A coupling approach for the generation of α,α-bis(enolate) equivalents: Regioselective synthesis of *gem*-difunctionalized ketones

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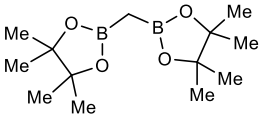
General Information

Solvents were purchased from standard chemical suppliers (Fisher, Sigma-Aldrich, VWR, Fluorochem) and dried over molecular sieves using the method of Williams[1] and degassed by sparging with dry nitrogen. 2,2,6,6-tetramethylpiperidine was distilled before use. Iodomethane was dried over molecular sieves. Other reagents were used as purchased. Reactions were performed under an atmosphere of dry nitrogen gas. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien 60F254 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm, and subsequently developed using vanillin or potassium permanganate as appropriate. Flash column chromatography was carried out using silica gel (Apollo Scientific 60Å particle size 40-63 micron). Melting points are uncorrected. Infra-red spectra were recorded on a Bruker Alpha-P ATR instrument on the neat compound. NMR spectra were recorded on a Bruker DPX-300, Bruker Avance III HD 300 MHz or Bruker Avance III HD 500 MHz instrument. For ^{1}H NMR spectra, chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard ($CDCl_3$ at 7.26 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q, (quartet), app (apparent), br (broad). Coupling constants (J) are quoted to the nearest 0.1 Hz. For proton decoupled ^{13}C NMR spectra, chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard ($CDCl_3$ at 77.16 ppm). Assignments were made using DEPT or PENDANT pulse sequences. For proton-decoupled ^{19}F NMR spectra, chemical shifts (δ) are quoted in parts per million (ppm) downfield of $CFCl_3$, using residual protonated solvent as internal standard ($CFCl_3$ at 376.38 MHz with respect to tetramethylsilane at 400.00 MHz). Low resolution mass spectra were recorded using electrospray ionization (ESI) techniques on an Agilent 6130R instrument. High resolution mass spectra were recorded using electrospray ionization (ESI) techniques on a Bruker Maxis instrument

Synthesis of geminal bis(boron) compounds

Compounds **S1,**[2] **S2,**[2] **S3,**[3] **S4,**[4] **S5**[4] **and S6**[5] were synthesized by known methods and displayed NMR and mass spectral data in full agreement with that reported in the literature



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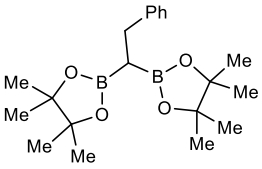

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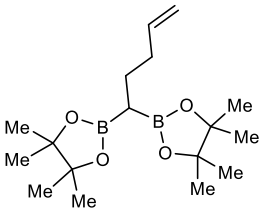

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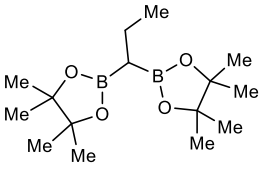

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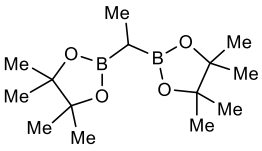

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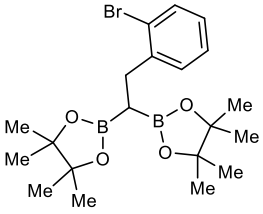

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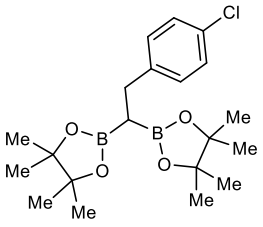
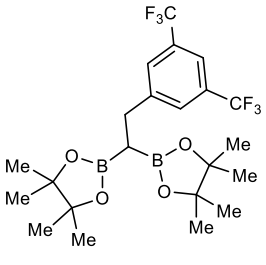


S7

2,2'-(2-(4-chlorophenyl)ethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)

A solution of LiTMP was prepared by the addition of nBuLi (1.32 mL, 2.5 M in hexanes, 3.3 mmol) to 2,2,6,6-tetramethylpiperidine (0.565 mL, 3.3 mmol) in THF (5 mL) at 0 °C. A solution of bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane **S1** in THF (1 mL) was added slowly to the LiTMP solution and stirred for 1 h. After this period a solution of 4-chlorobenzyl bromide (0.616 g, 3.0 mmol) in THF (2 mL) was added to the mixture, which was stirred at 0 °C for 2 h before warming to room temperature. The solution was diluted with diethyl ether (10 mL) and water (5 mL) and the organic layer separated. The aqueous layer was extracted with further portions of diethyl ether (3 x 10 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and evaporated. The crude material was purified by flash column chromatography on silica (EtOAc / hexanes, 10%) to give the title compound as a white solid (0.82 g, 70%); m.p. 60 – 61 °C; δ_H (400 MHz, $CDCl_3$) δ 7.20 – 7.13 (m, 4H, Ar**H**), 2.83 (d, *J* = 8.4 Hz, 2H, ArC**H₂**), 1.18 (s, 12H, BOC(C**H₃**)₂), 1.16 (s, 12H, BOC(C**H₃**)₂), 1.11 (t, *J* = 8.4 Hz, C**H**(B(pin))₂); δ_C (101 MHz, $CDCl_3$) δ 142.9 (C), 130.9 (C), 129.6 (2 x CH), 128.0 (2 x CH), 83.2 (4 x C), 30.7 (CH_2), 24.8 (4 x CH_3), 24.5 (4 x CH_3); HRMS (ES^+): Exact mass calculated for $C_{20}H_{31}B_2O_4ClNa$ $[M+Na]^+$: 415.1997, found: 415.2000.

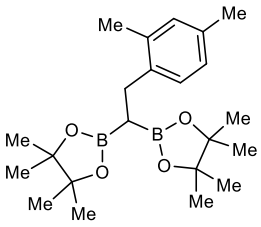


S8

2,2'-(2-(3,5-bis(trifluoromethyl)phenyl)ethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)

A solution of LiTMP was prepared by the addition of nBuLi (1.32 mL, 2.5 M in hexanes, 3.3 mmol) to 2,2,6,6-tetramethylpiperidine (0.565 mL, 3.3 mmol) in THF (5 mL) at 0 °C. A solution of bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane **S1** in THF (1 mL) was added slowly to the LiTMP solution and

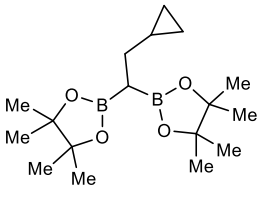
stirred for 1 h. After this period a solution of 3,5-bis(trifluoromethyl)benzyl bromide (0.921 g, 3.0 mmol) in THF (2 mL) was added to the mixture, which was stirred at 0 °C for 2 h before warming to room temperature. The solution was diluted with diethyl ether (10 mL) and water (5 mL) and the organic layer separated. The aqueous layer was extracted with further portions of diethyl ether (3 x 10 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and evaporated. The crude material was purified by flash column chromatography on silica (EtOAc / hexanes, 10%) to give the title compound as a colorless oil (0.92 g, 62%); δ_H (400 MHz, $CDCl_3$) δ 7.72 (s, 2H, Ar**H**), 7.65 (s, 1H, Ar**H**), 2.98 (d, *J* = 8.1 Hz, 2H, ArC**H₂**), 1.19 (s, 12H, BOC(C**H₃**)₂), 1.18 (s, 12H , BOC(C**H₃**)₂), 1.12 (t, *J* = 8.1 Hz, C**H**(B(pin))₂); δ_C (101 MHz, $CDCl_3$) δ 147.0 (s, C), 131.1 (q, *J* = 32.9 Hz, 2 x C), 128.8 (q, *J* = 2.5 Hz, 2 x CH), 123.5 (q, *J* = 273 Hz, CF_3), 119.5 (sept, *J* = 3.9 Hz, CH), 83.4 (s, 4 x C), 31.2 (s, CH_2), 24.7 (s, 4 x CH_3), 24.5 (s, 4 x CH_3); δ_F (376 MHz, $CDCl_3$) -62.9 (s); HRMS (ES^+): Exact mass calculated for $C_{22}H_{30}B_2O_4F_6Na$ $[M+Na]^+$: 517.2134, found: 517.2137.



S9

2,2'-(2-(2,4-dimethylphenyl)ethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)

A solution of LiTMP was prepared by the addition of nBuLi (1.32 mL, 2.5 M in hexanes, 3.3 mmol) to 2,2,6,6-tetramethylpiperidine (0.565 mL, 3.3 mmol) in THF (5 mL) at 0 °C. A solution of bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane **S1** in THF (1 mL) was added slowly to the LiTMP solution and stirred for 1 h. After this period a solution of 2,4-dimethylbenzyl bromide (0.398 g, 2.0 mmol) in THF (2 mL) was added to the mixture, which was stirred at 0 °C for 2 h before warming to room temperature. The solution was diluted with diethyl ether (10 mL) and water (5 mL) and the organic layer separated. The aqueous layer was extracted with further portions of diethyl ether (3 x 10 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and evaporated. The crude material was purified by flash column chromatography on silica (EtOAc / hexanes, 10%) to give the title compound as a colorless oil (0.51 g, 67%); δ_H (400 MHz, $CDCl_3$) δ 7.11 (d, *J* = 7.6 Hz, 1H, Ar**H**), 6.90 – 6.85 (m, 2H, Ar**H**), 2.81 (d, *J* = 8.0 Hz, 2H, ArC**H₂**), 2.27 (s, 3H, ArC**H₃**), 2.25 (s, 3H, ArC**H₃**), 1.19 (s, 24H, BOC(C**H₃**)₂), 1.11 (t, *J* = 8.0 Hz, C**H**(B(pin))₂); δ_C (101 MHz, $CDCl_3$) δ 139.4 (C), 135.7 (C), 134.6 (C), 130.6 (CH), 128.3 (CH), 126.1 (CH), 83.0 (4 x C), 27.9 (CH_2), 24.8 (4 x CH_3), 24.5 (4 x CH_3), 20.8 (CH_3), 19.3 (CH_3). HRMS (ES^+): Exact mass calculated for $C_{22}H_{36}B_2O_4Na$ $[M+Na]^+$: 409.2699, found: 409.2701.



S10

2,2'-(2-cyclopropylethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)

A solution of LiTMP was prepared by the addition of nBuLi (1.32 mL, 2.5 M in hexanes, 3.3 mmol) to 2,2,6,6-tetramethylpiperidine (0.565 mL, 3.3 mmol) in THF (5 mL) at 0 °C. A solution of bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane **S1** in THF (1 mL) was added slowly to the LiTMP solution and stirred for 1 h. After this period a solution of (bromomethyl)cyclopropane (0.405 g, 3.0 mmol) in THF (2 mL) was added to the mixture, which was stirred at 0 °C for 2 h before warming to room temperature. The solution was diluted with diethyl ether (10 mL) and water (5 mL) and the organic layer separated. The aqueous layer was extracted with further portions of diethyl ether (3 x 10 mL)

and the combined organic extracts were dried ($MgSO_4$), filtered and evaporated. The crude material was purified by flash column chromatography on silica (EtOAc / hexanes, 10%) to give the title compound as a colorless oil (0.62 g, 64%); δ_H (400 MHz, $CDCl_3$) δ 1.40 (t, J = 7.3 Hz, 2H, C**H₂**Cypro), 1.17 (s, 24H, BOC(C**H₃**)$_2$), 0.82 (t, J = 7.7 Hz, 1H, C**H**(B(pin))$_2$), 0.71 – 0.56 (m, 1H, CH_2C**H**(CH_2CH_2)), 0.32 – 0.26 (m, 2H, C**H₂**C**H₂**), 0.02 – -0.03 (m, 2H, C**H₂**C**H₂**); δ_C (101 MHz, $CDCl_3$) δ 82.9 (4 x C), 30.8 (CH_2), 24.8 (4 x CH_3), 24.6 (4 x CH_3), 13.5 (CH), 4.7 (2 x CH_2). HRMS (ES^+): Exact mass calculated for $C_{17}H_{32}B_2O_4Na$ $[M+Na]^+$: 345.2385, found: 345.2386.

Difluorinative and dimethylative coupling of esters with geminal bis(boron) compounds

General Procedure A: Difluorinative coupling of non-enolizable esters

Ester (0.40 mmol) and geminal bis(boron) compound (0.80 mmol) were mixed under nitrogen and dissolved in THF (1 mL). Sodium bis(trimethylsilyl)amide (0.50 mL, 2M in THF, 1.0 mmol) was added and the mixture heated to 50 °C for 15 minutes. After this period the mixture was cooled to room temperature, and a solution of *N*-fluorobenzenesulfonimide (378 mg, 1.2 mmol) in THF (1 mL) was added. After stirring for 15 minutes at room temperature the mixture was eluted through a short pad of silica (Et_2O) and concentrated. The compound was purified by flash column chromatography.

General Procedure B: Difluorinative coupling of enolizable esters

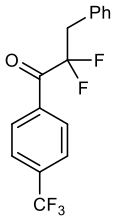
A solution of LiTMP was prepared by adding *n*-BuLi (0.32 mL, 0.8 mmol, 2.5 M in hexanes) to 2,2,6,6-tetramethylpiperidine (135 µL, 0.80 mmol) in THF (1 mL) and stirring at 0 °C for 15 minutes. Geminal bis(boron) compound (0.80 mmol) in THF (0.5 mL) was added and the mixture stirred for an additional 15 minutes at 0 °C. A solution of ester (0.40 mmol) in THF (0.5 mL) was added and the mixture heated to 50 °C for 15 minutes. After this period the mixture was cooled to room temperature, and a solution of *N*-fluorobenzenesulfonimide (378 mg, 1.2 mmol) in THF (1 mL) was added. After stirring for 15 minutes at room temperature the mixture was eluted through a short pad of silica (Et_2O) and concentrated. The compound was purified by flash column chromatography.

General Procedure C: Dimethylative coupling of non-enolizable esters

Ester (0.40 mmol) and geminal bis(boron) compound (0.80 mmol) were mixed under nitrogen and dissolved in THF (1 mL). Sodium bis(trimethylsilyl)amide (0.5 mL, 2M in THF, 1.0 mmol) was added and the mixture heated to 50 °C for 15 minutes. After this period the mixture was cooled to room temperature, and a solution of iodomethane (125 µL, 2.0 mmol) in THF (1 mL) was added. After stirring for 15 minutes at room temperature the mixture was eluted through a short pad of silica (Et_2O) and concentrated. The compound was purified by flash column chromatography.

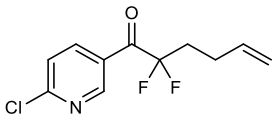
General Procedure D: Dimethylative coupling of enolizable esters

A solution of LiTMP was prepared by adding *n*-BuLi (0.32 mL, 0.8 mmol, 2.5 M in hexanes) to 2,2,6,6-tetramethylpiperidine (135 µL, 0.80 mmol) in THF (1 mL) and stirring at 0 °C for 15 minutes. Geminal bis(boron) compound (0.80 mmol) in THF (0.5 mL) was added and the mixture stirred for an additional 15 minutes at 0 °C. A solution of ester (0.40 mmol) in THF (0.5 mL) was added and the mixture heated to 50 °C for 15 minutes. After this period the mixture was cooled to room temperature, and a solution of iodomethane (125 µL, 2.0 mmol) in THF (1 mL) was added. After stirring for 15 minutes at room temperature the mixture was eluted through a short pad of silica (Et_2O) and concentrated. The compound was purified by flash column chromatography.



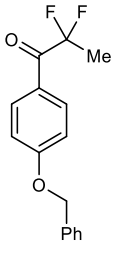
2,2-Difluoro-3-phenyl-1-(4-(trifluoromethyl)phenyl)propan-1-one (1a)

This compound was prepared using General Procedure A using ethyl 4-trifluoromethyl)benzoate (87 mg, 0.40 mmol), 2,2'-(2-phenylethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (287 mg, 0.80 mmol), sodium bis(trimethylsilyl)amide (0.5 mL, 2M in THF, 1.0 mmol), *N*-fluorobenzenesulfonimide (378 mg, 1.2 mmol) in THF (2 mL total). The compound was purified by flash column chromatography using Et_2O / hexane (2%) as eluent to yield the title compound as a colorless oil (69 mg, 55%); R_F = 0.63 (Et_2O / hexane (10%)); δ_H (500 MHz, $CDCl_3$) 8.10 (d, *J* = 8.2 Hz, 2H, Ar**H**), 7.72 (d, *J* = 8.2 Hz, 2H, Ar**H**), 7.35 – 7.28 (m, 5H, Ar**H**), 3.53 (t, *J* = 17.8 Hz, 2H, ArC**H₂**); δ_C (126 MHz, $CDCl_3$) δ 188.9 (t, *J* = 32.1 Hz, C), 135.3 (q, *J* = 32.9 Hz, C), 134.9 (s, C), 133.7 (s, C), 130.8 (s, 2 x CH), 130.4 (t, *J* = 3.4 Hz, 2 x CH), 128.5 (s, 2 x CH), 127.8 (s, CH), 125.6 (q, *J* = 3.6 Hz, 2 x CH), 123.3 (q, *J* = 272 Hz, CF_3), 118.2 (t, *J* = 255 Hz, CF_2), 39.9 (t, *J* = 23.0 Hz, CH_2); δ_F (282 MHz, $CDCl_3$) -63.4 (s ,3F), -98.7 (t, *J* = 17.8 Hz, 2F); HRMS (ES^+): Exact mass calculated for $C_{16}H_{11}NaOF_5$ $[M+Na]^+$: 337.0622, found: 337.0620.



1-(6-chloropyridin-3-yl)-2,2-difluorohex-5-en-1-one (1b)

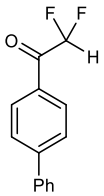
This compound was prepared using General Procedure A using ethyl 6-chloronicotinate (128 mg, 0.40 mmol), 2,2'-(pent-4-ene-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (258 mg, 0.80 mmol), sodium bis(trimethylsilyl)amide (0.5 mL, 2M in THF, 1.0 mmol), *N*-fluorobenzenesulfonimide (378 mg, 1.2 mmol) in THF (2 mL total). The compound was purified by flash column chromatography using Et_2O / hexane (2 → 10%) as eluent to yield the title compound as a colorless oil (59 mg, 60%); R_F = 0.22 (Et_2O / hexane (10%)); δ_H (400 MHz, $CDCl_3$) 9.09 (s, 1H, Ar**H**), 8.32 (dd, *J* = 8.4, 1.6 Hz, 1H, Ar**H**), 7.49 (d, *J* = 8.4 Hz, 1H, Ar**H**), 5.84 (ddt, *J* = 17.3, 10.4, 5.9 Hz, 1H, CH_2C**H**=CH_2), 5.10 (d, *J* = 17.3 Hz, 1H, CH_2CH=C**H₂**), 5.04 (d, *J* = 10.4 Hz, 1H, CH_2CH=C**H₂**), 2.38 – 2.22 (m, 4H, CF_2C**H₂**C**H₂**); δ_C (101 MHz, $CDCl_3$) 187.4 (s, C), 156.8 (s, C), 151.8 (t, *J* = 4.7 Hz, CH), 139.8 (t, *J* = 3.1 Hz, CH), 136.0 (s, CH), 126.5 (t, *J* = 2.8 Hz, C), 124.6 (s, CH), 119.3 (t, *J* = 252 Hz, CF_2) 115.9 (s, CH_2), 32.5 (t, *J* = 22.4 Hz, CH_2), 25.4 (t, *J* = 4.9 Hz, CH_2); δ_F (376 MHz, $CDCl_3$) -100.7 (t, *J* = 17.7 Hz); HRMS (ES^+): Exact mass calculated for $C_{11}H_{11}ClF_2NO$ $[M+H]^+$: 246.0497, found: 246.0494.



1-(4-(benzyloxy)phenyl)-2,2-difluoropropan-1-one (1c)

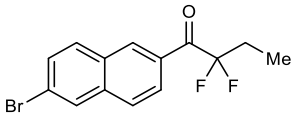
This compound was prepared using General Procedure A using methyl 4-benzyloxybenzoate (97 mg, 0.40 mmol), 2,2'-(ethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (226 mg, 0.80 mmol), sodium bis(trimethylsilyl)amide (0.5 mL, 2M in THF, 1.0 mmol), *N*-fluorobenzenesulfonimide (378 mg, 1.2 mmol) in THF (2 mL total). The compound was purified by flash column chromatography using Et_2O / hexane (2%) as eluent to yield the title compound as a white solid (79 mg, 71%); m.p. 40 - 41°C; R_F = 0.43 (Et_2O / hexane (10%)); IR 1694, 1598, 1571, 1510, 1422, 1310, 1229, 1165, 1132, 1103, 984, 921; δ_H (500 MHz, $CDCl_3$) 8.13 (d, *J* = 8.9 Hz, 2H, Ar**H**), 7.46 – 7.33 (m, 5H, Ar**H**), 7.04 (d, *J* = 8.9 Hz, 2H, Ar**H**), 5.16 (s, 2H, PhC**H₂**O), 1.88 (t, *J* = 19.5 Hz, 3H, C**H₃**); δ_C (126 MHz, $CDCl_3$) 187.6 (t, *J* = 31.5 Hz, C), 163.5 (s, C), 135.9 (s, C), 132.8 (t, *J* = 3.3 Hz, 2 x CH), 128.7 (s, 2 x CH), 128.3 (s, CH), 127.5 (s, 2 x CH), 124.6 (t, *J* = 2.8 Hz, C), 119.6 (t, *J* = 250 Hz, CF_2), 114.8 (s, 2 x CH), 70.2 (s, CH_2), 20.9 (t, *J* = 25.1 Hz, CH_3); δ_F (376 MHz,

$CDCl_3$) -92.2 (q, *J* = 19.5 Hz); HRMS (ES^+): Exact mass calculated for $C_{16}H_{14}NaO_2F_2$ $[M+Na]^+$: 299.0854, found: 299.0856.



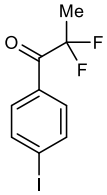
1-([1,1'-biphenyl]-4-yl)-2,2-difluoroethan-1-one (1d)

This compound was prepared using General Procedure A using methyl 4-phenylbenzoate (85 mg, 0.40 mmol), bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (214 mg, 0.80 mmol), sodium bis(trimethylsilyl)amide (0.5 mL, 2M in THF, 1.0 mmol), *N*-fluorobenzenesulfonimide (378 mg, 1.2 mmol) in THF (2 mL total). The compound was purified by flash column chromatography using Et_2O / hexane (2%) as eluent to yield the title compound as a yellow solid (83 mg, 89%); δ_H (500 MHz, $CDCl_3$) 8.16 (d, *J* = 8.3 Hz, 2H, Ar**H**), 7.75 (d, *J* = 8.3 Hz, 2H, Ar**H**), 7.65 (d, *J* = 7.5 Hz, 2H, Ar**H**), 7.50 (t, *J* = 7.5 Hz, 2H, Ar**H**), 7.44 (t, *J* = 7.5 Hz, 1H, Ar**H**), 6.32 (t, *J* = 53.5 Hz, 1H, CF_2**H**); δ_C (126 MHz, $CDCl_3$) 187.2 (t, *J* = 25.4 Hz, C), 147.6 (s, C), 139.4 (s, C), 130.3 (t, *J* = 2.2 Hz, 2 x CH), 130.1 (t, *J* = 1.8 Hz, C), 129.1 (s, 2 x CH), 128.7 (s, CH), 127.5 (s, 2 x CH), 127.3 (s, 2 x CH), 111.3 (t, *J* = 253.8 Hz, CF_2H); δ_F (282 MHz, $CDCl_3$) -121.7 (d, *J* = 53.5 Hz). Data in full agreement with the literature.[6]



1-(6-bromonaphthalen-2-yl)-2,2-difluorobutan-1-one (1e)

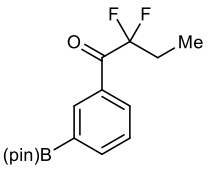
This compound was prepared using General Procedure A using methyl 6-bromo-2-naphthoate (106 mg, 0.40 mmol), 2,2'-(propane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (237 mg, 0.80 mmol), sodium bis(trimethylsilyl)amide (0.5 mL, 2M in THF, 1.0 mmol), *N*-fluorobenzenesulfonimide (378 mg, 1.2 mmol) in THF (2 mL total). The compound was purified by flash column chromatography using Et_2O / hexane (2%) as eluent to yield the title compound as a yellow solid (93 mg, 74%); m.p. 64 – 65 °C; R_F = 0.62 (Et_2O / hexane (10%)); IR 1702, 1616, 1460, 1383, 1278, 1140, 1115, 1064, 1055, 887, 812 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.67 (s, 1H, Ar**H**), 8.13 (d, *J* = 8.7 Hz, 1H, Ar**H**), 8.06 (s, 1H, Ar**H**), 7.87 (d, *J* = 8.7 Hz, 1H, Ar**H**), 7.83 (d, *J* = 8.7 Hz, 1H, Ar**H**), 7.66 (dd, *J* = 8.7, 1.7 Hz, 1H, Ar**H**), 2.35 – 2.21 (tq, *J* = 17.7, 7.5 Hz, 2H, CH_2C**H$_3$**), 1.15 (t, *J* = 7.5 Hz, 3H, CH_2C**H$_3$**); δ_C (126 MHz, $CDCl_3$) 189.1 (t, *J* = 31.6 Hz, C), 136.8 (s, C), 132.5 (t, *J* = 4.7 Hz, CH), 131.5 (s, CH), 130.7 (s, C), 130.5 (s, CH), 130.0 (s, CH), 129.6 (t, *J* = 2.6 Hz, C), 127.6 (s, CH), 126.1 (t, *J* = 1.9 Hz, CH), 123.8 (s, C), 120.2 (t, *J* = 252.6 Hz, CF_2), 27.4 (t, *J* = 23.6 Hz, CH_2), 5.8 (t, *J* = 5.6 Hz, CH_3); δ_F (376 MHz, $CDCl_3$) -101.4 (t, *J* = 17.7 Hz); HRMS (ES^+): Exact mass calculated for $C_{14}H_{11}NaOF_2Br$ (^{79}Br) $[M+Na]^+$: 334.9854, found: 334.9850.



2,2-difluoro-1-(4-iodophenyl)propan-1-one (1f)

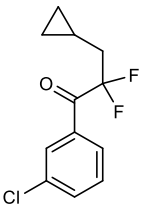
This compound was prepared using General Procedure A using ethyl 4-iodobenzoate (111 mg, 0.40 mmol), 2,2'-(ethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (226 mg, 0.80 mmol), sodium bis(trimethylsilyl)amide (0.5 mL, 2M in THF, 1.0 mmol), *N*-fluorobenzenesulfonimide (378 mg, 1.2 mmol) in THF (2 mL total). The compound was purified by flash column chromatography using Et_2O / hexane (2%) as eluent to yield the title compound as a pale yellow solid (73 mg, 62%); m.p. 42 – 43 °C; R_F = 0.64 (Et_2O / hexane (10%)); IR

1702, 1578, 1556, 1387, 1275, 1199, 1173, 1134, 1059, 990, 926, 867, 748 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.87 (d, *J* = 8.6 Hz, 2H, Ar**H**), 7.82 (d, *J* = 8.6 Hz, 2H, Ar**H**), 1.88 (t, *J* = 19.5 Hz, 3H, C**H₃**); δ_C (126 MHz, $CDCl_3$) 188.5 (t, *J* = 32.5 Hz, C), 138.1 (s, 2 x CH), 131.4 (t, *J* = 3.3 Hz, 2 x CH), 130.8 (t, *J* = 3.0 Hz, C), 119.3 (t, *J* = 250 Hz, CF_2), 102.9 (s, C), 20.6 (t, *J* = 24.8 Hz, CH_3); δ_F (282 MHz, $CDCl_3$) -92.8 (q, *J* = 19.5 Hz); HRMS (ES^+): Exact mass calculated for $C_9H_7NaOF_2I$ $[M+Na]^+$: 318.9402, found: 318.9401.



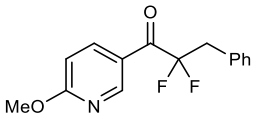
2,2-difluoro-1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)butan-1-one (1g)

This compound was prepared using General Procedure A using methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (105 mg, 0.40 mmol), 2,2'-(propane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (237 mg, 0.80 mmol), sodium bis(trimethylsilyl)amide (0.5 mL, 2M in THF, 1.0 mmol), *N*-fluorobenzenesulfonimide (378 mg, 1.2 mmol) in THF (2 mL total). The compound was purified by flash column chromatography using Et_2O / hexane (2%) as eluent to yield the title compound as a colorless oil (64 mg, 52%); R_F = 0.37 (Et_2O / hexane (10%)); IR 2978, 1703, 1601, 1359, 1326, 1264, 1138, 980, 698 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.51 (s, 1H, Ar**H**), 8.18 (d, *J* = 7.9 Hz, 1H, Ar**H**), 8.04 (d, *J* = 7.4 Hz, 1H, Ar**H**), 7.49 (t, *J* = 7.6 Hz, 1H, Ar**H**), 2.22 (tq, *J* = 17.6, 7.6 Hz, 2H, C**H₂**CH_3), 1.35 (s, 12H, BOC(C**H₃**)$_2$), 1.09 (t, *J* = 7.6 Hz, 3H, CH_2C**H₃**); δ_C (126 MHz, $CDCl_3$) 189.8 (t, *J* = 31.2 Hz, C), 140.3 (s, CH), 136.4 (t, *J* = 2.8 Hz, CH), 132.6 (t, *J* = 3.6 Hz, CH), 131.7 (t, *J* = 2.3 Hz, C), 128.0 (s, CH), 120.0 (t, *J* = 253 Hz, CF_2), 84.2 (s, C), 27.4 (t, *J* = 23.6 Hz, CH_2), 24.9 (s, CH_3), 5.8 (t, *J* = 5.6 Hz, CH_3) (quaternary carbon next to boron not visible); δ_F (282 MHz, $CDCl_3$) -102.2 (t, *J* = 17.6 Hz); HRMS (ES^+): Exact mass calculated for $C_{16}H_{21}NaO_3BF_2$ $[M+Na]^+$: 333.1447, found: 333.1449.



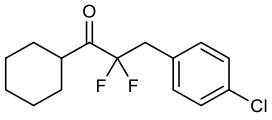
1-(3-chlorophenyl)-3-cyclopropyl-2,2-difluoropropan-1-one (1h)

This compound was prepared using General Procedure A using methyl 3-chlorobenzoate (68.2 mg, 0.40 mmol), 2,2'-(2-cyclopropylethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (258 mg, 0.80 mmol), sodium bis(trimethylsilyl)amide (0.5 mL, 2M in THF, 1.0 mmol), *N*-fluorobenzenesulfonimide (378 mg, 1.2 mmol) in THF (2 mL total). The compound was purified by flash column chromatography using Et_2O / hexane (2%) as eluent to yield the title compound as a pale yellow oil (72 mg, 74%); R_F = 0.60 (Et_2O / hexane (10%)); IR 1708, 1570, 1426, 1255, 1179, 1166, 1098, 1079, 1038, 1025, 971, 831, 747, 698, 674, 609 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.07 (br s, 1H, Ar**H**), 7.99 (d, *J* = 7.9 Hz, 1H, Ar**H**), 7.60 (d, *J* = 7.9 Hz, 1H, Ar**H**), 7.44 (t, *J* = 7.9 Hz, 1H, Ar**H**), 2.12 (td, *J* = 16.8, 7.1 Hz, 2H, CF_2C**H₂**), 0.92 – 0.83 (m, 1H, CF_2CH_2C**H**), 0.55 – 0.50 (m, 2H, C**H₂**C**H₂**), 0.19 – 0.13 (m, 2H, C**H₂**C**H₂**); δ_C (126 MHz, $CDCl_3$) 188.9 (t, *J* = 31.4 Hz, C), 135.0 (s, C), 134.1 (s, CH), 133.8 (t, *J* = 2.3 Hz, C), 130.18 – 129.81 (m, 2 x CH), 128.2 (t, *J* = 3.7 Hz, CH), 119.6 (t, *J* = 253.1 Hz, CF_2), 38.8 (t, *J* = 22.6 Hz, CH_2), 4.2 (s, 2 x CH_2), 3.6 (t, *J* = 6.1 Hz, CH); δ_F (282 MHz, $CDCl_3$) -99.4 (t, *J* = 16.8 Hz); HRMS (ES^+): Exact mass calculated for $C_{12}H_{11}NaOF_2Cl$ $[M+Na]^+$: 267.0359, found: 267.0359.



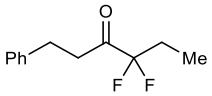
2,2-difluoro-1-(6-methoxypyridin-3-yl)-3-phenylpropan-1-one (1i)

Methyl 6-methoxynicotinate (418 mg, 2.5 mmol) and 2,2'-(2-phenylethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (1.79 g, 5.0 mmol) were mixed under nitrogen and dissolved in THF (5 mL). Sodium bis(trimethylsilyl)amide (3.0 mL, 2M in THF, 6.0 mmol) was added and the mixture heated to 50 °C for 15 minutes. After this period the mixture was cooled to room temperature, and a solution of *N*-fluorobenzenesulfonimide (2.37 g, 7.5 mmol) in THF (5 mL) was added. After stirring for 15 minutes at room temperature the mixture was eluted through a short pad of silica (Et_2O) and concentrated. The compound was purified by flash column chromatography using Et_2O / hexane (2% to 10%) as eluent to yield the title compound as a pale yellow oil (437 mg, 63%); R_F = 0.48 (Et_2O / hexane (10%)); IR 1696, 1594, 1495, 1455, 1299, 1280, 1181, 1011, 844, 72, 697 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.85 (s, 1H, Ar**H**), 8.10 (dd, *J* = 8.8, 2.2 Hz, 1H, Ar**H**), 7.30 – 7.22 (m, 5H, Ar**H**), 6.71 (d, *J* = 8.8 Hz, 1H, Ar**H**), 3.95 (s, 3H, OC**H₃**), 3.45 (t, *J* = 17.8 Hz, 2H, ArC**H₂**); δ_C (101 MHz, $CDCl_3$) 187.5 (t, *J* = 32.0 Hz, C), 167.1 (s, C), 151.5 (t, *J* = 5.5 Hz, CH), 141.6 (s, C), 139.7 (t, *J* = 2.5 Hz, CH), 131.1 (t, *J* = 3.6 Hz, C), 130.8 (s, 2 x CH), 128.4 (s, 2 x CH), 127.6 (s, CH), 118.3 (t, *J* = 254.2 Hz, CF_2), 111.2 (s, CH), 54.1 (s, CH_3), 39.9 (t, *J* = 23.2 Hz, CH_2); δ_F (376 MHz, $CDCl_3$) -98.9 (t, *J* = 17.8 Hz); HRMS (ES^+): Exact mass calculated for $C_{15}H_{14}NO_2F_2$ $[M+H]^+$: 278.0987, found: 278.0989.



3-(4-chlorophenyl)-1-cyclohexyl-2,2-difluoropropan-1-one (2a)

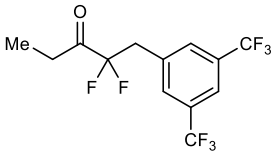
This compound was prepared using General Procedure B using methyl cyclohexanecarboxylate (56.9 mg, 0.40 mmol), 2,2'-(2-(4-chlorophenyl)ethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (314 mg, 0.80 mmol), 2,2,6,6-tetramethylpiperidine (135 µL, 0.80 mmol), *n*-BuLi (0.32 mL, 0.80 mmol, 2.5 M in hexanes), *N*-fluorobenzenesulfonimide (378 mg, 1.2 mmol) in THF (2 mL total). The compound was purified by flash column chromatography using Et_2O / hexane (2%) as eluent to yield the title compound as a pale yellow oil (86 mg, 75%); R_F = 0.62 (Et_2O / hexane (10%)); IR 2932, 2857, 1732, 1492, 1450, 1210, 1144, 1090, 1059, 1017, 978, 844, 747 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.28 (d, *J* = 8.4 Hz, 2H , Ar**H**), 7.16 (d, *J* = 8.4 Hz, 2H, Ar**H**), 3.27 (t, *J* = 16.9 Hz, 2H, ArC**H₂**), 2.71 (t, *J* = 8.6 Hz, 1H, O=CC**H**), 1.79 – 1.59 (m, 6H, cyclohexylC**H₂**), 1.23 – 1.13 (m, 4H, cyclohexylC**H₂**); δ_C (101 MHz, $CDCl_3$) 204.0 (t, *J* = 29.9 Hz, C), 133.7 (s, C), 132.1 (s, 2 × CH), 129.6 (t, *J* = 4.3 Hz, C), 128.9 – 128.2 (m, 2 × CH), 117.3 (t, *J* = 255.1 Hz, CF_2), 45.0 (s, CH), 38.6 (t, *J* = 23.7 Hz, CH_2), 27.9 (s, *J* = 12.1 Hz, CH_2), 25.5 (s, CH_2), 25.3 (s, CH_2); δ_F (376 MHz, $CDCl_3$) -104.9 (t, *J* = 16.9 Hz); HRMS (ES^+): Exact mass calculated for $C_{15}H_{17}NaClOF_2$ $[M+Na]^+$: 309.0828, found: 309.0825.



