flash column chromatography (Gradient: Hex to 8:2 to 6:4 Hex:MTBE). **4v** was obtained as a thick bright yellow oil. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm 1.40 (t, *J*=7.30 Hz, 3 H) 1.91 (dtt, *J*=16.00, 6.40, 6.40, 1.80, 1.80 Hz, 2 H) 1.96 (br. s., 1 H) 2.98 (t, *J*=8.20 Hz, 2 H) 3.71 (t, *J*=6.18 Hz, 2 H) 4.41 (q, *J*=7.02 Hz, 2 H) 6.77 (t, *J*=54.40 Hz, 1 H) 8.26 (d, *J*=1.83 Hz, 1 H) 9.02 (d, *J*=1.80 Hz, 1 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 14.04 (CH_3) 26.74 (CH_2) 33.75 (CH_2) 61.27 (CH_2) 61.76 (CH_2) 115.34 (t, $J_{C\text{-}F}$=242.10 Hz, CF_2H) 127.76 (C) 136.88 (C) 139.95 (CH) 147.33 (CH) 152.79 (t, $J_{C\text{-}C\text{-}F}$=24.60 Hz, C) 164.57 (s, C) **^{19}F NMR** ($CDCl_3$, 377 MHz) -115.00 (d, *J*=54.21 Hz) **FT-IR** (cm^{-1}, neat, ATR) 3372 (vw, v. br) 2983 (w br) 2941 (w, br) 2877 (vw, br) 1724 (m) 1368 (w) 1240 (m_ 1224 (m) 1144(s) 1113 (m) 1030 (vs) 835 (w) **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{12}H_{15}F_2NO_3$: 260.1093, found: 260.1100.

Large Scale Preparation of 1a



A 20 L reactor was charged sodium enolate, **2a** (0.58 kg, 92 wt%, 1.15 equiv.) and DMSO (3 L). The agitator was started and set for adequate mixing rate. The Temperature Control Unit (TCU) was started and the oil temperature was set to 20 – 25°C. The batch was agitated for about 15 min. A MTBE solution of butenone **1a** (1.9 kg, 25 wt%, 1 equiv.) was charged to the reactor over about 45min. The batch was agitated for about 2 h – 2.5 h 30 min at 20 – 25 °C. Ammonium formate (0.4 kg, 2 equiv.) though the manhole. The batch was agitated for about 1h at 20 – 25 °C. The batch was heated to 80 °C linearly over about 1h. Once the batch temperature reached 80 °C, the batch was agitated for 10 – 12 h. MTBE was slowly distilled out by applying vacuum (about 150 – 200 mmHg). The batch was cooled down to 10 – 12 °C over about 30 min. MTBE (5 L) was charged to the reactor. H_2O (5 L) was charged to the reactor at such rate where internal temperature is NMT 35 °C. The batch was heated to about 20 – 25 °C and agitated for about 15 min. The agitation was stopped to allow layers to settle and the bottom layer was drained. The batch was distilled at reduced pressure and a batch temperature of 30 – 40°C down to the minimum stirrable volume to afford **4a** (1.4 kg**,** 40.4 wt%, 90%) as an MTBE solution (see S3 for characterization).

Isolation of intermediate 3a



Sodium (3E)-2-(ethoxycarbonyl)-6,6-difluoro-5-oxohexa-1,3-dien-1-olate, 3a

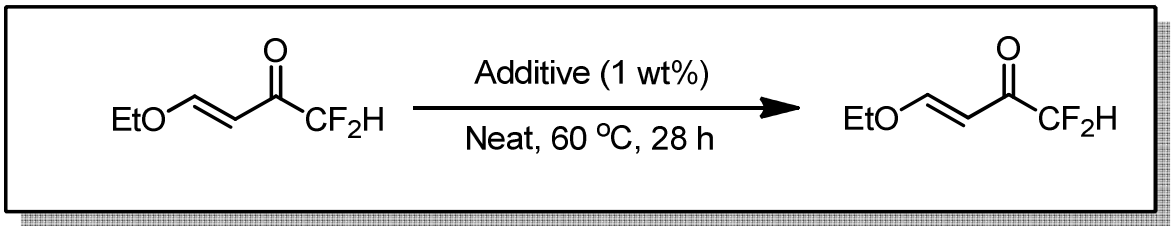
A reaction tube for a Mettler Toledo EasyMax^{TM} synthesis workstation was charged with the enolate **2a** (0.450 g, 92 wt%, 3 mmol, 1 equiv) and stir bar. The tube was sealed with a piercable cap and the contents were placed under a N_2 atmosphere *via* a N_2 inlet needle. MeCN (2.2 mL was added to the tube and the contents were stirred in the EasyMax^{TM} for 10 minutes at room temperature. After partial dissolution of **2a**, the butanone **1a** (0.993 g, 90.7 wt%, 6 mmol, 2 equiv) dissolved in MeCN (1 mL) was added dropwise to the tube. After complete addition, the reaction mixture was stirred at room temperature for 1.5 h and the heterogeneous solution gradually became bright yellow. Once complete conversion to the intermediate enolate was attained, [19] the contents of the tube were poured on to a medium porosity fritted funnel. The solid material was washed thoroughly with MTBE (≈ 100 mL). The light tan solid was transferred to a flask and allowed to dry under vacuum for 24 h to give the pure enolate **3a** (0.727 g, 80 % yield).

^{1}H NMR[20] (DMSO-d_6, 500 MHz, 353 K) δ ppm 1.22 (t, *J*=6.60 Hz, 3 H) 4.08 (q, *J*=7.15 Hz, 2 H) 5.96 (t, *J*=55.02 Hz, 1 H) 6.94 (br. s., 1 H) 8.00 (d, *J*=14.86 Hz, 1 H) 9.66 (br. s., 1 H) **^{13}C NMR** (DMSO-d_6, 125 MHz) δ ppm 14.26 (CH_3) 57.14 (CH_2) 101.42 (C) 102.75 (br. s., CH) 111.27 (t, $J_{C\text{-}F}$=249.27 Hz, CF_2H) 144.96 (CH) 168.57 (br. s, C) 183.88 (t, $J_{C\text{-}C\text{-}F}$=21.82 Hz, C) 185.47 (CH) **^{19}F NMR** (DMSO-d_6, 471 MHz) δ ppm -124.20 (d, *J*=59.71)

[19] Reaction progress was determined by UPLC-MS to determine reaction progress.
[20] Note that VT NMR was required for superior resolution of peaks in ^{1}H, ^{13}C, and ^{19}F spectra. We believe that this species has a high rotational barrier leading to rotomeric species. A ^{1}H NMR spectrum at 299 K is provided in the ^{1}H NMR Spectral Packet to support this assertion.

Stability Studies of 1a

Table S2: Determination of Optimal Stabilizer for 1a

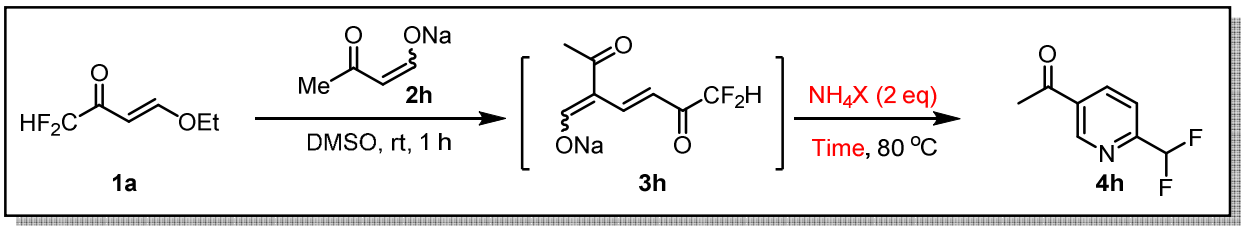


Entry	Additive (1 wt%)	Decomposition (%)[21]
1	NaOH	39
2	H_3PO_4	94
3	Benzoic acid	79
4	**BHT**	**12**
5	4-tert-butylcatechol	17
6	TEMPO	13
7	none	67
8	β-Carotene	85
9	Na_2CO_3	37
10	$NaHCO_3$	34

[21] Amount of decomposition determined by HPLC assay based on response factor using a standard curve

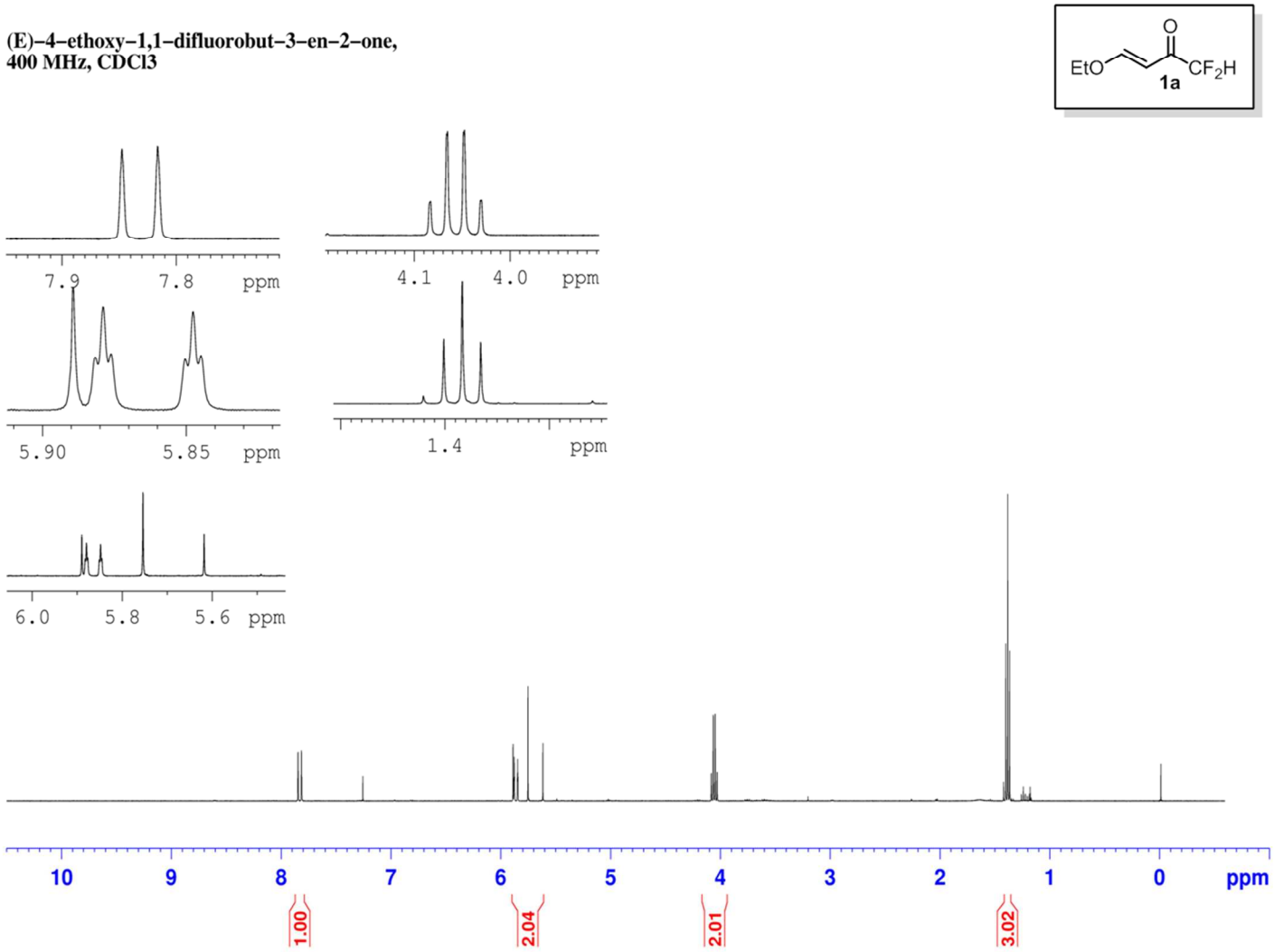
Screen of Various Ammonium Salt

Table S2: The Effect of Various Ammonium Salts on Pyridine Formation

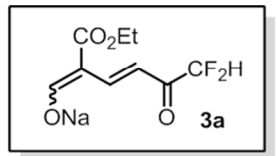


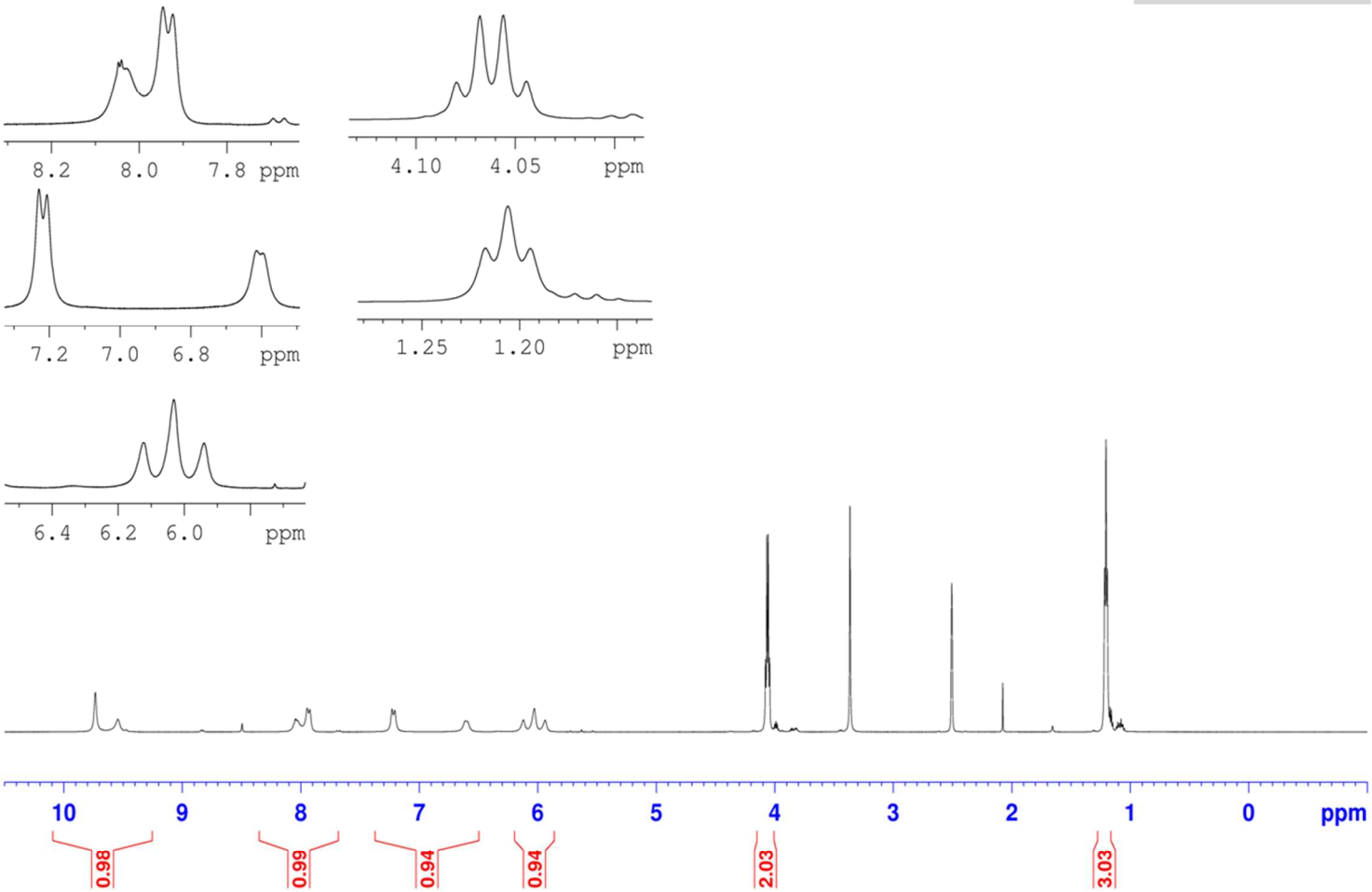
Entry	NH_4X	Time (h)	Isolated Yield (%)
1	$(NH_4)_2HPO_4$	24	0
2	$(NH_4)_2CO_3$	24	32
3	NH_4OAc	16	64
4	HCO_2NH_4	16	79
5	$NH_4O_2CCF_3$	48	45
6	NH_4BF_4	24	55
7	NH_4PF_6	24	51
8	NH_4Cl	48	41
9	NH_4Br	24	24
10	$NH_4O_2SCF_3$	16	37

^{1}H-NMR Spectra of Synthesized Compounds

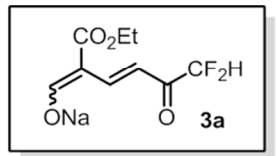


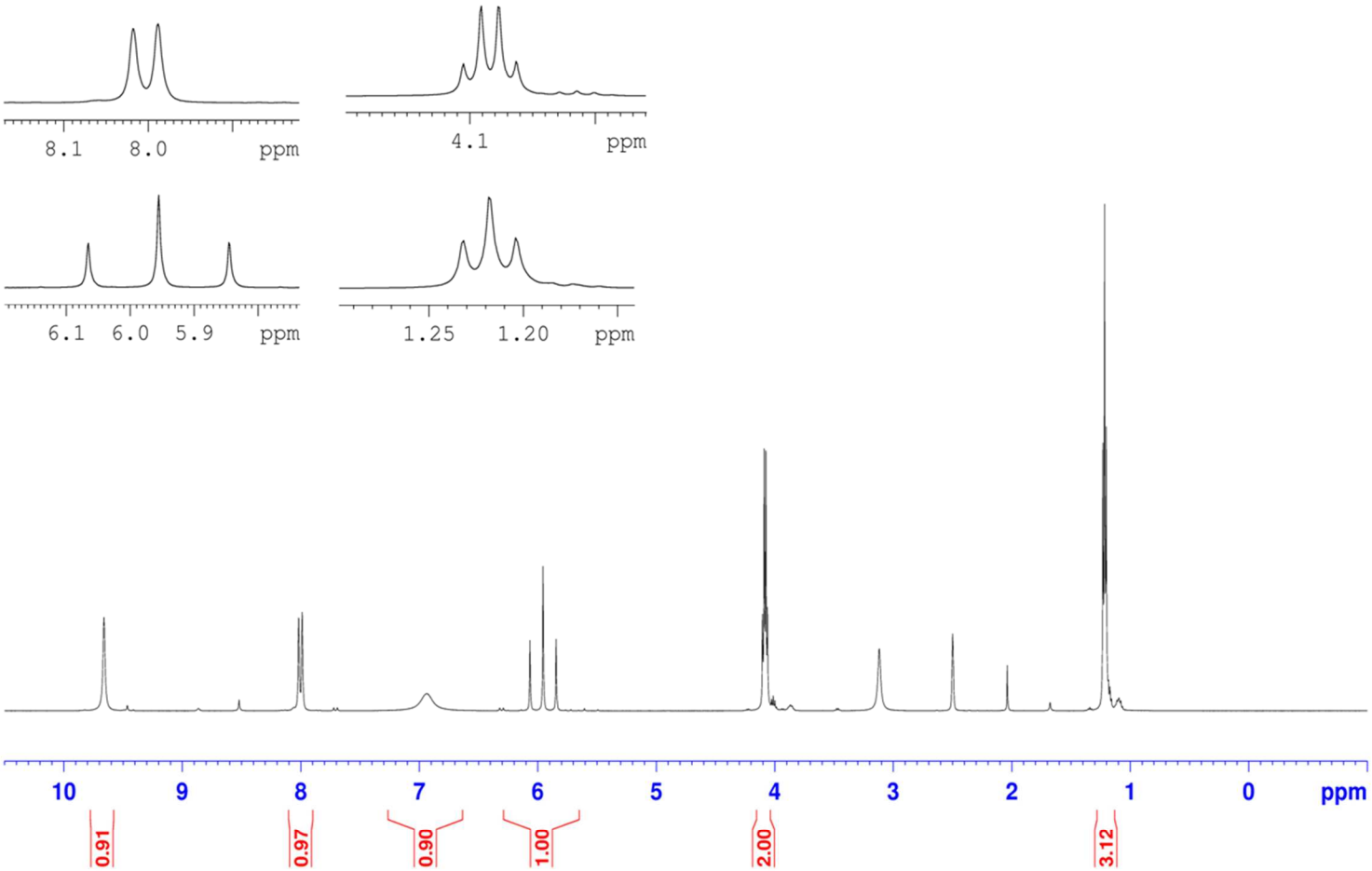
sodium (3E)–2–(ethoxycarbonyl)–6,6–difluoro–5–oxohexa–1,3–dien–1–olate
DMSO–d6, 600 MHz
T=299



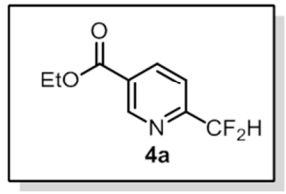


sodium (3E)−2−(ethoxycarbonyl)−6,6−difluoro−5−oxohexa−1,3−dien−1−olate
DMSO−d6, 500 MHz
T=353K

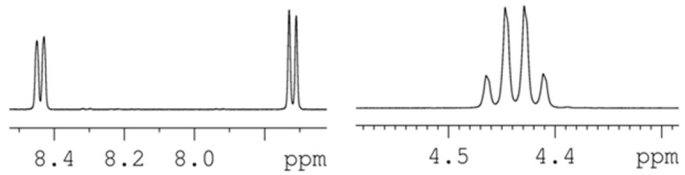


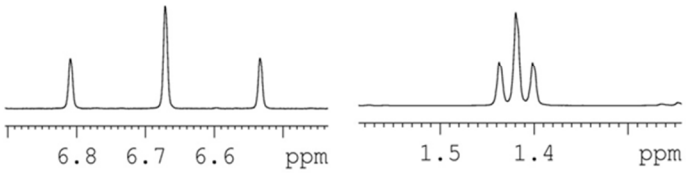


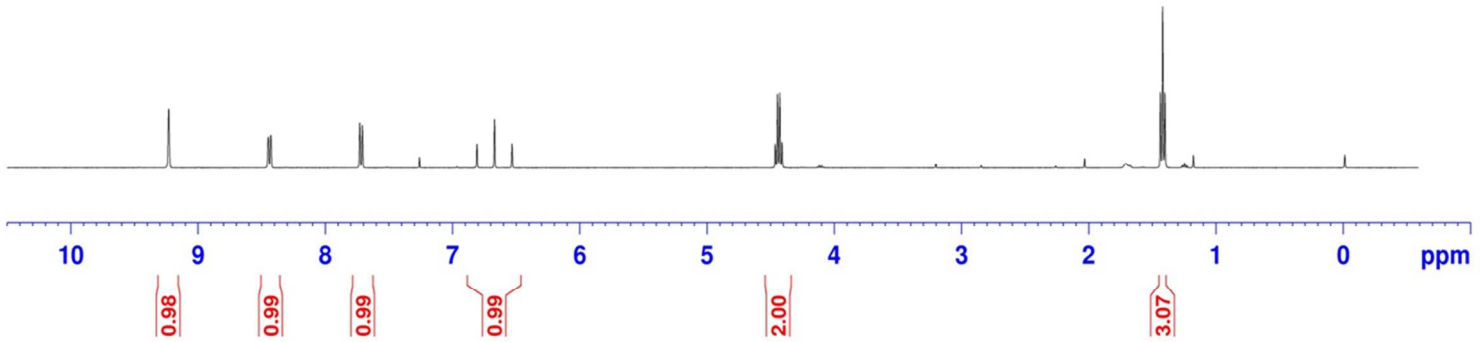
ethyl 6–(difluoromethyl)nicotinate
400 MHz, CDCl3



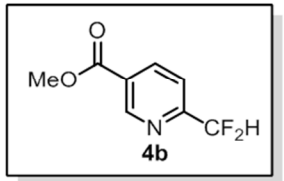
4a



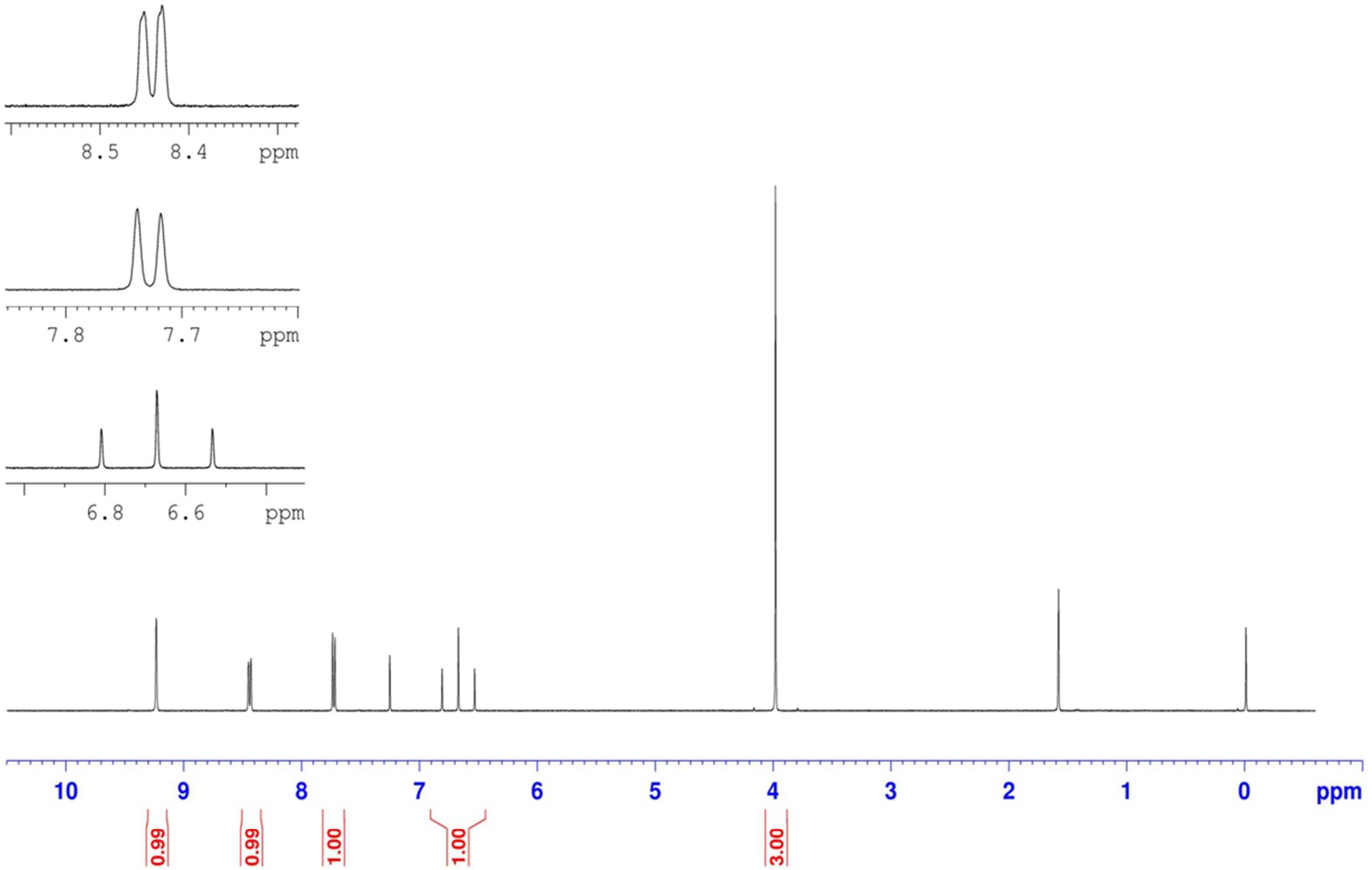




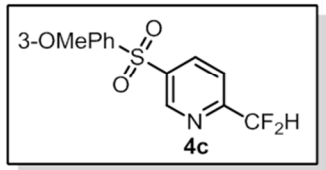
Methyl 6–(difluoromethyl)nicotinate
400 MHz, CDCl3

