Ligand-Promoted Alkylation of C(sp^3)–H and C(sp^2)–H Bonds

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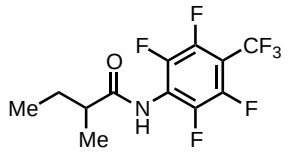
Table of Contents

General Information

Carboxylic acids or carboxylic chlorides and 2,3,5,6-tetrafluoro-4-(trifluoromethyl)aniline were obtained from the commercial sources or synthesized following literature procedures, and used to prepare the corresponding amides. Alkyl iodides were obtained either from the commercial sources or synthesized following literature procedures. AgOPiv was prepared by the reaction of pivalic acid and $AgNO_3$. Solvents were obtained from Sigma-Aldrich, Alfa-Aesar and Acros and used directly without further purification. Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F254. Visualization was carried out with UV light and Vogel's permanganate. ^{1}H NMR was recorded on Bruker AMX-400 instrument (400 MHz) or Bruker DRX-600 instrument (600 MHz). Chemical shifts were quoted in parts per million (ppm) referenced to 0.0 ppm for tetramethylsilane. The following abbreviations (or combinations thereof) were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q =quartet, m = multiplet, br = broad. Coupling constants, *J*, were reported in Hertz unit (Hz). ^{13}C NMR spectra were recorded on Bruker AMX-400 instrument (100 MHz) or Bruker DRX-600 instrument (150 MHz), and were fully decoupled by broad band proton decoupling. Chemical shifts were reported in ppm referenced to either the center line of a triplet at 77.0 ppm of chloroform-*d* or the center line of a multiplet at 29.84 ppm of acetone-d^6. In the ^{13}C NMR analysis, peaks that correspond to those of the polyfluoroarylamide auxiliary appeared as nearly invisible, complex sets of multiplets; they were omitted in the following spectroscopic analysis. High-resolution mass spectra (HRMS) were recorded on an Agilent Mass spectrometer using ESI-TOF (electrospray ionization-time of flight).

Substrate Structures



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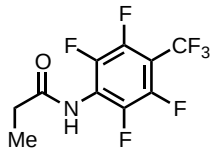

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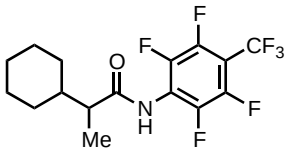

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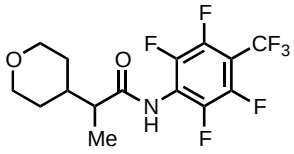

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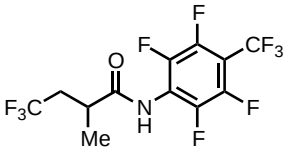

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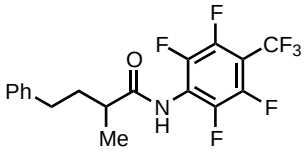

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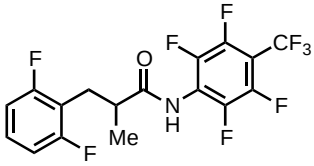

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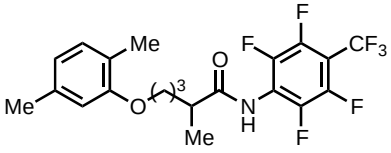

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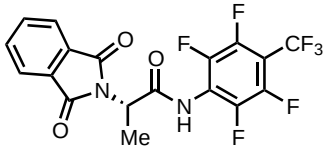

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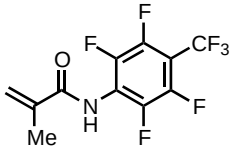

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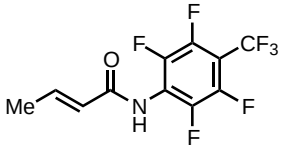

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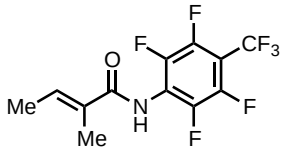

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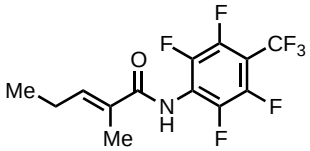

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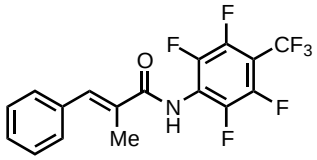

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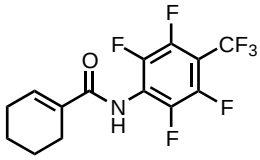

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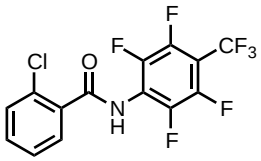

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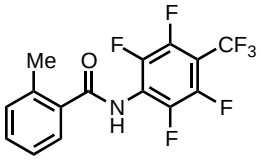

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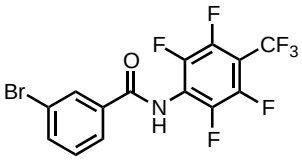

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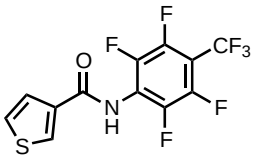

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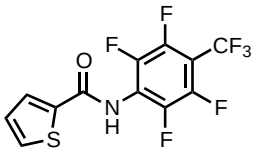

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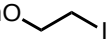

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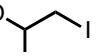

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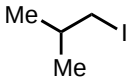

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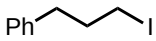
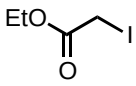


2d

2e

2f

2g



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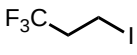

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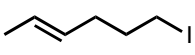
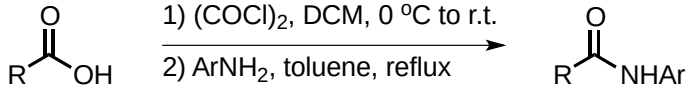


2j

2k

Experimental Section

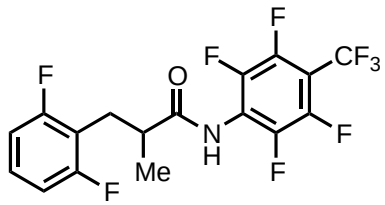
Substrate Preparation



General Procedure for the Preparation of Amide Substrates:[1] An acid chloride (5.0 mmol), prepared from the corresponding carboxylic acid and oxalyl chloride, was added dropwise to a vigorously stirring solution of 2,3,5,6-tetrafluoro-4-(trifluoromethyl)aniline (5.0 mmol) in toluene (5 mL). The reaction mixture was stirred overnight under reflux. The product mixture was concentrated in *vacuo* and was recrystallized from ethyl acetate/hexane to give the amide. Substrates **1a-f**,[2] **1h**[2], **1i**[3], **1p-r**[4] and **1s-t**[5] have been reported.

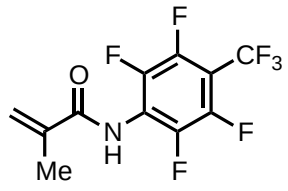
Alkyl iodides **2a-c**, **2e**, **2h** and **2i** are commercial available. **2d**, **2f** and **2g** were synthesized from corresponding alkyl bromides[6]. **2j** was synthesized from corresponding alcohol[6]. **2f** and **2i** have been reported[6].

General Procedure for the Preparation of AgOPiv: To a 250 mL round-bottom flask were added pivalic acid (49 mmol, 5.0 g) and 100 mL of water. Then 4.0 mL of ammonium hydroxide was added dropwise to the solution. Finally, the solution of $AgNO_3$ (50 mmol, 8.5 g) in water (25 mL) was added to the mixture. The reaction mixture was stirred at room temperature overnight. Upon completion, the reaction mixture was filtered and AgOPiv was washed with water and acetone twice.



3-(2,6-difluorophenyl)-2-methyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)propanamide (1g)

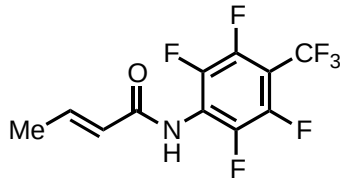
^{1}H NMR (400 MHz, acetone-d^6) δ 9.53 (br s, 1H), 7.37-7.30 (m, 1H), 7.03-6.96 (m, 2H), 3.14-3.05 (m, 2H), 2.92-2.86 (m, 1H), 1.25 (d, J = 6.0 Hz, 3H). ^{13}C NMR (150 MHz, acetone-d^6) δ 174.07, 162.59 (dd, J_1 = 8.7 Hz, J_2 = 244.4 Hz), 129.65 (t, J = 10.3 Hz), 115.63 (t, J = 20.2 Hz), 112.06 (dd, J_1 = 5.6 Hz, J_2 = 21.2 Hz), 41.10, 26.94, 17.71. HRMS (ESI-TOF) Calcd for $C_{17}H_{10}F_9NOH$ $[M+H]^+$: 416.0691, found: 416.0690.



***N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)methacrylamide (1j)**

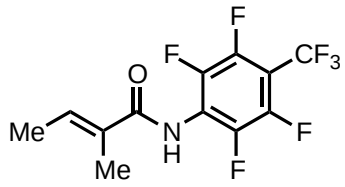
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (br s, 1H), 5.96-5.95 (m, 1H), 5.68-5.67 (m, 1H), 2.10-

2.09 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.44, 138.69, 123.01, 18.56. HRMS (ESI-TOF) Calcd for $C_{11}H_6F_7NOH$ $[M+H]^+$: 302.0410, found: 302.0409.



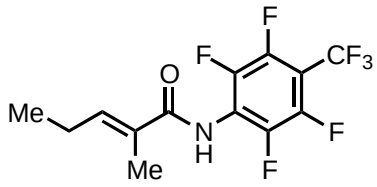
(*E*)-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)but-2-enamide (1k)

^{1}H NMR (400 MHz, acetone-d^6) δ 9.50 (br s, 1H), 7.07-6.98 (m, 1H), 6.30-6.25 (m, 1H), 1.92 (dd, J_1 = 1.6 Hz, J_2 = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d^6) δ 163.80, 144.18, 124.39, 17.96. HRMS (ESI-TOF) Calcd for $C_{11}H_6F_7NOH$ $[M+H]^+$: 302.0410, found: 302.0413.



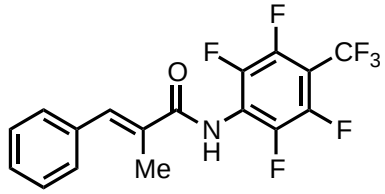
(*E*)-2-methyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)but-2-enamide (1l)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (br s, 1H), 6.74-6.68 (m, 1H), 1.98-1.97 (m, 3H), 1.90-1.87 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.38, 135.29, 130.88, 14.39, 12.44. HRMS (ESI-TOF) Calcd for $C_{12}H_8F_7NOH$ $[M+H]^+$: 316.0567, found: 316.0568.



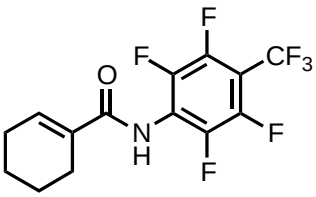
(*E*)-2-methyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)pent-2-enamide (1m)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (br s, 1H), 6.61-6.57 (m, 1H), 2.31-2.24 (m, 2H), 1.97-1.96 (m, 3H), 1.11 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.47, 142.05, 129.42, 22.06, 13.04, 12.63. HRMS (ESI-TOF) Calcd for $C_{13}H_{10}F_7NOH$ $[M+H]^+$: 330.0723, found: 330.0728.



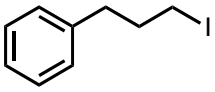
(*E*)-2-methyl-3-phenyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)acrylamide (1n)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.47-7.36 (m, 5H), 7.31 (br s, 1H), 2.26-2.25 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.86, 137.54, 135.00, 130.37, 129.54, 128.78, 128.59, 14.49. HRMS (ESI-TOF) Calcd for $C_{13}H_{10}F_7NOH$ $[M+H]^+$: 378.0723, found: 378.0722.



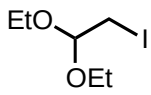
***N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)cyclohex-1-enecarboxamide (1o)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (br s, 1H), 6.92-6.89 (m, 1H), 2.40-2.35 (m, 2H), 2.31-2.25 (m, 2H), 1.79-1.73 (m, 2H), 1.70-1.64 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.55, 138.13, 132.15, 25.70, 24.23, 21.84, 21.22. HRMS (ESI-TOF) Calcd for $C_{14}H_{10}F_7NOH$ $[M+H]^+$: 342.0723, found: 342.0721.



(3-iodopropyl)benzene (2d)

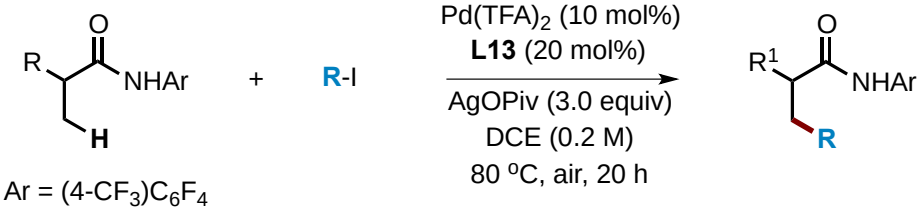
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.28 (m, 2H), 7.23-7.19 (m, 3H), 3.17 (t, *J* = 6.8 Hz, 2H), 2.73 (t, *J* = 7.2 Hz, 2H), 2.17-2.10 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.38, 128.53, 128.47, 126.15, 36.18, 34.86, 6.40.



1,1-diethoxy-2-iodoethane (2g)

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.62 (t, *J* = 5.6 Hz, 1H), 3.74-3.65 (m, 2H), 3.62-3.53 (m, 2H), 3.22 (t, *J* = 5.6 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 101.68, 62.17, 15.14, 5.59.

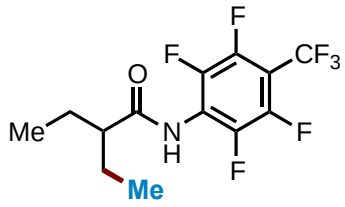
C(sp^3)–H Alkylation



Ar = (4-CF_3)C_6F_4

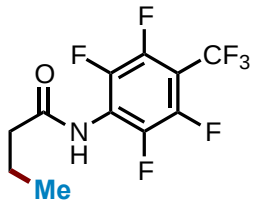
1 **2** **3**

General Procedures for the C(sp^3)–H Alkylation: Substrate **1** (0.1 mmol), $Pd(TFA)_2$ (0.01 mmol, 3.3 mg), **L13** (0.02 mmol, 3.9 mg) and AgOPiv (0.3 mmol, 62.7 mg) were weighed into a tube (10 mL) with a magnetic stir bar under air. The alkyl iodide **2** (0.25 mmol) and DCE (0.5 mL) were added, and the tube was sealed with a cap. The reaction mixture was stirred at 80 °C for 20 hours. Upon completion, the reaction mixture was cooled to room temperature and diluted with EtOAc. Then the reaction mixture was filtered through a short celite tube and purified by preparative thin-layer chromatography using hexane/EtOAc or hexane/EtOAc/DCM mixtures as the eluent.



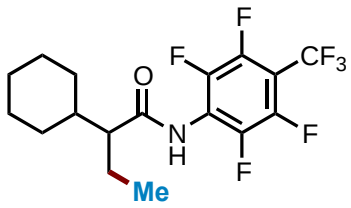
2-ethyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)butanamide (3a)

Substrate **1a** was alkylated following the general alkylation procedure. After purification by preparative thin-layer chromatography, **3a** was obtained as a white solid (23.4 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (br s, 1H), 2.28-2.21 (m, 1H), 1.80-1.57 (m, 4H), 0.99 (t, *J* = 7.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.80, 51.32, 25.76, 11.79. HRMS (ESI-TOF) Calcd for $C_{13}H_{12}F_7NOH$ $[M+H]^+$: 332.0880, found: 332.0880.



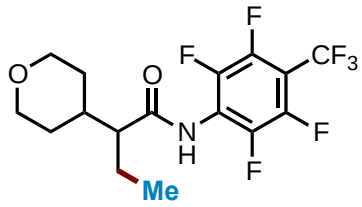
***N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)butyramide (3b)**

Substrate **1b** was alkylated following the general alkylation procedure. After purification by preparative thin-layer chromatography, **3b** was obtained as a white solid (15.1 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (br s, 1H), 2.46 (t, *J* = 7.6 Hz, 2H), 1.83-1.74 (m, 2H), 1.03 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.85, 38.14, 18.82, 13.44. HRMS (ESI-TOF) Calcd for $C_{11}H_8F_7NOH$ $[M+H]^+$: 304.0567, found: 304.0567.



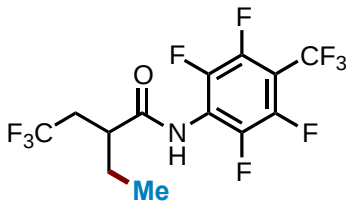
2-cyclohexyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)butanamide (3c)

Substrate **1c** was alkylated following the general alkylation procedure. After purification by preparative thin-layer chromatography, **3c** was obtained as a white solid (31.8 mg, 83%). ^{1}H NMR (400 MHz, acetone-d^6) δ 9.44 (br s, 1H), 2.36-2.30 (m, 1H), 1.91-1.88 (m, 1H), 1.79-1.55 (m, 7H), 1.29-1.10 (m, 4H), 1.06-0.99 (m, 1H), 0.95 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, acetone-d^6) δ 174.08, 55.46, 41.08, 31.68, 31.30, 27.16, 27.05, 27.02, 23.38, 12.25. HRMS (ESI-TOF) Calcd for $C_{17}H_{18}F_7NOH$ $[M+H]^+$: 386.1349, found: 386.1349.



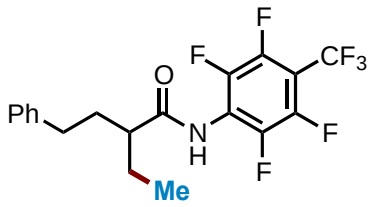
***N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-2-(tetrahydro-2*H*-pyran-4-yl)butanamide (3d)**

Substrate **1d** was alkylated following the general alkylation procedure. After purification by preparative thin-layer chromatography, **3d** was obtained as a white solid (24.0 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (br s, 1H), 4.04-3.96 (m, 2H), 3.44-3.35 (m, 2H), 2.11-2.05 (m, 1H), 1.93-1.83 (m, 1H), 1.78-1.64 (m, 4H), 1.50-1.31 (m, 2H), 1.00 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.70, 67.86, 67.75, 55.78, 37.52, 31.17, 30.66, 22.57, 11.76. HRMS (ESI-TOF) Calcd for $C_{16}H_{16}F_7NO_2H$ $[M+H]^+$: 388.1142, found: 388.1143.



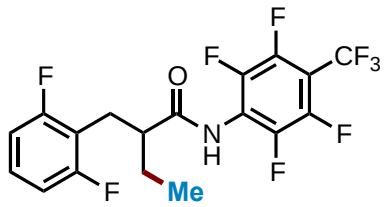
2-ethyl-4,4,4-trifluoro-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)butanamide (3e)

Substrate **1e** was alkylated following the general alkylation procedure. After purification by preparative thin-layer chromatography, **3e** was obtained as a white solid (30.0 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (br s, 1H), 2.82-2.66 (m, 2H), 2.32-2.20 (m, 1H), 1.90-1.80 (m, 1H), 1.78-1.66 (m, 1H), 1.05 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.62, 126.12 (q, *J* = 275.4 Hz), 42.70, 36.13 (q, *J* = 28.8 Hz), 26.48, 11.20. HRMS (ESI-TOF) Calcd for $C_{13}H_9F_{10}NOH$ $[M+H]^+$: 386.0597, found: 386.0596.



2-ethyl-4-phenyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)butanamide (3f)

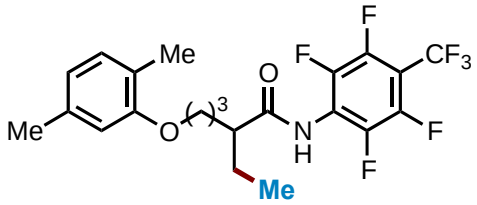
Substrate **1f** was alkylated following the general alkylation procedure. After purification by preparative thin-layer chromatography, **3f** was obtained as a white solid (26.3 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.28 (m, 2H), 7.22-7.17 (m, 3H), 7.12 (br s, 1H), 2.79-2.72 (m, 1H), 2.65-2.57 (m, 1H), 2.34-2.27 (m, 1H), 2.11-2.01 (m, 1H), 1.92-1.83 (m, 1H), 1.80-1.56 (m, 2H), 0.97 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.66, 141.10, 128.55, 128.31, 126.16, 48.46, 33.93, 33.34, 26.20, 11.66. HRMS (ESI-TOF) Calcd for $C_{19}H_{16}F_7NOH$ $[M+H]^+$: 408.1193, found: 408.1192.



2-(2,6-difluorobenzyl)-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)butanamide (3g)

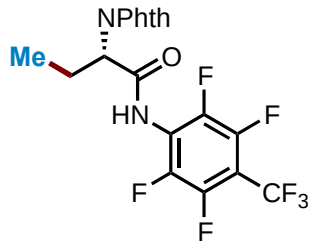
Substrate **1g** was alkylated following the general alkylation procedure. After purification by preparative thin-layer chromatography, **3g** was obtained as a white solid (30.5 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.16 (m, 1H), 6.95 (br s, 1H), 6.91-6.85 (m, 2H), 3.11-3.06 (m, 1H), 2.95-2.91 (m, 1H), 2.73-2.66 (m, 1H), 1.91-1.80 (m, 1H), 1.72-1.63 (m, 1H), 1.02 (t,

J = 7.6 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.45, 161.51 (dd, J_1 = 9.0 Hz, J_2 = 246.3 Hz), 128.46 (t, J = 10.5 Hz), 114.47 (t, J = 20.0 Hz), 111.29 (dd, J_1 = 5.1 Hz, J_2 = 21.3 Hz), 49.01, 25.71, 25.48, 11.62. HRMS (ESI-TOF) Calcd for $C_{18}H_{12}F_9NOH$ $[M+H]^+$: 430.0850, found: 430.0850.



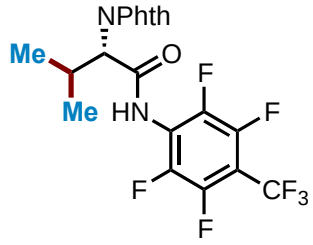
5-(2,5-dimethylphenoxy)-2-ethyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)pentanamide (3h)

Substrate **1h** was alkylated following the general alkylation procedure. After purification by preparative thin-layer chromatography, **3h** was obtained as a white solid (33.7 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (br s, 1H), 7.01 (d, J = 7.6 Hz, 1H), 6.67 (d, J = 7.6 Hz, 1H), 6.64 (s, 1H), 4.06-3.94 (m, 2H), 2.52-2.45 (m, 1H), 2.30 (s, 3H), 2.17 (s, 3H), 1.94-1.60 (m, 6H), 1.00 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.72, 156.70, 136.69, 130.44, 123.43, 121.10, 112.34, 67.92, 48.97, 29.77, 26.94, 26.07, 21.32, 15.86, 11.74. HRMS (ESI-TOF) Calcd for $C_{22}H_{22}F_7NO_2H$ $[M+H]^+$: 466.1611, found: 466.1612.



(*S*)-2-(1,3-dioxoisoindolin-2-yl)-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)butanamide (3i mono)

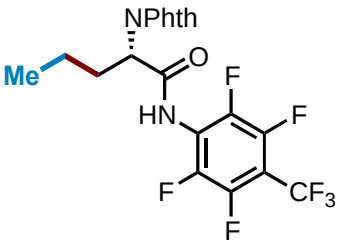
Substrate **1i** was alkylated following the general alkylation procedure. After purification by preparative thin-layer chromatography, **3i mono** was obtained as a white solid (27.5 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (br s, 1H), 7.92-7.90 (m, 2H), 7.81-7.79 (m, 2H), 4.98 (dd, J_1 = 6.8 Hz, J_2 = 9.2 Hz, 1H), 2.41-2.25 (m, 2H), 1.01 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.31, 167.08, 134.81, 131.22, 123.96, 57.14, 22.95, 10.62. HRMS (ESI-TOF) Calcd for $C_{19}H_{11}F_7N_2O_3H$ $[M+H]^+$: 449.0731, found: 449.0732.



(*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-methyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)butanamide (3i di)

Substrate **1i** was alkylated following the general alkylation procedure. After purification by

preparative thin-layer chromatography, **3i di** was obtained as a white solid (9.4 mg, 20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (br s, 1H), 7.95-7.92 (m, 2H), 7.83-7.81 (m, 2H), 4.67 (d, *J* = 11.6 Hz, 1H), 2.95-2.83 (m, 1H), 1.20 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.67, 166.57, 134.94, 131.01, 124.10, 63.47, 28.21, 19.32, 19.28. HRMS (ESI-TOF) Calcd for $C_{20}H_{13}F_7N_2O_3H$ $[M+H]^+$: 463.0887, found: 463.0888.



(*S*)-2-(1,3-dioxoisoindolin-2-yl)-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)pentanamide (3j)

Substrate **1i** was alkylated following the general alkylation procedure. After purification by preparative thin-layer chromatography, **3j** was obtained as a white solid (34.7 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (br s, 1H), 7.91-7.89 (m, 2H), 7.80-7.78 (m, 2H), 5.07 (dd, J_1 = 6.4 Hz, J_2 = 10.4 Hz, 1H), 2.37-2.18 (m, 2H), 1.42-1.33 (m, 2H), 0.97 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.30, 167.24, 134.80, 131.21, 123.96, 55.41, 31.35, 19.39, 13.33. HRMS (ESI-TOF) Calcd for $C_{20}H_{13}F_7N_2O_3H$ $[M+H]^+$: 463.0887, found: 463.0885. HPLC chiralcel ODH column (25% isopropanol in hexanes, 0.3 mL/min) t_r = 23.307 min (major), 32.473 min (minor): 99% ee.

Area % Report

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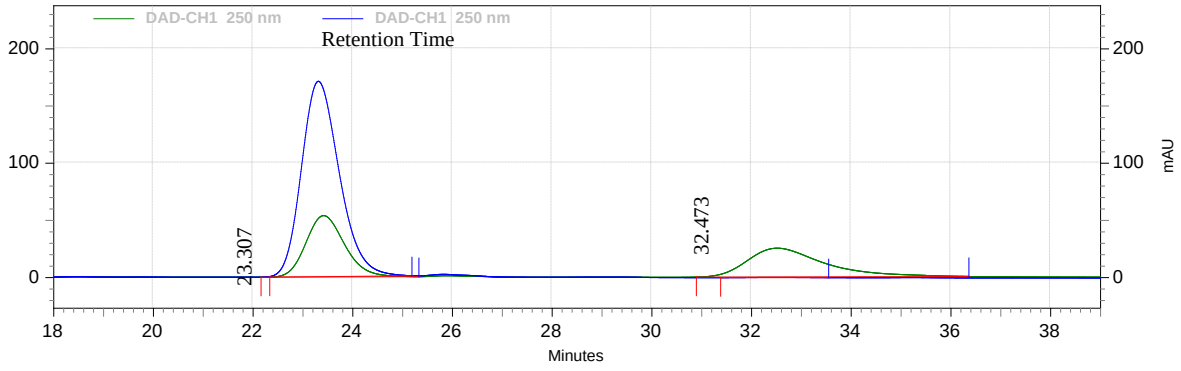

DAD-CH1

250 nm Results

Retention Time	Area	Area %	Height	Height %

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32.473	57342	0.16	824	0.12

Totals	36074520	100.00	684080	100.00

Area % Report

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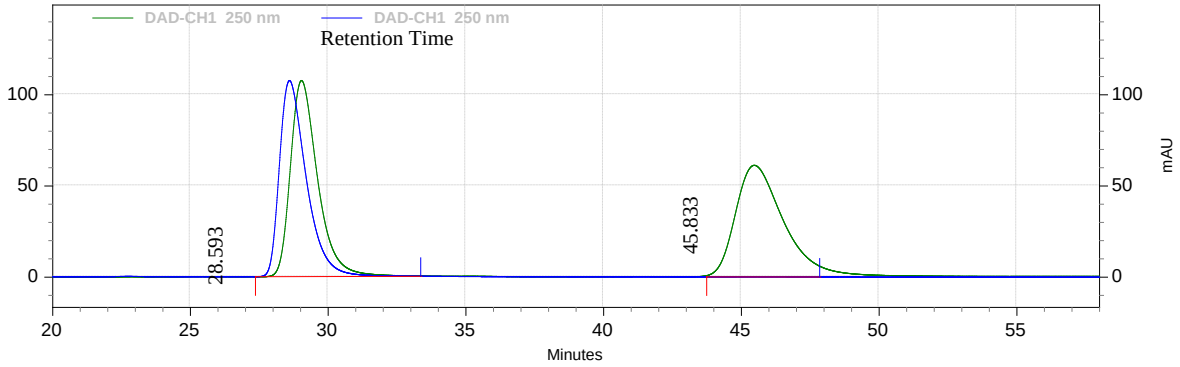

DAD-CH1
250 nm Results

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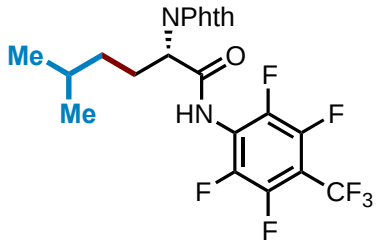
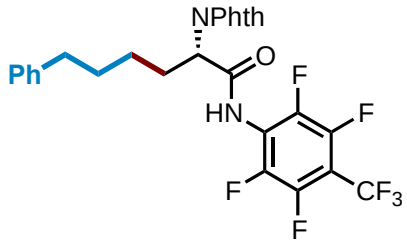


(*S*)-2-(1,3-dioxoisoindolin-2-yl)-5-methyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)hexanamide (3k)

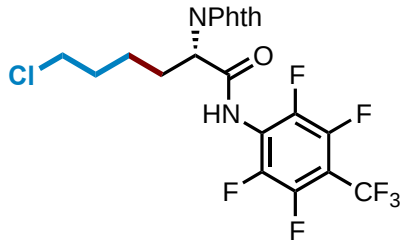
Substrate **1i** was alkylated following this alkylation procedure: Substrate **1i** (0.1 mmol, 43.4 mg), $Pd(TFA)_2$ (0.01 mmol, 3.3 mg), **L1** (0.02 mmol, 4.0 mg) and AgOPiv (0.3 mmol, 62.7 mg) were weighed into a tube (10 mL) with a magnetic stir bar under air. The alkyl iodide **2c**

(0.25 mmol, 46.0 mg) and DCE (0.5 mL) were added, and the tube was sealed with a cap. The reaction mixture was stirred at 80 °C for 20 hours. After purification by preparative thin-layer chromatography, **3k** was obtained as a white solid (19.9 mg, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (br s, 1H), 7.93-7.91 (m, 2H), 7.82-7.80 (m, 2H), 5.02 (dd, J_1 = 8.4 Hz, J_2 = 8.4 Hz, 1H), 2.31-2.56 (m, 2H), 1.66-1.57 (m, 1H), 1.32-1.13 (m, 2H), 0.89 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.32, 167.18, 134.83, 131.20, 124.00, 56.08, 35.02, 27.56, 27.46, 22.44, 22.24. HRMS (ESI-TOF) Calcd for $C_{22}H_{17}F_7N_2O_3H$ $[M+H]^+$: 491.1200, found: 491.1201.



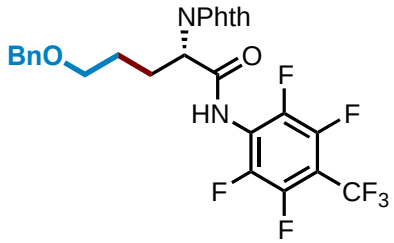
(*S*)-2-(1,3-dioxoisoindolin-2-yl)-6-phenyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)hexanamide (3l)

Substrate **1i** was alkylated following the general alkylation procedure. After purification by preparative thin-layer chromatography, **3l** was obtained as a white solid (30.1 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (br s, 1H), 7.90-7.88 (m, 2H), 7.80-7.81 (m, 2H), 7.23-7.19 (m, 2H), 7.12-7.10 (m, 3H), 5.04 (dd, J_1 = 6.8 Hz, J_2 = 9.2 Hz, 1H), 2.64-2.53 (m, 2H), 2.38-2.23 (m, 2H), 1.77-1.66 (m, 2H), 1.46-1.32 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.23, 167.10, 141.78, 134.78, 131.19, 128.29, 128.25, 125.74, 123.96, 55.49, 35.37, 30.40, 29.16, 25.52. HRMS (ESI-TOF) Calcd for $C_{27}H_{19}F_7N_2O_3H$ $[M+H]^+$: 553.1357, found: 553.1359.



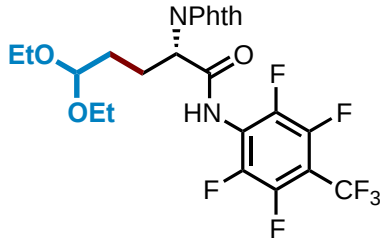
(*S*)-6-chloro-2-(1,3-dioxoisoindolin-2-yl)-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)hexanamide (3m)

Substrate 1i was alkylated following the general alkylation procedure. After purification by preparative thin-layer chromatography, **3m** was obtained as a white solid (41.4 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (br s, 1H), 7.91-7.89 (m, 2H), 7.81-7.79 (m, 2H), 5.05 (dd, J_1 = 8.0 Hz, J_2 = 8.0 Hz, 1H), 3.52 (t, J = 6.4 Hz, 2H), 2.35-2.29 (m, 2H), 1.90-1.78 (m, 2H), 1.58-1.47 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.17, 166.97, 134.87, 131.16, 123.98, 55.12, 44.29, 31.52, 28.53, 23.32. HRMS (ESI-TOF) Calcd for $C_{21}H_{14}ClF_7N_2O_3H$ $[M+H]^+$: 511.0654, found: 511.0653.



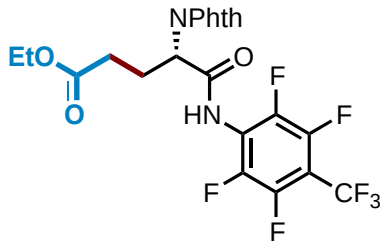
(*S*)-5-(benzyloxy)-2-(1,3-dioxoisoindolin-2-yl)-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)pentanamide (3n)

Substrate **1i** was alkylated following the general alkylation procedure. After purification by preparative thin-layer chromatography, **3n** was obtained as a colorless oil (48.6 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (br s, 1H), 7.87-7.85 (m, 2H), 7.76-7.74 (m, 2H), 7.35-7.21 (m, 5H), 5.10 (dd, J_1 = 7.6 Hz, J_2 = 8.4 Hz, 1H), 4.50 (s, 2H), 3.60 (t, J = 6.0 Hz, 2H), 2.60-2.51 (m, 1H), 2.37-2.27 (m, 1H), 1.85-1.73 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.00, 167.04, 137.51, 134.52, 131.41, 128.38, 127.88, 127.81, 123.73, 73.35, 69.34, 54.49, 26.64, 26.23. HRMS (ESI-TOF) Calcd for $C_{27}H_{19}F_7N_2O_4H$ $[M+H]^+$: 569.1306, found: 569.1305.



(*S*)-2-(1,3-dioxoisoindolin-2-yl)-5,5-diethoxy-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)pentanamide (3o)

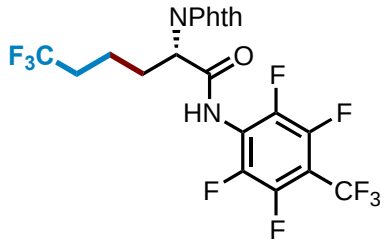
Substrate **1i** was alkylated following the general alkylation procedure. After purification by preparative thin-layer chromatography, **3o** was obtained as a white solid (37.1 mg, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (br s, 1H), 7.88-7.86 (m, 2H), 7.78-7.76 (m, 2H), 5.14 (dd, J_1 = 7.2 Hz, J_2 = 8.8 Hz, 1H), 4.58 (t, J = 5.2 Hz, 1H), 3.70-3.62 (m, 2H), 3.56-3.47 (m, 2H), 2.56-2.47 (m, 1H), 2.38-2.28 (m, 1H), 1.77-1.73 (m, 2H), 1.21 (t, J = 7.2 Hz, 3H), 1.20 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.03, 167.03, 134.60, 131.38, 123.78, 102.13, 62.03, 61.96, 54.61, 30.16, 24.59, 15.19, 15.16. HRMS (ESI-TOF) Calcd for $C_{24}H_{21}F_7N_2O_5Na$ $[M+Na]^+$: 573.1231, found: 573.1234.



(*S*)-ethyl-4-(1,3-dioxoisoindolin-2-yl)-5-oxo-5-((2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)amino)pentanoate (3p)

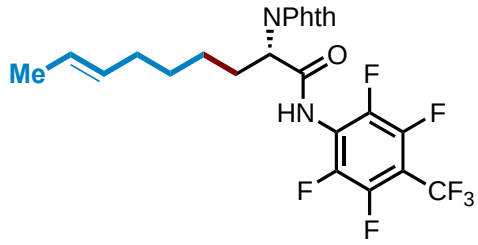
Substrate **1i** was alkylated following this alkylation procedure: Substrate **1i** (0.1 mmol, 43.4 mg), $Pd(TFA)_2$ (0.01 mmol, 3.3 mg), **L1** (0.02 mmol, 4.0 mg) and AgOPiv (0.3 mmol, 62.7 mg) were weighed into a tube (10 mL) with a magnetic stir bar under air. The alkyl iodide **2h**

(0.25 mmol, 53.5 mg) and DCE (0.5 mL) were added, and the tube was sealed with a cap. The reaction mixture was stirred at 80 °C for 20 hours. After purification by preparative thin-layer chromatography, **3p** was obtained as a colorless oil (43.5 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (br s, 1H), 7.89-7.87 (m, 2H), 7.79-7.77 (m, 2H), 5.09 (dd, J_1 = 5.6 Hz, J_2 = 8.8 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 2.70-2.56 (m, 2H), 2.53-2.40 (m, 2H), 1.23 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.96, 167.89, 166.58, 134.64, 131.36, 123.80, 61.17, 53.87, 30.97, 24.73, 14.01. HRMS (ESI-TOF) Calcd for $C_{22}H_{15}F_7N_2O_5H$ $[M+H]^+$: 521.0942, found: 521.0943.