4,4-difluoro-1-phenylhexan-3-one (2b)

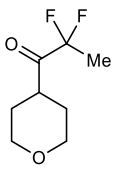
This compound was prepared using General Procedure B using ethyl hydrocinnamate (71 mg, 0.40 mmol), 2,2'-(propane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (237 mg, 0.80 mmol), 2,2,6,6-tetramethylpiperidine (135 µL, 0.80 mmol), *n*-BuLi (0.32 mL, 0.80 mmol, 2.5 M in hexanes), *N*-fluorobenzenesulfonimide (378 mg, 1.2 mmol) in THF (2 mL total). The compound was purified by flash column chromatography using Et_2O / hexane (2%) as eluent to yield the title compound as a colorless oil (53 mg, 62%); δ_H (500 MHz, $CDCl_3$) 7.33 – 7.19 (m, 5H,

Ar**H**), 3.04 – 2.99 (m, 2H, ArC**H₂**), 2.98 – 2.93 (m, 2H, O=CC**H₂**), 2.06 – 1.91 (tq *J* = 17.4, 7.6 Hz, 2H, C**H₂**CH_3), 0.98 (t, *J* = 7.6 Hz, 3H, CH_2C**H₃**); δ_C (126 MHz, $CDCl_3$) 200.5 (t, *J* = 31.7 Hz, C), 140.2 (s, C), 128.5 (s, 2 x CH), 128.3 (s, 2 x CH), 126.3 (s, CH), 118.5 (t, *J* = 251.4 Hz, CF_2), 38.1 (s, CH_2), 28.6 (s, *J* = 4.3 Hz, CH_2), 25.9 (t, *J* = 23.7 Hz, CH_2), 5.5 (t, *J* = 5.5 Hz, CH_3); δ_F (282 MHz, $CDCl_3$) -109.2 (t, *J* = 17.4 Hz); HRMS (ES^+): Exact mass calculated for $C_{12}H_{14}NaF_2O$ $[M+Na]^+$: 235.0910, found: 235.0924.



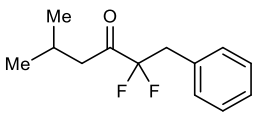
1-(3,5-bis(trifluoromethyl)phenyl)-2,2-difluoropentan-3-one (2c)

This compound was prepared using General Procedure B using ethyl propionate (41 mg, 0.40 mmol), 2,2'-(2-(3,5-bis(trifluoromethyl)phenyl)ethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (395 mg, 0.80 mmol), 2,2,6,6-tetramethylpiperidine (135 µL, 0.80 mmol), *n*-BuLi (0.32 mL, 0.80 mmol, 2.5 M in hexanes), *N*-fluorobenzenesulfonimide (378 mg, 1.2 mmol) in THF (2 mL total). The compound was purified by flash column chromatography using Et_2O / hexane (2%) as eluent to yield the title compound as a colorless oil (58 mg, 43%); R_F = 0.41 (Et_2O / hexane (10%)); δ_H (500 MHz, $CDCl_3$) 7.83 (s, 1H, Ar**H**), 7.73 (s, 2H, Ar**H**), 3.44 (t, *J* = 17.0 Hz, 2H, ArC**H₂**), 2.66 (q, *J* = 7.2 Hz, 2H, C**H₂**CH_3), 1.08 (t, *J* = 7.2 Hz, 3H, CH_2C**H₃**); δ_C (126 MHz, $CDCl_3$) 200.9 (t, *J* = 31.3 Hz, C), 133.8 (t, *J* = 3.7 Hz, C), 131.9 (q, *J* = 33.5 Hz, 2 x C), 130.9 (d, *J* = 2.8 Hz, 2 x CH), 123.1 (q, *J* = 273 Hz, 2 × CF_3), 121.9 – 121.7 (m, CH), 116.1 (t, *J* = 255 Hz, CF_2), 38.3 (t, *J* = 23.6 Hz, CH_2), 29.8 (d, *J* = 4.8 Hz, CH_2), 6.5 (s, CH_3); δ_F (282 MHz, $CDCl_3$) -63.0 (s), -105.6 (t, *J* = 17.0 Hz); HRMS (ES^-): Exact mass calculated for $C_{13}H_9OF_8$ $[M-H]^-$: 333.0531, found: 333.0548.



2,2-difluoro-1-(tetrahydro-2H-pyran-4-yl)propan-1-one (2d)

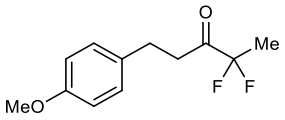
This compound was prepared using General Procedure B using methyl tetrahydro-2H-pyran-4-carboxylate (58 mg, 0.40 mmol), 2,2'-(ethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (226 mg, 0.80 mmol), 2,2,6,6-tetramethylpiperidine (135 µL, 0.80 mmol), *n*-BuLi (0.32 mL, 0.80 mmol, 2.5 M in hexanes), *N*-fluorobenzenesulfonimide (378 mg, 1.2 mmol) in THF (2 mL total). The compound was purified by flash column chromatography using Et_2O / hexane (2%) as eluent to yield the title compound as a colorless oil (47 mg, 66%); R_F = 0.60 (Et_2O / hexane (10%)); δ_H (500 MHz, $CDCl_3$) 4.01 (dt, *J* = 11.5, 3.3 Hz, 2H, OC**H₂**), 3.52 – 3.43 (m, 2H, OC**H₂**), 3.15 (pent, *J* = 7.7 Hz, 1H, O=CC**H**), 1.81 – 1.75 (m, 4H, OCH_2C**H₂**), 1.70 (t, *J* = 19.4 Hz, 3H, C**H₃**); δ_C (126 MHz, $CDCl_3$) 201.7 (t, *J* = 31.5 Hz, C), 118.2 (t, *J* = 250 Hz, CF_2), 67.0 (s, CH_2), 41.5 (s, CH), 27.9 (s, CH_2), 19.7 (t, *J* = 24.9 Hz, CH_3); δ_F (376 MHz, $CDCl_3$) -99.3 (s); *m/z* ES^+ $C_8H_{12}F_2O_2$ requires $[M+Na]^+$ 201.1; found 201.1.



2,2-difluoro-5-methyl-1-phenylhexan-3-one (2e)

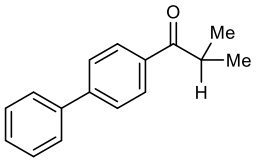
This compound was prepared using General Procedure B using ethyl isovalerate (52 mg, 0.40 mmol), 2,2'-(2-phenylethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (287 mg, 0.80 mmol), 2,2,6,6-tetramethylpiperidine (135 µL, 0.80 mmol), *n*-BuLi (0.32 mL, 0.80 mmol, 2.5 M in hexanes), *N*-fluorobenzenesulfonimide (378 mg, 1.2

mmol) in THF (2 mL total). The compound was purified by flash column chromatography using Et_2O / hexane (2%) as eluent to yield the title compound as a colorless oil (55 mg, 61%); δ_H (500 MHz, $CDCl_3$) 7.34 – 7.22 (m, 5H, Ar**H**), 3.30 (t, *J* = 17.0 Hz, 2H, ArC**H₂**), 2.35 (d, *J* = 6.7 Hz, 2H, O=CC**H₂**), 2.15 – 2.01 (sept, *J* = 6.7 Hz, 1H, C**H**$(CH_3)_2$), 0.85 (d, *J* = 6.7 Hz, 6H, CH(C**H₃**$)_2$); δ_C (126 MHz, $CDCl_3$) 201.2 (t, *J* = 30.7 Hz, C), 131.0 (t, *J* = 4.3 Hz, C), 130.7 (s, 2 x CH), 128.5 (s, 2 x CH), 127.7 (s, CH), 117.0 (t, *J* = 254.2 Hz, CF_2), 45.8 (s, CH_2), 39.2 (t, *J* = 23.6 Hz, CH_2), 23.4 (s, CH), 22.3 (s, 2 x CH_3); δ_F (282 MHz, $CDCl_3$) -105.6 (t, *J* = 17.0 Hz); HRMS (ES^+): Exact mass calculated for $C_{13}H_{16}NaF_2O$ $[M+Na]^+$: 249.1061, found: 249.1065.



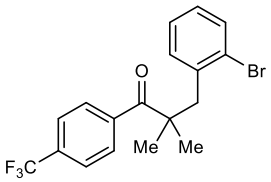
4,4-difluoro-1-(4-methoxyphenyl)pentan-3-one (2f)

This compound was prepared using General Procedure B using methyl 3-(4-methoxyphenyl)propionate (78 mg, 0.40 mmol), 2,2'-(ethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (226 mg, 0.80 mmol), 2,2,6,6-tetramethylpiperidine (135 µL, 0.80 mmol), *n*-BuLi (0.32 mL, 0.80 mmol, 2.5 M in hexanes), *N*-fluorobenzenesulfonimide (378 mg, 1.2 mmol) in THF (2 mL total). The compound was purified by flash column chromatography using Et_2O / hexane (2%) as eluent to yield the title compound as a colorless oil (48 mg, 53%); δ_H (500 MHz, $CDCl_3$) 7.12 (d, *J* = 8.5 Hz, 2H, Ar**H**), 6.83 (d, *J* = 8.6 Hz, 2H, Ar**H**), 3.79 (s, 3H, OC**H₃**), 2.99 (t, *J* = 7.3 Hz, 2H, ArC**H₂**), 2.89 (t, *J* = 7.3 Hz, 2H, O=CC**H₂**), 1.66 (t, *J* = 19.2 Hz, 3H, CF_2C**H₃**); δ_C (126 MHz, $CDCl_3$) 200.1 (t, *J* = 32.2 Hz, C), 158.1 (s, C), 132.2 (s, C), 129.2 (s, 2 × CH), 117.6 (t, *J* = 248.9 Hz, CF_2), 113.9 (s, 2 × CH), 55.2 (s, CH_3), 37.5 (s, CH_2), 27.8 (s, CH_2), 19.2 (t, *J* = 25.0 Hz, CH_3); δ_F (282 MHz, $CDCl_3$) -100.2 (q, *J* = 19.2 Hz); HRMS (ES^+): Exact mass calculated for $C_{12}H_{14}NaF_2O_2$ $[M+Na]^+$: 251.0854, found: 251.0860.



1-([1,1'-biphenyl]-4-yl)-2-methylpropan-1-one (3a)

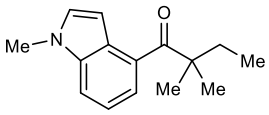
This compound was prepared using General Procedure C using methyl 4-phenylbenzoate (85 mg, 0.40 mmol), bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (214 mg, 0.80 mmol), sodium bis(trimethylsilyl)amide (0.5 mL, 2M in THF, 1.0 mmol), iodomethane (125 µL, 2.0 mmol) in THF (2 mL total). The compound was purified by flash column chromatography using Et_2O / hexane (2%) as eluent to yield the title compound as a yellow solid (53 mg, 59%); δ_H (300 MHz, $CDCl_3$) 8.06 (d, *J* = 7.7 Hz, 2H, Ar**H**), 7.71 (d, *J* = 7.6 Hz, 2H, Ar**H**), 7.66 (d, *J* = 7.4 Hz, 2H, Ar**H**), 7.54 – 7.39 (m, 3H, Ar**H**), 3.62 (sept, *J* = 6.8 Hz, 1H, C**H**$(CH_3)_2$), 1.28 (d, *J* = 6.8 Hz, 6H, CH(C**H₃**$)_2$). *m/z* ES^+ $C_{16}H_{16}O$ requires $[M+Na]^+$ 247.1; found 247.1. Data in full agreement with the literature[7]



3-(2-bromophenyl)-2,2-dimethyl-1-(4-(trifluoromethyl)phenyl)propan-1-one (3b)

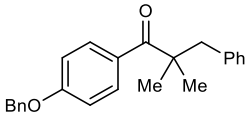
This compound was prepared using General Procedure C using ethyl 4-trifluoromethyl)benzoate (87 mg, 0.40 mmol), 2,2'-(2-(2-bromophenyl)ethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (350 mg, 0.80 mmol), sodium bis(trimethylsilyl)amide (0.5 mL, 2M in THF, 1.0 mmol), iodomethane (125 µL, 2.0 mmol) in

THF (2 mL total). The compound was purified by flash column chromatography using Et_2O / hexane (2%) as eluent to yield the title compound as a colorless oil (132 mg, 86%); R_F = 0.45 (Et_2O / hexane (10%)); IR 1682, 1469, 1322, 1167, 1125, 1066, 1017, 967, 949, 844, 749 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.70 – 7.56 (m, 5H, Ar**H**), 7.24 – 7.13 (m, 2H, Ar**H**), 7.09 (t, *J* = 7.5 Hz, 1H, Ar**H**), 3.32 (s, 2H, ArC**H₂**), 1.33 (s, 6H, C(C**H₃**)₂); δ_C (101 MHz, $CDCl_3$) 209.0 (s, C), 142.5 (s, C), 137.5 (s, C), 133.3 (s, CH), 132.3 (q, *J* = 32.8 Hz, C), 132.0 (s, CH), 128.3 (s, CH), 127.6 (s, 2 x CH), 127.2 (s, CH), 126.2 (s, C), 125.2 (q, *J* = 3.7 Hz, 2 x CH), 49.6 (s, C), 43.7 (s, CH_2), 25.7 (s, 2 × CH_3) (CF_3 not observed); δ_F (282 MHz, $CDCl_3$) -63.0 (s); HRMS (ES^+): Exact mass calculated for $C_{18}H_{16}NaOF_3Br$ (^{79}Br) $[M+Na]^+$: 407.0229, found: 407.0232.



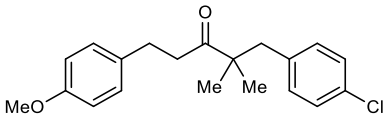
2,2-dimethyl-1-(1-methyl-1H-indol-4-yl)butan-1-one (3c)

This compound was prepared using General Procedure C using methyl 1-methyl-1H-indole-4-carboxylate (76 mg, 0.40 mmol), 2,2'-(propane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (237 mg, 0.80 mmol), sodium bis(trimethylsilyl)amide (0.5 mL, 2M in THF, 1.0 mmol), iodomethane (125 µL, 2.0 mmol) in THF (2 mL total). The compound was purified by flash column chromatography using Et_2O / hexane (2→ 10%) as eluent to yield the title compound as an orange oil (58 mg, 63%); R_F = 0.19 (Et_2O / hexane (10%)); δ_H (400 MHz, $CDCl_3$) 7.39 (d, *J* = 8.2 Hz, 1H, Ar**H**), 7.36 (d, *J* = 7.3 Hz, 1H, Ar**H**), 7.20 (d, *J* = 7.8 Hz, 1H, Ar**H**), 7.11 (d, *J* = 3.1 Hz, 1H, Ar**H**), 6.66 (d, *J* = 3.1 Hz, 1H, Ar**H**), 3.80 (s, 3H, NC**H₃**), 1.84 (q, *J* = 7.5 Hz, 2H, C**H₂**CH_3), 1.32 (s, 6H, C(C**H₃**)₂), 0.90 (t, *J* = 7.5 Hz, 3H, CH_2C**H₃**); δ_C (101 MHz, $CDCl_3$) 211.1 (C), 137.2 (C), 131.8 (C), 130.1 (CH), 126.8 (C), 120.1 (CH), 118.0 (CH), 111.3 (CH), 101.4 (CH), 48.6 (C), 33.5 (CH_2), 25.5 (CH_3), 24.8 (CH_3), 24.5 (CH_3); HRMS (ES^+): Exact mass calculated for $C_{15}H_{19}NaNO$ $[M+Na]^+$: 252.1359, found: 252.1360.



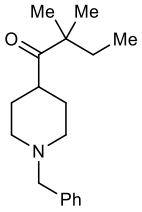
1-(4-(benzyloxy)phenyl)-2,2-dimethyl-3-phenylpropan-1-one (3d)

This compound was prepared using General Procedure C using methyl 4-benzyloxybenzoate (97 mg, 0.40 mmol), 2,2'-(2-phenylethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (287 mg, 0.80 mmol), sodium bis(trimethylsilyl)amide (0.5 mL, 2M in THF, 1.0 mmol), iodomethane (125 µL, 2.0 mmol) in THF (2 mL total). The compound was purified by flash column chromatography using Et_2O / hexane (2%) as eluent to yield the title compound as a colorless oil (68 mg, 49%); R_F = 0.27 (Et_2O / hexane (10%)); IR 1663, 1598, 1491, 1455, 1417, 1252, 1228, 1167, 1118, 1046, 838, 697 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.73 (d, *J* = 8.9 Hz, 2H, Ar**H**), 7.46 – 7.32 (m, 6H, Ar**H**), 7.19 (d, *J* = 8.4 Hz, 2H, Ar**H**), 6.98 (t, *J* = 8.6 Hz, 4H, Ar**H**), 5.12 (s, 2H, OC**H₂**Ph), 3.06 (s, 2H, ArC**H₂**), 1.32 (s, 6H, C(C**H₃**)₂); δ_C (101 MHz, $CDCl_3$) 205.9 (C), 161.2 (C), 136.5 (C), 132.3 (C), 131.7 (2 × CH), 131.1 (C), 130.7 (CH), 130.6 (2 × CH), 128.7 (2 × CH), 128.2 (2 × CH), 128.1 (CH), 127.5 (2 × CH), 114.2 (2 × CH), 70.1 (CH_2), 48.5 (C), 45.9 (CH_2), 26.3 (2 × CH_3); HRMS (ES^+): Exact mass calculated for $C_{24}H_{24}NaO_2$ $[M+Na]^+$: 367.1674, found: 367.1670.



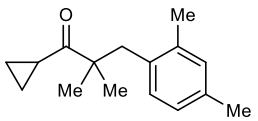
1-(4-chlorophenyl)-5-(4-methoxyphenyl)-2,2-dimethylpentan-3-one (3e)

This compound was prepared using General Procedure D using methyl 3-(4-methoxyphenyl)propionate (78 mg, 0.40 mmol), 2,2'-(2-(4-chlorophenyl)ethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (314 mg, 0.80 mmol), 2,2,6,6-tetramethylpiperidine (135 µL, 0.80 mmol), *n*-BuLi (0.32 mL, 0.80 mmol, 2.5 M in hexanes), iodomethane (125 µL, 2.0 mmol) in THF (2 mL total). The compound was purified by flash column chromatography using Et_2O / hexane (2%) as eluent to yield the title compound as a colorless oil (95 mg, 72%); R_F = 0.25 (Et_2O / hexane (10%)); δ_H (400 MHz, $CDCl_3$) 7.18 (d, *J* = 8.1 Hz, 2H, Ar**H**), 7.06 (d, *J* = 8.5 Hz, 2H, Ar**H**), 6.94 (d, *J* = 8.1 Hz, 2H, Ar**H**), 6.81 (d, *J* = 8.5 Hz, 2H, Ar**H**), 3.78 (s, 3H, OC**H₃**), 2.78 (t, *J* = 7.4 Hz, 2H, ArC**H₂**CH_2), 2.74 (s, 2H, ArC**H₂**), 2.65 (t, *J* = 7.4 Hz, 2H, $ArCH_2$C**H₂**), 1.07 (s, 6H, C(C**H₃**)$_2$); δ_C (101 MHz, $CDCl_3$) 214.3 (C), 157.9 (C), 136.3 (C), 133.3 (C), 132.2 (C), 131.5 (2 × CH), 129.4 (2 × CH), 128.1 (2 × CH), 113.8 (2 × CH), 55.2 (CH_3), 48.2 (C), 44.7 (CH_2), 40.2 (CH_2), 28.9 (CH_2), 24.2 (2 × CH_3); HRMS (ES^+): Exact mass calculated for $C_{20}H_{23}NaClO_2$ (^{35}Cl) $[M+Na]^+$: 353.1279, found: 353.1271.



1-(1-benzylpiperidin-4-yl)-2,2-dimethylbutan-1-one (3f)

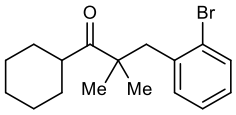
This compound was prepared using General Procedure D using ethyl 1-benzylpiperidine-4-carboxylate (78 mg, 0.40 mmol), 2,2'-(propane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (237 mg, 0.80 mmol), 2,2,6,6-tetramethylpiperidine (135 µL, 0.80 mmol), *n*-BuLi (0.32 mL, 0.80 mmol, 2.5 M in hexanes), iodomethane (125 µL, 2.0 mmol) in THF (2 mL total). The compound was purified by flash column chromatography using Et_2O / hexane (2 → 10 %) as eluent to yield the title compound as a yellow oil (68 mg, 62%); δ_H (300 MHz, $CDCl_3$) 7.36 – 7.21 (m, 5H, Ar**H**), 3.52 (s, 2H, ArC**H₂**), 2.93 (d, *J* = 11.2 Hz, 2H, NC**H₂**), 2.80 (t, *J* = 11.0 Hz, 1H, O=CC**H**), 2.00 (t, *J* = 11.6 Hz, 2H, NC**H₂**), 1.77 (q, *J* = 12.1 Hz, 2H, C**H₂**CH_3), 1.63 – 1.49 (m, 4H, NCH_2C**H₂**), 1.09 (s, 6H, C(C**H₃**)$_2$), 0.78 (t, *J* = 7.4 Hz, 3H, CH_2C**H₃**); δ_C (75 MHz, $CDCl_3$) 218.1 (C), 138.0 (C), 129.2 (2 × CH), 128.2 (2 × CH), 127.1 (CH), 63.2 (CH_2), 53.0 (CH_2), 48.6 (C), 42.9 (CH), 31.9 (CH_2), 29.3 (CH_2), 23.4 (2 × CH_3), 9.2 (CH_3); HRMS (ES^+): Exact mass calculated for $C_{18}H_{28}NO$ $[M+H]^+$: 274.2165, found: 274.2155.



1-cyclopropyl-3-(2,4-dimethylphenyl)-2,2-dimethylpropan-1-one (3g)

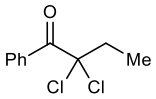
This compound was prepared using General Procedure D using ethyl cyclopropanecarboxylate (34 mg, 0.30 mmol), 2,2'-(2-(2,4-dimethylphenyl)ethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (287 mg, 0.60 mmol), 2,2,6,6-tetramethylpiperidine (101 µL, 0.60 mmol), *n*-BuLi (0.24 mL, 0.60 mmol, 2.5 M in hexanes), iodomethane (94 µL, 1.5 mmol) in THF (2 mL total). The compound was purified by flash column chromatography using Et_2O / hexane (2%) as eluent to yield the title compound as a colorless oil (45 mg, 65%); R_F = 0.37 (Et_2O / hexane (10%)); IR 1713, 1688, 1469, 1443, 1377, 1362, 1219, 1053, 1022, 821 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.99 – 6.88 (m, 3H, Ar**H**), 2.92 (s, 2H, ArC**H₂**), 2.28 (s, 6H, 2 x ArC**H₃**), 2.22 – 2.11 (m, 1H, O=CC**H**), 1.18 (s, 6H, C(C**H₃**)$_2$), 1.06 – 0.97 (m, 2H, C**H₂**C**H₂**), 0.90 – 0.81 (m, 2H, C**H₂**C**H₂**); δ_C (75 MHz, $CDCl_3$) 215.4 (C), 136.8 (C), 135.7 (C), 133.2 (C), 131.2 (CH), 130.6 (CH), 126.2 (CH), 49.2

(C), 40.5 (CH_2), 24.2 (2 × CH_3), 20.8 (CH_3), 20.3 (CH_3), 16.5 (CH), 11.4 (2 × CH_2); HRMS (ES^+): Exact mass calculated for $C_{16}H_{22}NaO$ $[M+Na]^+$: 253.1563, found: 253.1561.



3-(2-bromophenyl)-1-cyclohexyl-2,2-dimethylpropan-1-one (3h)

This compound was prepared using General Procedure D using methyl cyclohexanecarboxylate (57 mg, 0.40 mmol), 2,2'-(2-(2-bromophenyl)ethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (350 mg, 0.80 mmol), 2,2,6,6-tetramethylpiperidine (135 µL, 0.80 mmol), *n*-BuLi (0.32 mL, 0.80 mmol, 2.5 M in hexanes), iodomethane (125 µL, 2.0 mmol) in THF (2 mL total). The compound was purified by flash column chromatography using Et_2O / hexane (2%) as eluent to yield the title compound as a colorless oil (79 mg, 61%); R_F = 0.51 (Et_2O / hexane (10%)); δ_H (300 MHz, $CDCl_3$) 7.55 (d, *J* = 8.0 Hz, 1H, Ar**H**), 7.17 (t, *J* = 7.9 Hz, 2H, Ar**H**), 7.05 (t, *J* = 7.3 Hz, 1H, Ar**H**), 3.08 (s, 2H, ArC**H₂**), 2.89 (t, *J* = 11.1 Hz, 1H, O=CC**H**), 1.85 – 1.58 (m, 6H, cyclohexyl**H**), 1.52 – 1.27 (m, 4H, cyclohexyl**H**), 1.16 (s, 6H, C(C**H₃**)₂); δ_C (75 MHz, $CDCl_3$) 218.3 (C), 138.0 (C), 133.0 (CH), 132.3 (q, *J* = 33.0 Hz, C), 132.2 (CH), 127.9 (CH), 126.9 (CH), 126.3 (C), 49.7 (C), 45.4 (CH_2), 41.8 (CH), 39.3 (CH_2), 29.9 (2 × CH_2), 25.8 (2 × CH_2), 23.6 (2 × CH_3); HRMS (ES^+): Exact mass calculated for $C_{17}H_{23}NaBrO$ (^{79}Br) $[M+Na]^+$: 345.0824, found: 345.0826.



2,2-dichloro-1-phenylbutan-1-one (4)

Ethyl benzoate (60 mg, 0.40 mmol) and 2,2'-(propane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (237 mg, 0.80 mmol) were mixed under nitrogen and dissolved in THF (1 mL). Sodium bis(trimethylsilyl)amide (0.5 mL, 2M in THF, 1.0 mmol) was added and the mixture heated to 50 °C for 15 minutes. After this period the mixture was cooled to room temperature, and a solution of trichloroisocyanuric acid (93 mg, 0.40 mmol) in THF (1 mL) was added. After stirring for 15 minutes at room temperature the mixture was eluted through a short pad of silica (Et_2O) and concentrated. The compound was purified by flash column chromatography to yield the title compound as a colorless oil (58 mg, 67%); δ_H (400 MHz, $CDCl_3$) 8.28 (d, *J* = 7.4 Hz, 2H, Ar**H**), 7.58 (t, *J* = 7.4 Hz, 1H, Ar**H**), 7.46 (t, *J* = 7.7 Hz, 2H, Ar**H**), 2.54 (q, *J* = 7.2 Hz, 2H, C**H₂**CH_3), 1.26 (t, *J* = 7.2 Hz, 3H, CH_2C**H₃**); δ_C (101 MHz, $CDCl_3$) 188.5 (s, C), 133.4 (s, CH), 132.1 (s, C), 130.9 (s, 2 × CH), 128.1 (s, 2 × CH), 88.4 (s, CCl_2), 37.8 (s, CH_2), 9.2 (s, CH_3). This data is in full agreement with the literature.[8]

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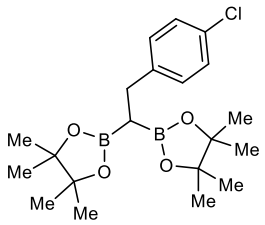
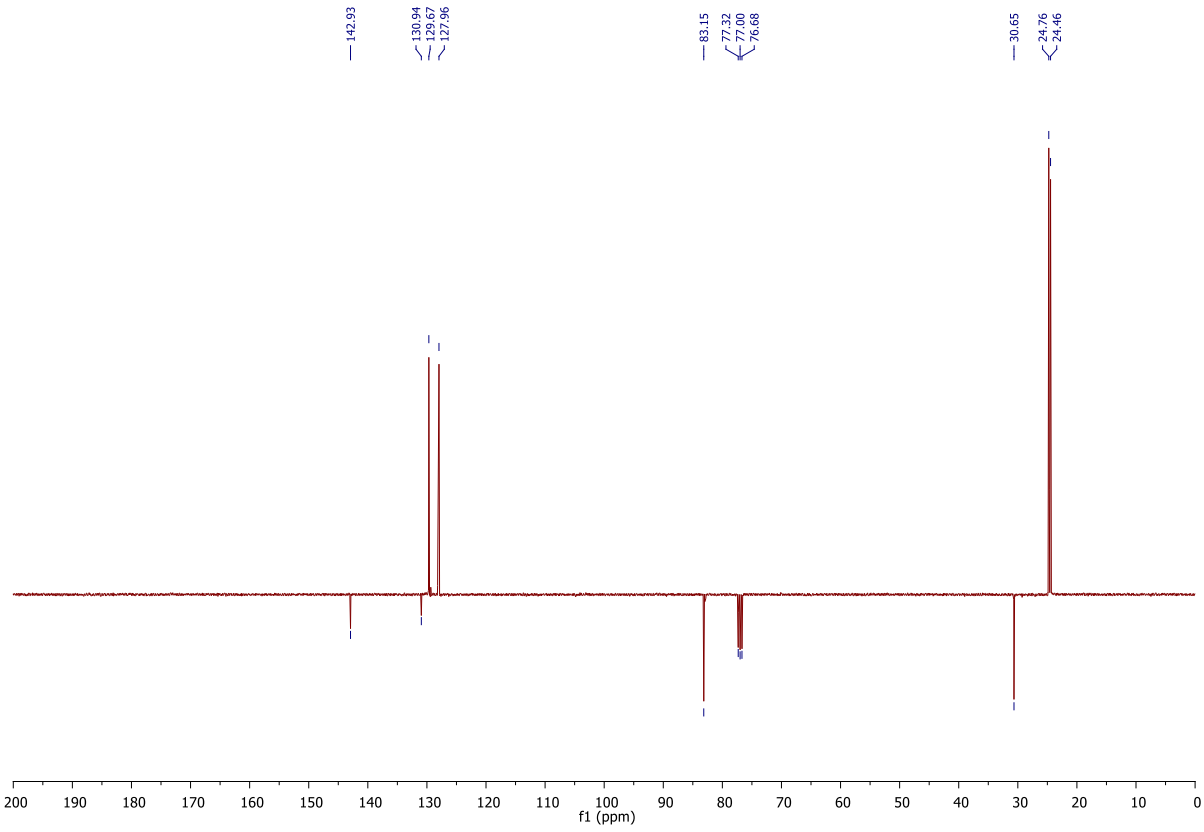
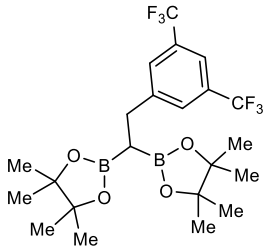


S7

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B
O
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O
O

S8

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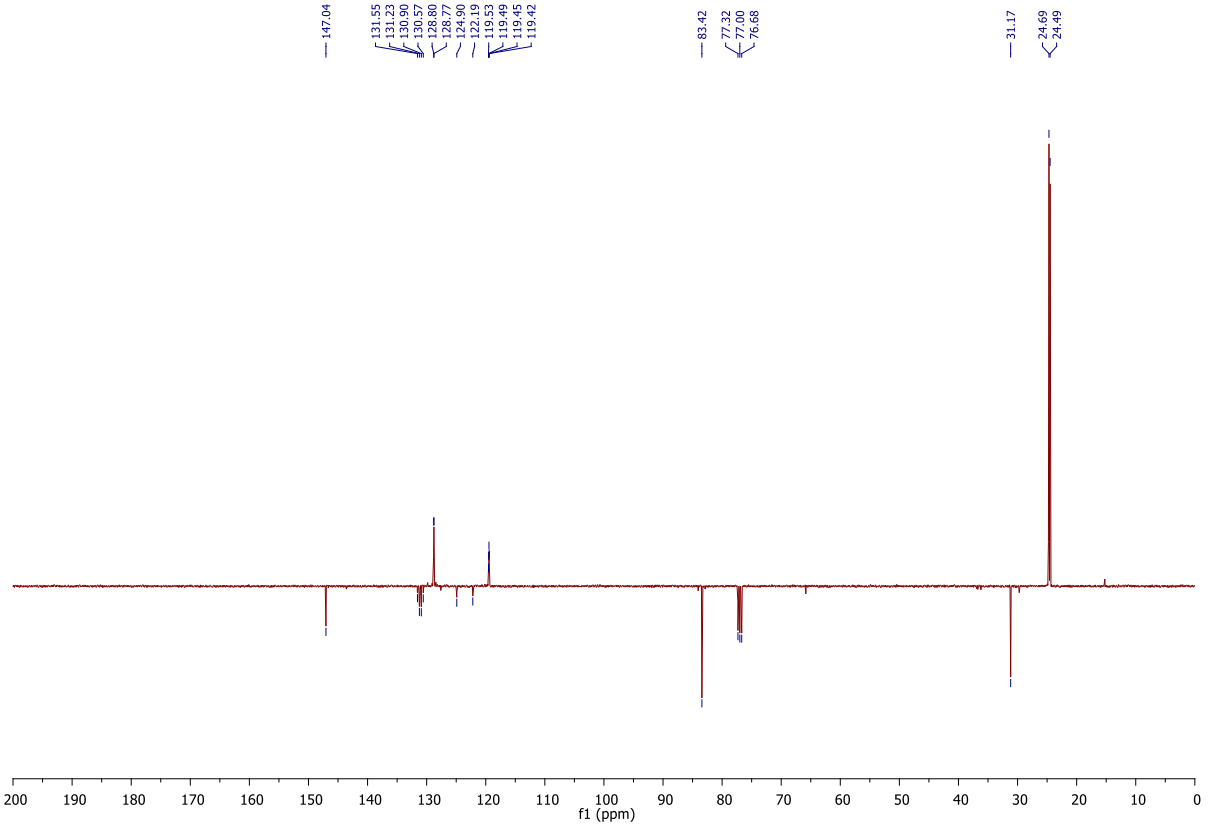
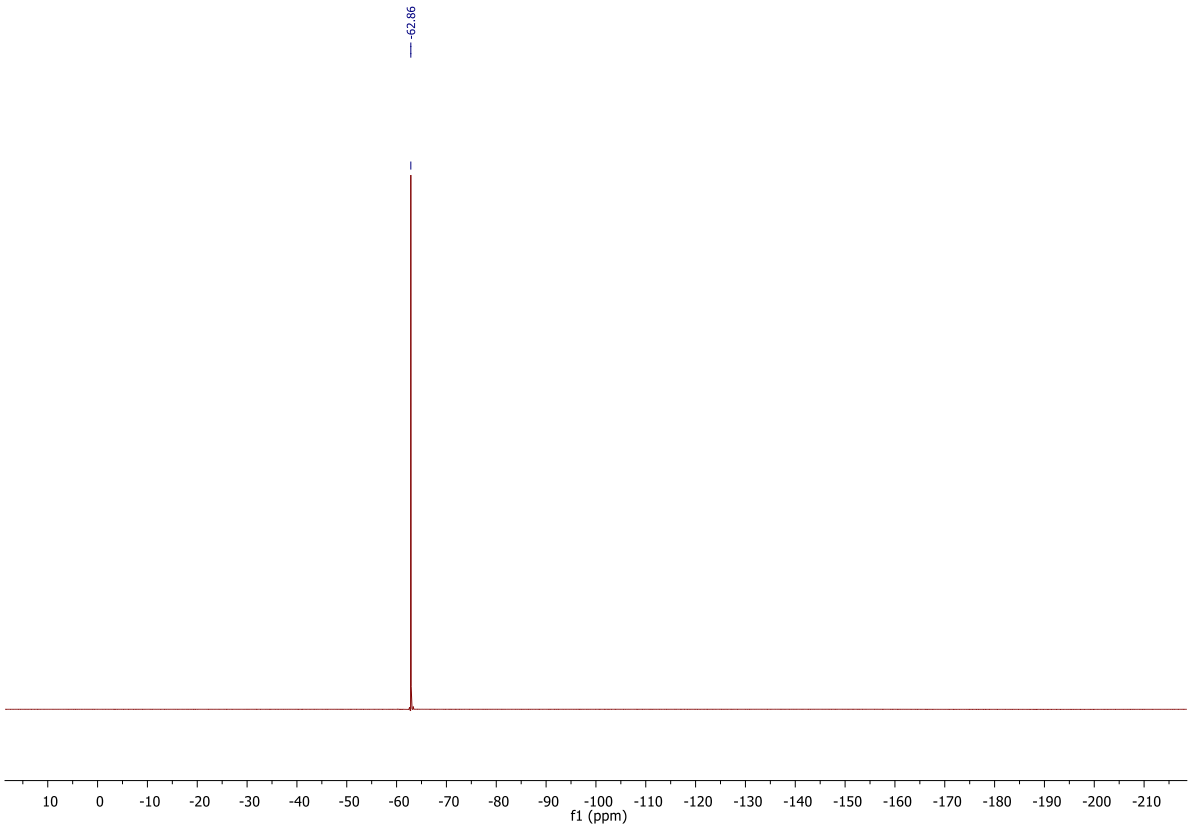
0.0
f1 (ppm)


147.04
131.55
131.23
130.90
130.57
128.80
128.77
124.90
122.19
119.53
119.49
119.45
119.42
83.42
77.32
77.00
76.68
31.17
24.69
24.49
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