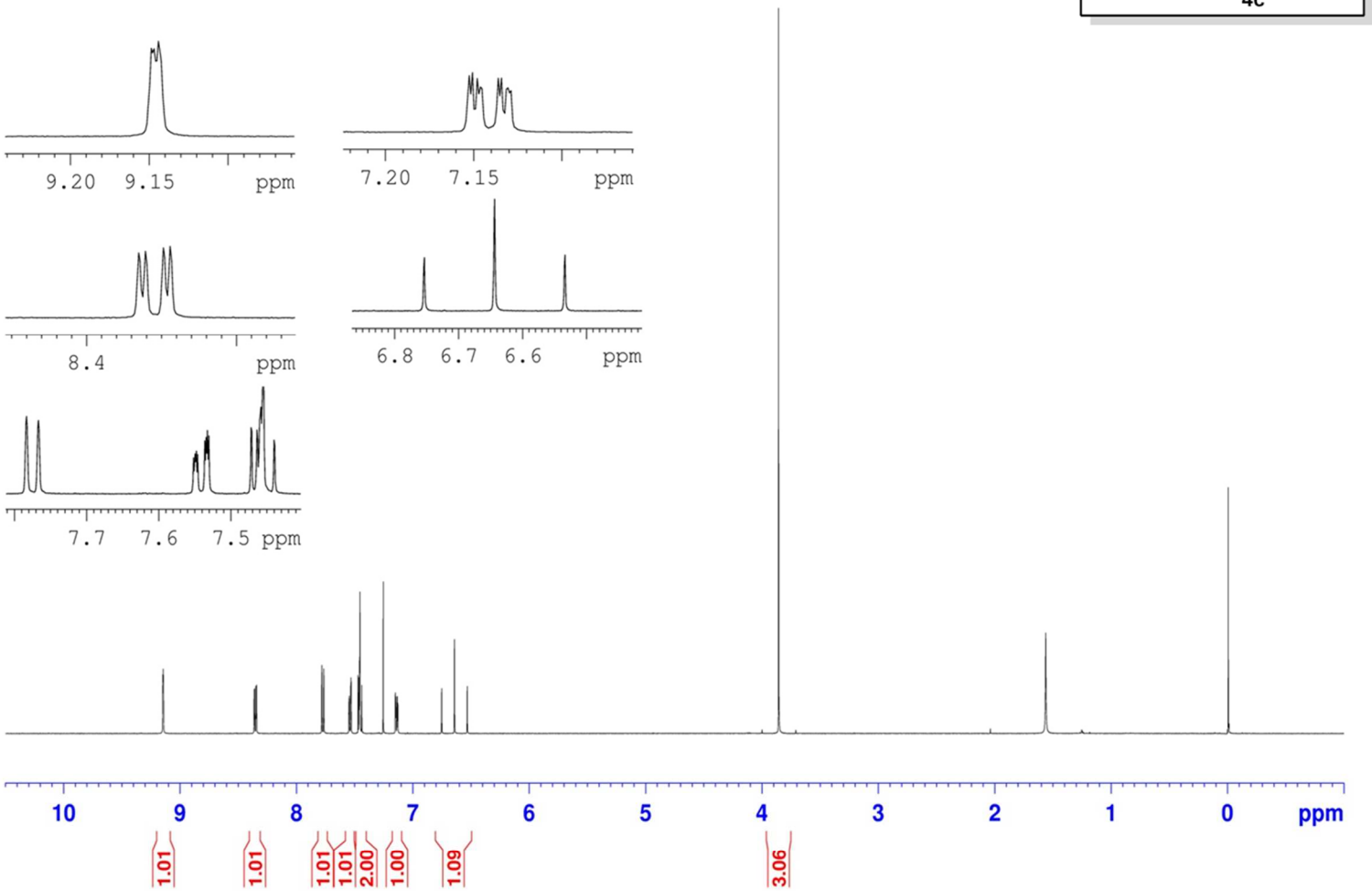


4b

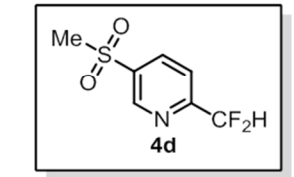


2–(Difluoromethyl)–5–((3–methoxyphenyl)sulfonyl)pyridine
500 MHz, CDCl3

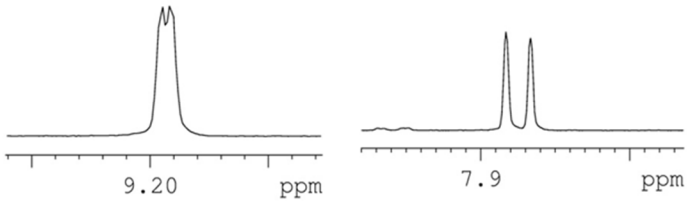


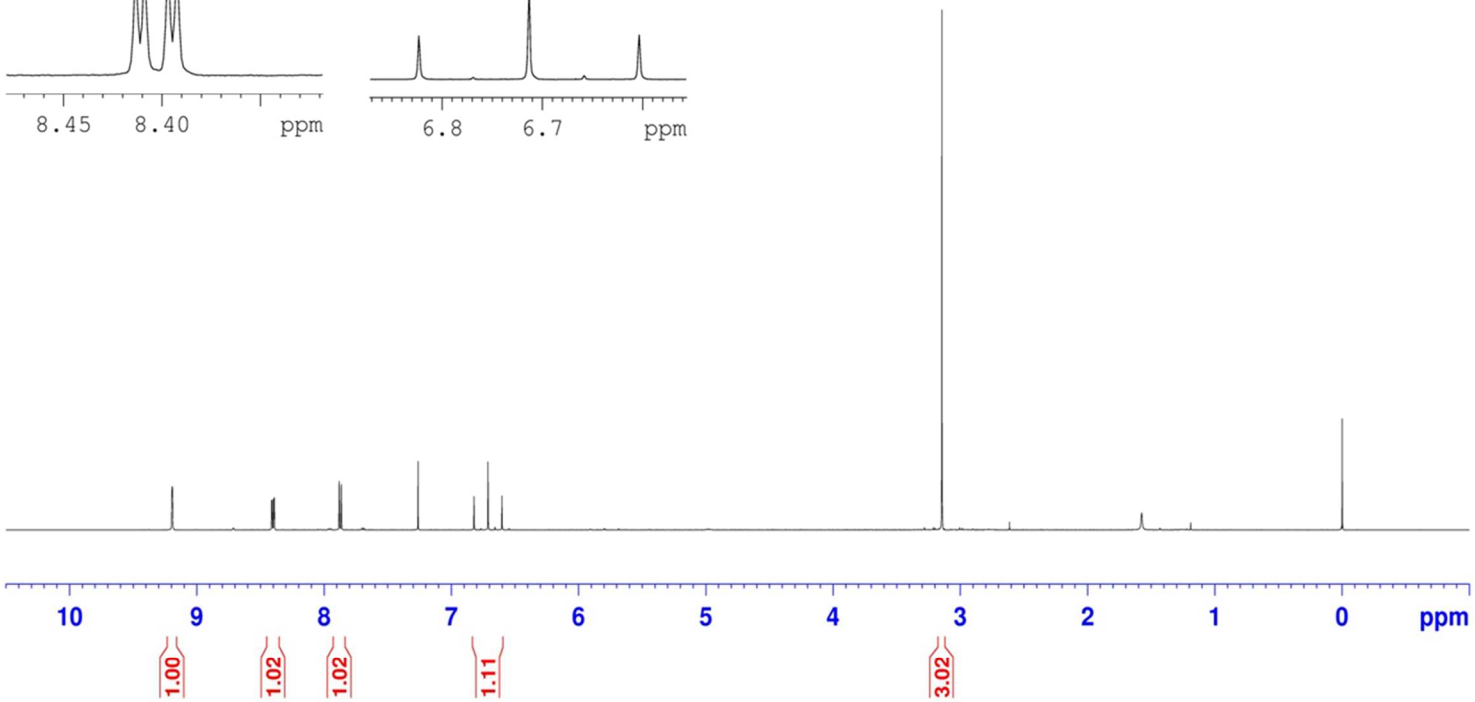


2–(Difluoromethyl)–5–(methylsulfonyl)pyridine
500 MHz, CDCl3

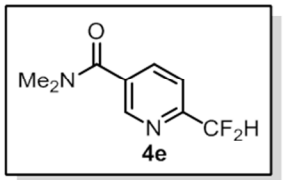


4d

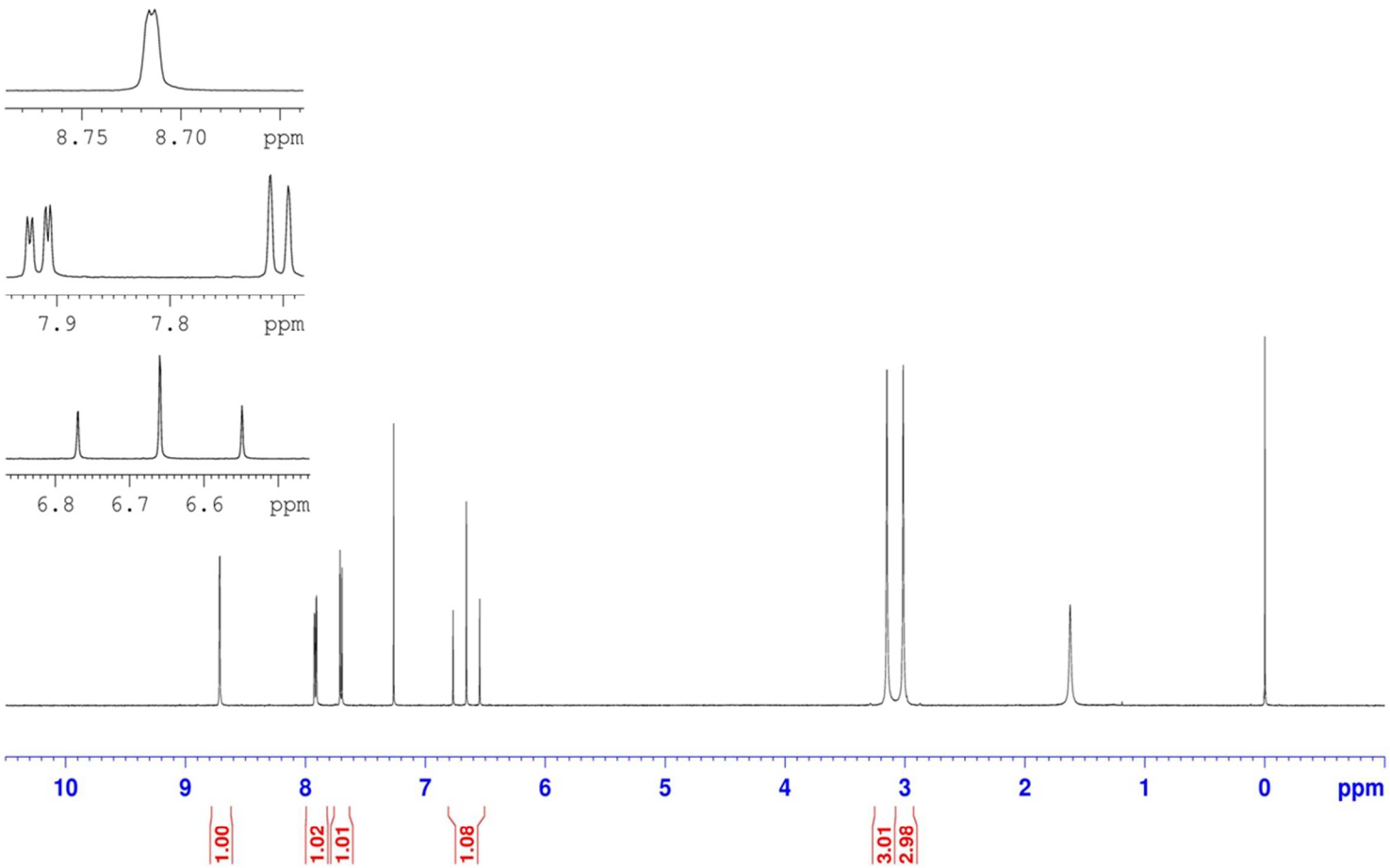




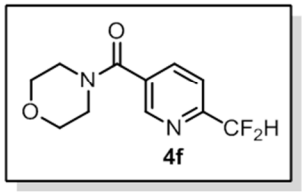
6–(Difluoromethyl)–N,N–dimethylnicotinamide
500 MHz, CDCl3



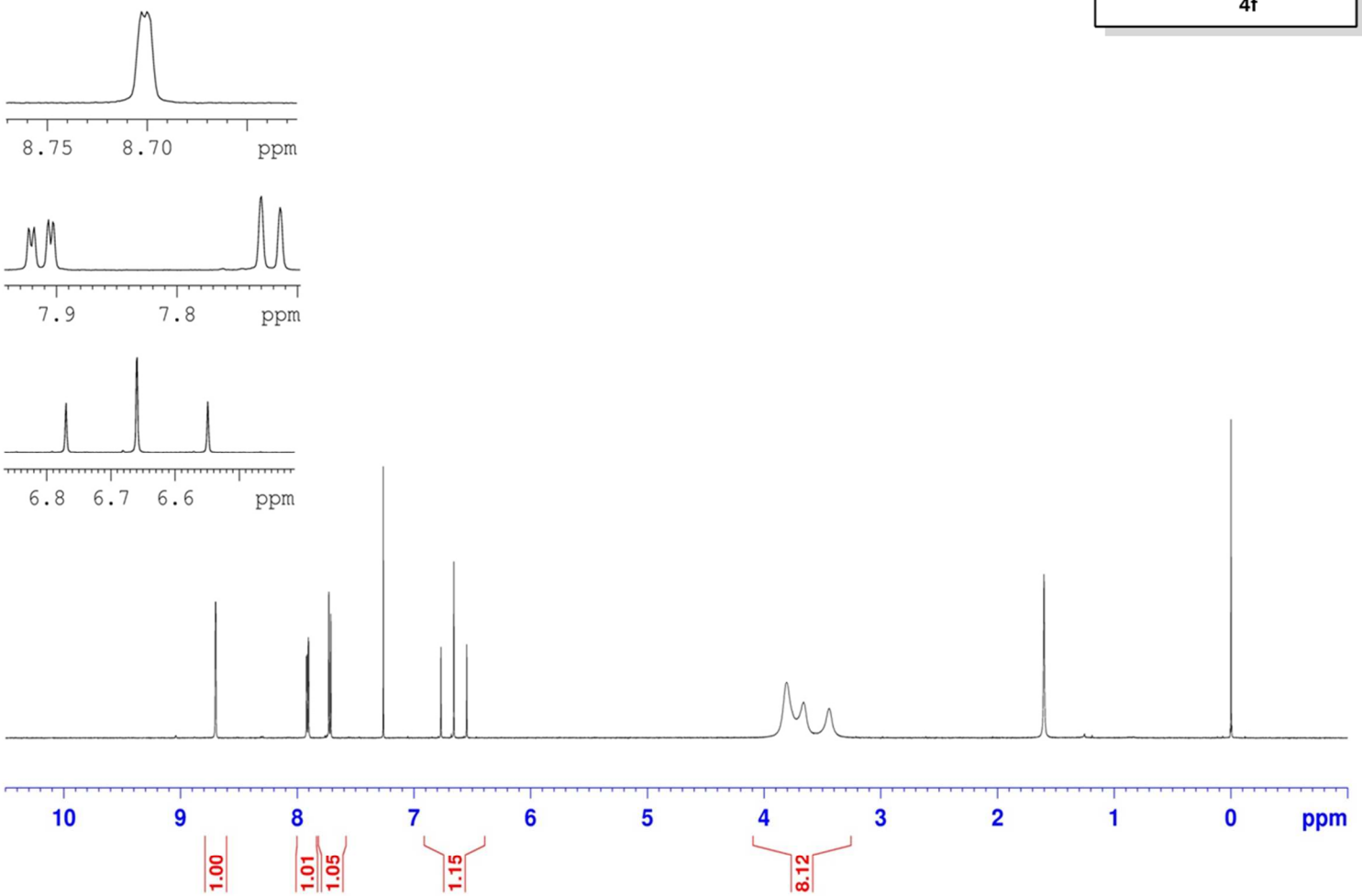
4e



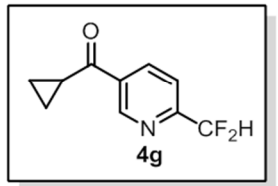
(6–(Difluoromethyl)pyridin–3–yl)(morpholino)methanone
500 MHz, CDCl3

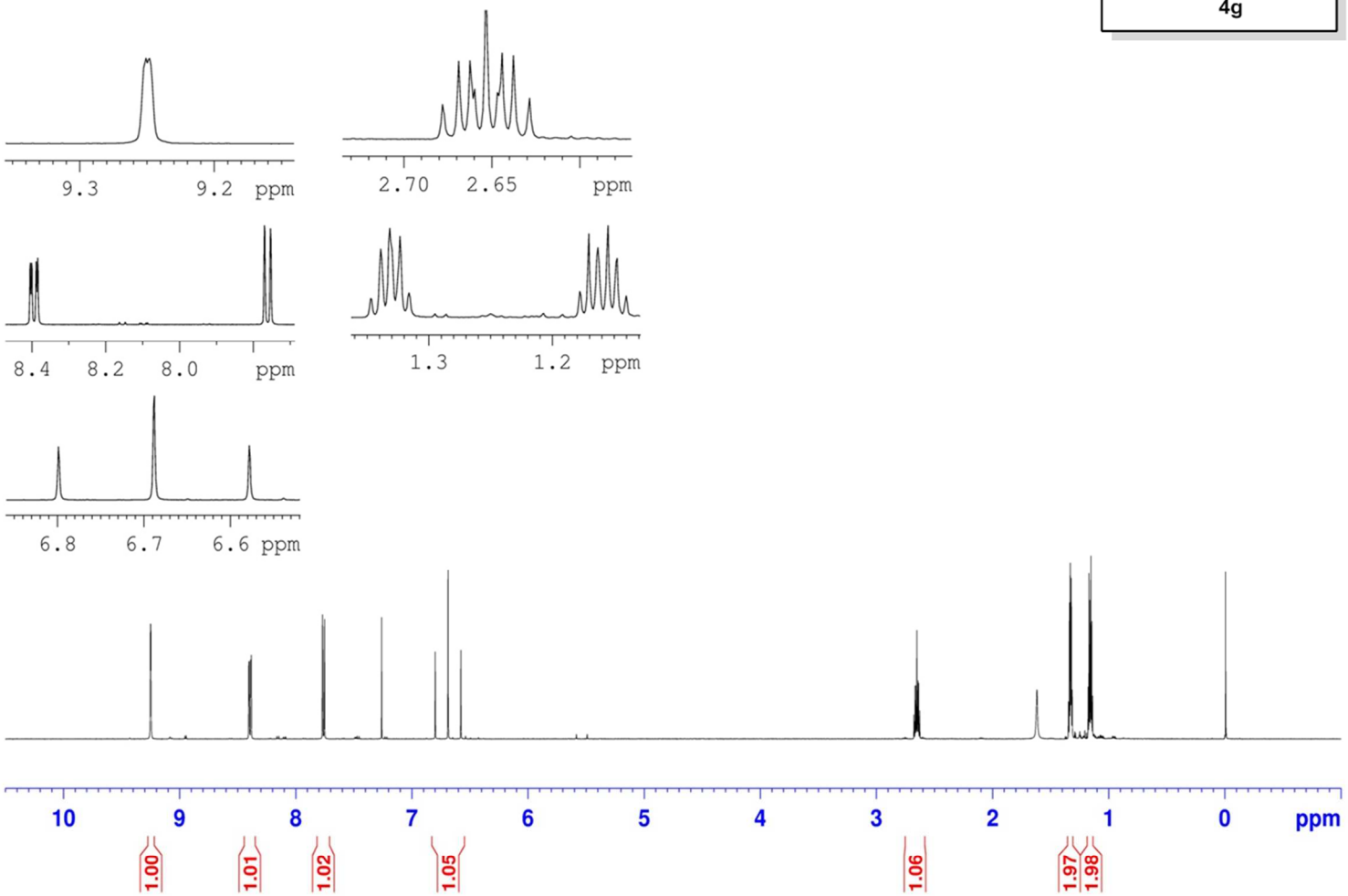


4f

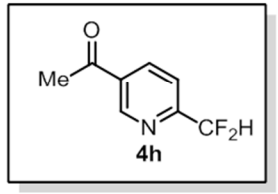


Cyclopropyl(6–(difluoromethyl)pyridin–3–yl)methanone
500 MHz, CDCl3

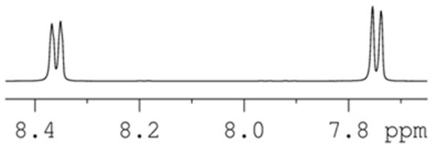


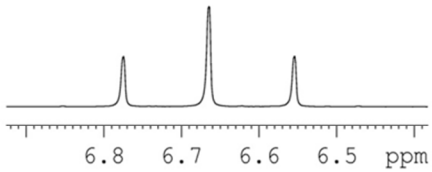


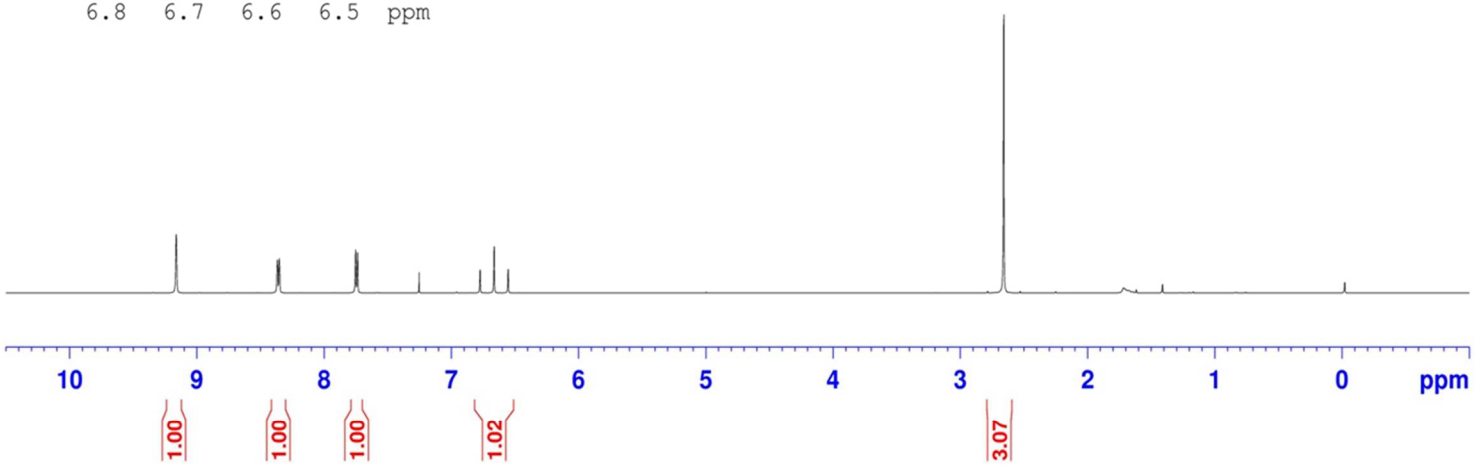
1–(6–(Difluoromethyl)pyridin–3–yl)ethanone
500 MHz, CDCl3



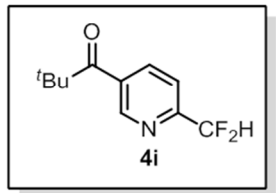
4h



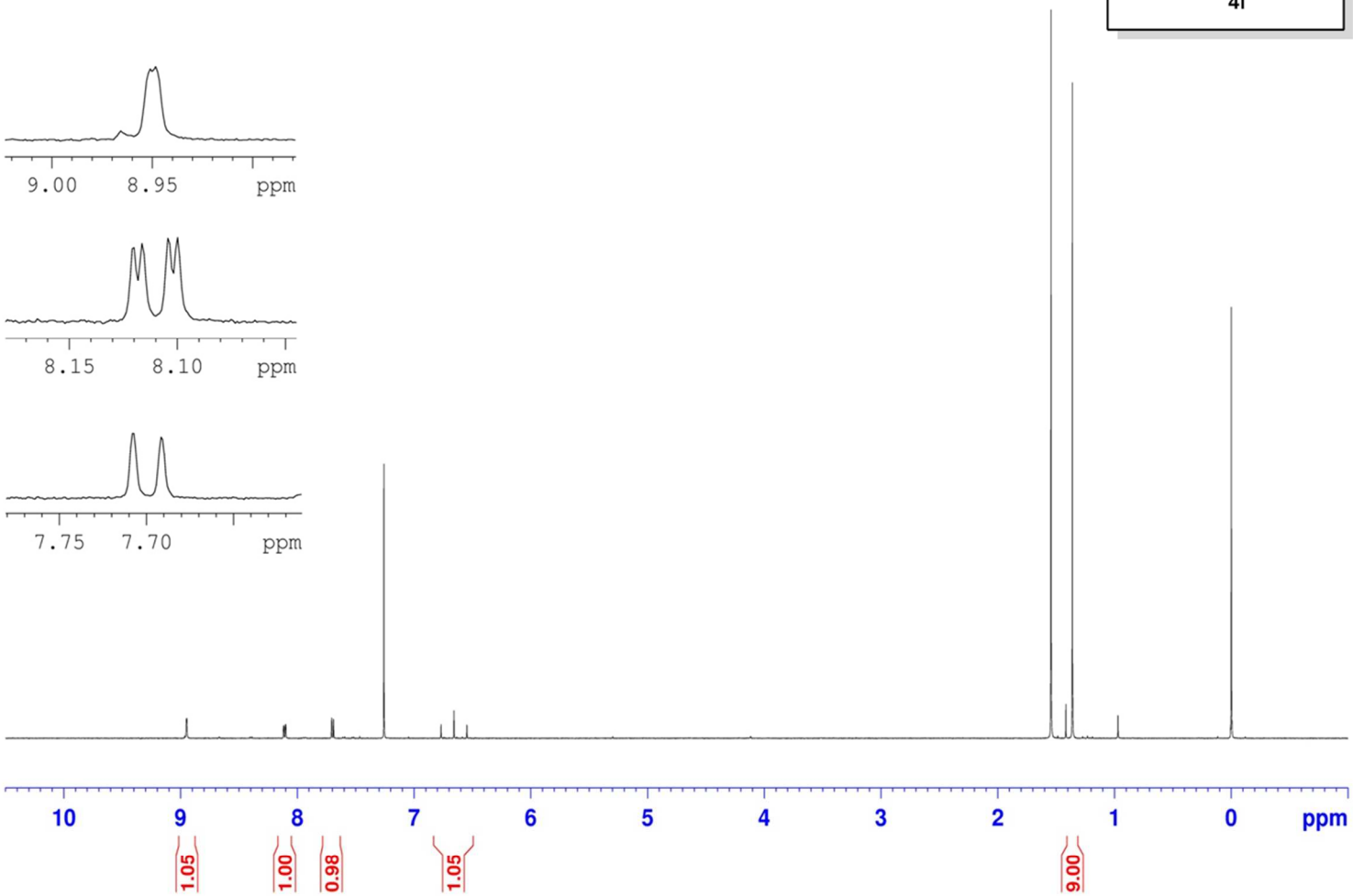




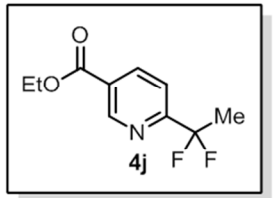
1–(6–(difluoromethyl)pyridin–3–yl)–2,2–dimethylpropan–1–one
500 MHz,CDCl3

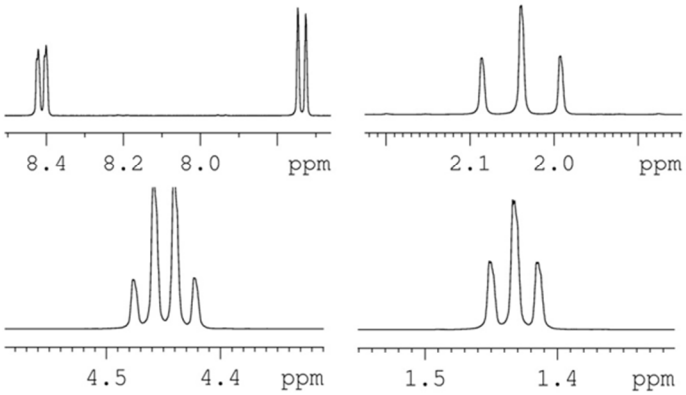


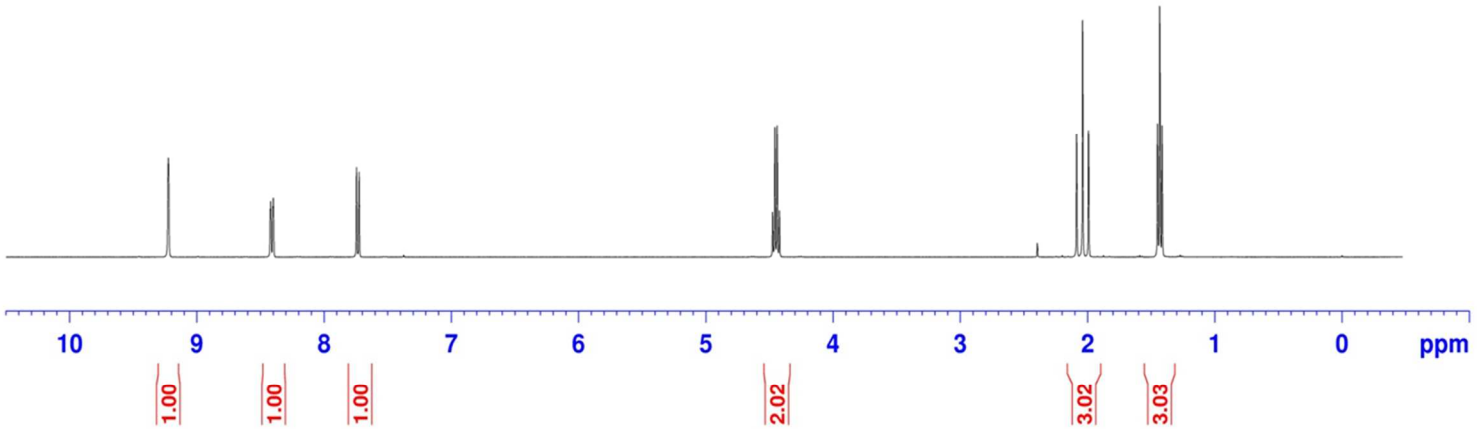
4i



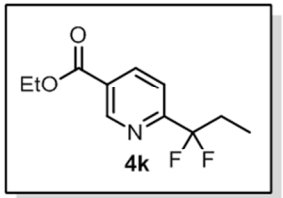
Ethyl 6–(1,1–difluoroethyl)nicotinate
400 MHz, CDCl3

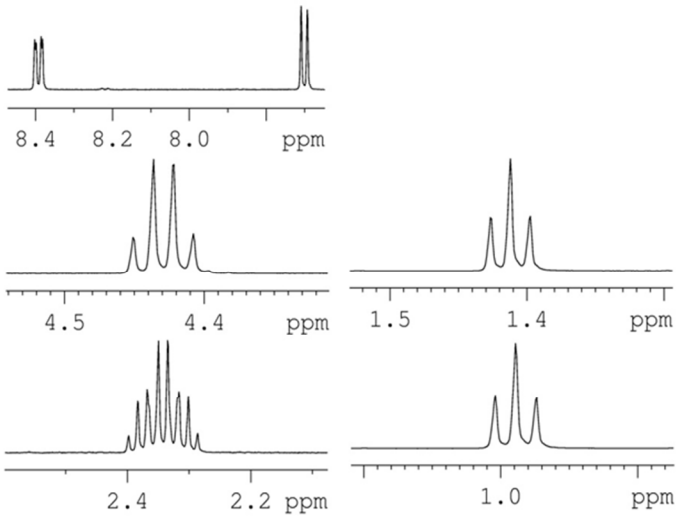


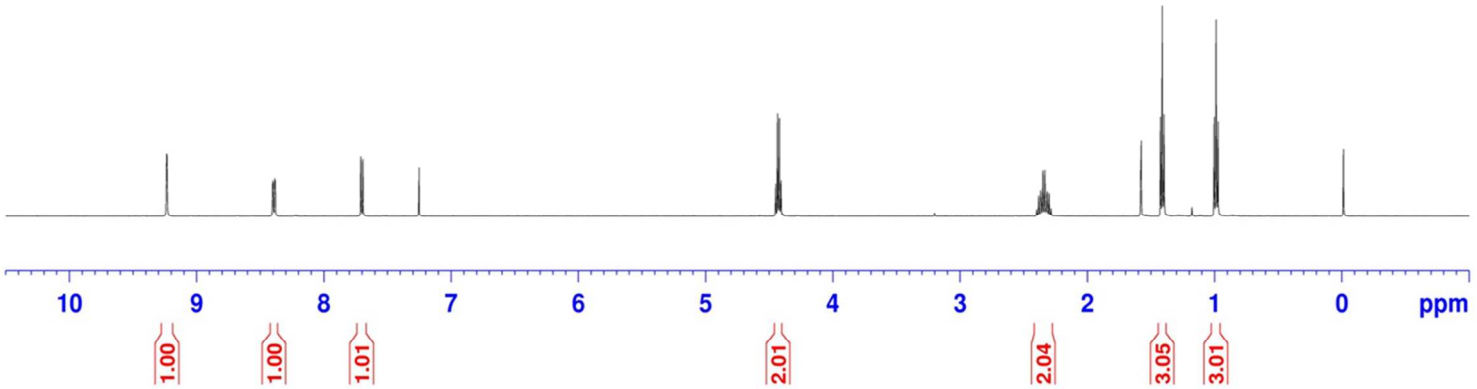




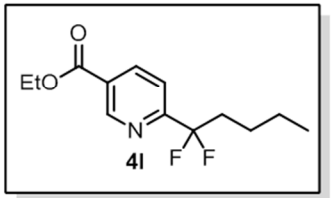
ethyl 6–(1,1–difluoropropyl)nicotinate
500 MHz, CDCl3



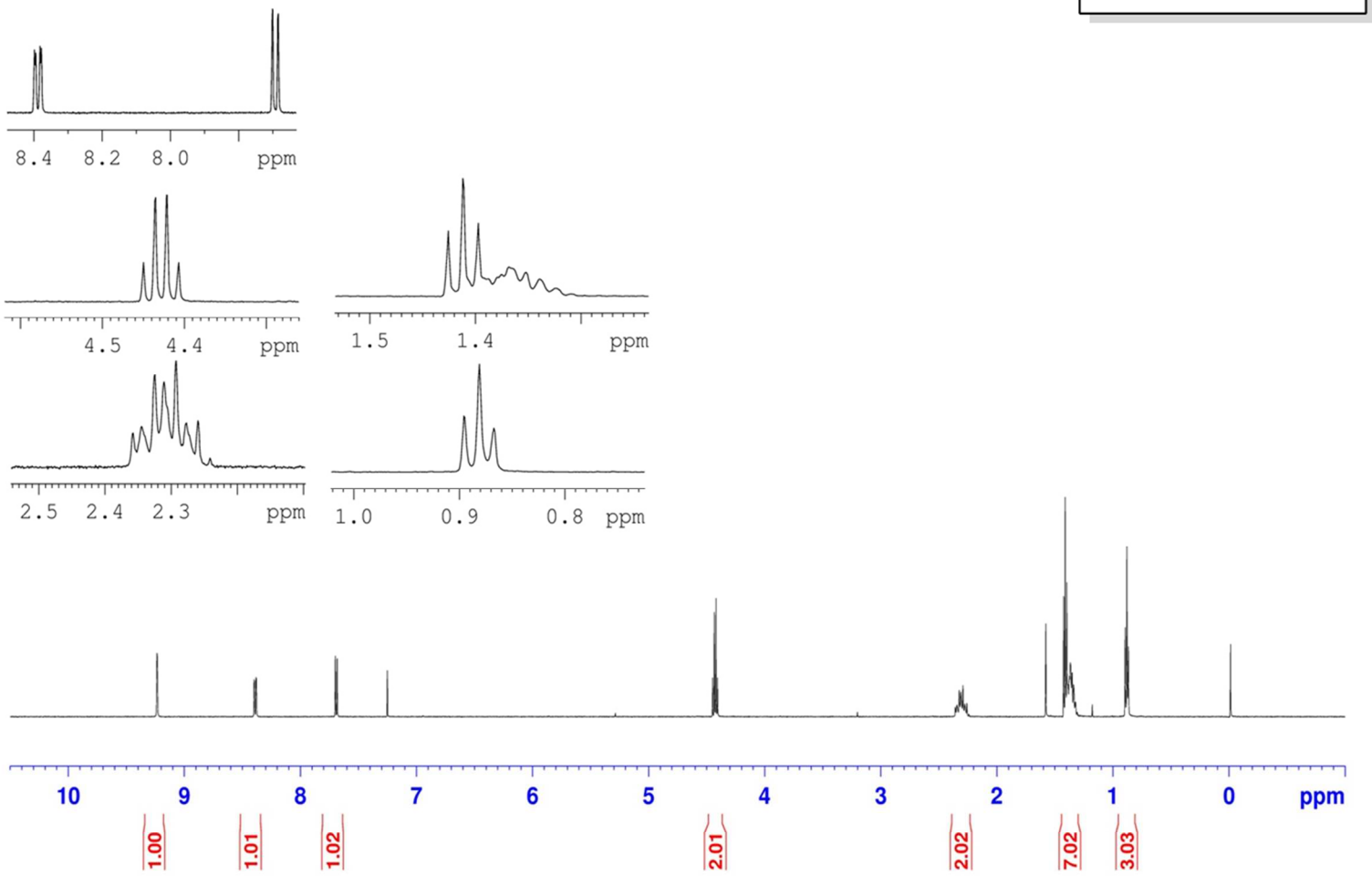




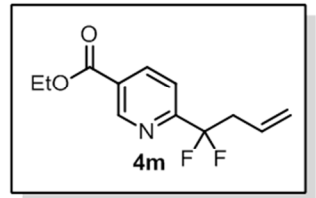
ethyl 6–(1,1–difluoropentyl)nicotinate
500 MHz, CDCl3