(*S*)-2-(1,3-dioxoisoindolin-2-yl)-6,6,6-trifluoro-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)hexanamide (3q)

Substrate **1i** was alkylated following this alkylation procedure: Substrate **1i** (0.1/1.0 mmol, 43.4/434 mg), $Pd(TFA)_2$ (0.01/0.1 mmol, 3.3/33.2 mg), **L1** (0.02/0.2 mmol, 4.0/40.2 mg) and AgOPiv (0.3/3.0 mmol, 62.7/627 mg) were weighed into a tube (10/100 mL) with a magnetic stir bar under air. The alkyl iodide **2i** (0.25/2.5 mmol, 56.0/560 mg) and DCE (0.5/5.0 mL) were added, and the tube was sealed with a cap. The reaction mixture was stirred at 80 °C for 20 hours. After purification by preparative thin-layer chromatography/flash column chromatography, **3q** was obtained as a white solid (42.6/457 mg, 80%/86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (br s, 1H), 7.90-7.88 (m, 2H), 7.81-7.79 (m, 2H), 5.04 (dd, J_1 = 7.2 Hz, J_2 = 8.8 Hz, 1H), 2.41-2.32 (m, 2H), 2.25-2.09 (m, 2H), 1.70-1.56 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.03, 166.67, 134.96, 131.06, 126.62 (q, J = 275.0 Hz), 124.04, 54.51, 32.94 (q, J = 28.8 Hz), 28.24, 18.83-18.75. HRMS (ESI-TOF) Calcd for $C_{21}H_{12}F_{10}N_2O_3H$ $[M+H]^+$: 531.0761, found: 531.0762.

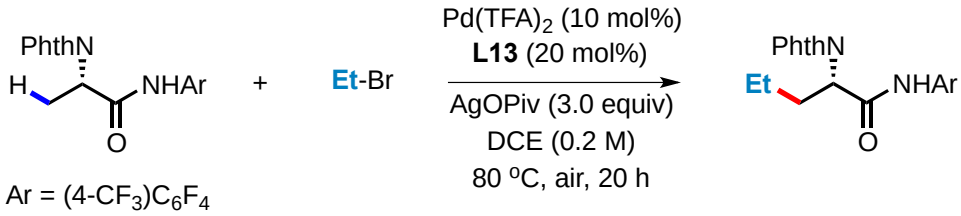


(*S*,*E*)-2-(1,3-dioxoisoindolin-2-yl)-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)non-7-enamide (3r)

Substrate **1i** was alkylated following the general alkylation procedure. After purification by preparative thin-layer chromatography, **3r** was obtained as a white solid (22.4 mg, 43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (br s, 1H), 7.93-7.91 (m, 2H), 7.82-7.80 (m, 2H), 5.44-5.35 (m, 1H), 5.34-5.26 (m, 1H), 5.06 (dd, J_1 = 7.6 Hz, J_2 = 9.2 Hz, 1H), 2.32-2.26 (m, 2H), 2.04-1.99 (m, 2H), 1.55 (d, J = 6.4 Hz, 3H), 1.48-1.30 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.29, 167.14, 134.82, 131.23, 129.77, 124.36, 123.98, 55.72, 29.33, 28.64, 26.36, 25.63,

12.72. HRMS (ESI-TOF) Calcd for $C_{24}H_{19}F_7N_2O_3H$ [M+H]$^+$: 517.1357, found: 517.1356.

C(sp^3)–H Alkylation with Ethyl bromide

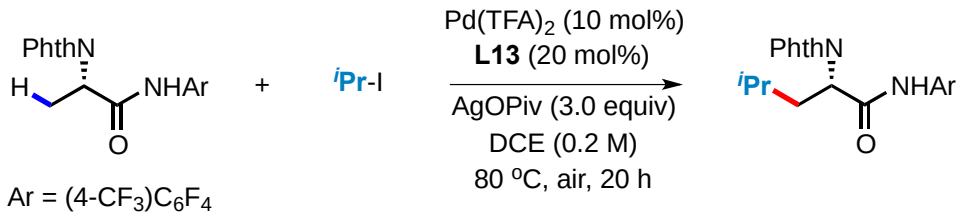


1i **2l** **3j**

36% (^{1}H NMR)

General Procedures for the C(sp^3)–H Alkylation with Ethyl bromide: Substrate **1i** (0.1 mmol, 43.4 mg), Pd(TFA)$_2$ (0.01 mmol, 3.3 mg), **L13** (0.02 mmol, 3.9 mg) and AgOPiv (0.3 mmol, 62.7 mg) were weighed into a tube (10 mL) with a magnetic stir bar under air. The ethyl bromide **2l** (0.25 mmol, 27.2 mg) and DCE (0.5 mL) were added, and the tube was sealed with a cap. The reaction mixture was stirred at 80 °C for 20 hours. Upon completion, the reaction mixture was analyzed through ^{1}H NMR by using CH_2Br_2 as an internal standard.

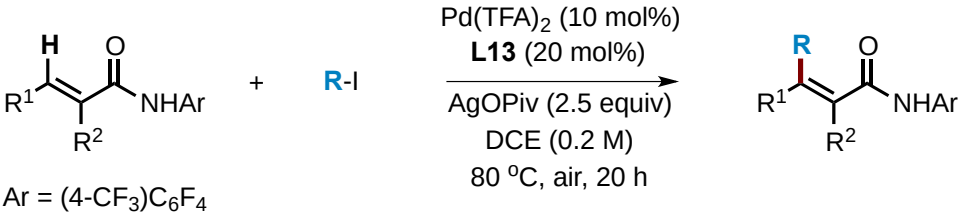
C(sp^3)–H Alkylation with Isopropyl Iodide



1i **2m** **No Reaction**

General Procedures for the C(sp^3)–H Alkylation with Isopropyl Iodide: Substrate **1i** (0.1 mmol, 43.4 mg), Pd(TFA)$_2$ (0.01 mmol, 3.3 mg), **L13** (0.02 mmol, 3.9 mg) and AgOPiv (0.3 mmol, 62.7 mg) were weighed into a tube (10 mL) with a magnetic stir bar under air. The isopropyl iodide **2m** (0.25 mmol, 41.8 mg) and DCE (0.5 mL) were added, and the tube was sealed with a cap. The reaction mixture was stirred at 80 °C for 20 hours. Upon completion, the reaction mixture was analyzed through ^{1}H NMR by using CH_2Br_2 as an internal standard.

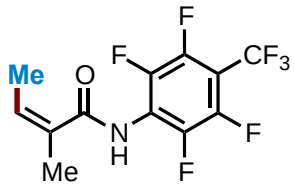
Vinylic C(sp^2)–H Alkylation



1 **2** **3**

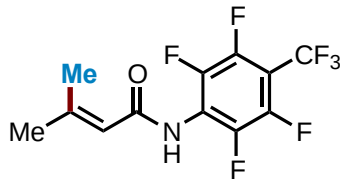
General Procedures for the Vinylic C(sp^2)–H Alkylation: Substrate **1** (0.1 mmol), Pd(TFA)$_2$ (0.01 mmol, 3.3 mg), **L13** (0.02 mmol, 3.9 mg) and AgOPiv (0.25 mmol, 52.2 mg)

were weighed into a tube (10 mL) with a magnetic stir bar under air. The alkyl iodide **2** (0.25 mmol) and DCE (0.5 mL) were added, and the tube was sealed with a cap. The reaction mixture was stirred at 80 °C for 20 hours. Upon completion, the reaction mixture was cooled to room temperature and diluted with EtOAc. Then the reaction mixture was filtered through a short celite tube and purified by preparative thin-layer chromatography using hexane/EtOAc or hexane/EtOAc/DCM mixtures as the eluent.



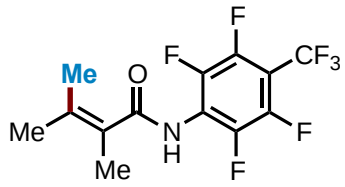
(*Z*)-2-methyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)but-2-enamide (3s)

Substrate **1j** was alkylated following the general alkylation procedure. After purification by preparative thin-layer chromatography, **3s** was obtained as a white solid (22.6 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (br s, 1H), 6.00-5.94 (m, 1H), 2.04-2.03 (m, 3H), 1.97-1.95 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.70, 133.76, 130.08, 20.67, 15.56. HRMS (ESI-TOF) Calcd for $C_{12}H_8F_7NOH$ $[M+H]^+$: 316.0567, found: 316.0565.



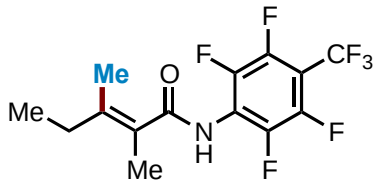
3-methyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)but-2-enamide (3t)

Substrate **1k** was alkylated following the general alkylation procedure. After purification by preparative thin-layer chromatography, **3t** was obtained as white solid (23.5 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (br s, 1H), 5.83 (s, 1H), 2.23 (s, 3H), 1.96 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.54, 158.41, 115.95, 27.60, 20.38. HRMS (ESI-TOF) Calcd for $C_{12}H_8F_7NOH$ $[M+H]^+$: 316.0567, found: 316.0568.



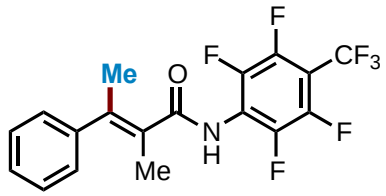
2,3-dimethyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)but-2-enamide (3u)

Substrate **1l** was alkylated following the general alkylation procedure. After purification by preparative thin-layer chromatography, **3u** was obtained as a white solid (23.8 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (br s, 1H), 1.95 (s, 6H), 1.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.15, 138.31, 124.84, 22.45, 20.88, 16.09. HRMS (ESI-TOF) Calcd for $C_{13}H_{10}F_7NOH$ $[M+H]^+$: 330.0723, found: 330.0724.



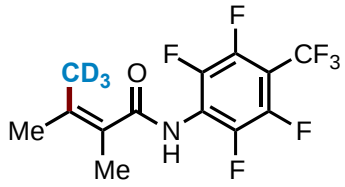
(*E*)-2,3-dimethyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)pent-2-enamide (3v)

Substrate **1m** was alkylated following the general alkylation procedure. After purification by preparative thin-layer chromatography, **3v** was obtained as a white solid (20.0 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (br s, 1H), 2.16 (q, *J* = 7.6 Hz, 2H), 1.96 (s, 3H), 1.93 (s, 3H), 1.05 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.32, 143.26, 124.38, 27.56, 19.84, 15.52, 11.68. HRMS (ESI-TOF) Calcd for $C_{14}H_{12}F_7NOH$ $[M+H]^+$: 344.0880, found: 344.0879.



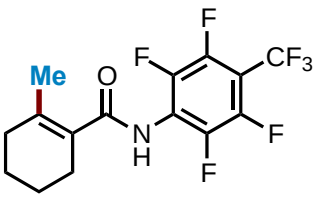
(*E*)-2-methyl-3-phenyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)but-2-enamide (3w)

Substrate **1n** was alkylated following the general alkylation procedure. After purification by preparative thin-layer chromatography, **3w** was obtained as a white solid (26.4 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.37 (m, 2H), 7.34-7.30 (m, 1H), 7.20-7.18 (m, 3H), 2.25-2.24 (m, 3H), 1.91-1.90 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.89, 141.84, 141.61, 128.49, 127.49, 127.34, 126.96, 22.82, 17.73. HRMS (ESI-TOF) Calcd for $C_{18}H_{12}F_7NOH$ $[M+H]^+$: 392.0880, found: 392.0880.



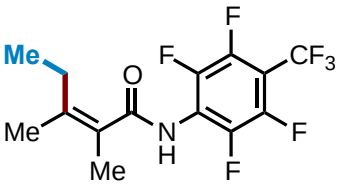
(*Z*)-4,4,4-deuterium-2,3-dimethyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)but-2-enamide (3x)

Substrate **1l** was alkylated following the general alkylation procedure. After purification by preparative thin-layer chromatography, **3x** was obtained as a white solid (22.7 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (br s, 1H), 1.96 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.11, 138.34, 124.86, 20.84, 16.09. HRMS (ESI-TOF) Calcd for $C_{13}H_7D_3F_7NOH$ $[M+H]^+$: 333.0909, found: 333.0910.



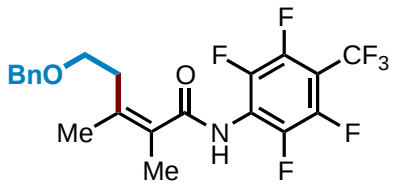
2-methyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)cyclohex-1-enecarboxamide (3y)

Substrate **1o** was alkylated following the general alkylation procedure. After purification by preparative thin-layer chromatography, **3y** was obtained as a white solid (32.3 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (br s, 1H), 2.34-2.31 (m, 2H), 2.13-2.10 (m, 2H), 1.94 (s, 3H), 1.72-1.63 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.33, 141.30, 126.72, 32.18, 26.85, 22.08, 21.42. HRMS (ESI-TOF) Calcd for $C_{15}H_{12}F_7NOH$ $[M+H]^+$: 356.0880, found: 356.0880.



(*Z*)-2,3-dimethyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)pent-2-enamide (3z)

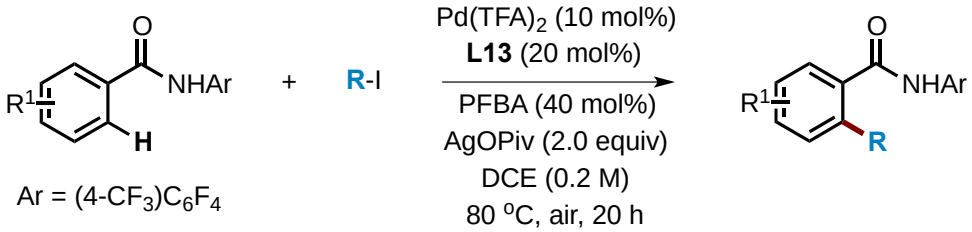
Substrate **1l** was alkylated following this alkylation procedure: Substrate **1l** (0.1 mmol, 31.5 mg), $Pd(TFA)_2$ (0.01 mmol, 3.3 mg), **L1** (0.02 mmol, 4.0 mg), K_2HPO_4 (0.1 mmol, 17.4 mg) and AgOPiv (0.25 mmol, 52.2 mg) were weighed into a tube (10 mL) with a magnetic stir bar under air. The alkyl iodide **2b** (0.25 mmol, 39.0 mg) and DCE (0.5 mL) were added, and the tube was sealed with a cap. The reaction mixture was stirred at 80 ^{o}C for 20 hours. After purification by preparative thin-layer chromatography, **3z** was obtained as a white solid (22.0 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (br s, 1H), 2.28 (q, *J* = 7.6 Hz, 2H), 1.95 (s, 3H), 1.78 (s, 3H), 1.08 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.15, 143.27, 124.39, 29.23, 17.84, 16.20, 13.04. HRMS (ESI-TOF) Calcd for $C_{14}H_{12}F_7NOH$ $[M+H]^+$: 344.0880, found: 344.0882.



(*Z*)-5-(benzyloxy)-2,3-dimethyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)pent-2-enamide (3aa)

Substrate **1l** was alkylated following the general alkylation procedure. After purification by preparative thin-layer chromatography, **3aa** was obtained as a colorless oil (27.4 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.28-7.20 (m, 5H), 4.55 (s, 2H), 3.75 (t, *J* = 5.6 Hz, 2H), 2.62 (t, *J* = 5.6 Hz, 2H), 1.97 (s, 3H), 1.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.55, 136.66, 135.83, 129.23, 128.44, 128.20, 128.02, 73.74, 67.37, 36.51, 18.62, 16.72. HRMS (ESI-TOF) Calcd for $C_{21}H_{18}F_7NO_2H$ $[M+H]^+$: 450.1298, found: 450.1298.

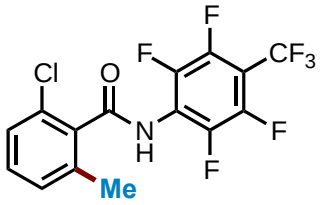
Aromatic C(sp^2)–H Alkylation



Ar = (4-CF_3)C_6F_4

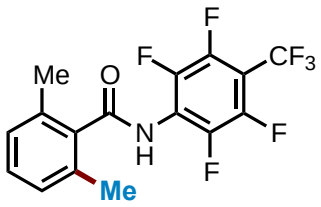
1 **2** **3**

General Procedures for the Aromatic C(sp^2)–H Alkylation: Substrate **1** (0.1 mmol), $Pd(TFA)_2$ (0.01 mmol, 3.3 mg), **L13** (0.02 mmol, 3.9 mg), PFBA (0.04 mmol, 8.4 mg) and AgOPiv (0.2 mmol, 41.8 mg) were weighed into a tube (10 mL) with a magnetic stir bar under air. The alkyl iodide **2** (0.25 mmol) and DCE (0.5 mL) were added, and the tube was sealed with a cap. The reaction mixture was stirred at 80 °C for 20 hours. Upon completion, the reaction mixture was cooled to room temperature and diluted with EtOAc. Then the reaction mixture was filtered through a short celite tube and purified by preparative thin-layer chromatography using hexane/EtOAc or hexane/EtOAc/DCM mixtures as the eluent.



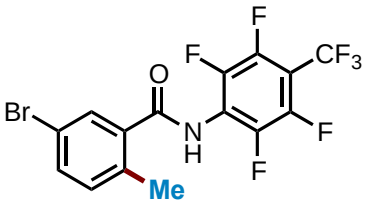
2-chloro-6-methyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)benzamide (3ab)

Substrate **1p** was alkylated following the general alkylation procedure. After purification by preparative thin-layer chromatography, **3ab** was obtained as a white solid (30.9 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (br s, 1H), 7.29-7.23 (m, 2H), 7.16-7.14 (m, 1H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.90, 137.62, 134.40, 130.88, 130.39, 128.82, 126.96, 19.24. HRMS (ESI-TOF) Calcd for $C_{15}H_6ClF_7NO$ $[M-H]^-$: 384.0032, found: 384.0026.



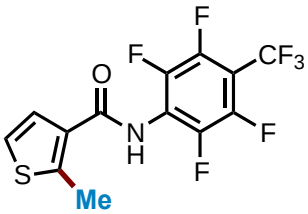
2,6-dimethyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)benzamide (3ac)

Substrate **1q** was alkylated following the general alkylation procedure. After purification by preparative thin-layer chromatography, **3ac** was obtained as a white solid (32.3 mg, 88%). ^{1}H NMR (400 MHz, acetone-d^6) δ 9.83 (br s, 1H), 7.27-7.23 (m, 1H), 7.13-7.11 (m, 2H), 2.39 (s, 6H). ^{13}C NMR (100 MHz, acetone-d^6) δ 168.48, 137.46, 135.18, 130.10, 128.32, 19.24. HRMS (ESI-TOF) Calcd for $C_{16}H_{10}F_7NOH$ $[M+H]^+$: 366.0723, found: 366.0722.



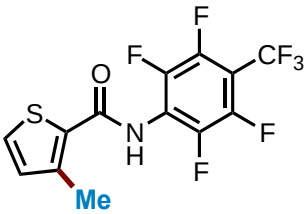
5-bromo-2-methyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)benzamide (3ad)

Substrate **1r** was alkylated following the general alkylation procedure. After purification by preparative thin-layer chromatography, **3ad** was obtained as a white solid (33.4 mg, 78%). ^{1}H NMR (400 MHz, acetone-d^6) δ 9.86 (br s, 1H), 7.79 (d, J = 2.0 Hz, 1H), 7.62 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H), 2.46 (s, 3H). ^{13}C NMR (100 MHz, acetone-d^6) δ 166.41, 137.23, 137.14, 134.52, 134.00, 131.34, 119.46, 19.45. HRMS (ESI-TOF) Calcd for $C_{15}H_6BrF_7NO$ [M-H]$^-$: 427.9526, found: 427.9530.



2-methyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)thiophene-3-carboxamide (3ae)

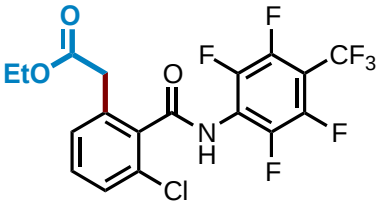
Substrate **1s** was alkylated following this alkylation procedure: Substrate **1s** (0.1 mmol, 34.3 mg), $Pd(OAc)_2$ (0.01 mmol, 2.3 mg), **L11** (0.02 mmol, 5.4 mg), AgOAc (0.3 mmol, 50.1 mg) were weighed into a tube (10 mL) with a magnetic stir bar under air. The alkyl iodide **2a** (0.25 mmol, 35.5 mg) and DCE (1.5 mL) were added, and the tube was sealed with a cap. The reaction mixture was stirred at 90 °C for 20 hours. After purification by preparative thin-layer chromatography, **3ae** was obtained as a white solid (24.6 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (br s, 1H), 7.28 (d, J = 5.4 Hz, 1H), 7.15 (d, J = 5.4 Hz, 1H), 2.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.12, 149.35, 129.01, 126.08, 122.81, 15.17. HRMS (ESI-TOF) Calcd for $C_{13}H_6F_7NOSH$ [M+H]$^+$: 358.0131, found: 358.0130.



3-methyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)thiophene-2-carboxamide (3af)

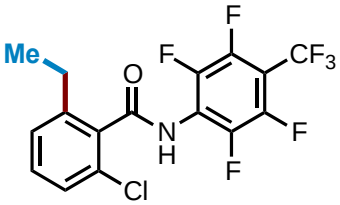
Substrate **1t** was alkylated following this alkylation procedure: Substrate **1t** (0.1 mmol, 34.3 mg), $Pd(OAc)_2$ (0.01 mmol, 2.3 mg), **L11** (0.02 mmol, 5.4 mg), AgOAc (0.3 mmol, 50.1 mg) were weighed into a tube (10 mL) with a magnetic stir bar under air. The alkyl iodide **2a** (0.25 mmol, 35.5 mg) and DCE (1.5 mL) were added, and the tube was sealed with a cap. The reaction mixture was stirred at 90 °C for 20 hours. After purification by preparative thin-layer

chromatography, **3af** was obtained as a white solid (29.3 mg, 82%). ^{1}H NMR (400 MHz, acetone-d^{6}) δ 9.45 (br s, 1H), 7.67 (d, J = 5.2 Hz, 1H), 7.08 (d, J = 5.2 Hz, 1H), 2.56 (s, 3H). ^{13}C NMR (100 MHz, acetone-d^{6}) δ 161.46, 145.36, 132.94, 129.92, 129.39, 15.86. HRMS (ESI-TOF) Calcd for $C_{13}H_6F_7NOSH$ $[M+H]^+$: 358.0131, found: 358.0130.



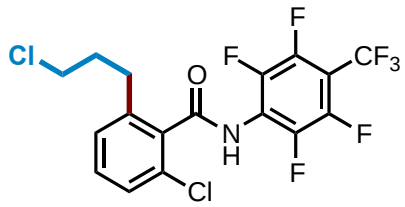
ethyl 2-(3-chloro-2-((2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)carbamoyl)phenyl)acetate (3ae)

Substrate **1q** was alkylated following this alkylation procedure: Substrate **1q** (0.1 mmol, 37.2 mg), $Pd(TFA)_2$ (0.01 mmol, 3.3 mg), **L1** (0.02 mmol, 4.0 mg), PFBA (0.04 mmol, 8.4 mg) and AgOPiv (0.2 mmol, 41.8 mg) were weighed into a tube (10 mL) with a magnetic stir bar under air. The alkyl iodide **2h** (0.25 mmol, 53.5 mg) and DCE (0.5 mL) were added, and the tube was sealed with a cap. The reaction mixture was stirred at 80 ^{o}C for 20 hours. After purification by preparative thin-layer chromatography, **3ae** was obtained as a white solid (31.3 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (br s, 1H), 7.42-7.34 (m, 2H), 7.21-7.19 (m, 1H), 4.18 (q, J = 7.2 Hz, 2H), 3.78 (s, 2H), 1.28 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.12, 164.46, 135.36, 133.22, 131.81, 131.08, 129.12, 128.86, 61.92, 38.81, 14.01. HRMS (ESI-TOF) Calcd for $C_{18}H_{11}ClF_7NO_3H$ $[M+H]^+$: 458.0388, found: 458.0384.



2-chloro-6-ethyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)benzamide (3af)

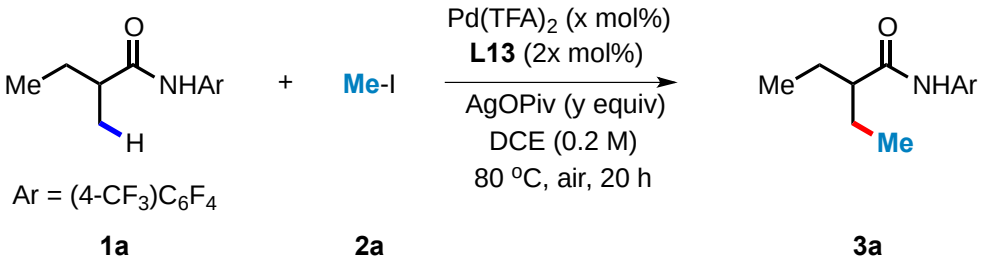
Substrate **1q** was alkylated following this alkylation procedure: Substrate **1q** (0.1 mmol, 37.2 mg), $Pd(TFA)_2$ (0.01 mmol, 3.3 mg), **L1** (0.02 mmol, 4.0 mg), PFBA (0.04 mmol, 8.4 mg) and AgOPiv (0.3 mmol, 62.7 mg) were weighed into a tube (10 mL) with a magnetic stir bar under air. The alkyl iodide **2b** (0.25 mmol, 39.0 mg) and DCE (0.5 mL) were added, and the tube was sealed with a cap. The reaction mixture was stirred at 80 ^{o}C for 20 hours. After purification by preparative thin-layer chromatography, **3af** was obtained as a white solid (24.7 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (br s, 1H), 7.36-7.32 (m, 1H), 7.29-7.26 (m, 1H), 7.23-7.22 (m, 1H), 2.74 (q, J = 7.6 Hz, 2H), 1.27 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.74, 143.95, 133.98, 131.16, 130.32, 127.36, 127.04, 26.54, 15.64. HRMS (ESI-TOF) Calcd for $C_{16}H_8ClF_7NO$ $[M-H]^-$: 398.0188, found: 398.0187.



2-chloro-6-(3-chloropropyl)-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)benzamide (3ag)

Substrate **1q** was alkylated following this alkylation procedure: Substrate **1q** (0.1 mmol, 37.2 mg), $Pd(TFA)_2$ (0.01 mmol, 3.3 mg), **L1** (0.02 mmol, 4.0 mg), PFBA (0.04 mmol, 8.4 mg) and AgOPiv (0.3 mmol, 62.7 mg) were weighed into a tube (10 mL) with a magnetic stir bar under air. The alkyl iodide **2e** (0.25 mmol, 51.0 mg) and DCE (0.5 mL) were added, and the tube was sealed with a cap. The reaction mixture was stirred at 80 ^{o}C for 20 hours. After purification by preparative thin-layer chromatography, **3af** was obtained as a white solid (35.8 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (br s, 1H), 7.35-7.27 (m, 2H), 7.23-7.21 (m, 1H), 3.53 (t, *J* = 6.4 Hz, 2H), 2.84 (t, *J* = 7.6 Hz, 2H), 2.13-2.06 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.74, 140.66, 134.35, 131.14, 130.60, 128.19, 127.55, 44.02, 33.78, 30.62. HRMS (ESI-TOF) Calcd for $C_{17}H_9Cl_2F_7NO$ $[M-H]^-$: 445.9955, found: 445.9951.

Reducing the loadings of Catalyst and AgOPiv



1a **2a** **3a**

General Procedures for Reducing the loadings of Catalyst and AgOPiv: Substrate **1a** (0.1 mmol, 31.7 mg), $Pd(TFA)_2$ (x mmol), **L13** (2x mmol) and AgOPiv (y mmol) were weighed into a tube (10 mL) with a magnetic stir bar under air. The methyl iodide **2a** (0.25 mmol, 35.5 mg) and DCE (0.5 mL) were added, and the tube was sealed with a cap. The reaction mixture was stirred at 80 ^{o}C for 20 hours. Upon completion, the reaction mixture was analyzed through ^{1}H NMR by using CH_2Br_2 as an internal standard.

Entry	Conditions	3a (%)[a]
1	$Pd(TFA)_2$ (10 mol%), L13 (20 mol%), AgOPiv (3.0 equiv)	81
2	$Pd(TFA)_2$ (5 mol%), L13 (10 mol%), AgOPiv (3.0 equiv)	63
3	$Pd(TFA)_2$ (10 mol%), L13 (20 mol%), AgOPiv (1.5 equiv)	58
4	$Pd(TFA)_2$ (5 mol%), L13 (10 mol%), AgOPiv (1.5 equiv)	53

[a] ^{1}H NMR yield using CH_2Br_2 as an internal standard.

References

(1) (a) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3680. (b) Wasa, M.; Chan, K. S. L.; Zhang, X.-G.; He, J.; Miura, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 18570.

(2) He, J.; Wasa, M.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 3387.

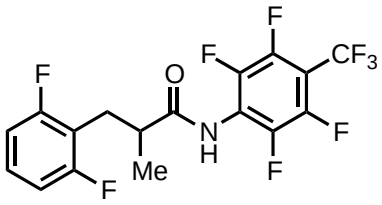
(3) He, J.; Li, S.-H.; Deng, Y.-Q.; Fu, H.-Y.; Laforteza, B. N.; Spangler, J. E.; Homs, A.; Yu, J.-Q. *Science* **2014**, *343*, 1216.

(4) Chan, K. S. L.; Wasa, M.; Wang, X.-S.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 9081.

(5) Shang, M.; Zeng, S.-H.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. *Org. Lett.* **2013**, *15*, 5286.

(6) Zhao, Y.-S.; Chen, G. *Org. Lett.* **2011**, *13*, 4850.