-62.86
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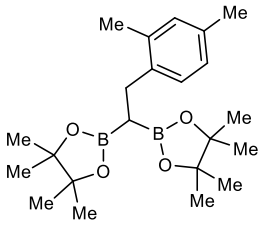
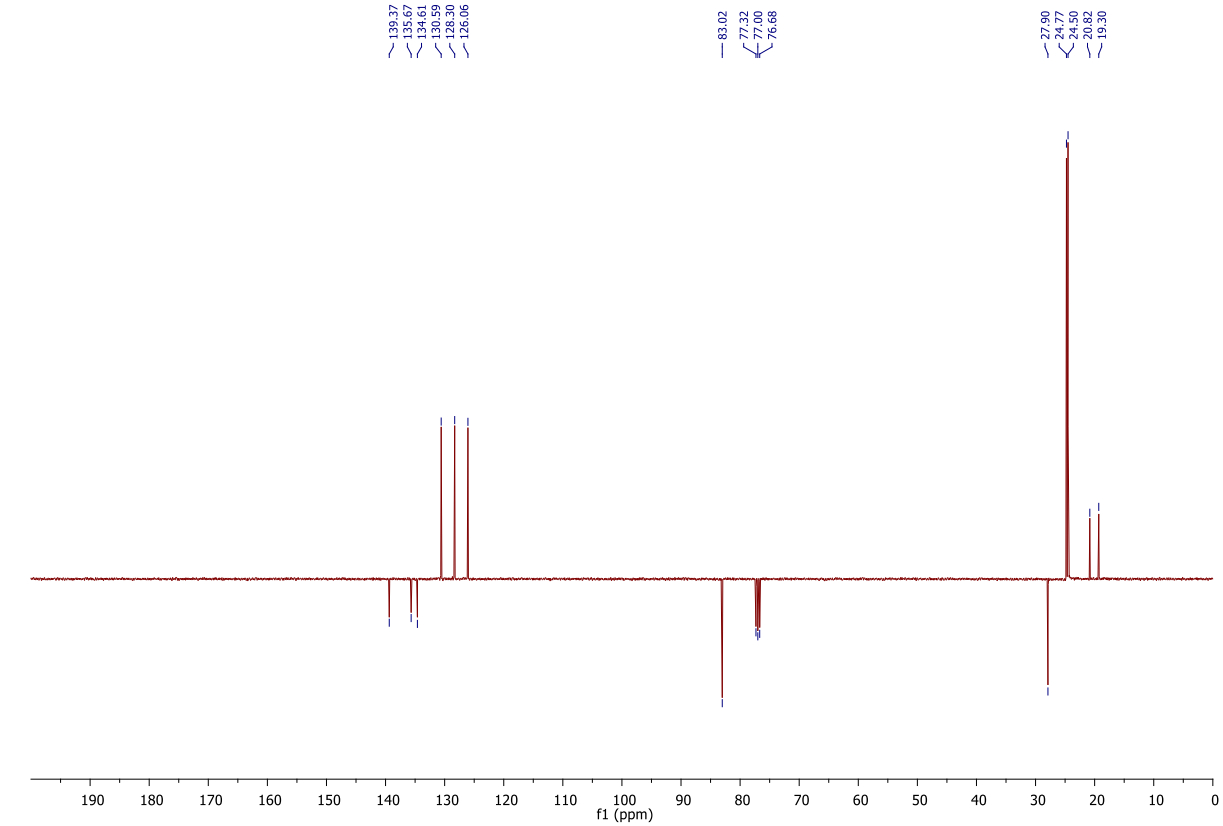
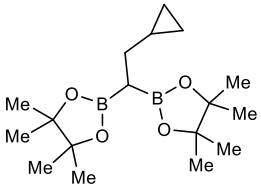
f1 (ppm)


Me
Me
O
B
O
B
O
O
Me
Me
Me
Me
Me
Me
Me
Me

S9

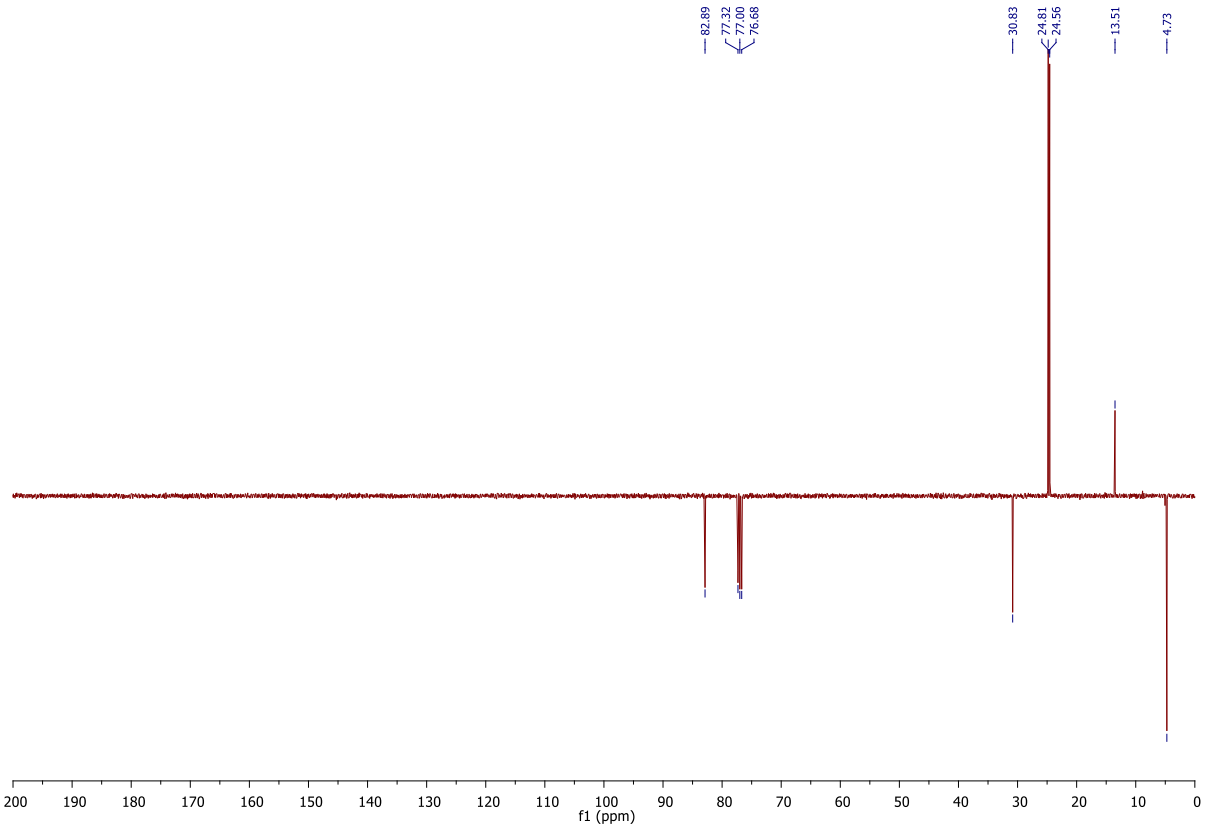
1.000
1.990
1.964
2.940
2.901
24.434
1.207
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

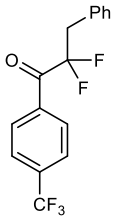

139.37
135.67
134.61
130.59
128.30
126.06
83.02
77.32
77.00
76.68
27.90
24.77
24.50
20.82
19.30
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Me
Me
Me
Me
O
B
O
B
O
O
Me
Me
Me
Me

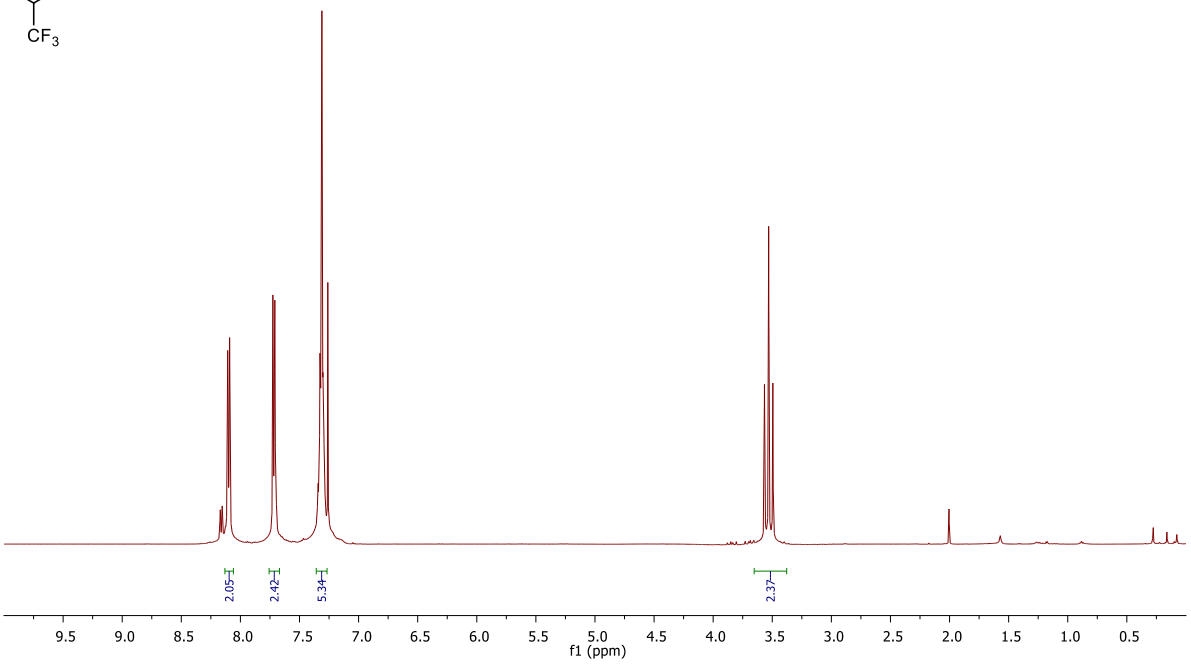
S10

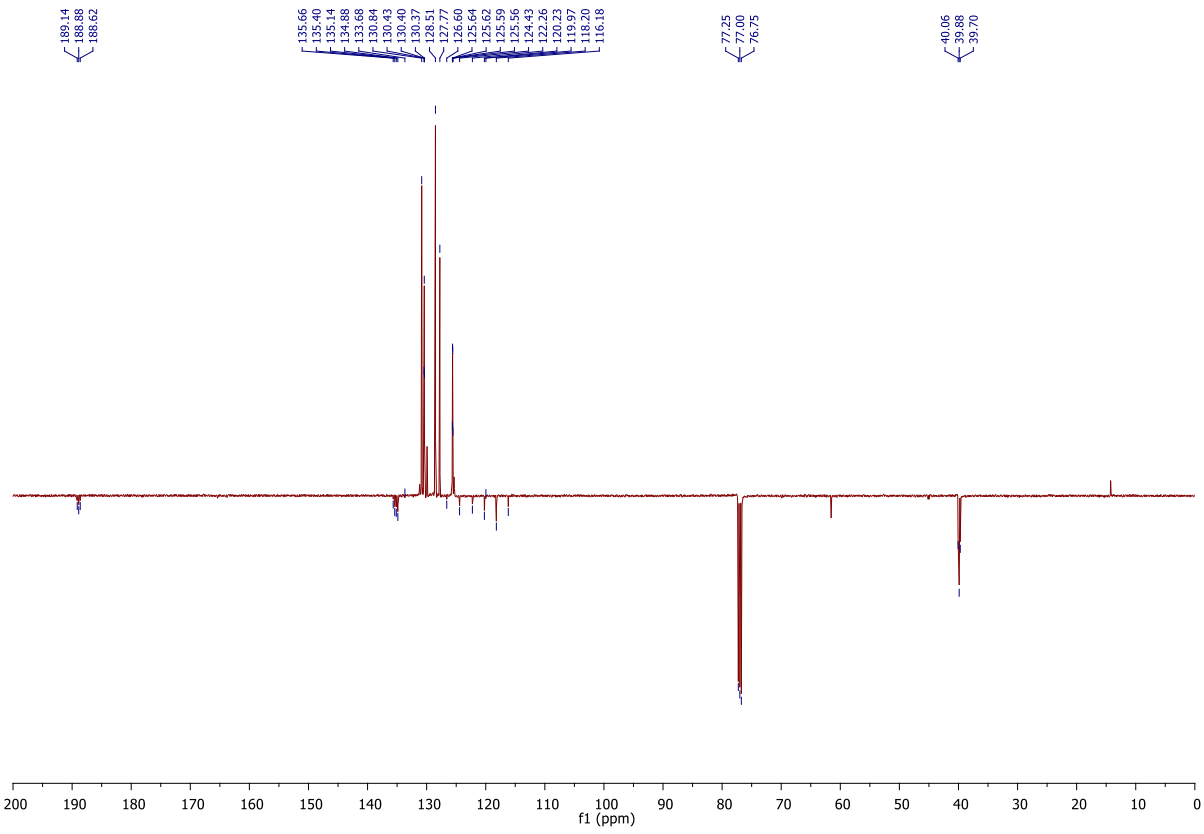
1.949
24.513
1.000
1.025
2.010
1.928
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

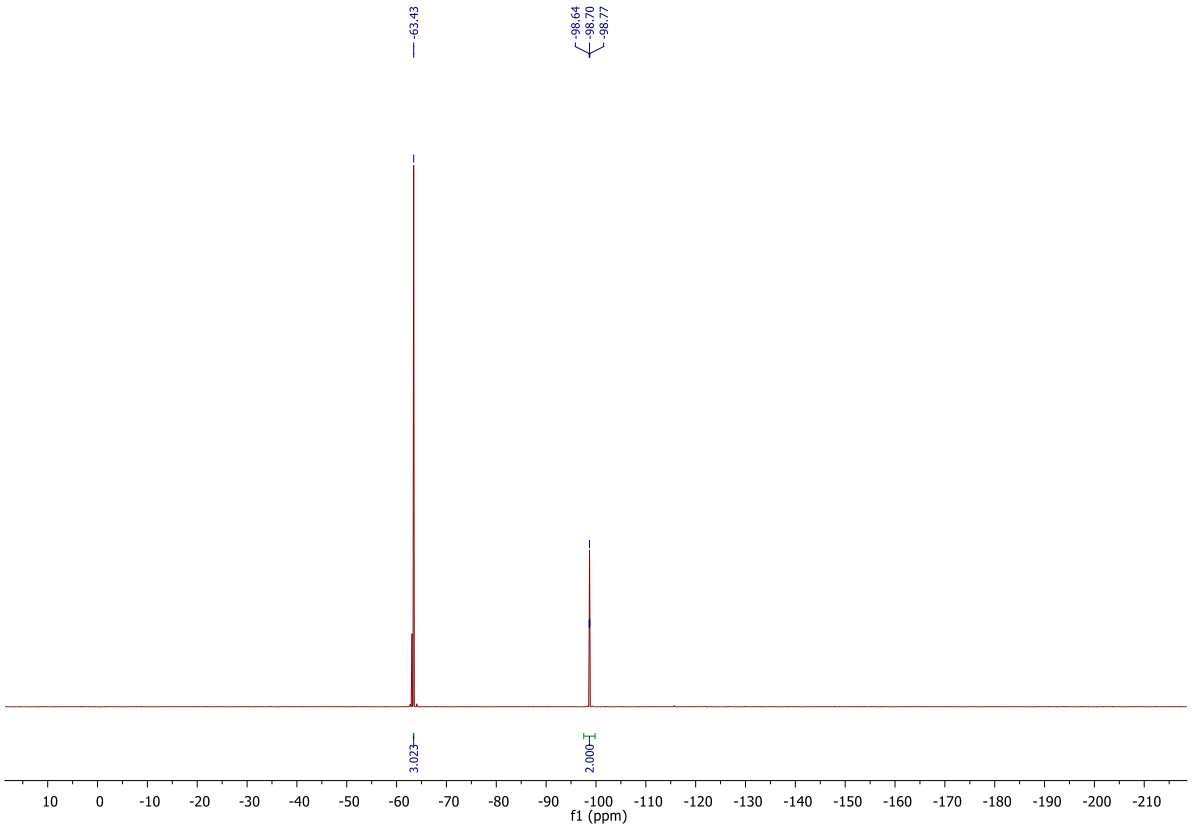

82.89
77.32
77.00
76.68
30.83
24.81
24.56
13.51
4.73
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

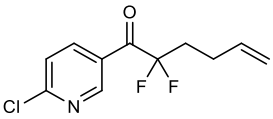


2,2-Difluoro-3-phenyl-1-(4-(trifluoromethyl)phenyl)propan-1-one (1a)

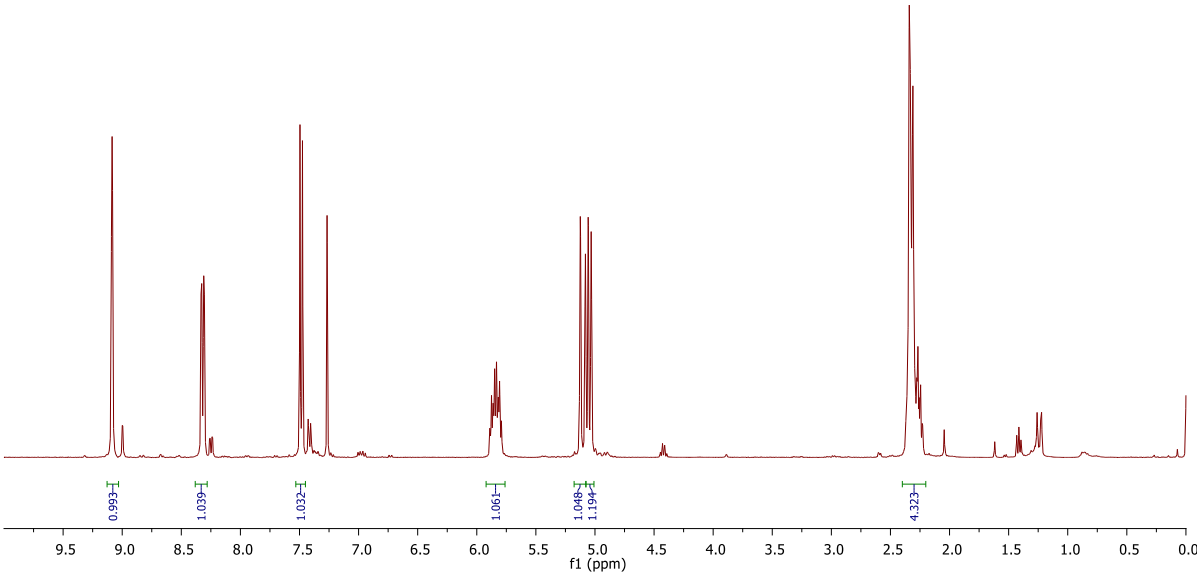


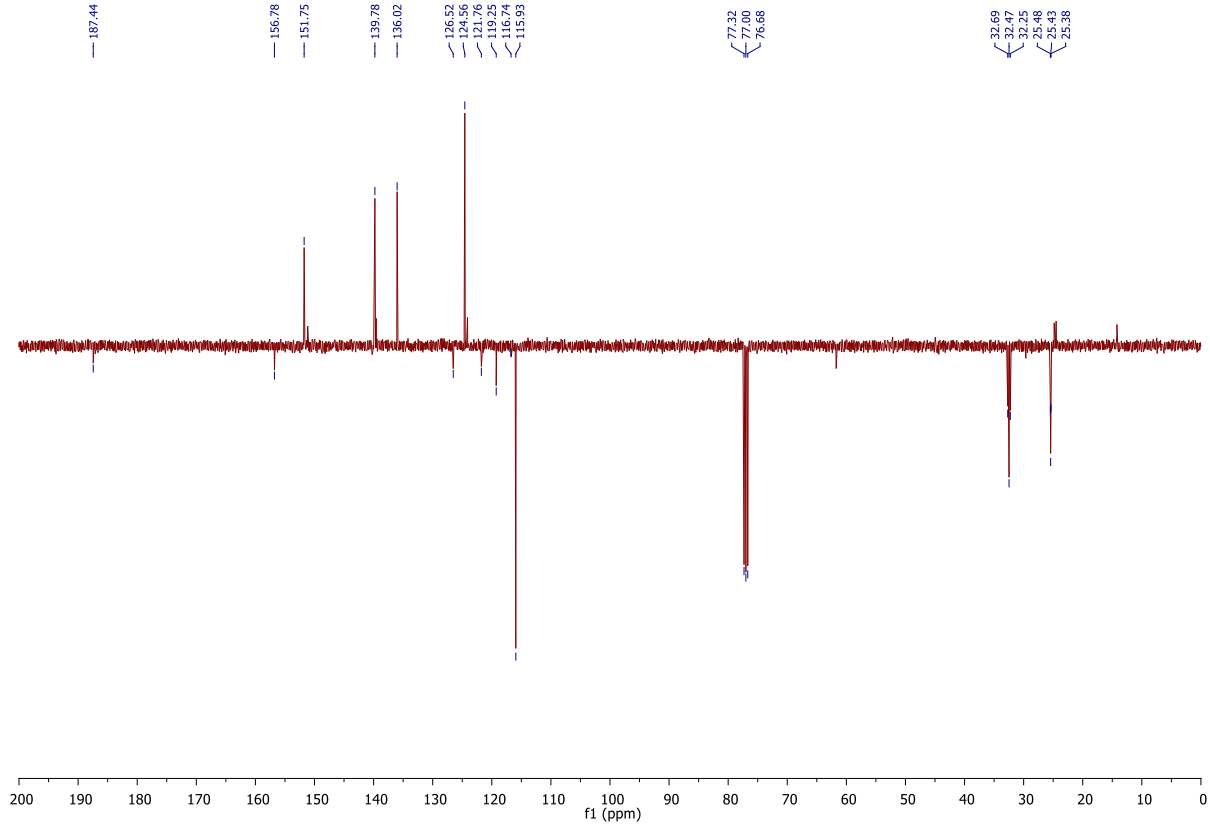


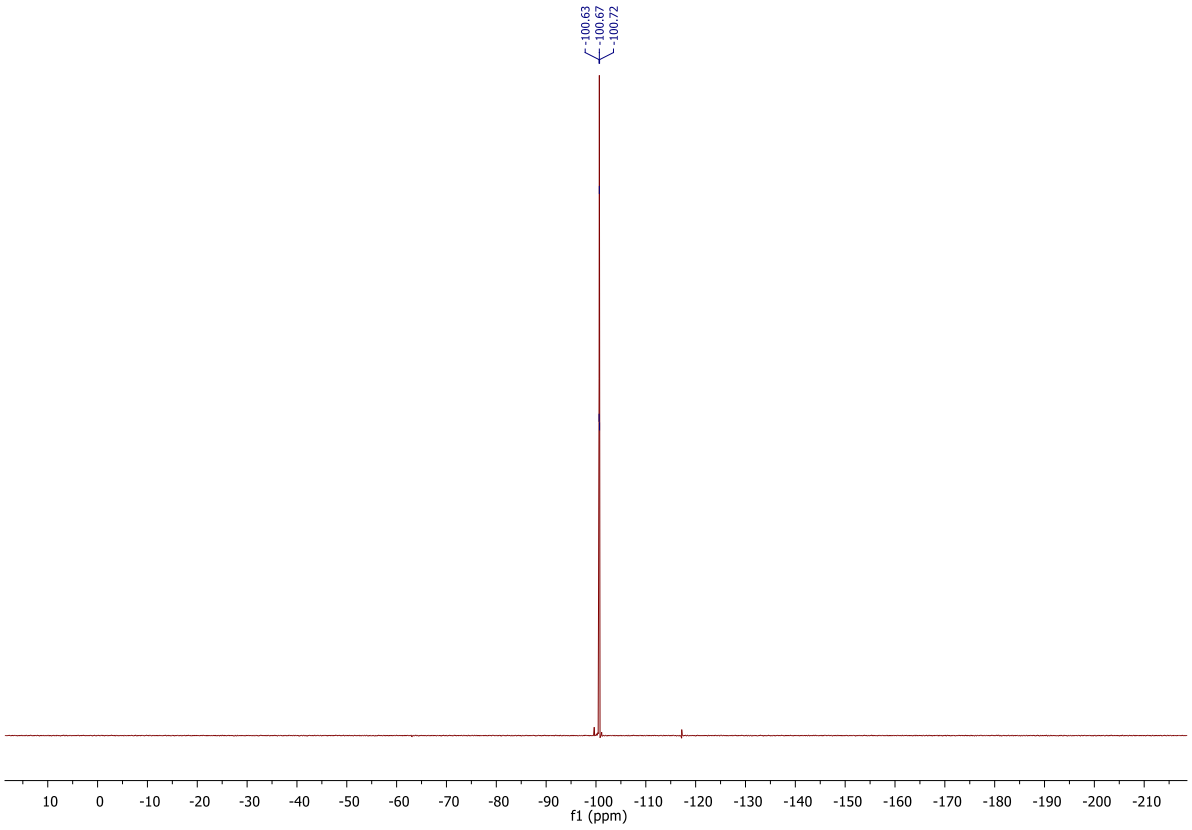

-63.43
-98.64
-98.70
-98.77
3.023
2.000
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)



1-(6-chloropyridin-3-yl)-2,2-difluorohex-5-en-1-one (1b)






-100.63
-100.67
-100.72
10
0
-10
-20
-30
-40
-50
-60
-70
-80
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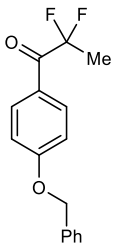
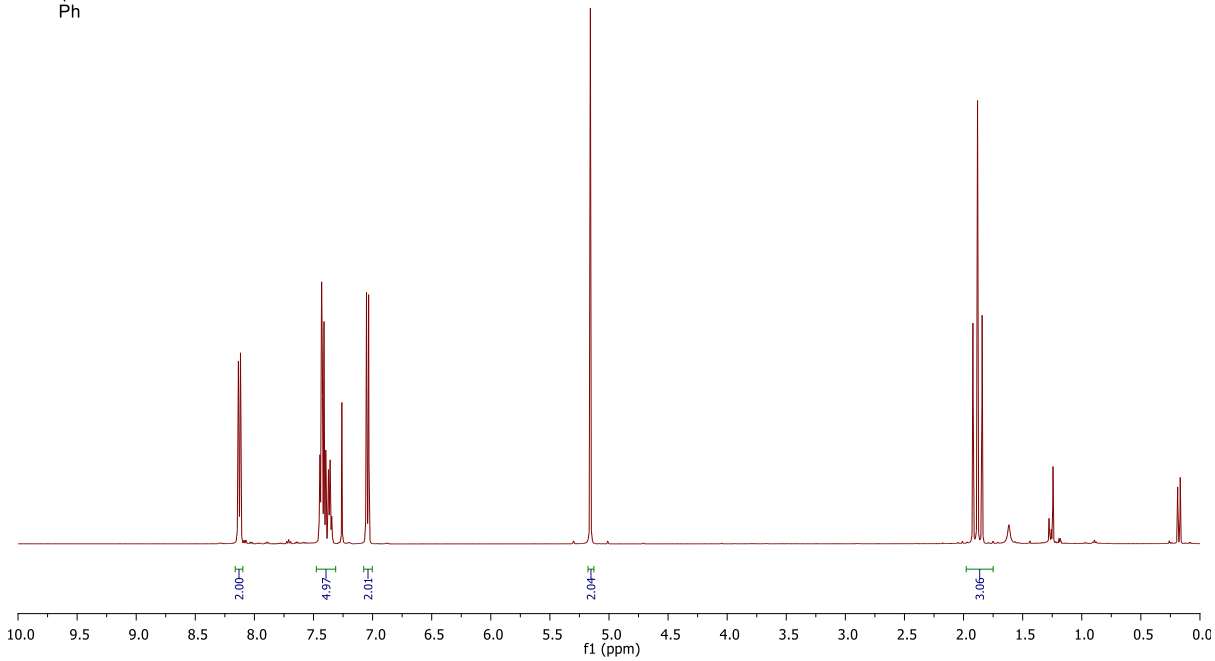
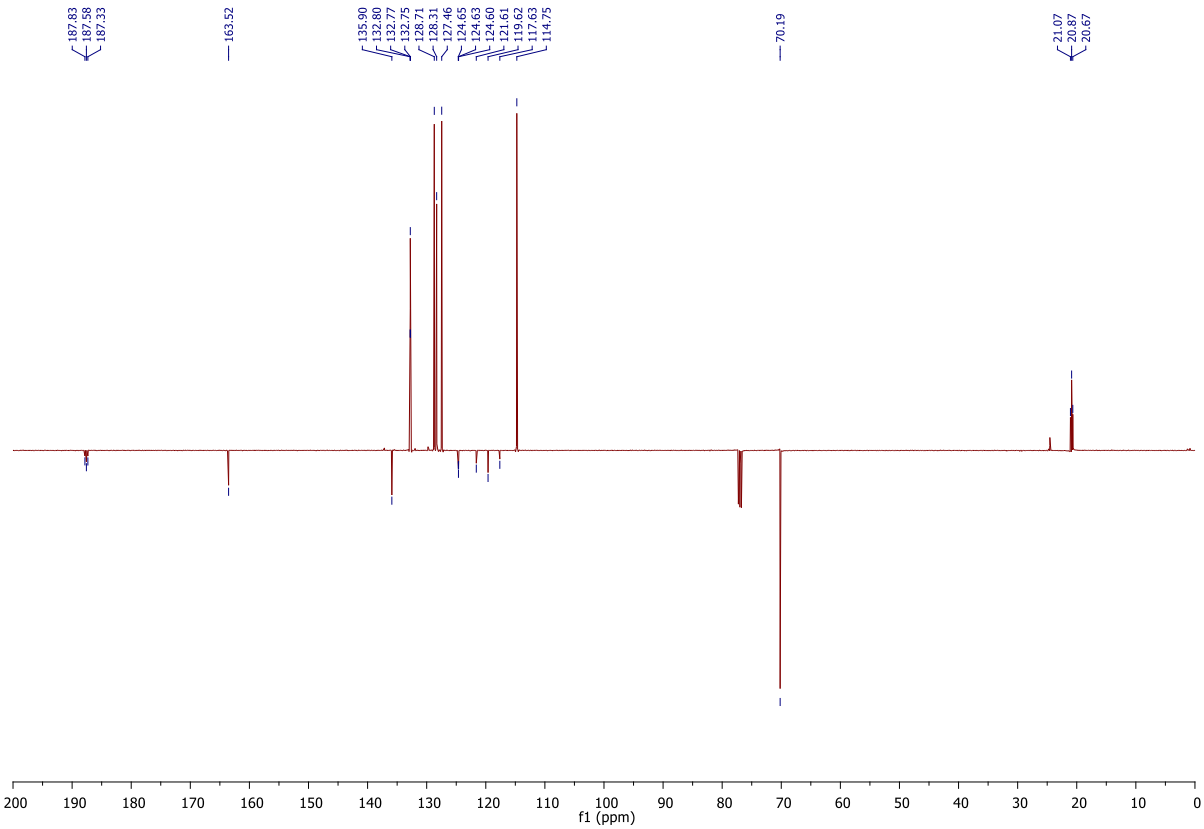
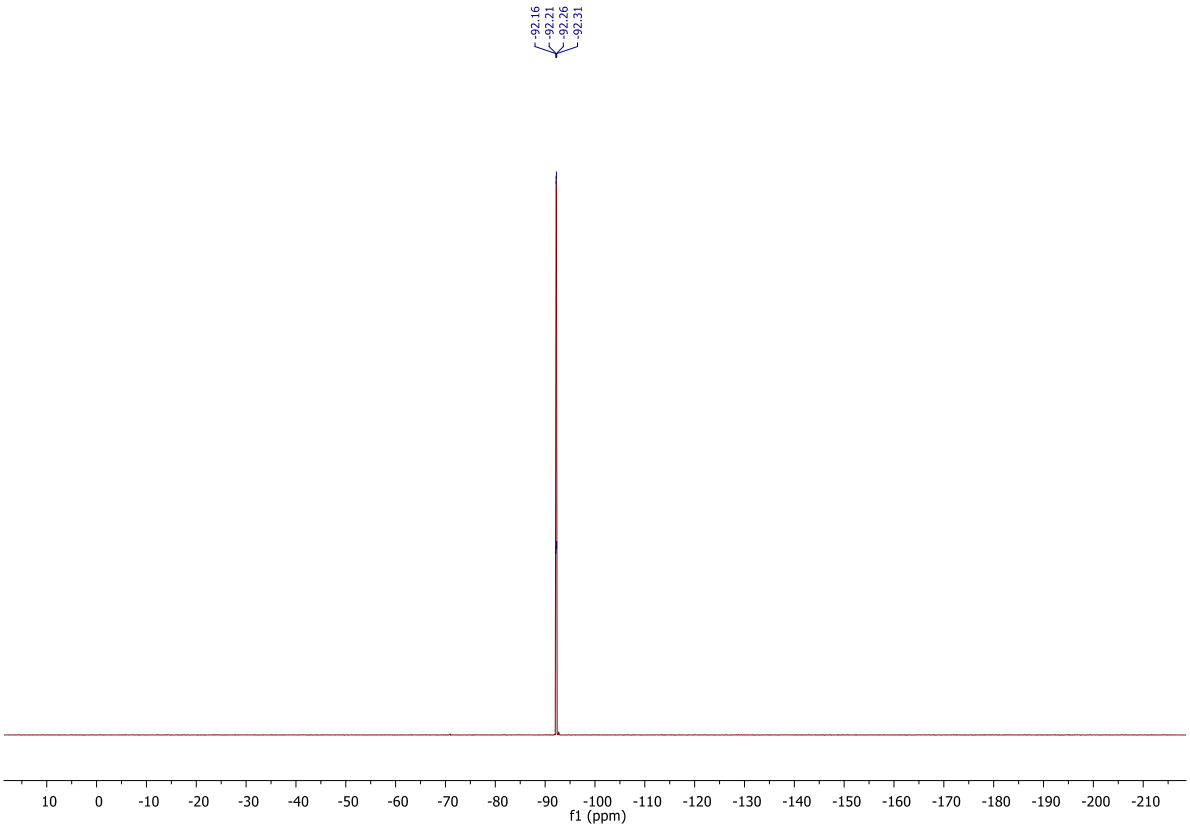
-170
-180
-190
-200
-210
f1 (ppm)

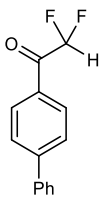


1-(4-(benzyloxy)phenyl)-2,2-difluoropropan-1-one (1c)

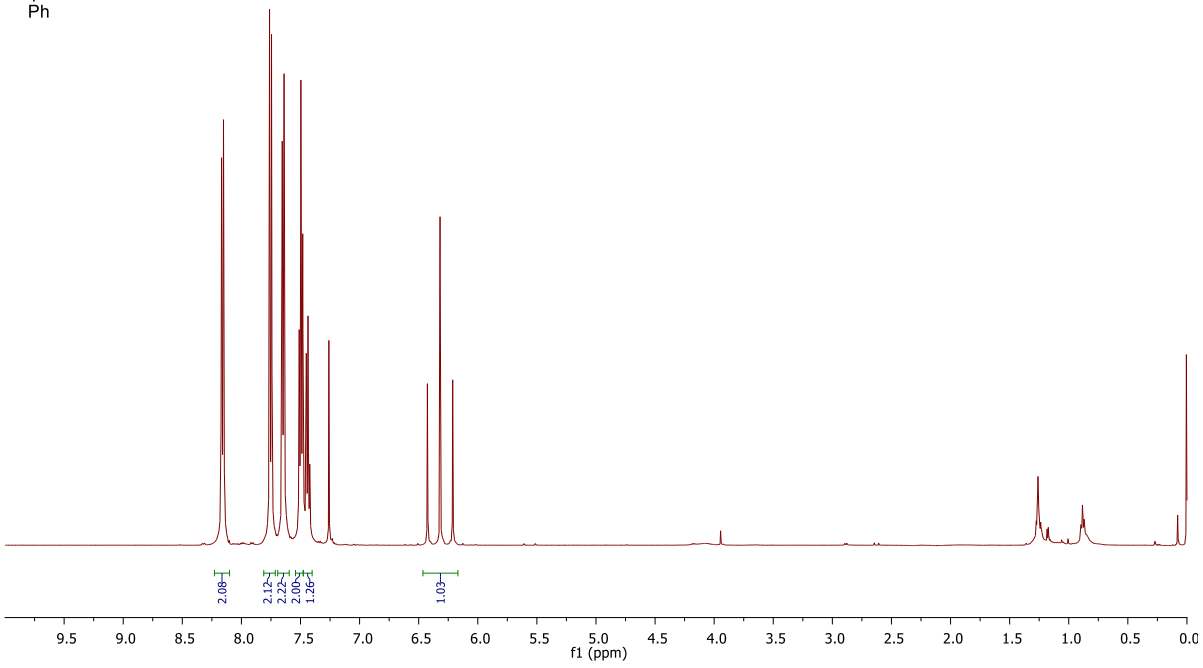


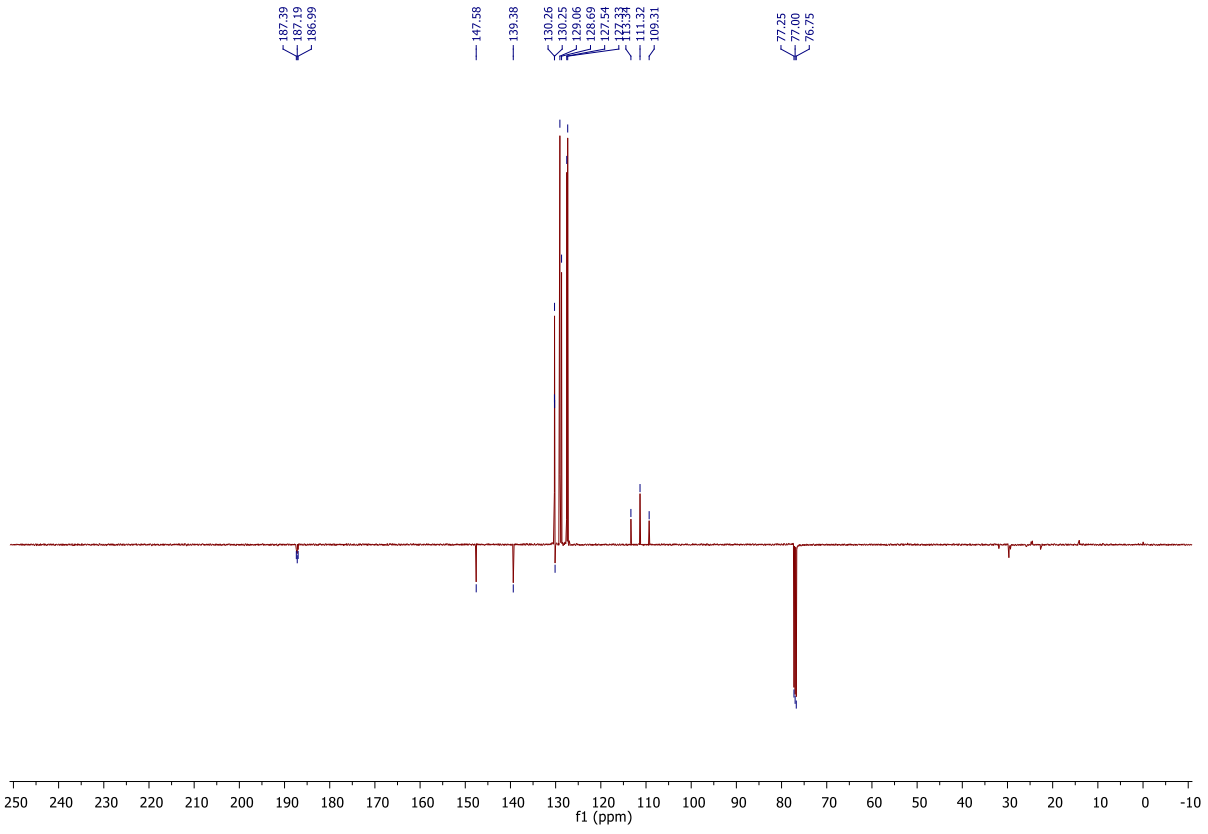


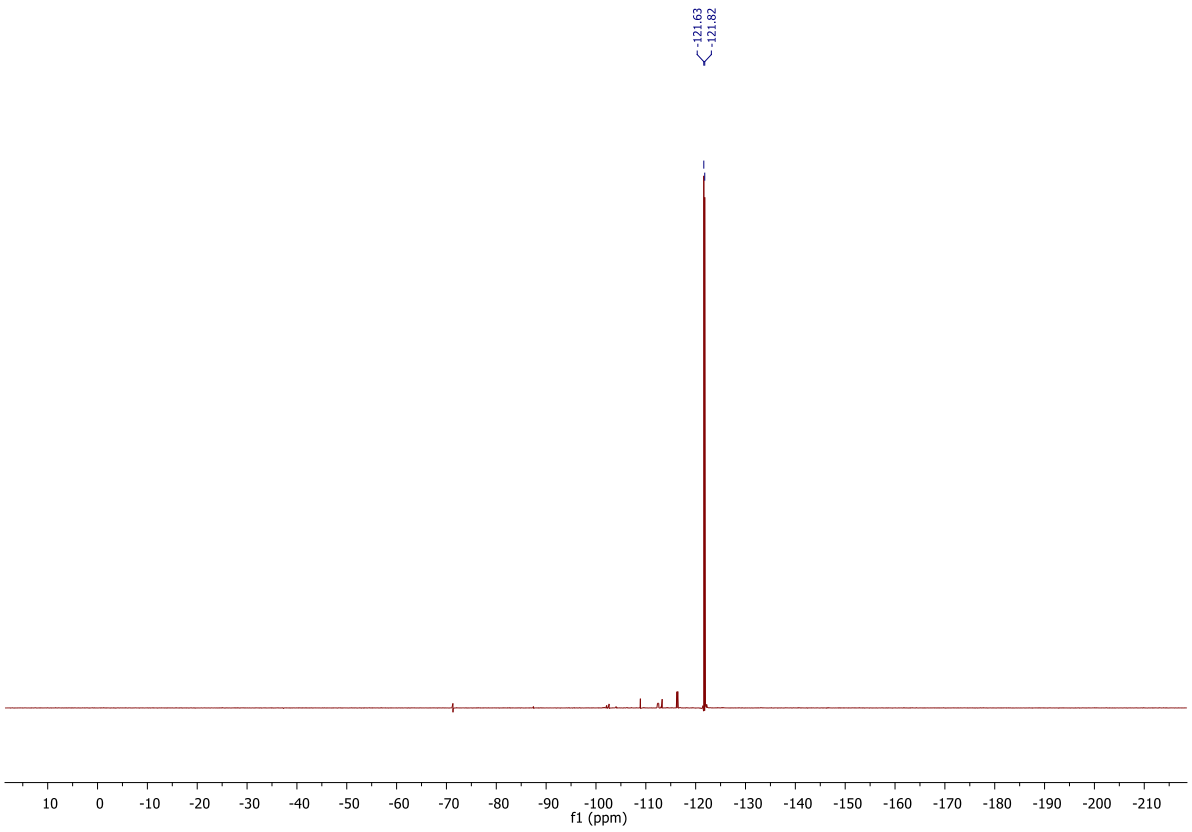

-92.16
-92.21
-92.26
-92.31
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)