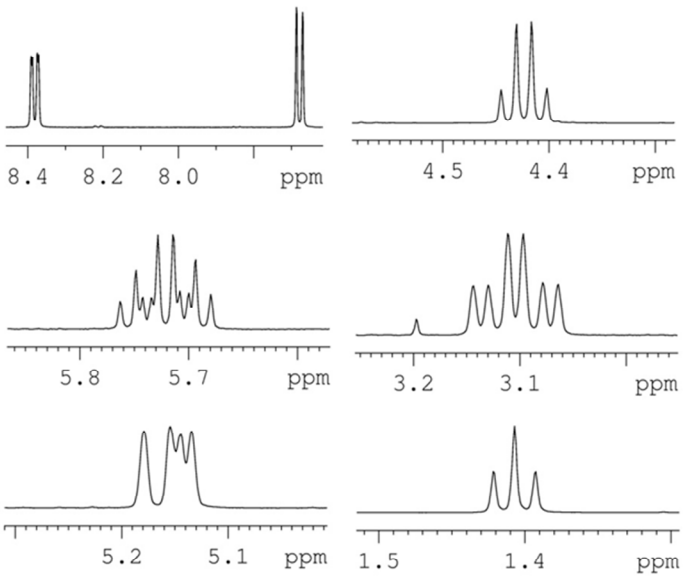


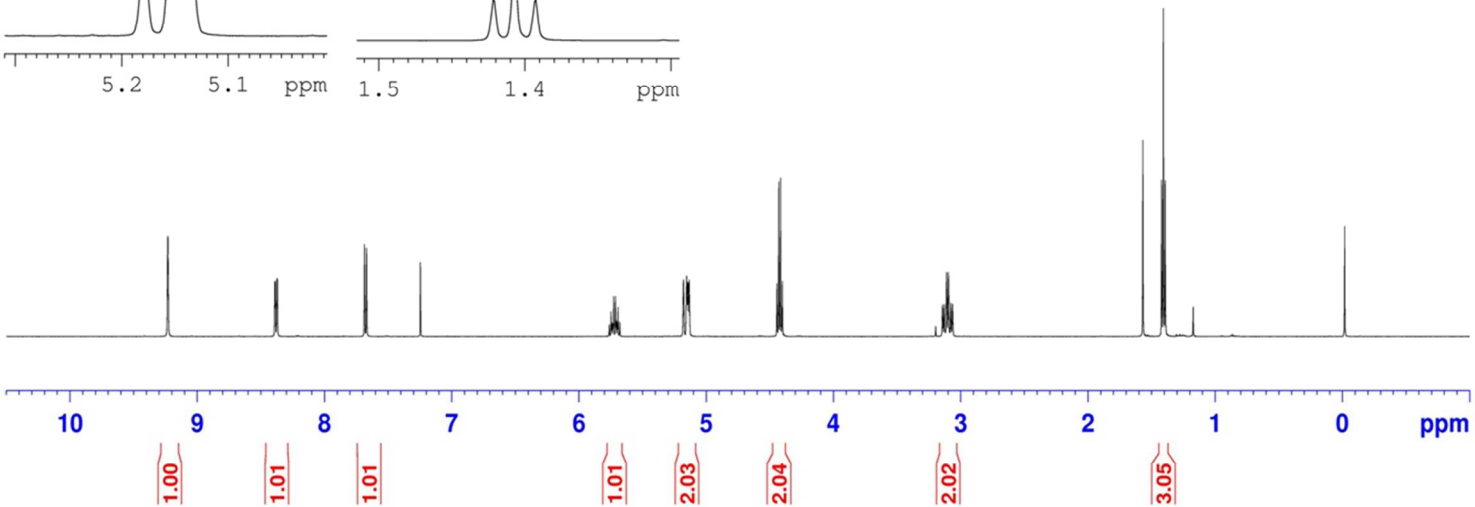
4l



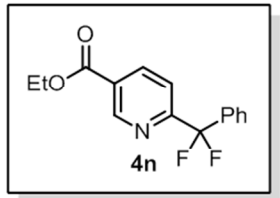
ethyl 6–(1,1–difluorobut–3–en–1–yl)nicotinate
500 MHz, CDCl3

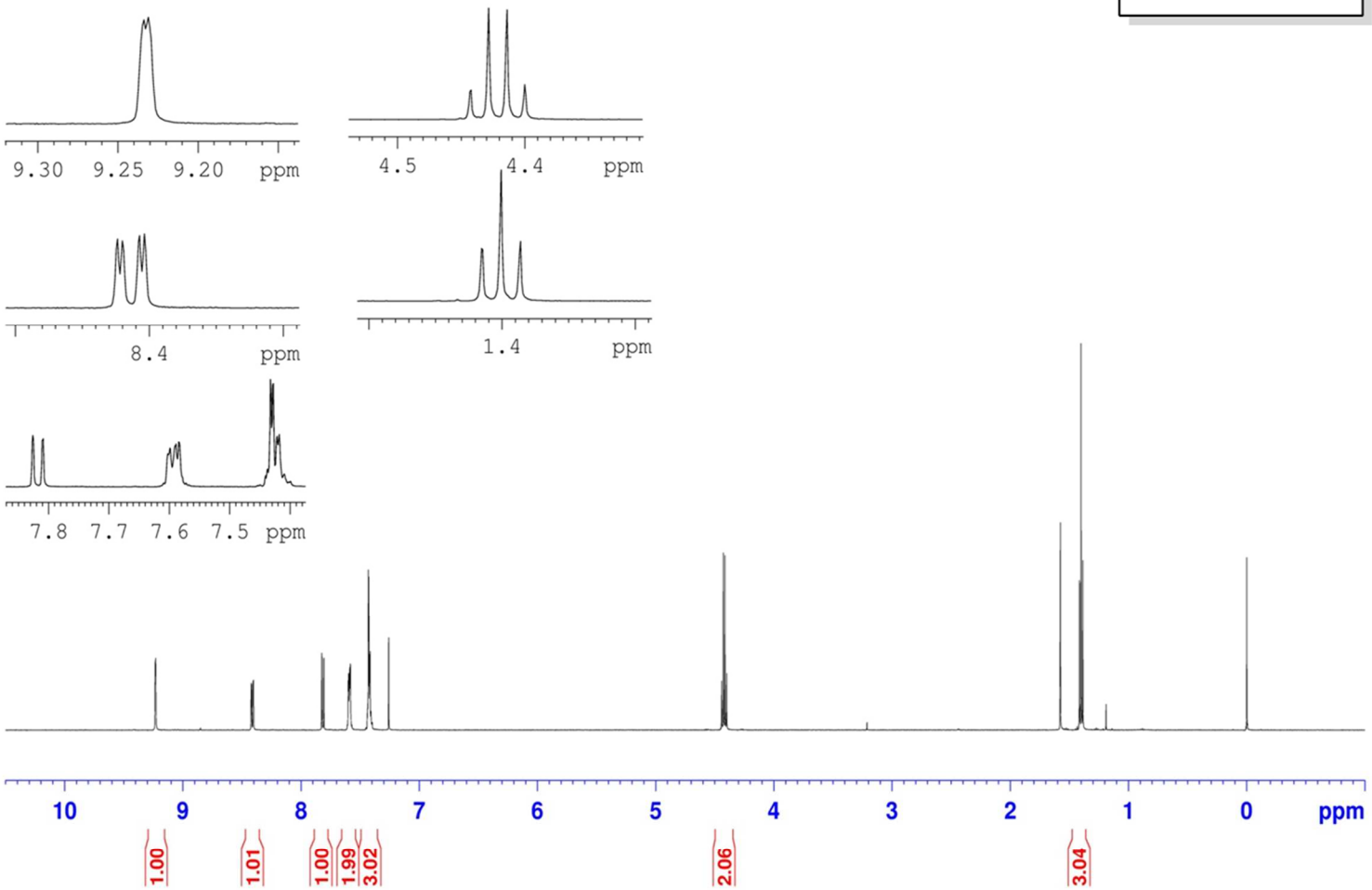




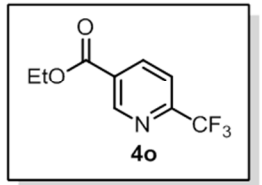


Ethyl 6–(difluoro(phenyl)methyl)nicotinate
500 MHz, CDCl3

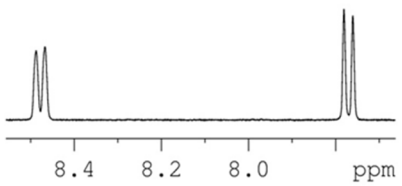


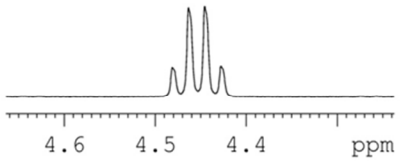


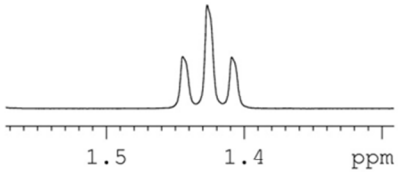
ethyl 6–(trifluoromethyl)nicotinate
400 MHz, CDCl3

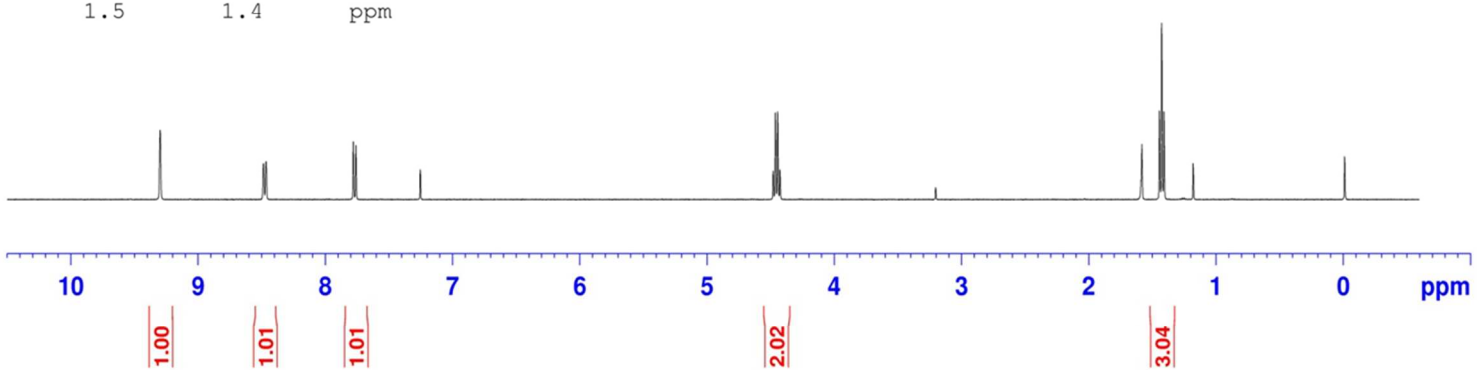


4o

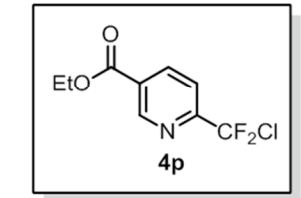




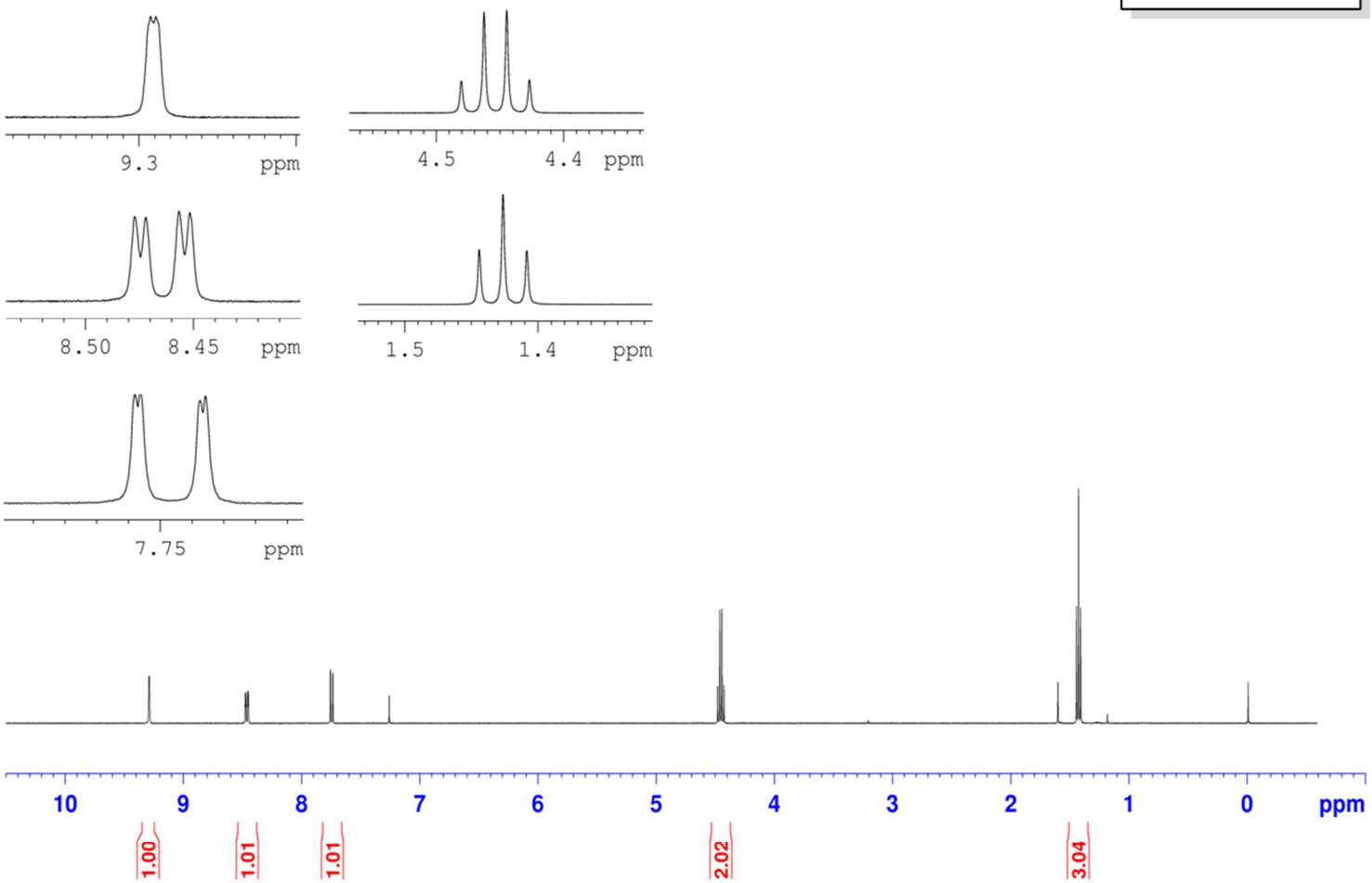




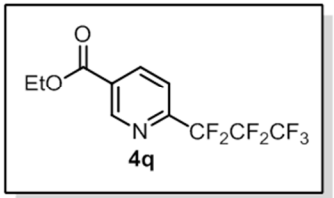
Ethyl 6–(chlorodifluoromethyl)nicotinate
400 MHz, CDCl3



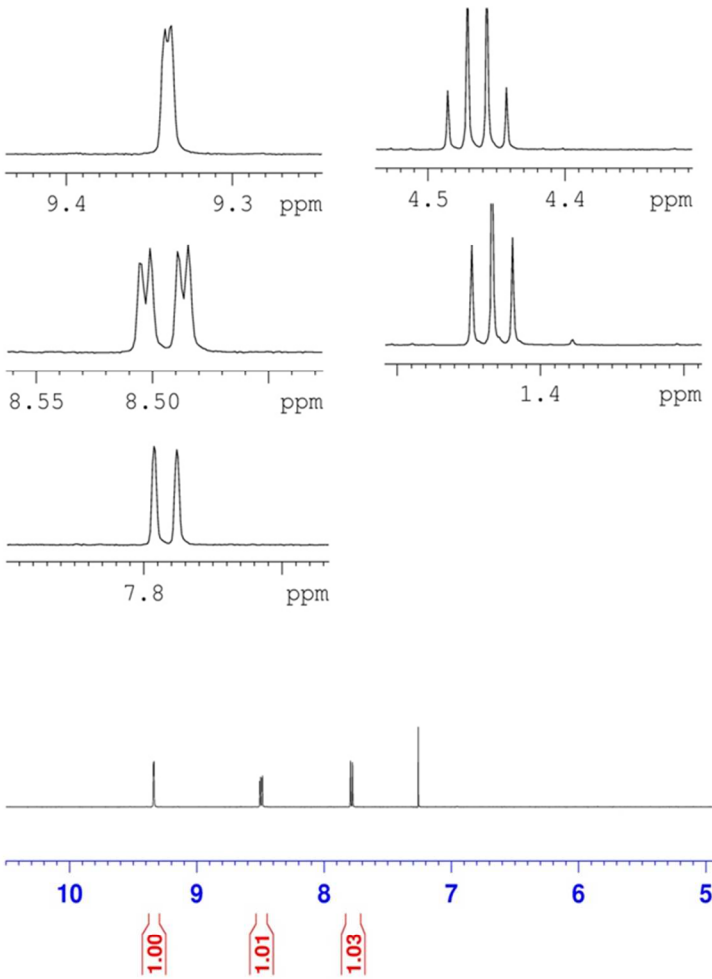
4p



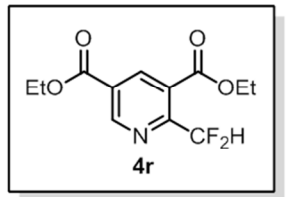
ethyl 6–(perfluoropropyl)nicotinate
500 MHz, CDCl3



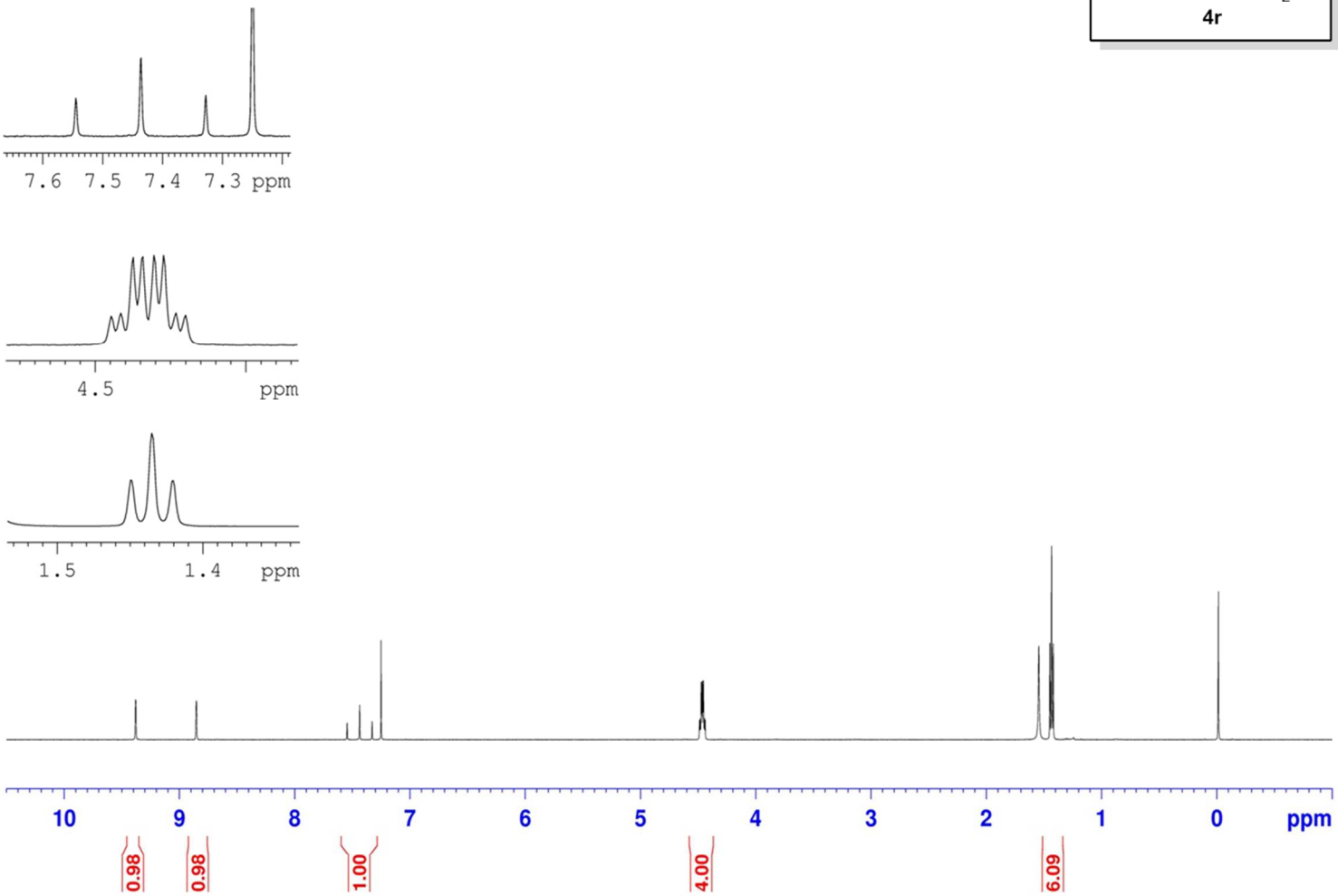
4q



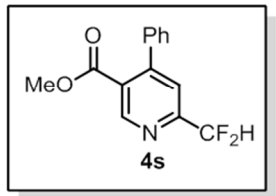
Diethyl 2–(difluoromethyl)pyridine–3,5–dicarboxylate
500 MHz, CDCl3



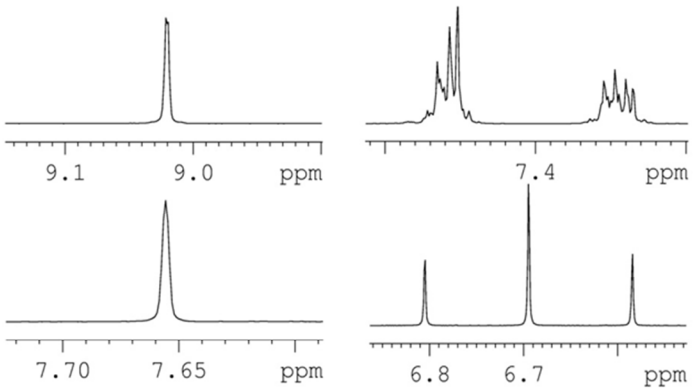
4r

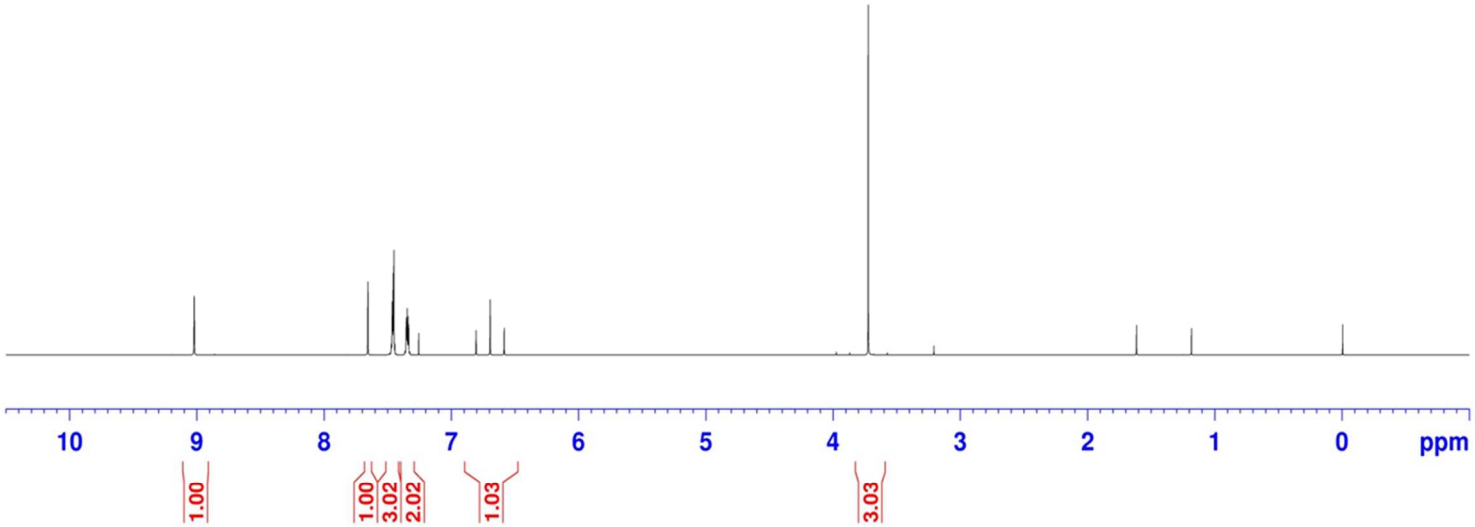


Methyl 6–(difluoromethyl)–4–phenylnicotinate
500 MHz, CDCl3

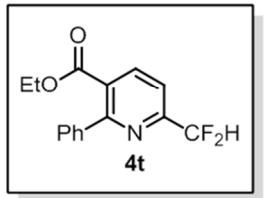


4s

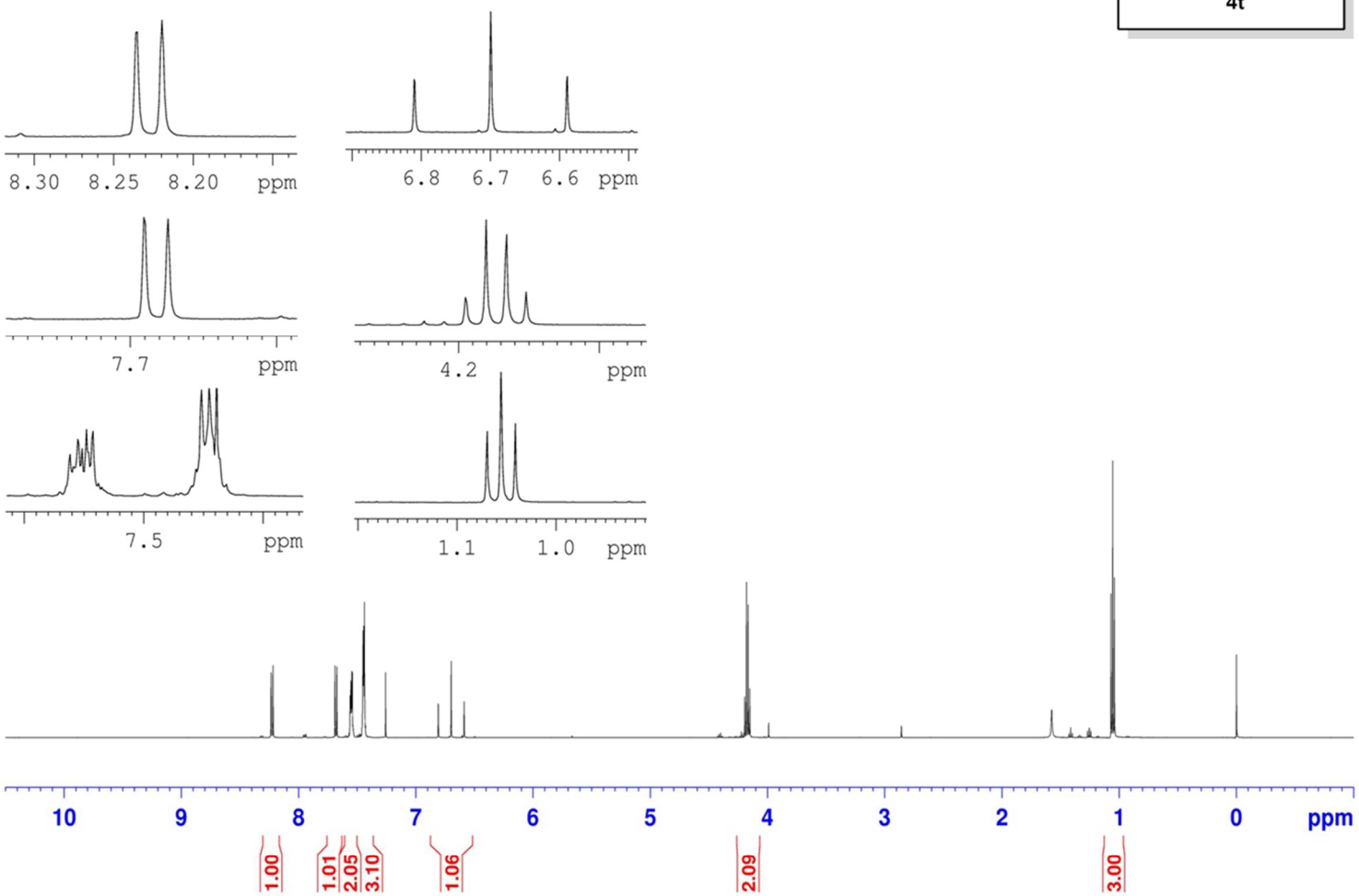




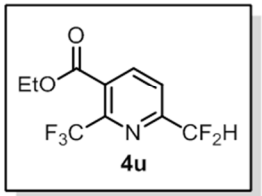
Ethyl 6–(difluoromethyl)–2–phenylnicotinate
500 MHz, CDCl3