^{1}H and ^{13}C NMR Spectra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O
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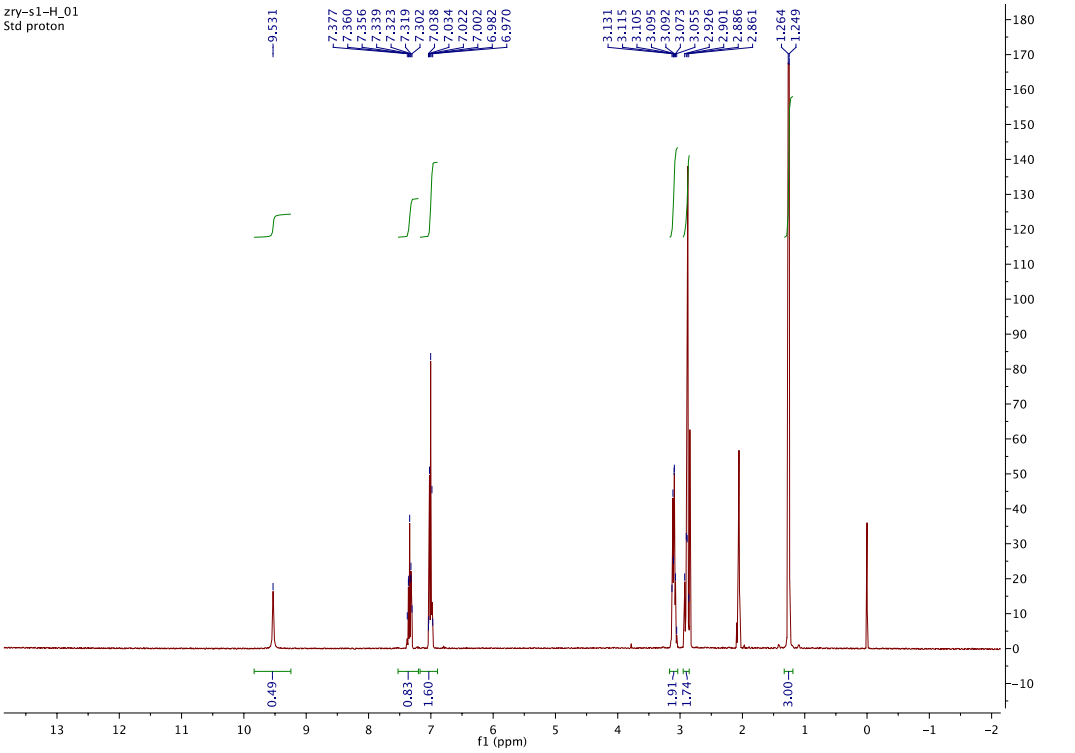
F
CF3
N
H
F
Me
F
F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7.319
7.302
7.038
7.034
7.022
7.002
6.982
6.970
3.131
3.115
3.105
3.095
3.092
3.073
3.055
2.926
2.901
2.886
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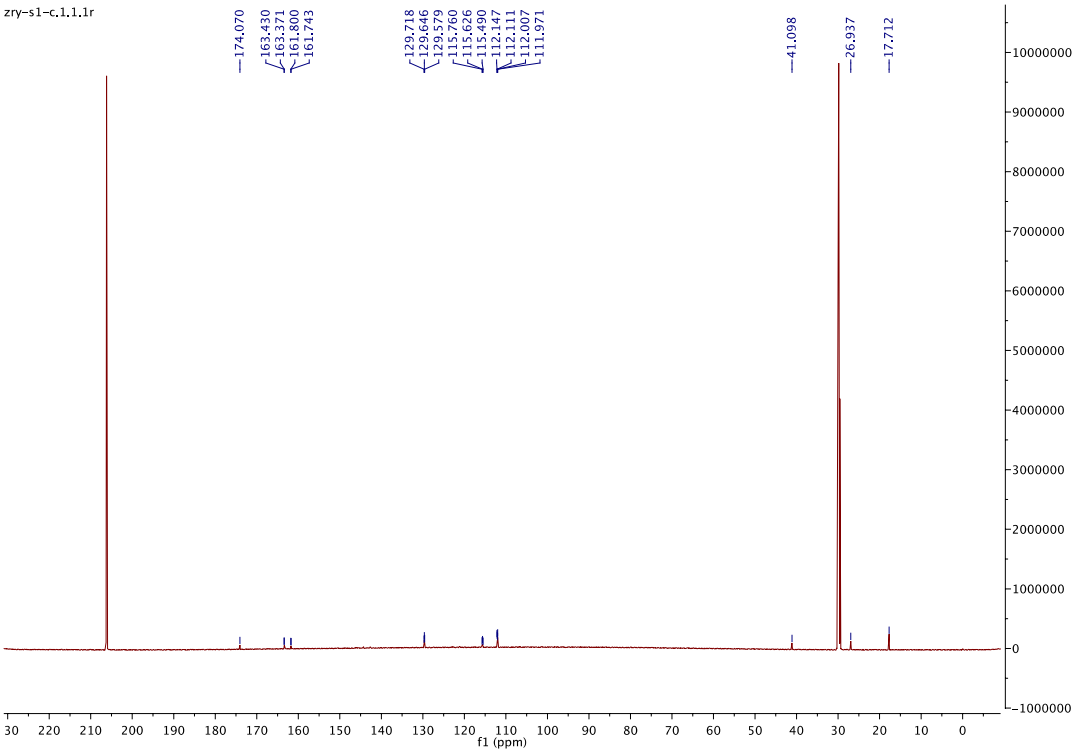
1.91
1.74
3.00
f1 (ppm)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115.490
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26.937
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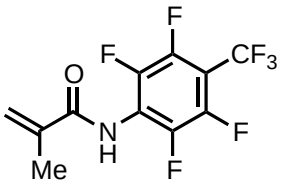
f1 (ppm)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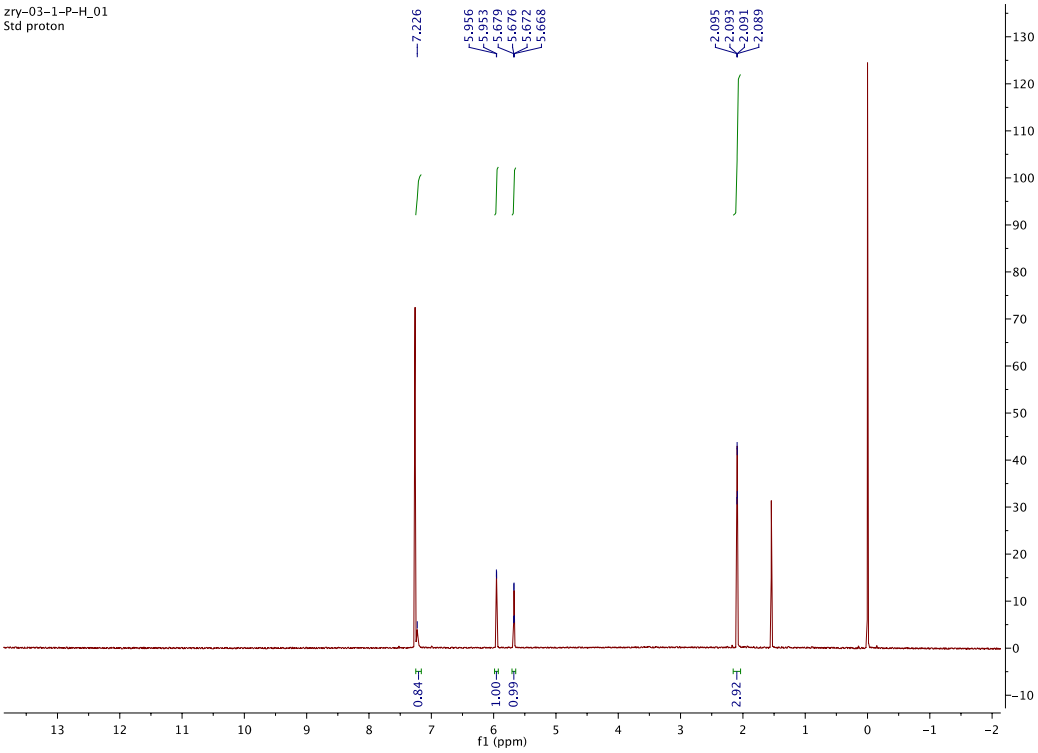
H
F
Me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2.091
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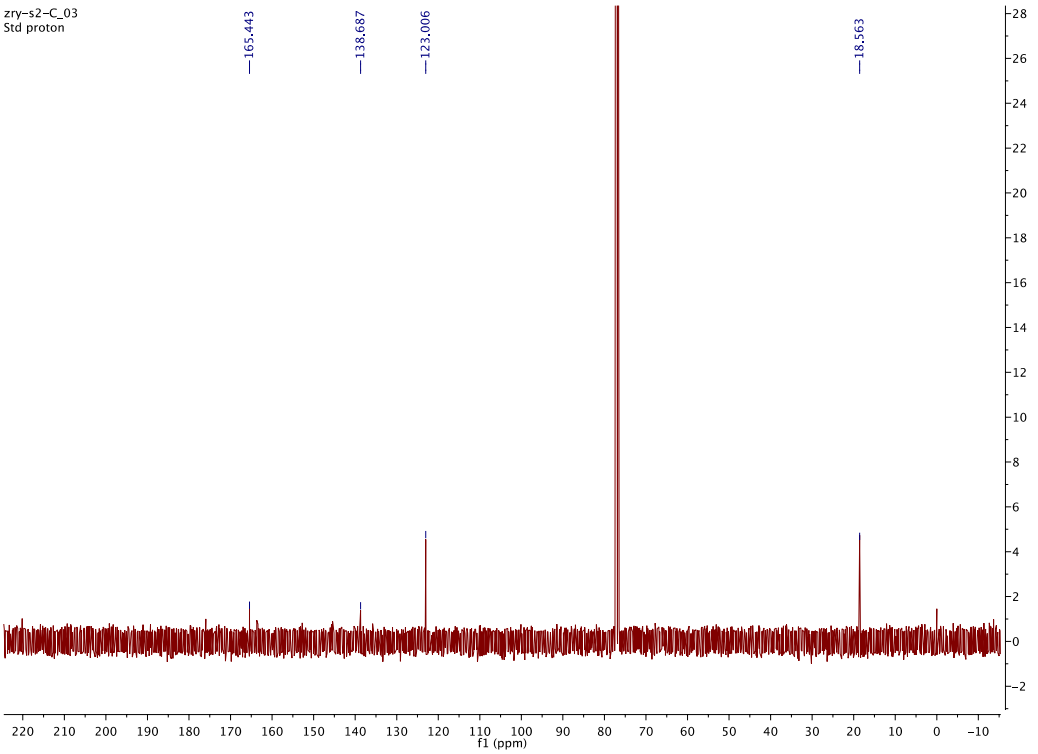
0.99
2.92
f1 (ppm)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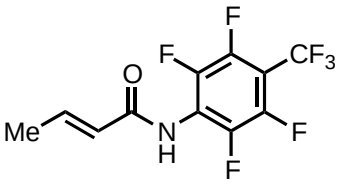
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N
H
F
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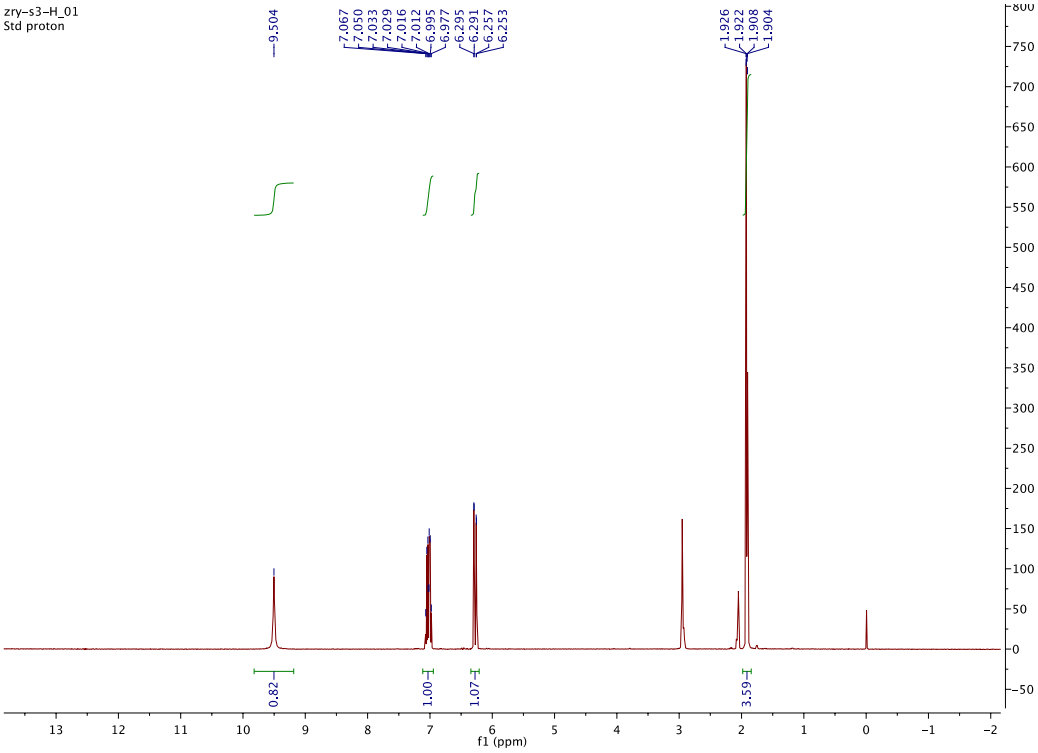
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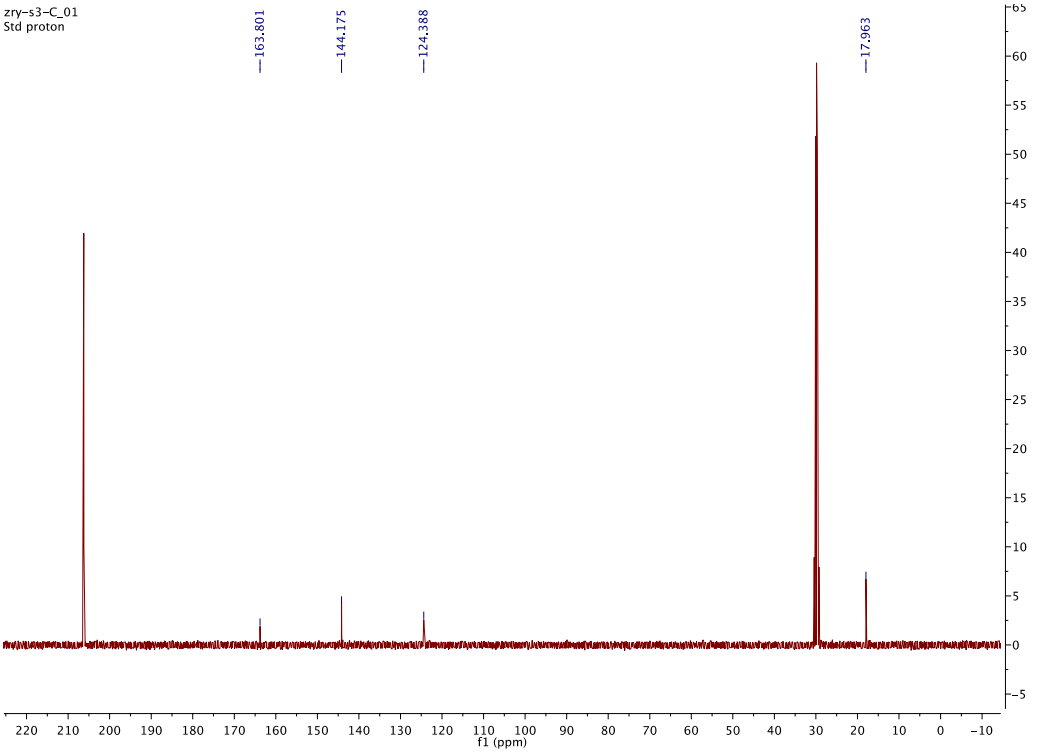
f1 (ppm)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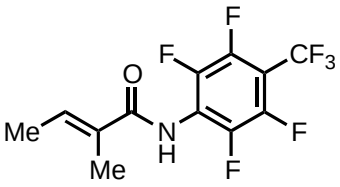
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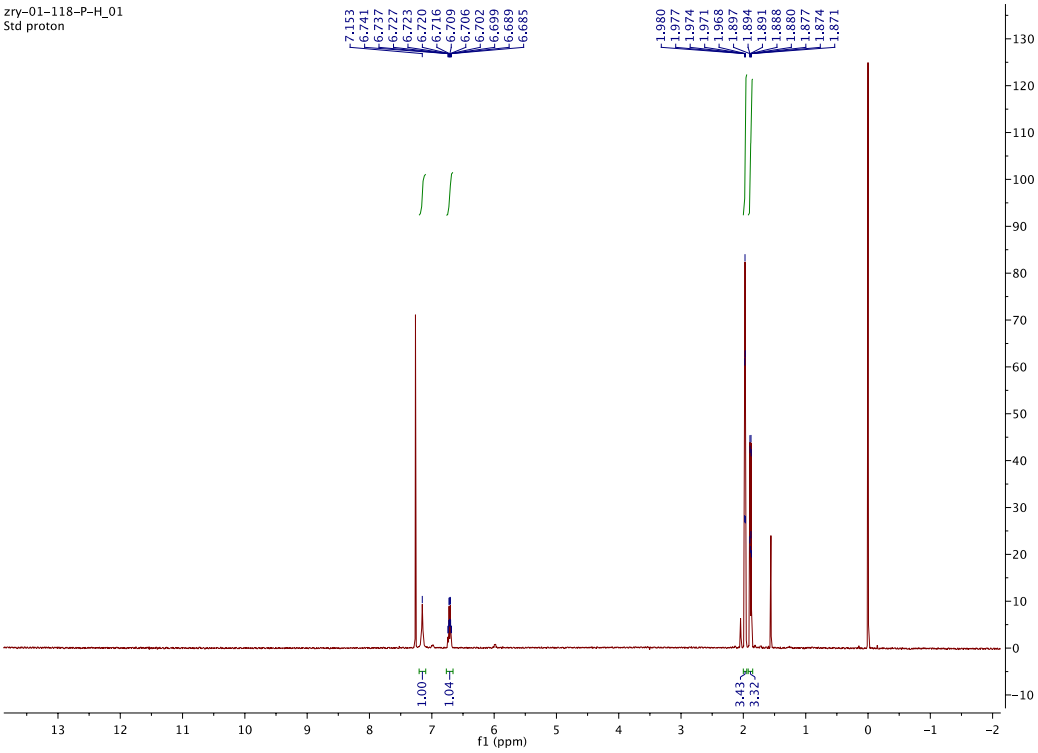
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6.699
6.689
6.685
1.980
1.977
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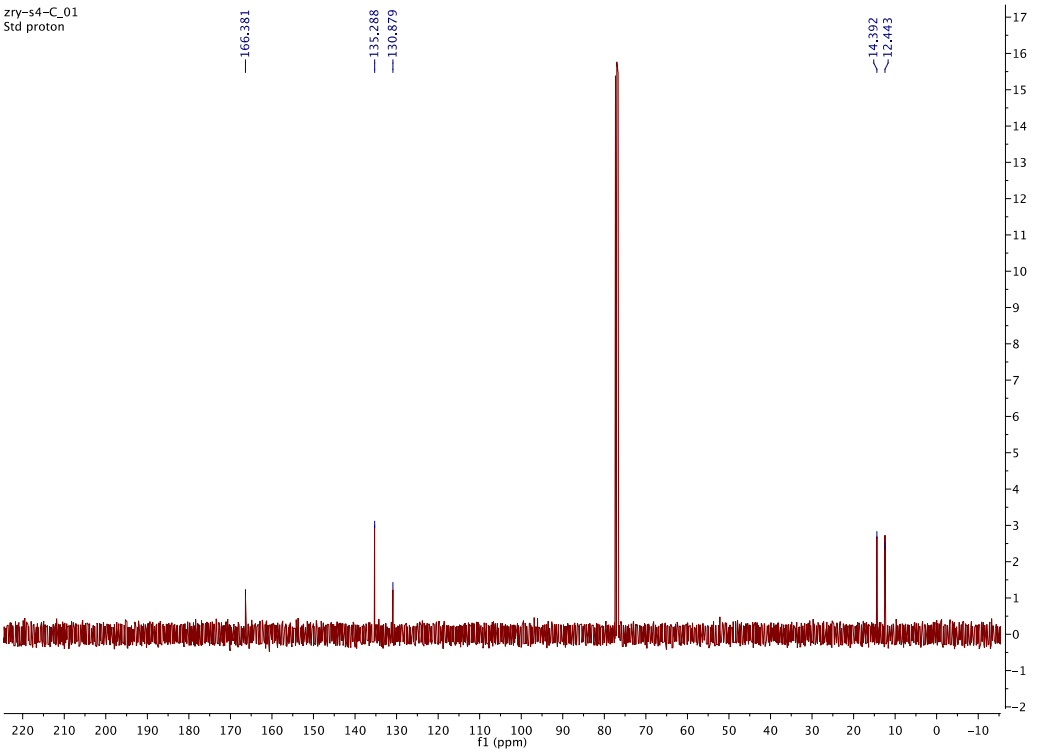
3.32
f1 (ppm)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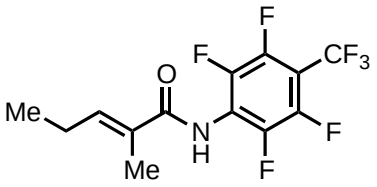
f1 (ppm)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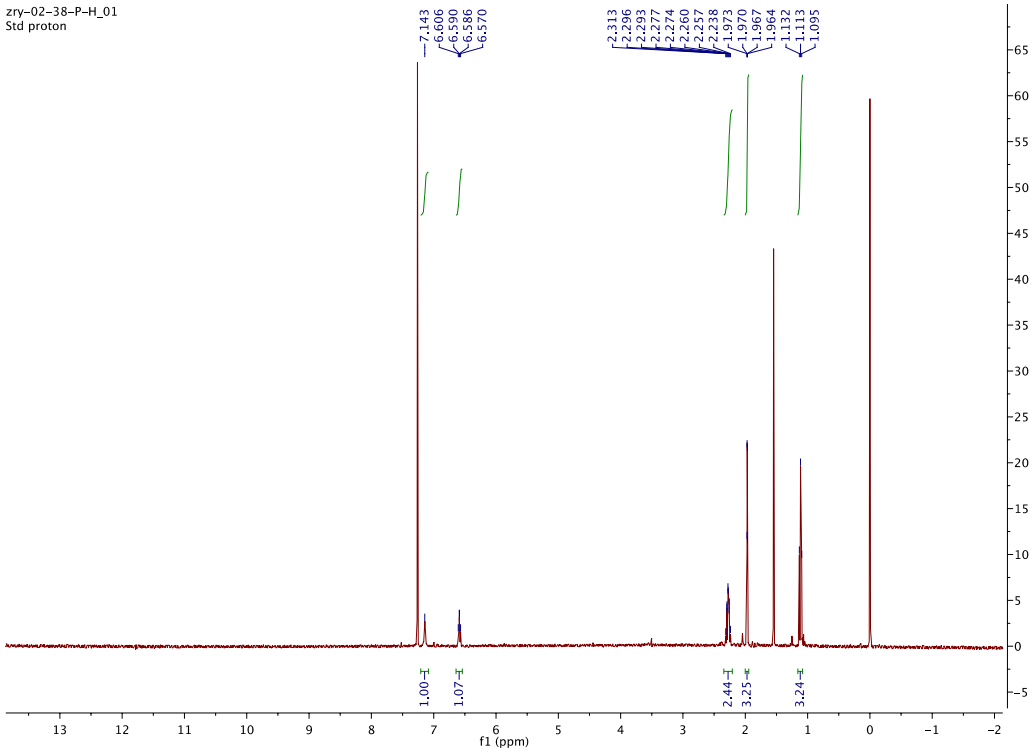
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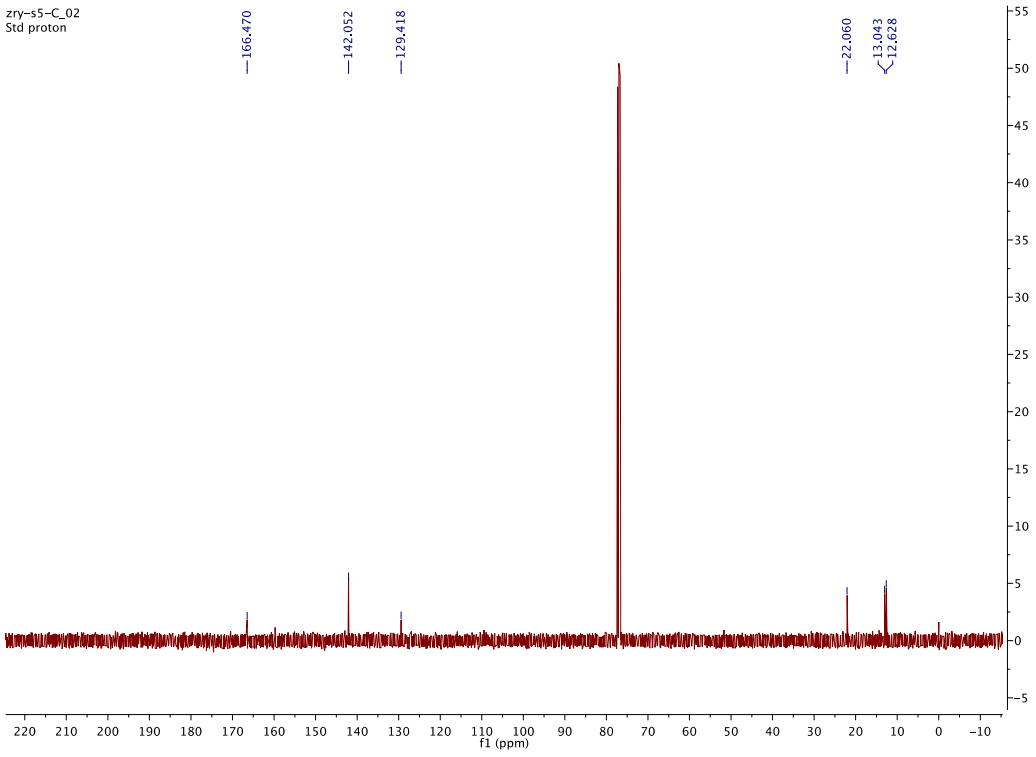
3.24
f1 (ppm)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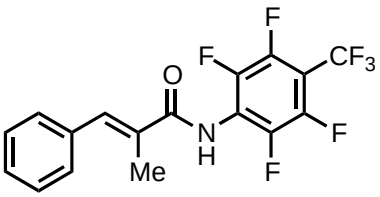
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N
H
F
Me
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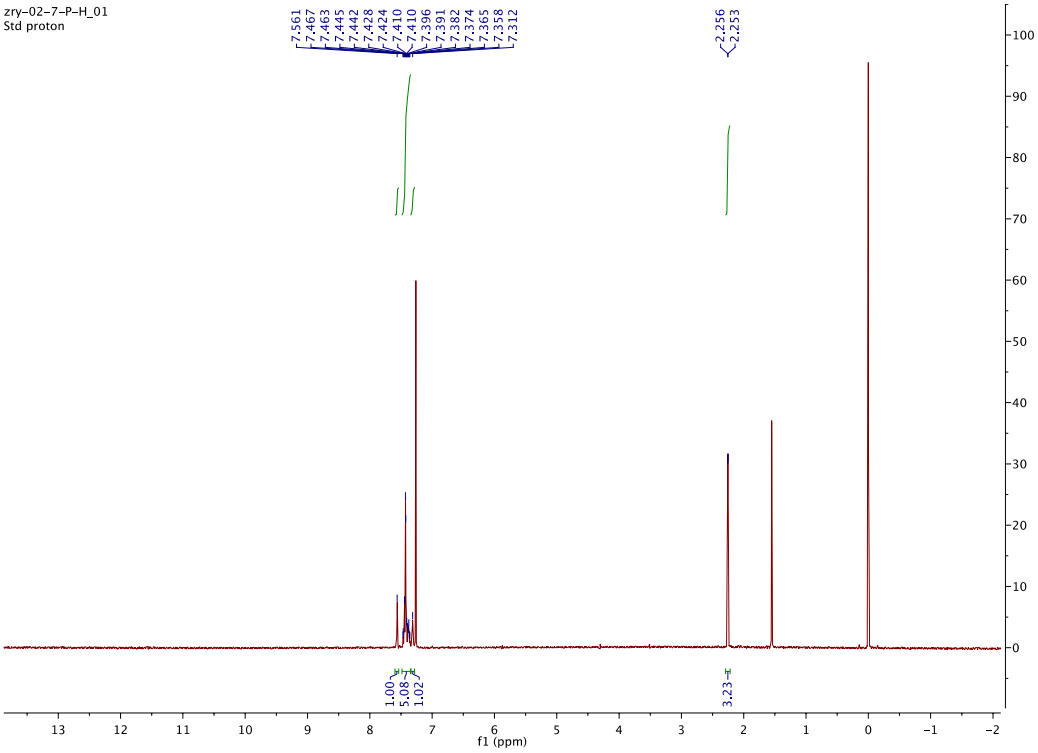
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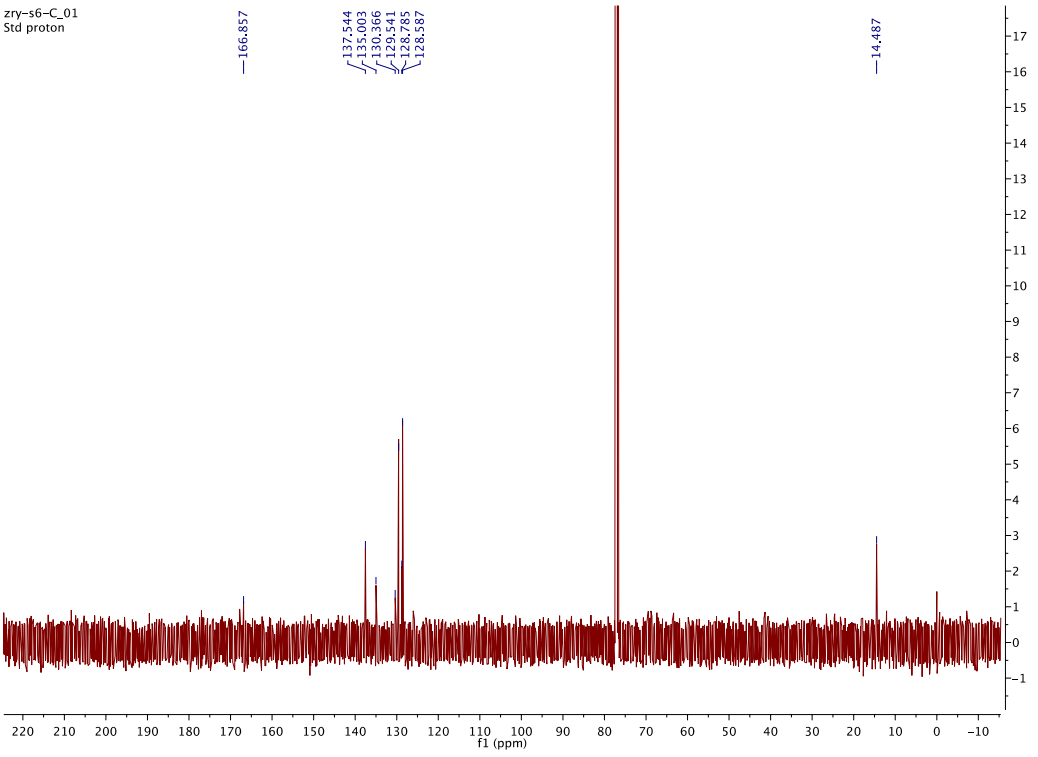
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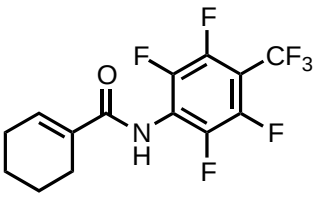
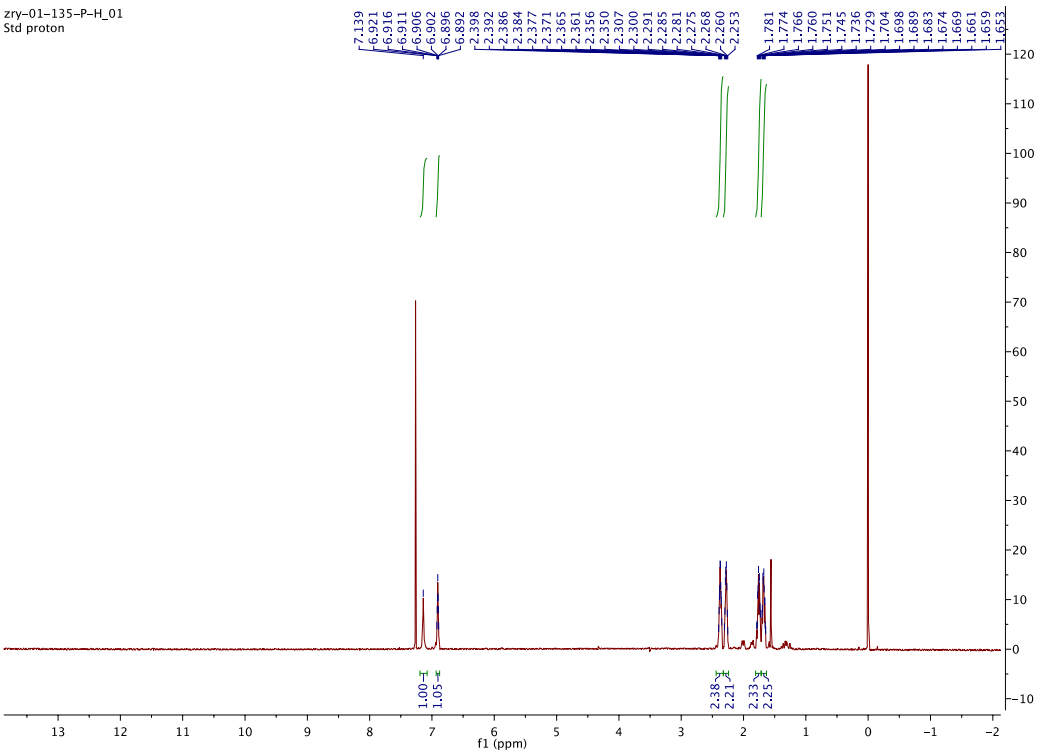
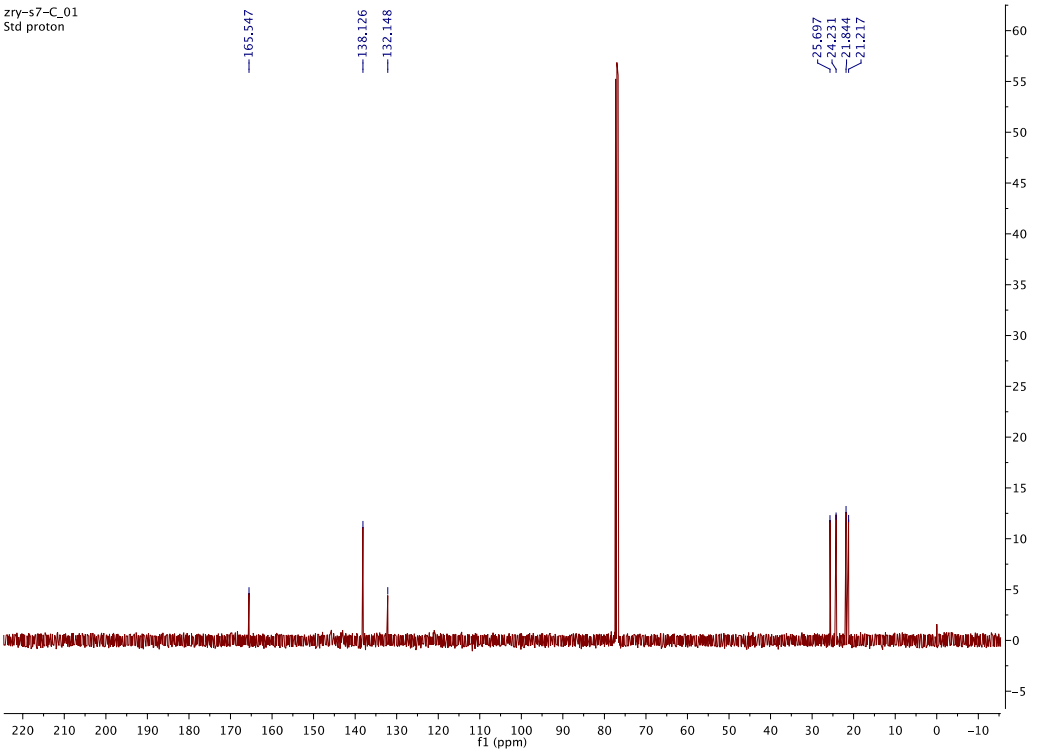
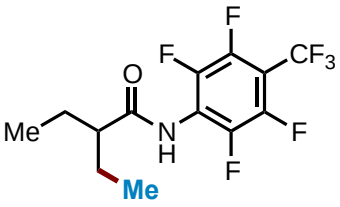
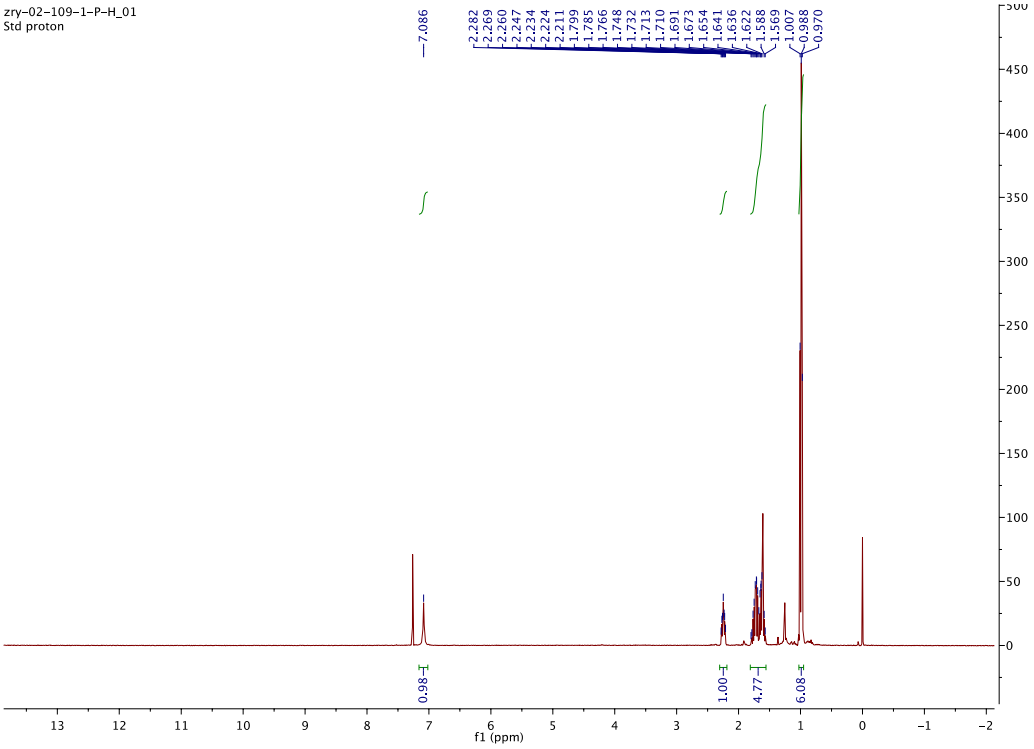
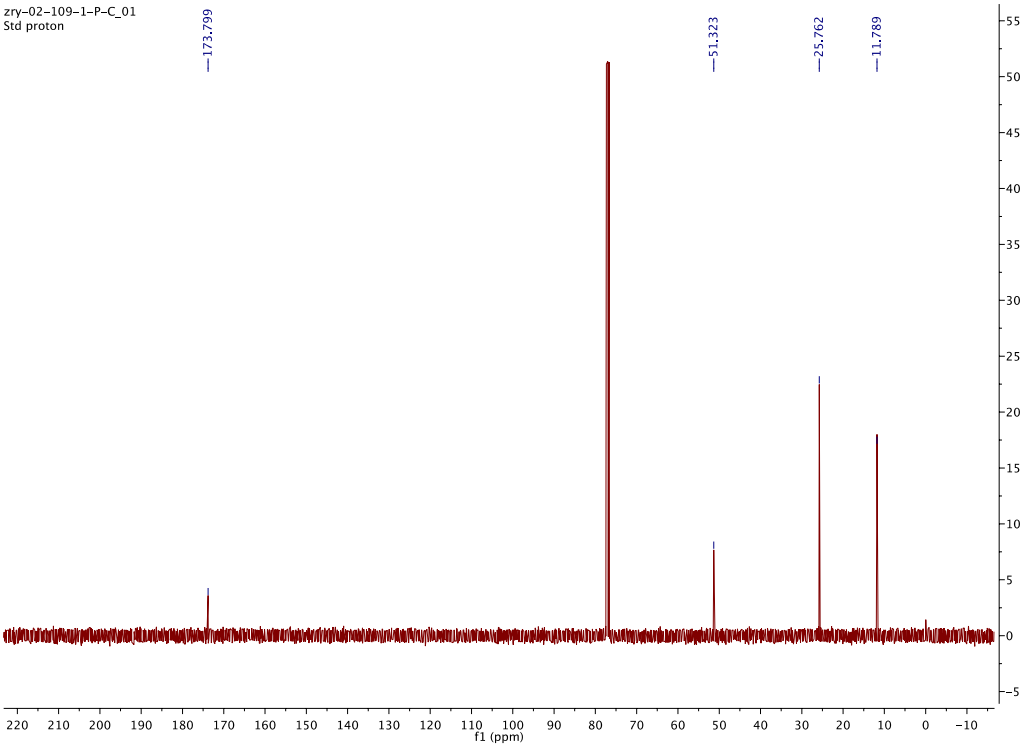

F
F
CF3
O
N
H
F
F

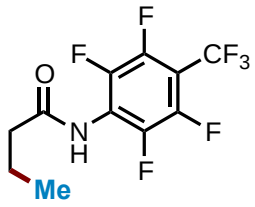

zry-01-135-P-H_01
Std proton
7.139
6.921
6.916
6.911
6.906
6.902
6.896
6.892
2.398
2.392
2.386
2.384
2.377
2.371
2.365
2.361
2.356
2.350
2.307
2.300
2.291
2.285
2.281
2.275
2.268
2.260
2.253
1.781
1.774
1.766
1.760
1.751
1.745
1.736
1.729
1.704
1.698
1.689
1.683
1.674
1.669
1.661
1.659
1.653
1.00
1.05
2.38
2.21
2.33
2.25
f1 (ppm)

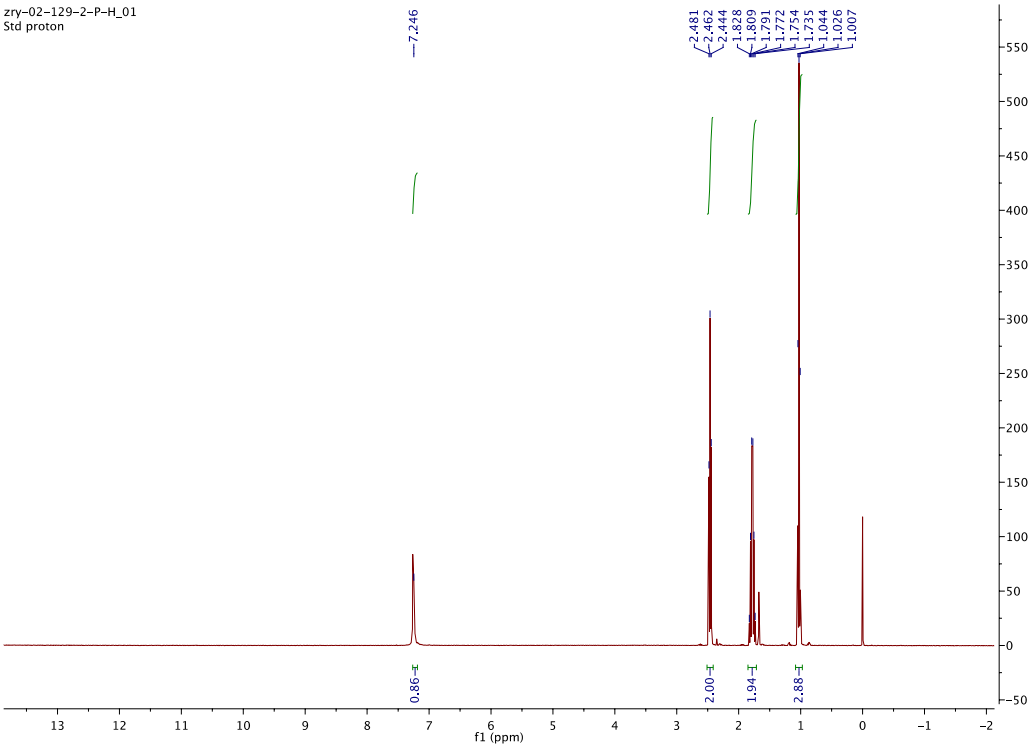

zry-s7-C_01
Std proton
165.547
138.126
132.148
25.697
24.231
21.844
21.217
f1 (ppm)