1-([1,1'-biphenyl]-4-yl)-2,2-difluoroethan-1-one (1d)






-121.63
-121.82
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
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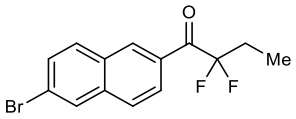
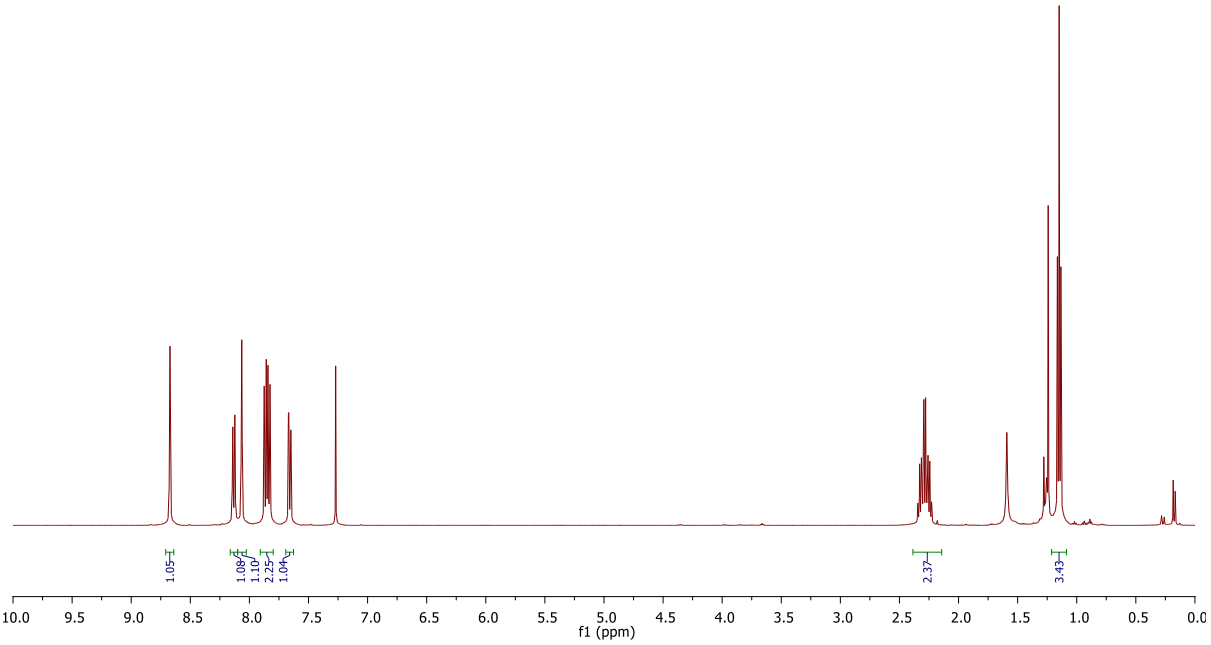
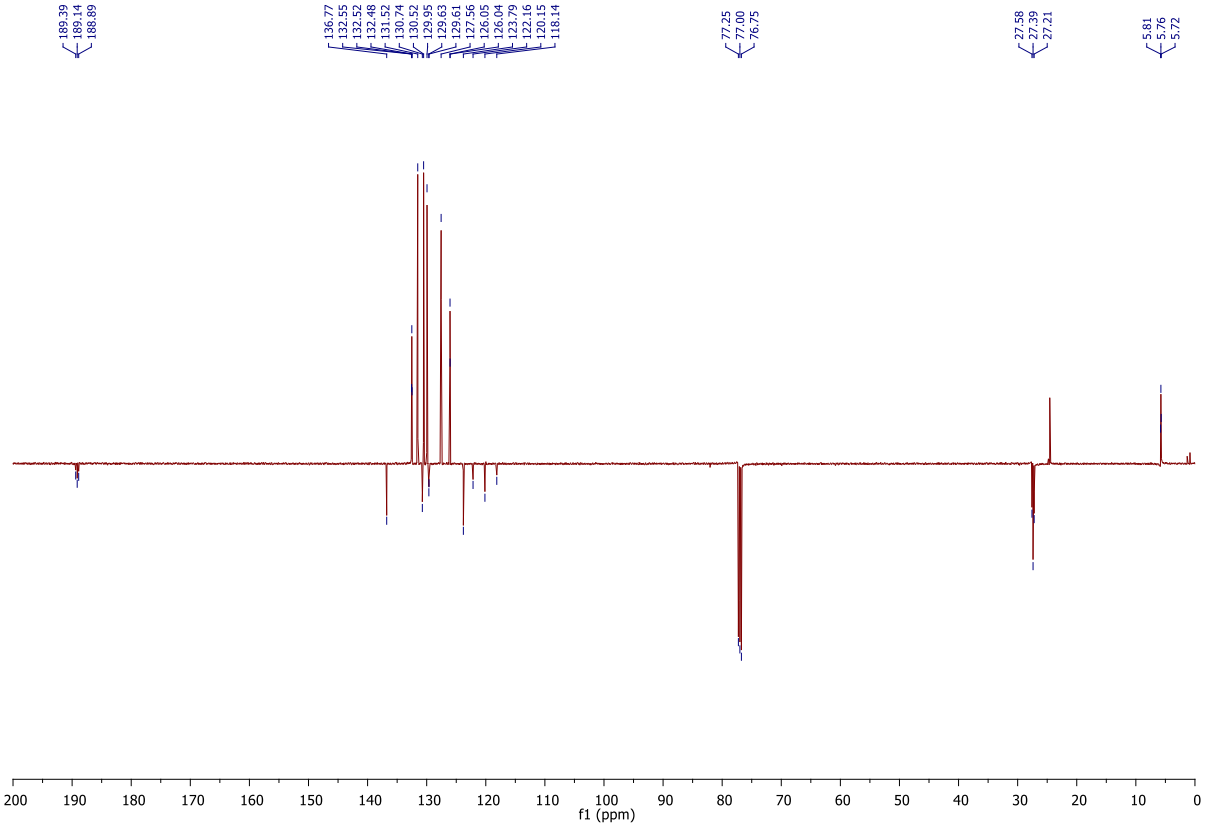
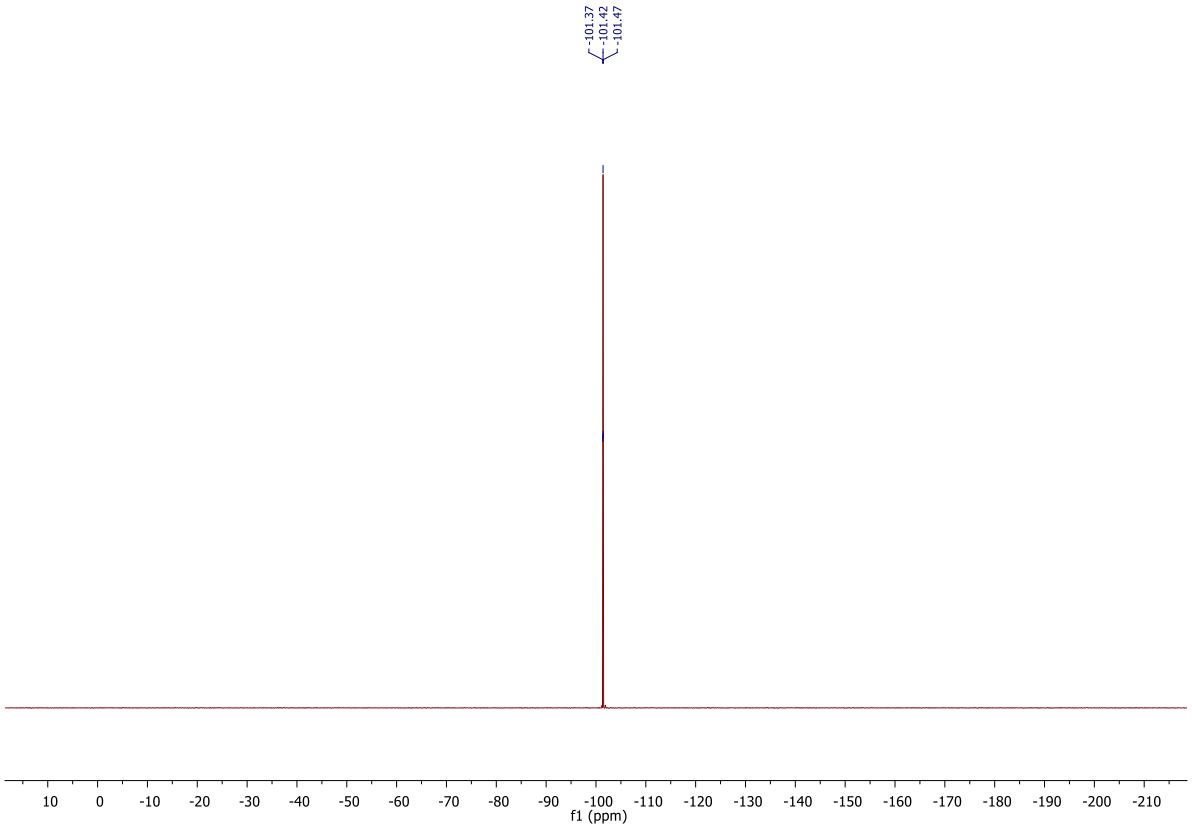
-170
-180
-190
-200
-210
f1 (ppm)



1-(6-bromonaphthalen-2-yl)-2,2-difluorobutan-1-one (1e)



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-101.42
-101.47
10
0
-10
-20
-30
-40
-50
-60
-70
-80
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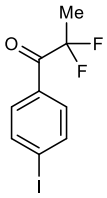
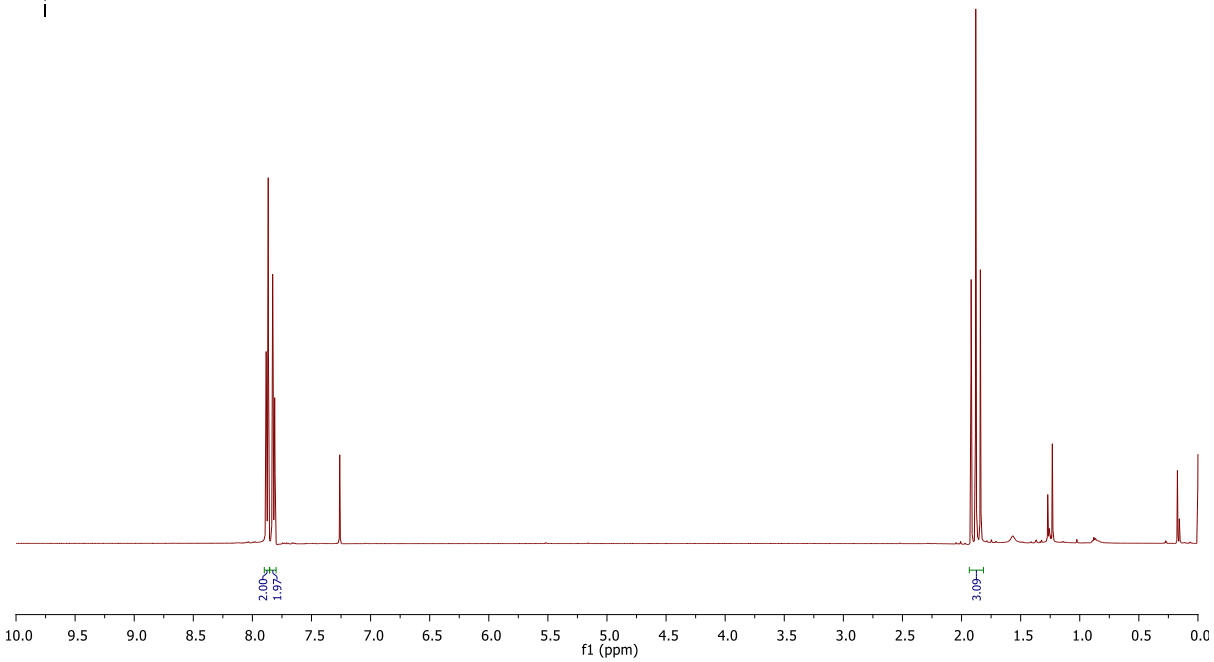
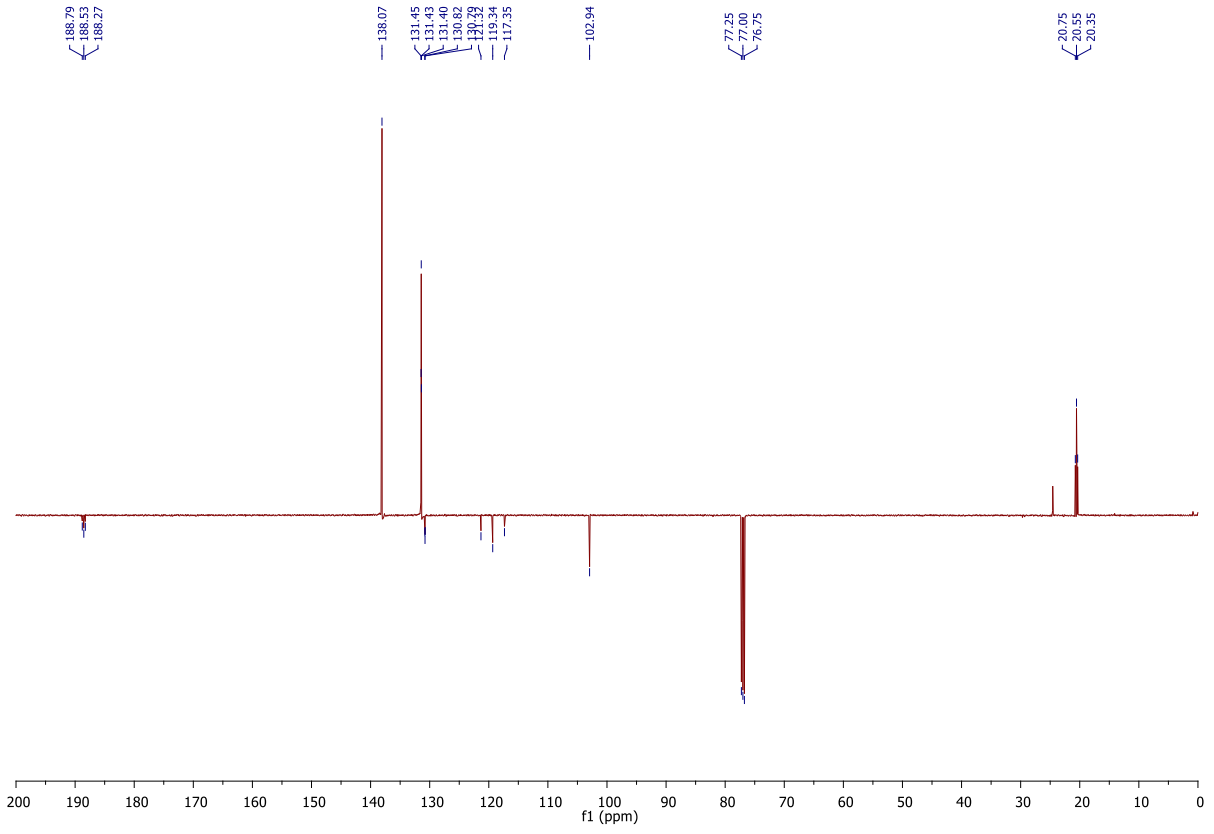
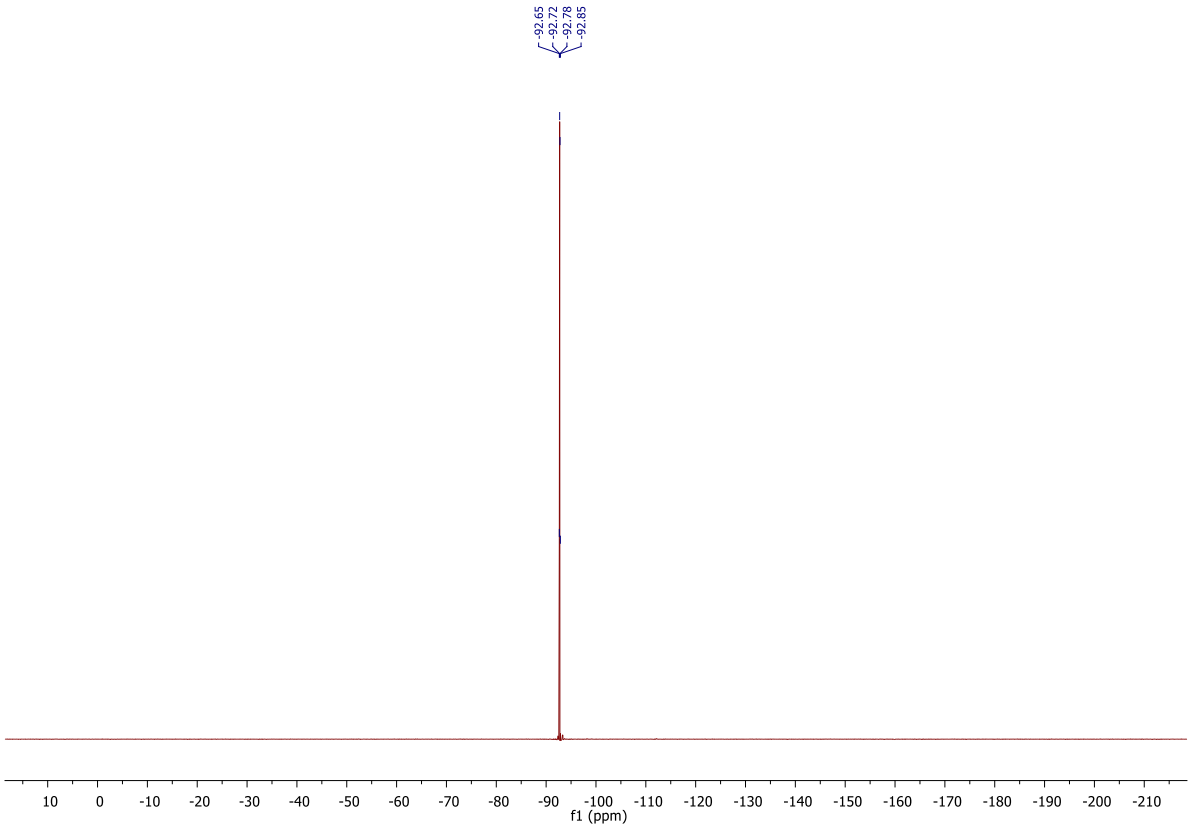
-170
-180
-190
-200
-210
f1 (ppm)

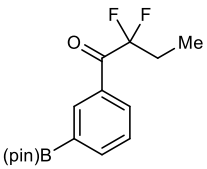


2,2-difluoro-1-(4-iodophenyl)propan-1-one (1f)

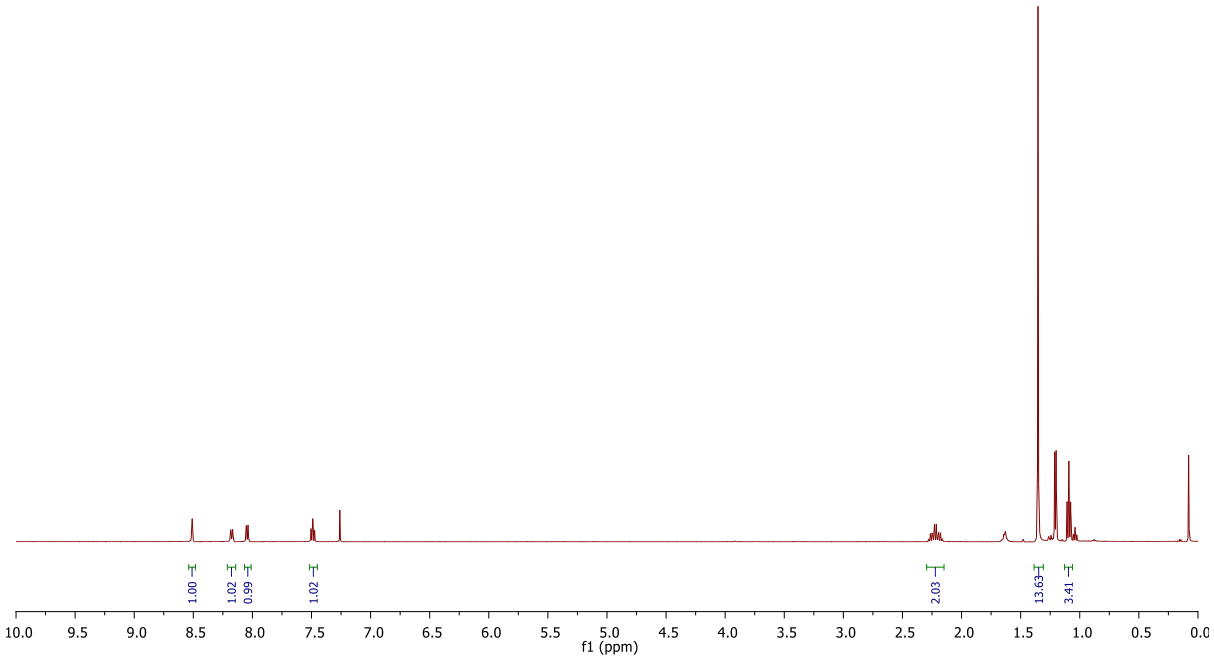


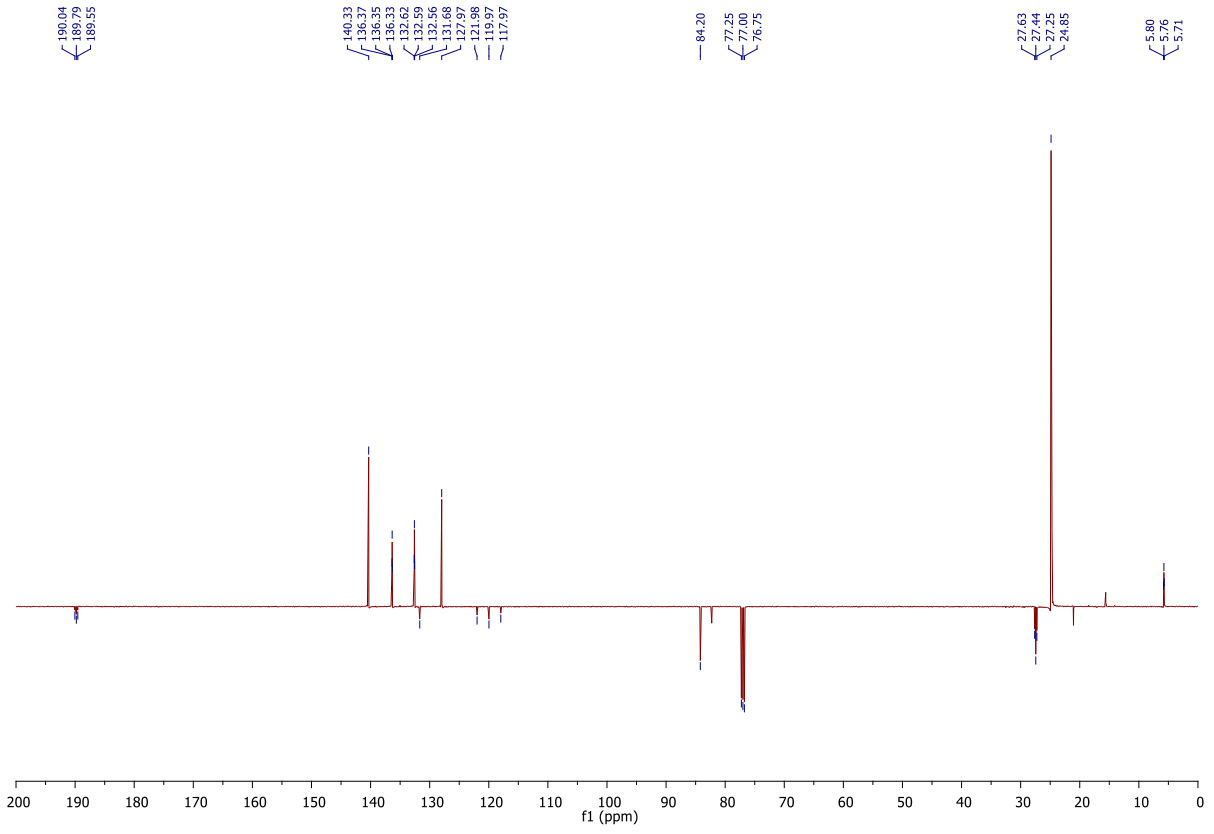


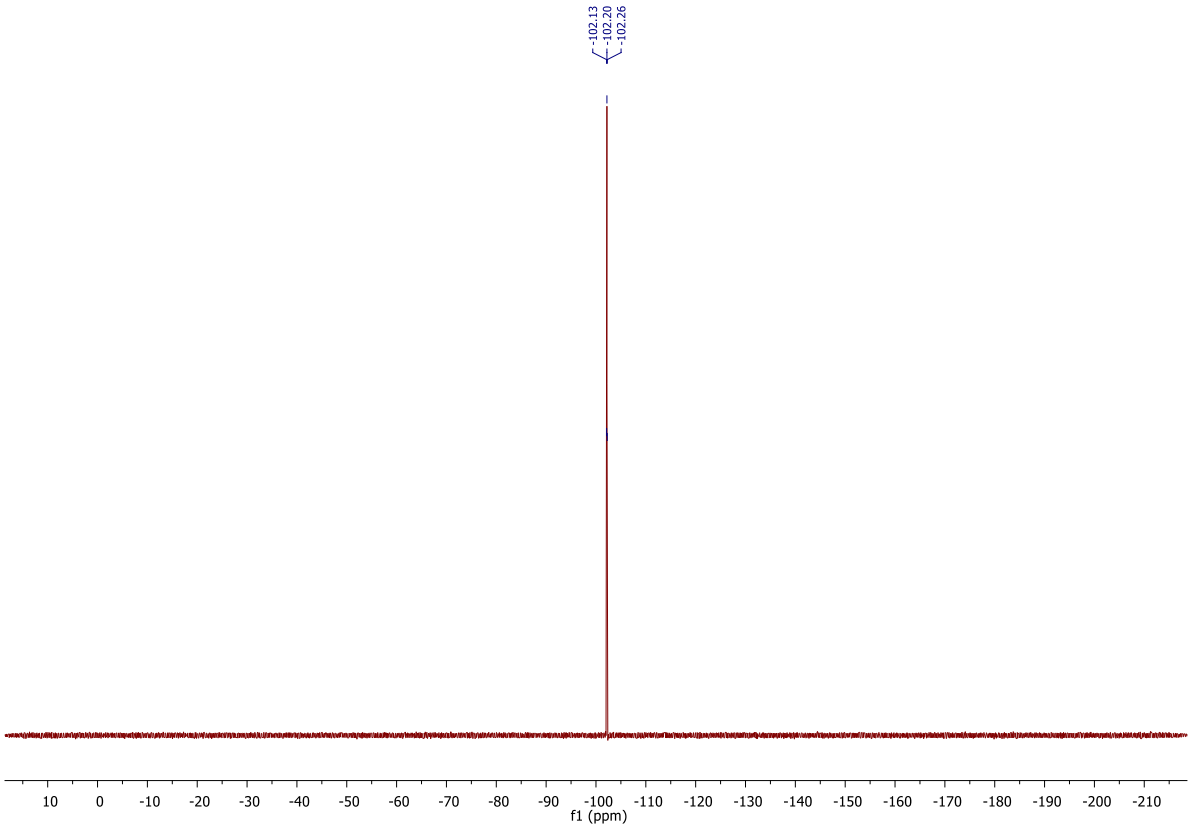

-92.65
-92.72
-92.78
-92.85
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)



2,2-difluoro-1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)butan-1-one (1g)






-102.13
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-102.26
10
0
-10
-20
-30
-40
-50
-60
-70
-80
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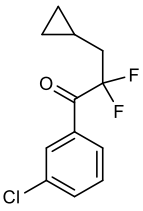
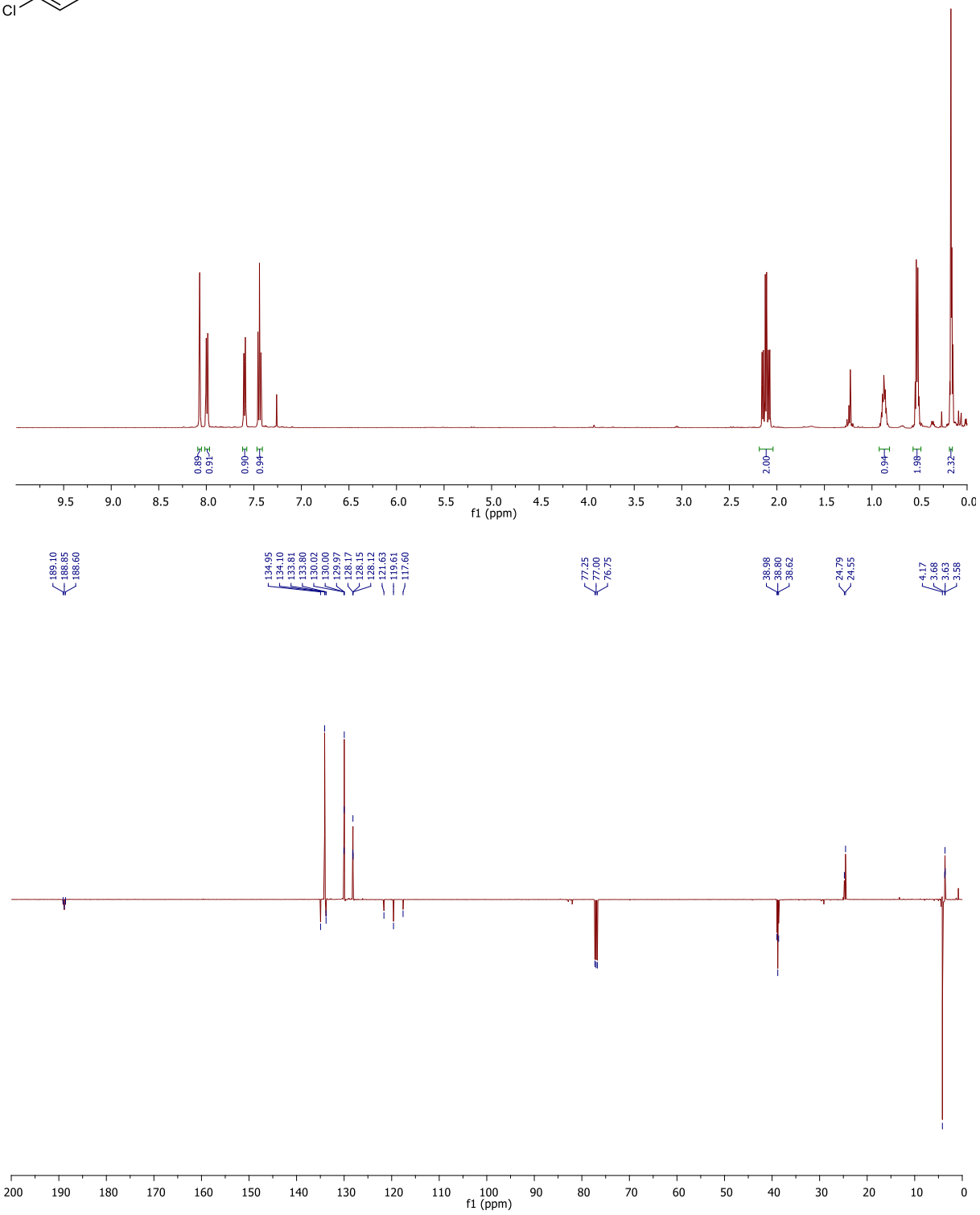
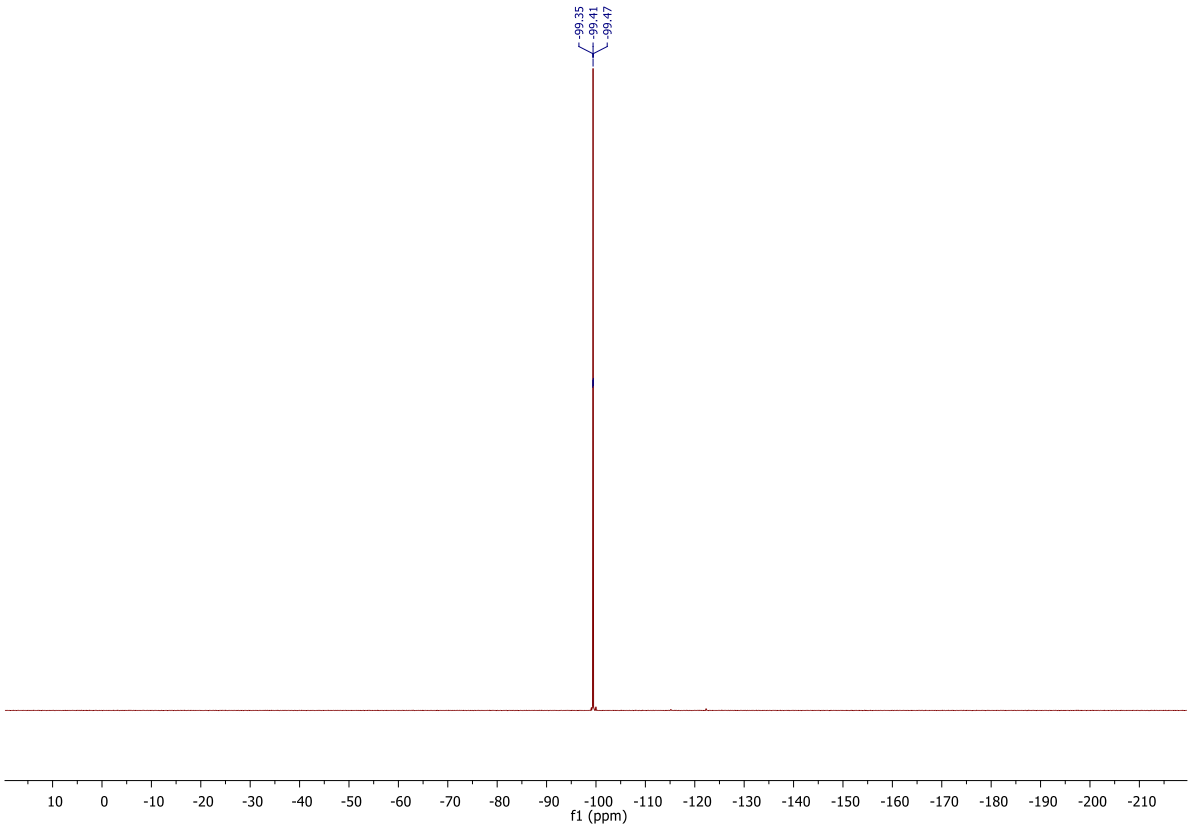
-170
-180
-190
-200
-210
f1 (ppm)