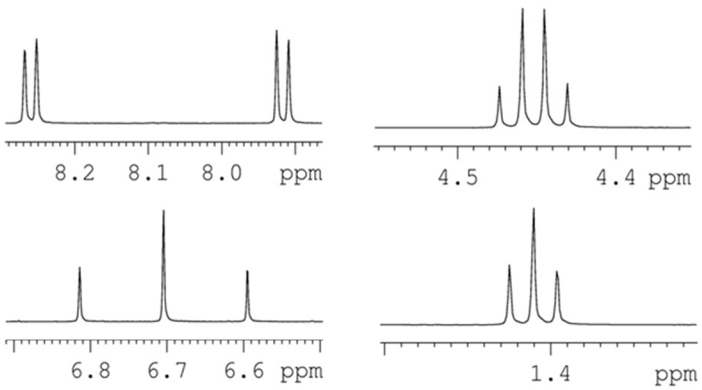
4t

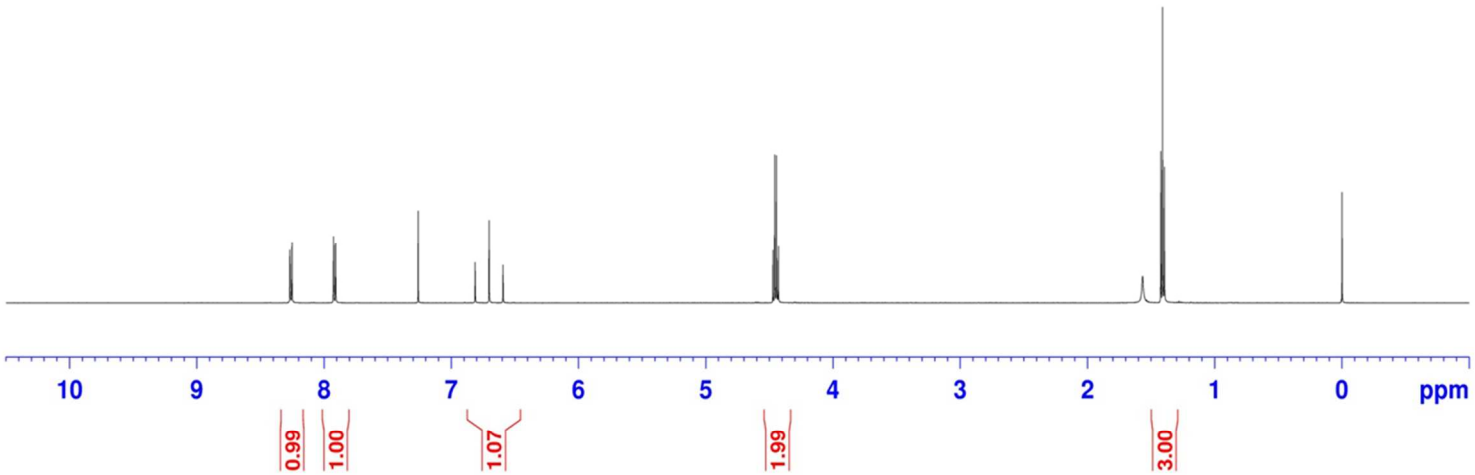


Ethyl 6–(difluoromethyl)–2–(trifluoromethyl)nicotinate
500 MHz, CDCl3

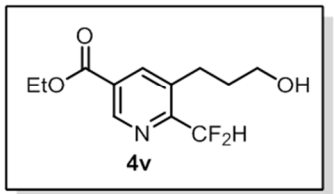


4u

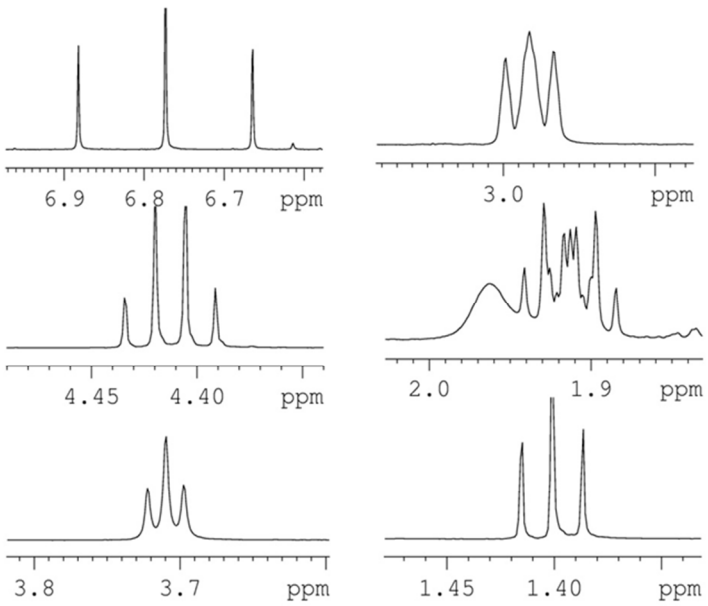


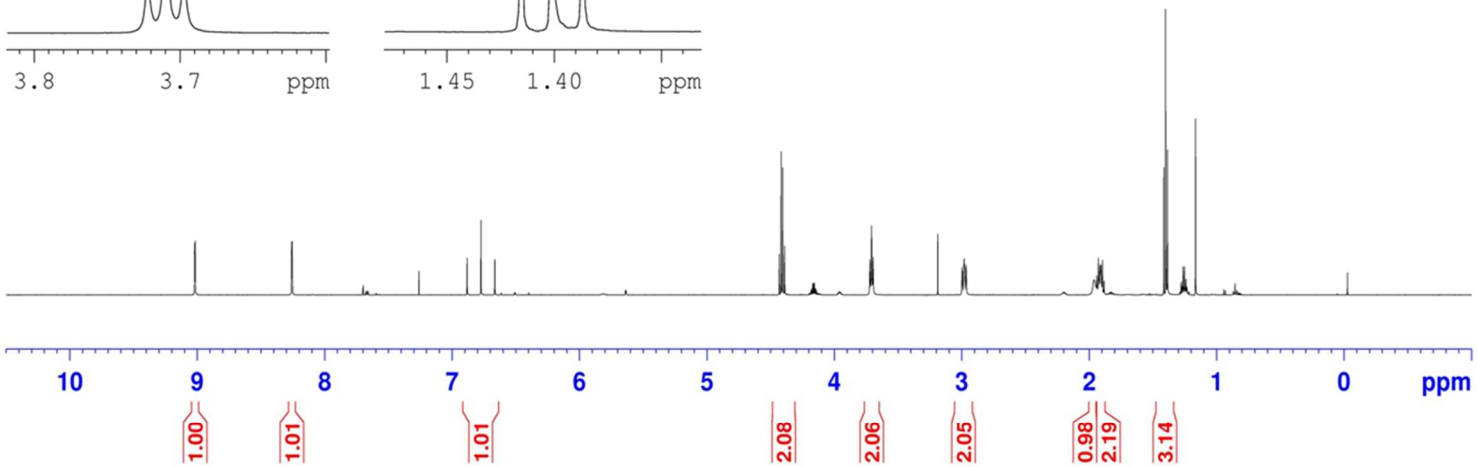


ethyl 6–(difluoromethyl)–5–(3–hydroxypropyl)nicotinate
500 MHz CDCl3

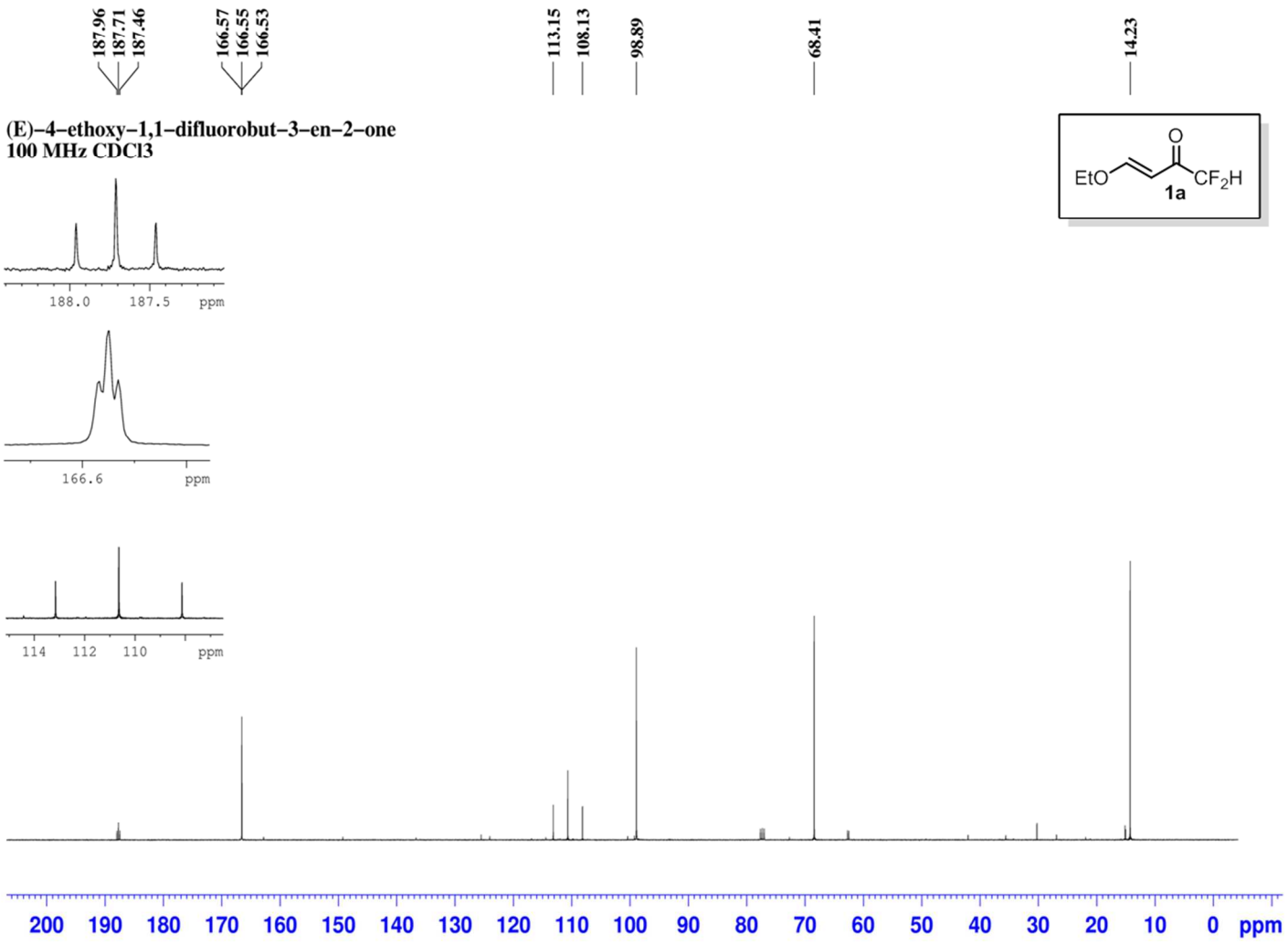


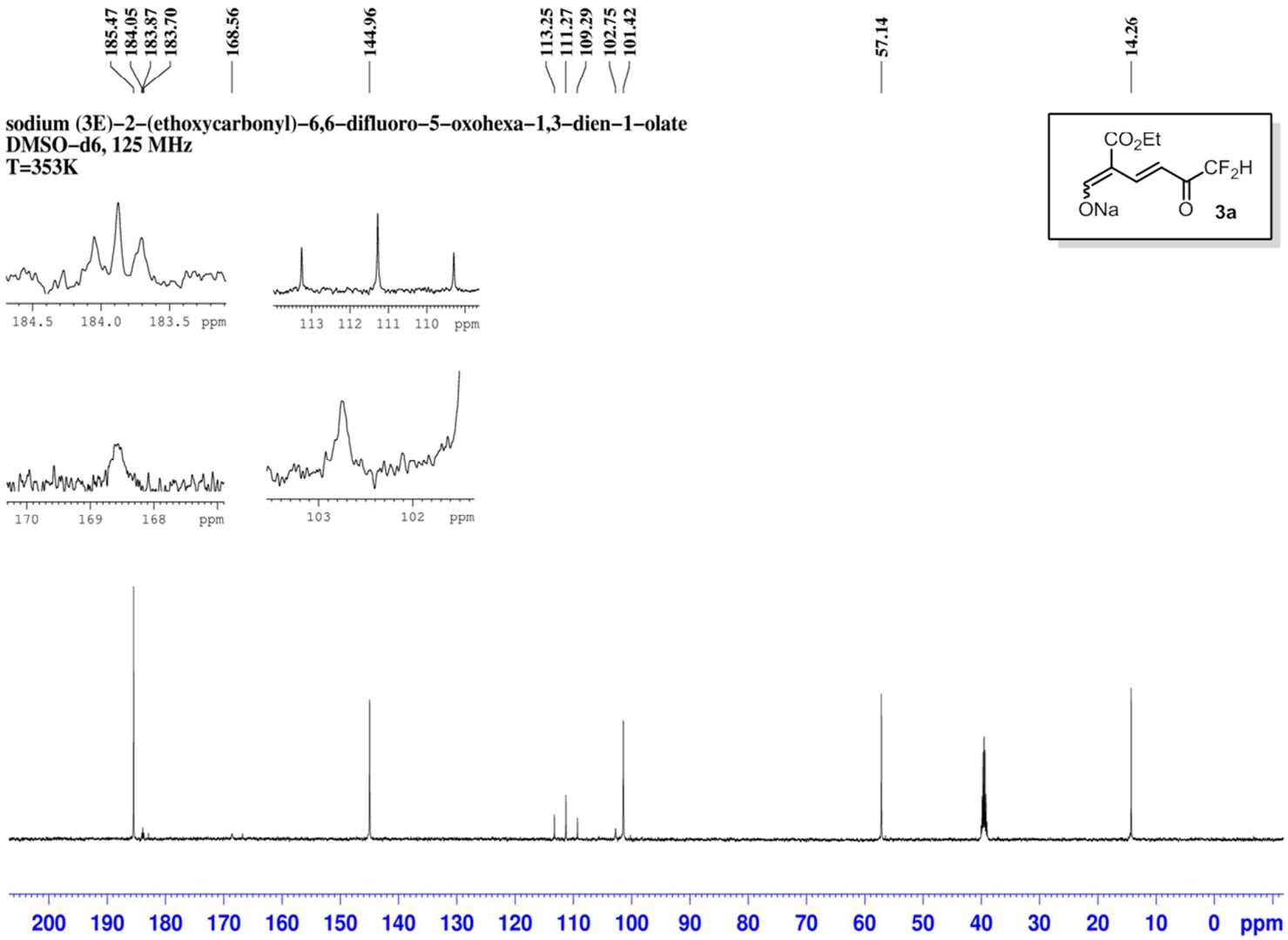
4v

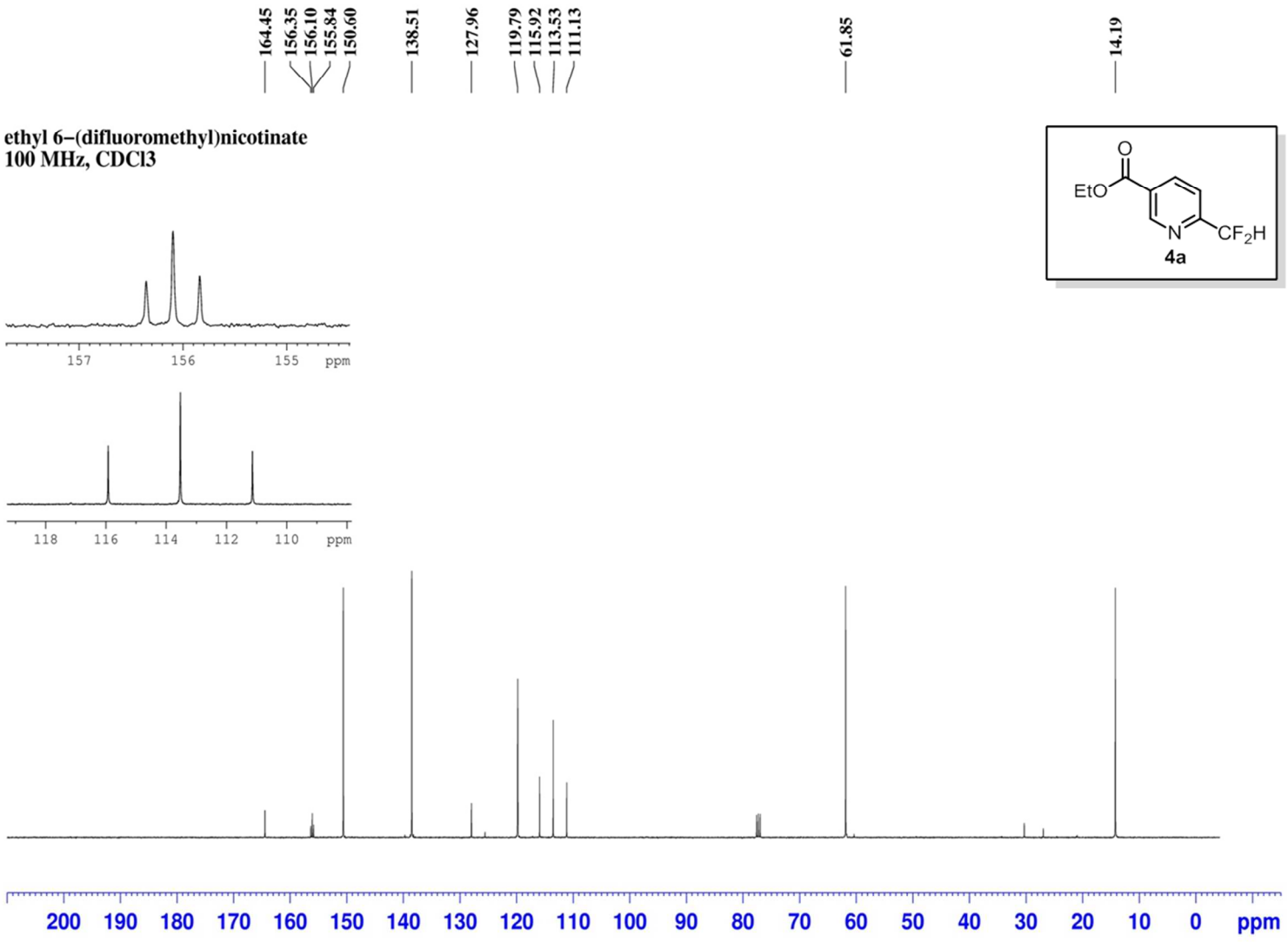


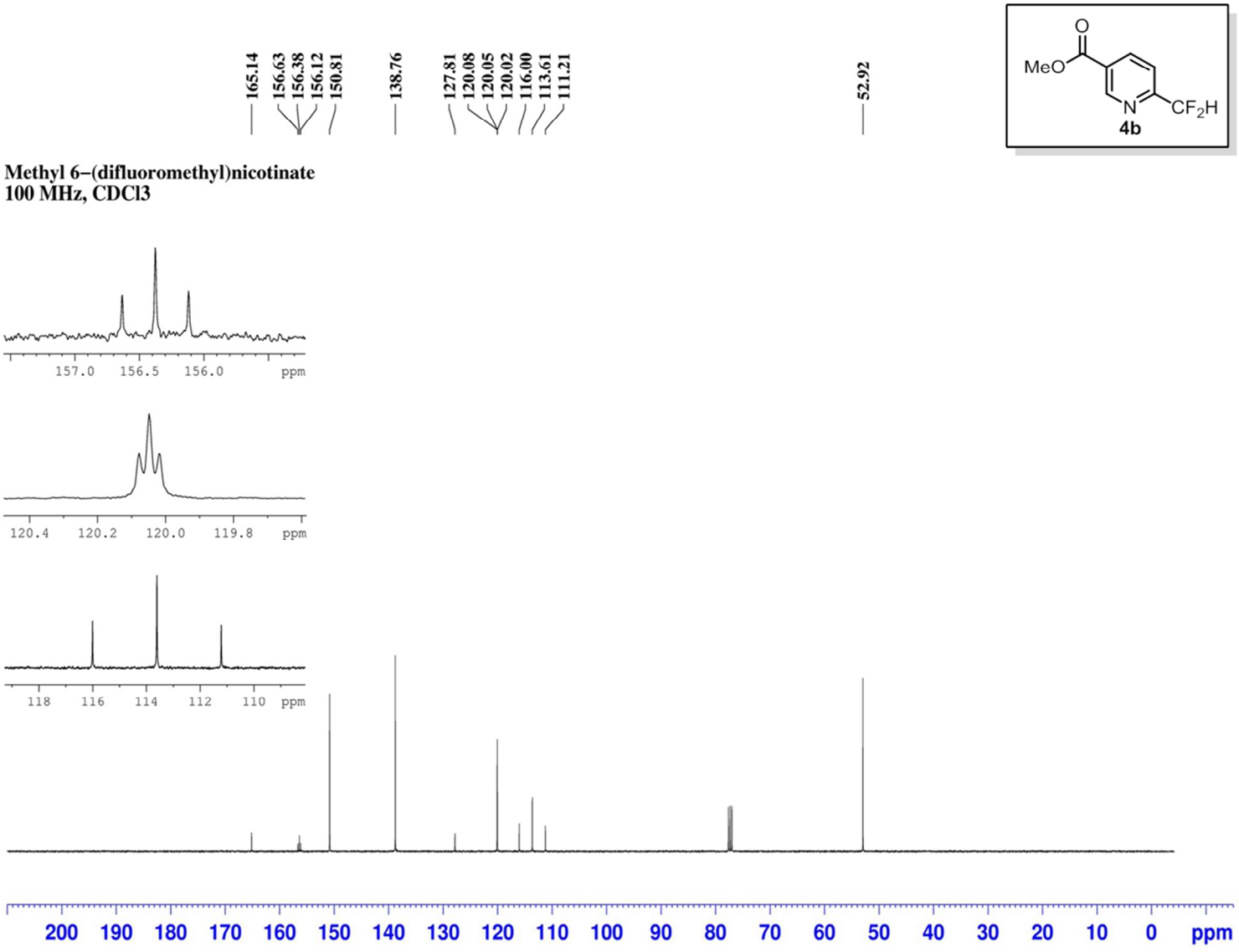


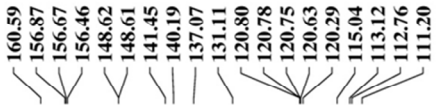
^{13}C-NMR Spectra of Synthesized Compounds



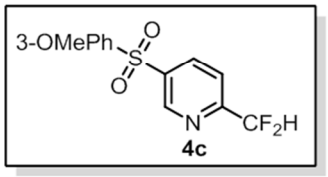

185.47
184.05
183.87
183.70
168.56
144.96
113.25
111.27
109.29
102.75
101.42
57.14
14.26
sodium (3E)−2−(ethoxycarbonyl)−6,6−difluoro−5−oxohexa−1,3−dien−1−olate
DMSO−d6, 125 MHz
T=353K
CO2Et
CF2H
ONa
O
3a
184.5 184.0 183.5 ppm
113 112 111 110 ppm
170 169 168 ppm
103 102 ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

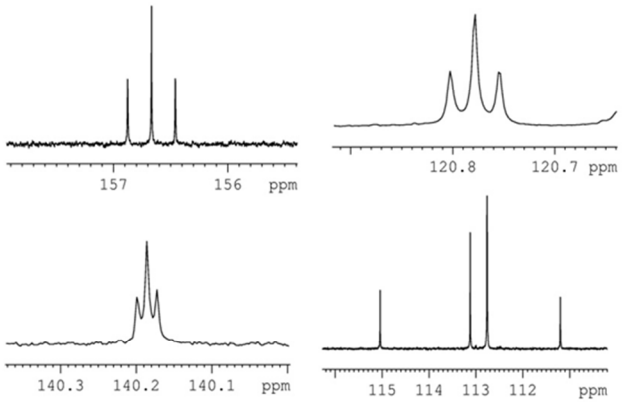

164.45
156.35
156.10
155.84
150.60
138.51
127.96
119.79
115.92
113.53
111.13
61.85
14.19
ethyl 6−(difluoromethyl)nicotinate
100 MHz, CDCl3
EtO
O
N
CF2H
4a
157
156
155
ppm
118
116
114
112
110
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

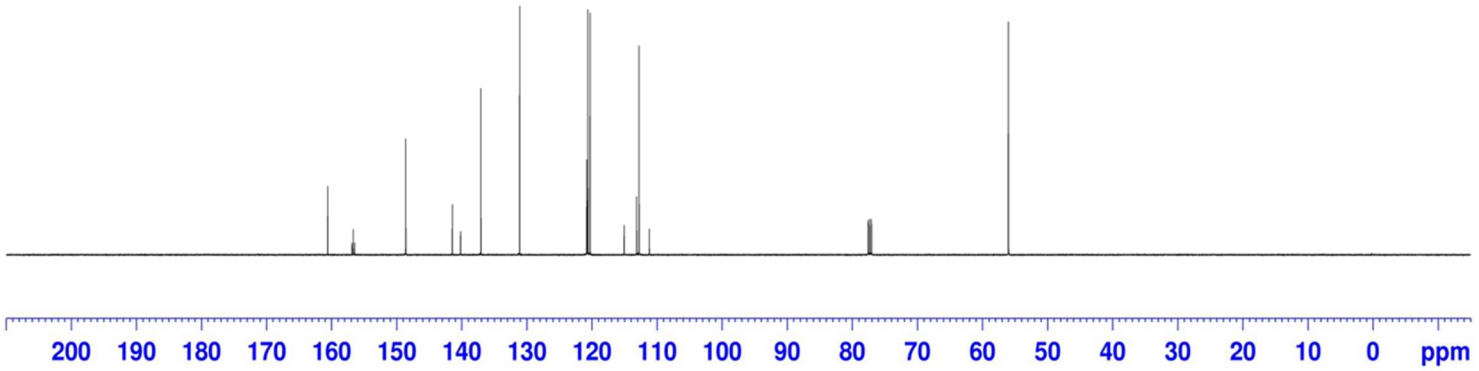

165.14
156.63
156.38
156.12
150.81
138.76
127.81
120.08
120.05
120.02
116.00
113.61
111.21
52.92
MeO
O
N
CF2H
4b
Methyl 6−(difluoromethyl)nicotinate
100 MHz, CDCl3
157.0 156.5 156.0 ppm
120.4 120.2 120.0 119.8 ppm
118 116 114 112 110 ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

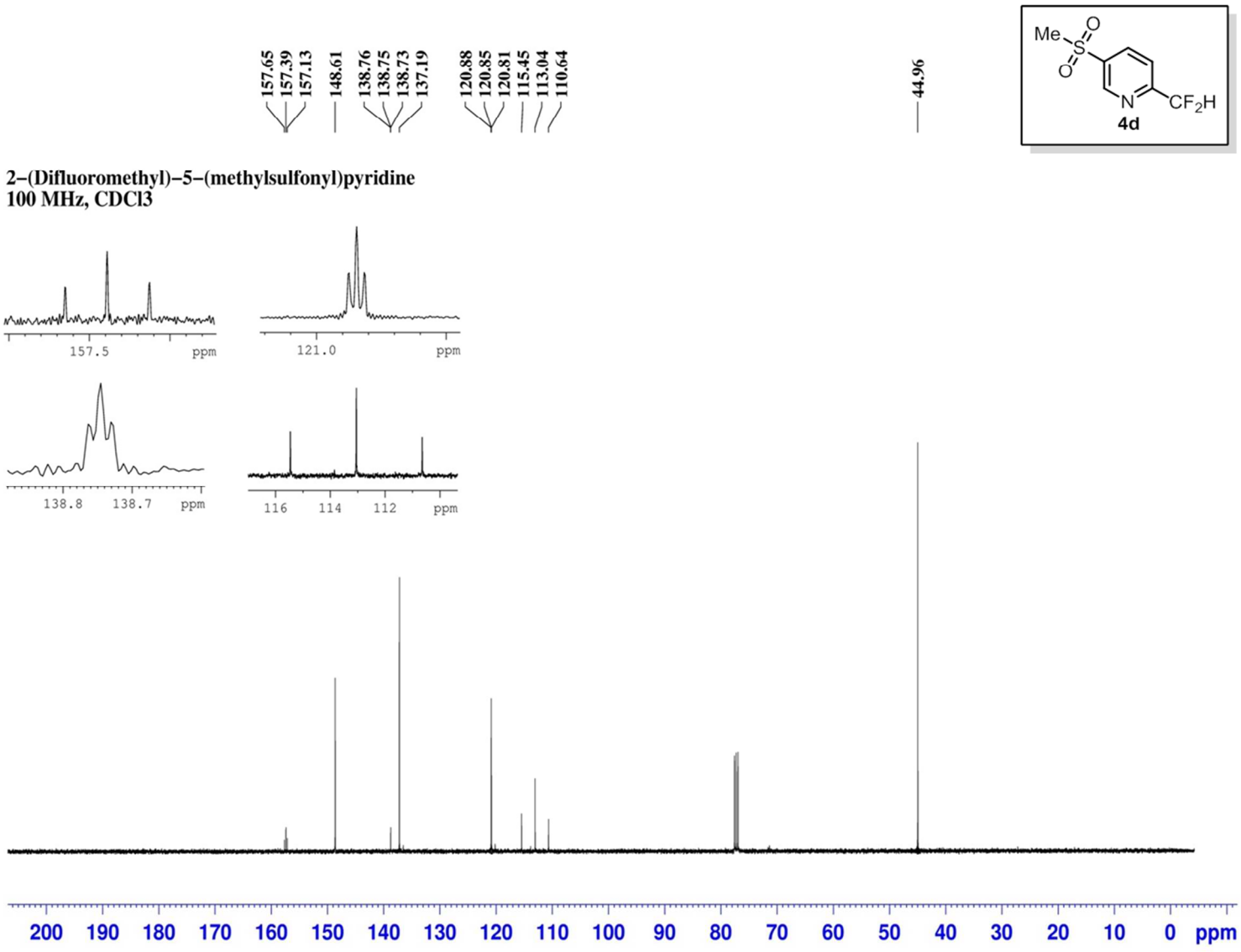


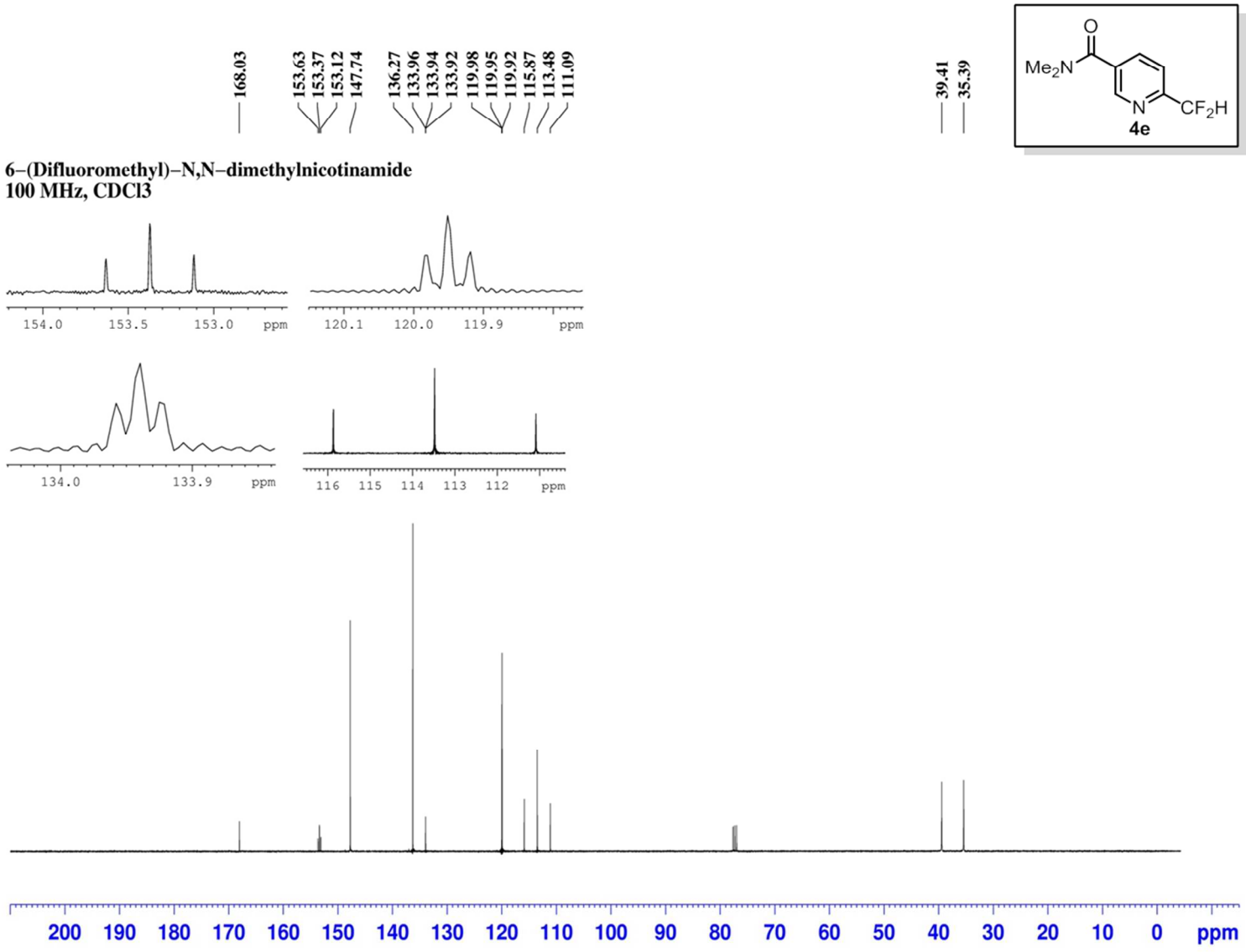
2-(Difluoromethyl)-5-((3-methoxyphenyl)sulfonyl)pyridine
125 MHz, CDCl3

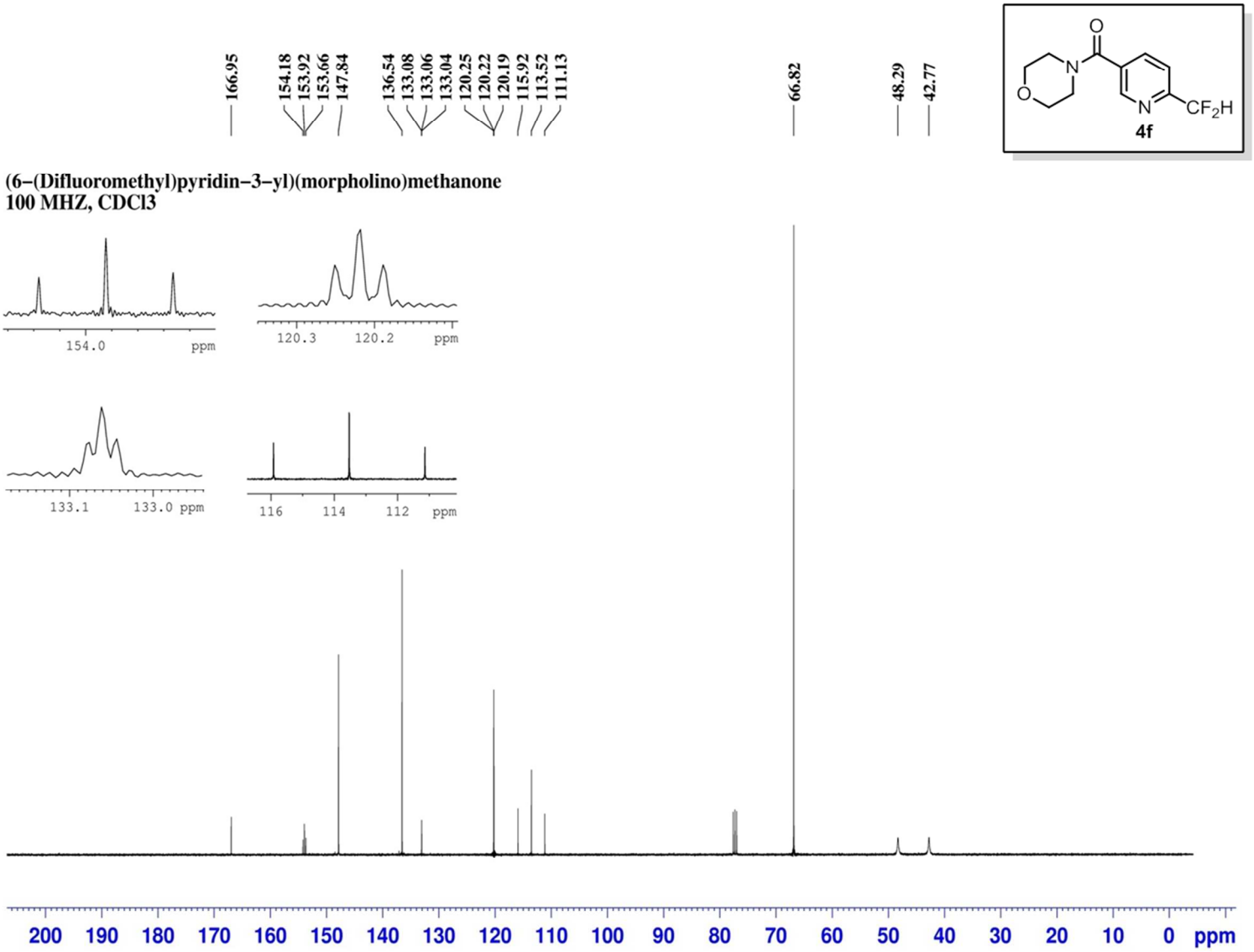


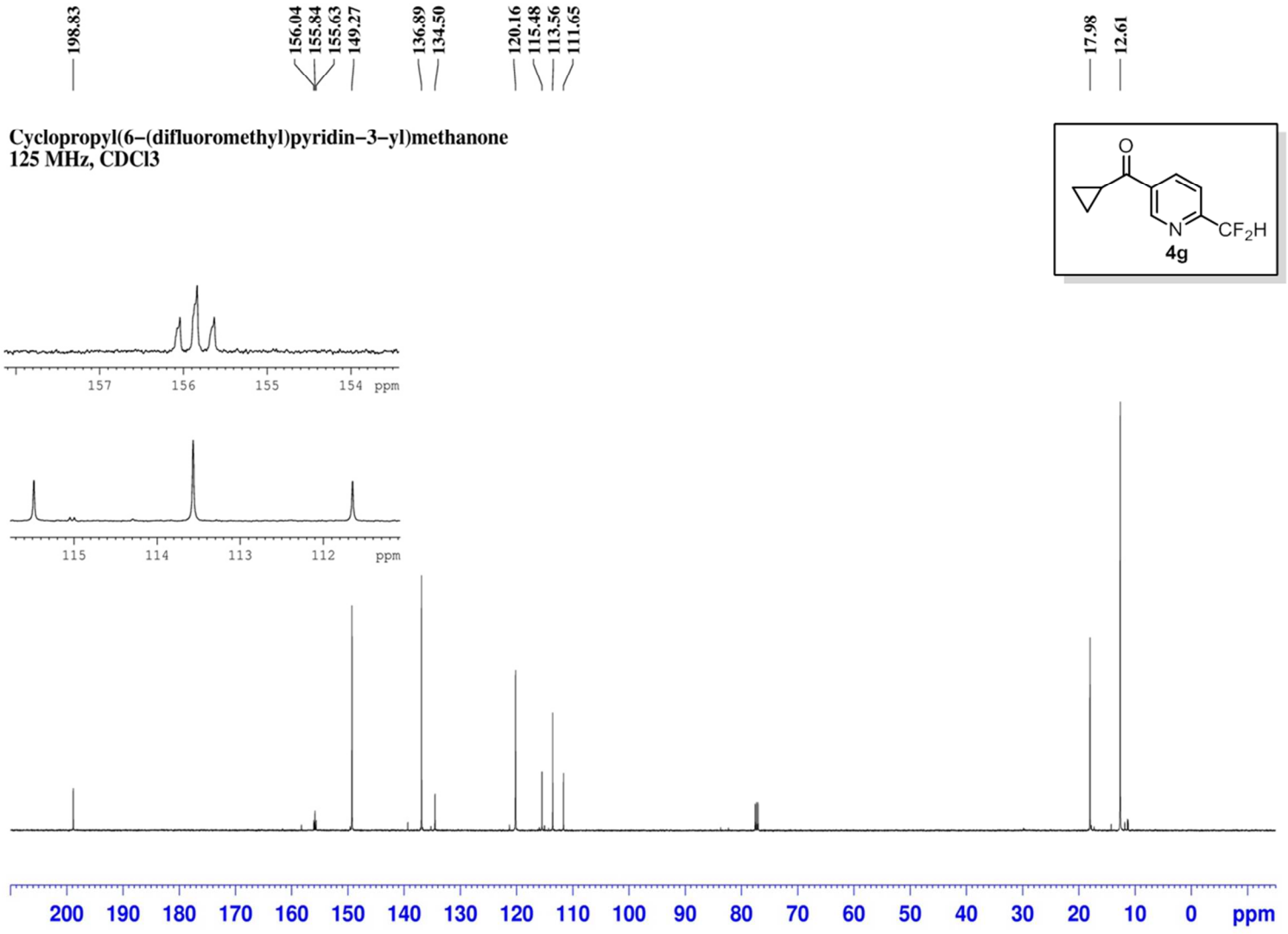


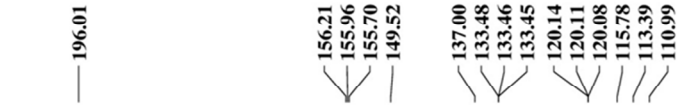


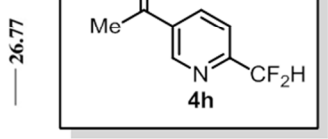

157.65
157.39
157.13
148.61
138.76
138.75
138.73
137.19
120.88
120.85
120.81
115.45
113.04
110.64
44.96
Me
O
O
S
N
CF2H
4d
2−(Difluoromethyl)−5−(methylsulfonyl)pyridine
100 MHz, CDCl3
157.5
ppm
121.0
ppm
138.8
138.7
ppm
116
114
112
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