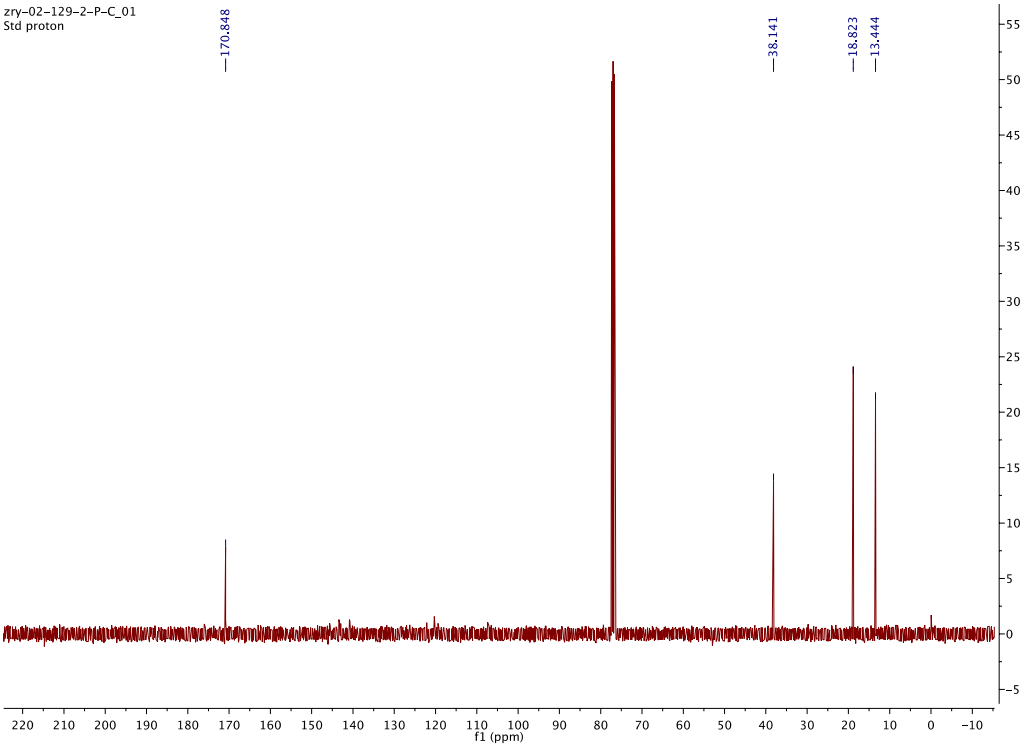

F
F
CF3
O
Me
N
H
F
F
Me

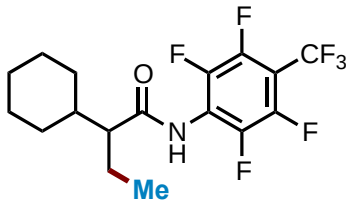

zry-02-109-1-P-H_01
Std proton
7.086
2.282
2.269
2.260
2.247
2.234
2.224
2.211
1.799
1.785
1.766
1.748
1.732
1.713
1.710
1.691
1.673
1.654
1.641
1.636
1.622
1.588
1.569
1.007
0.988
0.970
0.98
1.00
4.77
6.08
f1 (ppm)

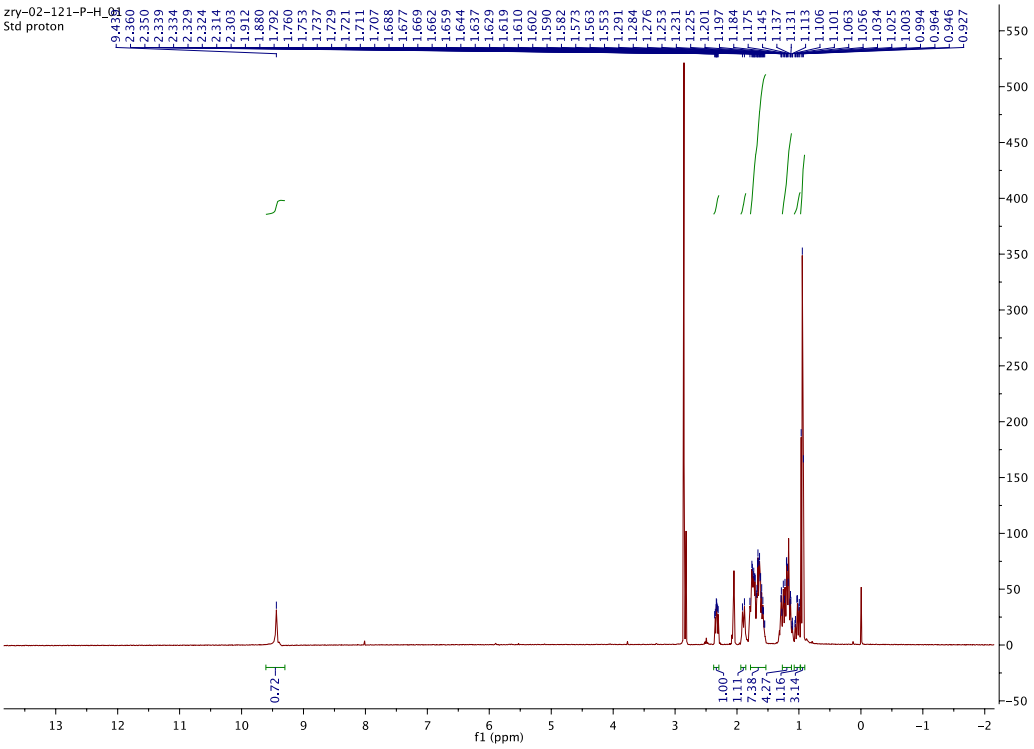

zry-02-109-1-P-C_01
Std proton
173.799
51.323
25.762
11.789
f1 (ppm)

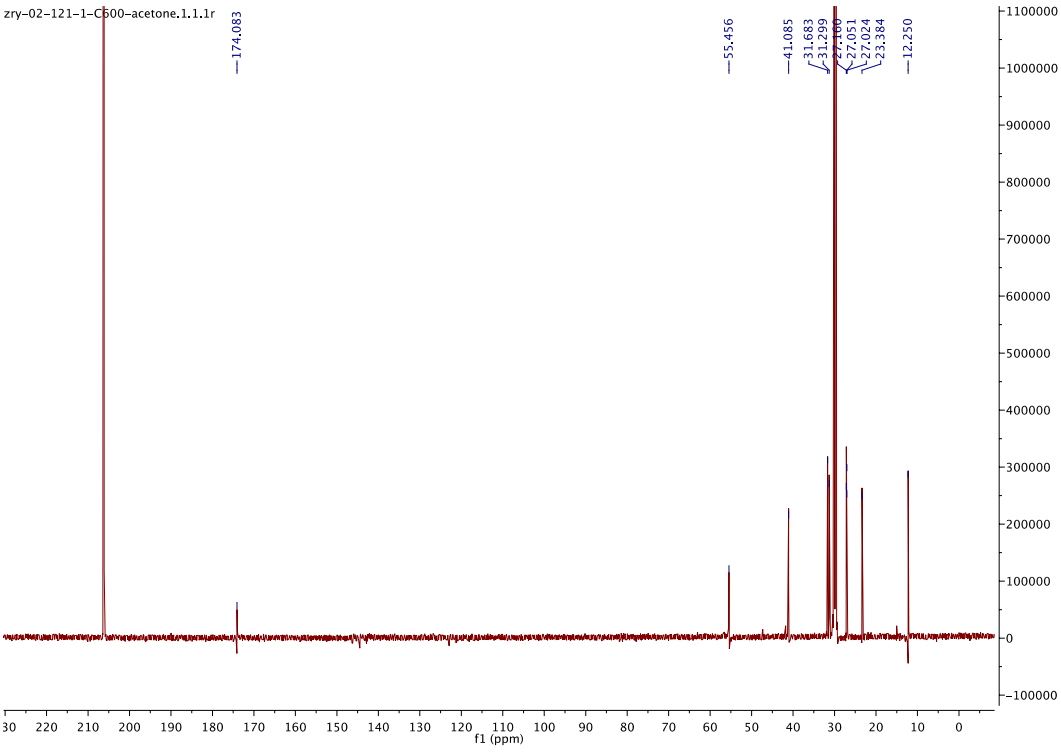

F
F
CF3
O
N
H
F
F
Me

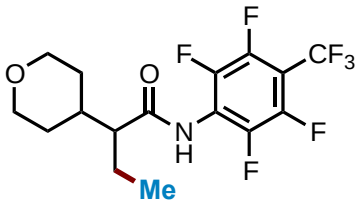

zry-02-129-2-P-H_01
Std proton
7.246
2.481
2.462
2.444
1.828
1.809
1.791
1.772
1.754
1.735
1.044
1.026
1.007
0.86
2.00
1.94
2.88
f1 (ppm)

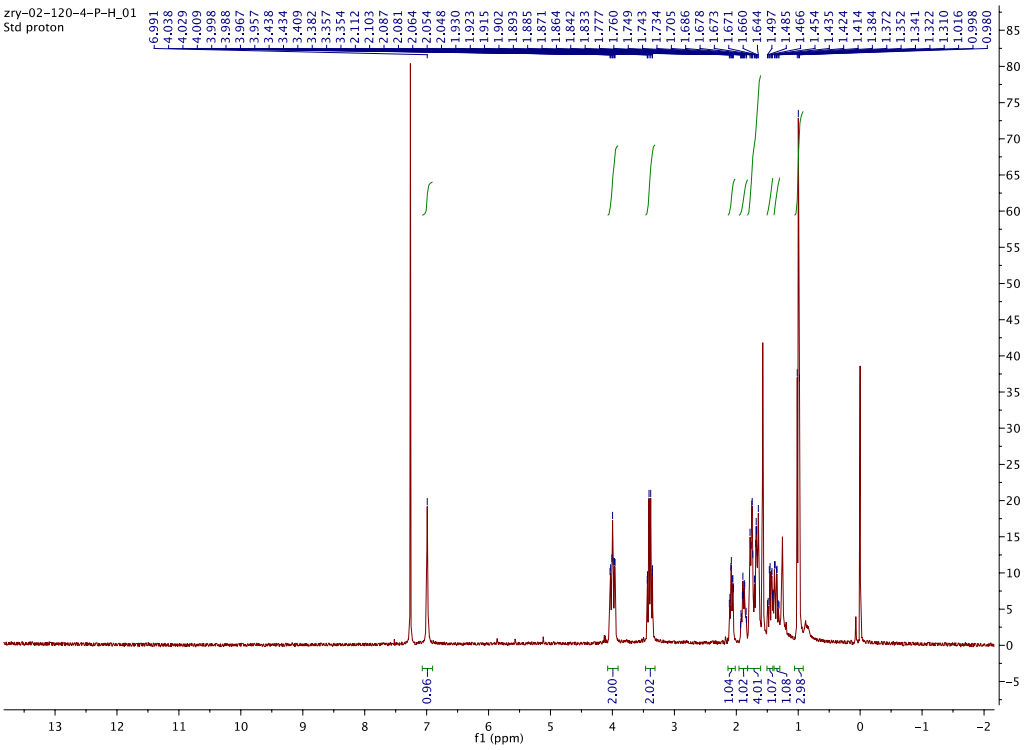

zry-02-129-2-P-C_01
Std proton
170.848
38.141
18.823
13.444
f1 (ppm)

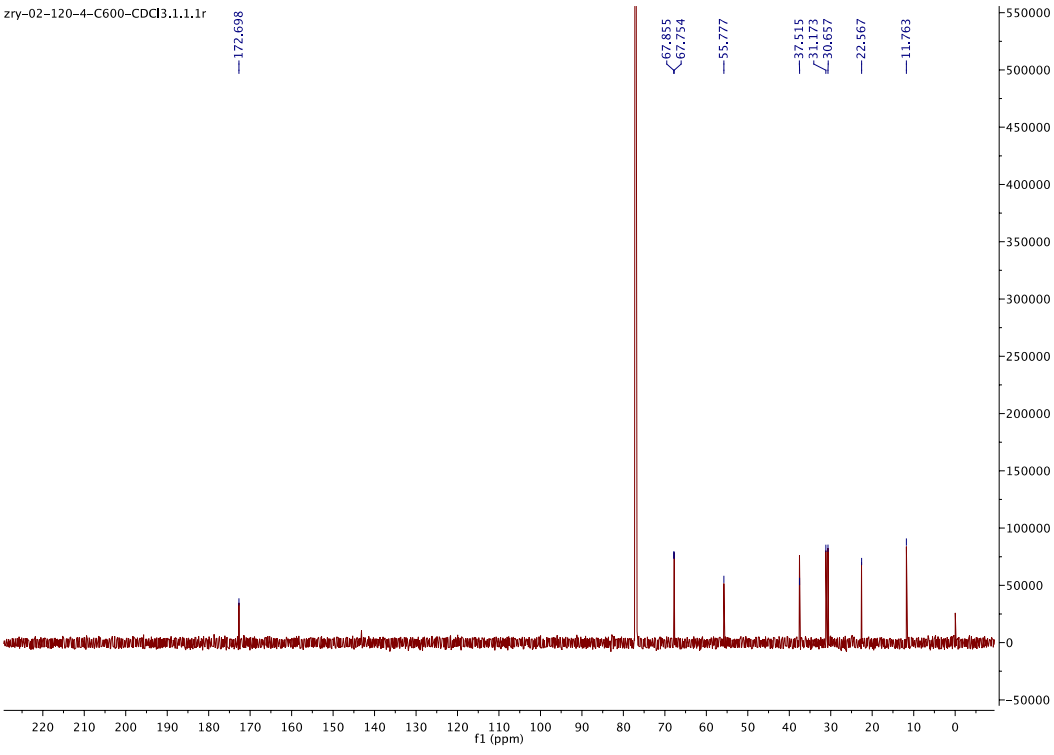

F
F
CF3
O
N
H
F
F
Me

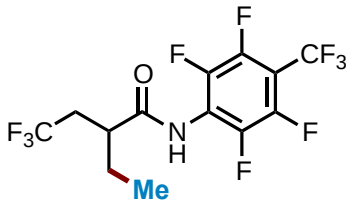

zry-02-121-P-H_01
Std proton
f1 (ppm)

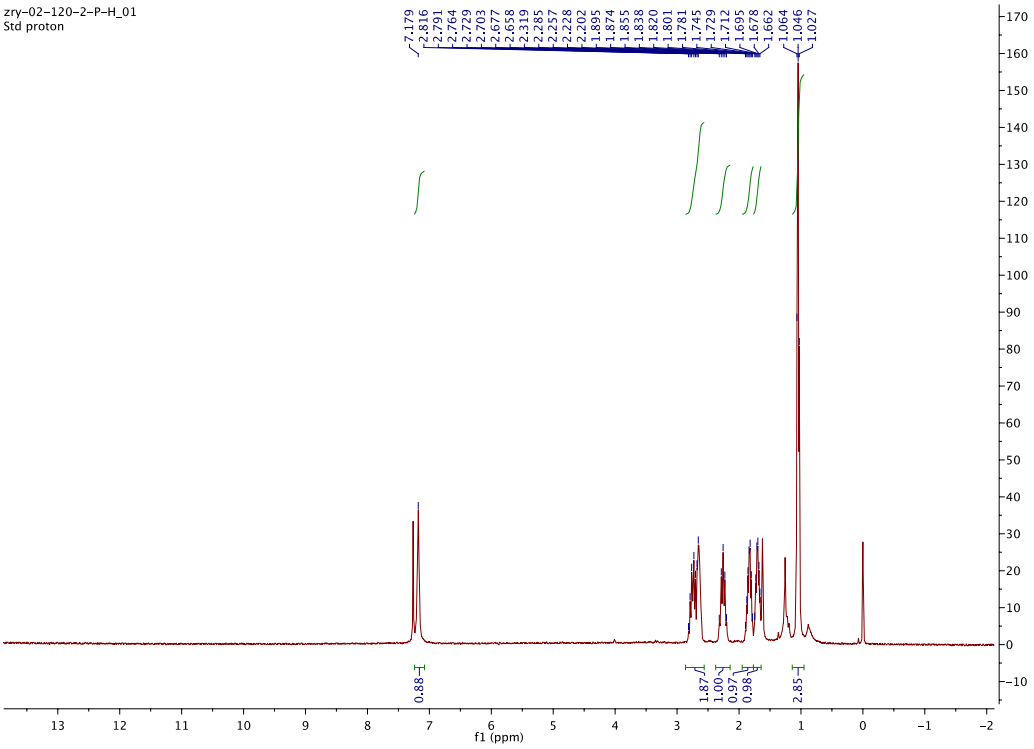

zry-02-121-1-C600-acetone.1.1.1r
174.083
55.456
41.085
31.683
31.299
27.660
27.051
27.024
23.384
12.250
f1 (ppm)

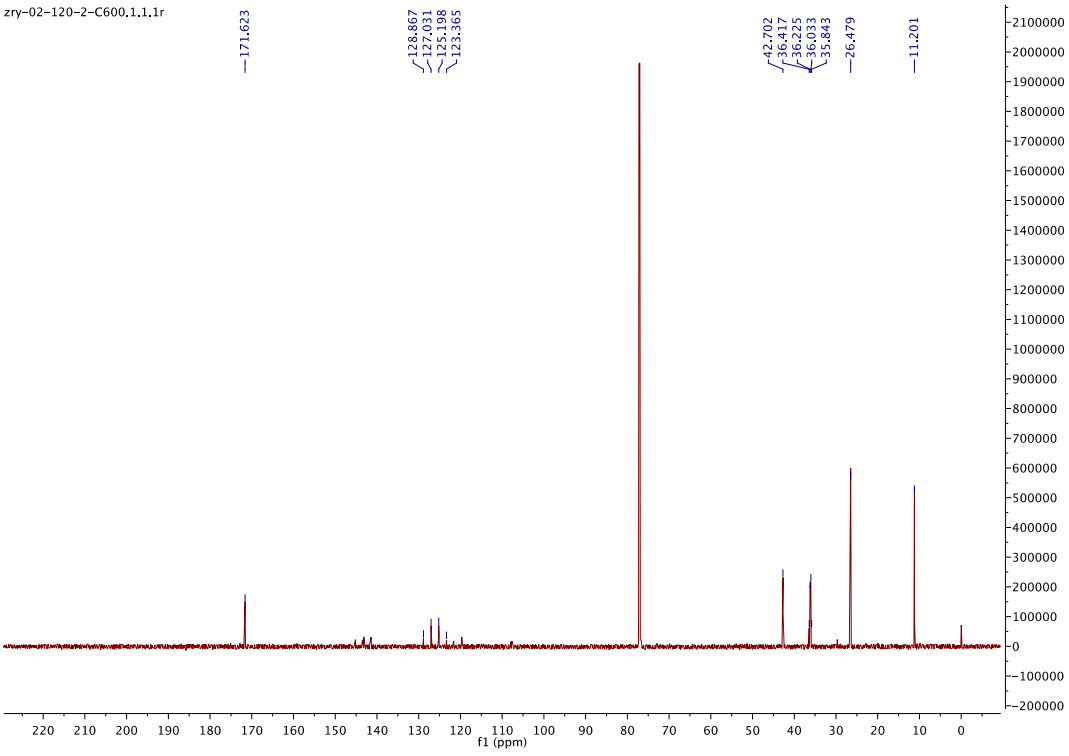

F
F
CF3
O
O
N
H
F
F
Me

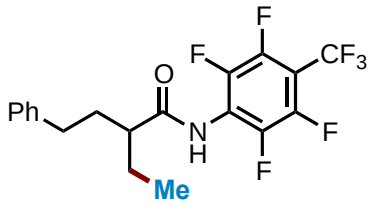

zry-02-120-4-P-H_01
Std proton
f1 (ppm)

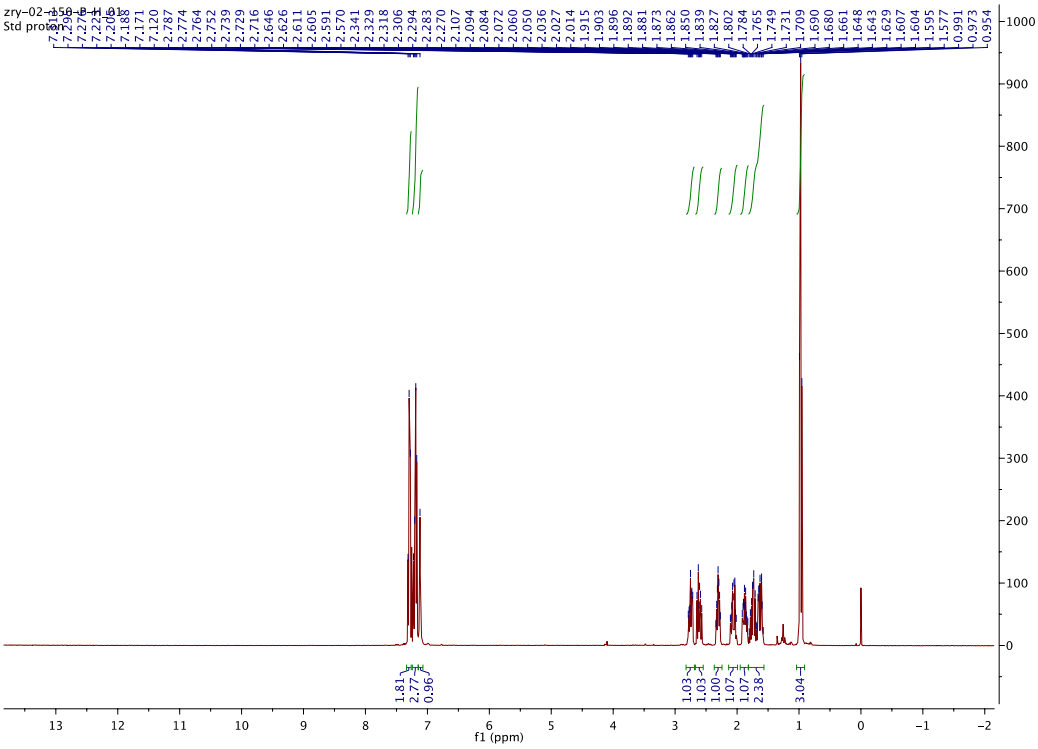

zry-02-120-4-C600-CDCl3.1.1.1r
172.698
67.855
67.754
55.777
37.515
31.173
30.657
22.567
11.763
f1 (ppm)

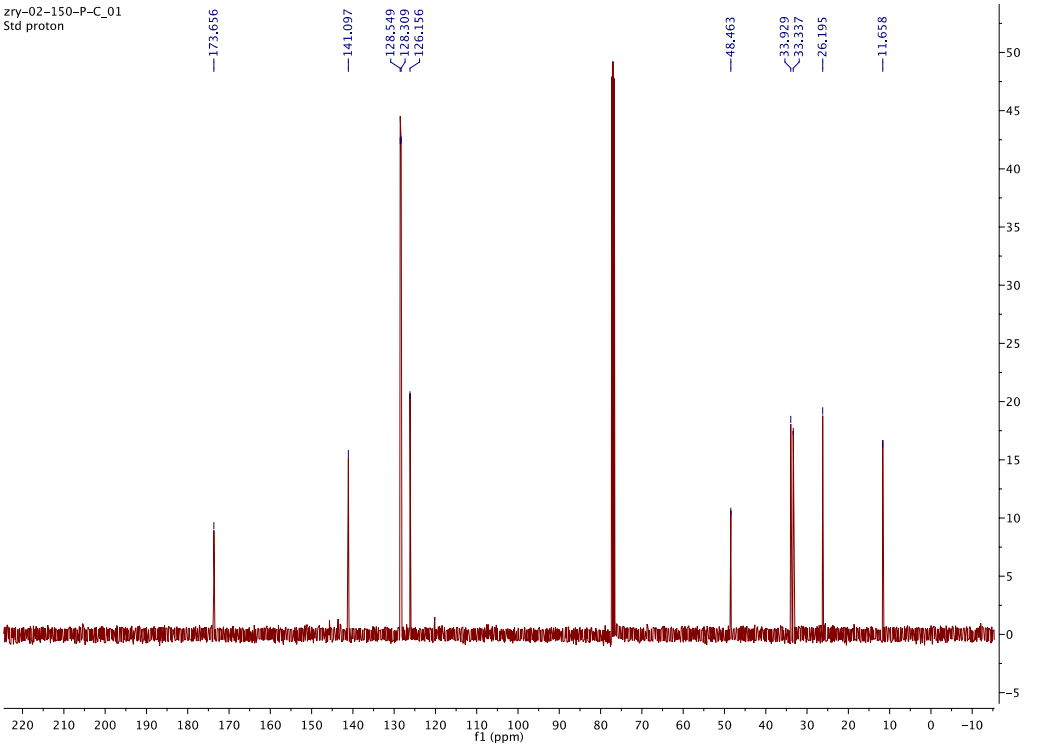

F
F
CF3
O
F3C
N
H
F
F
Me

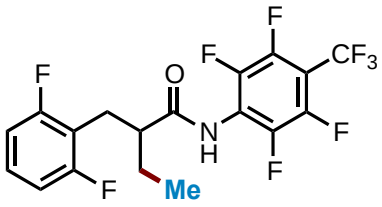

zry-02-120-2-P-H_01
Std proton
7.179
2.816
2.791
2.764
2.729
2.703
2.677
2.658
2.319
2.285
2.257
2.228
2.202
1.895
1.874
1.855
1.838
1.820
1.801
1.781
1.745
1.729
1.712
1.695
1.678
1.662
1.064
1.046
1.027
0.88
1.87
1.00
0.97
0.98
2.85
f1 (ppm)

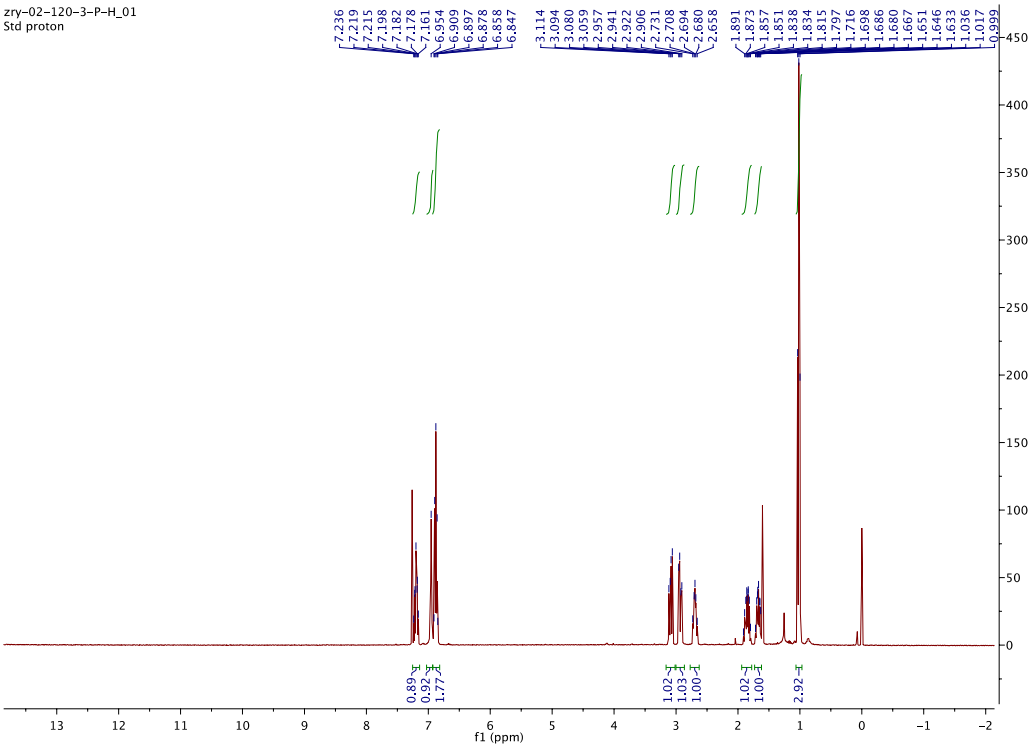

zry-02-120-2-C600.1.1.1r
171.623
128.867
127.031
125.198
123.365
42.702
36.417
36.225
36.033
35.843
26.479
11.201
f1 (ppm)

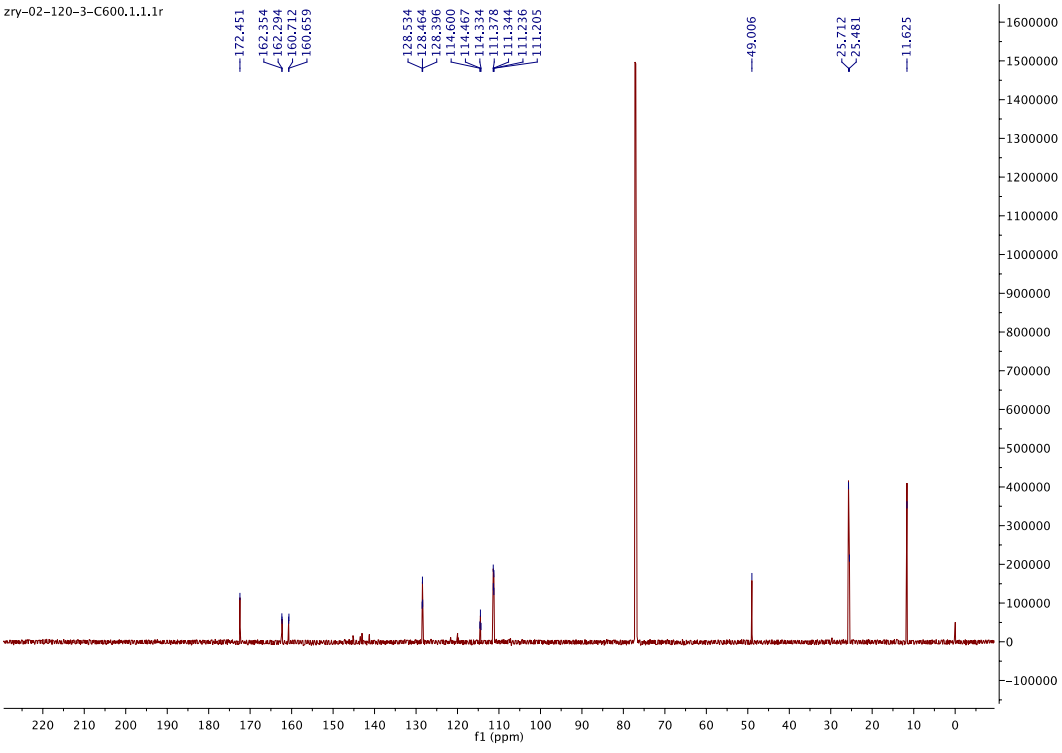

F
F
CF3
O
Ph
N
H
F
F
Me

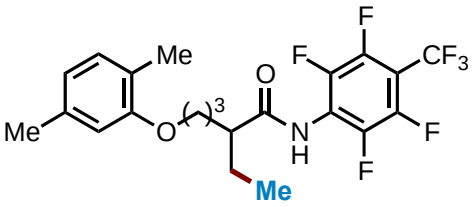

zry-02-150-P-H_01
Std proton
1.81
2.77
0.96
1.03
1.03
1.00
1.07
1.07
2.38
3.04
f1 (ppm)

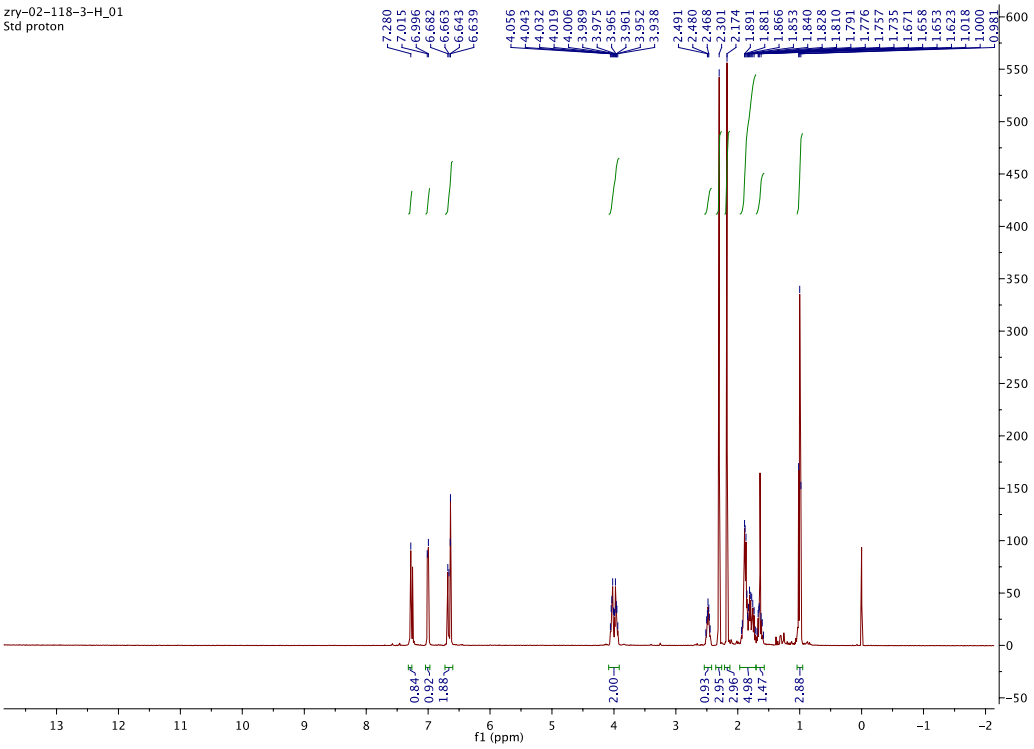

zry-02-150-P-C_01
Std proton
173.656
141.097
128.549
128.309
126.156
48.463
33.929
33.337
26.195
11.658
f1 (ppm)

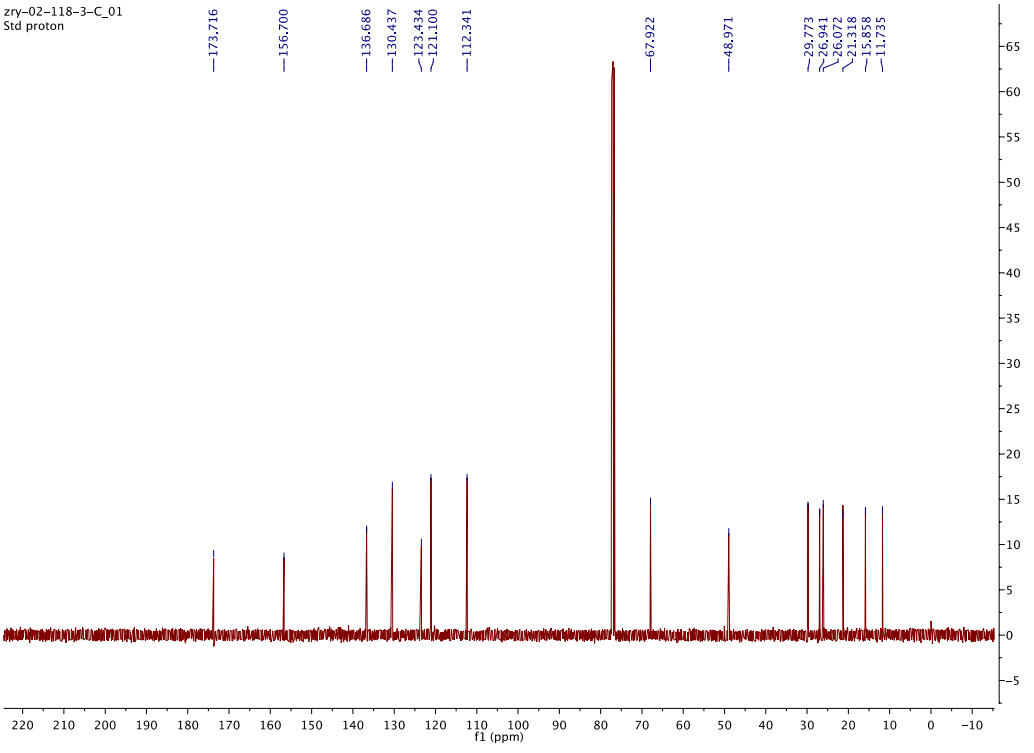

F
O
F
F
CF3
N
H
F
F
F
Me

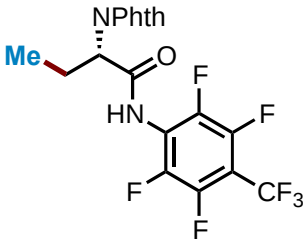

zry-02-120-3-P-H_01
Std proton
7.236
7.219
7.215
7.198
7.182
7.178
7.161
6.954
6.909
6.897
6.878
6.858
6.847
3.114
3.094
3.080
3.059
2.957
2.941
2.922
2.906
2.731
2.708
2.694
2.680
2.658
1.891
1.873
1.857
1.851
1.838
1.834
1.815
1.797
1.716
1.698
1.686
1.680
1.667
1.651
1.646
1.633
1.036
1.017
0.999
0.89
0.92
1.77
1.02
1.03
1.00
1.02
1.00
2.92
f1 (ppm)

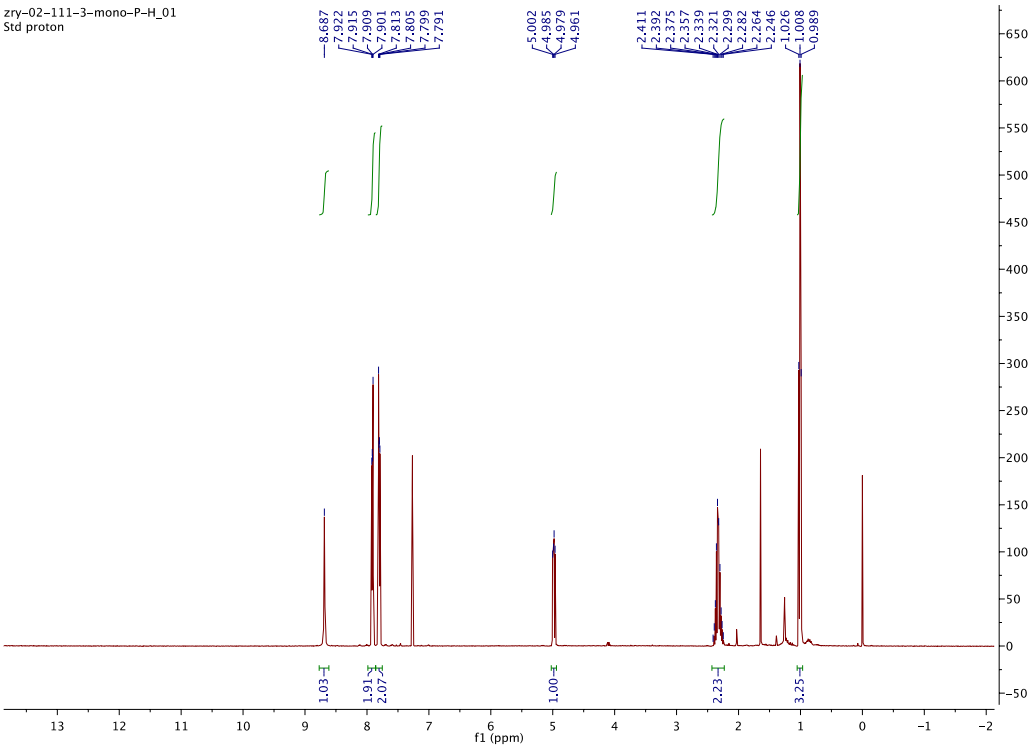

zry-02-120-3-C600.1.1.1r
172.451
162.354
162.294
160.712
160.659
128.534
128.464
128.396
114.600
114.467
114.334
111.378
111.344
111.236
111.205
49.006
25.712
25.481
11.625
f1 (ppm)