1-(3-chlorophenyl)-3-cyclopropyl-2,2-difluoropropan-1-one (1h)




-99.35
-99.41
-99.47
10
0
-10
-20
-30
-40
-50
-60
-70
-80
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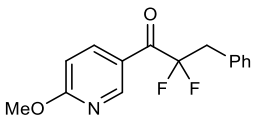
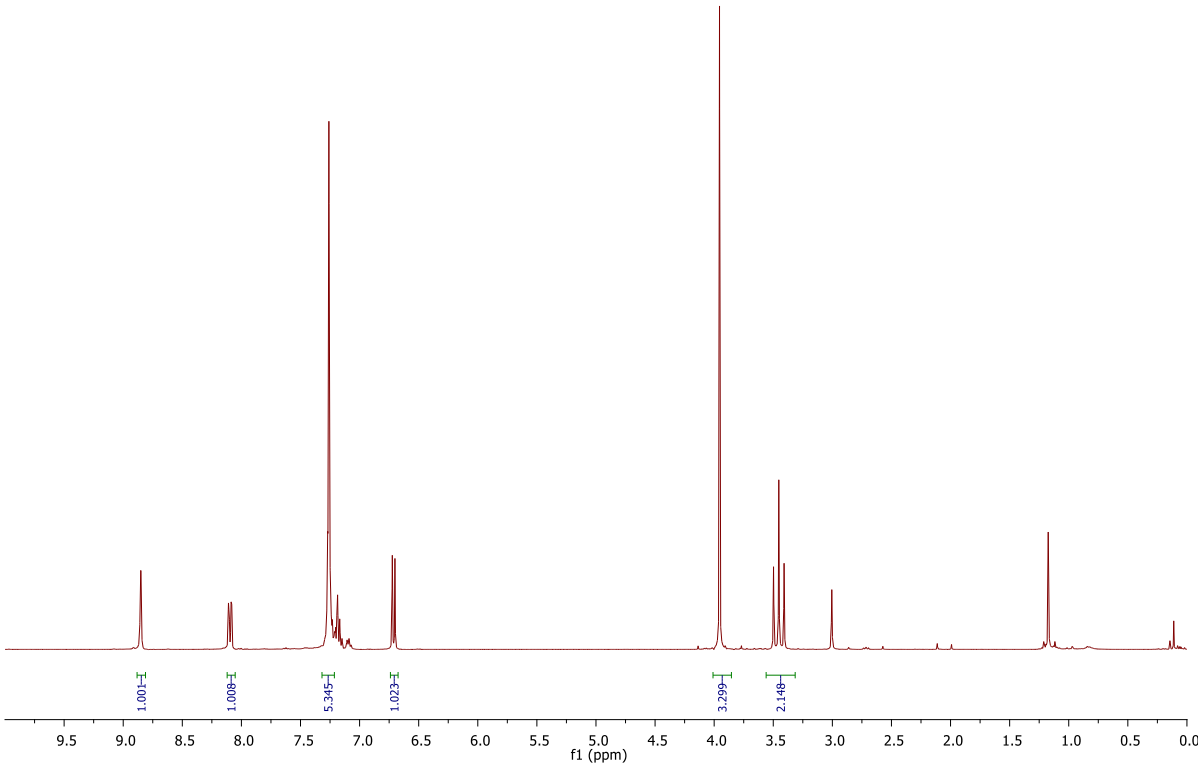
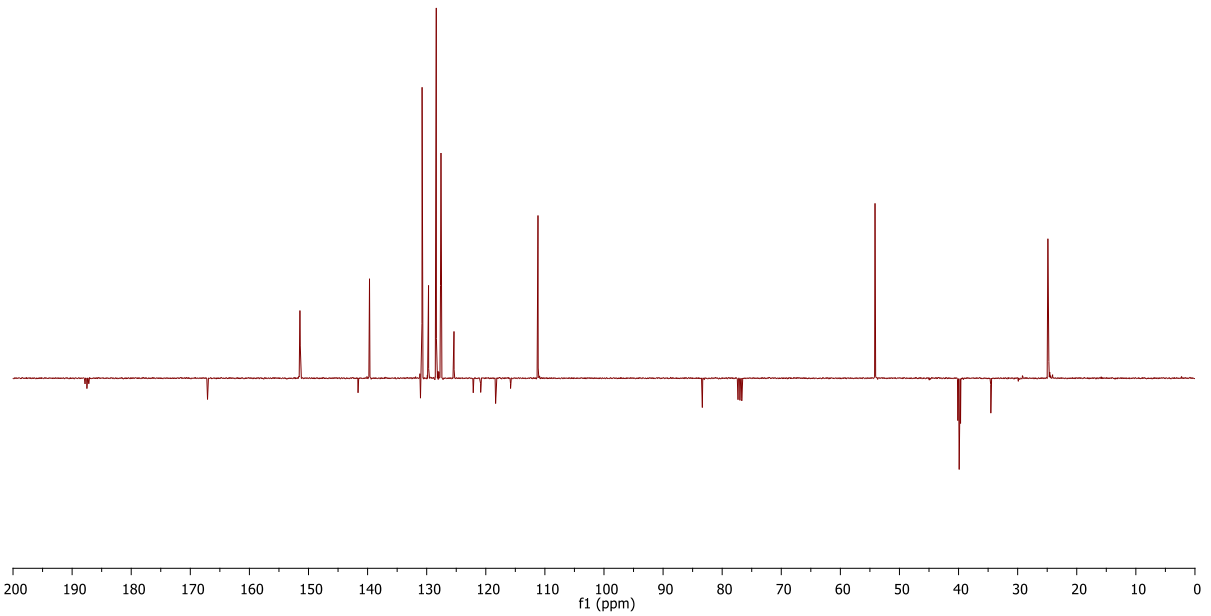
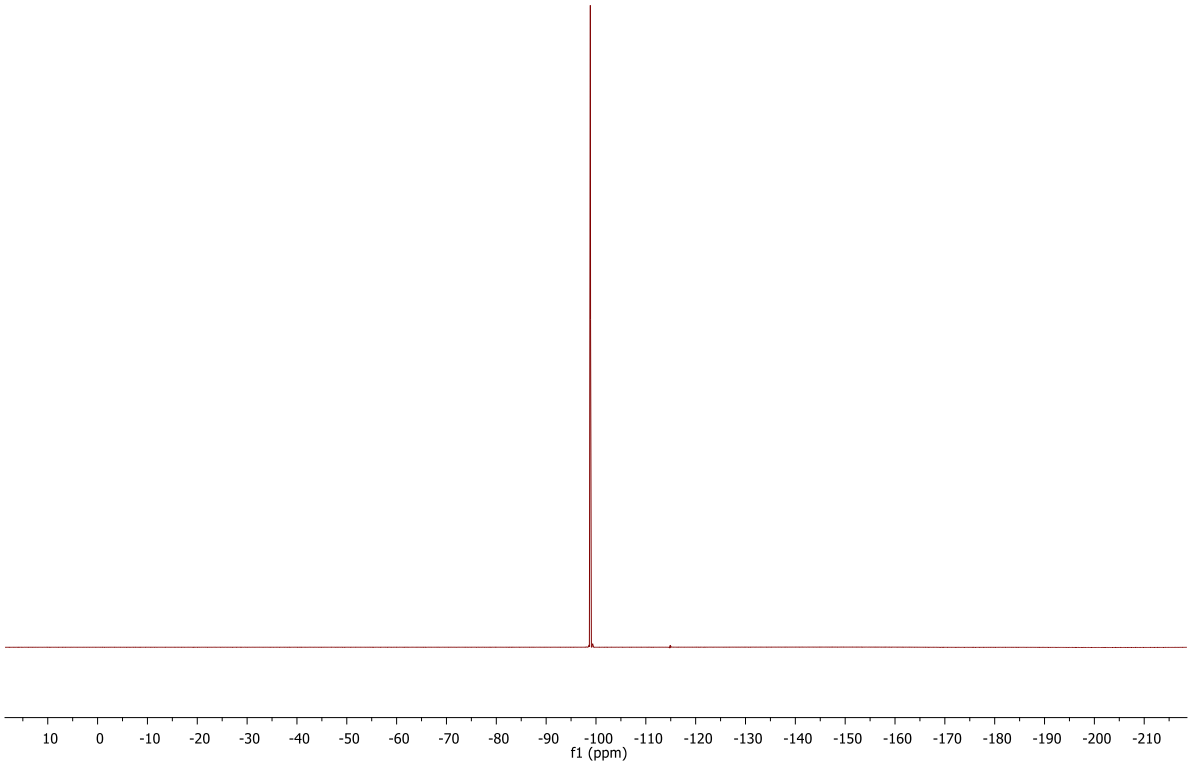
-170
-180
-190
-200
-210
f1 (ppm)



2,2-difluoro-1-(6-methoxypyridin-3-yl)-3-phenylpropan-1-one (1i)






10
0
-10
-20
-30
-40
-50
-60
-70
-80
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-100
-110
-120
-130
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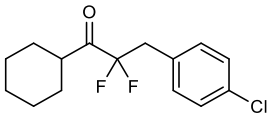
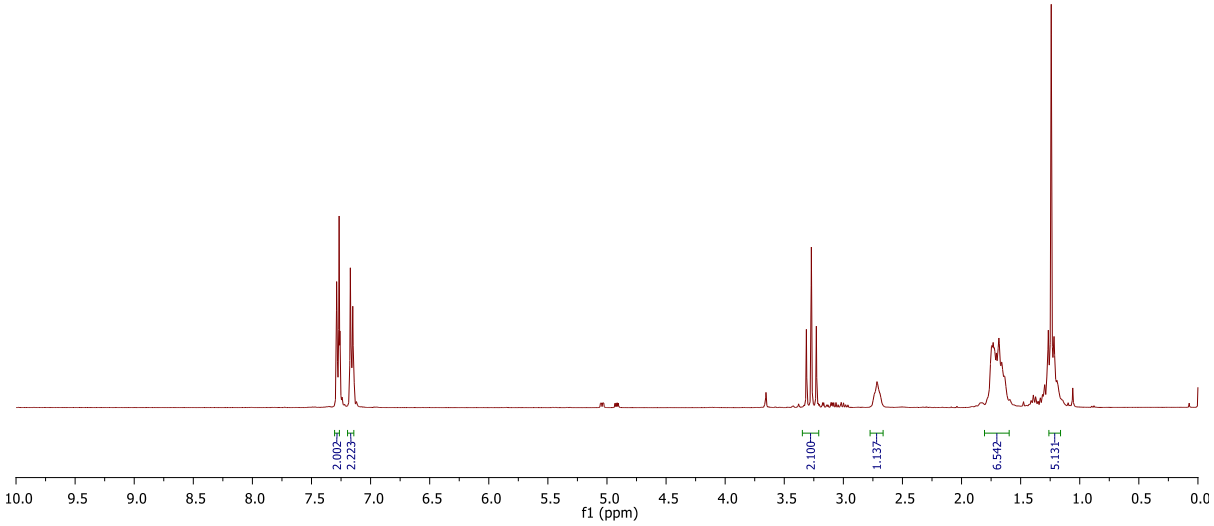
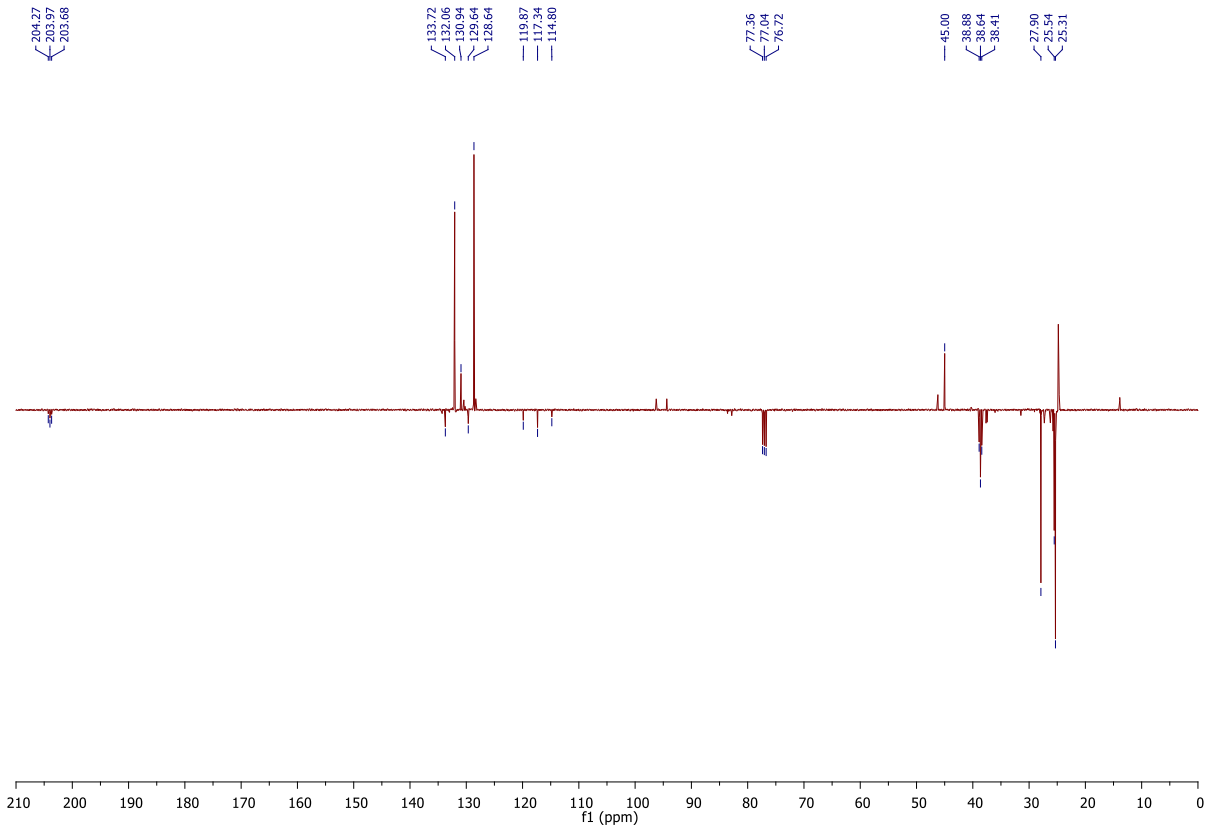
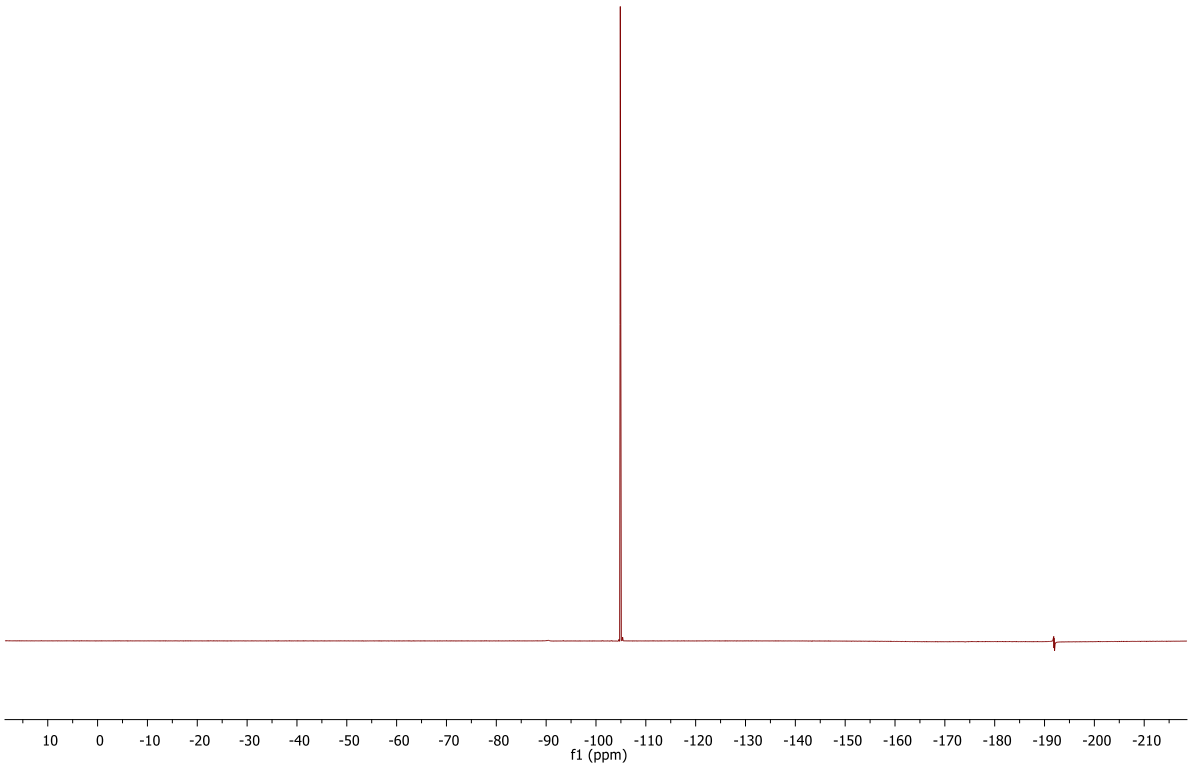
-170
-180
-190
-200
-210
f1 (ppm)

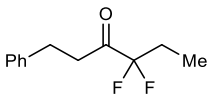


3-(4-chlorophenyl)-1-cyclohexyl-2,2-difluoropropan-1-one (2a)

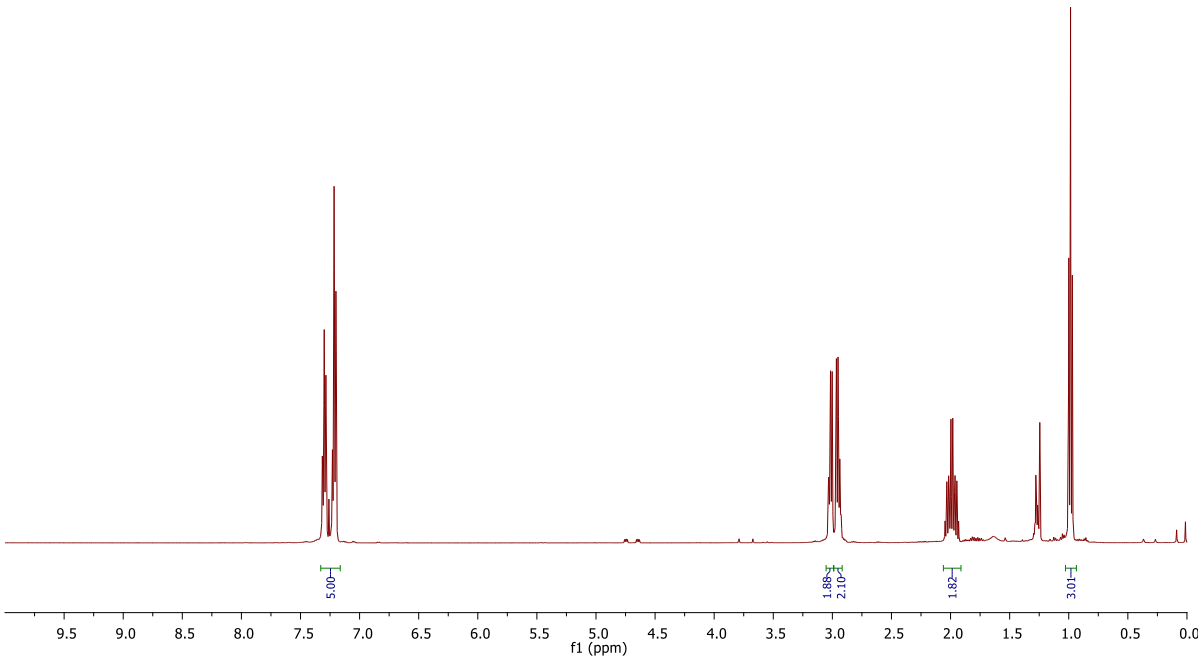


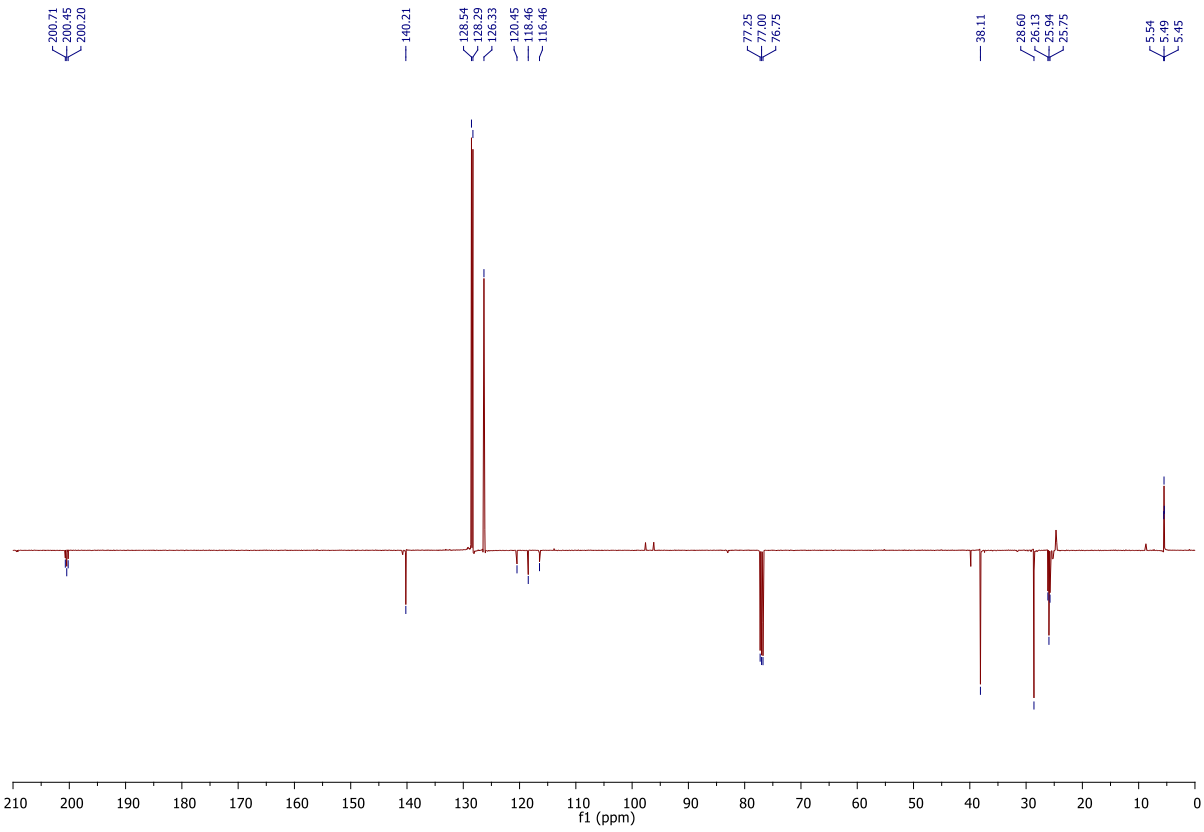


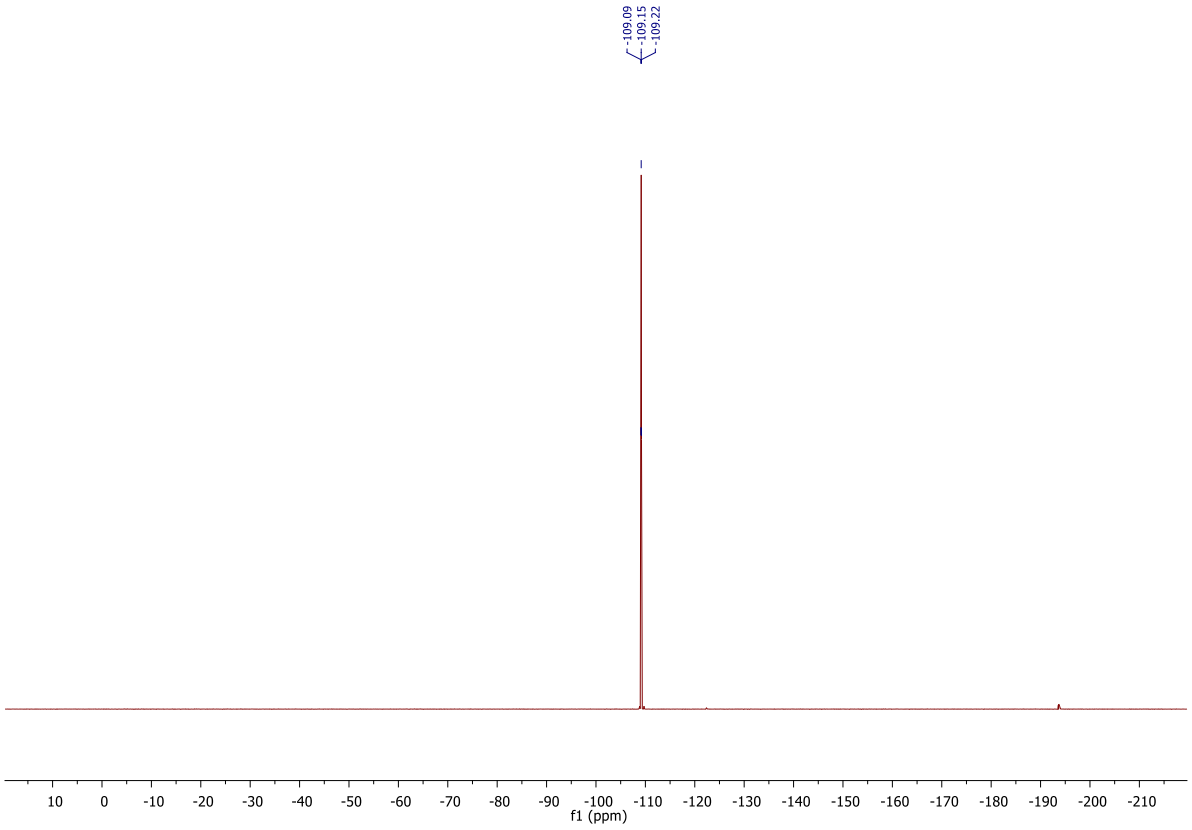

10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)



4,4-difluoro-1-phenylhexan-3-one (2b)



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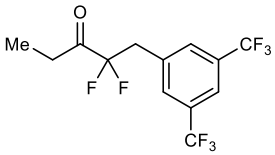
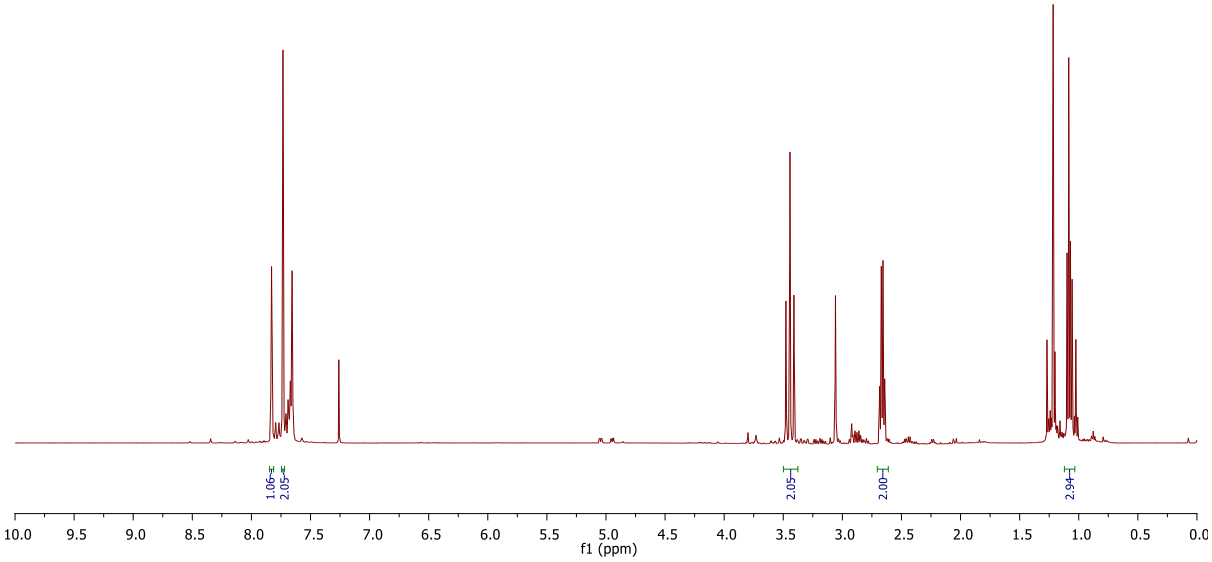
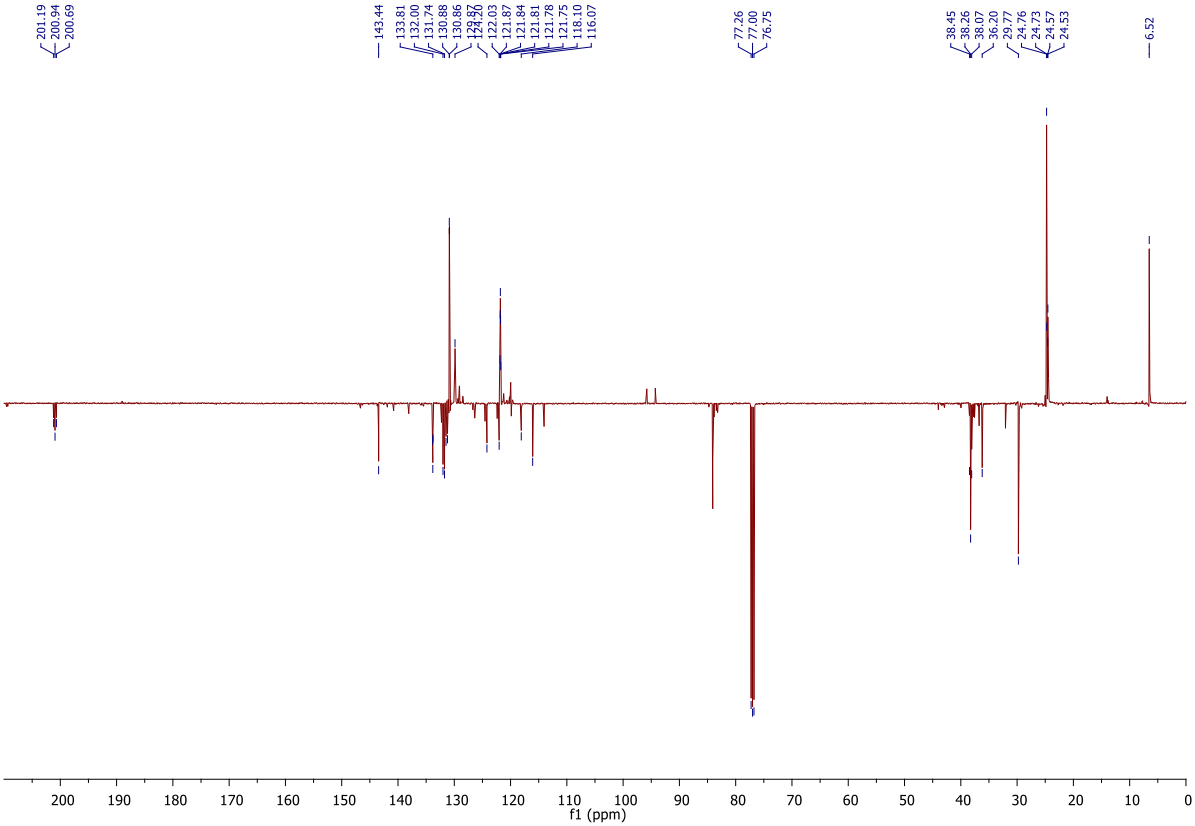
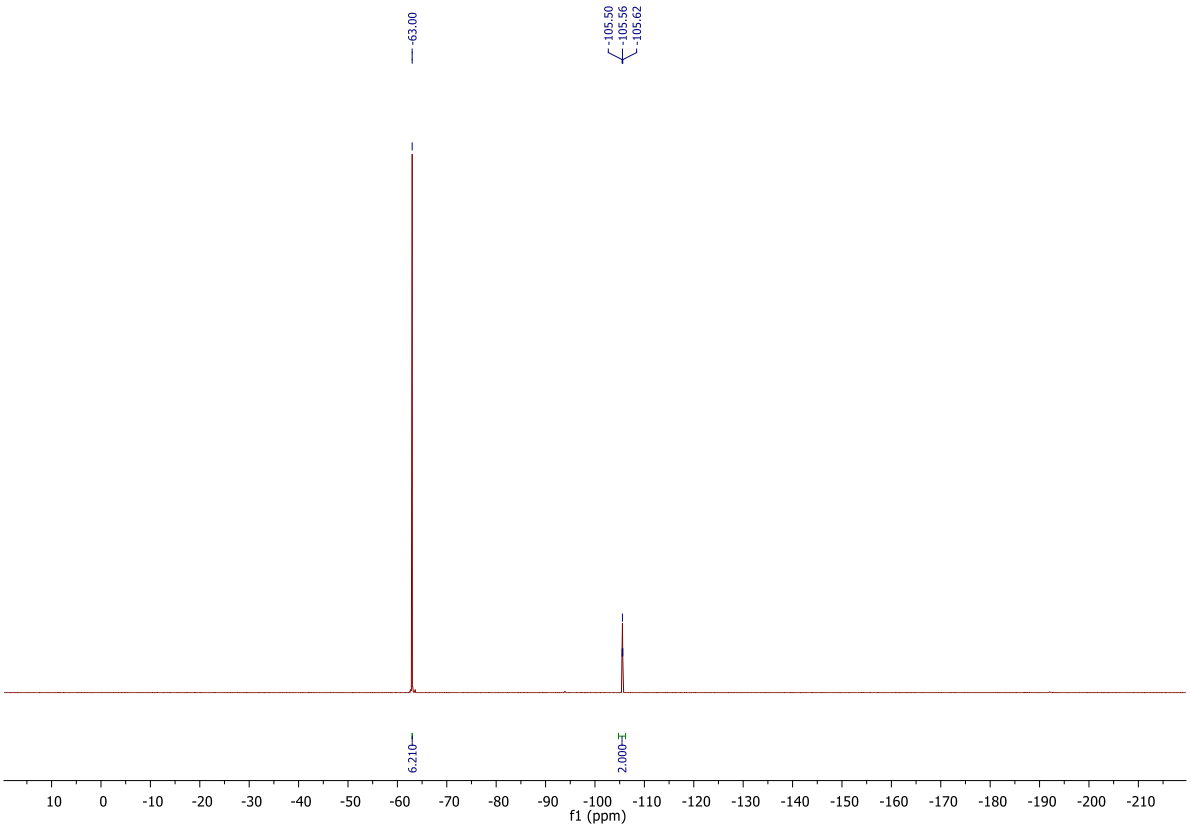
f1 (ppm)



1-(3,5-bis(trifluoromethyl)phenyl)-2,2-difluoropentan-3-one (2c)