168.03
153.63
153.37
153.12
147.74
136.27
133.96
133.94
133.92
119.98
119.95
119.92
115.87
113.48
111.09
39.41
35.39
Me2N
O
N
CF2H
4e
6–(Difluoromethyl)–N,N–dimethylnicotinamide
100 MHz, CDCl3
154.0
153.5
153.0
ppm
120.1
120.0
119.9
ppm
134.0
133.9
ppm
116
115
114
113
112
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

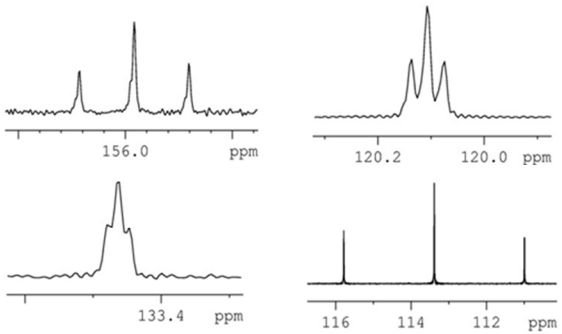

166.95
154.18
153.92
153.66
147.84
136.54
133.08
133.06
133.04
120.25
120.22
120.19
115.92
113.52
111.13
66.82
48.29
42.77
O
N
O
N
CF2H
4f
(6−(Difluoromethyl)pyridin−3−yl)(morpholino)methanone
100 MHZ, CDCl3
154.0
ppm
120.3
120.2
ppm
133.1
133.0 ppm
116
114
112
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

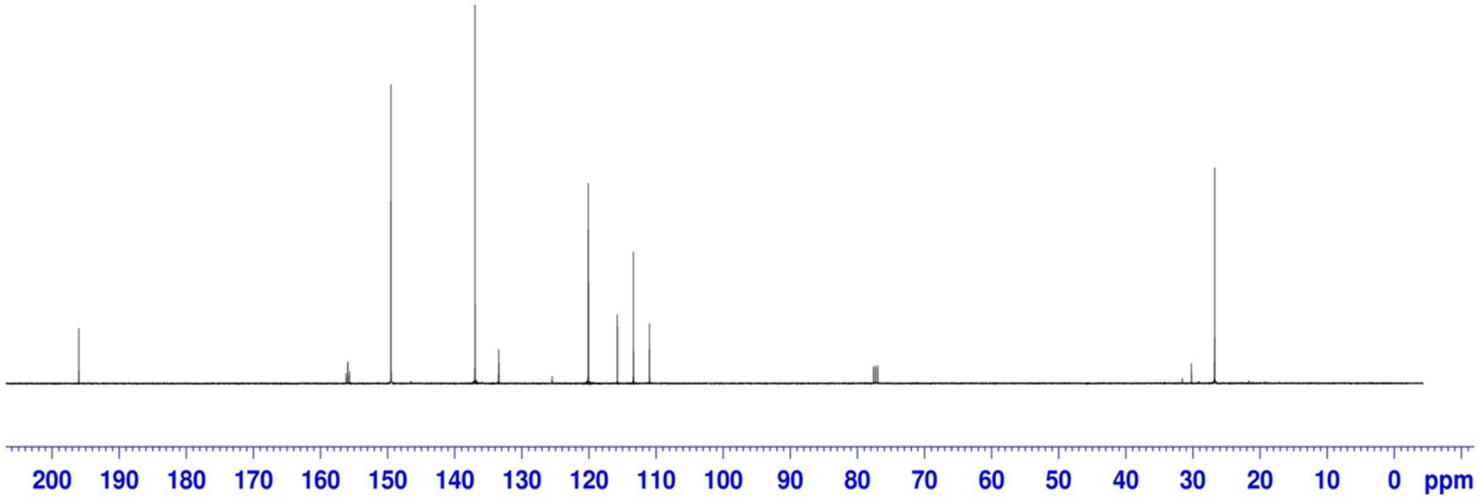

198.83
156.04
155.84
155.63
149.27
136.89
134.50
120.16
115.48
113.56
111.65
17.98
12.61
Cyclopropyl(6−(difluoromethyl)pyridin−3−yl)methanone
125 MHz, CDCl3
O
N
CF2H
4g
157
156
155
154 ppm
115
114
113
112
ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

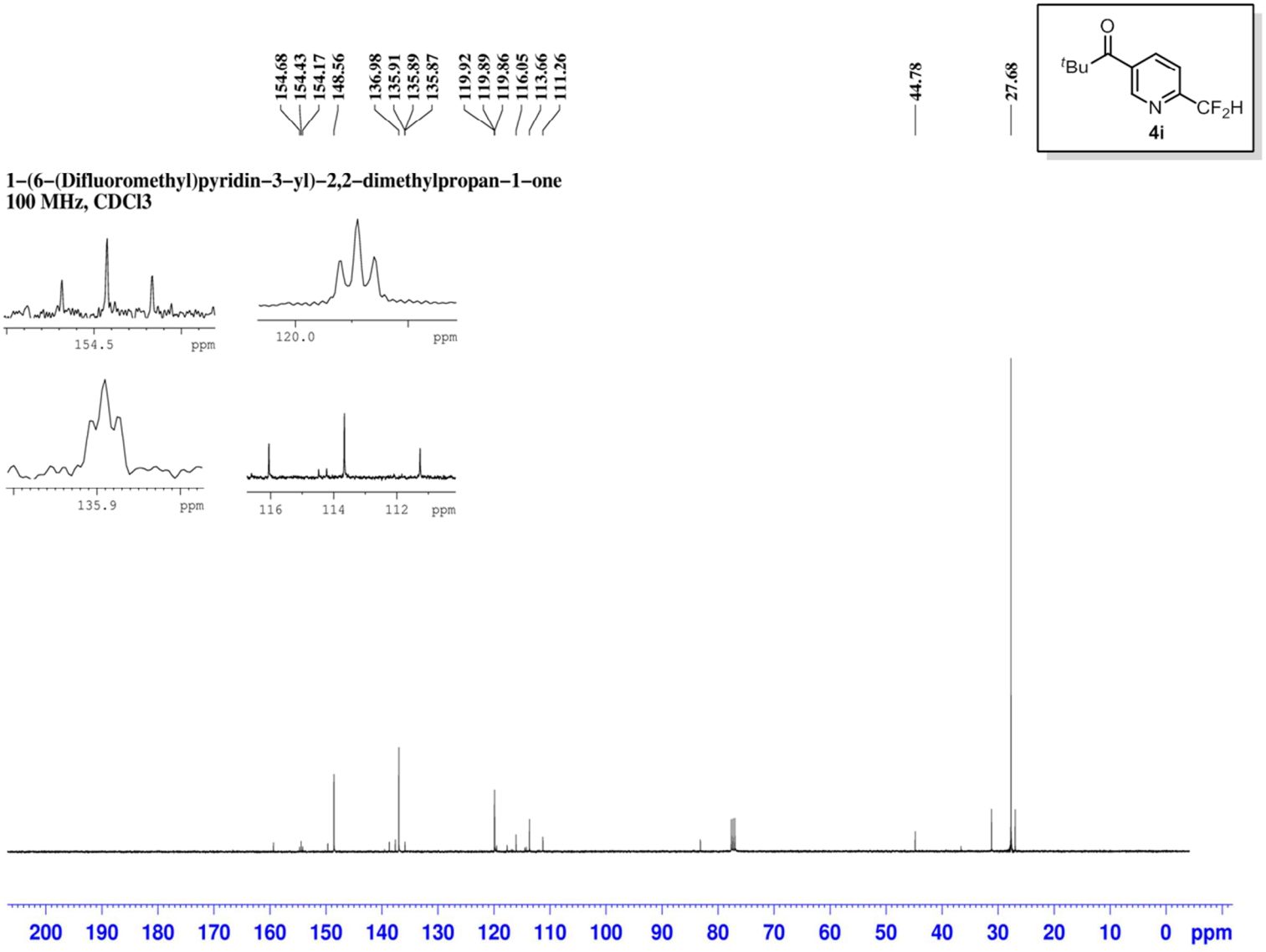


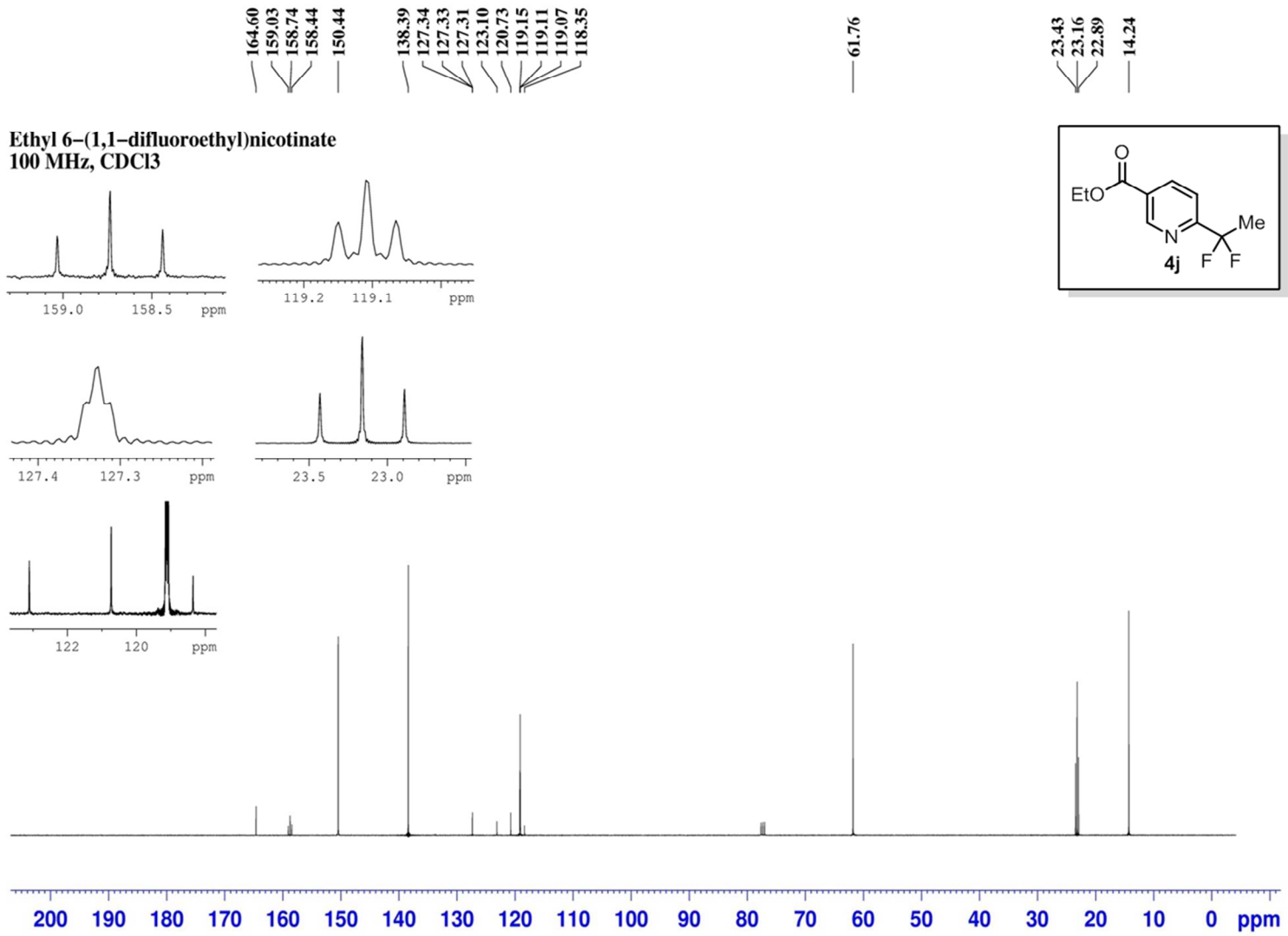


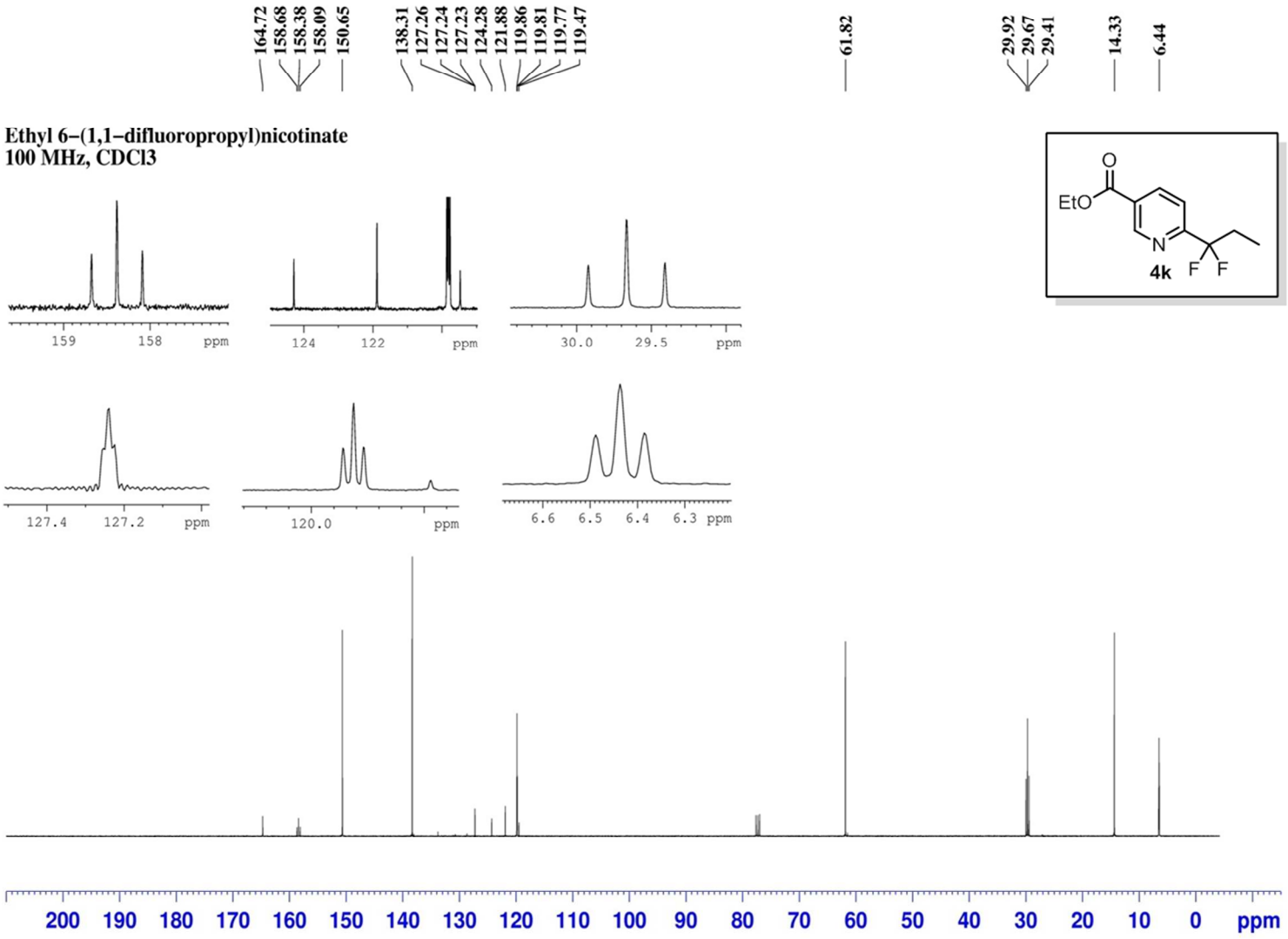
1−(6−(Difluoromethyl)pyridin−3−yl)ethanone
100 MHz, CDCl3

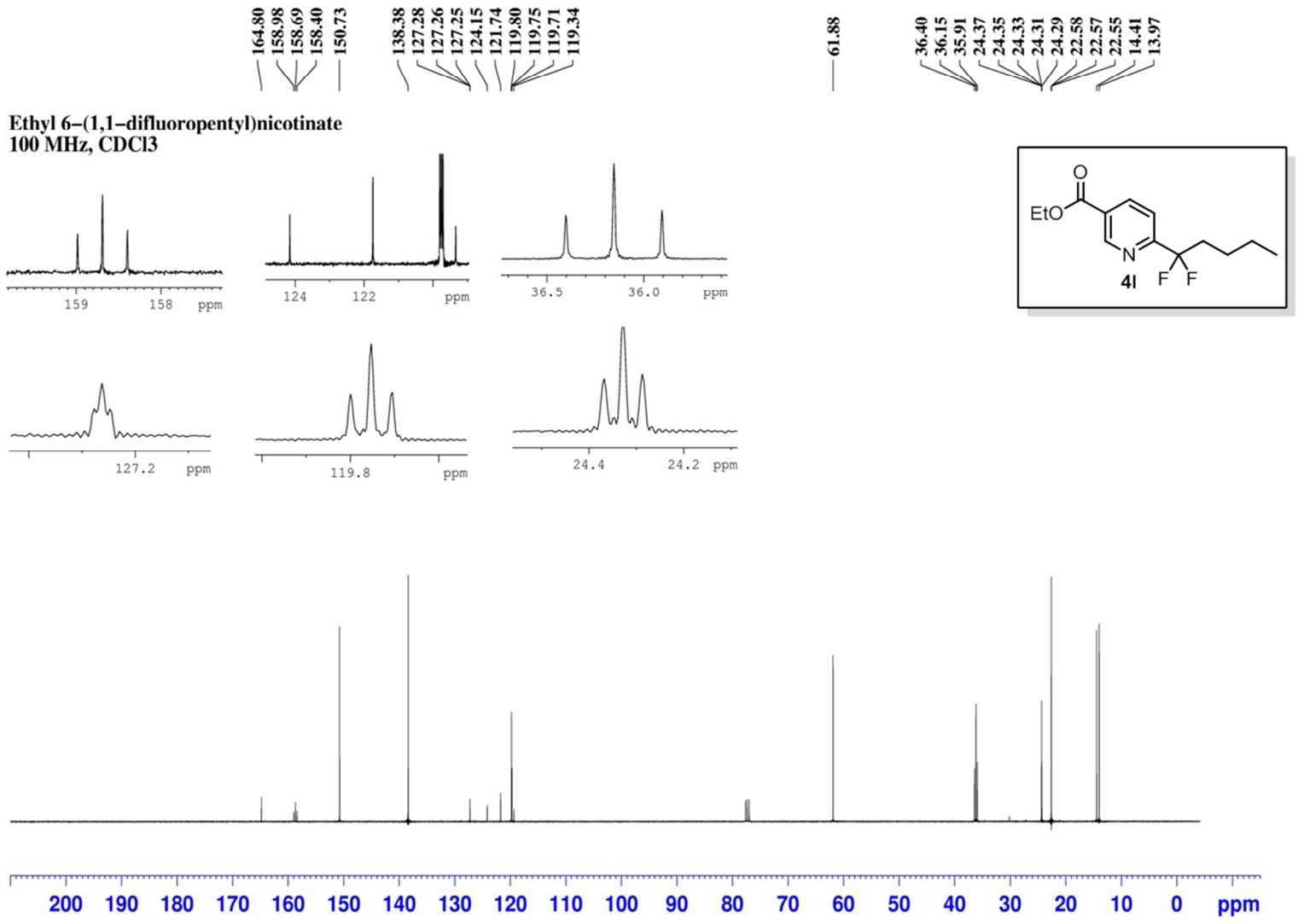


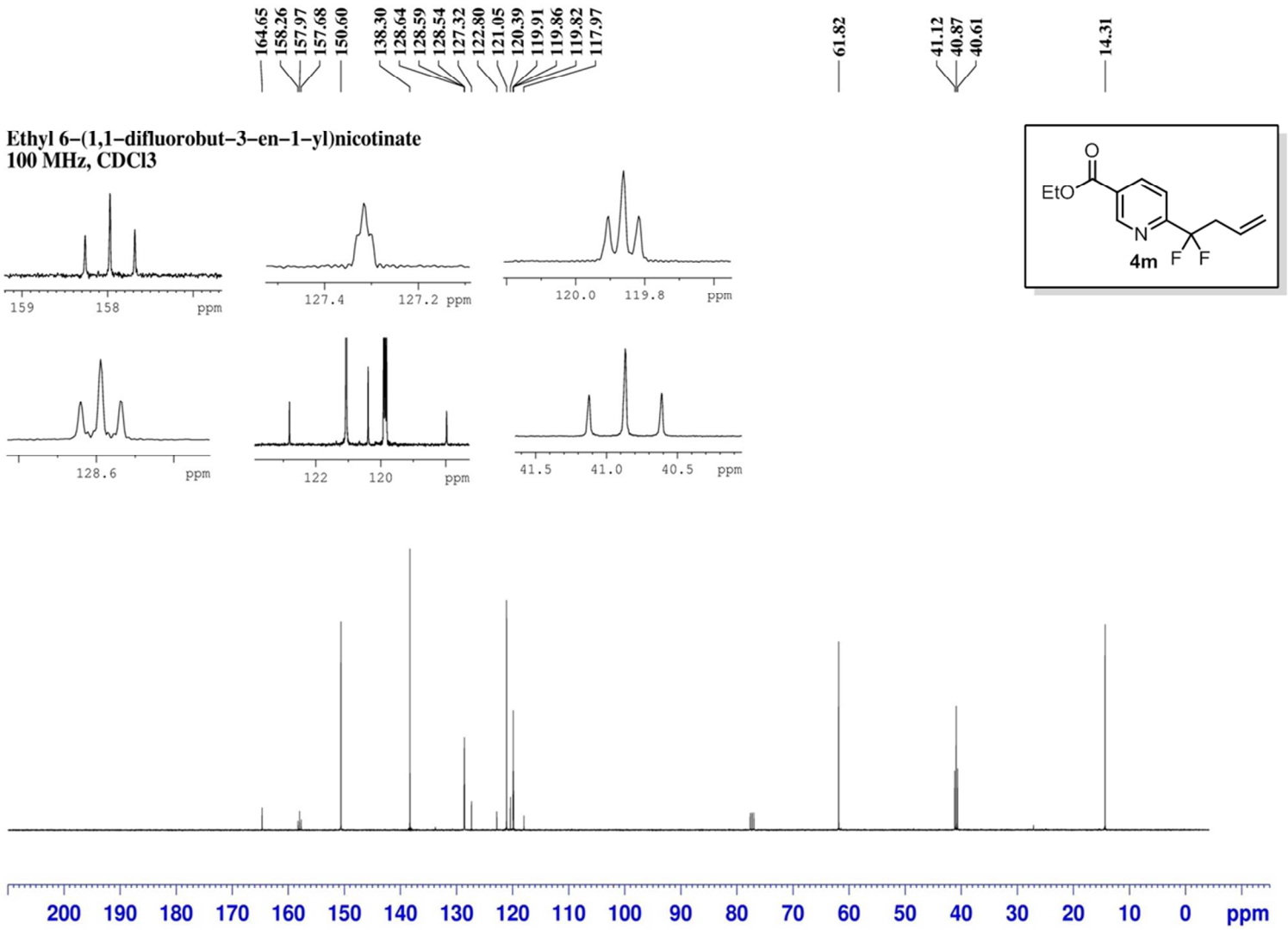


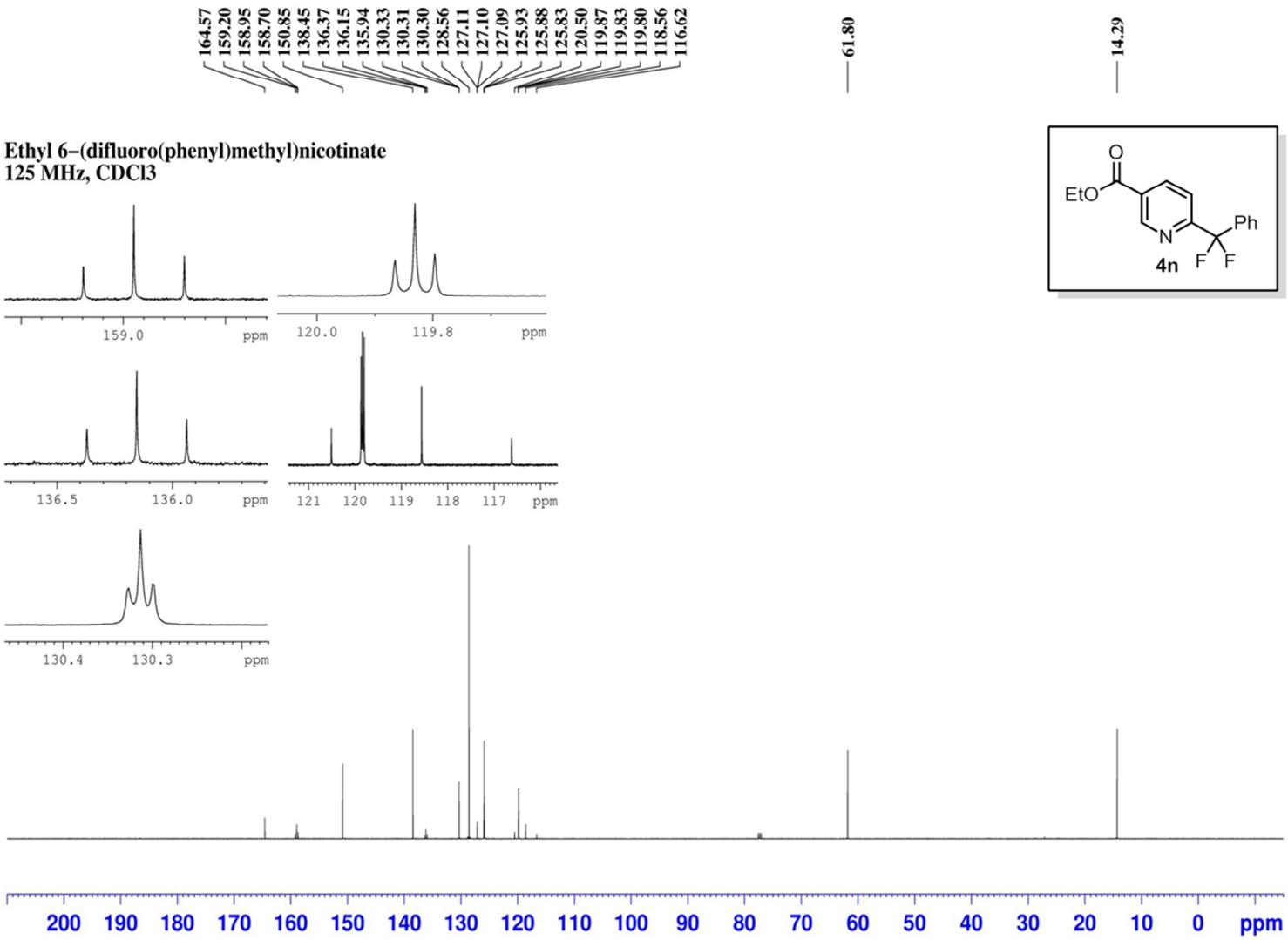

154.68
154.43
154.17
148.56
136.98
135.91
135.89
135.87
119.92
119.89
119.86
116.05
113.66
111.26
44.78
27.68
tBu
O
N
CF2H
4i
1-(6-(Difluoromethyl)pyridin-3-yl)-2,2-dimethylpropan-1-one
100 MHz, CDCl3
154.5
ppm
120.0
ppm
135.9
ppm
116
114
112
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

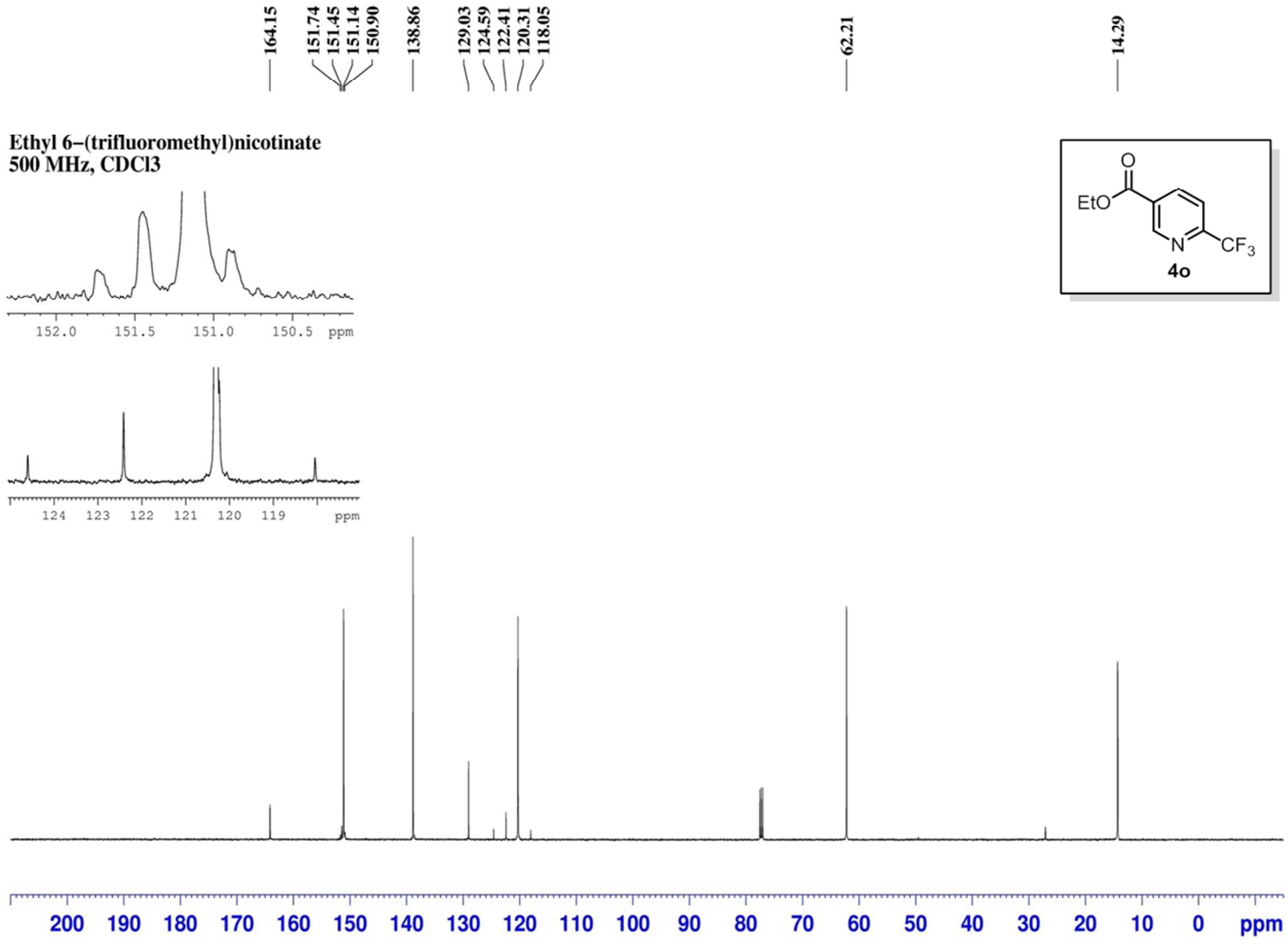

164.60
159.03
158.74
158.44
150.44
138.39
127.34
127.33
127.31
123.10
120.73
119.15
119.11
119.07
118.35
61.76
23.43
23.16
22.89
14.24
Ethyl 6−(1,1−difluoroethyl)nicotinate
100 MHz, CDCl3
EtO
O
N
Me
F F
4j
159.0
158.5
ppm
119.2
119.1
ppm
127.4
127.3
ppm
23.5
23.0
ppm
122
120
ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