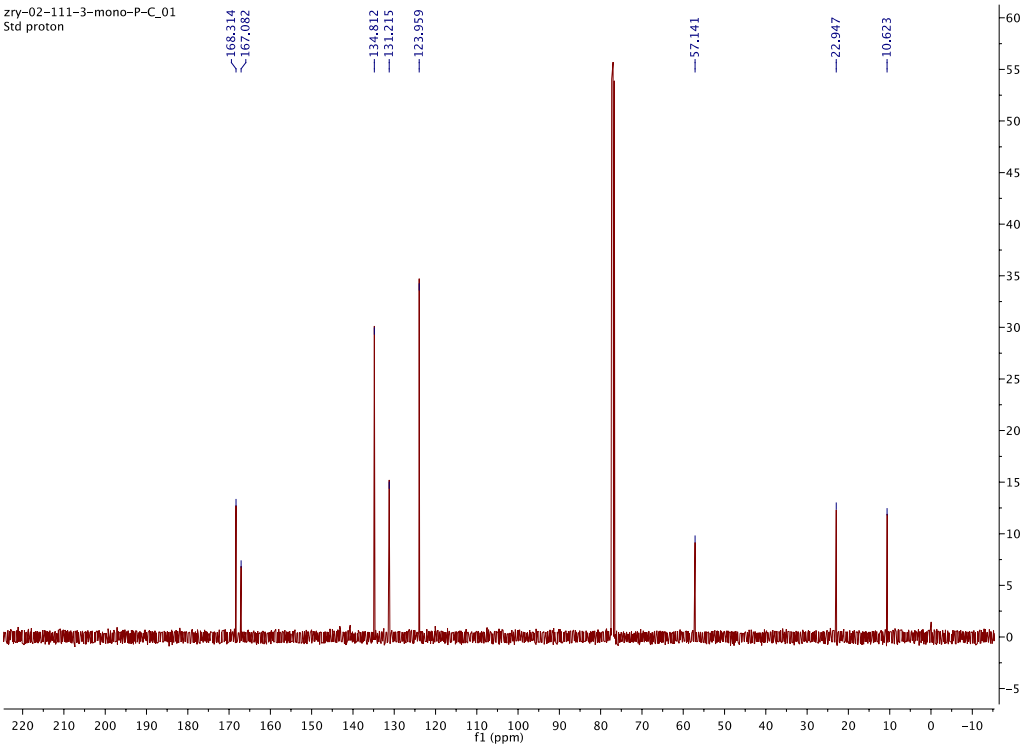

F
Me
F
CF3
O
3
O
N
H
F
Me
F
Me

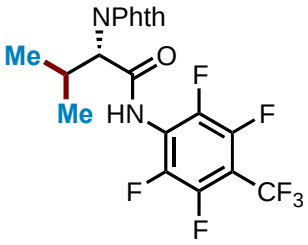

zry-02-118-3-H_01
Std proton
f1 (ppm)

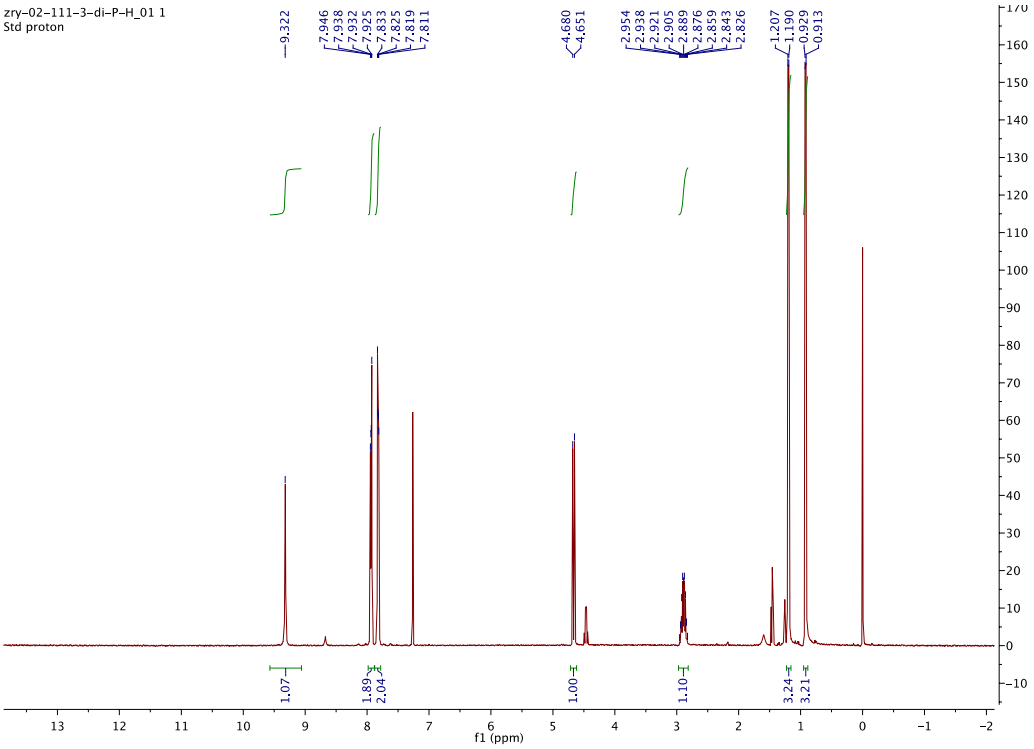

zry-02-118-3-C_01
Std proton
173.716
156.700
136.686
130.437
123.434
121.100
112.341
67.922
48.971
29.773
26.941
26.072
21.318
15.858
11.735
f1 (ppm)

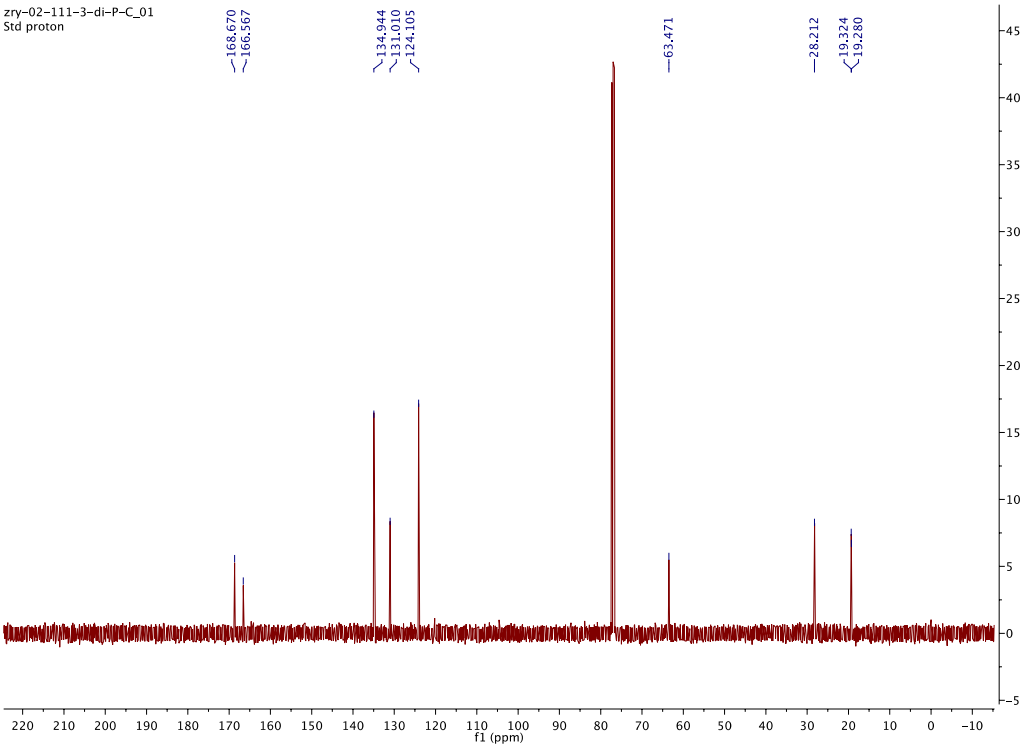

NPhth
Me
O
HN
F
F
F
F
CF3

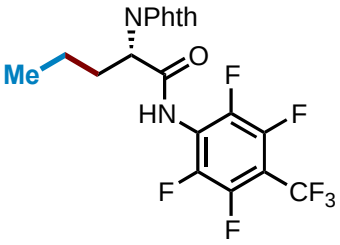

zry-02-111-3-mono-P-H_01
Std proton
8.687
7.922
7.915
7.909
7.901
7.813
7.805
7.799
7.791
5.002
4.985
4.979
4.961
2.411
2.392
2.375
2.357
2.339
2.321
2.299
2.282
2.264
2.246
1.026
1.008
0.989
1.03
1.91
2.07
1.00
2.23
3.25
f1 (ppm)

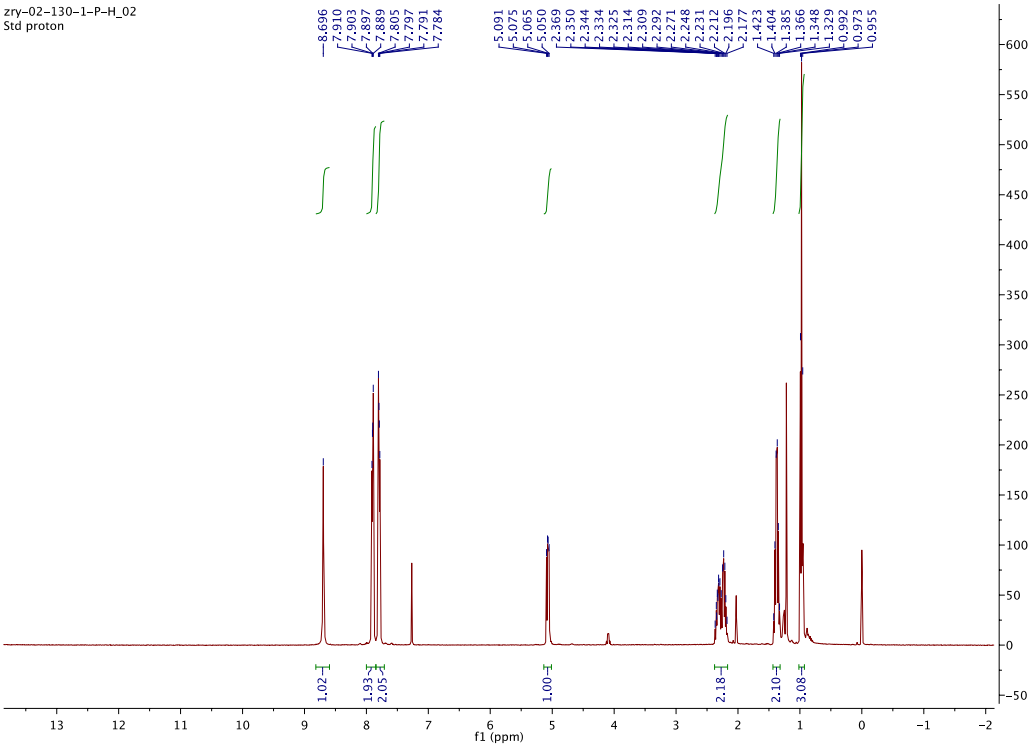

zry-02-111-3-mono-P-C_01
Std proton
168.314
167.082
134.812
131.215
123.959
57.141
22.947
10.623
f1 (ppm)

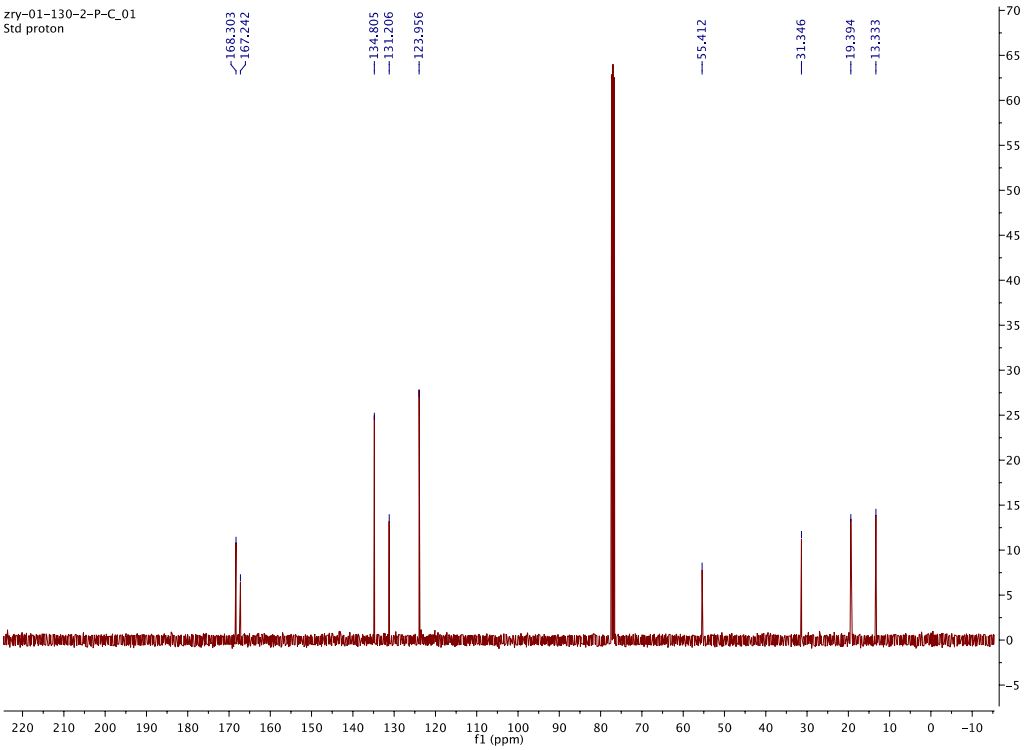

NPhth
Me
O
F
Me
HN
F
F
CF3
F

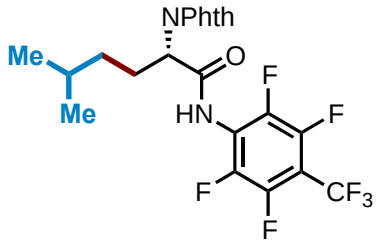

zry-02-111-3-di-P-H_01 1
Std proton
9.322
7.946
7.938
7.932
7.925
7.833
7.825
7.819
7.811
4.680
4.651
2.954
2.938
2.921
2.905
2.889
2.876
2.859
2.843
2.826
1.207
1.190
0.929
0.913
1.07
1.89
2.04
1.00
1.10
3.24
3.21
f1 (ppm)

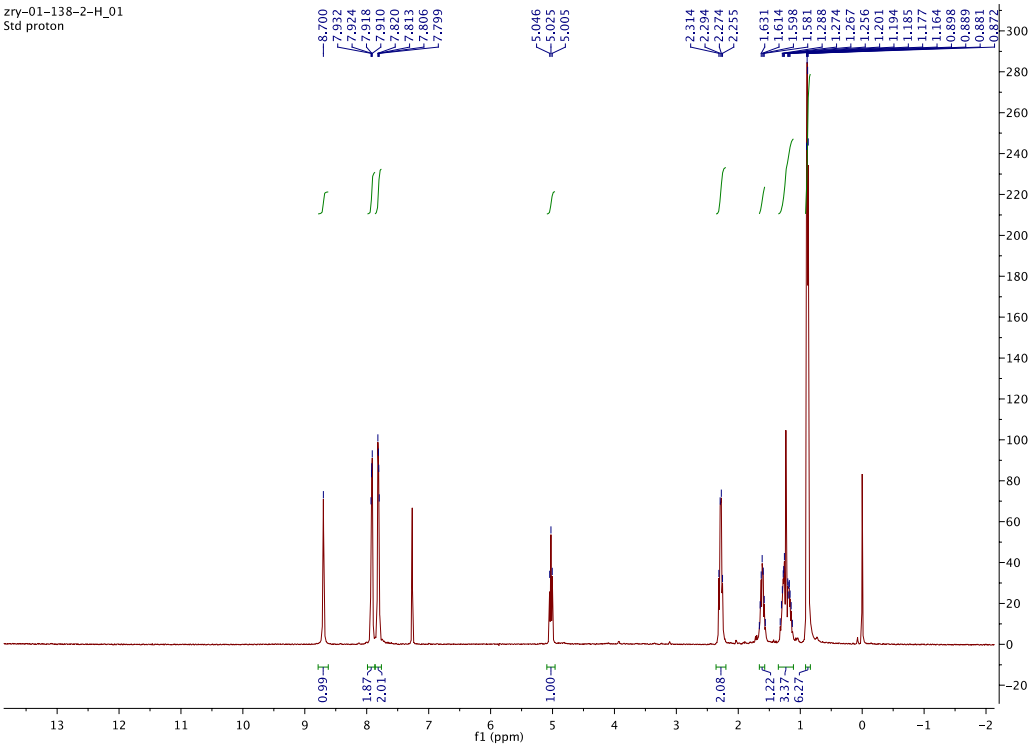

zry-02-111-3-di-P-C_01
Std proton
168.670
166.567
134.944
131.010
124.105
63.471
28.212
19.324
19.280
f1 (ppm)

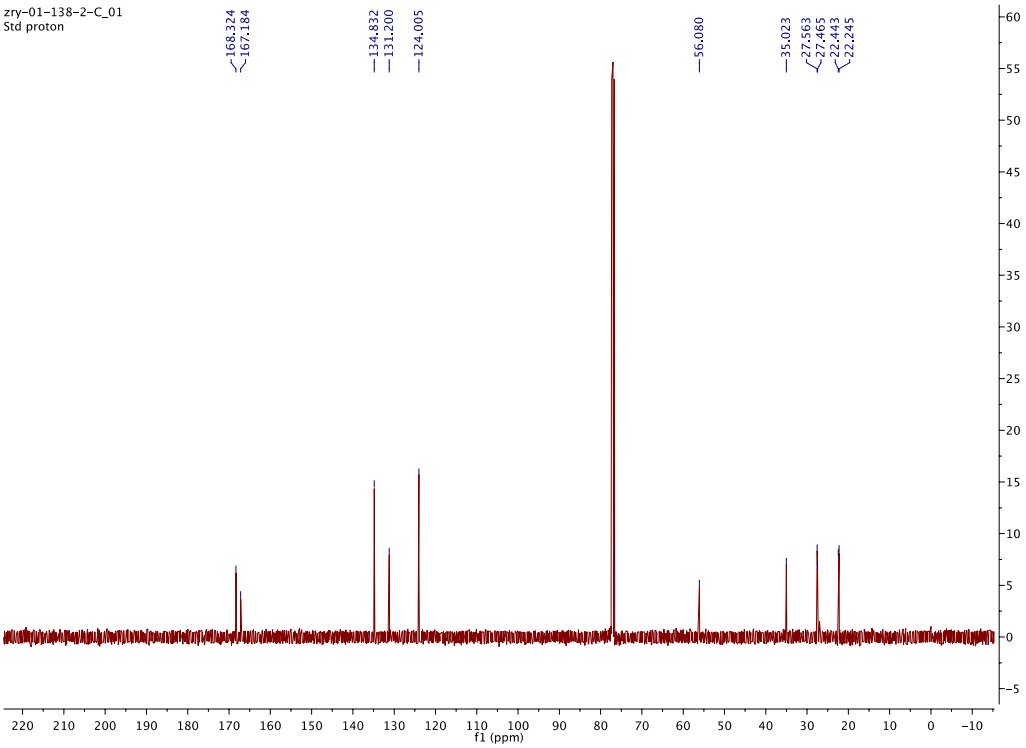

NPhth
Me
O
HN
F
F
F
F
CF3

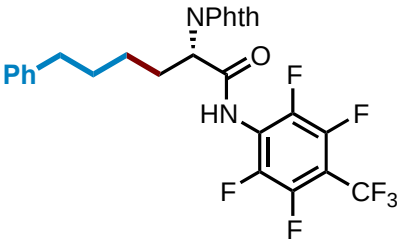

zry-02-130-1-P-H_02
Std proton
8.696
7.910
7.903
7.897
7.889
7.805
7.797
7.791
7.784
5.091
5.075
5.065
5.050
2.369
2.350
2.344
2.334
2.325
2.314
2.309
2.292
2.271
2.248
2.231
2.212
2.196
2.177
1.423
1.404
1.385
1.366
1.348
1.329
0.992
0.973
0.955
1.02
1.93
2.05
1.00
2.18
2.10
3.08
f1 (ppm)

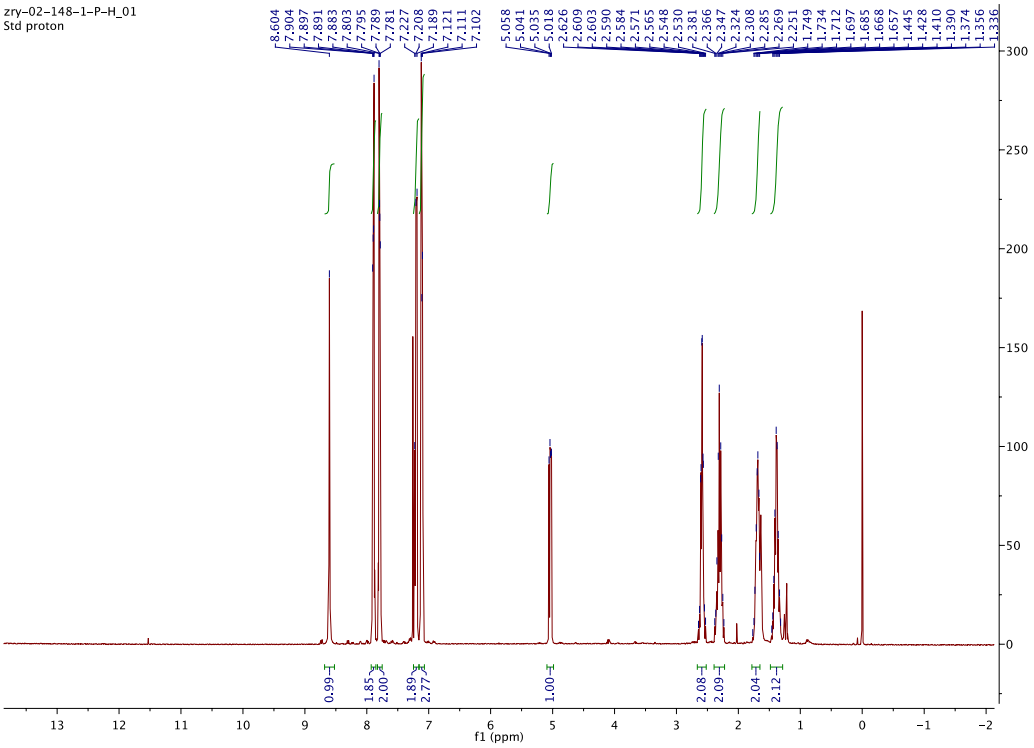

zry-01-130-2-P-C_01
Std proton
168.303
167.242
134.805
131.206
123.956
55.412
31.346
19.394
13.333
f1 (ppm)

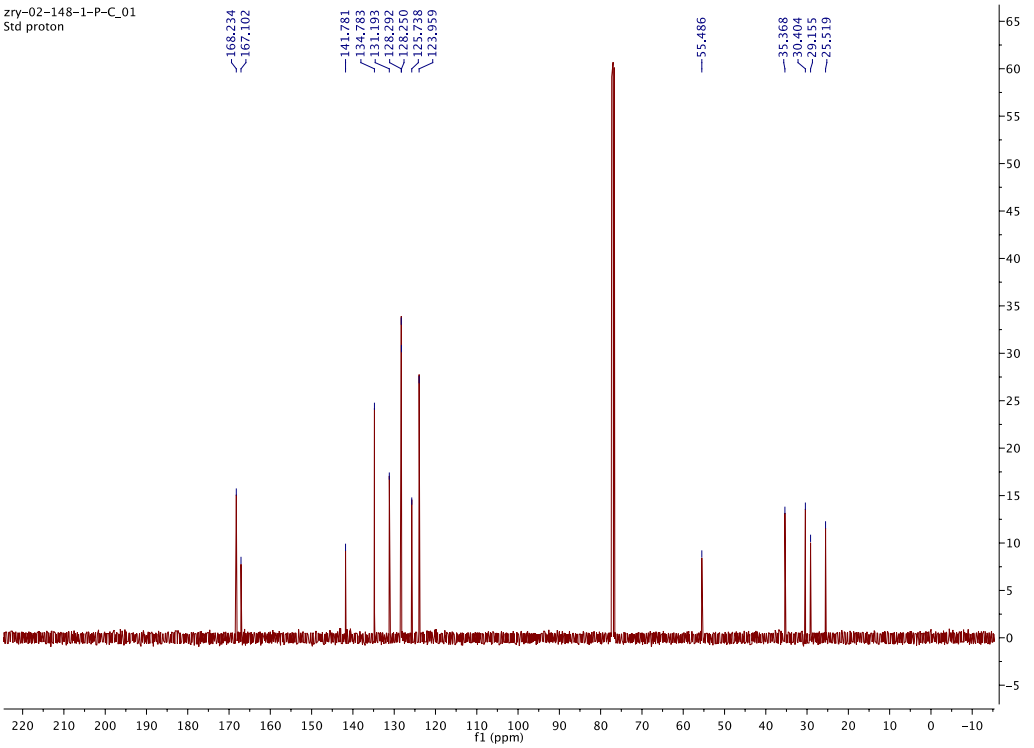

NPhth
Me
Me
O
HN
F
F
F
F
CF3

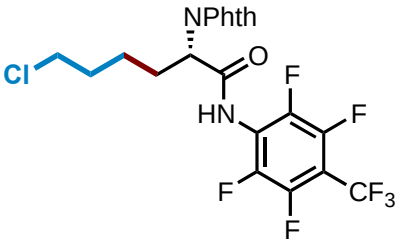

zry-01-138-2-H_01
Std proton
f1 (ppm)

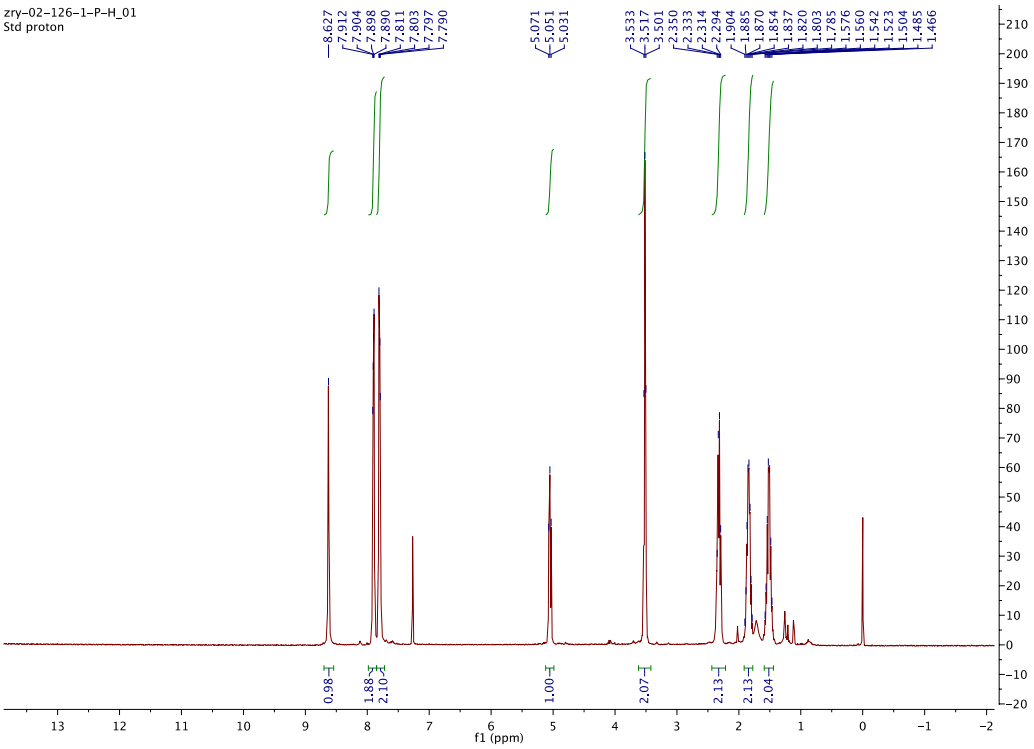

zry-01-138-2-C_01
Std proton
f1 (ppm)

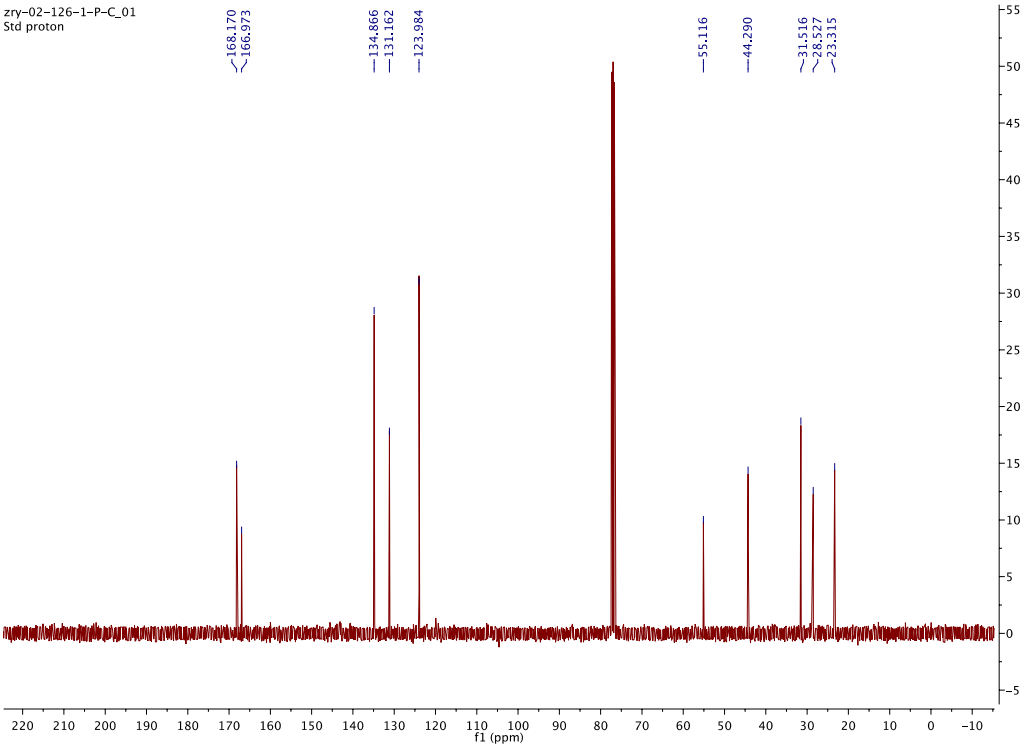

NPhth
Ph
O
HN
F
F
F
F
CF3

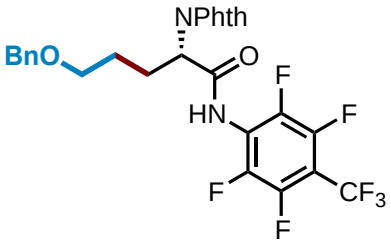

zry-02-148-1-P-H_01
Std proton
f1 (ppm)

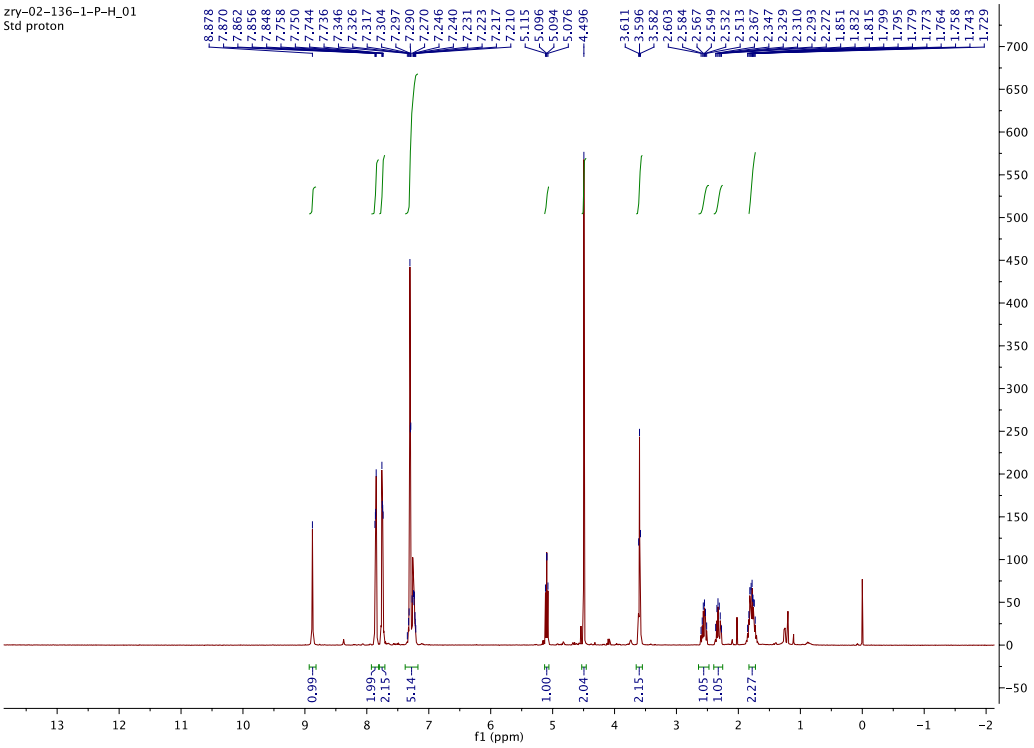

zry-02-148-1-P-C_01
Std proton
f1 (ppm)

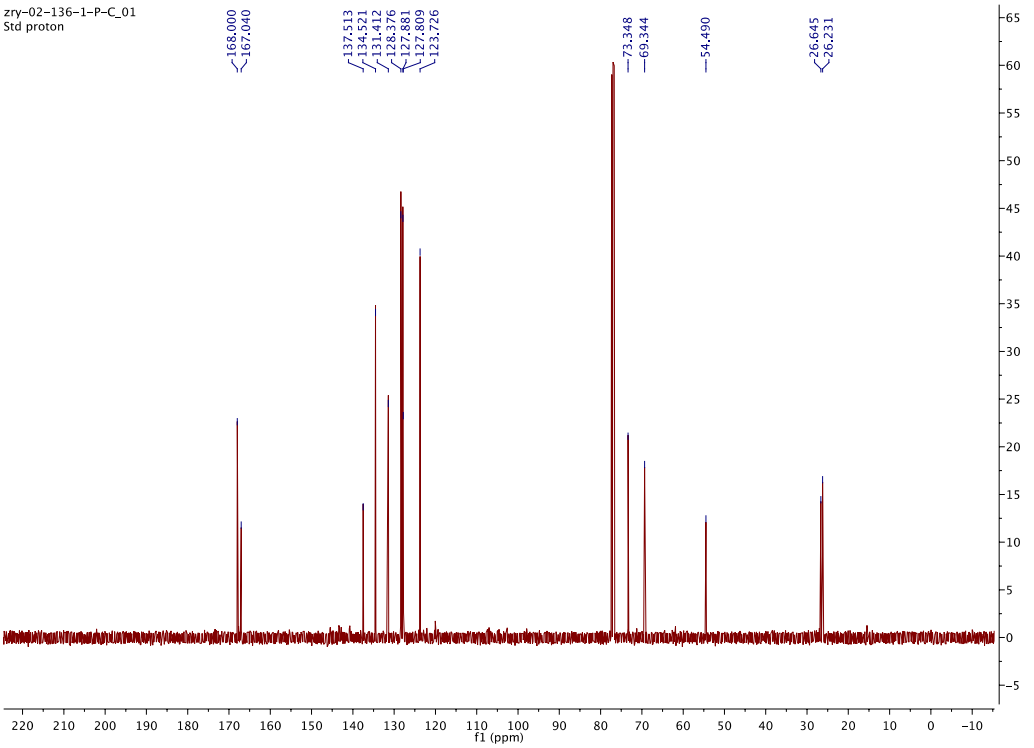

NPhth
Cl
O
HN
F
F
F
F
CF3

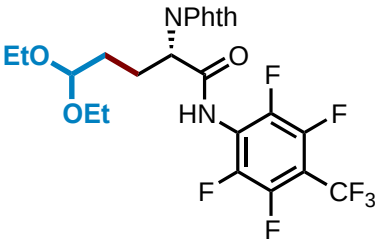

zry-02-126-1-P-H_01
Std proton
8.627
7.912
7.904
7.898
7.890
7.811
7.803
7.797
7.790
5.071
5.051
5.031
3.533
3.517
3.501
2.350
2.333
2.314
2.294
1.904
1.885
1.870
1.854
1.837
1.820
1.803
1.785
1.576
1.560
1.542
1.523
1.504
1.485
1.466
0.98
1.88
2.10
1.00
2.07
2.13
2.13
2.04
f1 (ppm)