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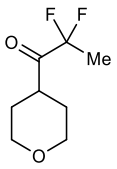
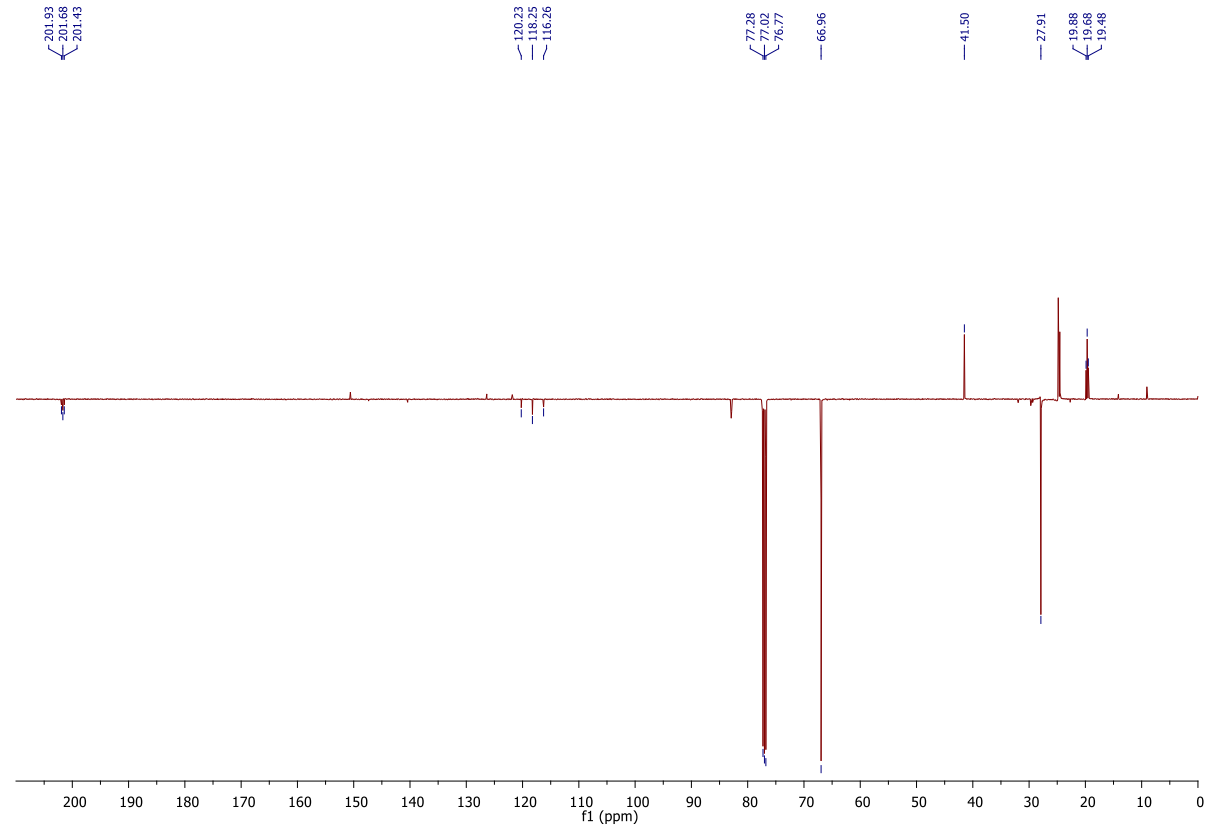
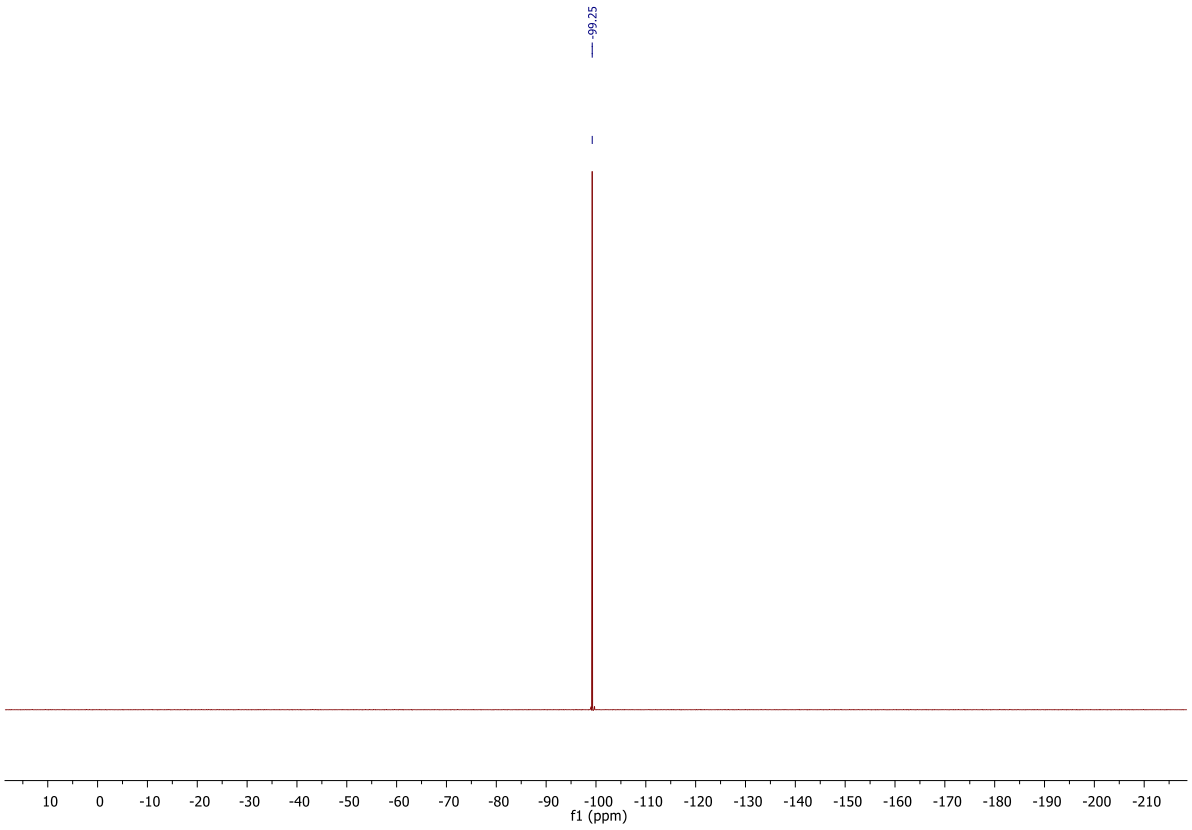
f1 (ppm)



2,2-difluoro-1-(tetrahydro-2H-pyran-4-yl)propan-1-one (2d)

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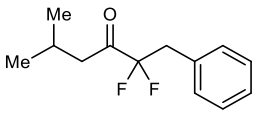
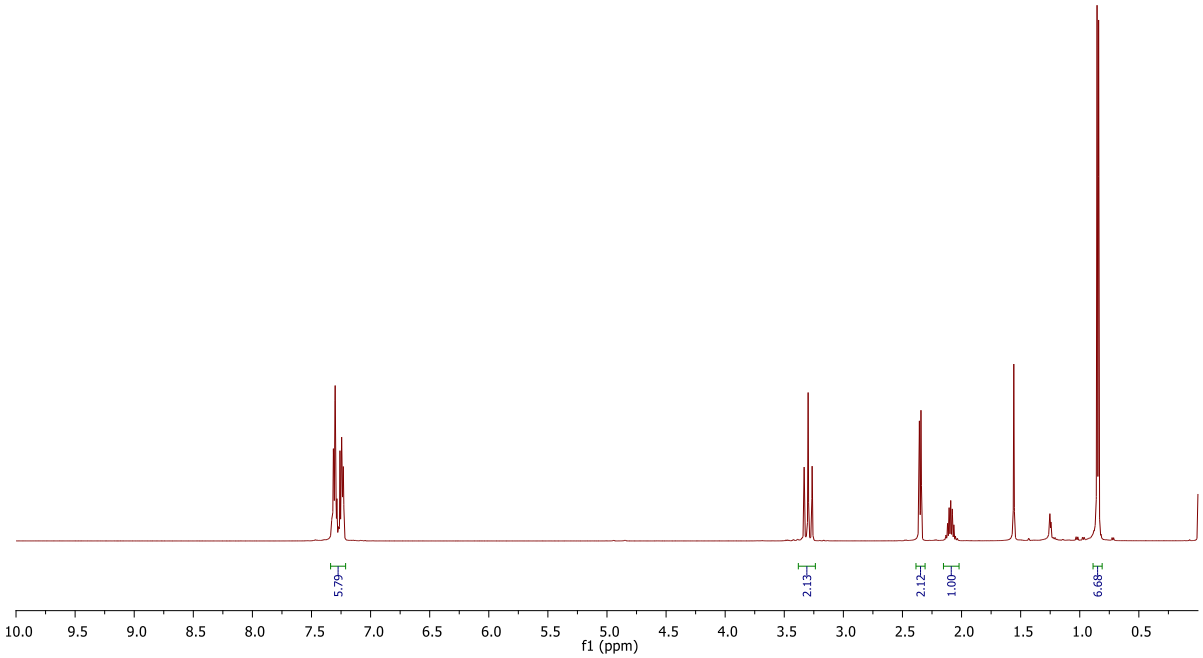
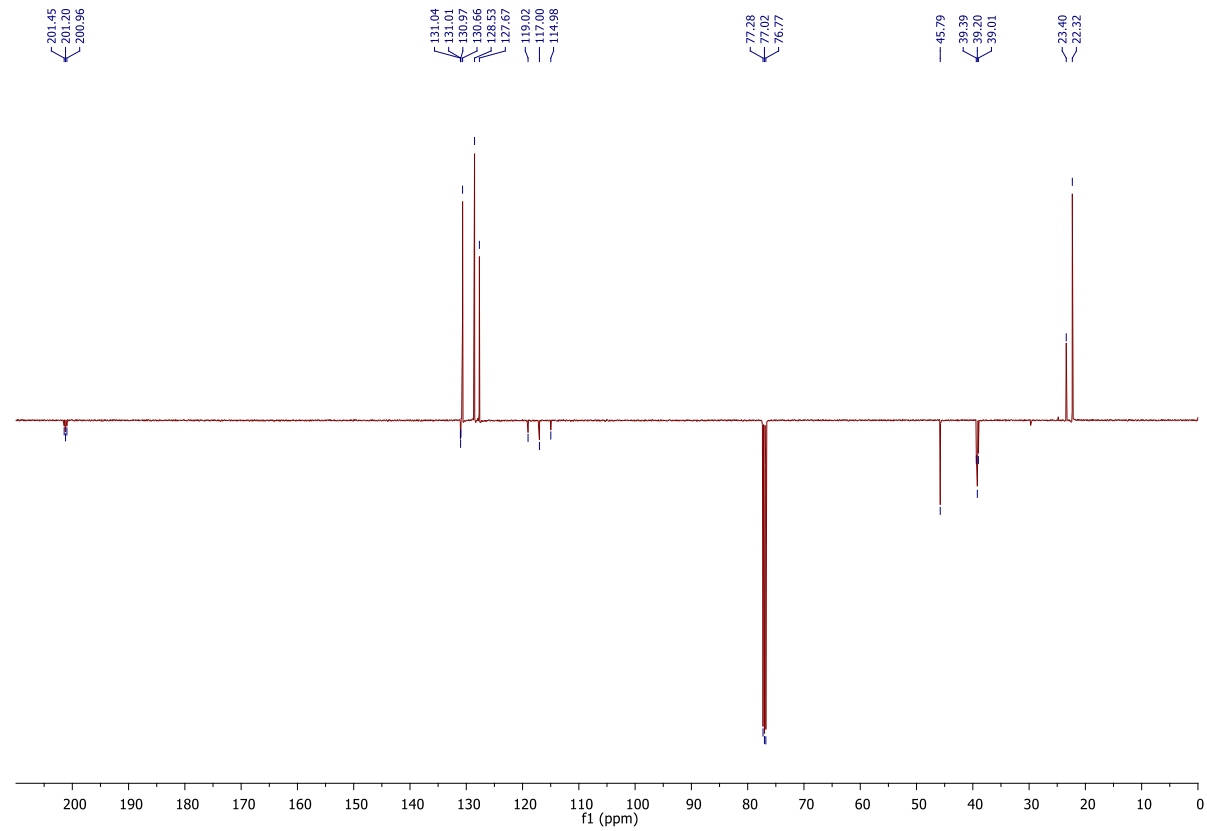
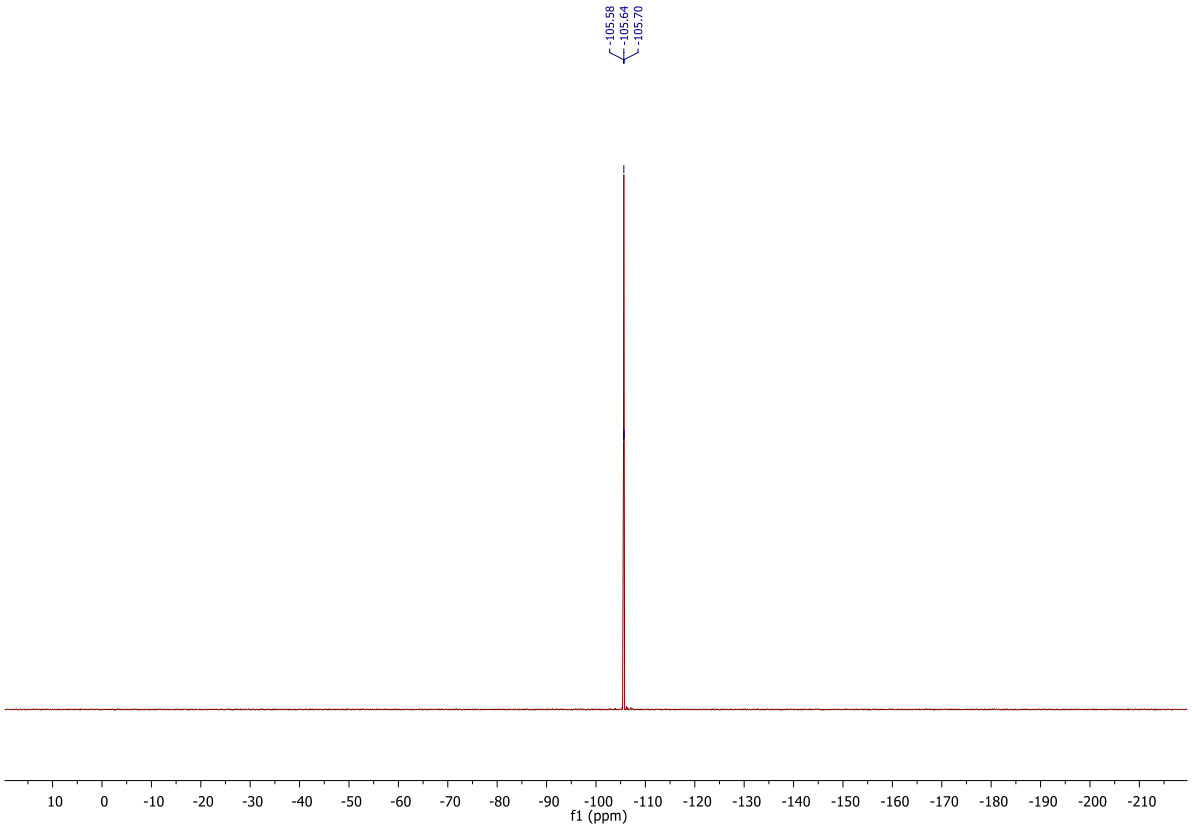
f1 (ppm)



2,2-difluoro-5-methyl-1-phenylhexan-3-one (2e)



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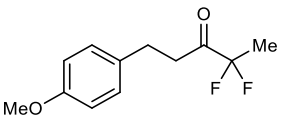
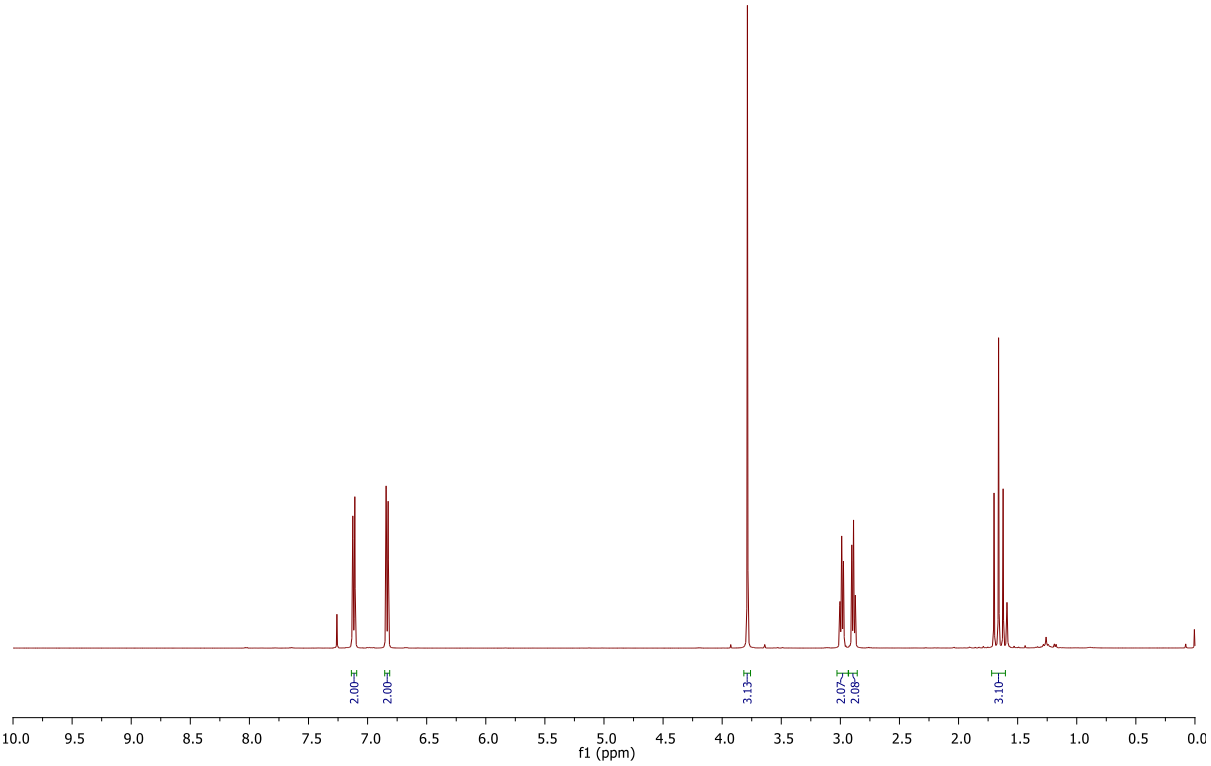
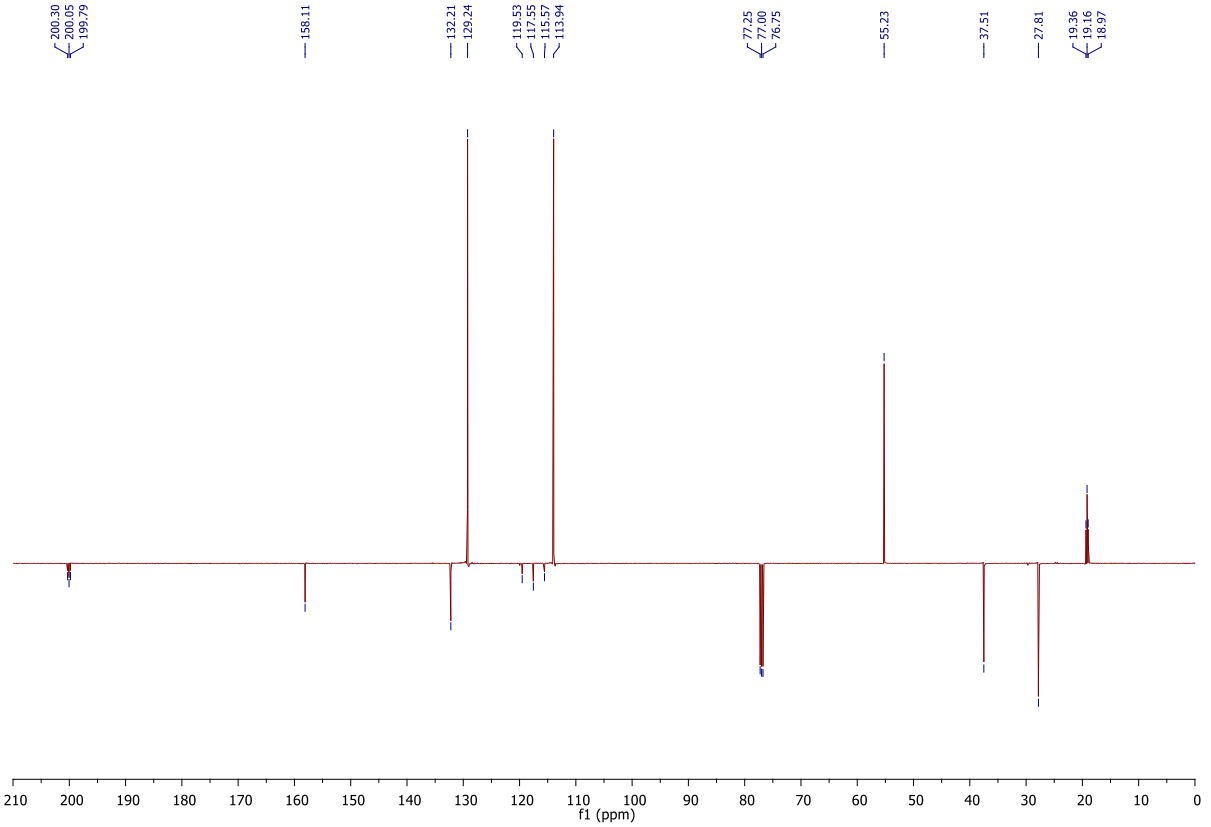
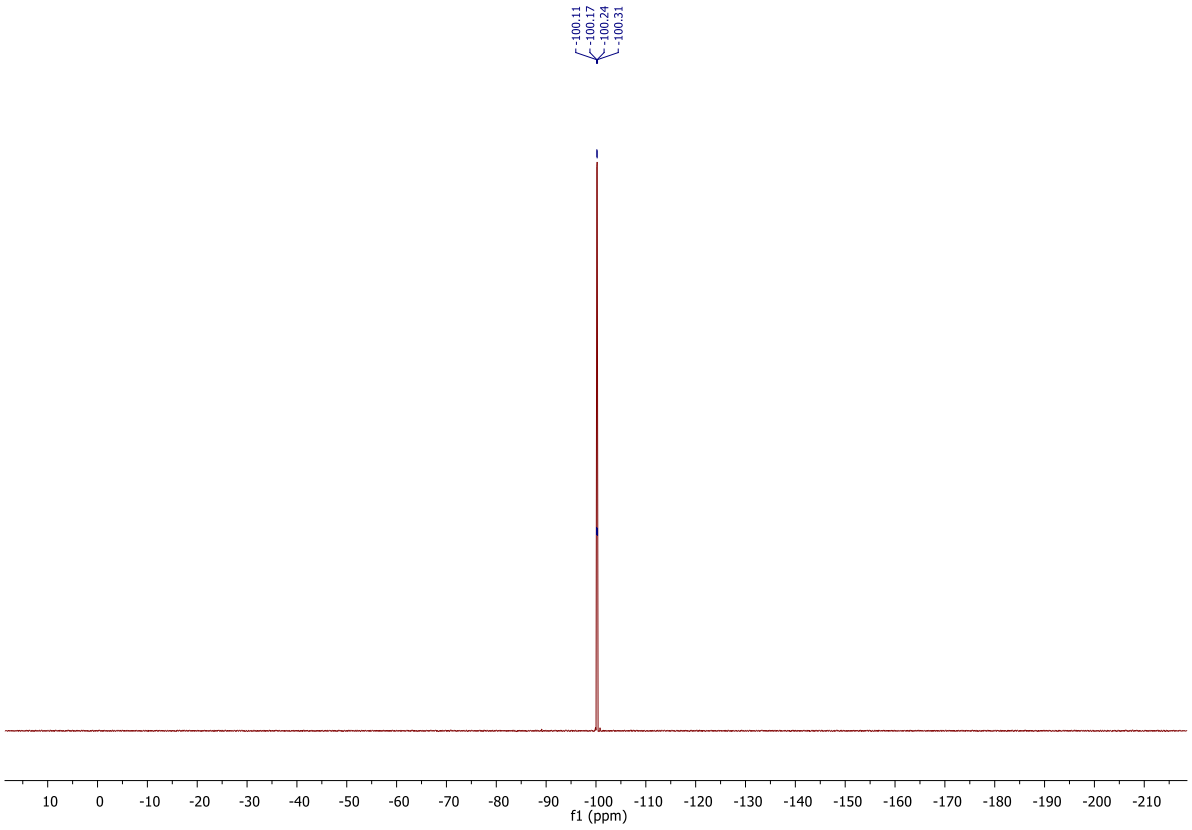
f1 (ppm)



4,4-difluoro-1-(4-methoxyphenyl)pentan-3-one (2f)



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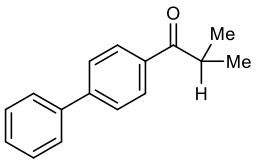
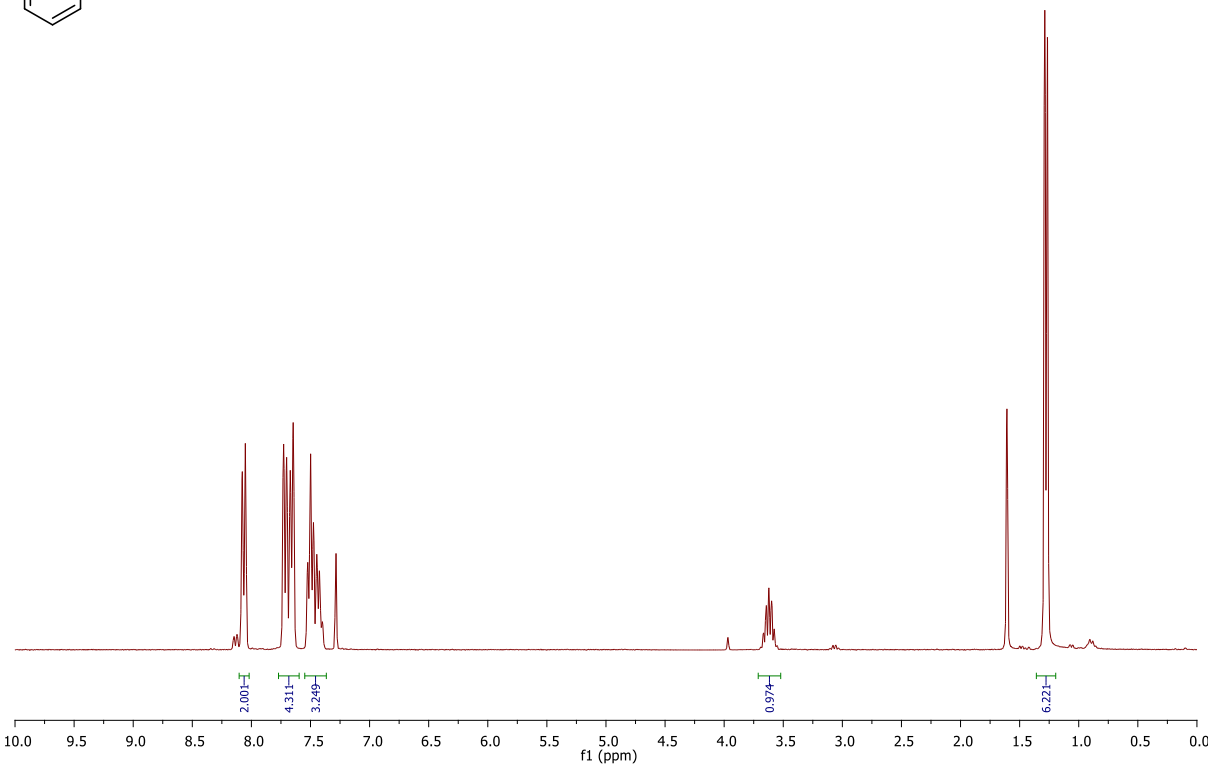
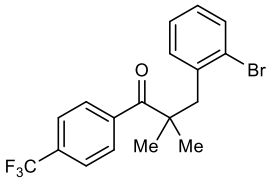
f1 (ppm)

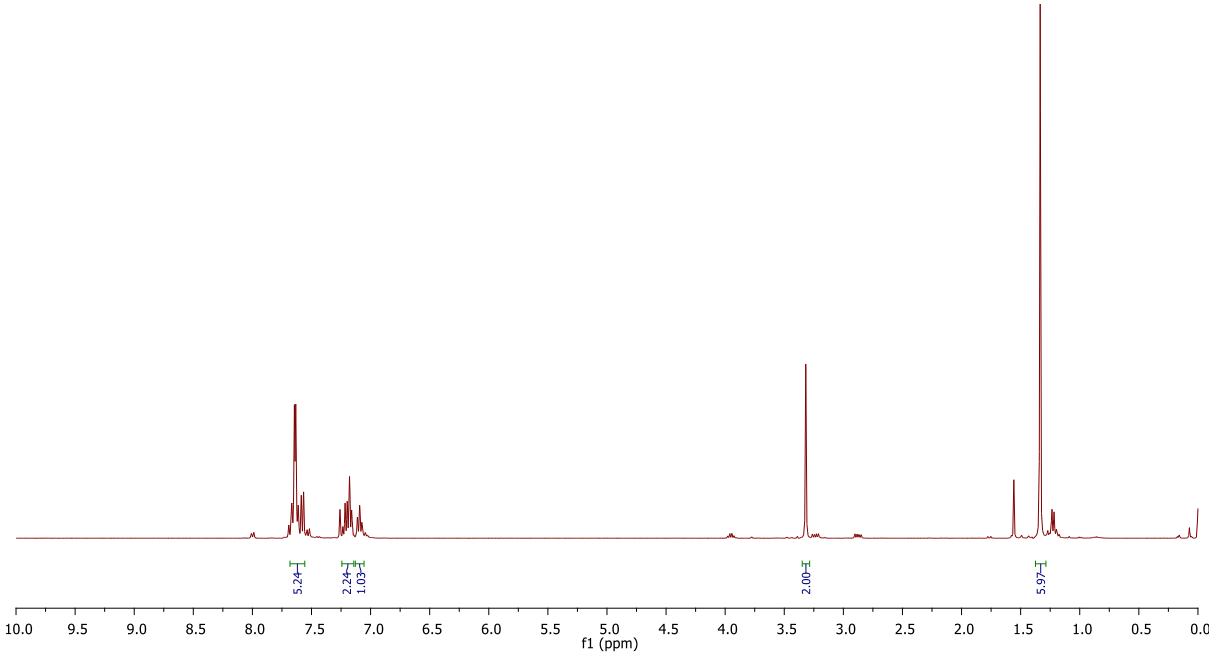


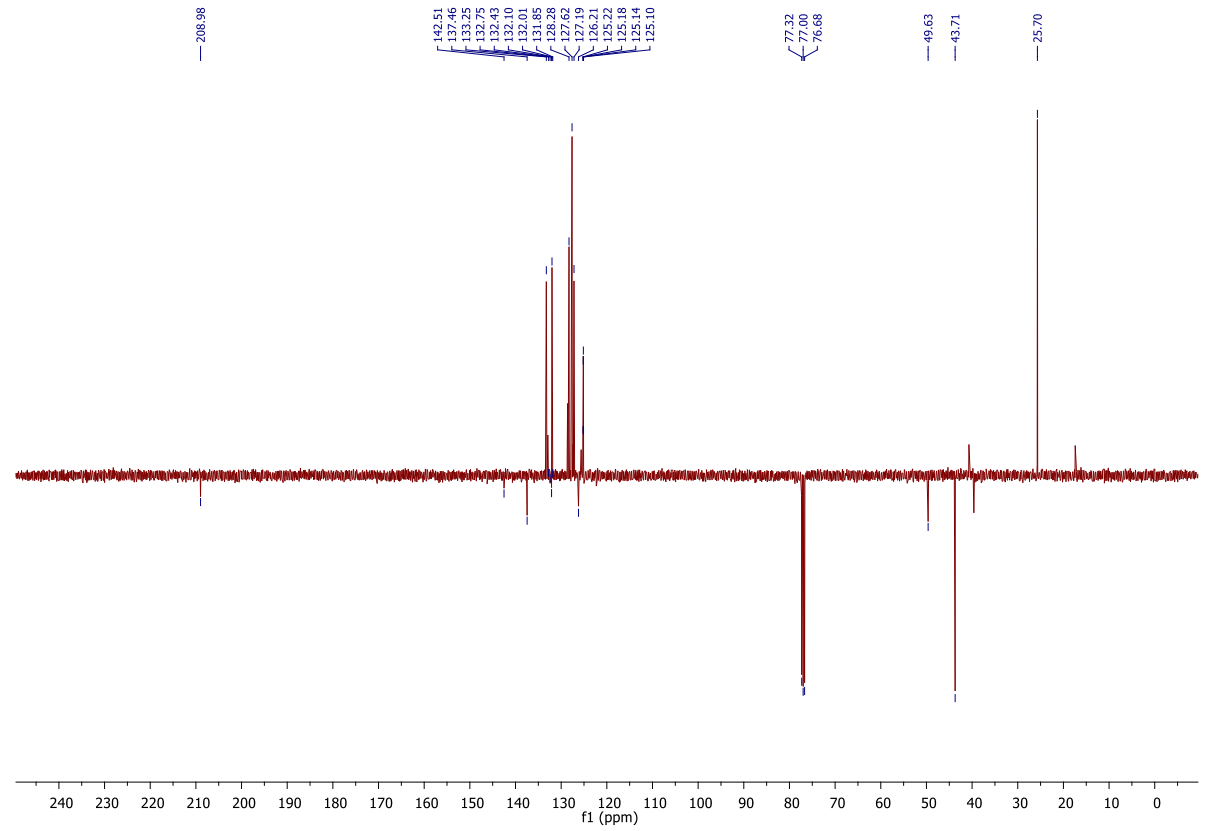
1-([1,1'-biphenyl]-4-yl)-2-methylpropan-1-one (3a)

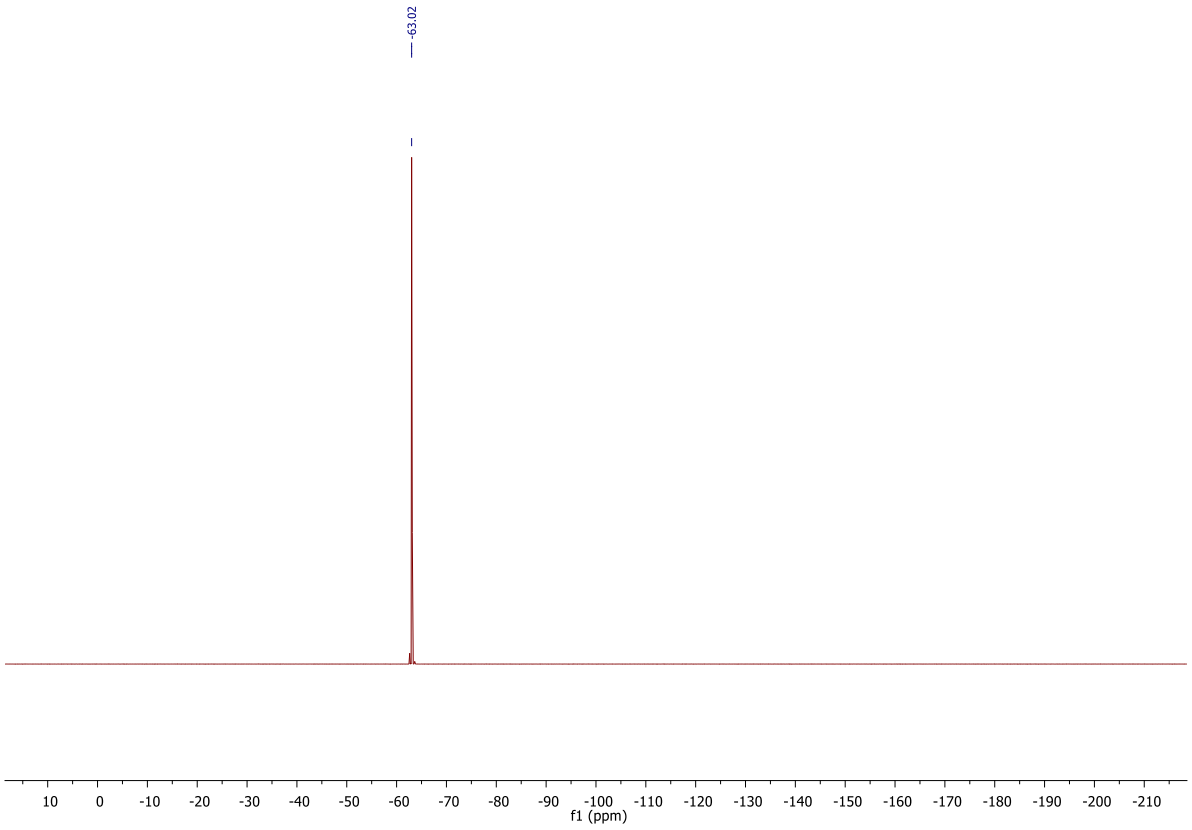




3-(2-bromophenyl)-2,2-dimethyl-1-(4-(trifluoromethyl)phenyl)propan-1-one (3b)