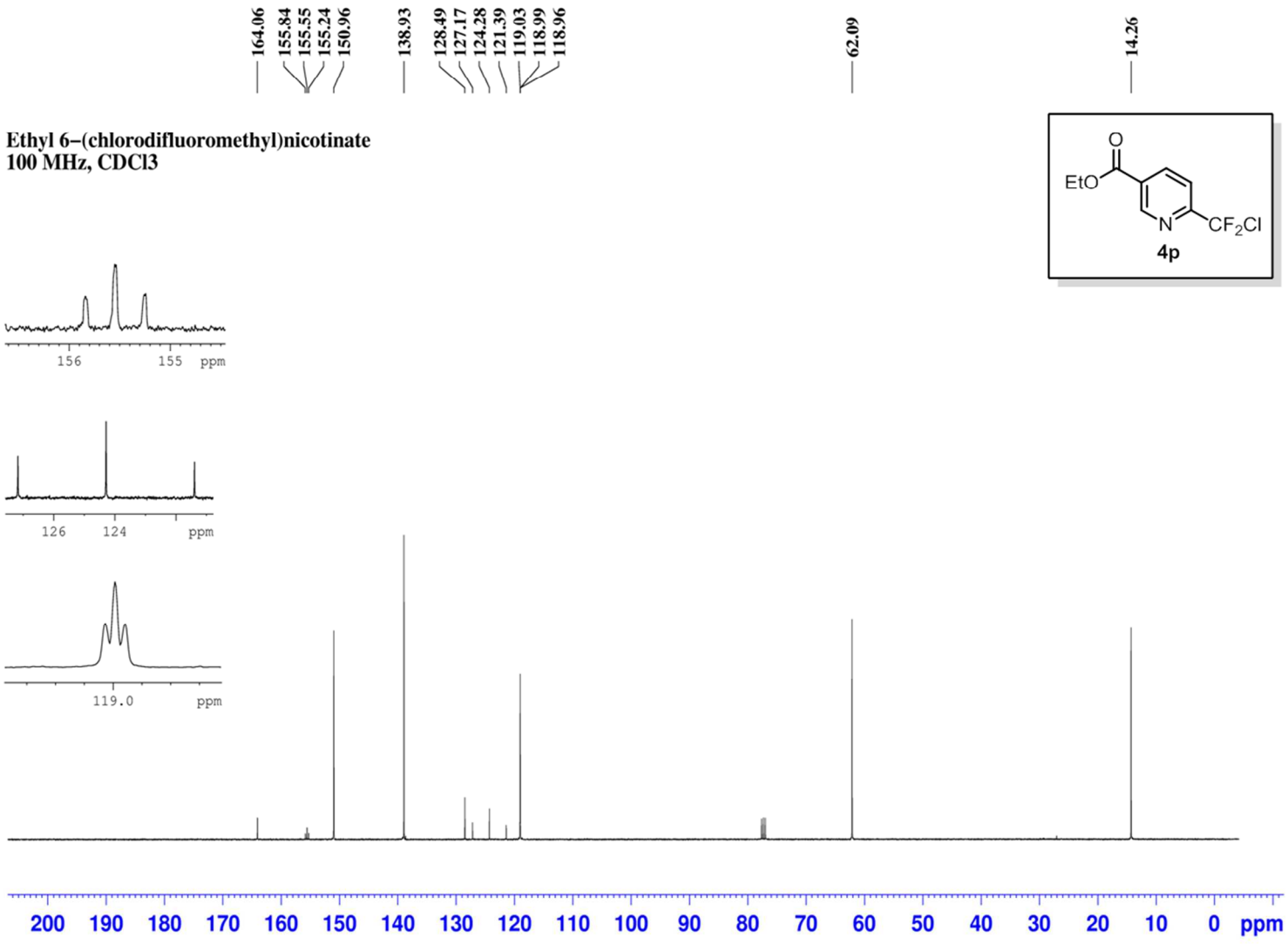

164.72
158.68
158.38
158.09
150.65
138.31
127.26
127.24
127.23
124.28
121.88
119.86
119.81
119.77
119.47
61.82
29.92
29.67
29.41
14.33
6.44
Ethyl 6−(1,1−difluoropropyl)nicotinate
100 MHz, CDCl3
EtO
O
N
F
F
4k
159
158
ppm
124
122
ppm
30.0
29.5
ppm
127.4
127.2
ppm
120.0
ppm
6.6
6.5
6.4
6.3
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

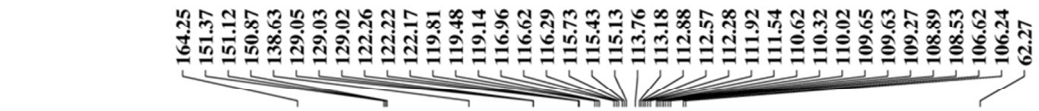

164.80
158.98
158.69
158.40
150.73
138.38
127.28
127.26
127.25
124.15
121.74
119.80
119.75
119.71
119.34
61.88
36.40
36.15
35.91
24.37
24.35
24.33
24.31
24.29
22.58
22.57
22.55
14.41
13.97
Ethyl 6–(1,1–difluoropentyl)nicotinate
100 MHz, CDCl3
159
158
ppm
124
122
ppm
36.5
36.0
ppm
127.2
ppm
119.8
ppm
24.4
24.2
ppm
EtO
O
N
F
F
4l
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


164.65
158.26
157.97
157.68
150.60
138.30
128.64
128.59
128.54
127.32
122.80
121.05
120.39
119.91
119.86
119.82
117.97
61.82
41.12
40.87
40.61
14.31
Ethyl 6-(1,1-difluorobut-3-en-1-yl)nicotinate
100 MHz, CDCl3
159
158
ppm
127.4
127.2 ppm
120.0
119.8
ppm
128.6
ppm
122
120
ppm
41.5
41.0
40.5
ppm
EtO
O
N
F F
4m
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

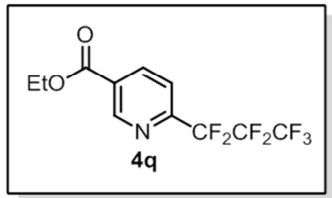

164.57
159.20
158.95
158.70
150.85
138.45
136.37
136.15
135.94
130.33
130.31
130.30
128.56
127.11
127.10
127.09
125.93
125.88
125.83
120.50
119.87
119.83
119.80
118.56
116.62
61.80
14.29
Ethyl 6–(difluoro(phenyl)methyl)nicotinate
125 MHz, CDCl3
EtO
O
N
Ph
F F
4n
159.0
ppm
120.0
119.8
ppm
136.5
136.0
ppm
121
120
119
118
117
ppm
130.4
130.3
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

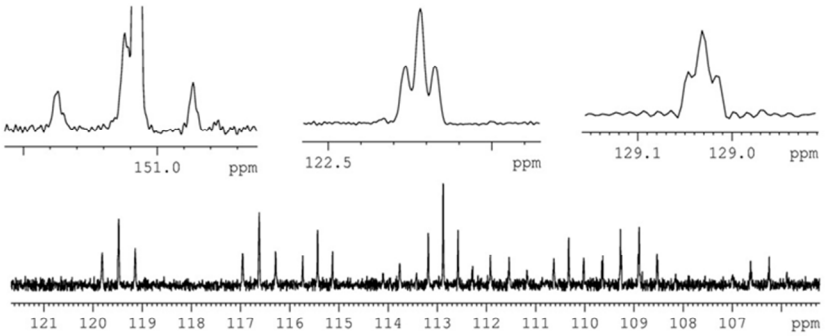

164.15
151.74
151.45
151.14
150.90
138.86
129.03
124.59
122.41
120.31
118.05
62.21
14.29
Ethyl 6–(trifluoromethyl)nicotinate
500 MHz, CDCl3
152.0
151.5
151.0
150.5
ppm
124
123
122
121
120
119
ppm
EtO
O
N
CF3
4o
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

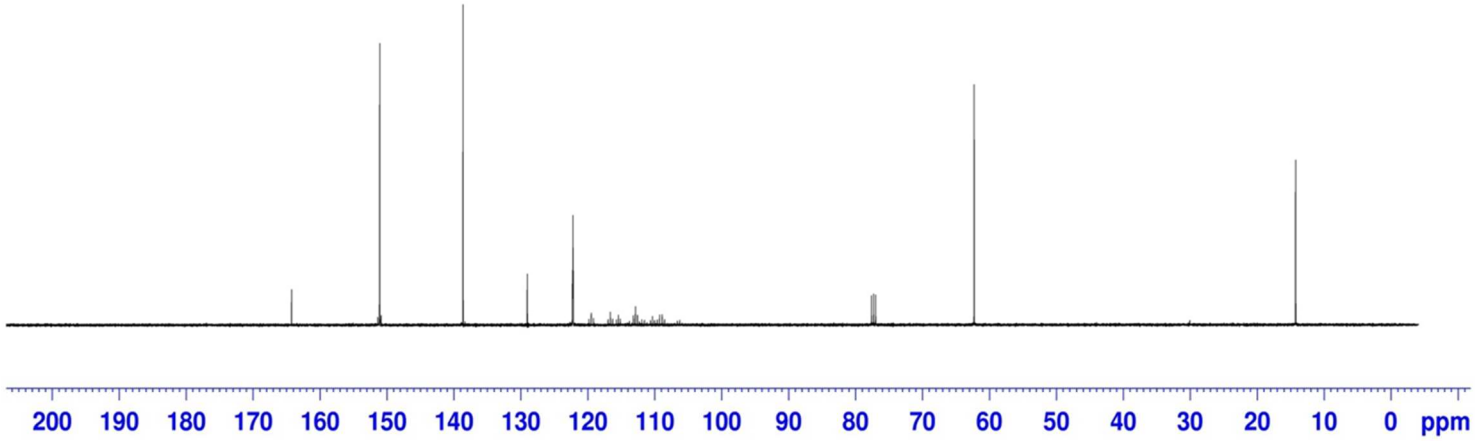

164.06
155.84
155.55
155.24
150.96
138.93
128.49
127.17
124.28
121.39
119.03
118.99
118.96
62.09
14.26
Ethyl 6–(chlorodifluoromethyl)nicotinate
100 MHz, CDCl3
EtO
O
N
CF2Cl
4p
156
155
ppm
126
124
ppm
119.0
ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

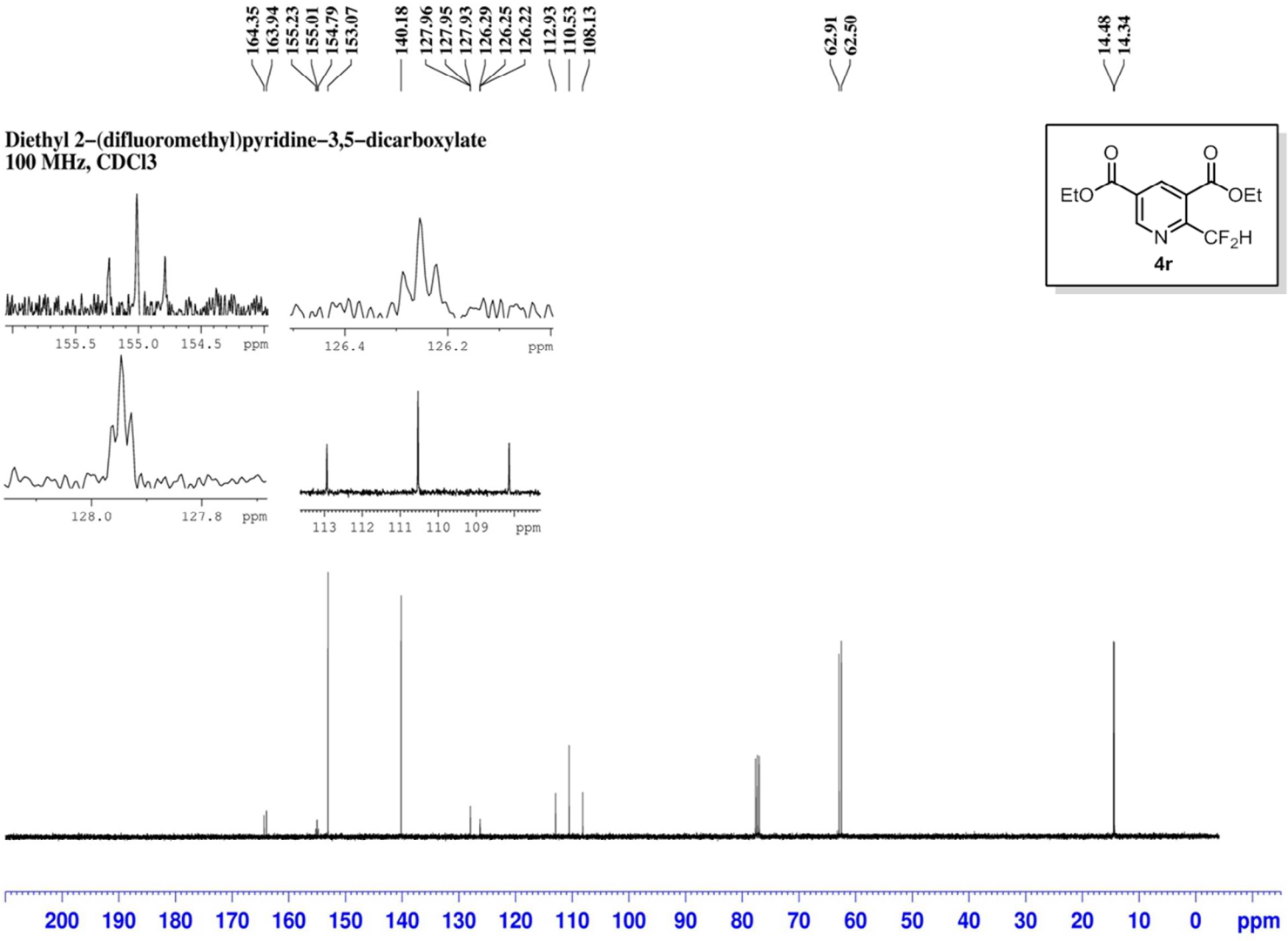


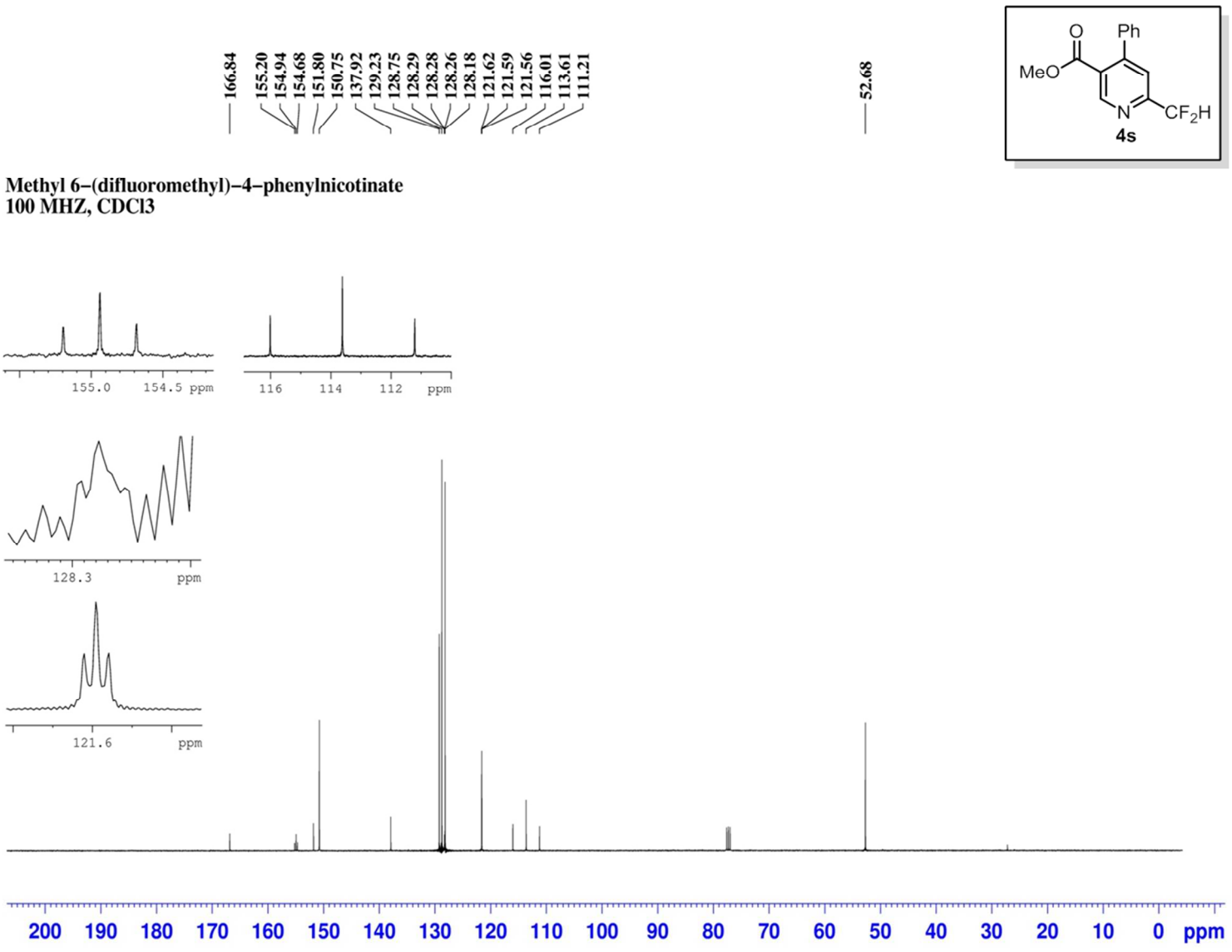
ethyl 6−(perfluoropropyl)nicotinate
100 MHz, CDCl3

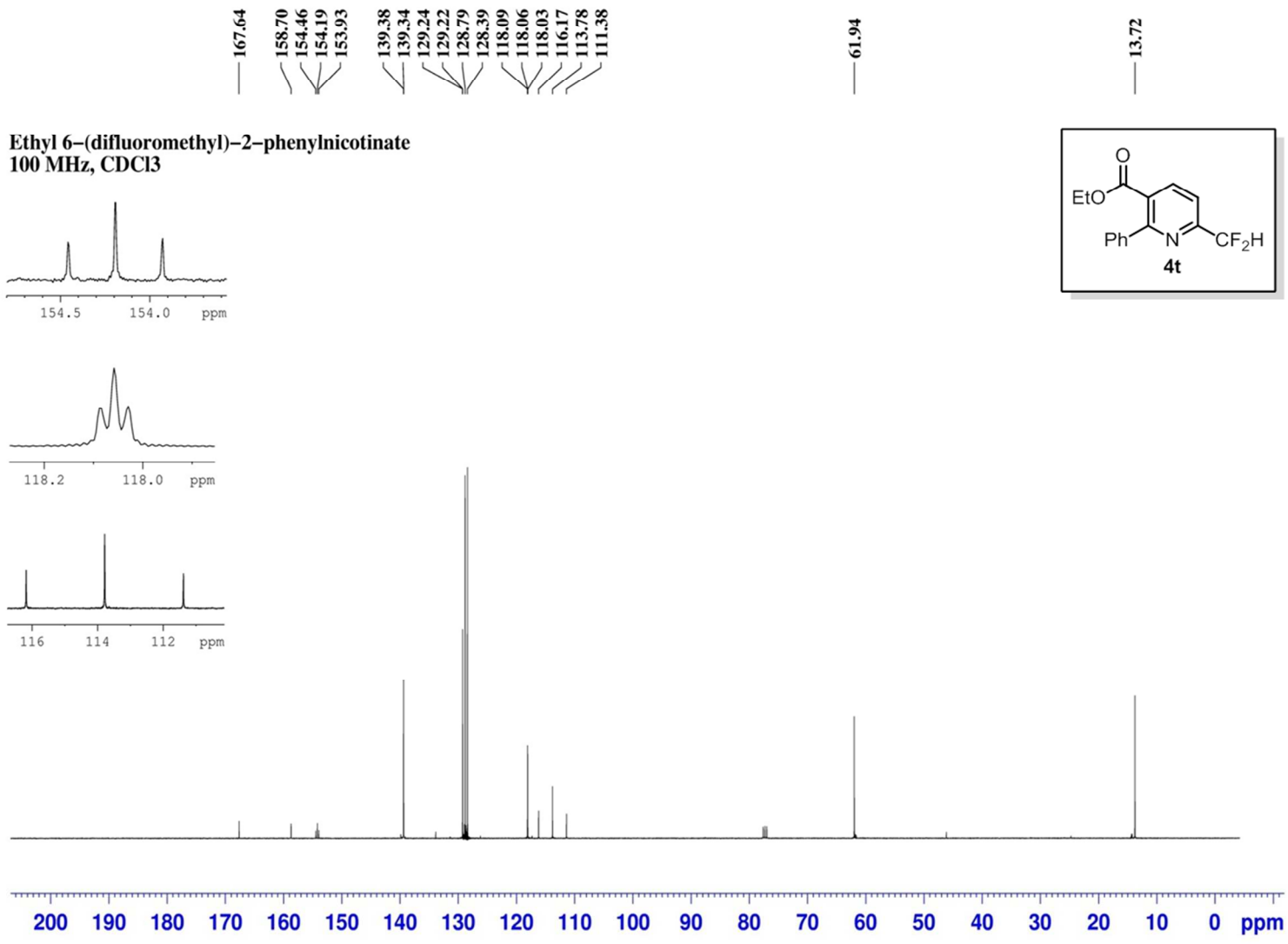




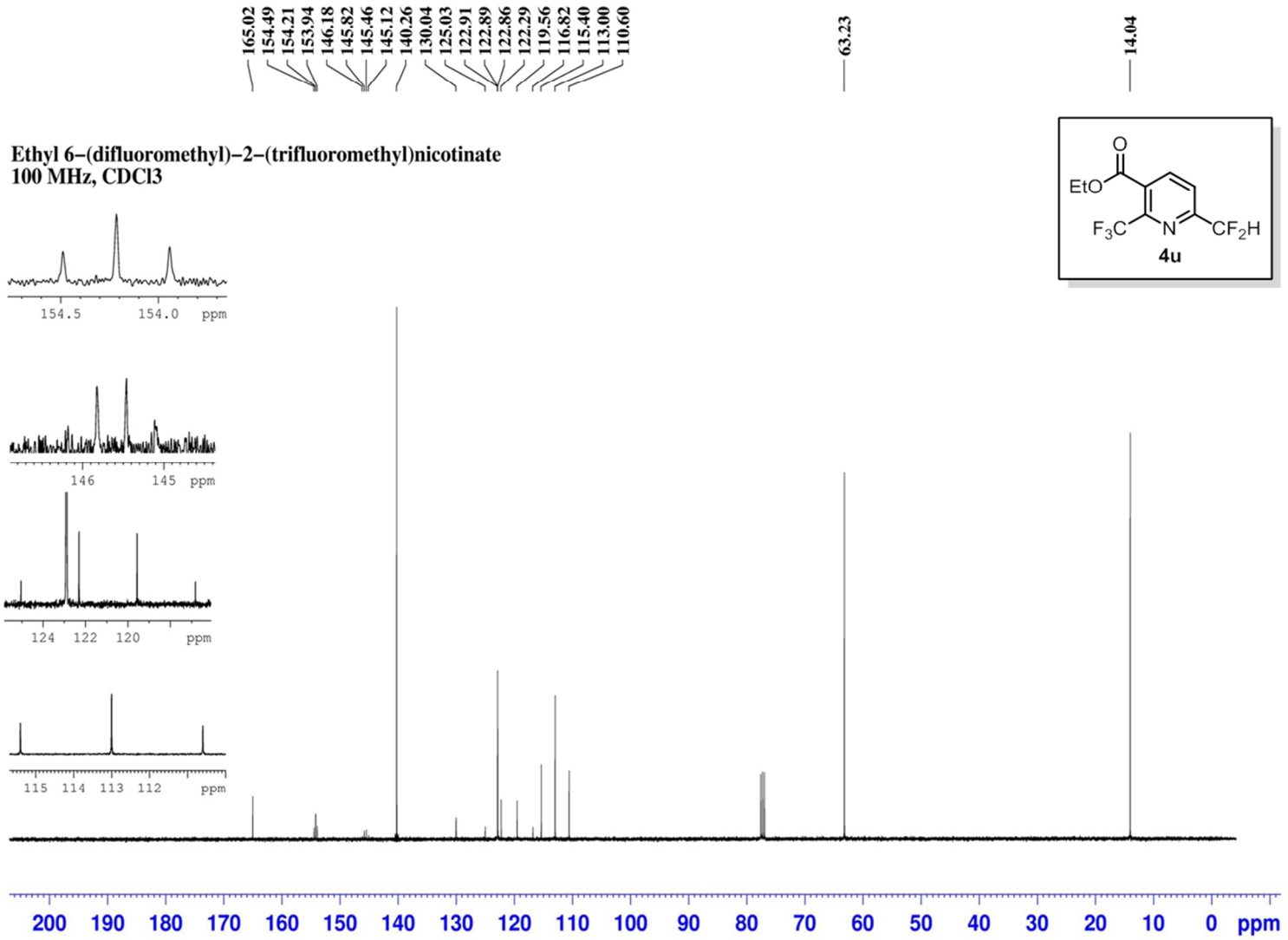


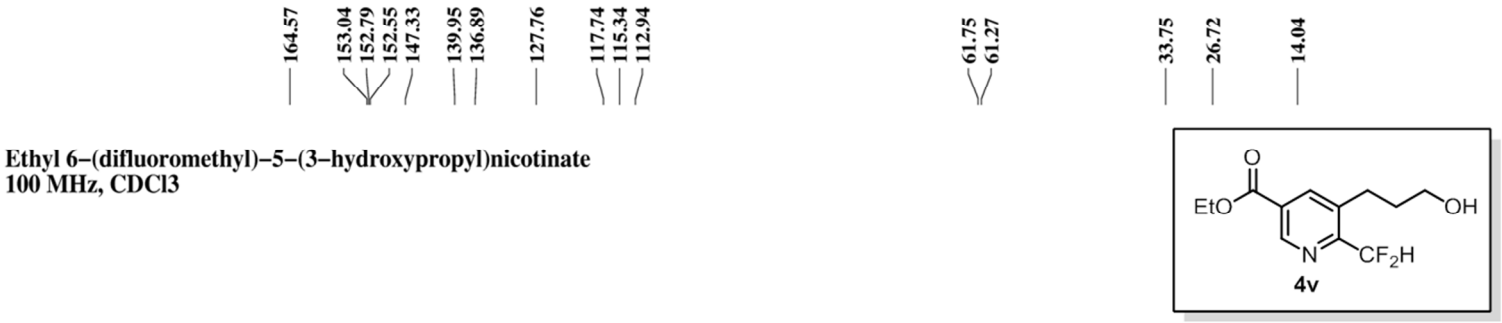

164.35
163.94
155.23
155.01
154.79
153.07
140.18
127.96
127.95
127.93
126.29
126.25
126.22
112.93
110.53
108.13
62.91
62.50
14.48
14.34
Diethyl 2−(difluoromethyl)pyridine−3,5−dicarboxylate
100 MHz, CDCl3
155.5 155.0 154.5 ppm
126.4 126.2 ppm
128.0 127.8 ppm
113 112 111 110 109 ppm
EtO
O
O
OEt
N
CF2H
4r
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


166.84
155.20
154.94
154.68
151.80
150.75
137.92
129.23
128.75
128.29
128.28
128.26
128.18
121.62
121.59
121.56
116.01
113.61
111.21
52.68
MeO
O
Ph
N
CF2H
4s
Methyl 6−(difluoromethyl)−4−phenylnicotinate
100 MHZ, CDCl3
155.0
154.5 ppm
116
114
112
ppm
128.3
ppm
121.6
ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


167.64
158.70
154.46
154.19
153.93
139.38
139.34
129.24
129.22
128.79
128.39
118.09
118.06
118.03
116.17
113.78
111.38
61.94
13.72
Ethyl 6−(difluoromethyl)−2−phenylnicotinate
100 MHz, CDCl3
154.5
154.0
ppm
118.2
118.0
ppm
116
114
112
ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

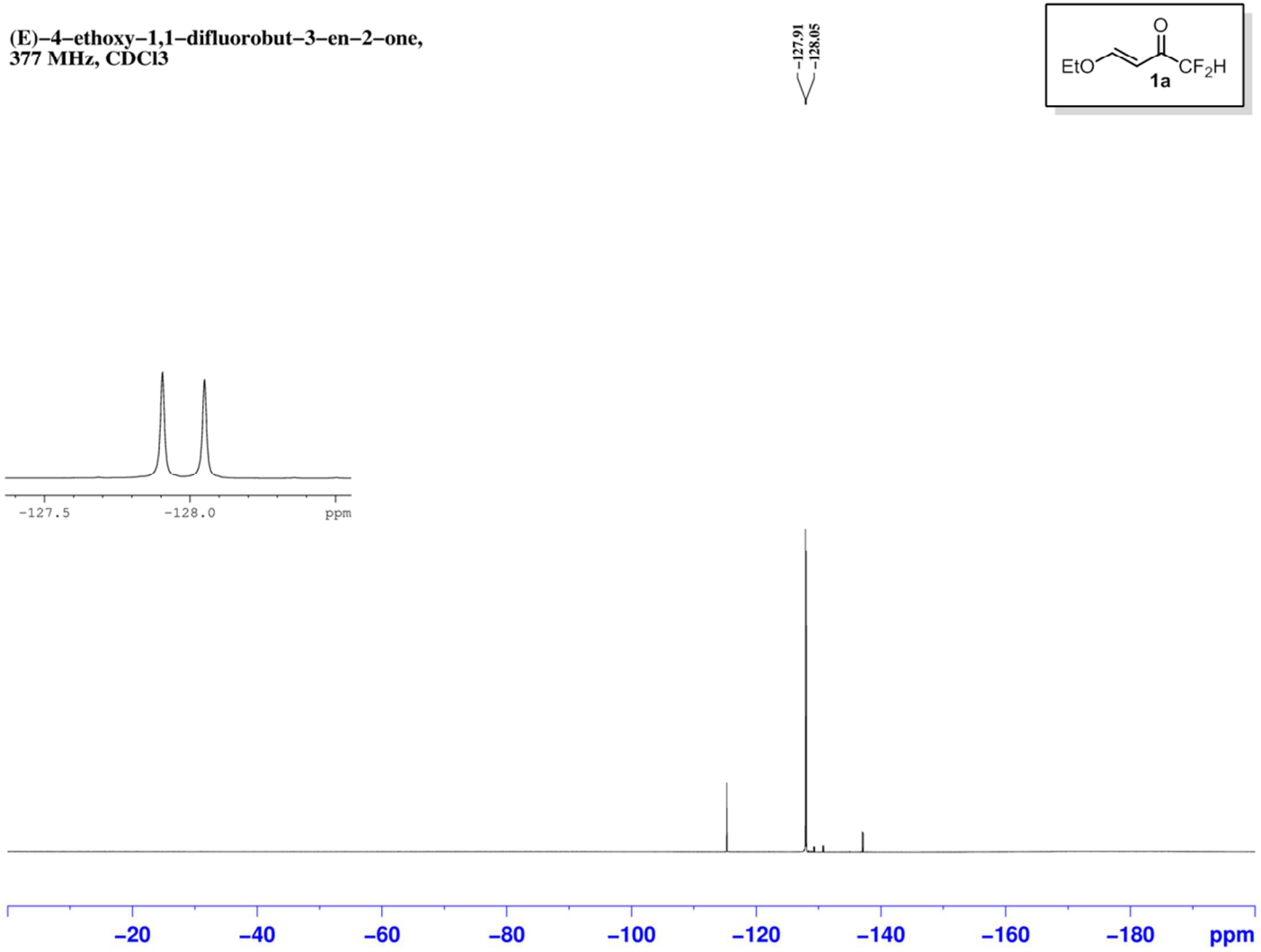
O
EtO
Ph
N
CF2H
4t


165.02
154.49
154.21
153.94
146.18
145.82
145.46
145.12
140.26
130.04
125.03
122.91
122.89
122.86
122.29
119.56
116.82
115.40
113.00
110.60
63.23
14.04
Ethyl 6–(difluoromethyl)–2–(trifluoromethyl)nicotinate
100 MHz, CDCl3
EtO
O
F3C
N
CF2H
4u
154.5
154.0
ppm
146
145
ppm
124
122
120
ppm
115
114
113
112
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