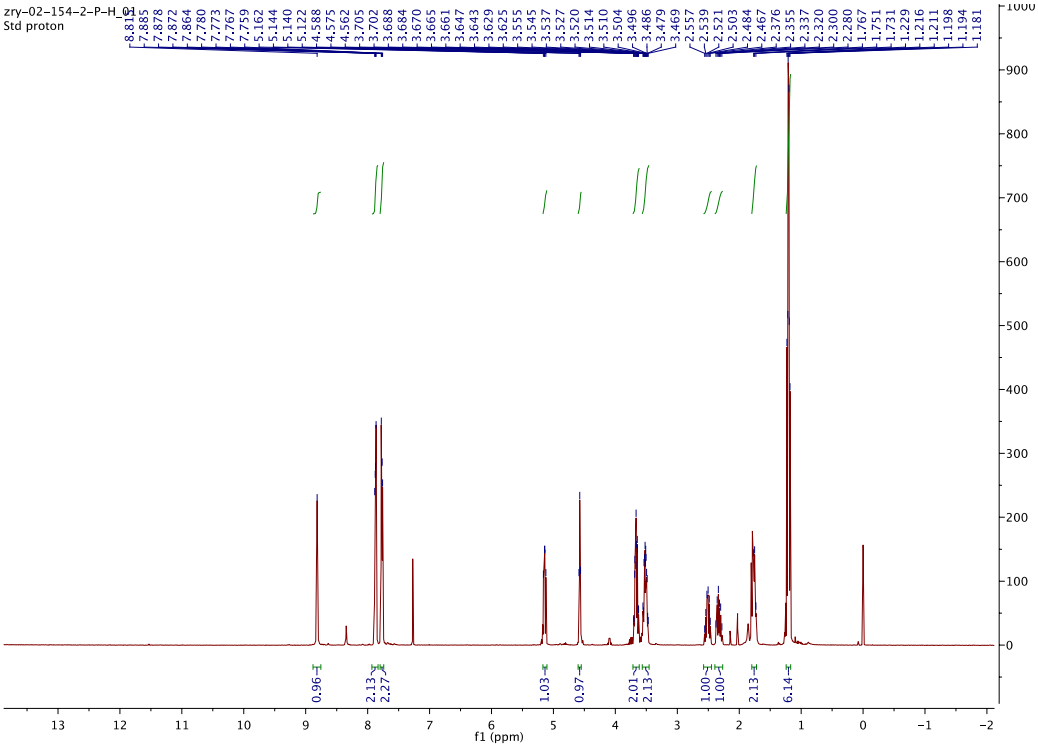

zry-02-126-1-P-C_01
Std proton
168.170
166.973
134.866
131.162
123.984
55.116
44.290
31.516
28.527
23.315
f1 (ppm)

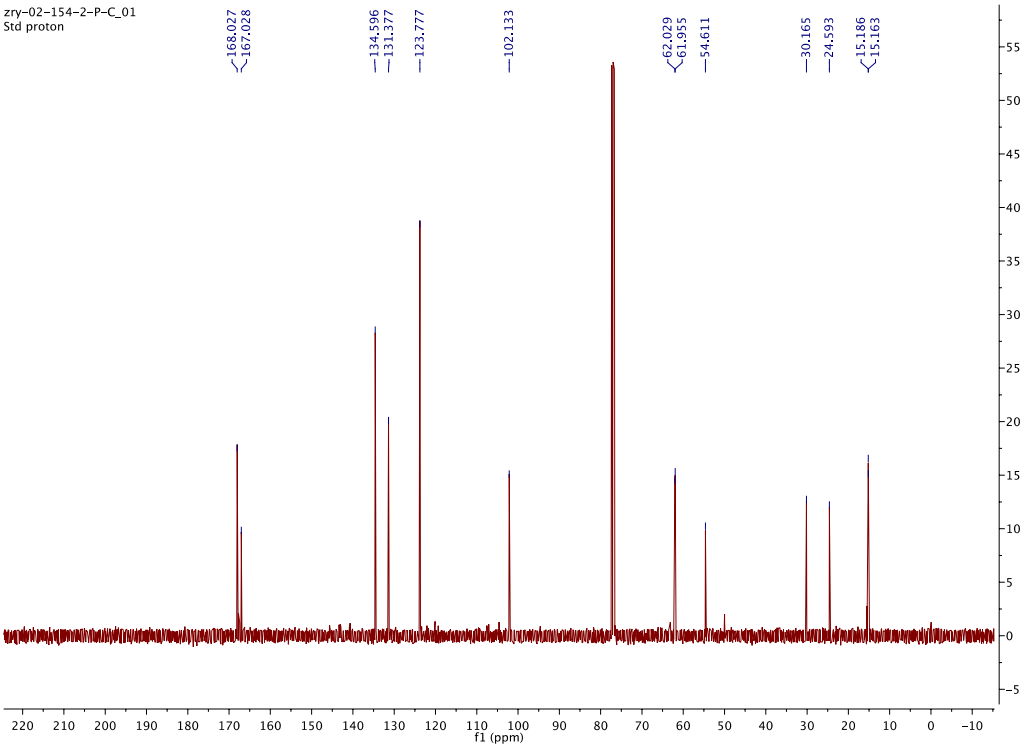

NPhth
BnO
O
HN
F
F
F
F
CF3

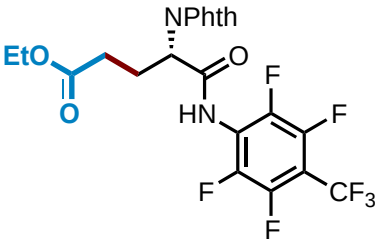

zry-02-136-1-P-H_01
Std proton
f1 (ppm)

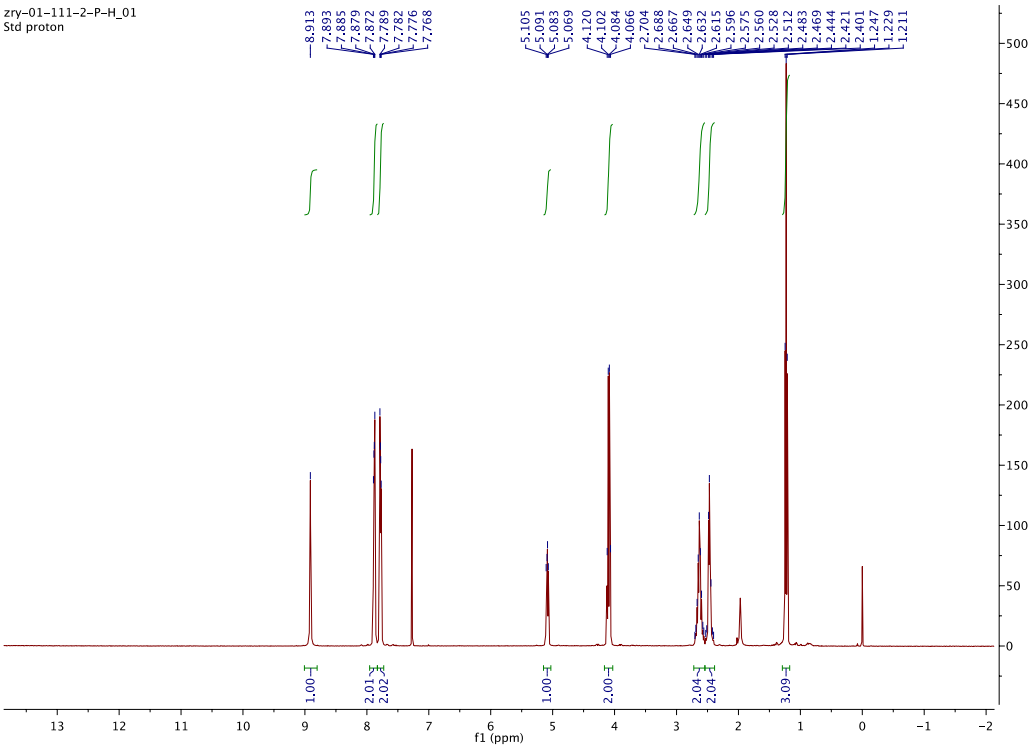

zry-02-136-1-P-C_01
Std proton
f1 (ppm)

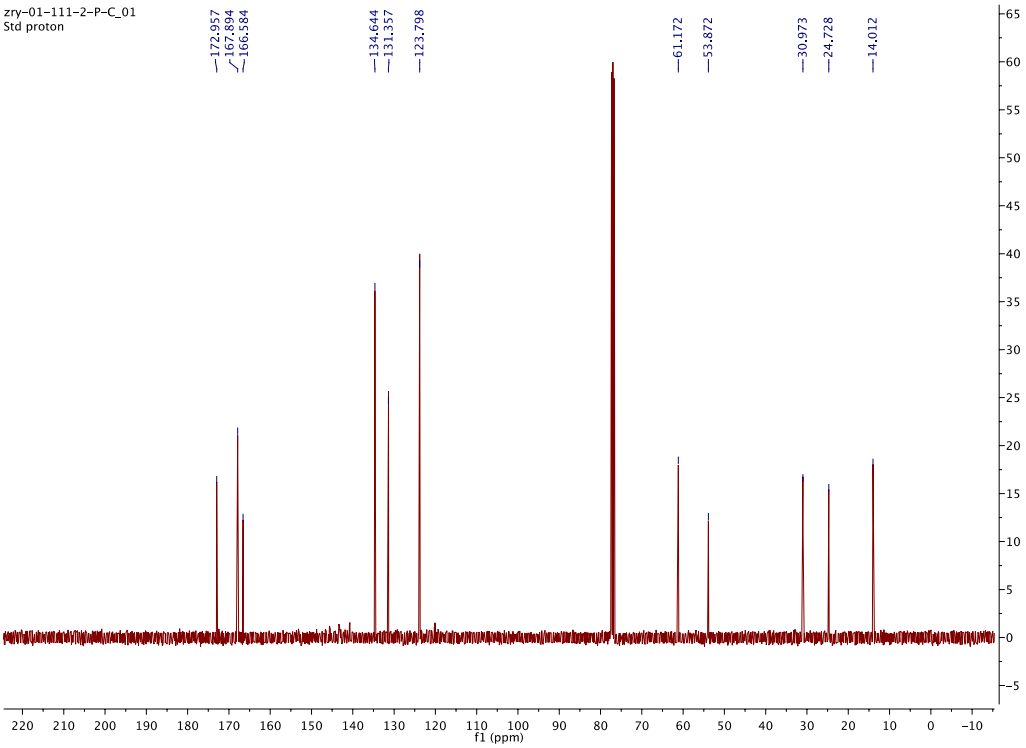

NPhth
EtO
OEt
O
HN
F
F
F
F
CF3

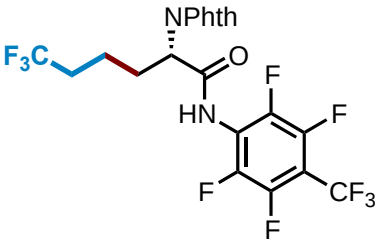

zry-02-154-2-P-H_01
Std proton
f1 (ppm)

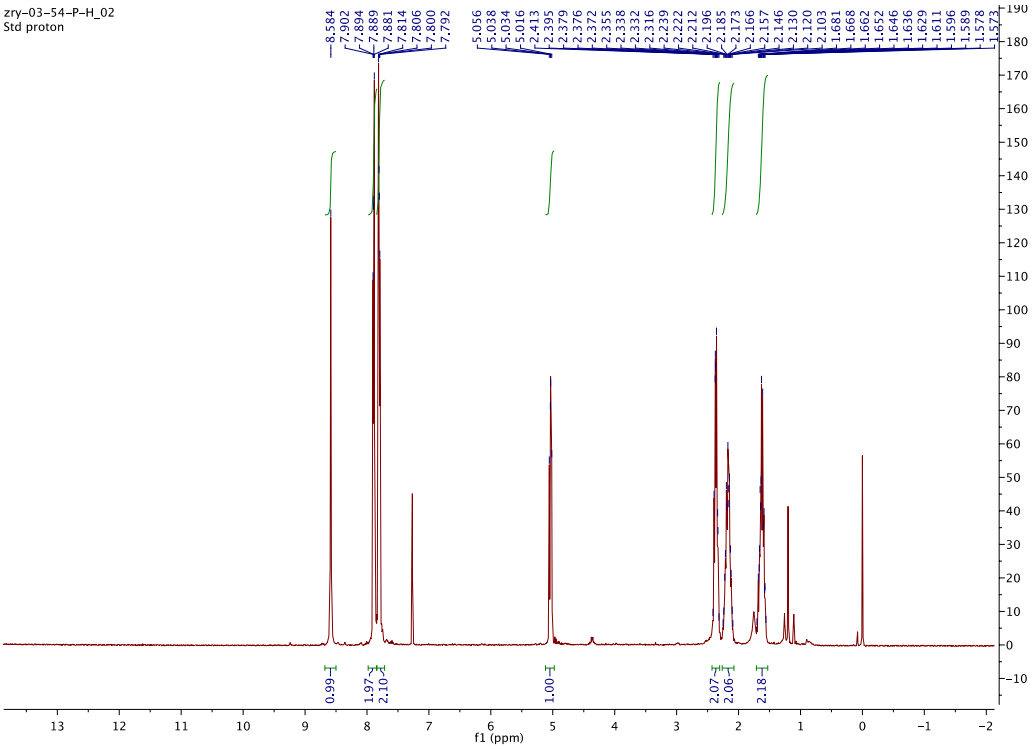

zry-02-154-2-P-C_01
Std proton
f1 (ppm)

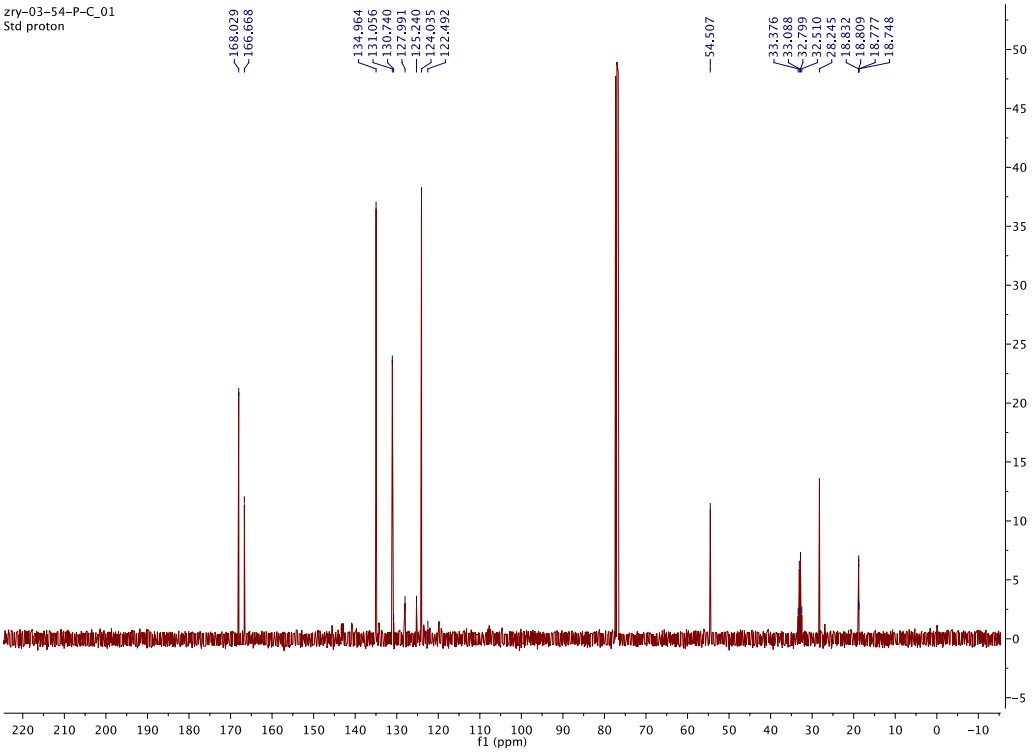

NPhth
EtO
O
O
HN
F
F
F
F
CF_3

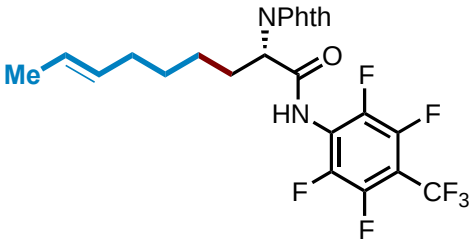

zry-01-111-2-P-H_01
Std proton
f1 (ppm)

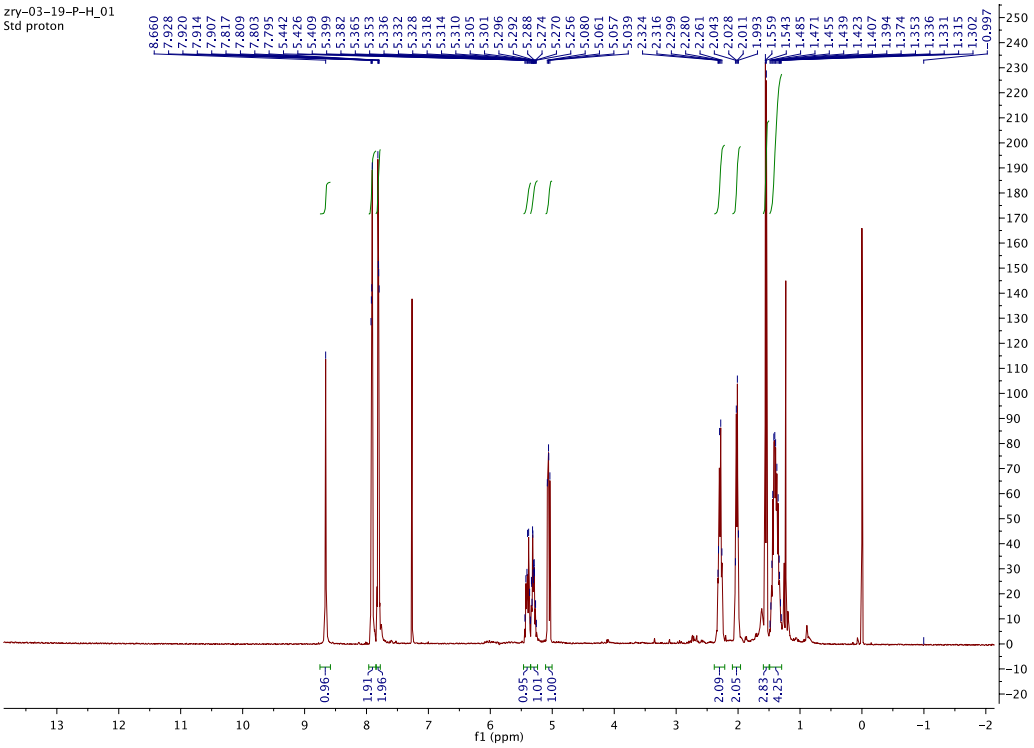

zry-01-111-2-P-C_01
Std proton
f1 (ppm)

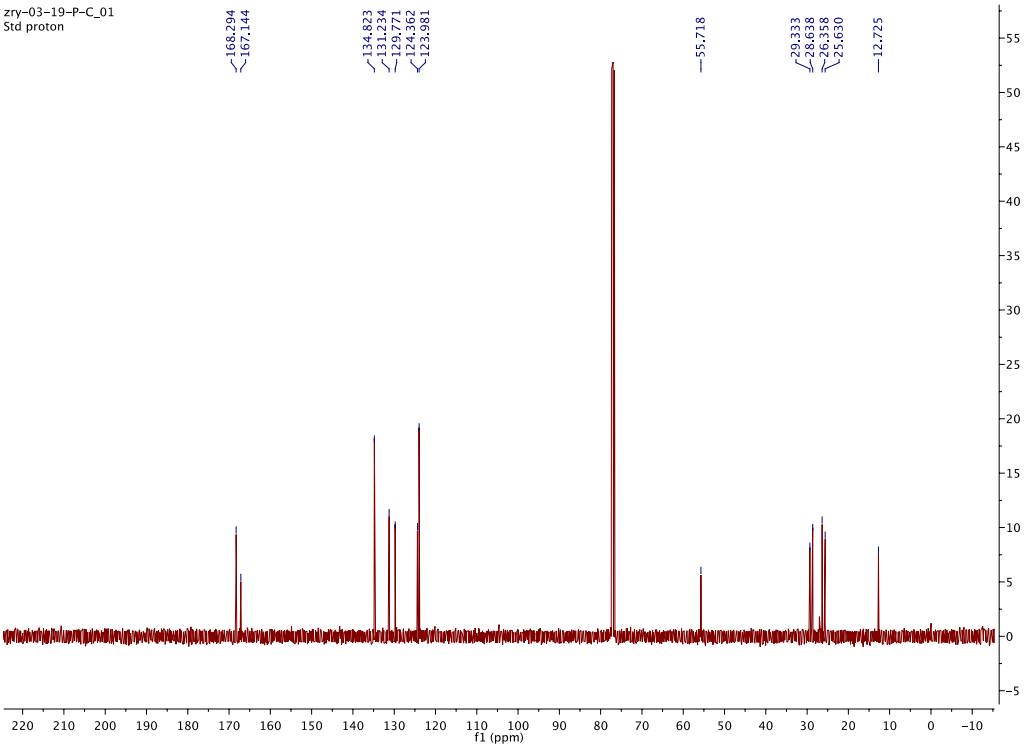

NPhth
F3C
O
HN
F
F
F
F
CF3

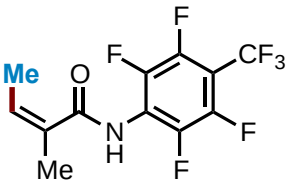

zry-03-54-P-H_02
Std proton
f1 (ppm)

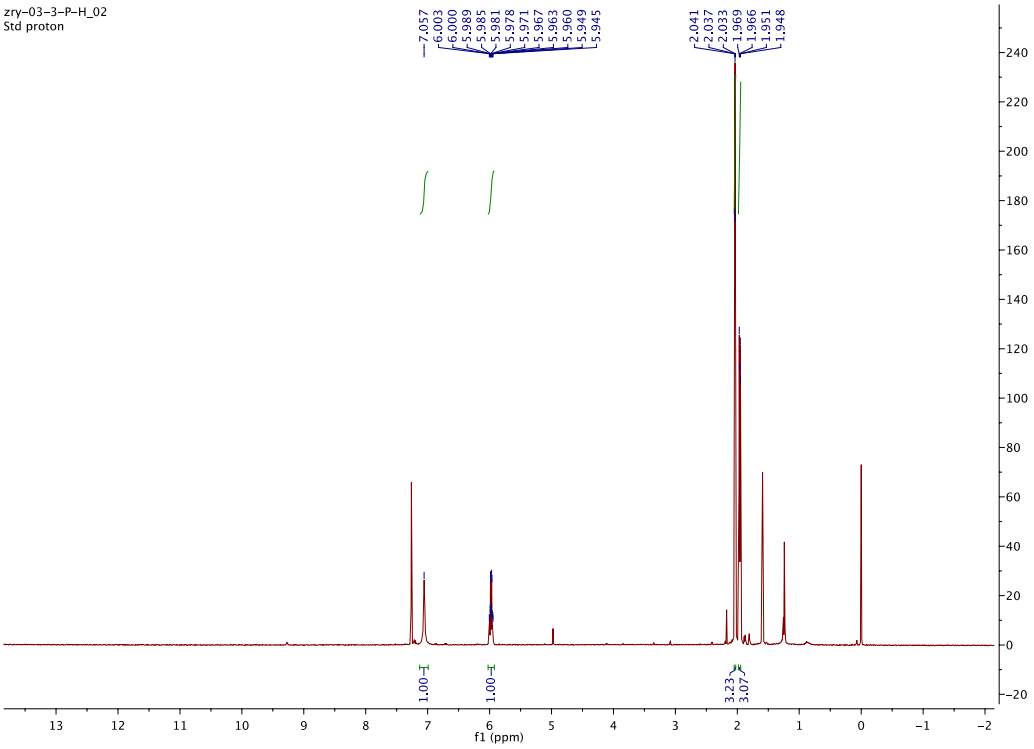

zry-03-54-P-C_01
Std proton
f1 (ppm)

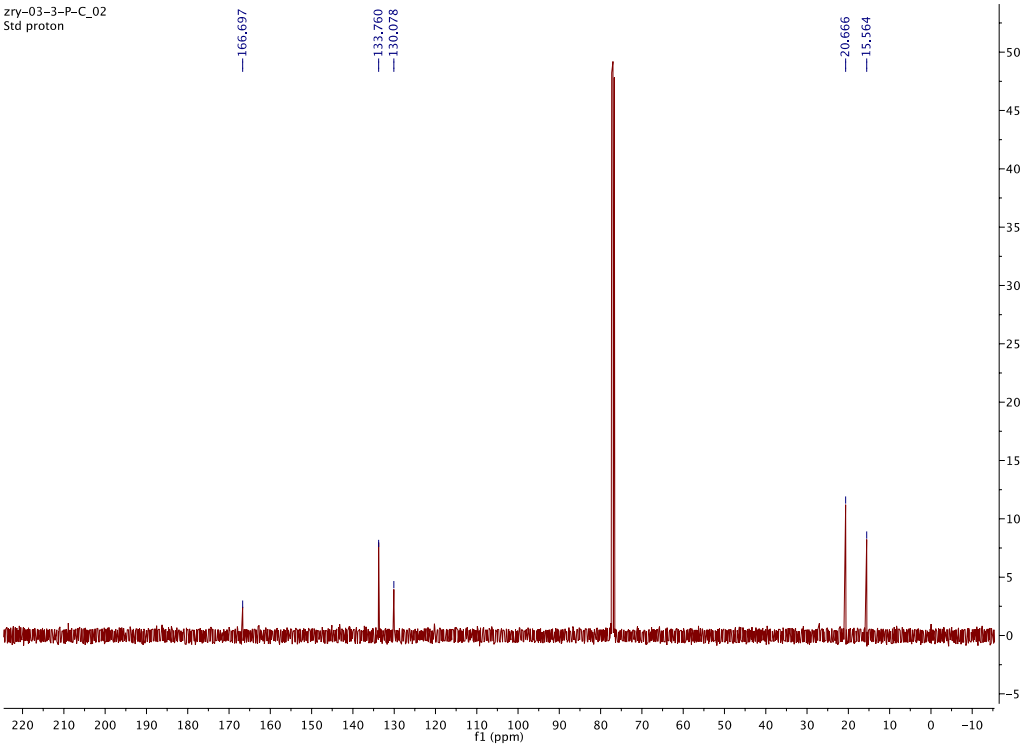

NPhth
Me
O
HN
F
F
F
F
CF3

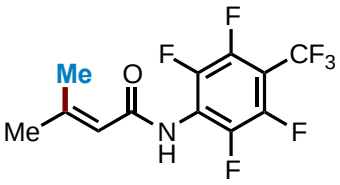

zry-03-19-P-H_01
Std proton
f1 (ppm)

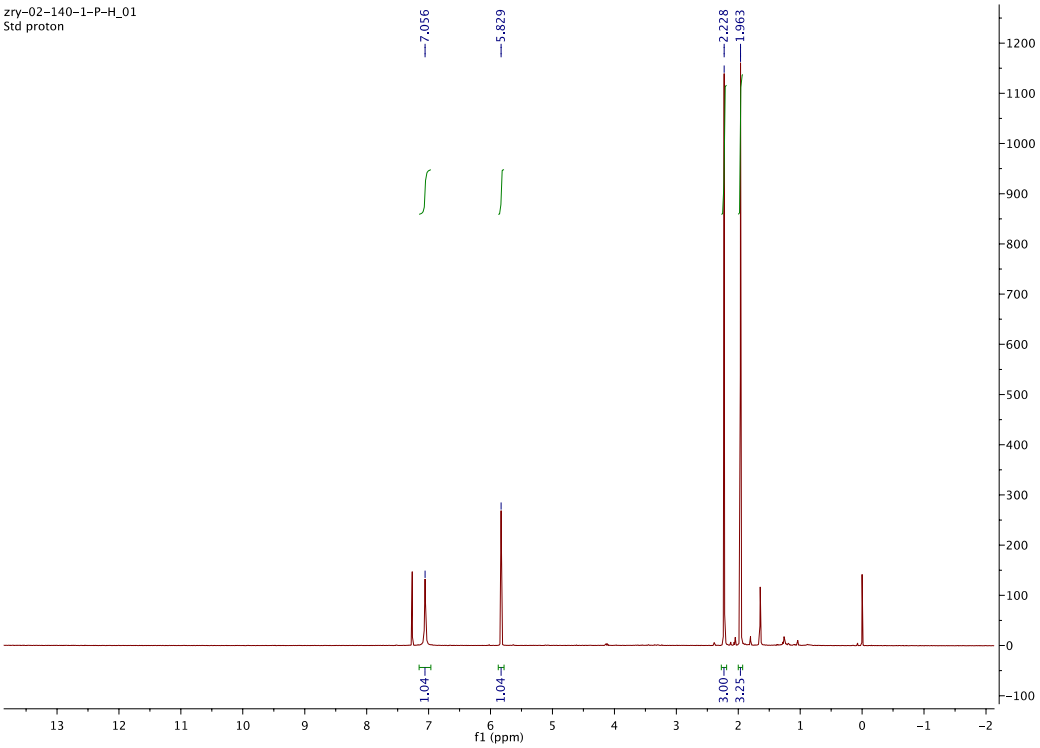

zry-03-19-P-C_01
Std proton
168.294
167.144
134.823
131.234
129.771
124.362
123.981
55.718
29.333
28.638
26.358
25.630
12.725
f1 (ppm)

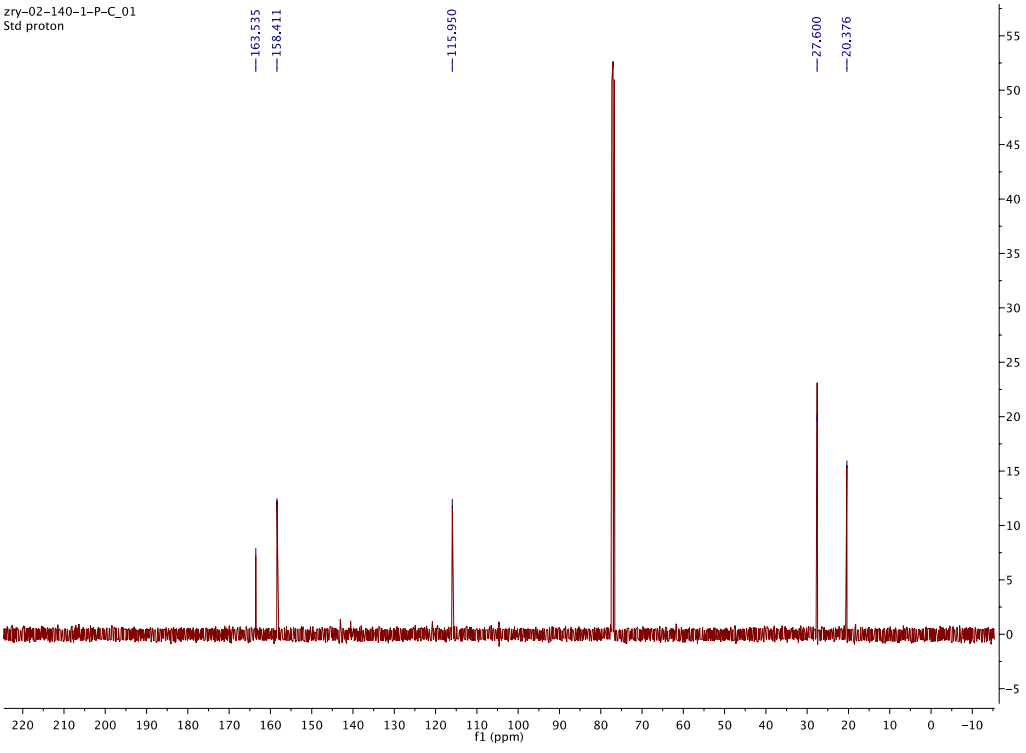

F
F
CF3
Me
O
N
H
F
Me
F

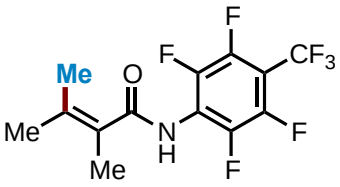

zry-03-3-P-H_02
Std proton
7.057
6.003
6.000
5.989
5.985
5.981
5.978
5.971
5.967
5.963
5.960
5.949
5.945
2.041
2.037
2.033
1.969
1.966
1.951
1.948
1.00
1.00
3.23
3.07
f1 (ppm)

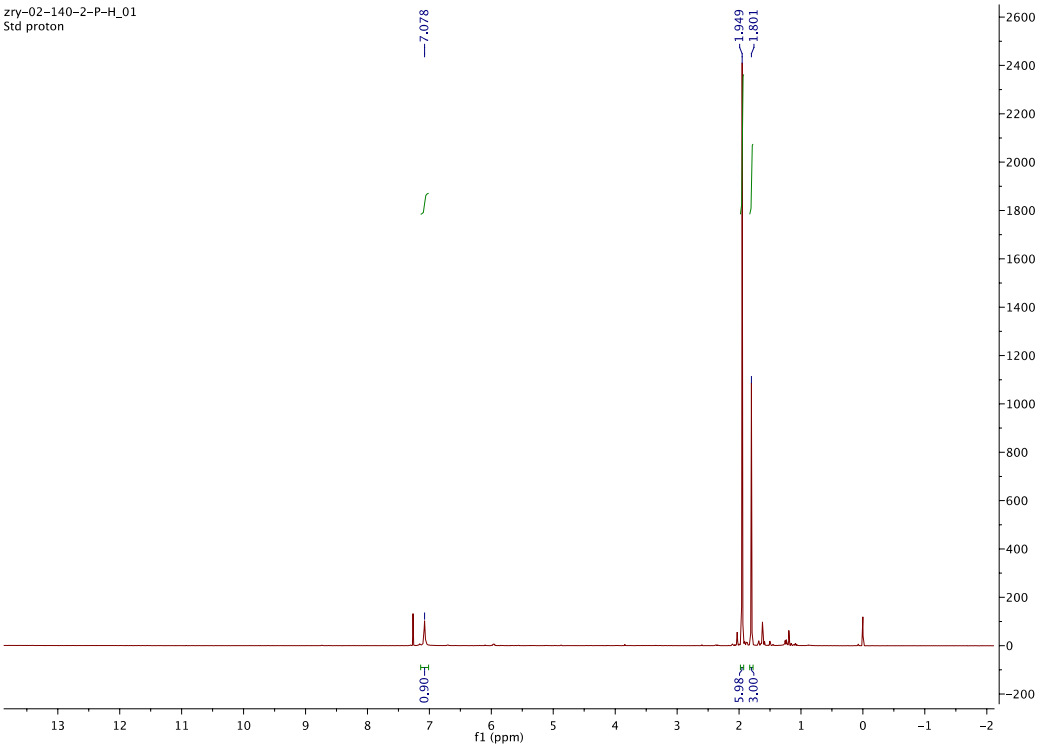

zry-03-3-P-C_02
Std proton
166.697
133.760
130.078
20.666
15.564
f1 (ppm)

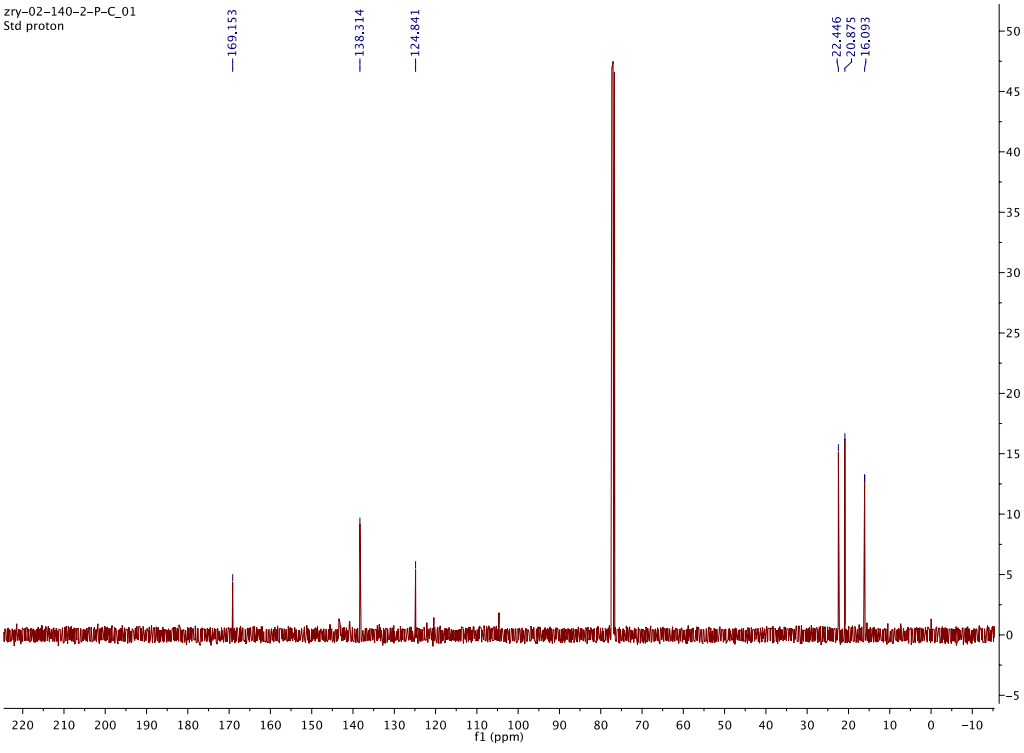

F
F
CF3
Me
O
Me
N
H
F
F

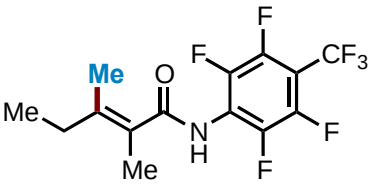

zry-02-140-1-P-H_01
Std proton
7.056
5.829
2.228
1.963
1.04
1.04
3.00
3.25
f1 (ppm)

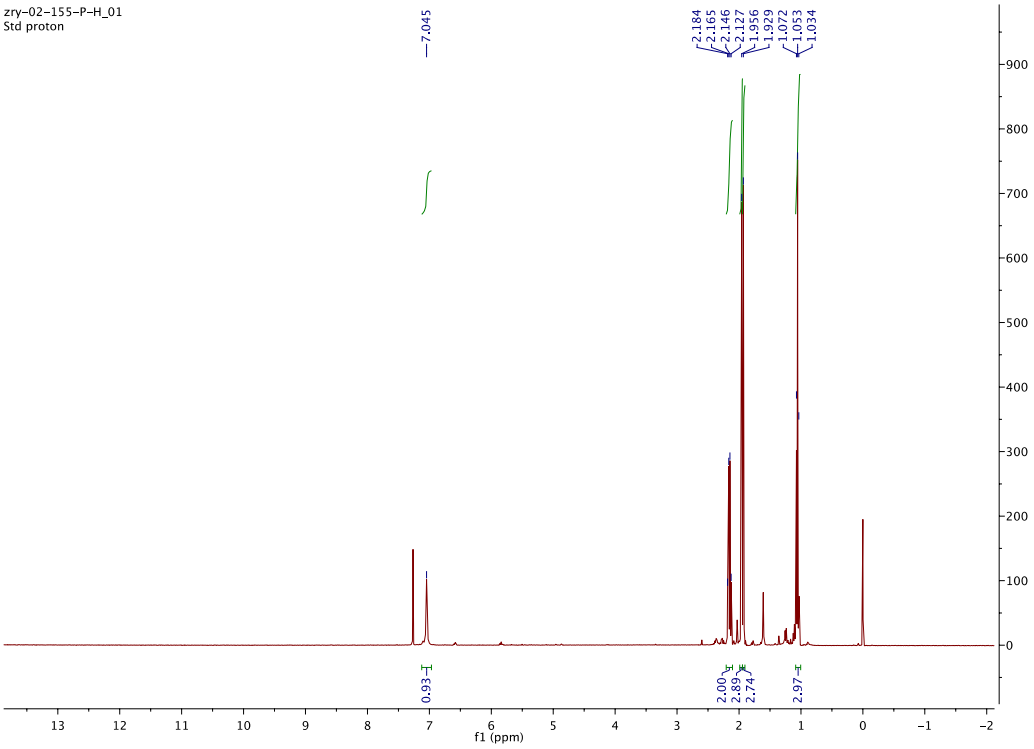

zry-02-140-1-P-C_01
Std proton
163.535
158.411
115.950
27.600
20.376
f1 (ppm)