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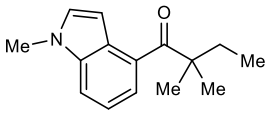
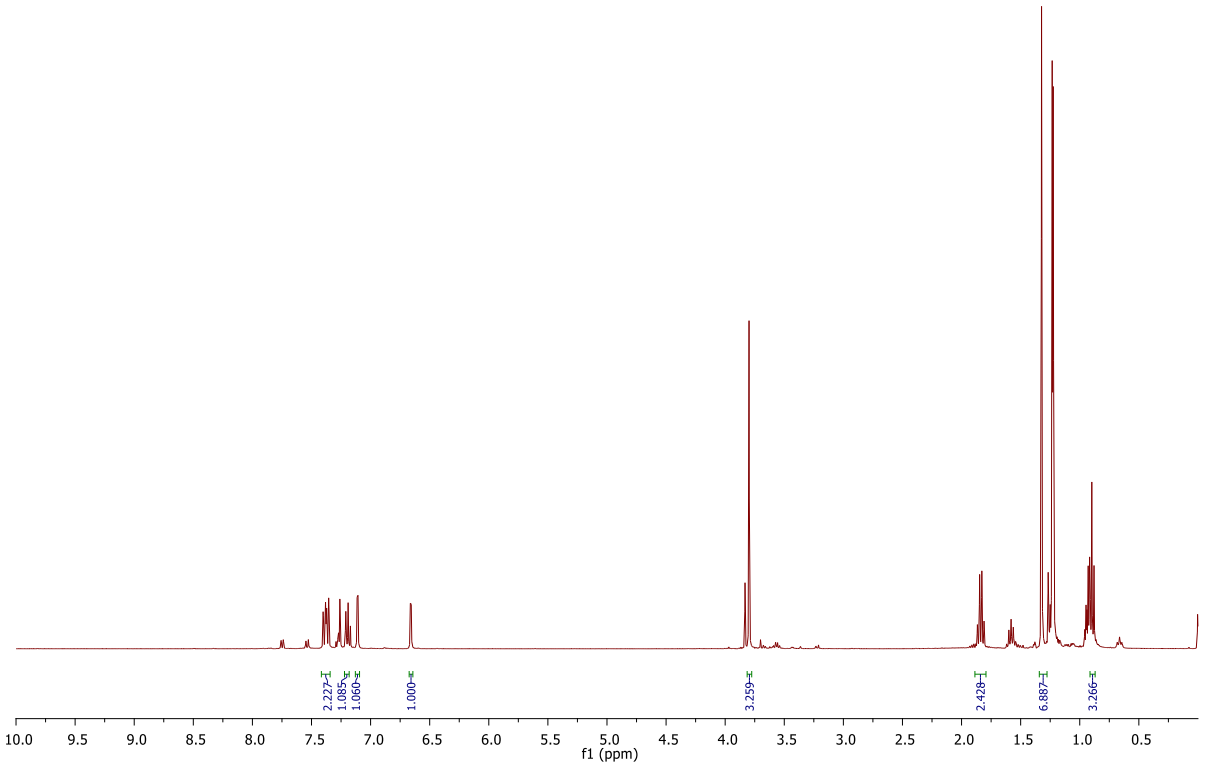
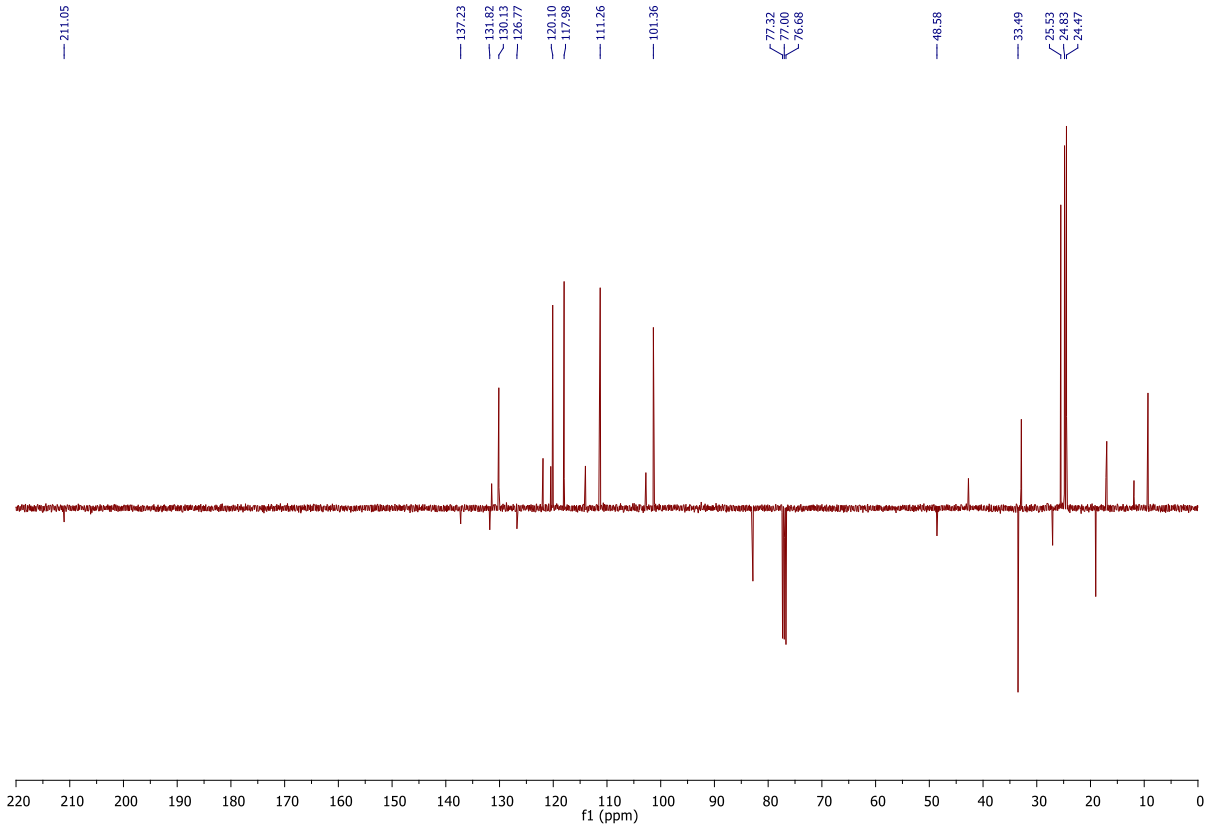
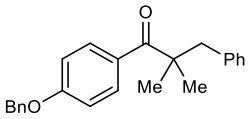
f1 (ppm)



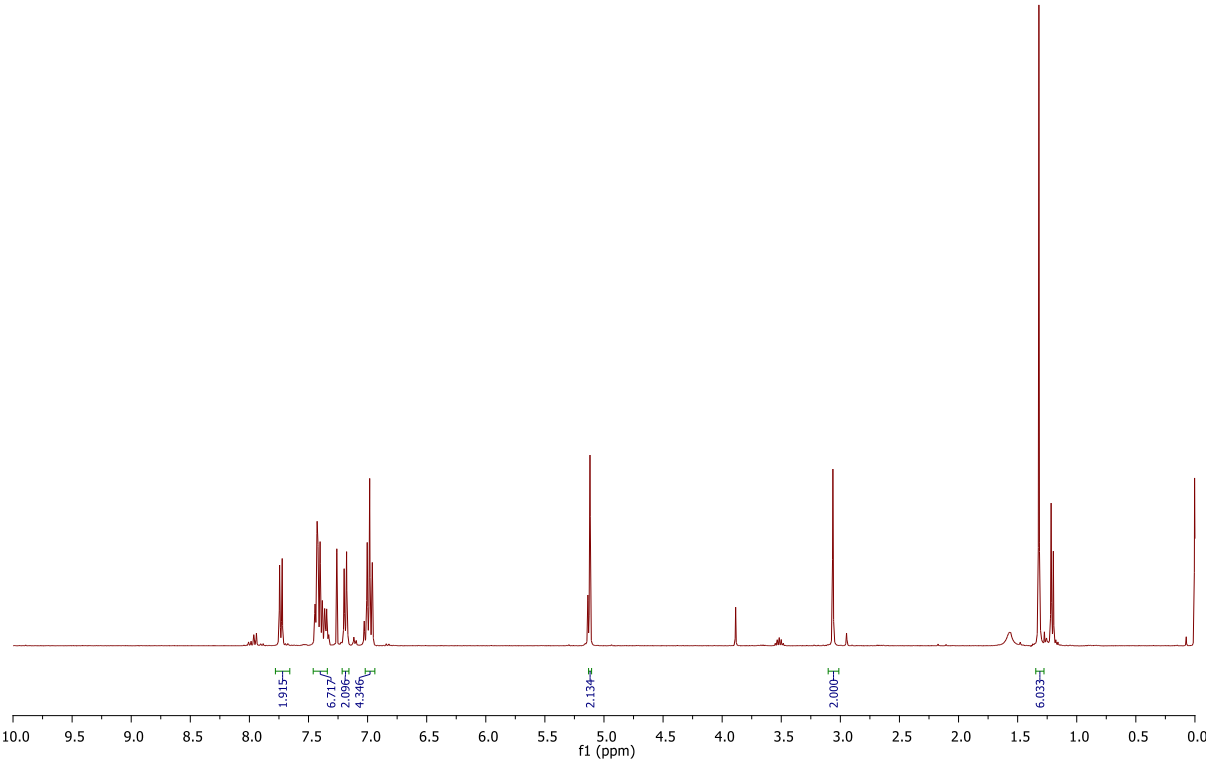
2,2-dimethyl-1-(1-methyl-1H-indol-4-yl)butan-1-one (3c)

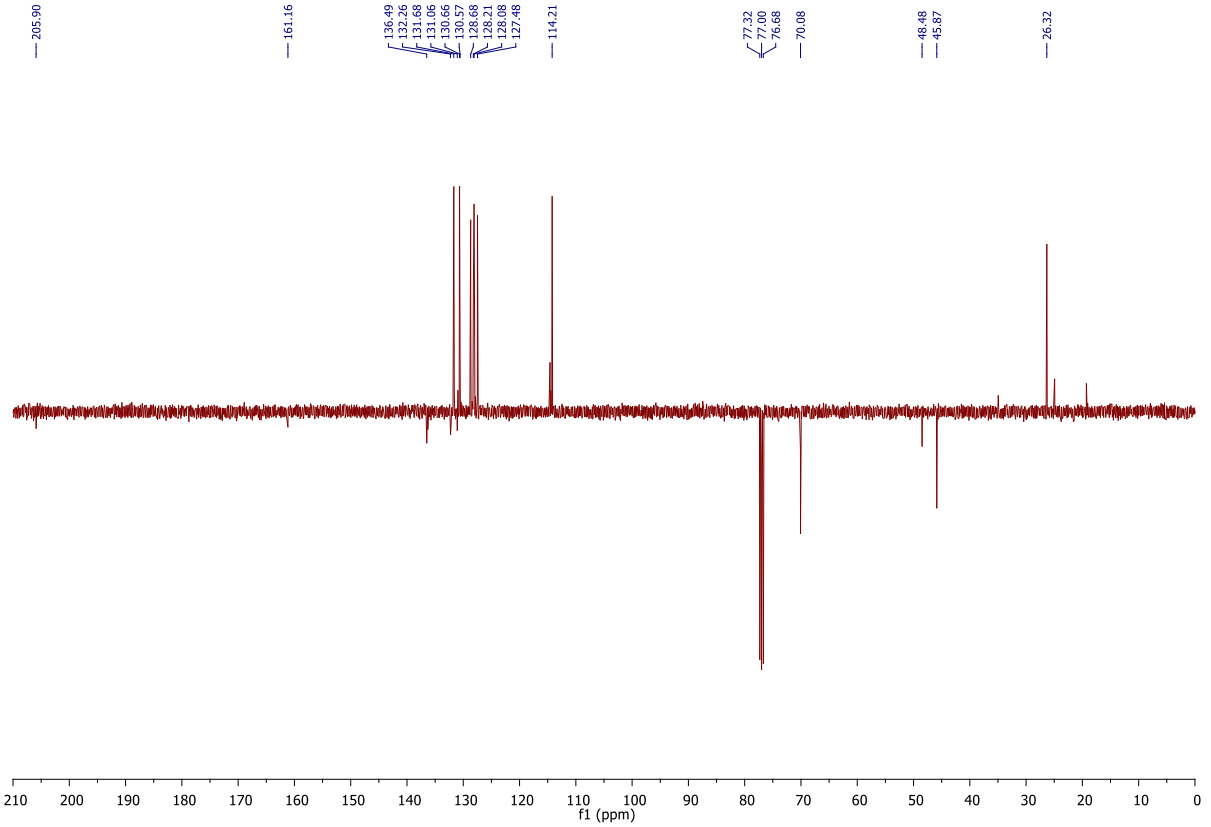


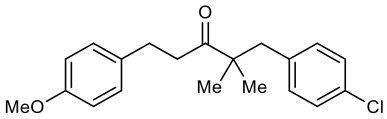




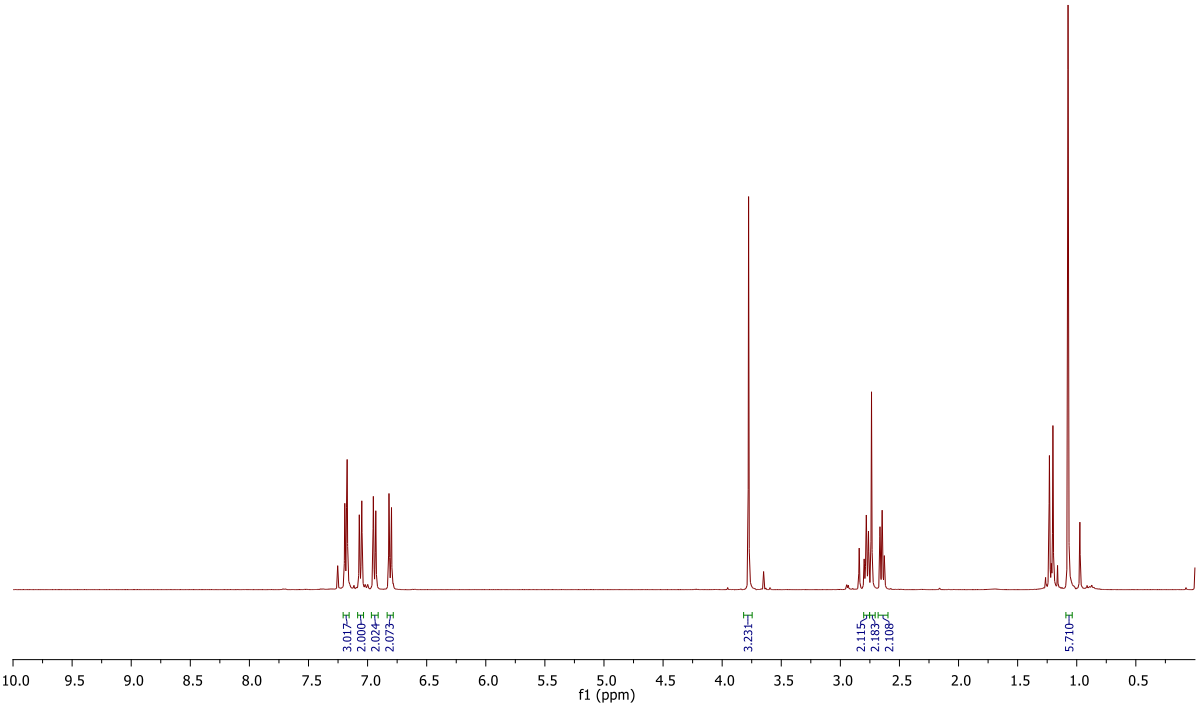
1-(4-(benzyloxy)phenyl)-2,2-dimethyl-3-phenylpropan-1-one (3d)

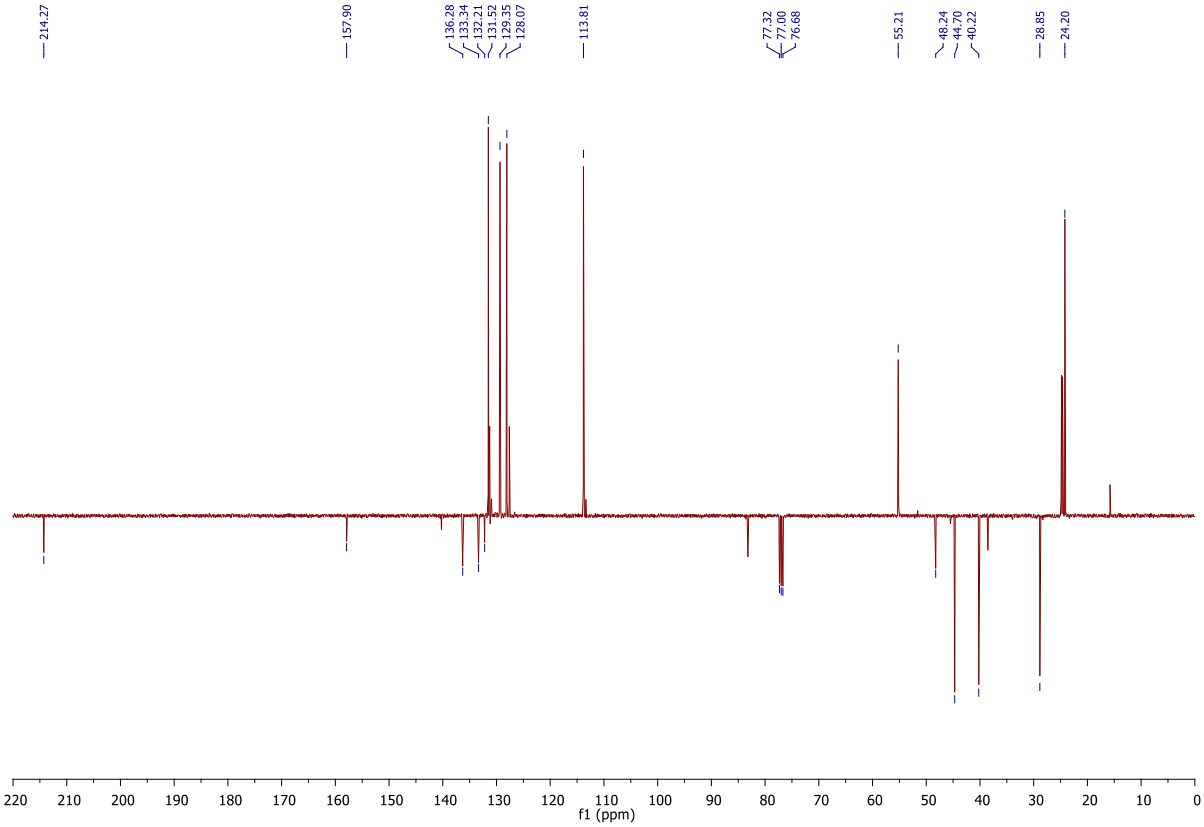


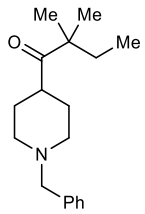




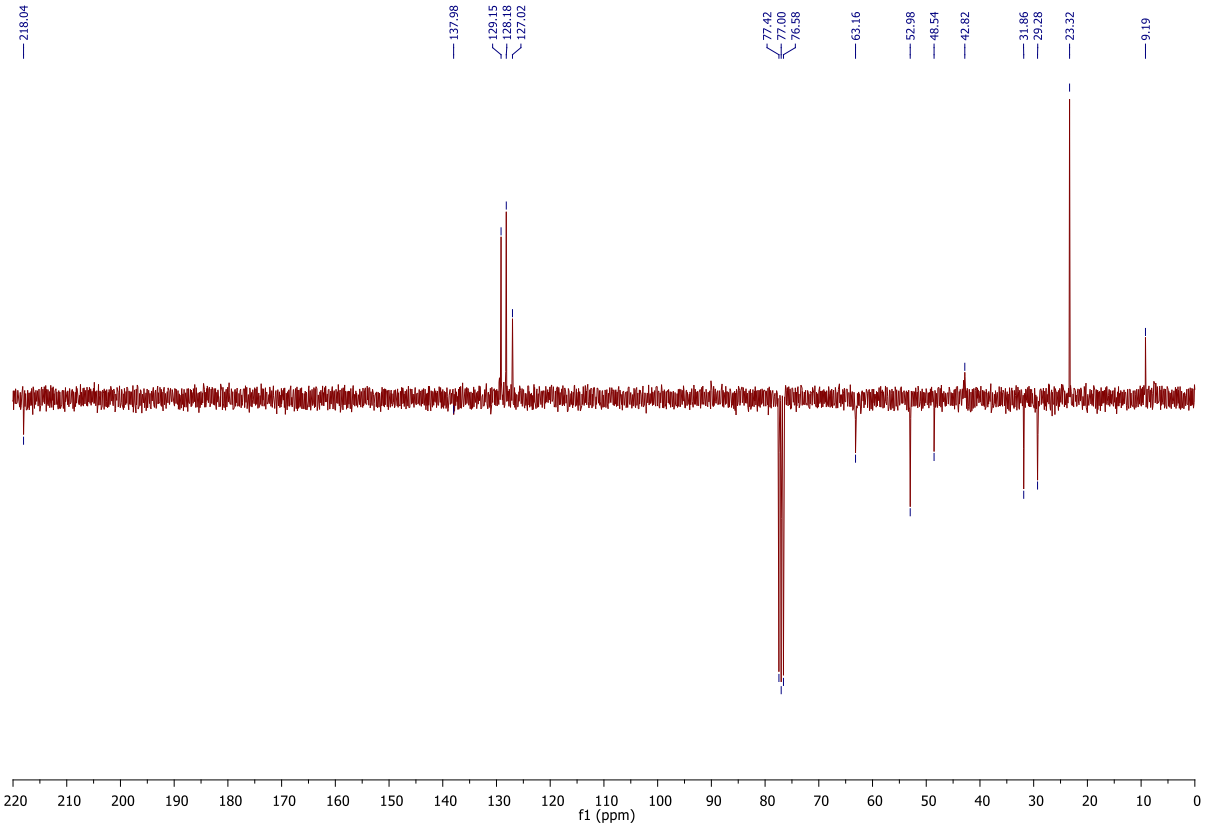
1-(4-chlorophenyl)-5-(4-methoxyphenyl)-2,2-dimethylpentan-3-one (3e)

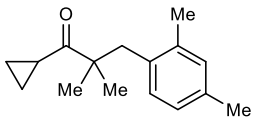




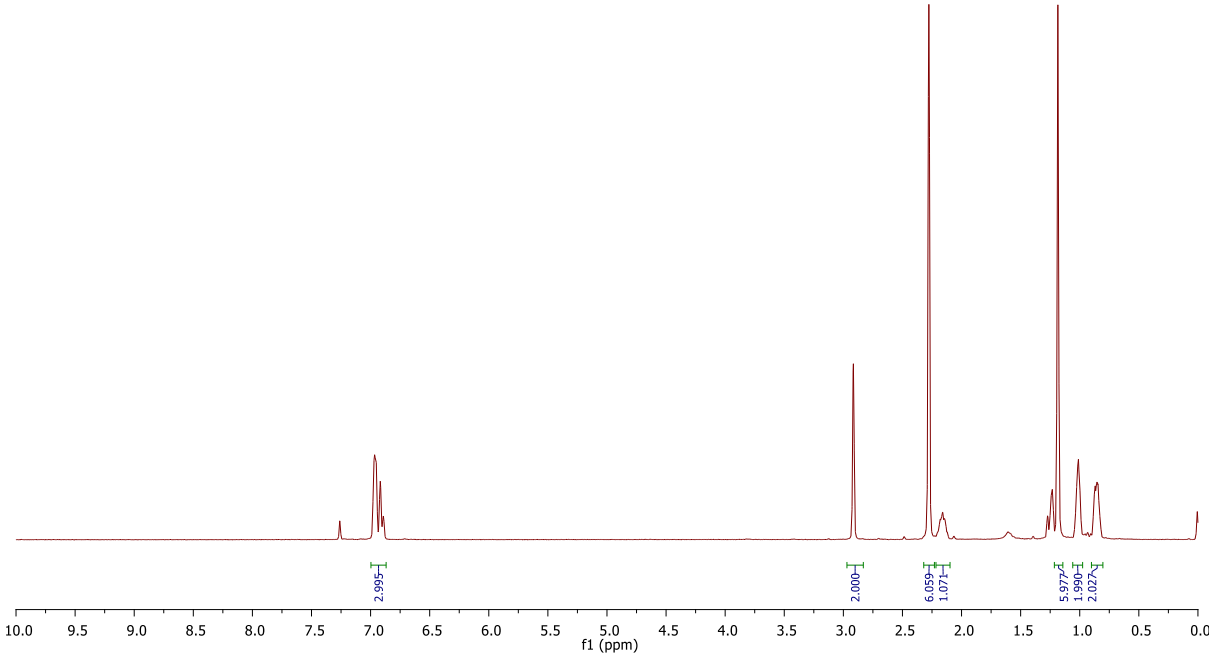


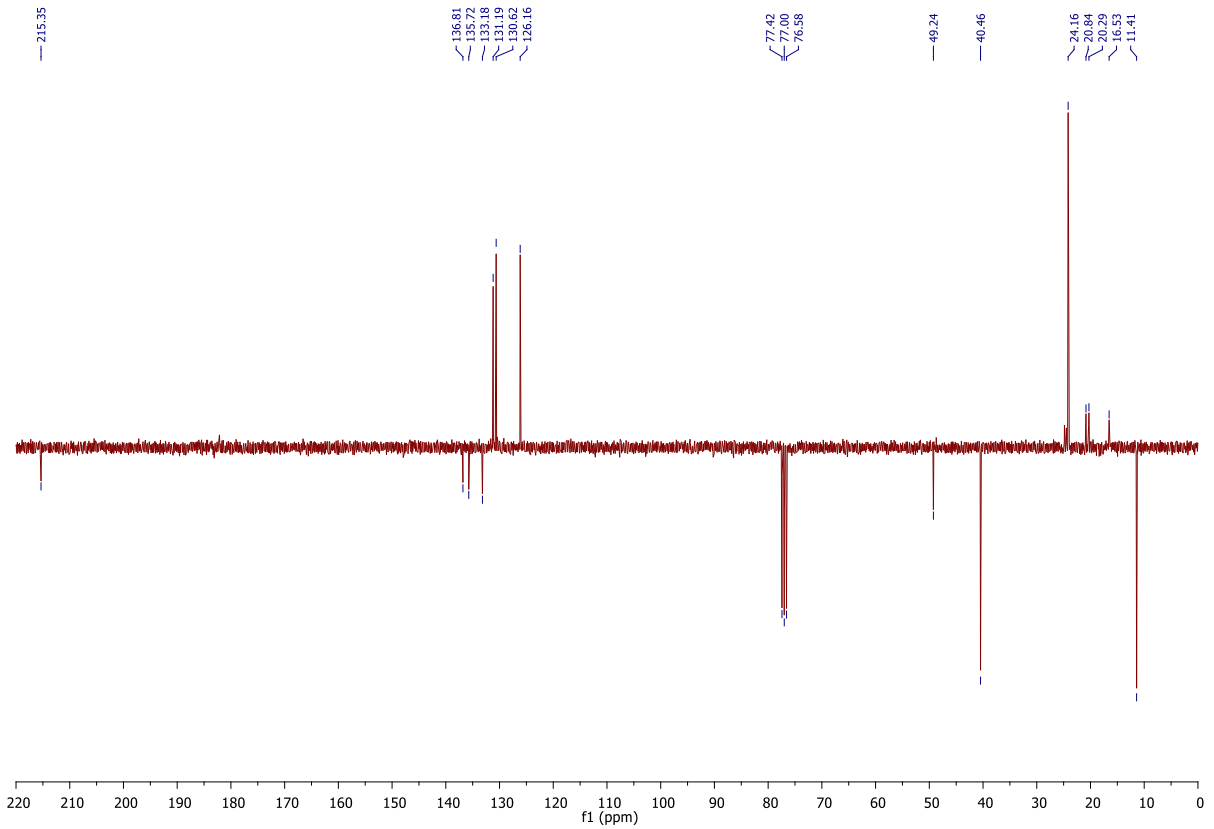
1-(1-benzylpiperidin-4-yl)-2,2-dimethylbutan-1-one (3f)

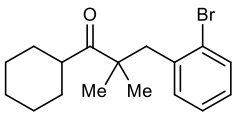




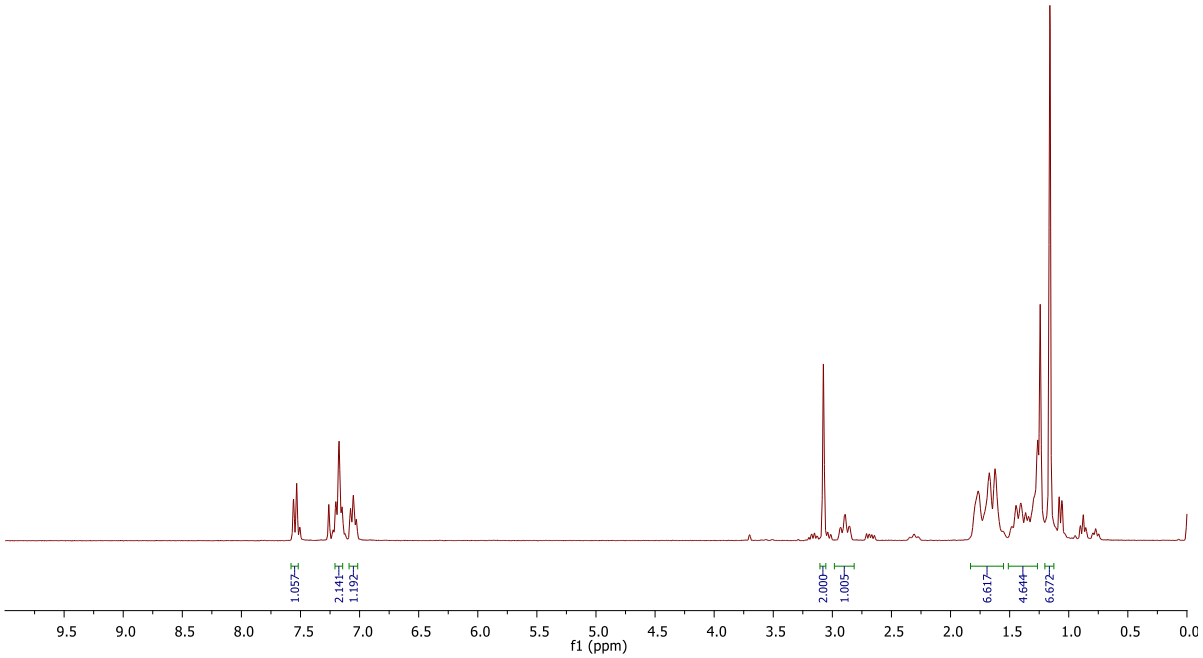
1-cyclopropyl-3-(2,4-dimethylphenyl)-2,2-dimethylpropan-1-one (3g)

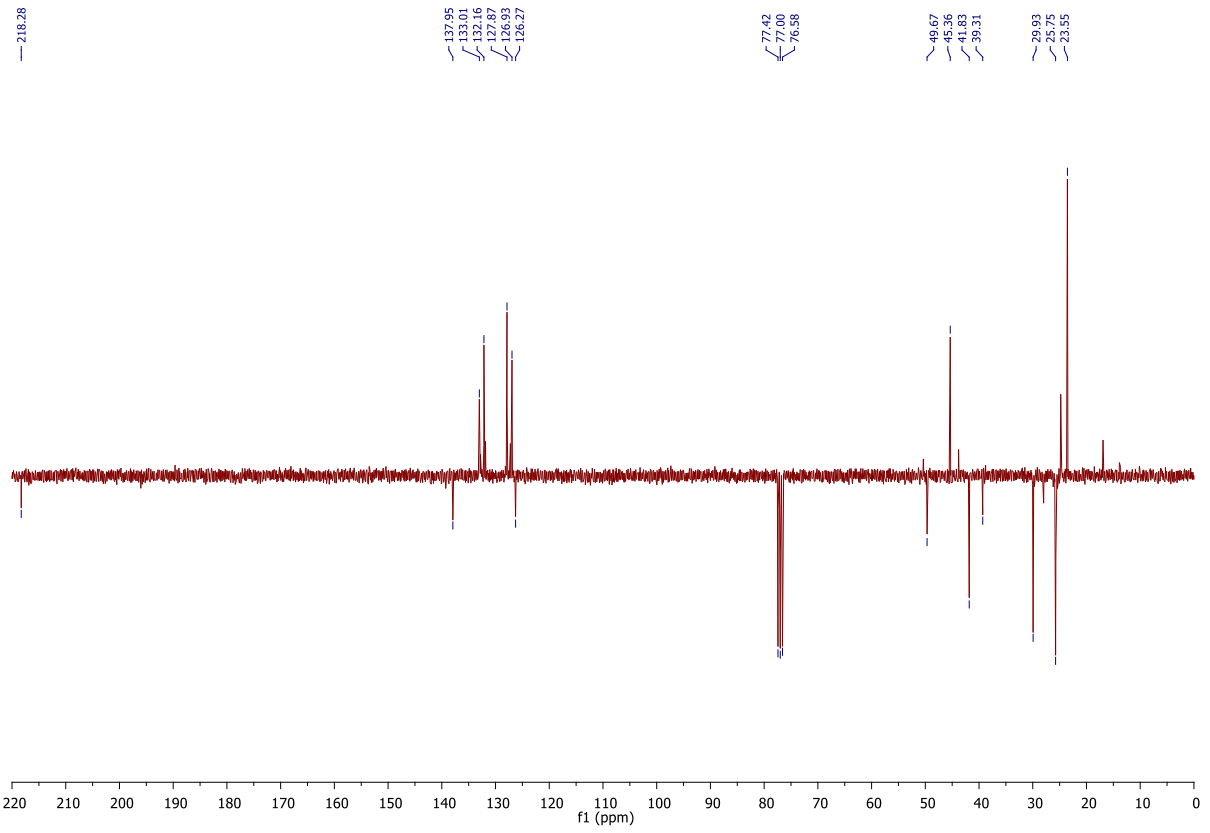


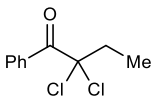




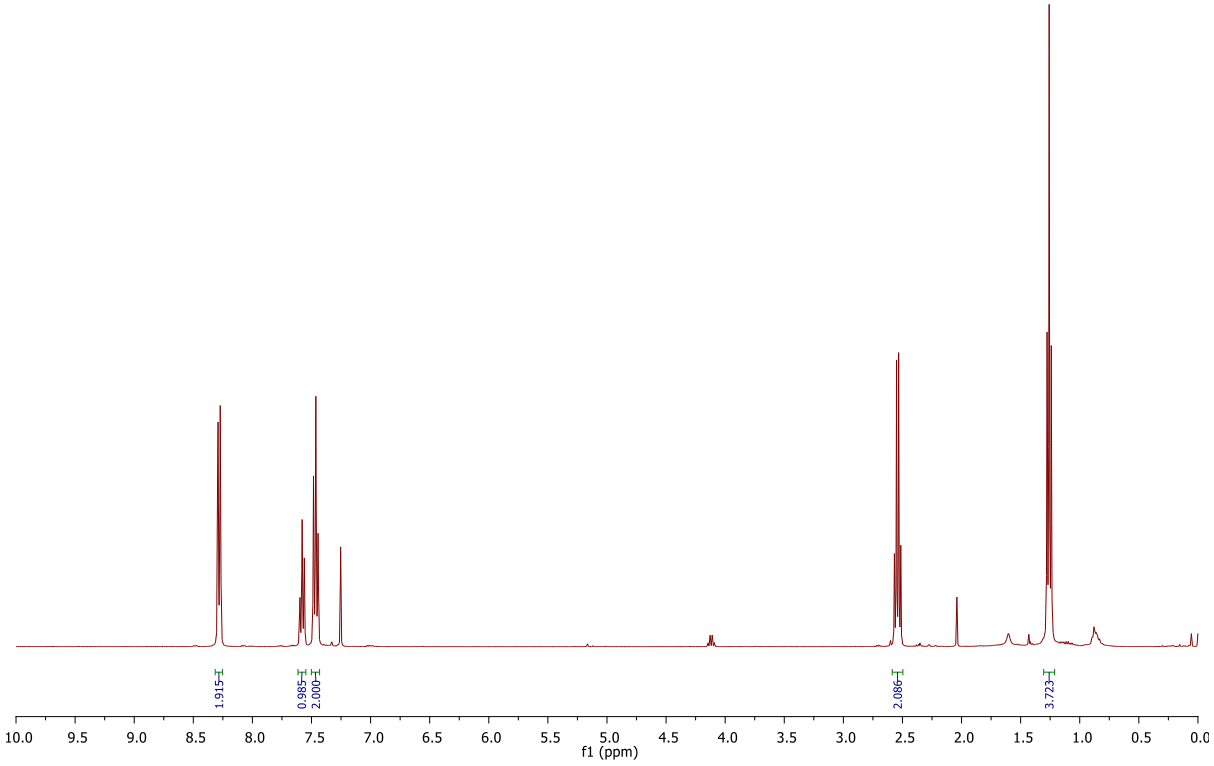
3-(2-bromophenyl)-1-cyclohexyl-2,2-dimethylpropan-1-one (3h)

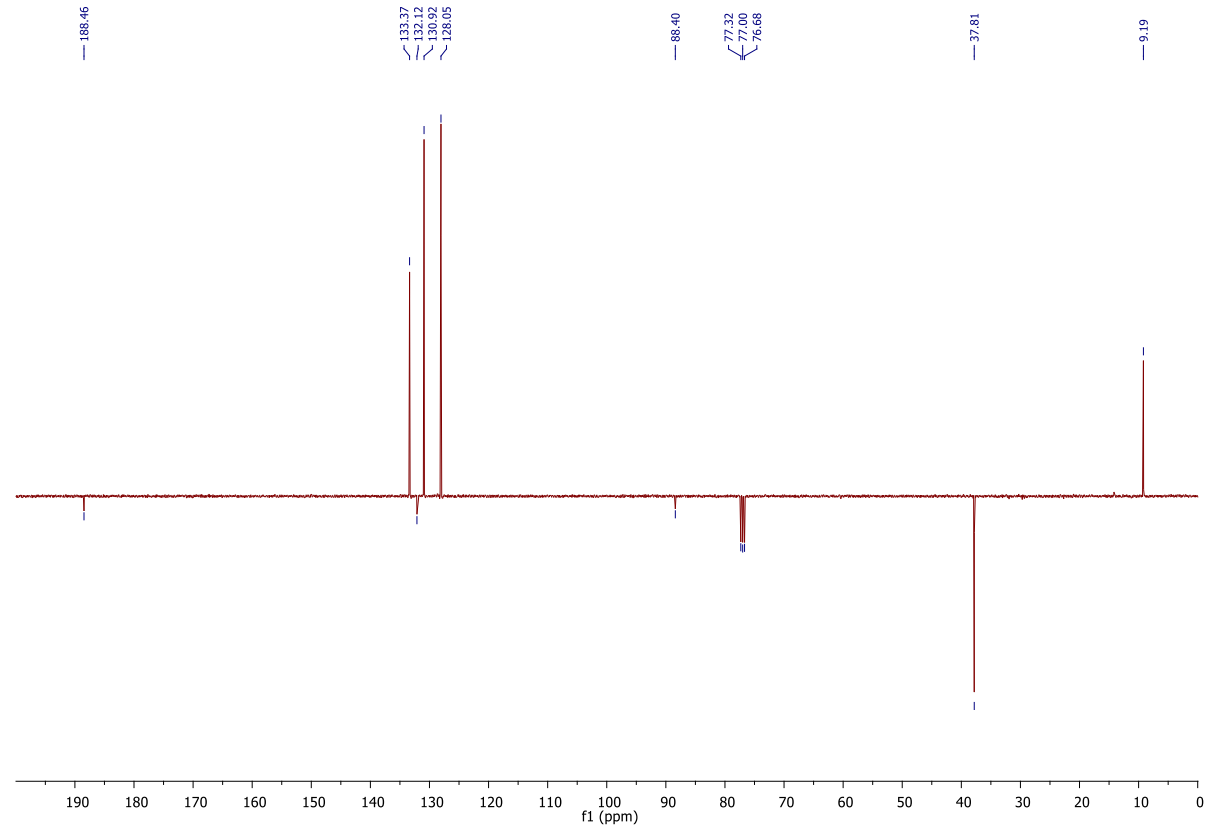






2,2-dichloro-1-phenylbutan-1-one (4)



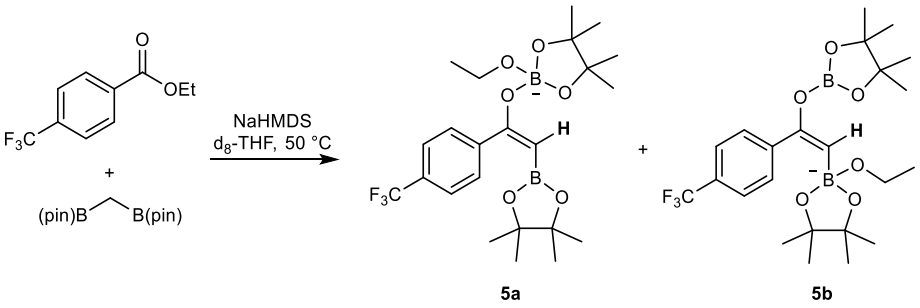


Mechanistic Studies

A series of experiments were performed to indicate the presence of an α-boryl boron enolate and to confirm its reactivity with electrophiles.