164.57
153.04
152.79
152.55
147.33
139.95
136.89
127.76
117.74
115.34
112.94
61.75
61.27
33.75
26.72
14.04
Ethyl 6−(difluoromethyl)−5−(3−hydroxypropyl)nicotinate
100 MHz, CDCl3
O
EtO
OH
N
CF2H
4v
153.0
152.5
ppm
118
116
114
ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

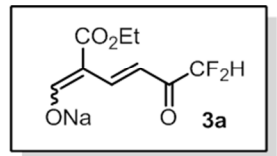
^{19}F-NMR Spectra of Synthesized Compounds

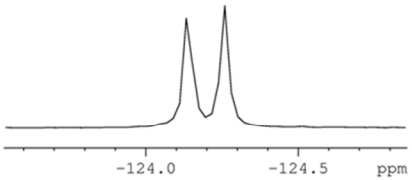
(E)–4–ethoxy–1,1–difluorobut–3–en–2–one,
377 MHz, CDCl3

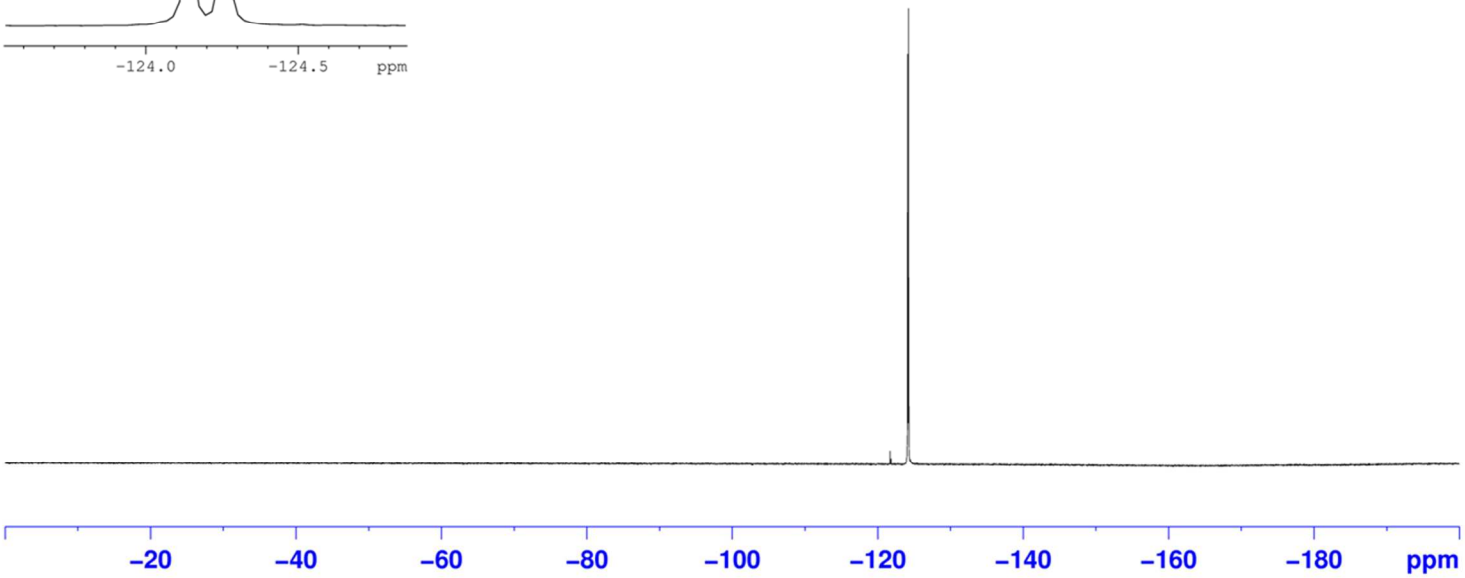


sodium (3E)–2–(ethoxycarbonyl)–6,6–difluoro–5–oxohexa–1,3–dien–1–olate
DMSO–d6, 471 MHz
T=353K

-124.14
-124.26

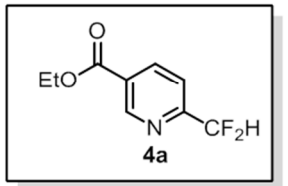




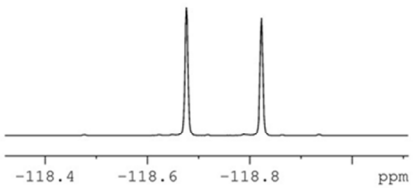


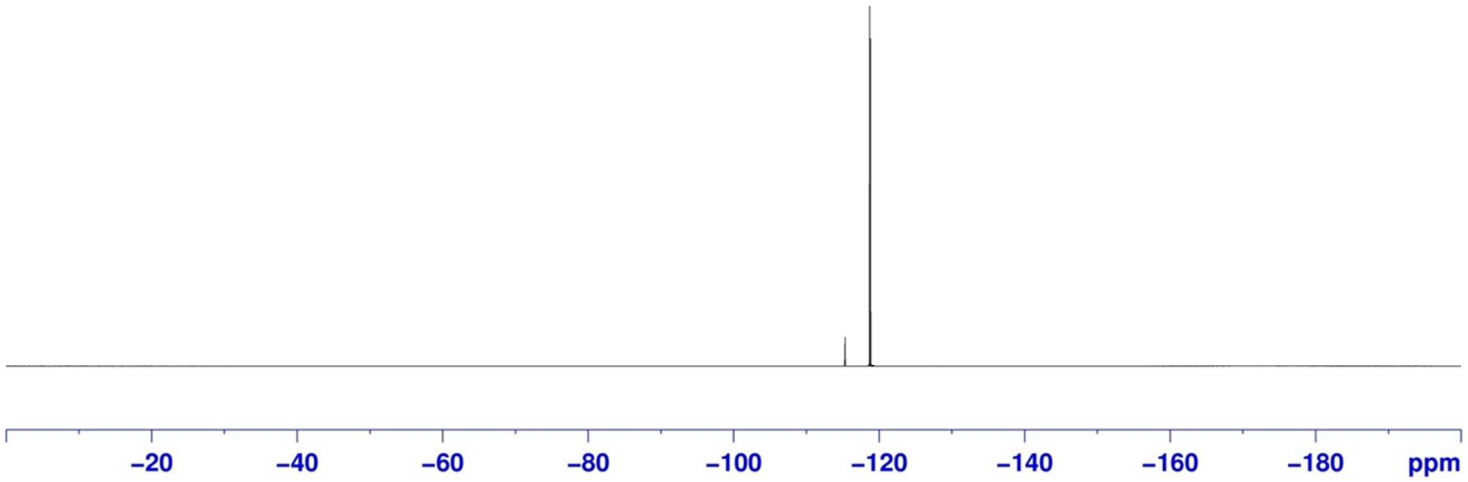
Ethyl 6–(difluoromethyl)nicotinate
377 MHz, CDCl3

-118.68
-118.82

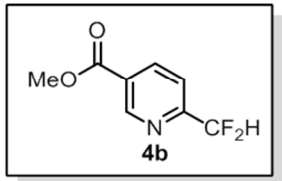


4a

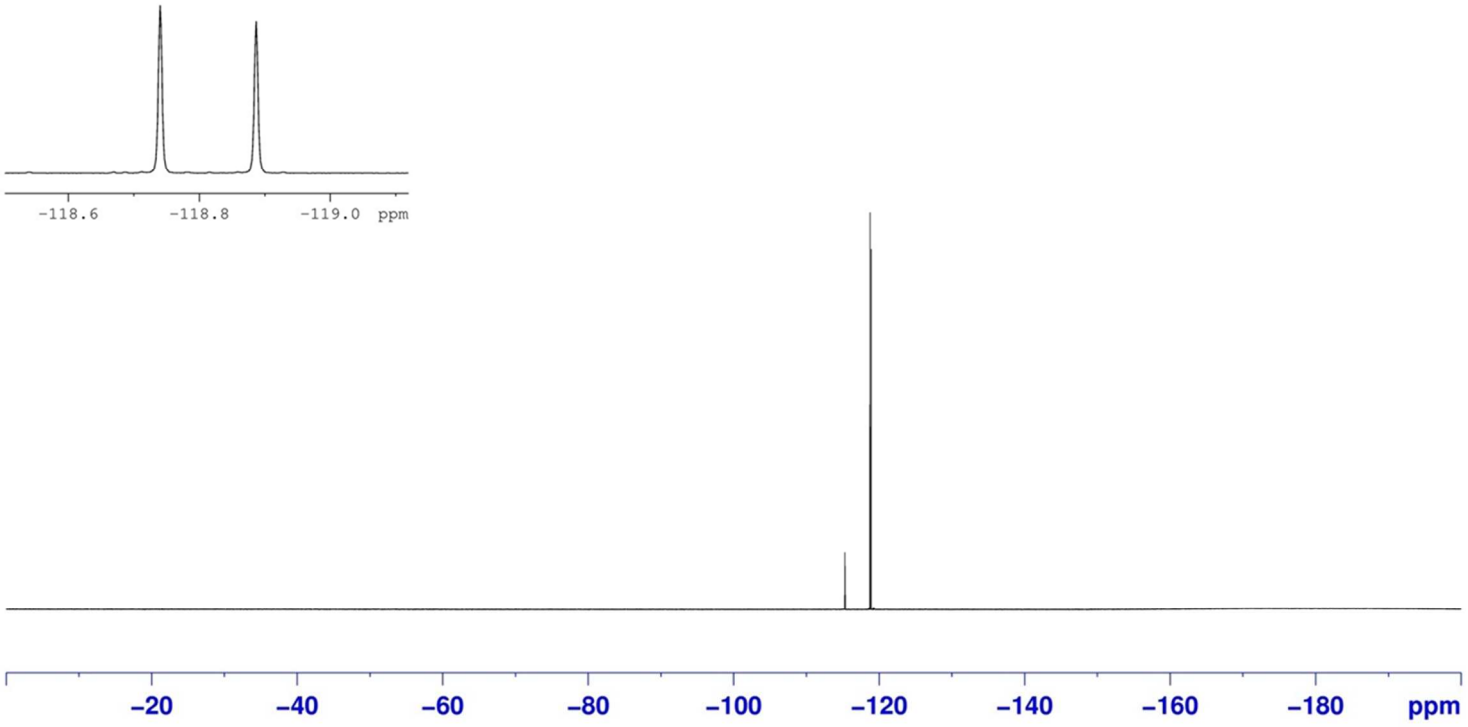




Methyl 6–(difluoromethyl)nicotinate
377 MHz, CDCl3

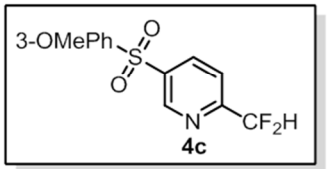


4b

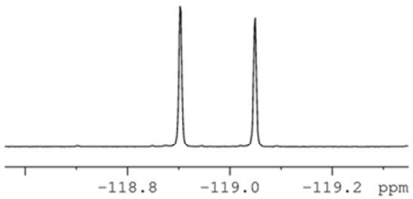


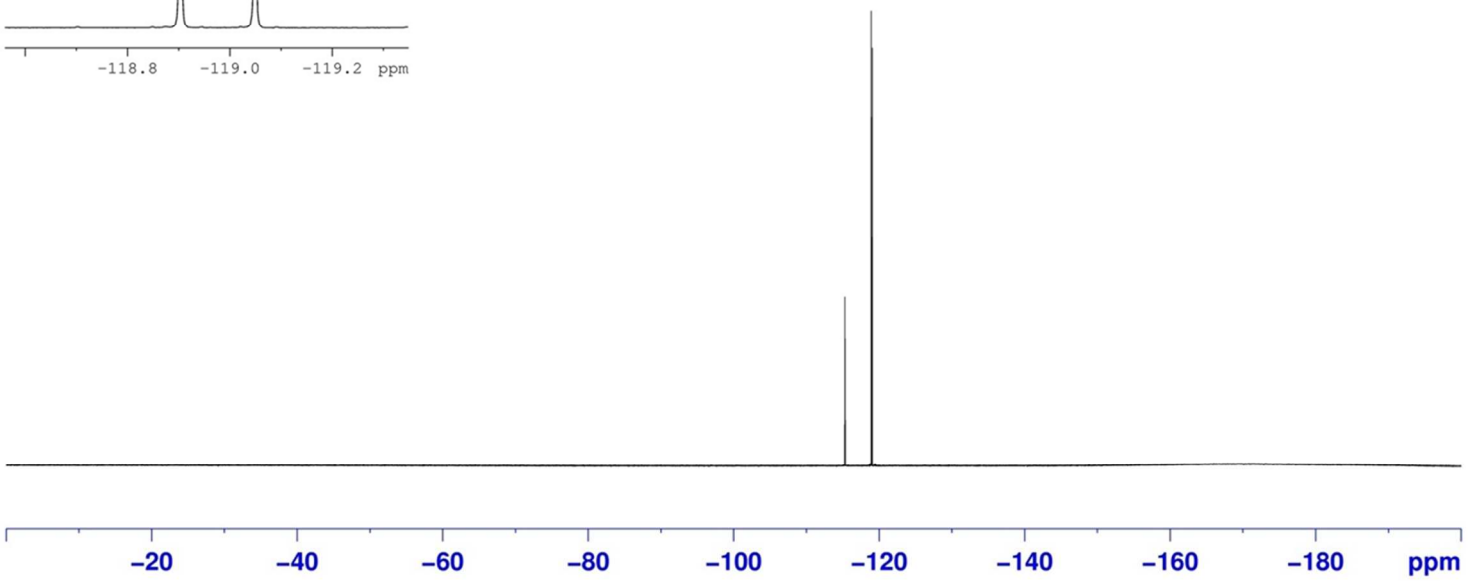
2–(Difluoromethyl)–5–((3–methoxyphenyl)sulfonyl)pyridine
377 MHZ, CDCl3

-118.90
-119.05



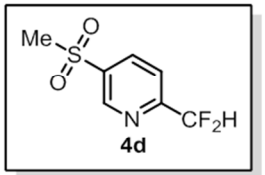
4c



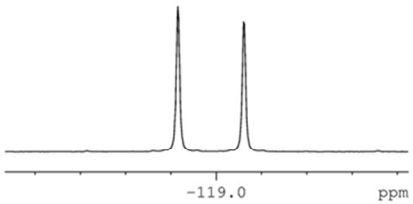


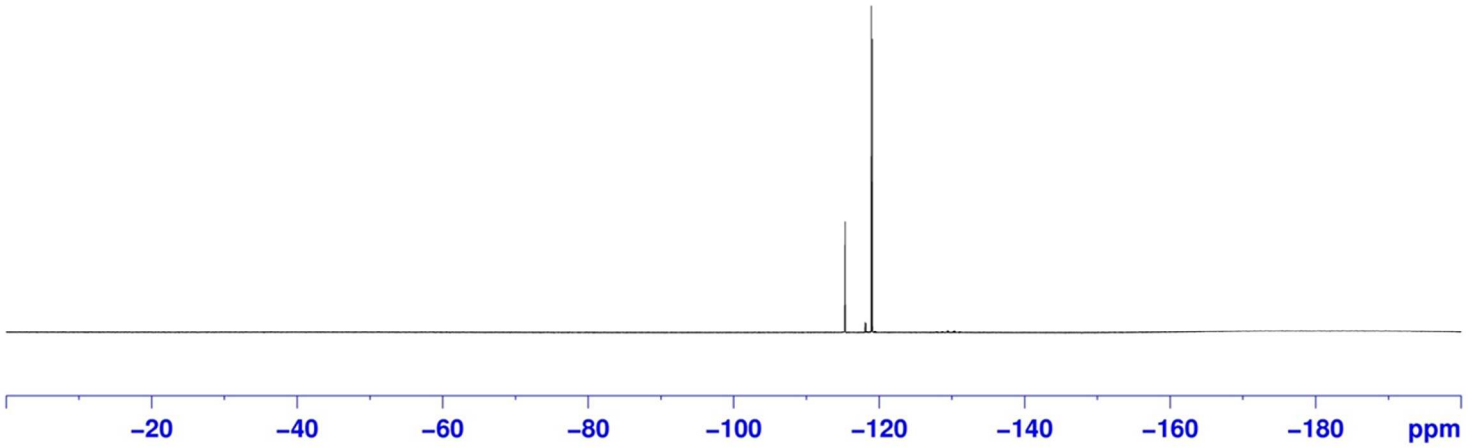
2–(Difluoromethyl)–5–(methylsulfonyl)pyridine
377 MHz, CDCl3

-118.92
-119.06

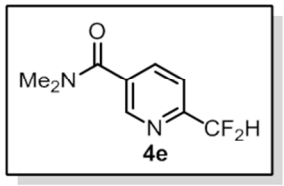


4d

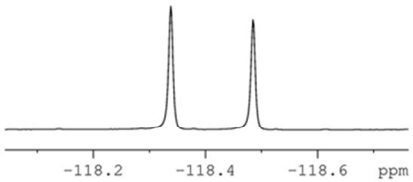


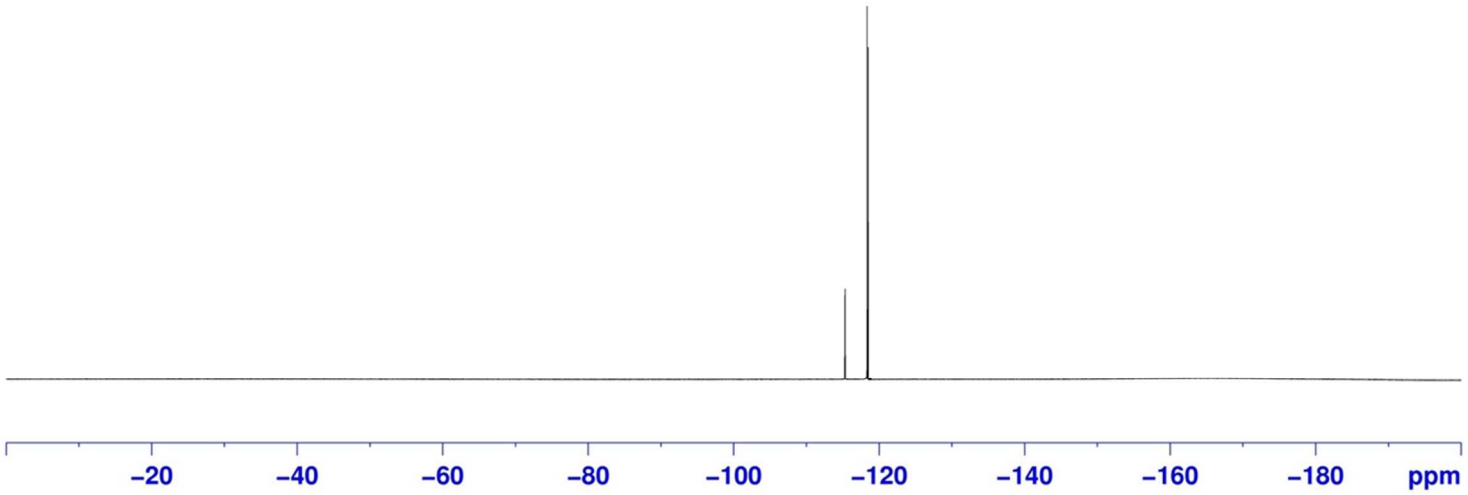


6–(Difluoromethyl)–N,N–dimethylnicotinamide
377 MHz, CDCl3

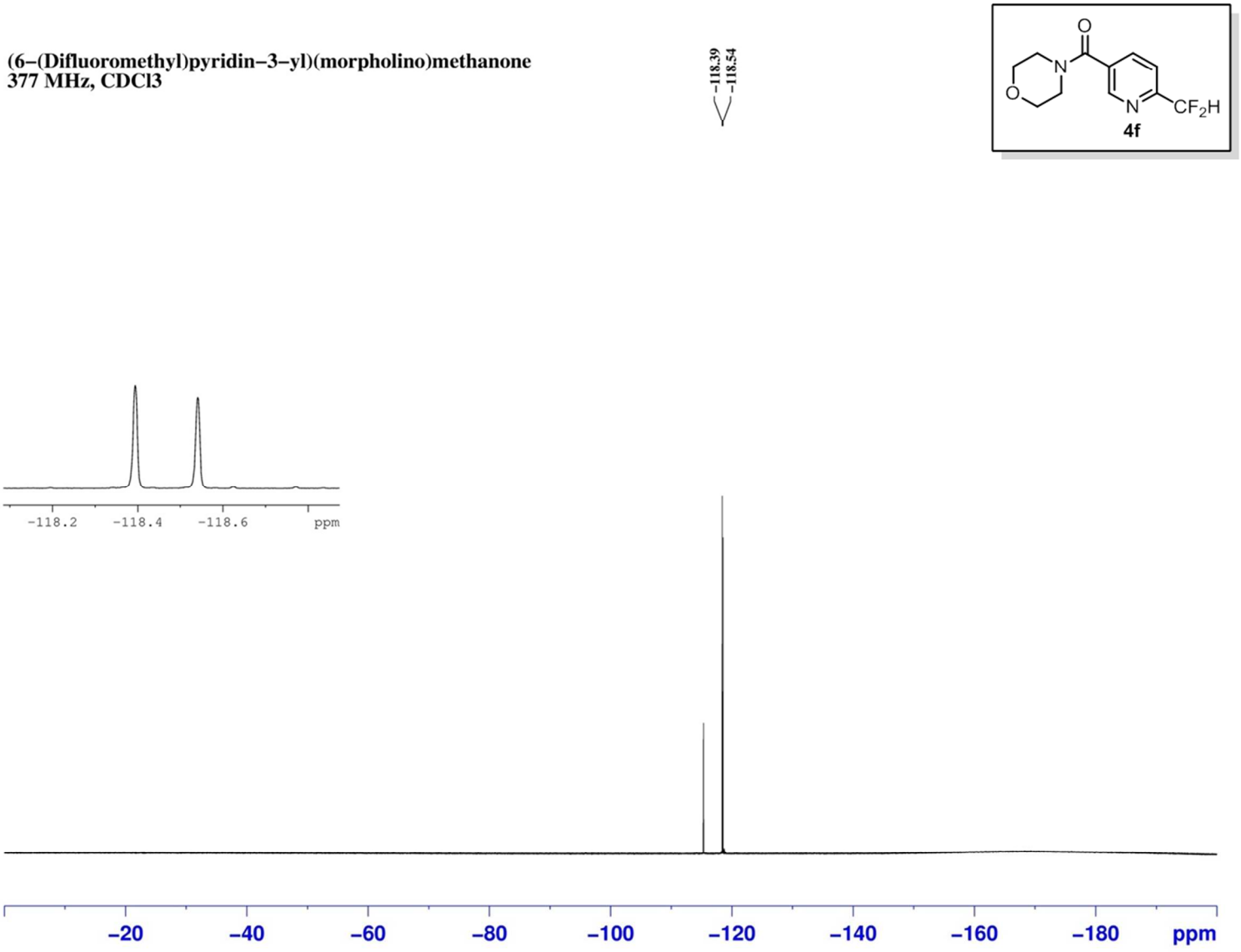


4e

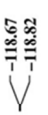


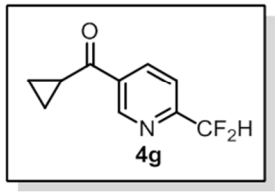


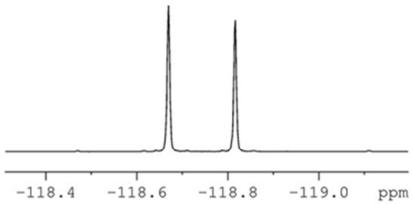
(6–(Difluoromethyl)pyridin–3–yl)(morpholino)methanone
377 MHz, CDCl3

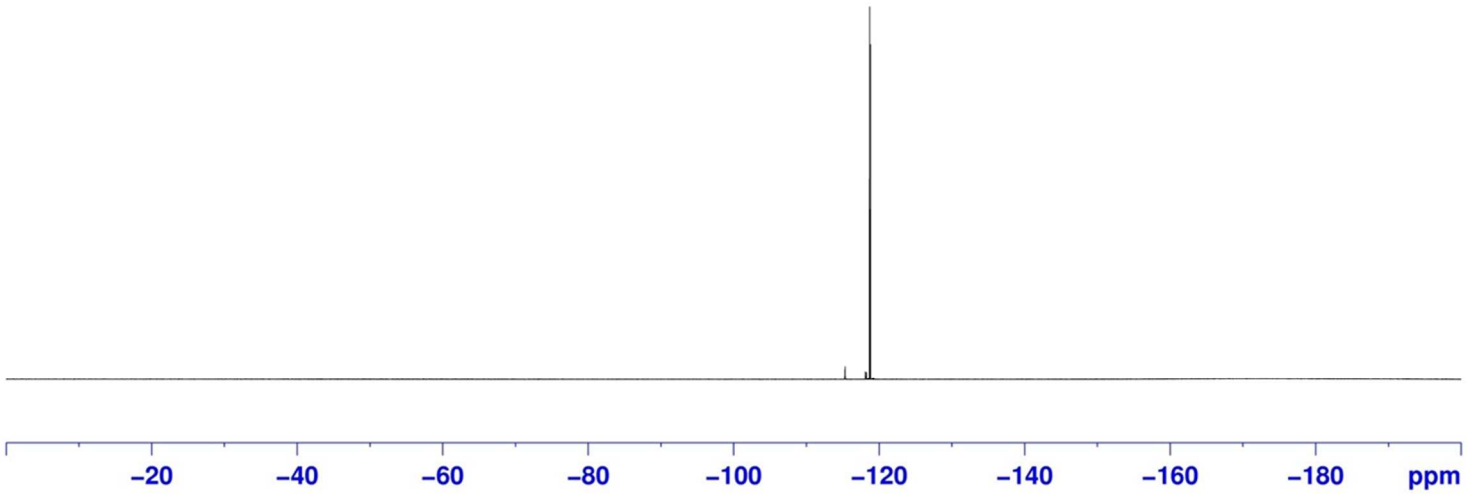


Cyclopropyl(6−(difluoromethyl)pyridin−3−yl)methanone
377 MHz, CDCl3

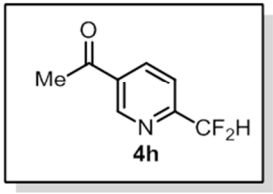


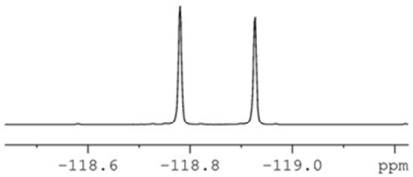


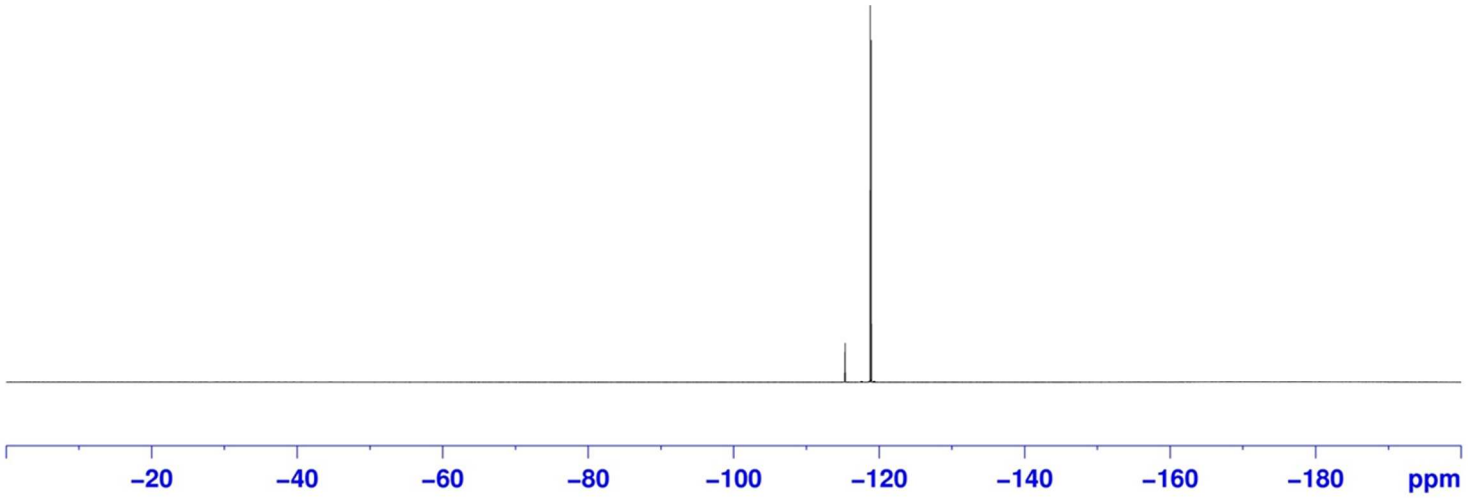




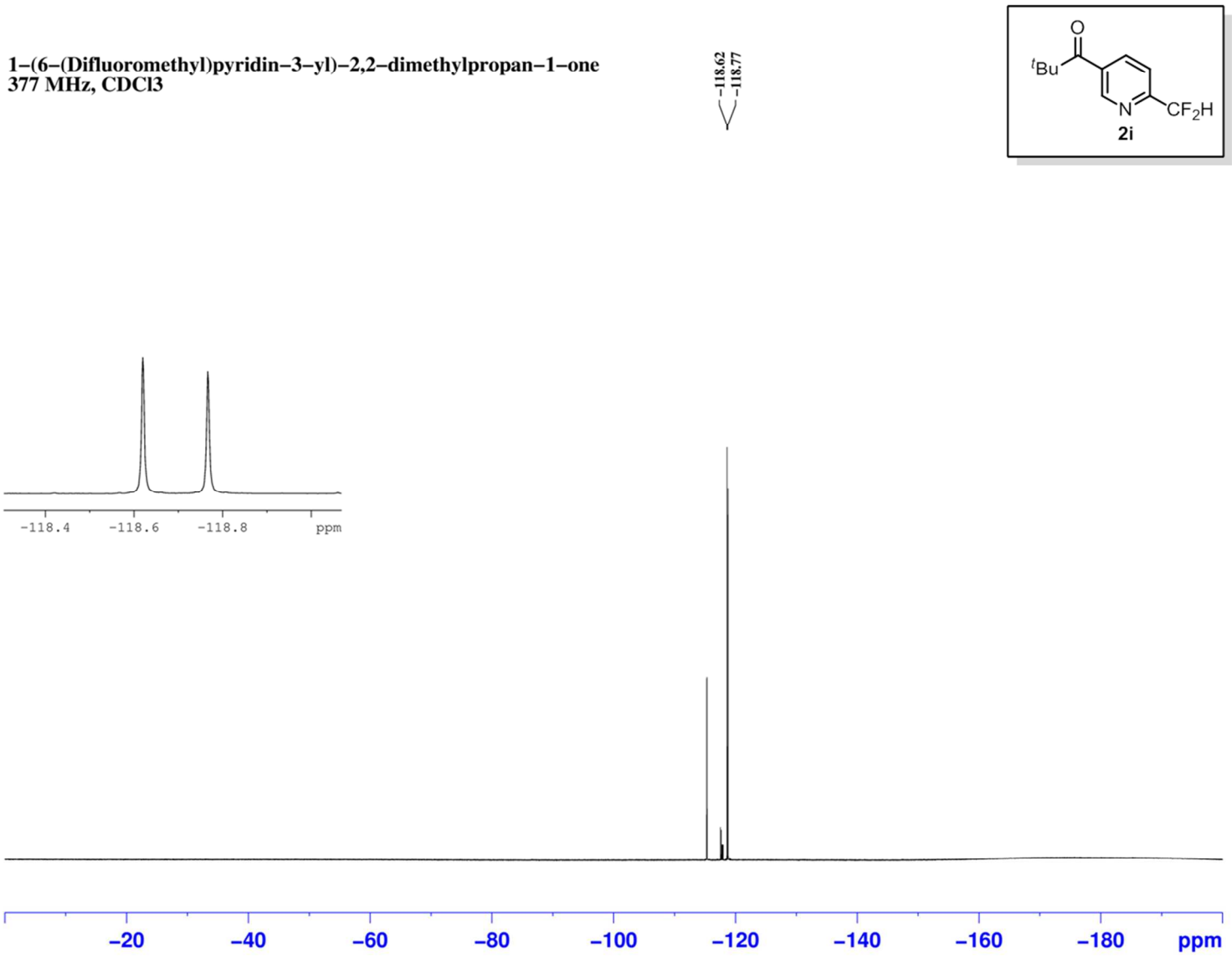
1–(6–(Difluoromethyl)pyridin–3–yl)ethanone
377 MHz, CDCl3