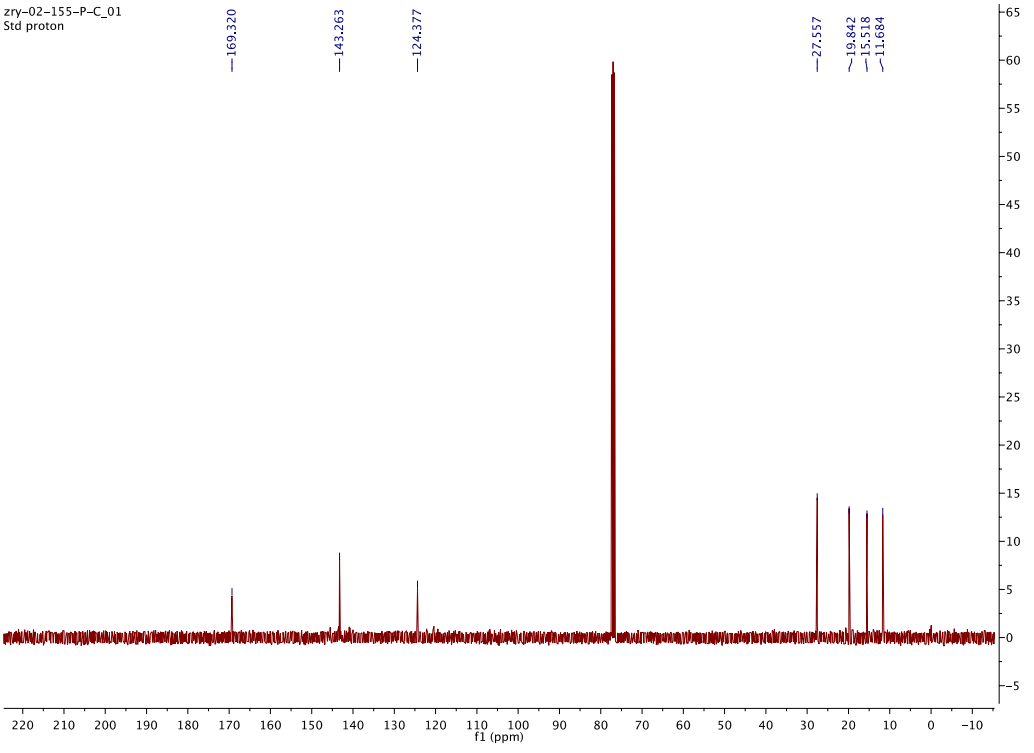

F
F
CF3
Me
O
Me
N
H
F
Me
F

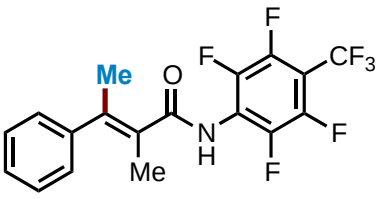

zry-02-140-2-P-H_01
Std proton
7.078
1.949
1.801
0.90
5.98
3.00
f1 (ppm)

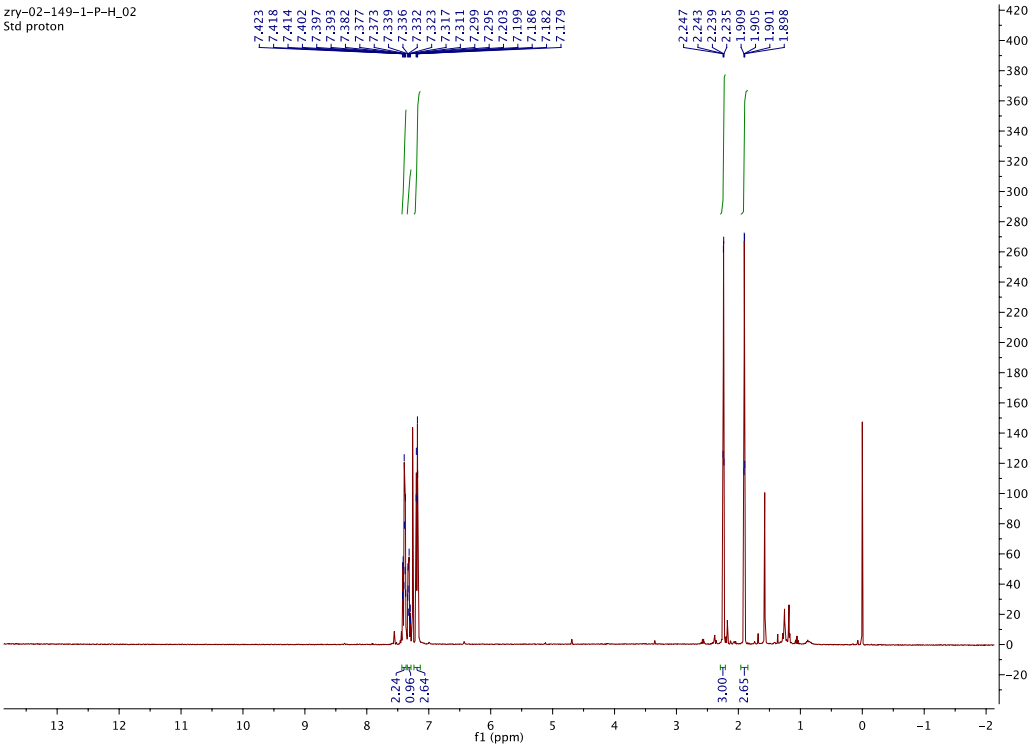

zry-02-140-2-P-C_01
Std proton
169.153
138.314
124.841
22.446
20.875
16.093
f1 (ppm)

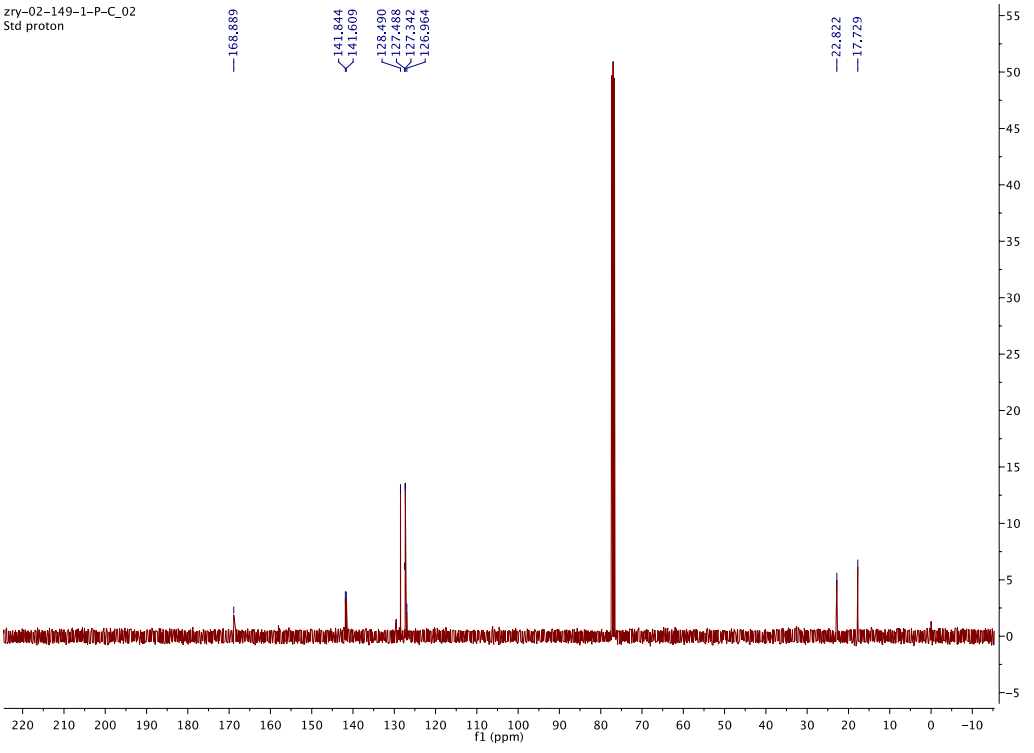

F
F
CF3
Me
O
Me
N
H
F
Me

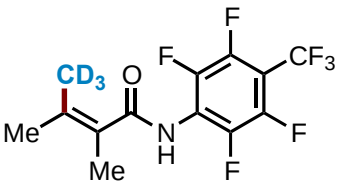

zry-02-155-P-H_01
Std proton
7.045
2.184
2.165
2.146
2.127
1.956
1.929
1.072
1.053
1.034
0.93
2.00
2.89
2.74
2.97
f1 (ppm)

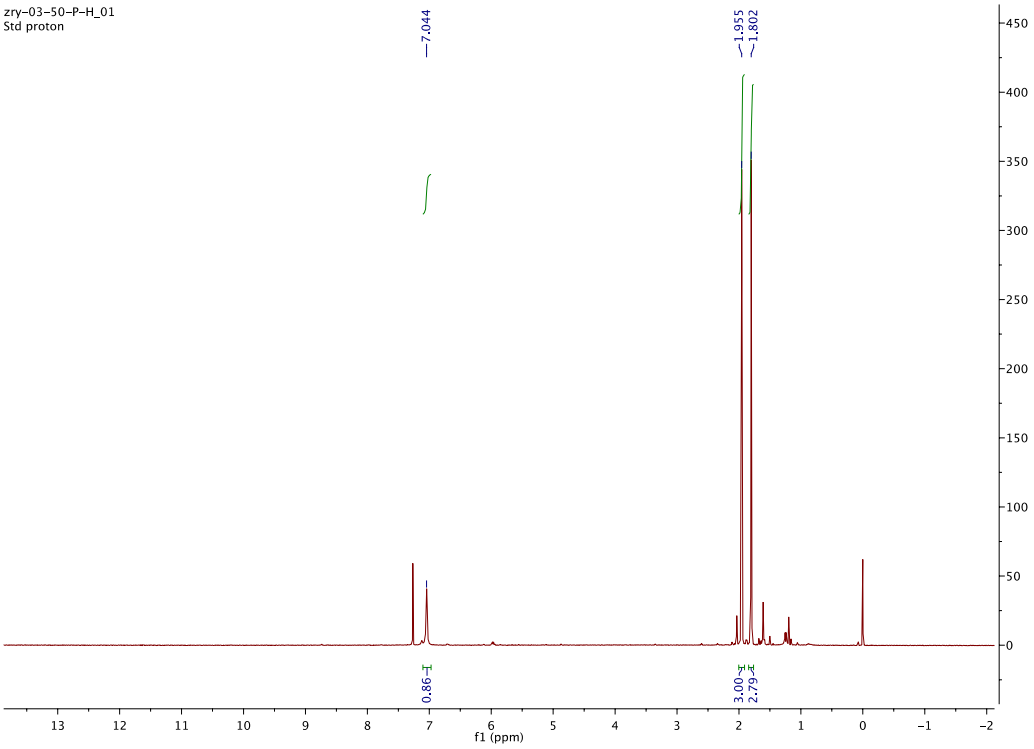

zry-02-155-P-C_01
Std proton
169.320
143.263
124.377
27.557
19.842
15.518
11.684
f1 (ppm)

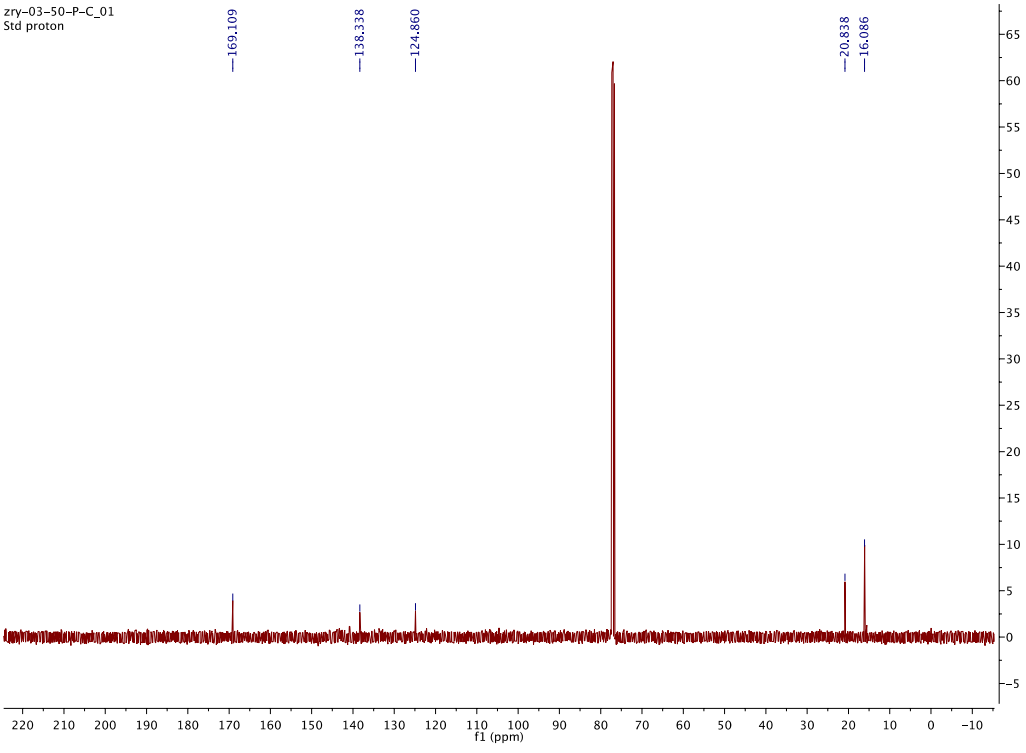

F
F
CF3
Me
O
F
N
H
Me
F

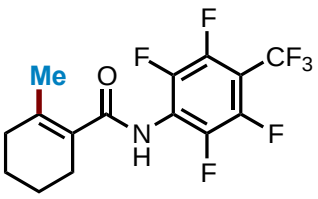

zry-02-149-1-P-H_02
Std proton
7.423
7.418
7.414
7.402
7.397
7.393
7.382
7.377
7.373
7.339
7.336
7.332
7.323
7.317
7.311
7.299
7.295
7.203
7.199
7.186
7.182
7.179
2.247
2.243
2.239
2.235
1.909
1.905
1.901
1.898
2.24
0.96
2.64
3.00
2.65
f1 (ppm)

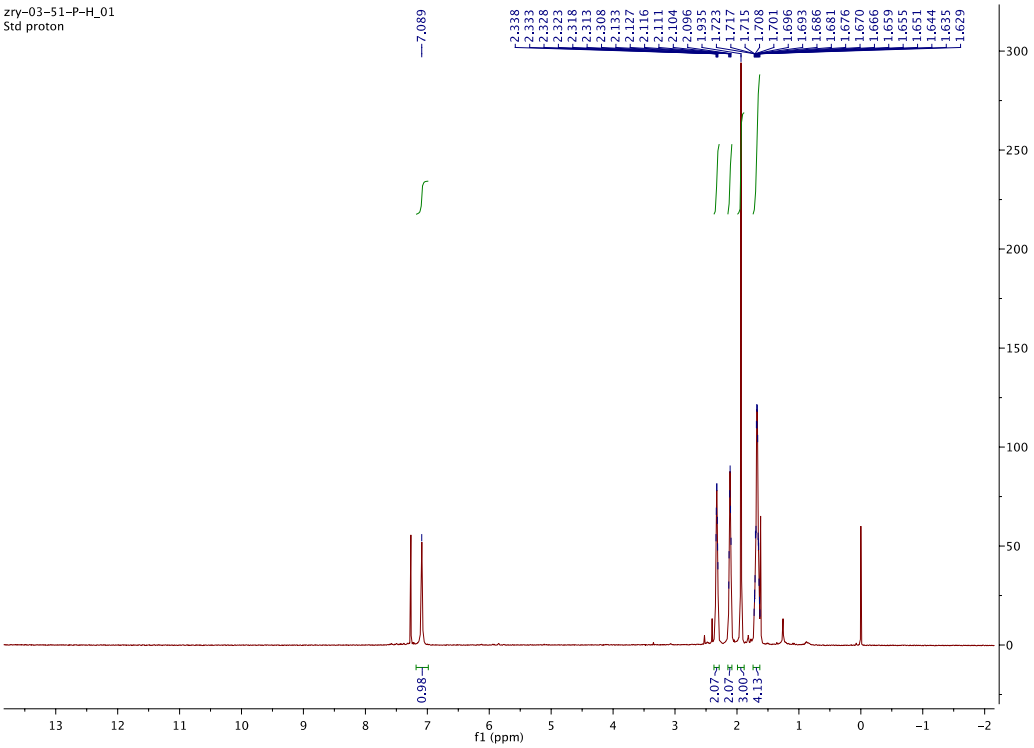

zry-02-149-1-P-C_02
Std proton
168.889
141.844
141.609
128.490
127.488
127.342
126.964
22.822
17.729
f1 (ppm)

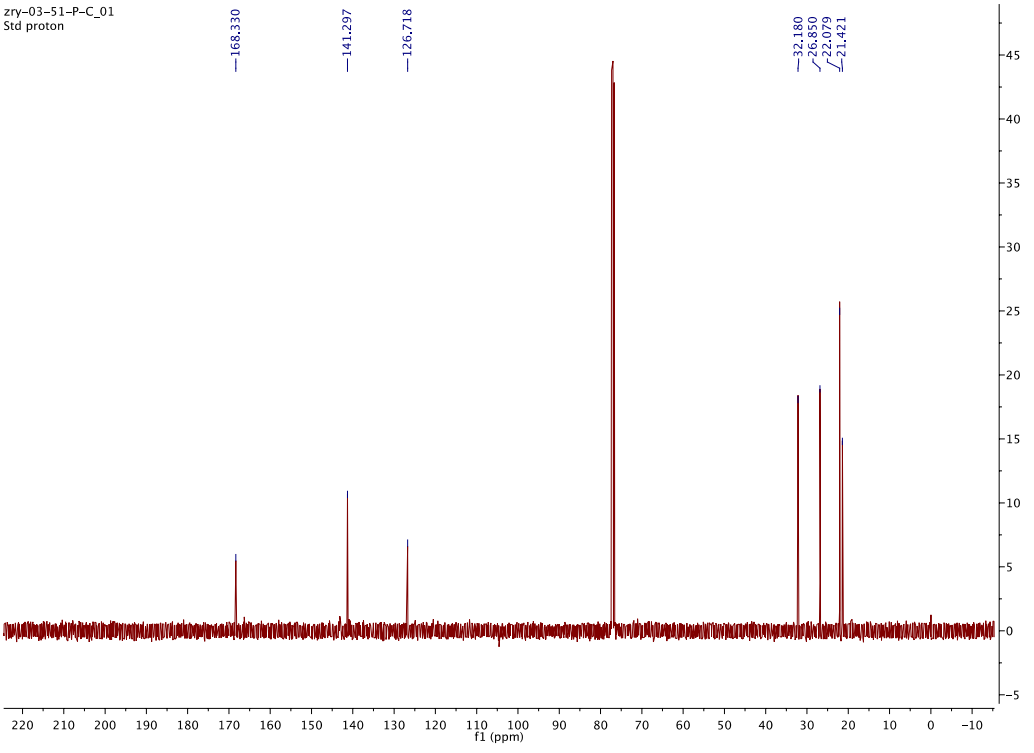

F
F
CF3
CD3
O
Me
N
H
F
Me
F

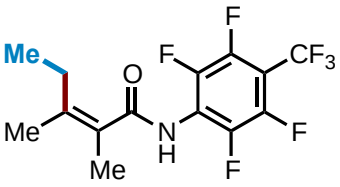

zry-03-50-P-H_01
Std proton
7.044
1.955
1.802
0.86
3.00
2.79
f1 (ppm)

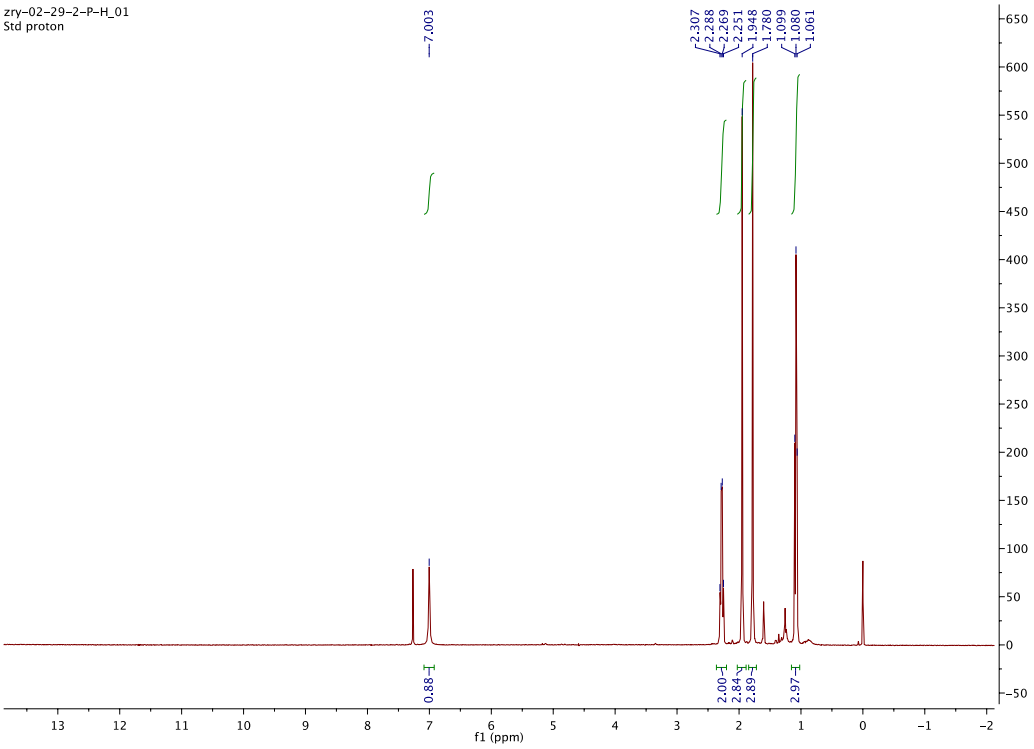

zry-03-50-P-C_01
Std proton
169.109
138.338
124.860
20.838
16.086
f1 (ppm)

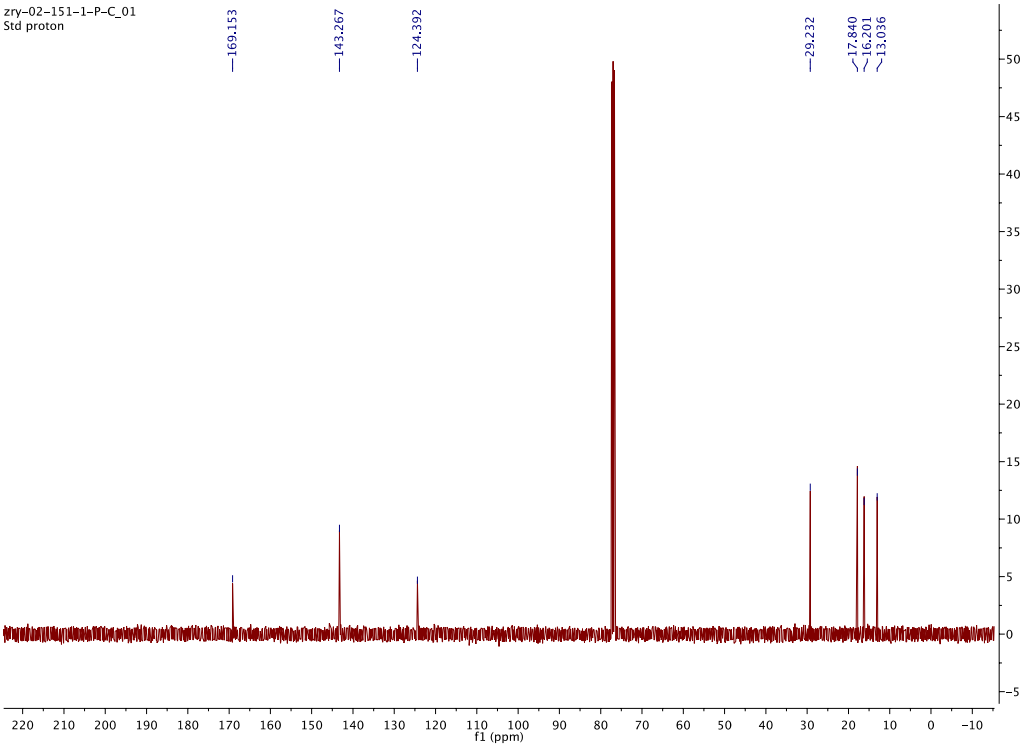

Me
O
N
H
F
F
CF3
F
F

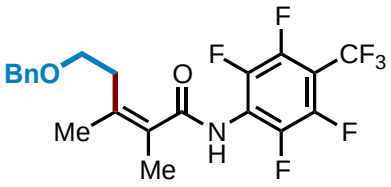

zry-03-51-P-H_01
Std proton
7.089
2.338
2.333
2.328
2.323
2.318
2.313
2.308
2.133
2.127
2.116
2.111
2.104
2.096
1.935
1.723
1.717
1.715
1.708
1.701
1.696
1.693
1.686
1.681
1.676
1.670
1.666
1.659
1.655
1.651
1.644
1.635
1.629
0.98
2.07
2.07
3.00
4.13
f1 (ppm)

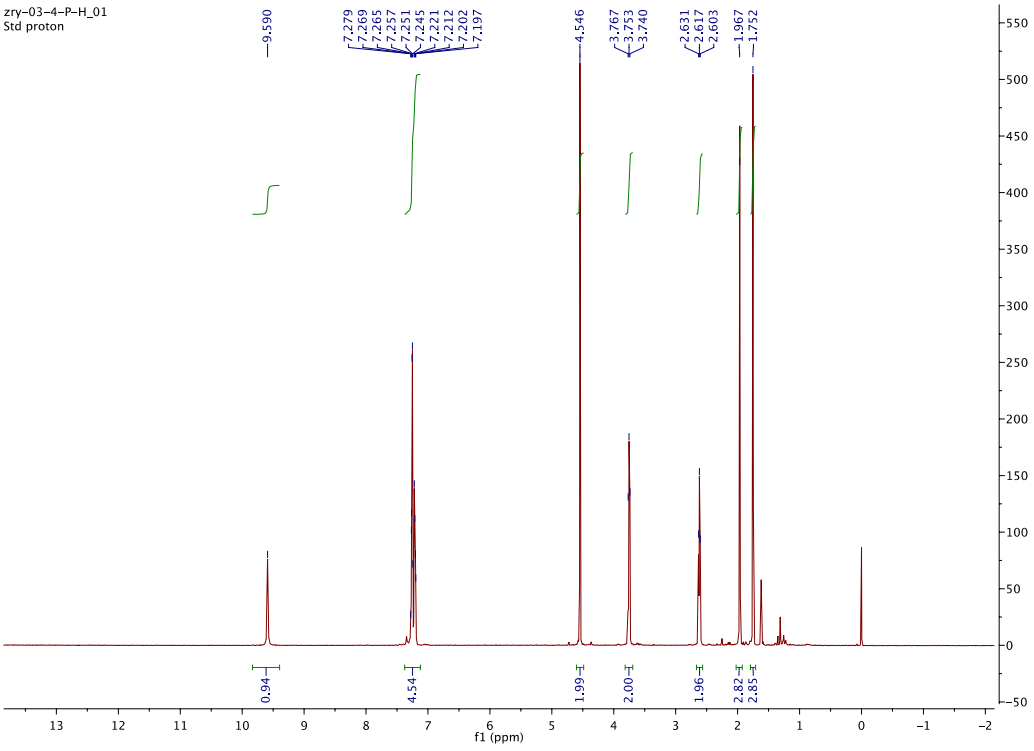

zry-03-51-P-C_01
Std proton
168.330
141.297
126.718
32.180
26.850
22.079
21.421
f1 (ppm)

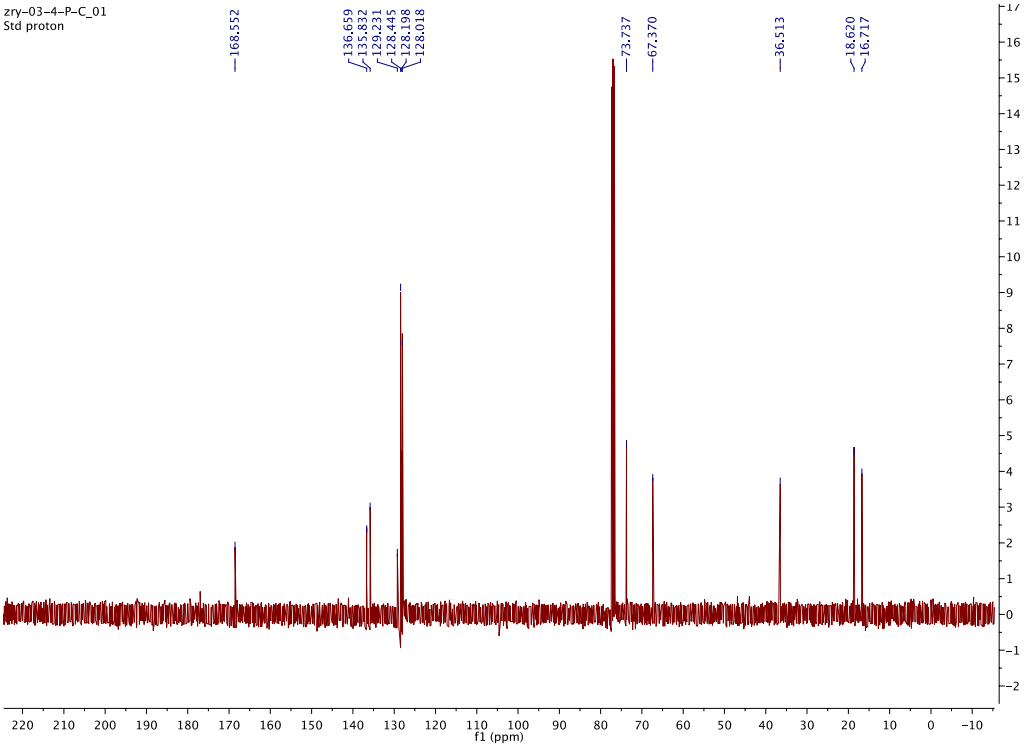

Me
O
F
F
CF3
Me
N
H
F
F
Me

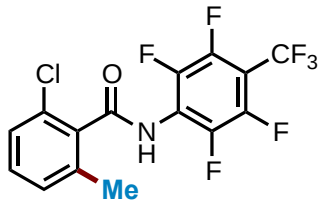

zry-02-29-2-P-H_01
Std proton
7.003
2.307
2.288
2.269
2.251
1.948
1.780
1.099
1.080
1.061
0.88
2.00
2.84
2.89
2.97
f1 (ppm)

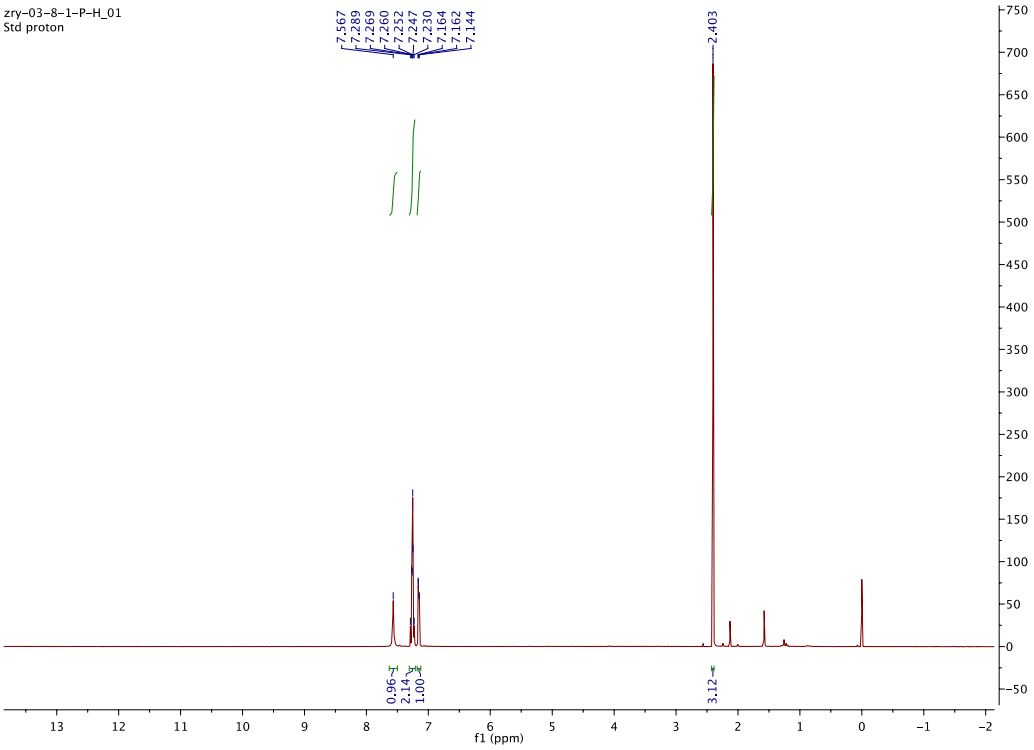

zry-02-151-1-P-C_01
Std proton
169.153
143.267
124.392
29.232
17.840
16.201
13.036
f1 (ppm)

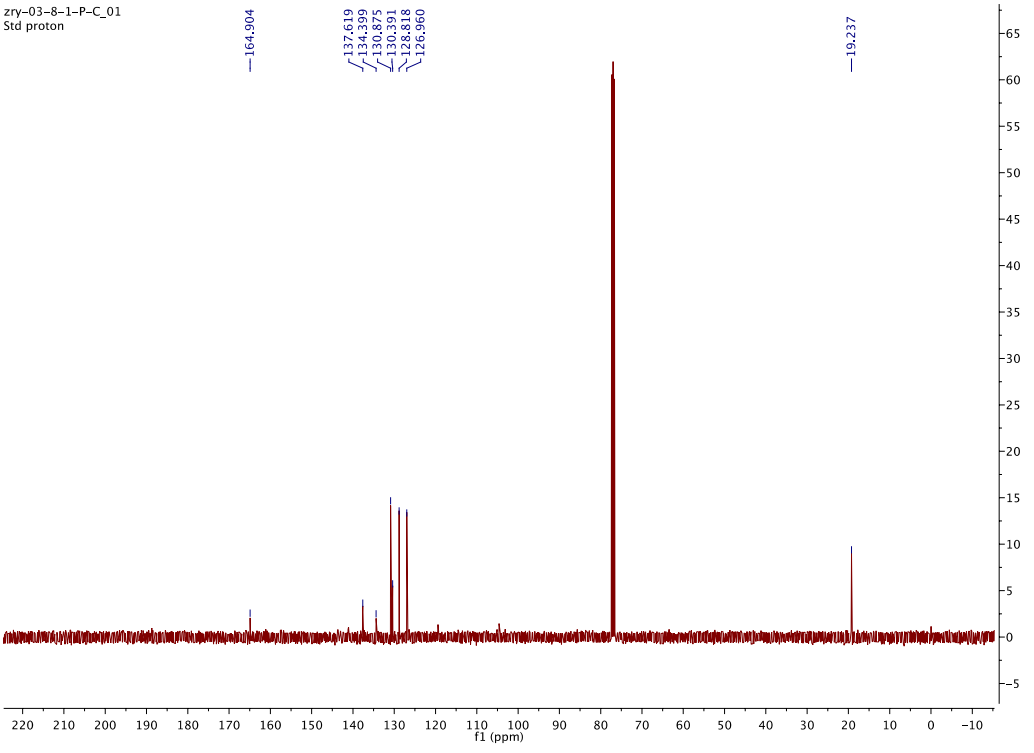

BnO
O
Me
Me
N
H
F
F
CF3
F
F

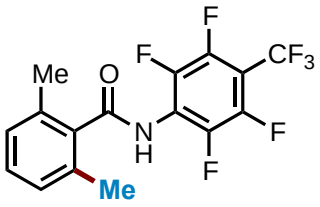

zry-03-4-P-H_01
Std proton
9.590
7.279
7.269
7.265
7.257
7.251
7.245
7.221
7.212
7.202
7.197
4.546
3.767
3.753
3.740
2.631
2.617
2.603
1.967
1.752
0.94
4.54
1.99
2.00
1.96
2.82
2.85
f1 (ppm)