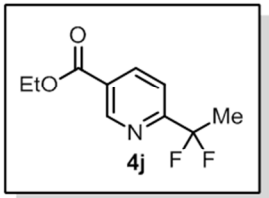


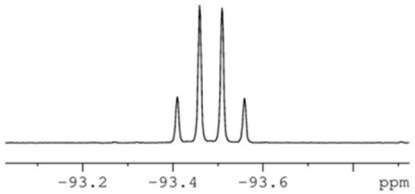


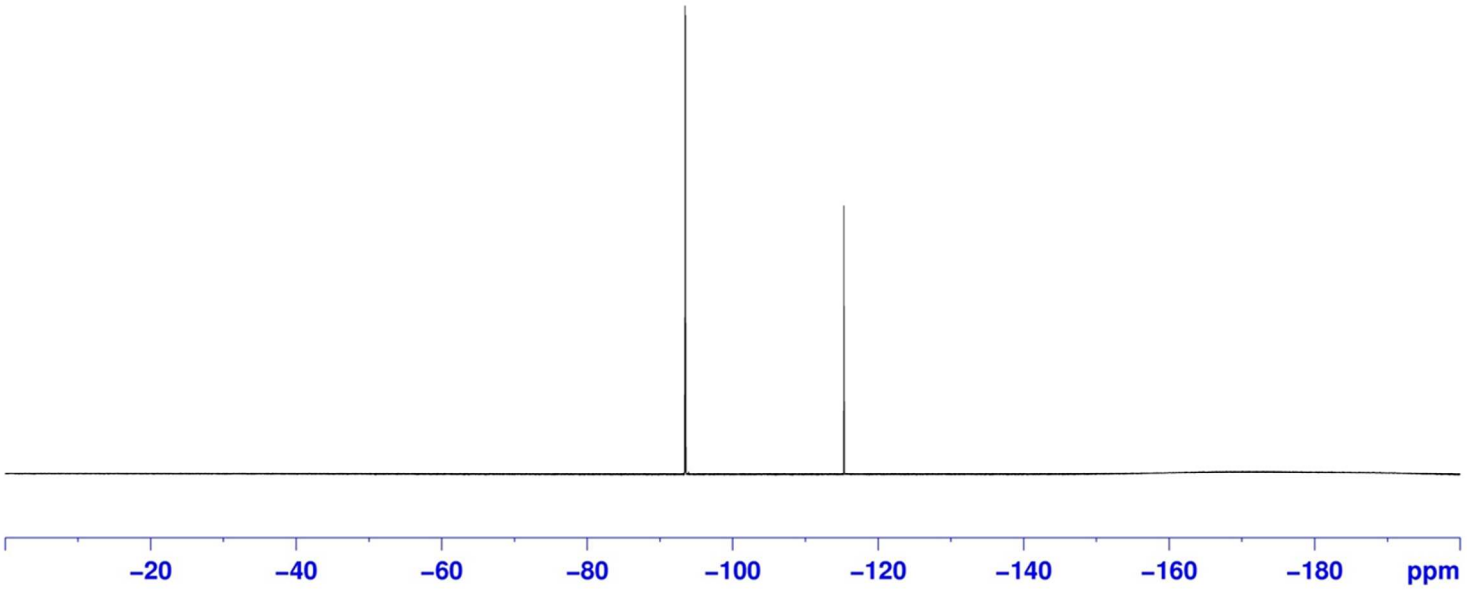
1–(6–(Difluoromethyl)pyridin–3–yl)–2,2–dimethylpropan–1–one
377 MHz, CDCl3



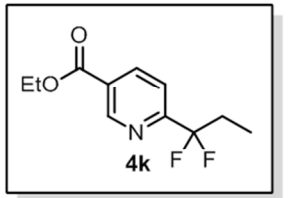
Ethyl 6–(1,1–difluoroethyl)nicotinate
377 MHz, CDCl3

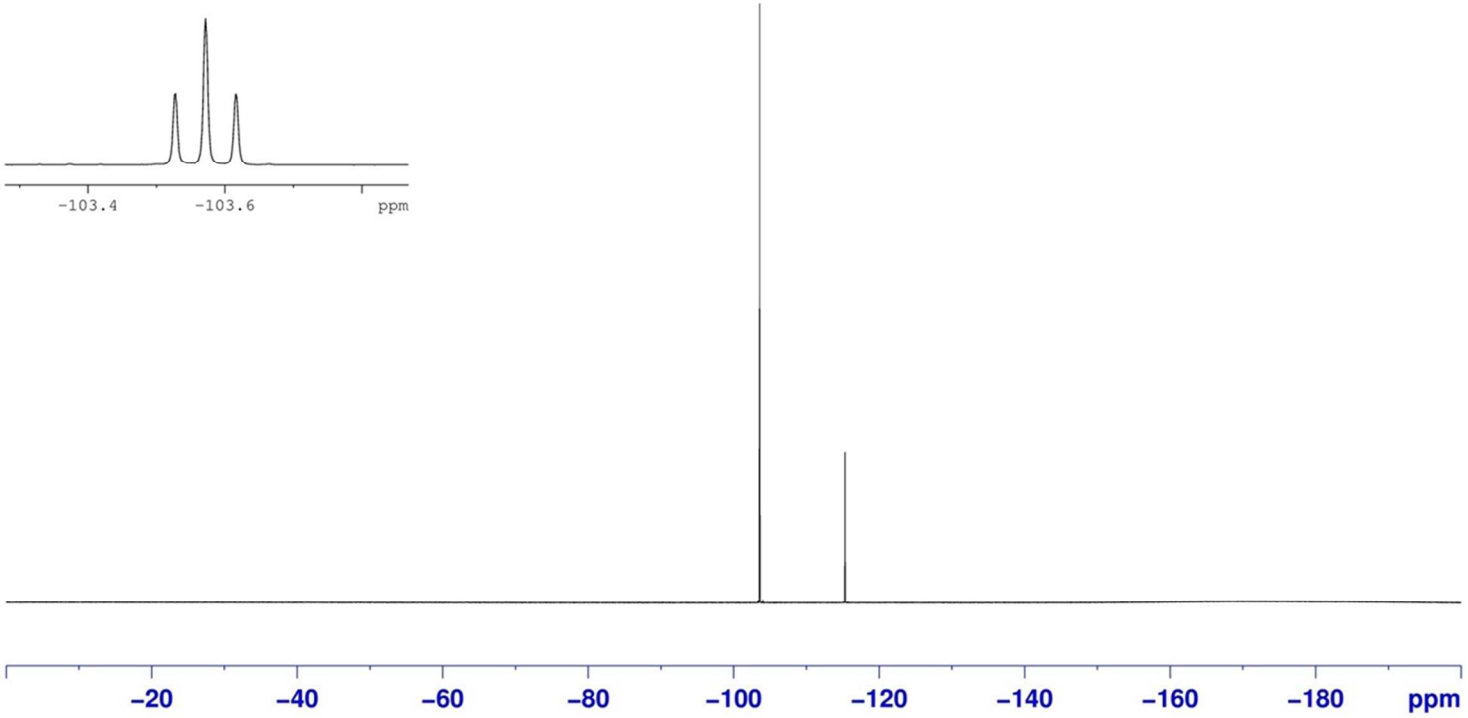




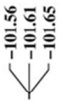


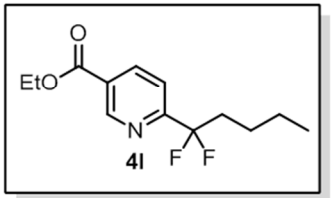
Ethyl 6−(1,1−difluoropropyl)nicotinate
377 MHz, CDCl3

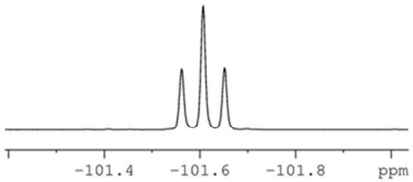




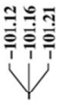
Ethyl 6−(1,1−difluoropentyl)nicotinate
377 MHz, CDCl3

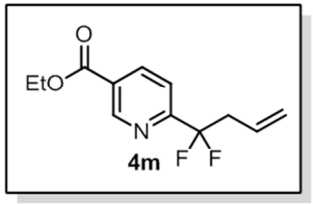


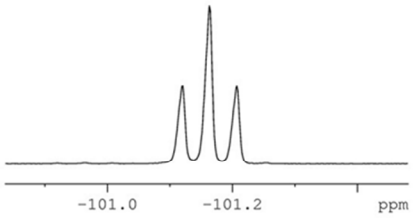




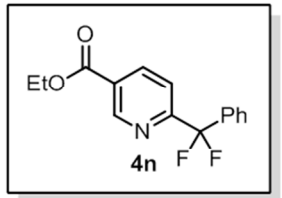
Ethyl 6–(1,1–difluorobut–3–en–1–yl)nicotinate
377 MHz, CDCl3



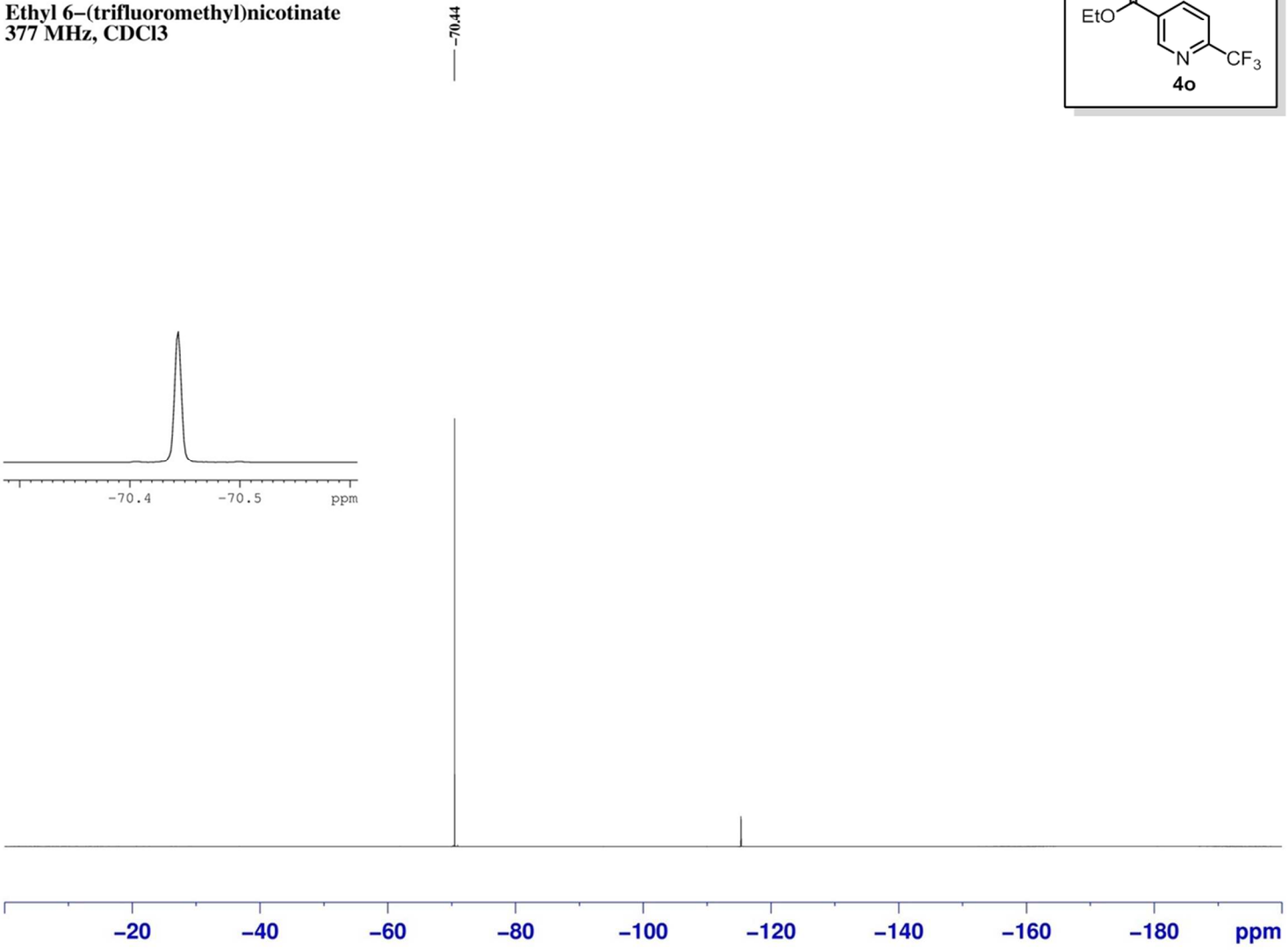




Ethyl 6–(difluoro(phenyl)methyl)nicotinate
377 MHz, CDCl3

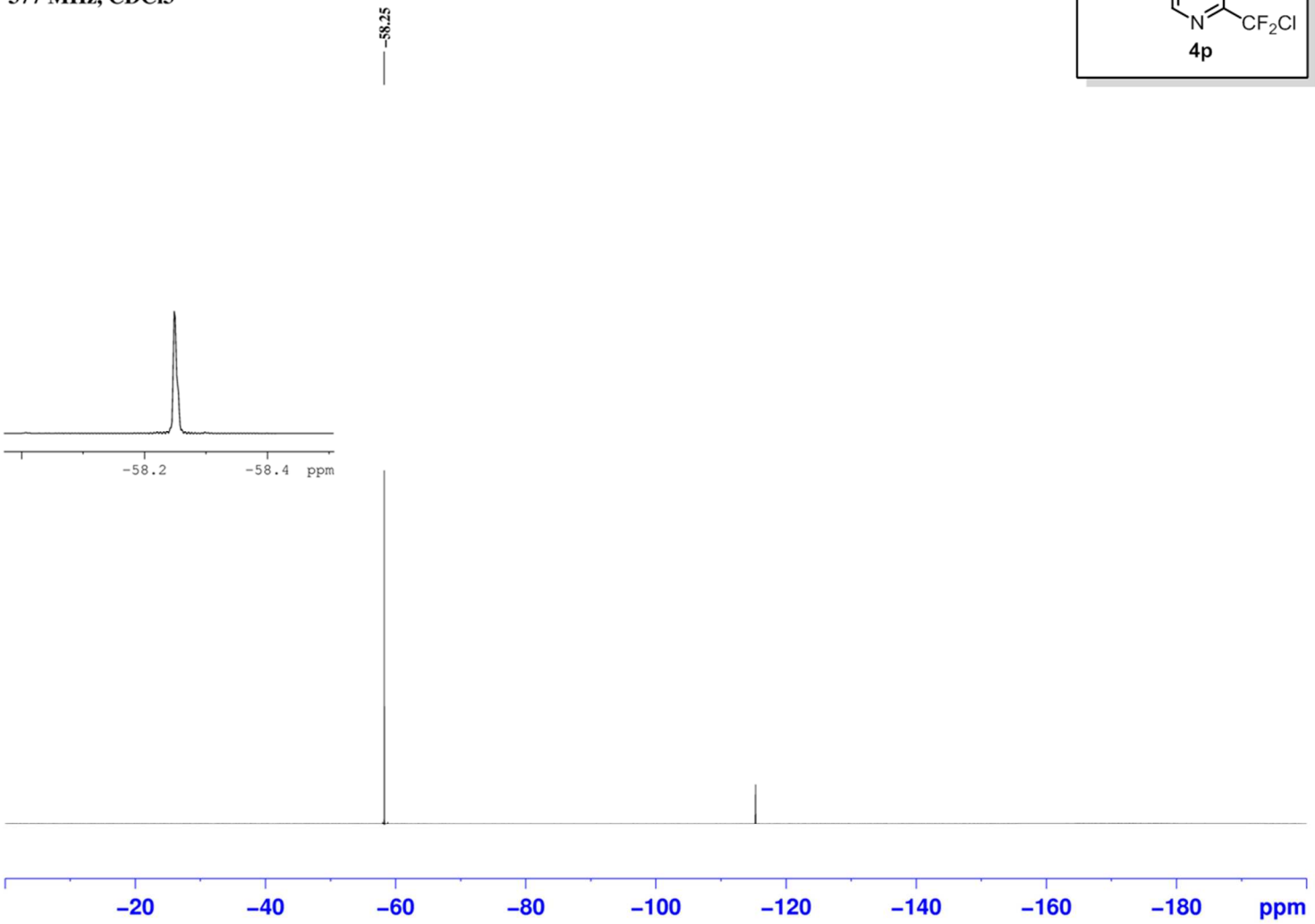


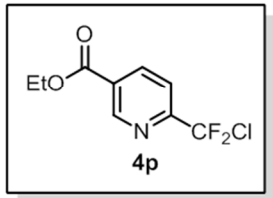
Ethyl 6–(trifluoromethyl)nicotinate
377 MHz, CDCl3



4o

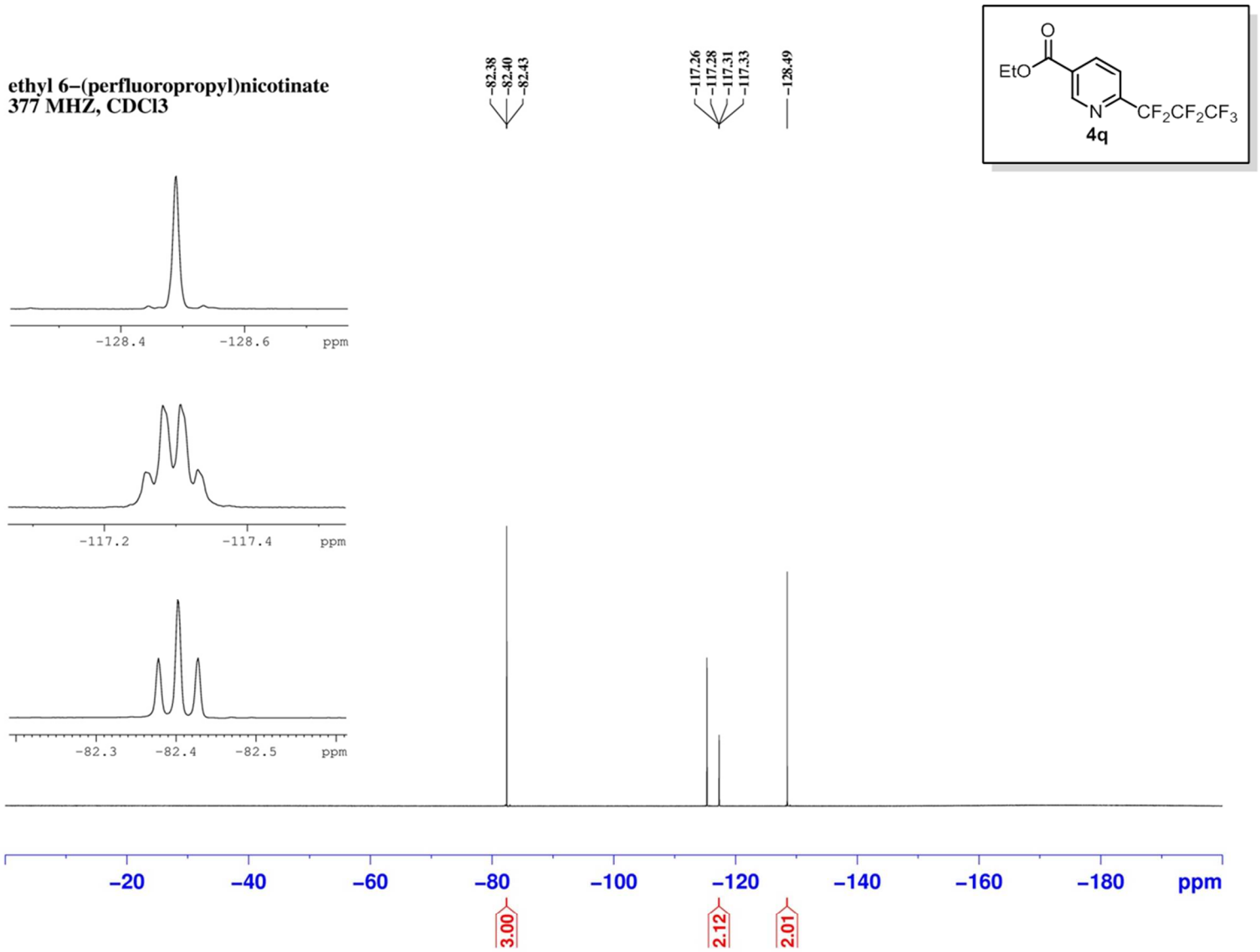
Ethyl 6–(chlorodifluoromethyl)nicotinate
377 MHz, CDCl3





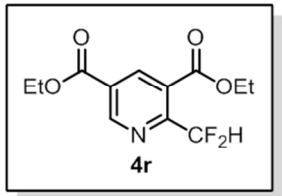
4p

ethyl 6–(perfluoropropyl)nicotinate
377 MHZ, CDCl3

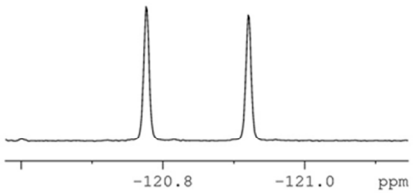


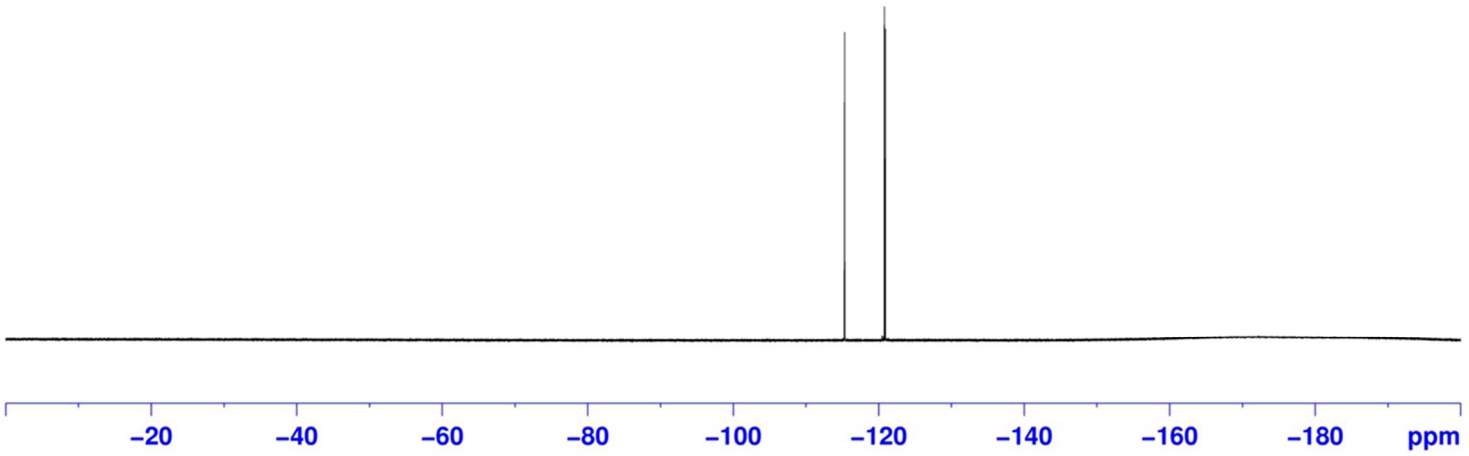
Diethyl 2–(difluoromethyl)pyridine–3,5–dicarboxylate
377 MHz, CDCl3

-120.78
-120.92



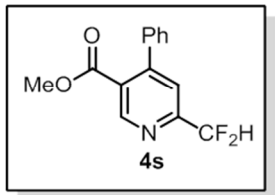
4r



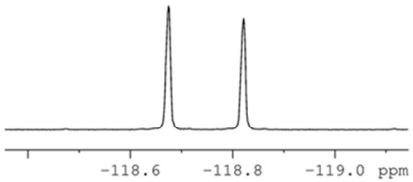


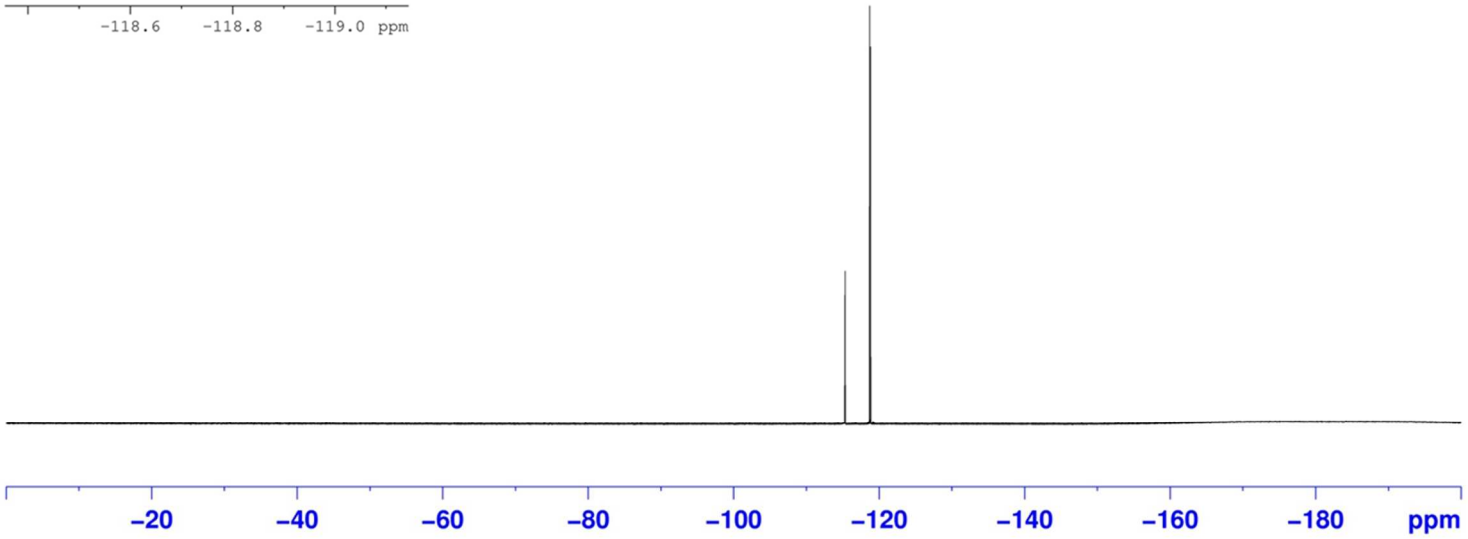
Methyl 6–(difluoromethyl)–4–phenylnicotinate
377 MHz, CDCl3

-118.68
-118.82



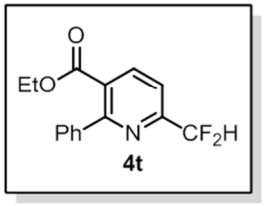
4s



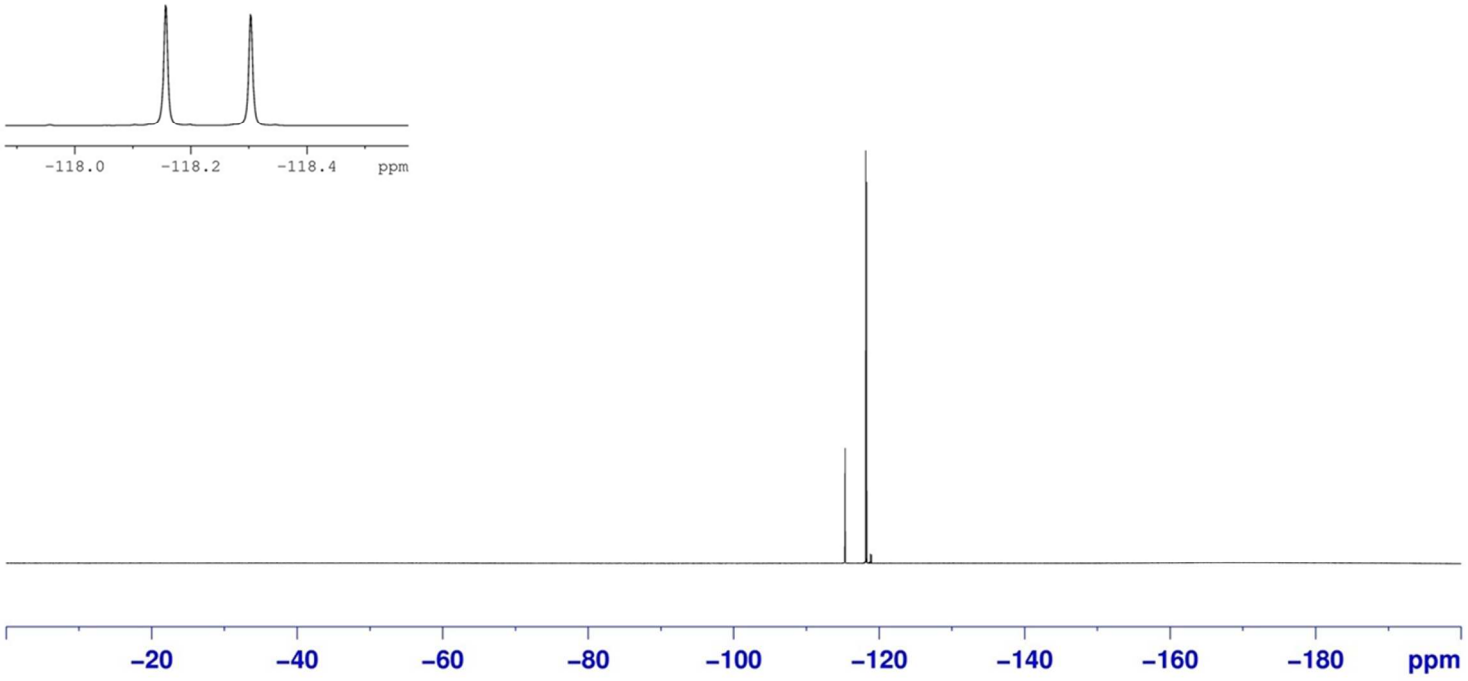


Ethyl 6−(difluoromethyl)−2−phenylnicotinate
377 MHz, CDCl3

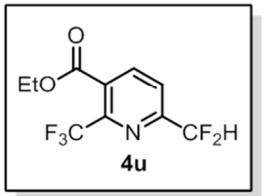
−118.16
−118.30



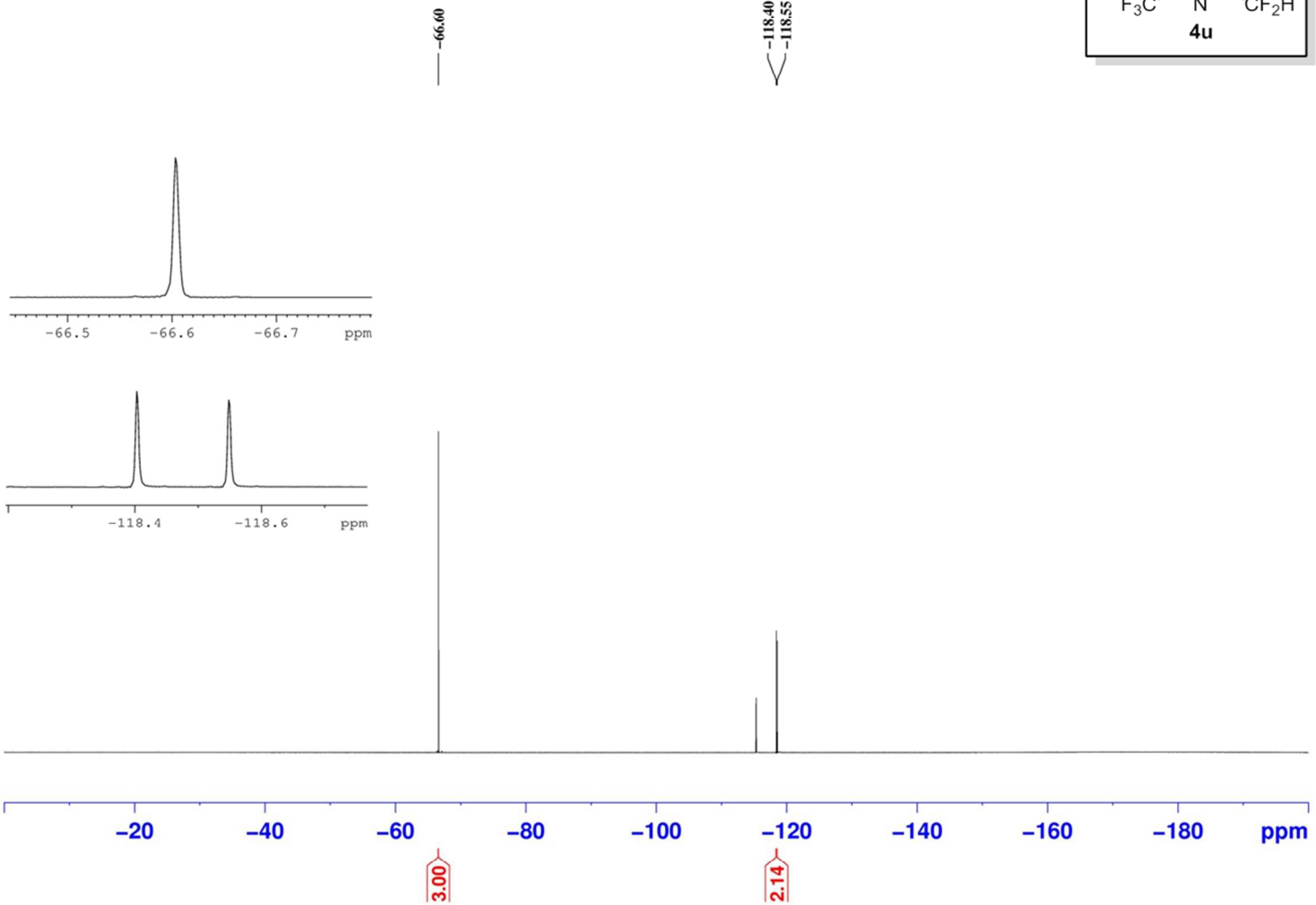
4t



Ethyl 6–(difluoromethyl)–2–(trifluoromethyl)nicotinate
377 MHz, CDCl3

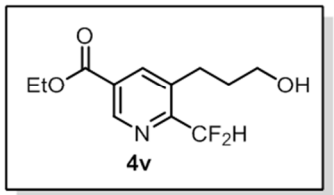


4u



ethyl 6−(difluoromethyl)−5−(3−hydroxypropyl)nicotinate
377 MHz, CDCl3

−114.93
−115.07



4v