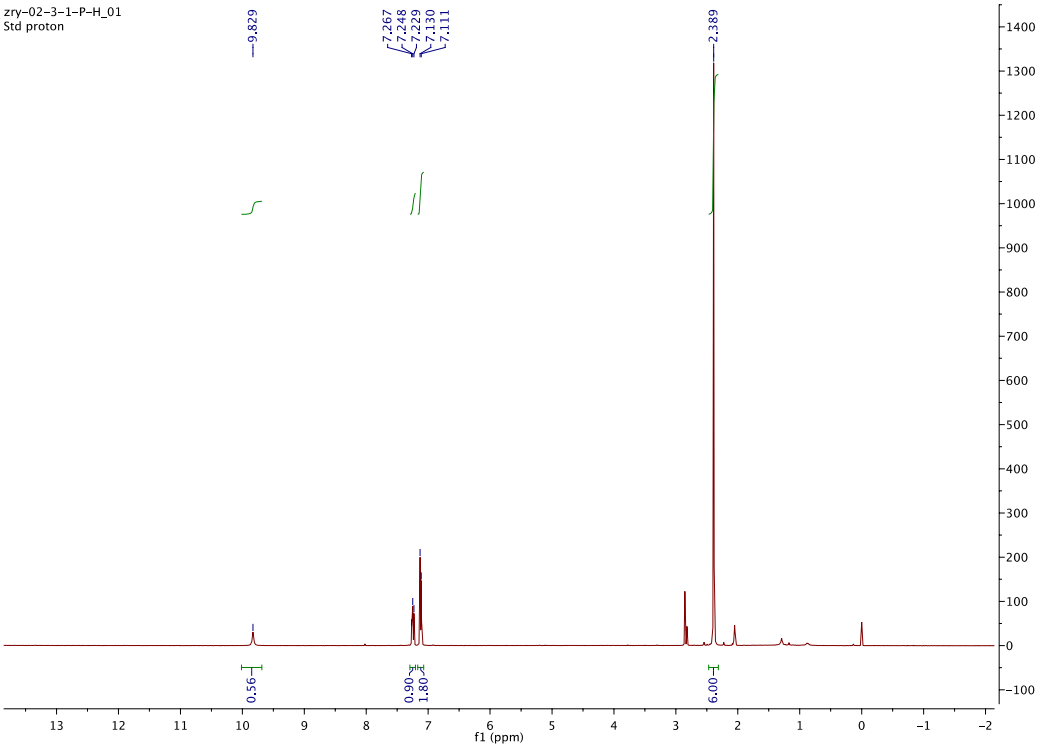

zry-03-4-P-C_01
Std proton
168.552
136.659
135.832
129.231
128.445
128.198
128.018
73.737
67.370
36.513
18.620
16.717
f1 (ppm)

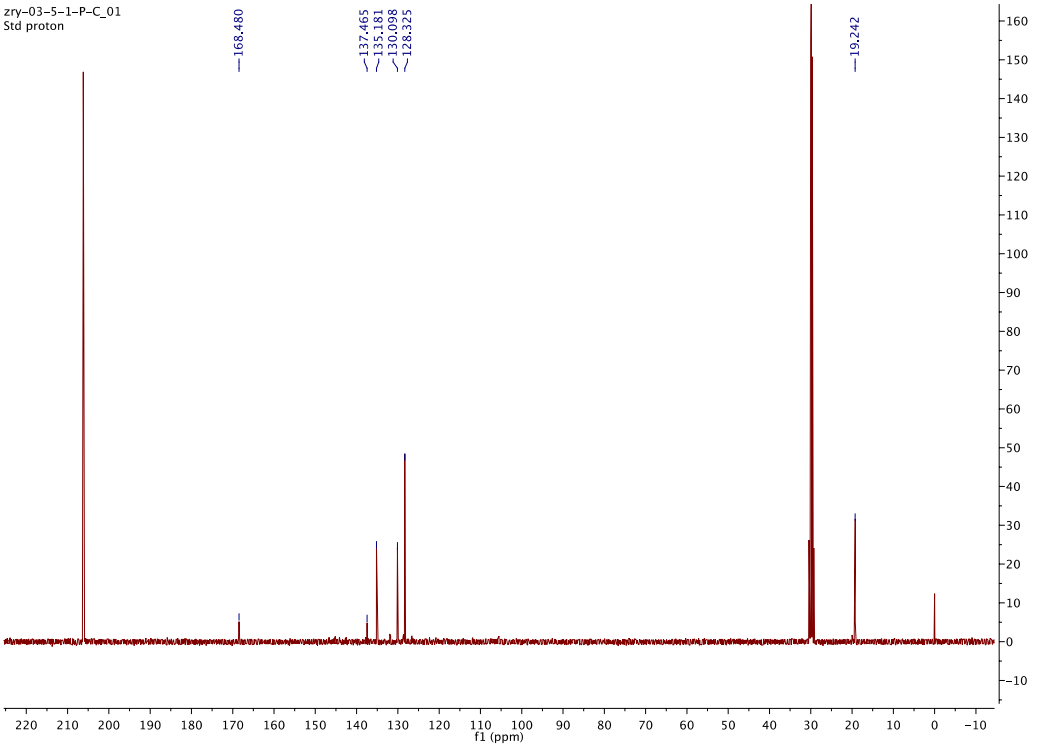

F
F
CF3
Cl
O
N
H
F
F
Me

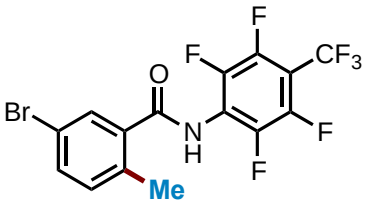

zry-03-8-1-P-H_01
Std proton
7.567
7.289
7.269
7.260
7.252
7.247
7.230
7.164
7.162
7.144
2.403
0.96
2.14
1.00
3.12
f1 (ppm)

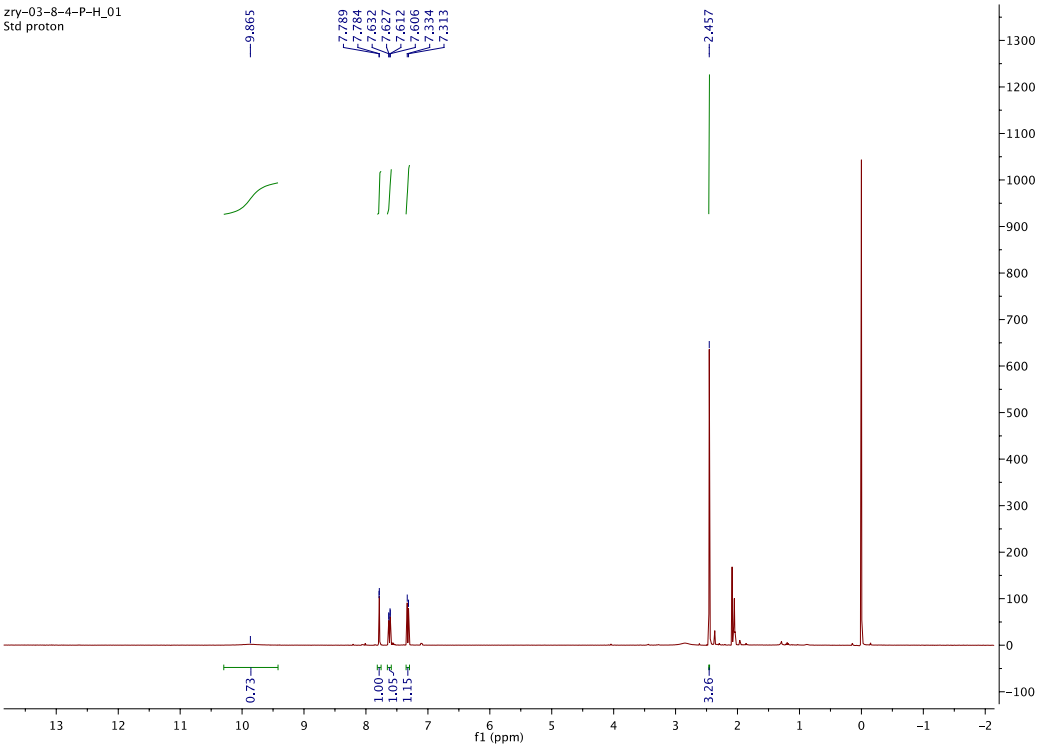

zry-03-8-1-P-C_01
Std proton
164.904
137.619
134.399
130.875
130.391
128.818
126.960
19.237
f1 (ppm)

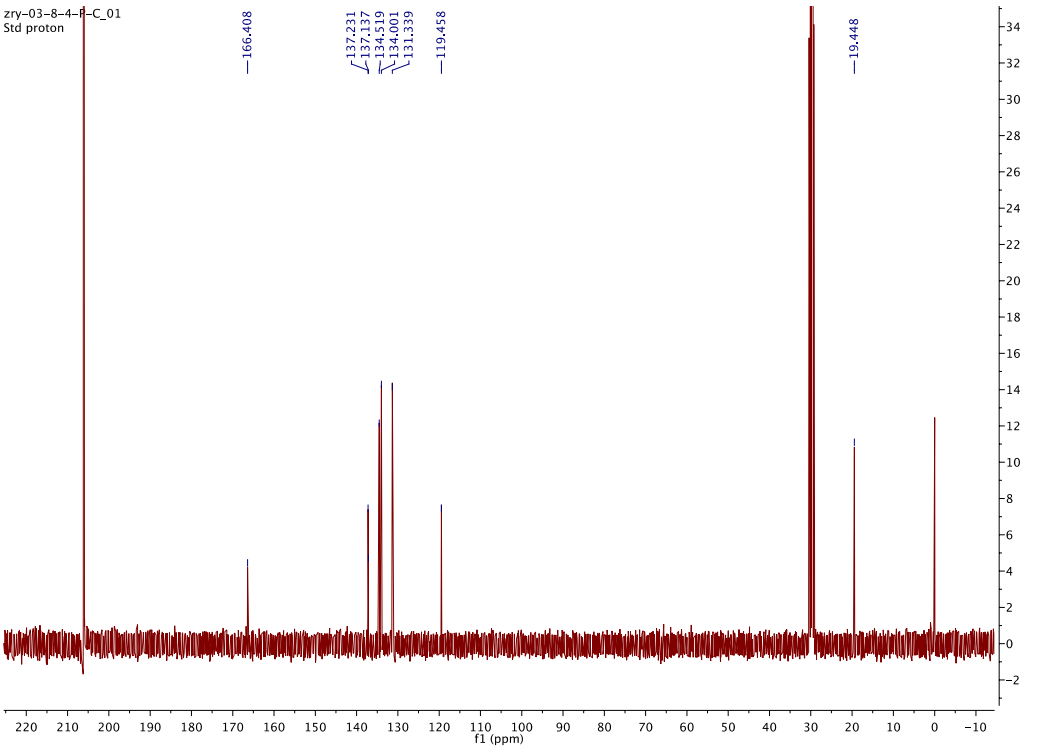

F
F
CF3
Me
O
N
H
F
F
Me

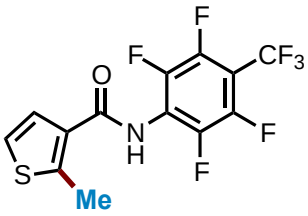

zry-02-3-1-P-H_01
Std proton
9.829
7.267
7.248
7.229
7.130
7.111
2.389
0.56
0.90
1.80
6.00
f1 (ppm)

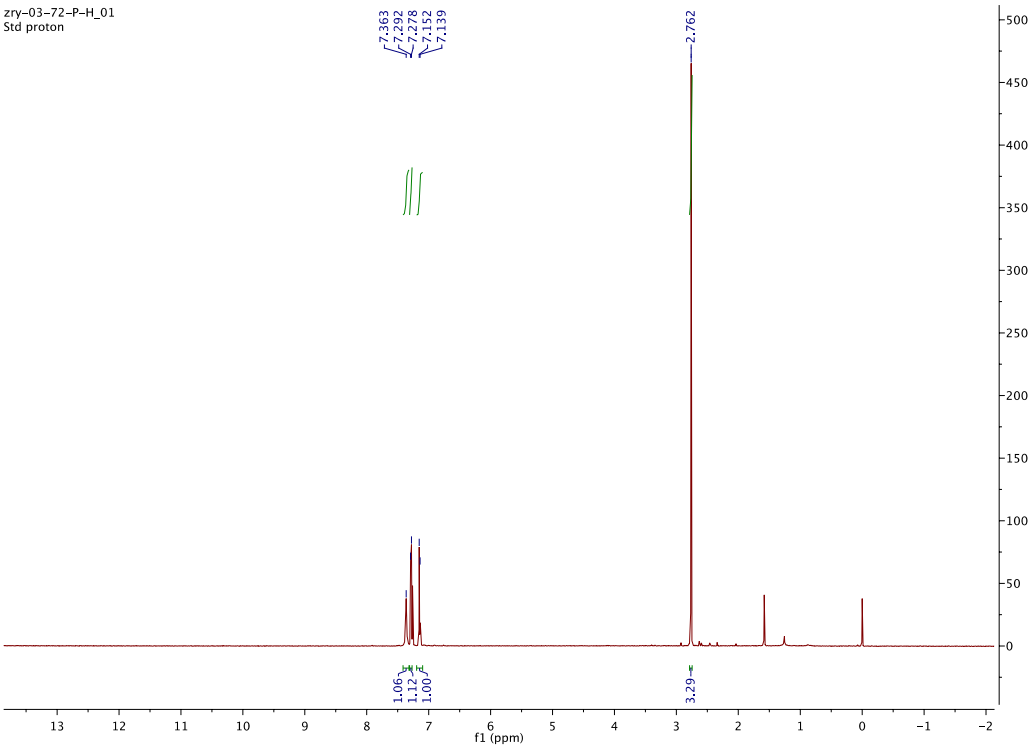

zry-03-5-1-P-C_01
Std proton
168.480
137.465
135.181
130.098
128.325
19.242
f1 (ppm)

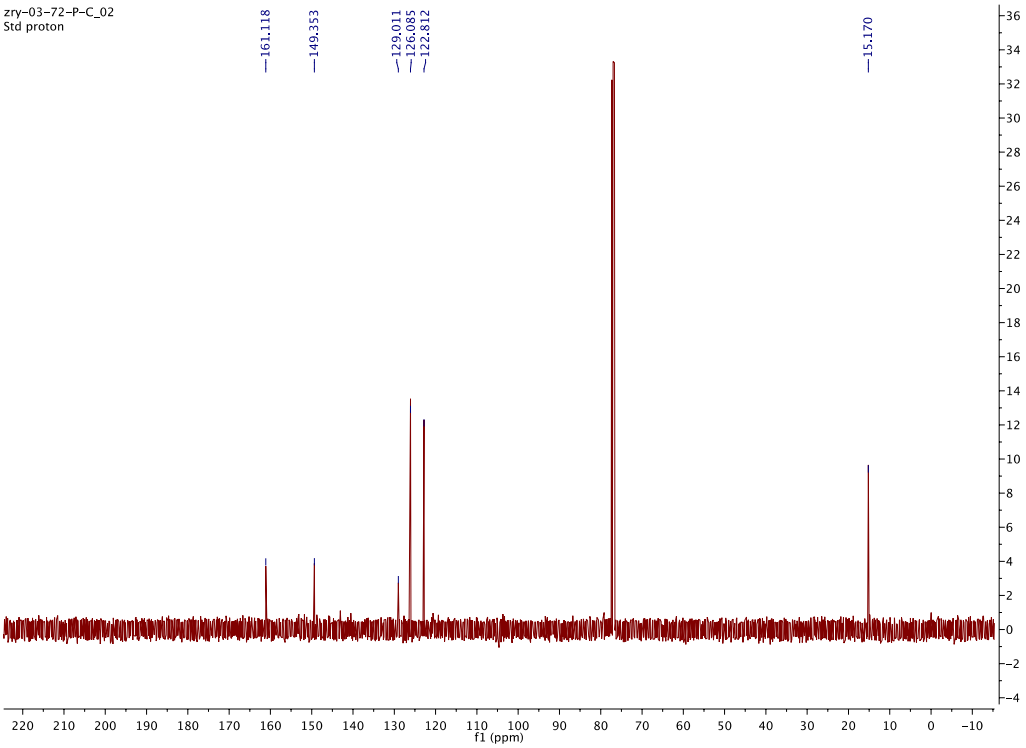

F
F
CF3
O
Br
N
H
F
F
Me

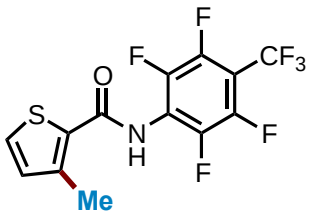

zry-03-8-4-P-H_01
Std proton
9.865
7.789
7.784
7.632
7.627
7.612
7.606
7.334
7.313
2.457
0.73
1.00
1.05
1.15
3.26
f1 (ppm)

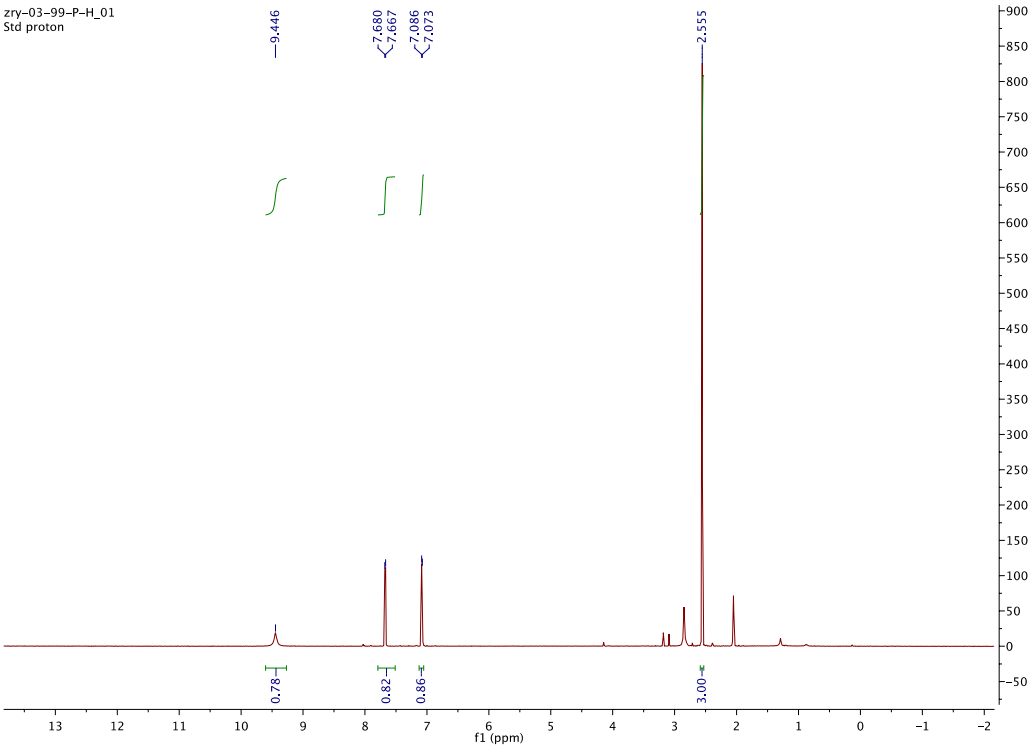

zry-03-8-4-P-C_01
Std proton
166.408
137.231
137.137
134.519
134.001
131.339
119.458
19.448
f1 (ppm)

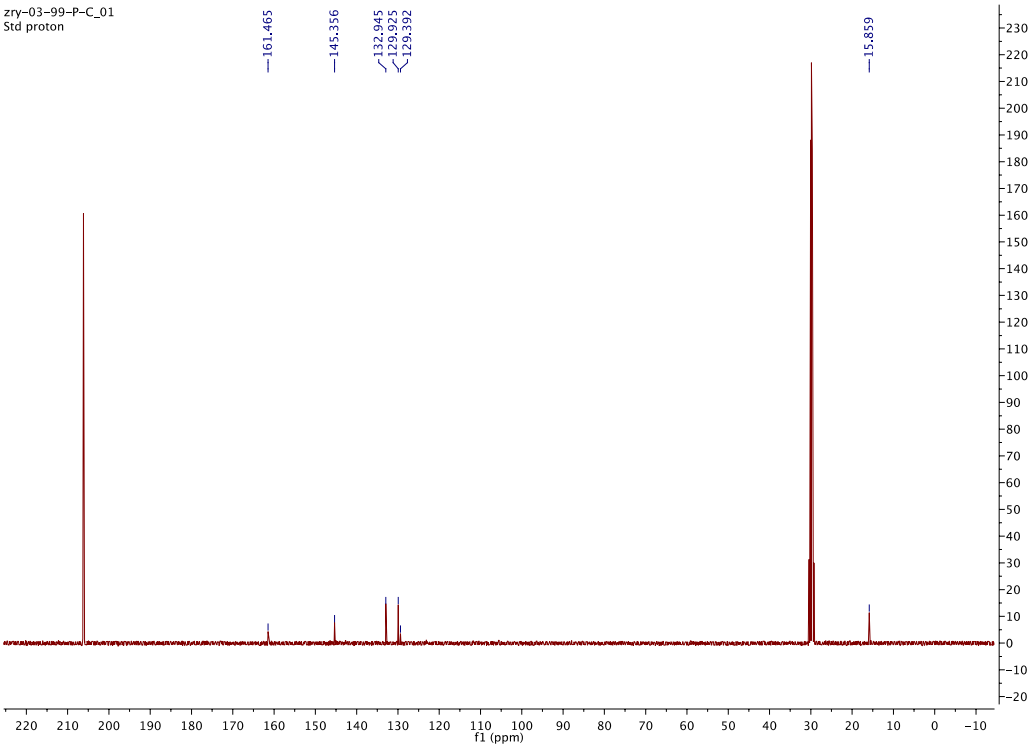

F
F
CF3
O
N
H
F
S
Me

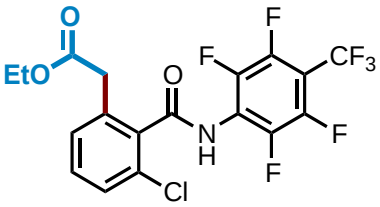

zry-03-72-P-H_01
Std proton
7.363
7.292
7.278
7.152
7.139
2.762
1.06
1.12
1.00
3.29
f1 (ppm)

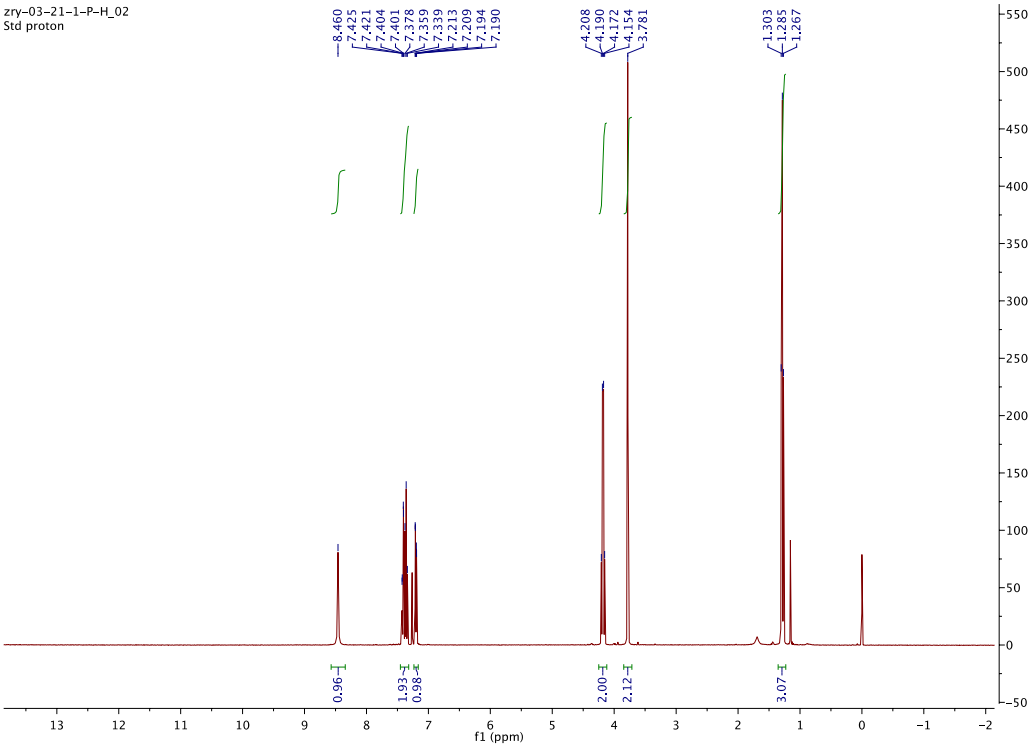

zry-03-72-P-C_02
Std proton
161.118
149.353
129.011
126.085
122.812
15.170
f1 (ppm)

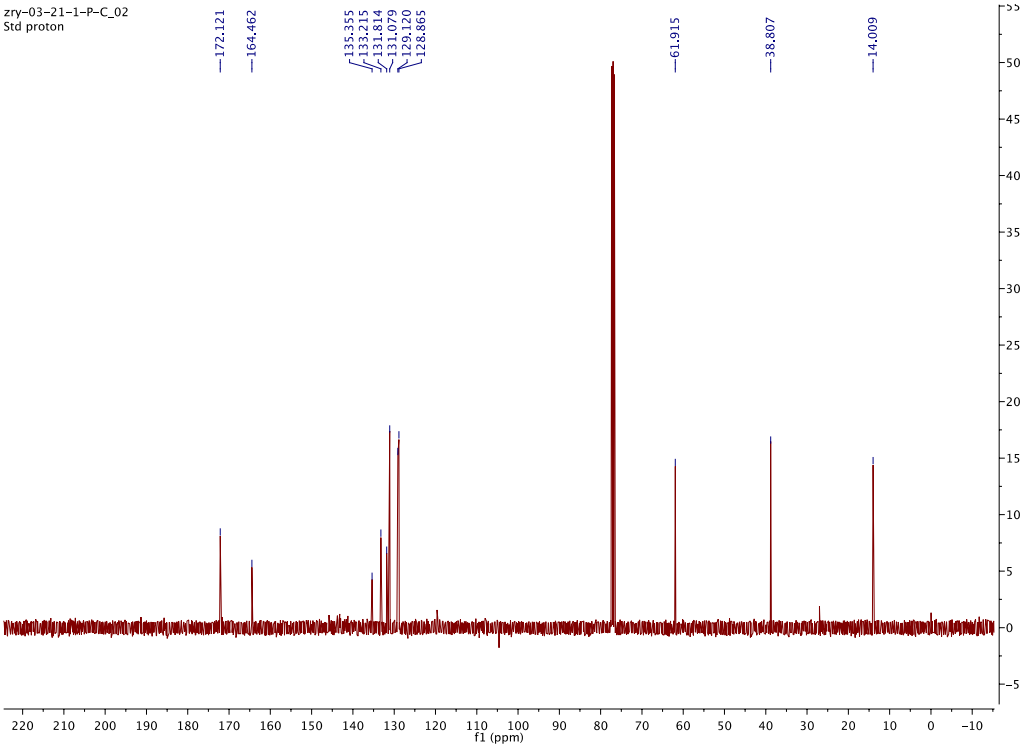

F
F
CF3
O
S
N
H
F
F
Me

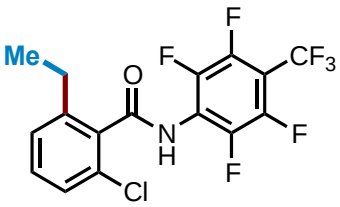

zry-03-99-P-H_01
Std proton
9.446
7.680
7.667
7.086
7.073
2.555
0.78
0.82
0.86
3.00
f1 (ppm)

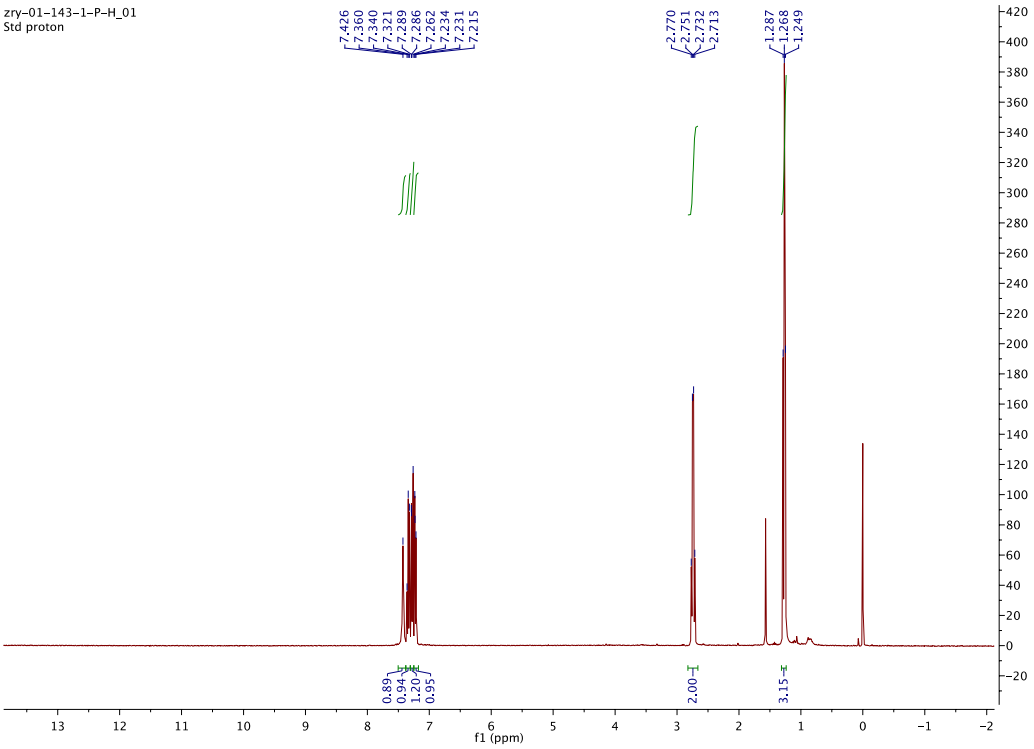

zry-03-99-P-C_01
Std proton
161.465
145.356
132.945
129.925
129.392
15.859
f1 (ppm)

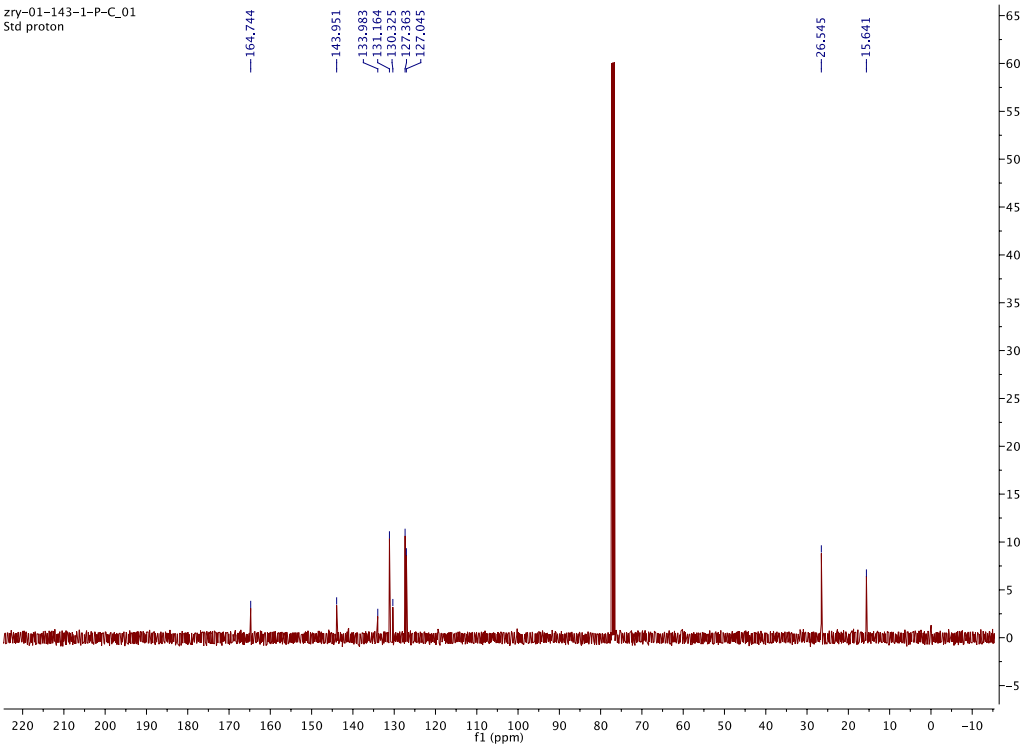

O
EtO
O
N
H
F
F
CF3
F
F
Cl

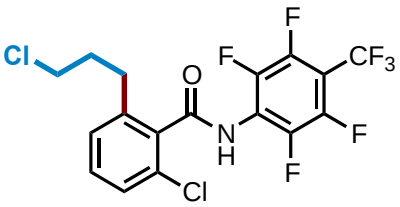

zry-03-21-1-P-H_02
Std proton
8.460
7.425
7.421
7.404
7.401
7.378
7.359
7.339
7.213
7.209
7.194
7.190
4.208
4.190
4.172
4.154
3.781
1.303
1.285
1.267
0.96
1.93
0.98
2.00
2.12
3.07
f1 (ppm)

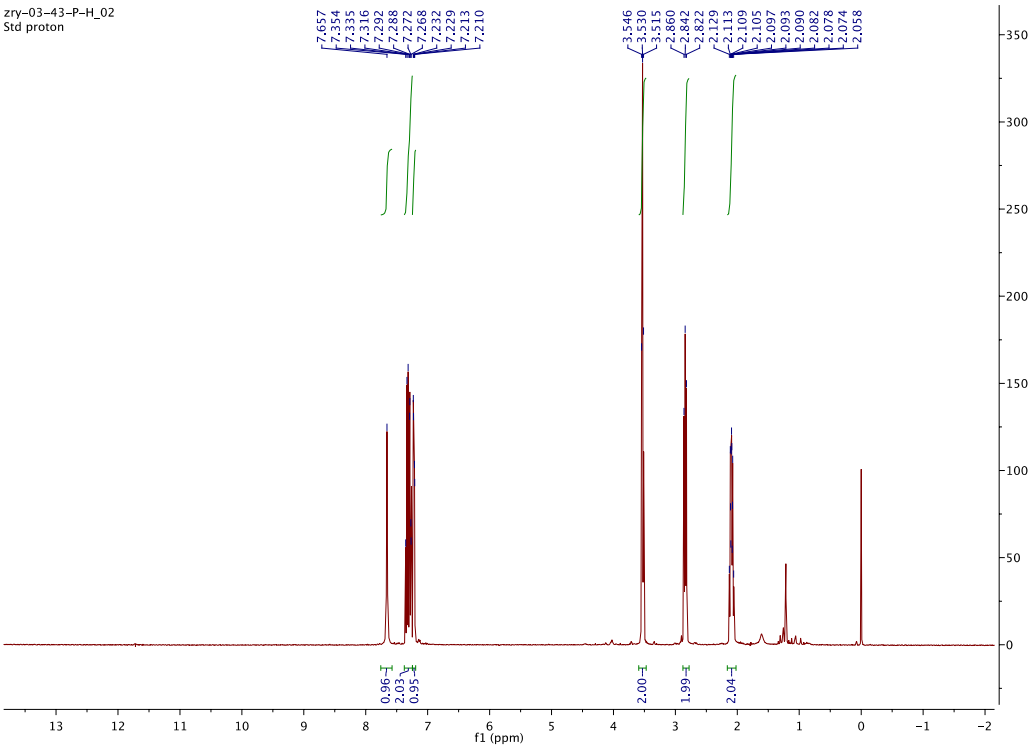

zry-03-21-1-P-C_02
Std proton
172.121
164.462
135.355
133.215
131.814
131.079
129.120
128.865
61.915
38.807
14.009
f1 (ppm)

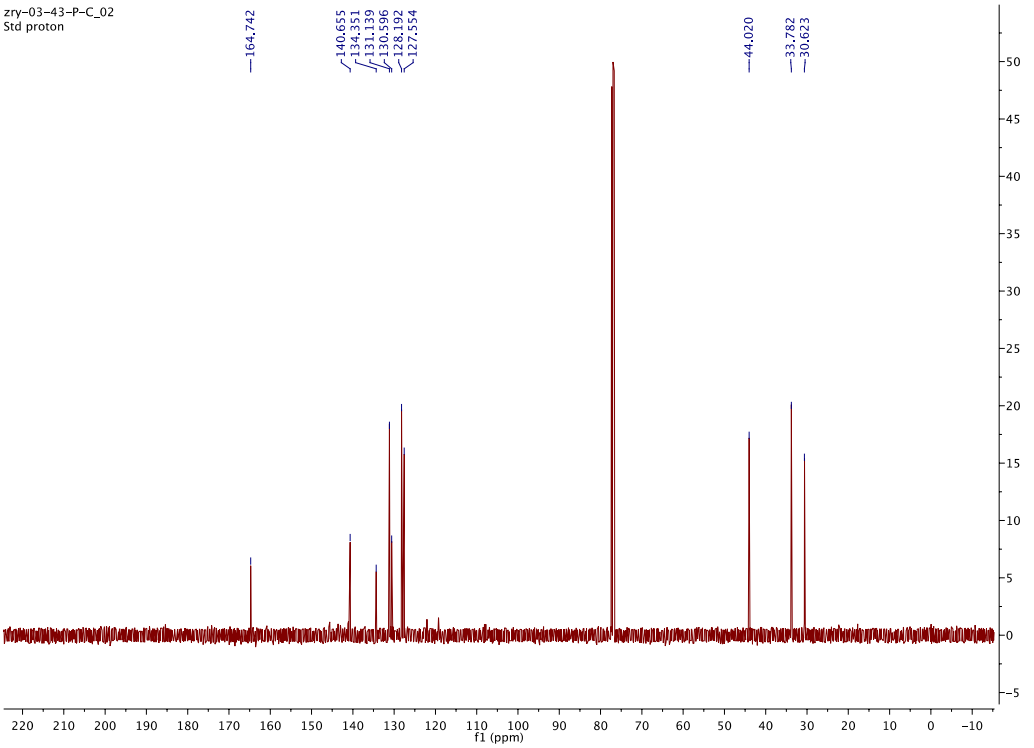

Me
O
N
H
F
F
CF3
F
F
Cl


zry-01-143-1-P-H_01
Std proton
7.426
7.360
7.340
7.321
7.289
7.286
7.262
7.234
7.231
7.215
2.770
2.751
2.732
2.713
1.287
1.268
1.249
0.89
0.94
1.20
0.95
2.00
3.15
f1 (ppm)


zry-01-143-1-P-C_01
Std proton
164.744
143.951
133.983
131.164
130.325
127.363
127.045
26.545
15.641
f1 (ppm)


Cl
O
N
H
F
F
CF3
F
F
Cl


zry-03-43-P-H_02
Std proton
7.657
7.354
7.335
7.316
7.292
7.288
7.272
7.268
7.232
7.229
7.213
7.210
3.546
3.530
3.515
2.860
2.842
2.822
2.129
2.113
2.109
2.105
2.097
2.093
2.090
2.082
2.078
2.074
2.058
0.96
2.03
0.95
2.00
1.99
2.04
f1 (ppm)


zry-03-43-P-C_02
Std proton
164.742
140.655
134.351
131.139
130.596
128.192
127.554
44.020
33.782
30.623
f1 (ppm)