Synthesis and observation of boron enolate

Firstly, ester was reacted with 1 equivalent of bis(boron) compound in the presence of NaHMDS as base but without the addition of electrophile. The species formed in this reaction was analysed by NMR and proposed to be α-boryl boron enolate **5.** Coordination of released ethoxide ion to boron is important in this species, forming species in which the *O*-bound **5a** and *C*-bound **5b** boron atoms were quaternized. This observation is supported by ^{1}H, ^{13}C and ^{11}B NMR (see pg S65 for more details).



Procedure: Ethyl 4-trifluoromethyl)benzoate (44 mg, 0.20 mmol) and bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (54 mg, 0.20 mmol) were dissolved in dried d^{8}-THF (0.5 mL) under nitrogen. Sodium bis(trimethylsilyl)amide (125 µL, 2M in THF (non-deuterated), 0.25 mmol) was added and the mixture heated to 50 °C for 15 minutes. After this period the mixture was cooled and transferred using a dried syringe to an NMR tube sealed with parafilm under nitrogen and spectra obtained.

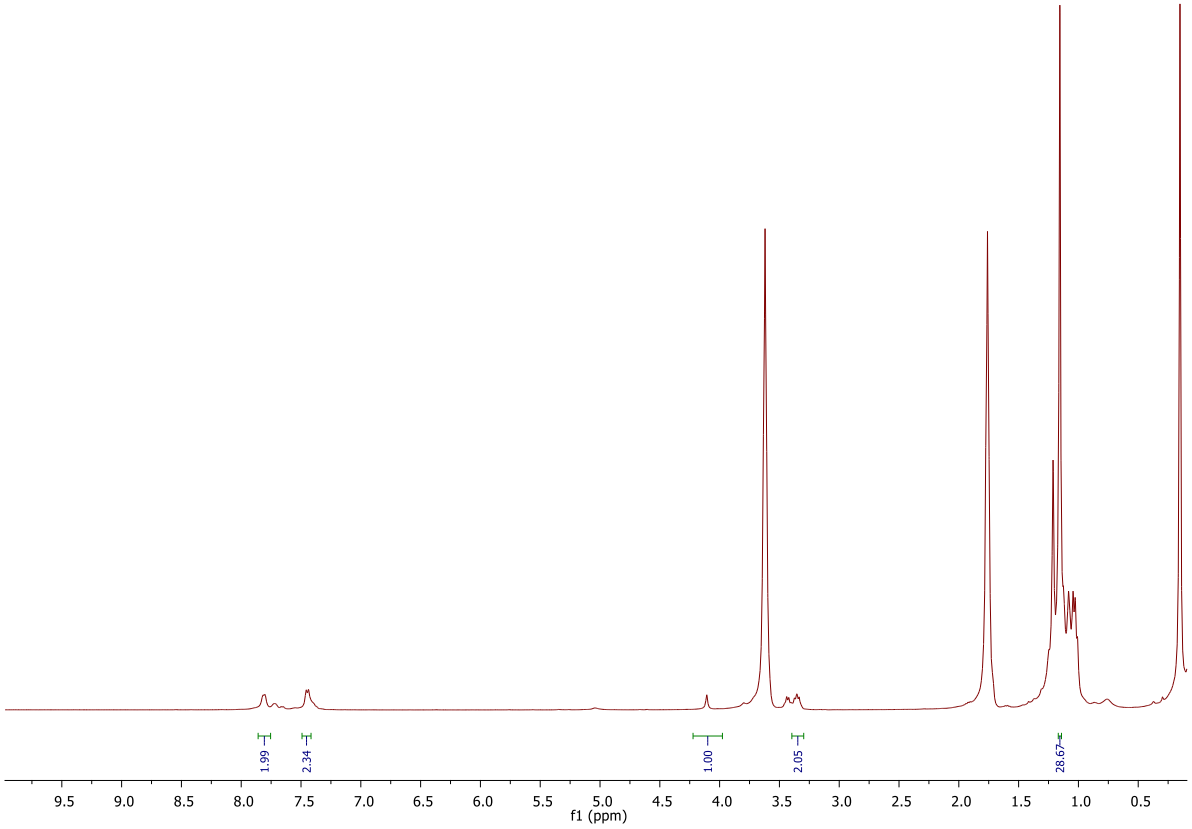
δ_H (400 MHz, d_8-THF) 7.81 (d, *J* = 7.0 Hz, 2H, Ar**H**), 7.45 (d, *J* = 7.0 Hz, Ar**H**), 4.12 (br s, C=C**H**), 3.35 (app pent, *J* = 7.4 Hz, BOC**H₂**CH_3) 1.16 (s, 27H, BOC(C**H₃**)$_2$ with $BOCH_2C$**H₃** obscured);

δ_C (100 MHz, d_8-THF) δ 181.4, 152.0, 128.9 (q, *J* = 31.5 Hz) 127.1, 125.4 (q, *J* = 272 Hz), 124.6 (q, *J* = 3.6 Hz), 82.0, 81.5, 78.0, 57.04, 56.95, 24.7, 19.3, 19.0;

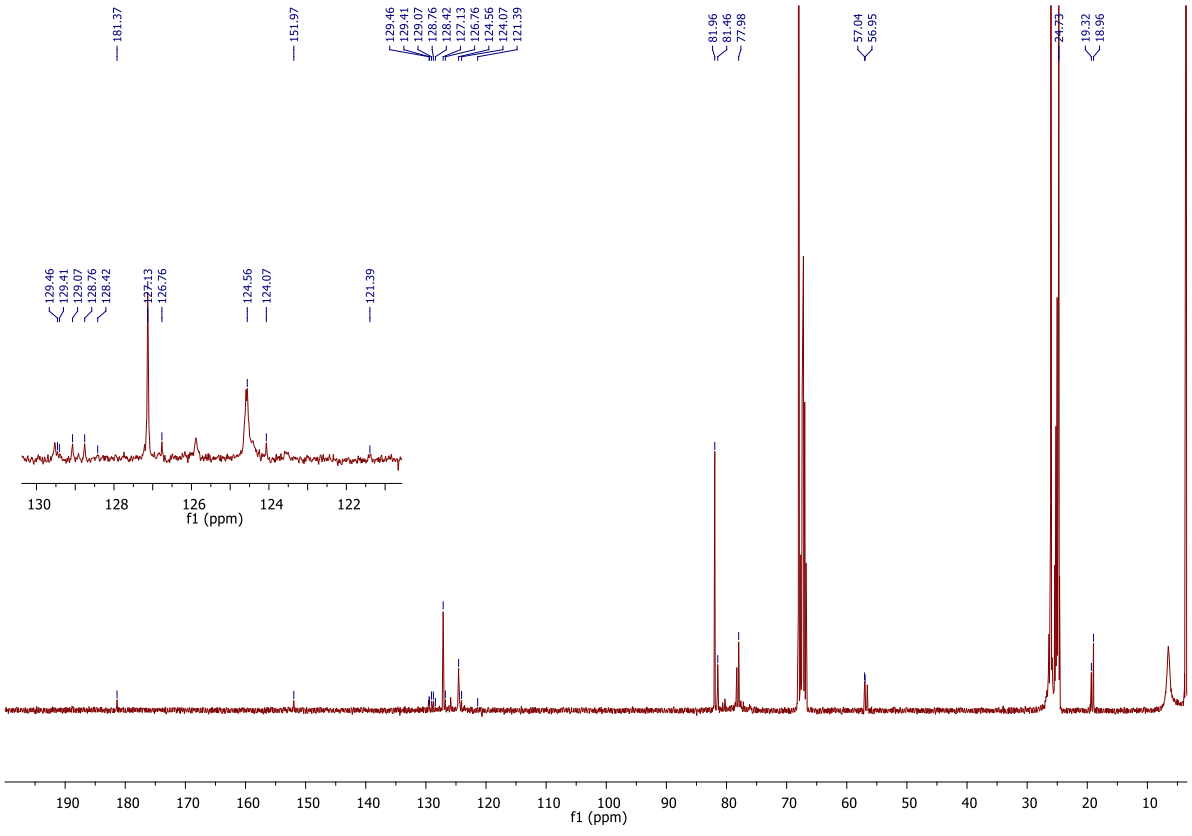
δ_F (376 MHz, d_8-THF) -62.75 (3F, s);

δ_B (160 MHz, d_8-THF) 25.4 (br s, 1B), 7.58 (br s, 0.5B), 5.55 (br s, 0.5B)

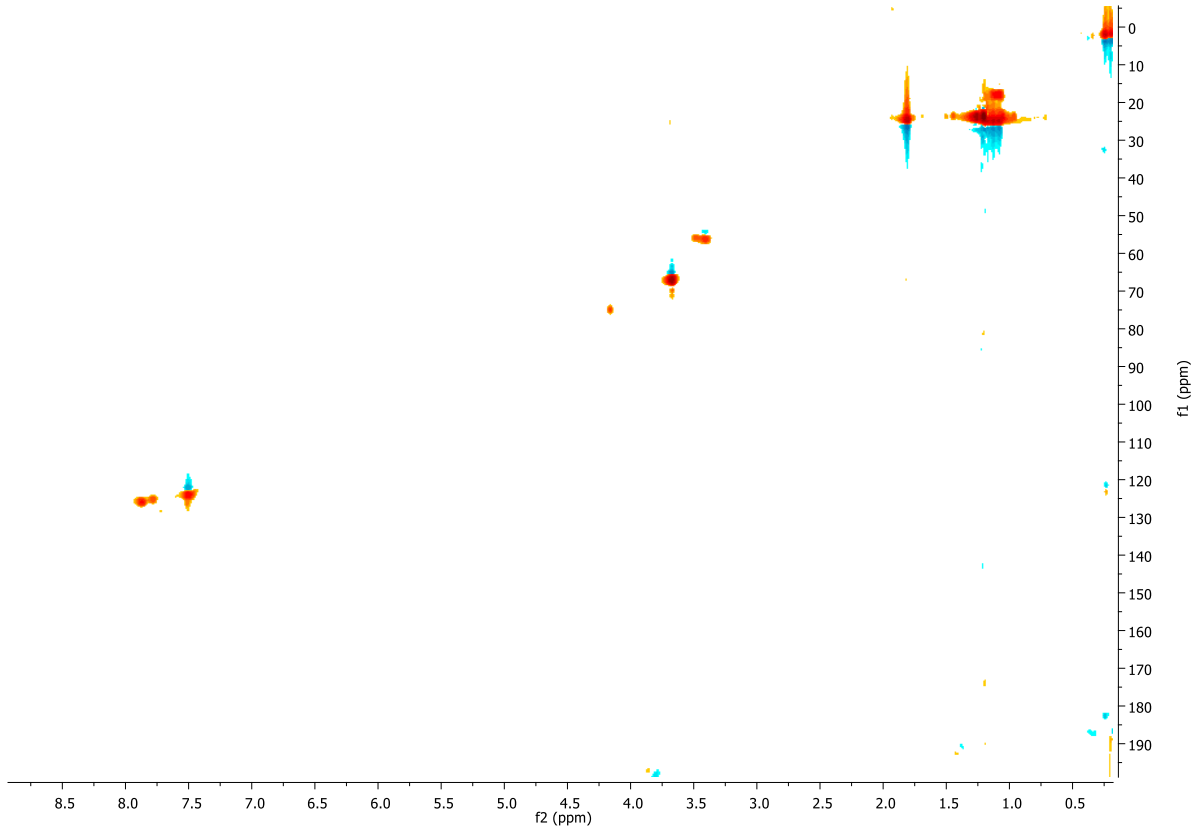
^{1}H NMR



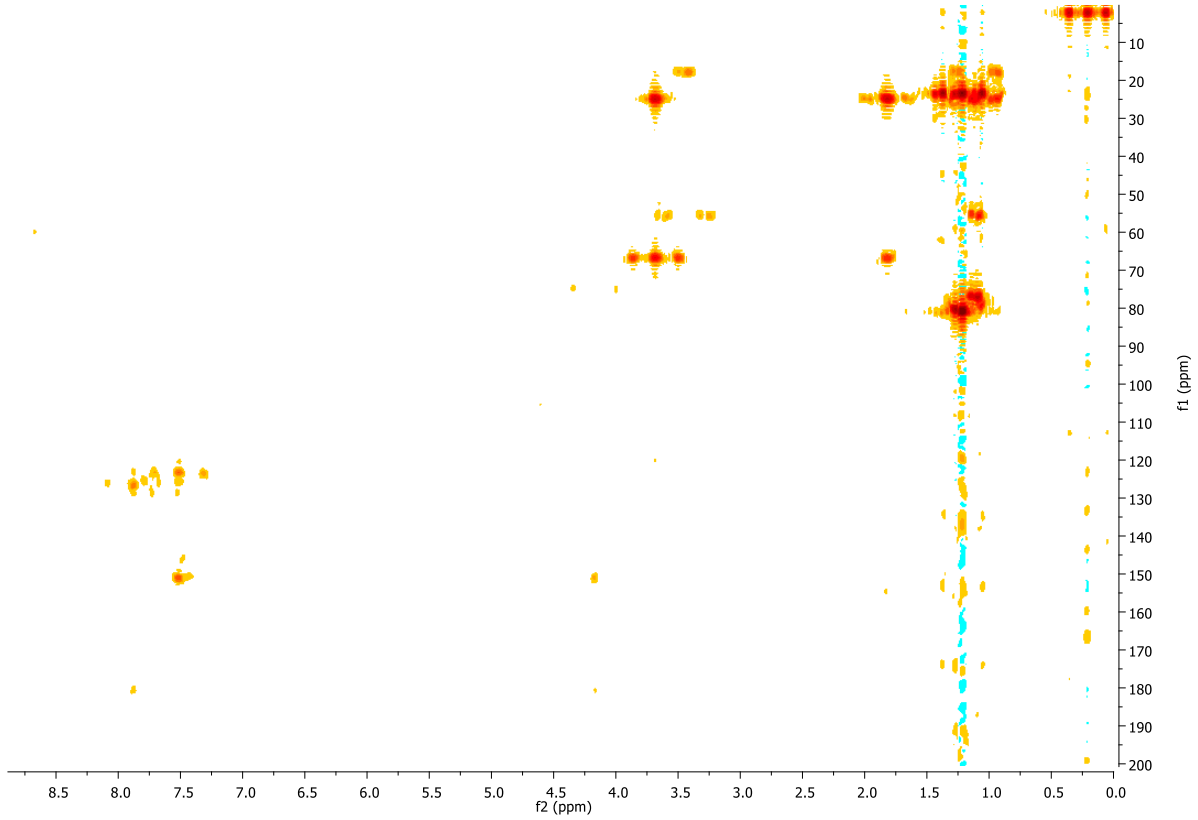
^{13}C NMR



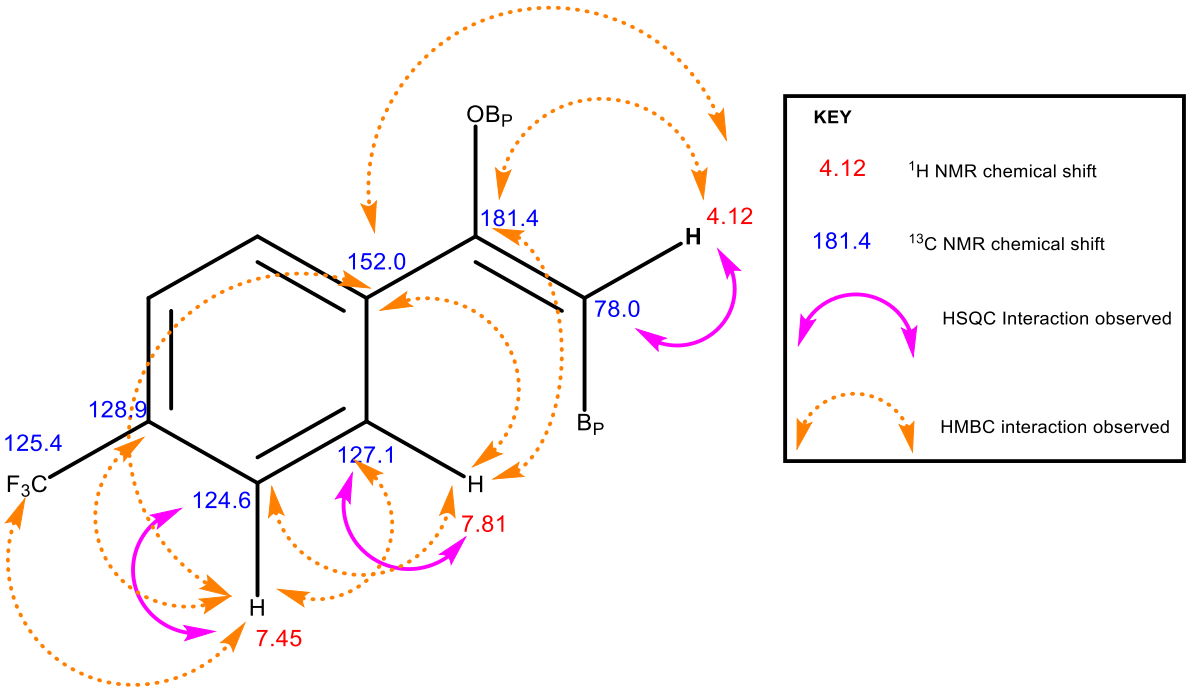
HSQC



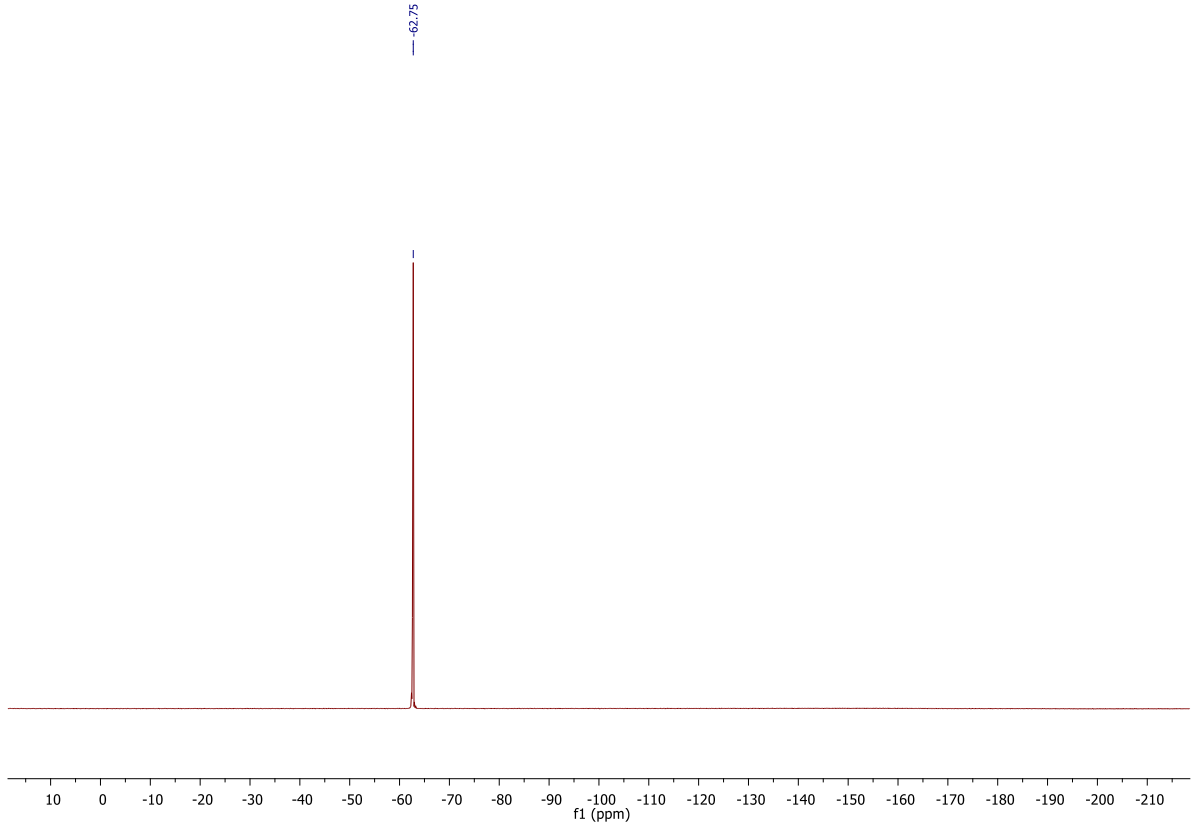
HMBC



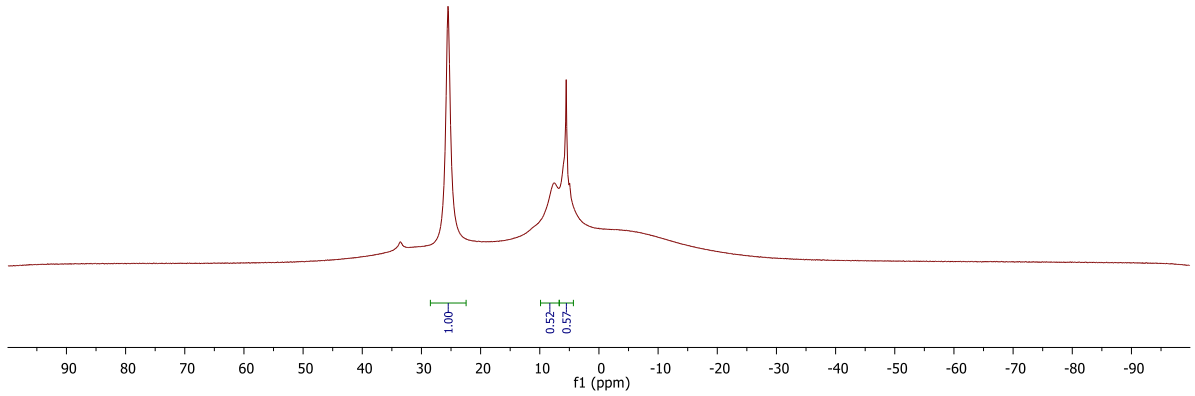
Complete summary of HSQC / HMBC interactions observed

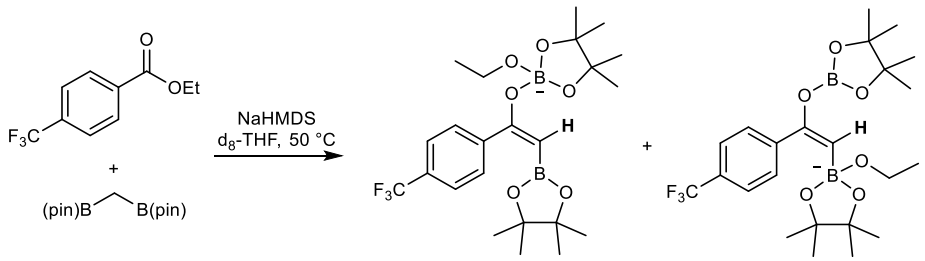


^{19}F NMR



^{11}B NMR





5a **5b**

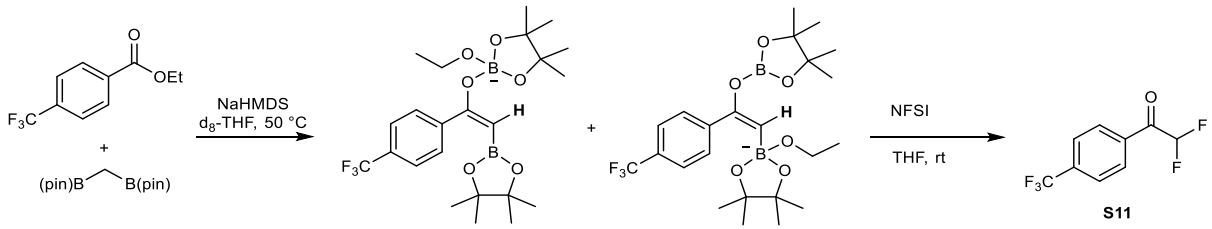
^{11}B NMR would indicate that coordination of ethoxide ion (released on substitution of the ester) to boron is important in this system, which in turn may promote higher reactivity with electrophiles. Two boron environments are observed at 7.6 and 5.6 ppm, both chemical shifts indicative of quaternized boron species, likely to be *O*-bound **5a** and *C*-bound **5b** quaternary boron species. These are in an approximately 1:1 ratio as there is likely to be little preference for which boron atom ethoxide ion binds to. The unquaternized boron environments are shown at 25.4 ppm, where peaks for the *O*-bound **5a** and *C*-bound **5b** species are seemingly overlapping. A 1:1 ratio is observed between the quaternized and unquaternized boron environments. This is consistent with the 1 equivalent of ethoxide ion released on ester substitution, which is only therefore able to complex with 50% of the available boron atoms.

^{1}H and ^{13}C NMR also support this coordination of ethoxide, with an apparent pentet (integration 2) at 3.35 ppm (likely two closely overlapping quartets) in ^{1}H NMR, and pairs of peaks in the ^{13}C NMR at around 57 and 19 ppm which would represent similar OCH_2CH_3 groups.

Control experiments to confirm reaction of boron enolate with NFSI / MeI

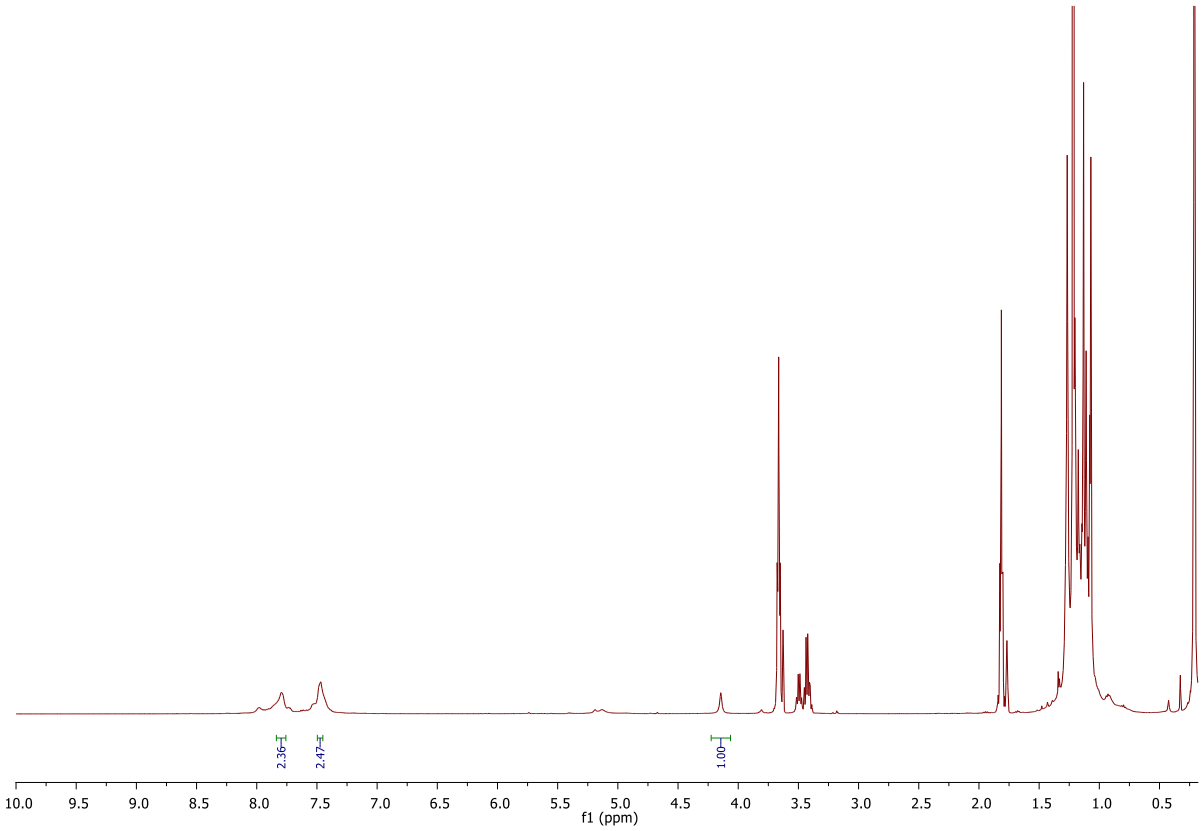
Control experiments were then performed to confirm that this proposed boron enolate species did indeed undergo electrophilic trapping with both NFSI and MeI. A solution of boron enolate was prepared as above and observed by NMR to ensure it matched the above data. A solution of NFSI or MeI was then added to confirm that the expected difluorinated or dimethylated species were indeed produced.

Fluorination:

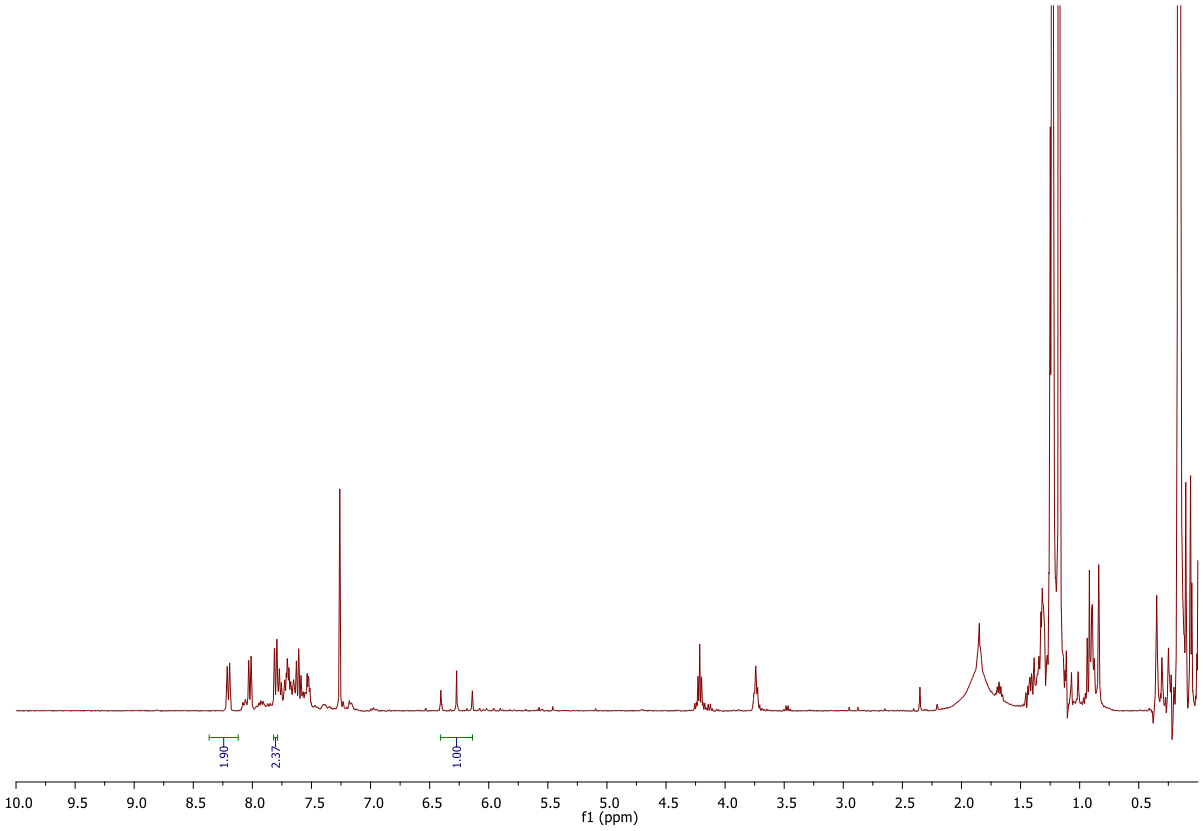


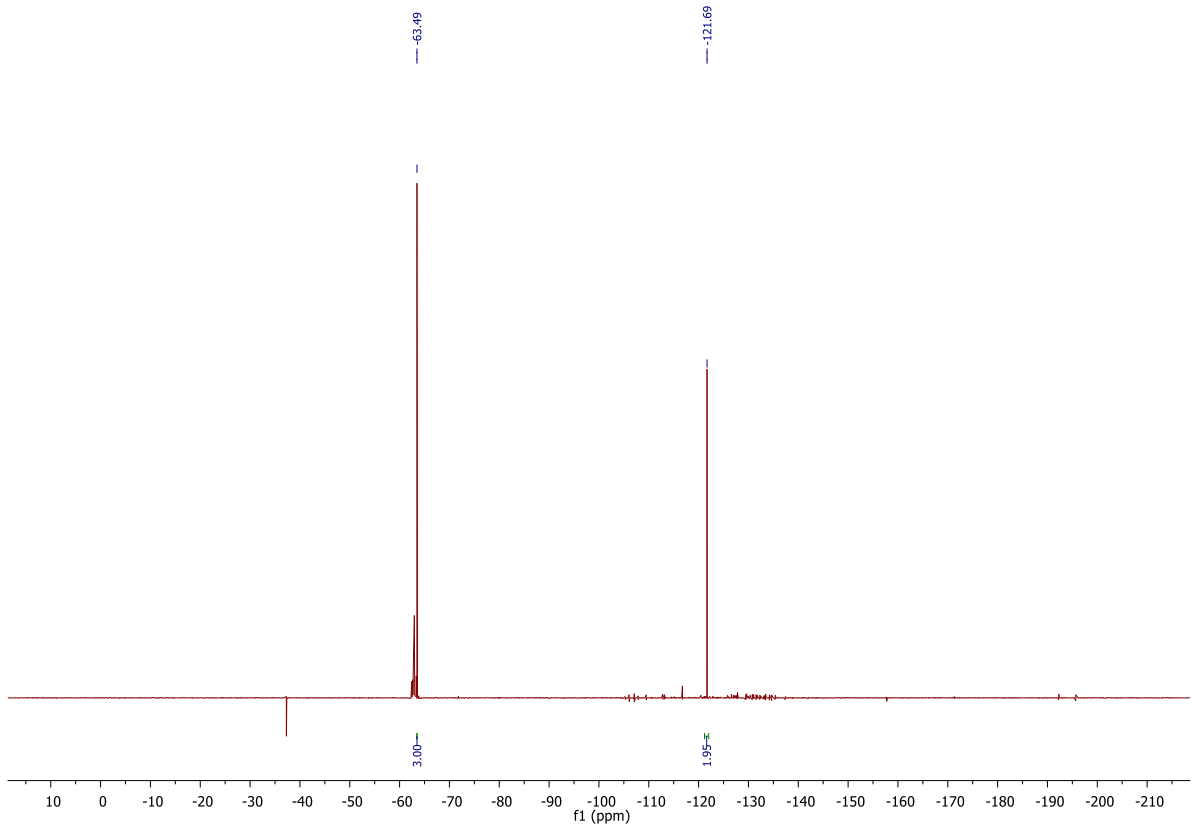
Ethyl 4-trifluoromethyl)benzoate (22 mg, 0.10 mmol) and bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (54 mg, 0.20 mmol) were dissolved in dry d^8-THF (0.5 mL) under nitrogen. Sodium bis(trimethylsilyl)amide (125 µL, 2M in THF, 0.25 mmol) was added and the mixture heated to 50 °C for 15 minutes. After this period the mixture was cooled and transferred using a dried syringe to an NMR tube sealed with parafilm under nitrogen. After an NMR spectrum was obtained to confirm the presence of the boron enolate, NFSI (95 mg, 0.3 mmol) in THF (0.5 mL) was added and the mixture agitated over 15 minutes. The reaction mixture was then eluted (Et_2O) through a short plug of silica gel to remove solid materials before evaporation of solvent and dissolution in $CDCl_3$ to obtain an NMR spectrum. This confirmed the presence of *2,2-difluoro-1-(4-(trifluoromethyl)phenyl)ethan-1-one* **S11**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (2H, d, *J* = 8.2 Hz), 7.80 (2H, d, *J* = 8.2 Hz), 6.27 (1H, t, *J* = 53.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.5 (3F, s), -121.7 (2F, s). Data in agreement with the literature.[6]

Stage 1 – boron enolate

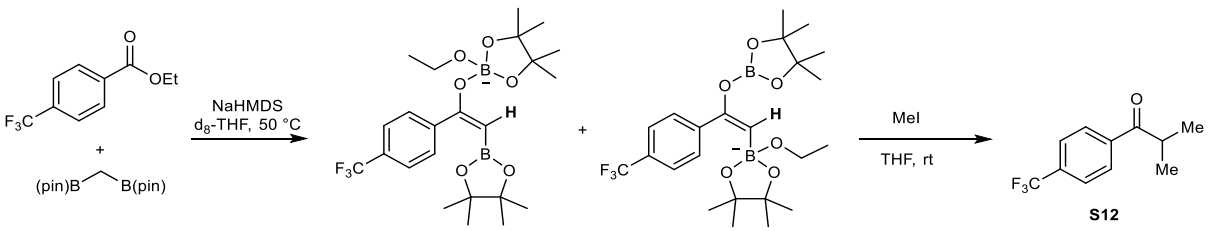


Stage 2: Difluorination



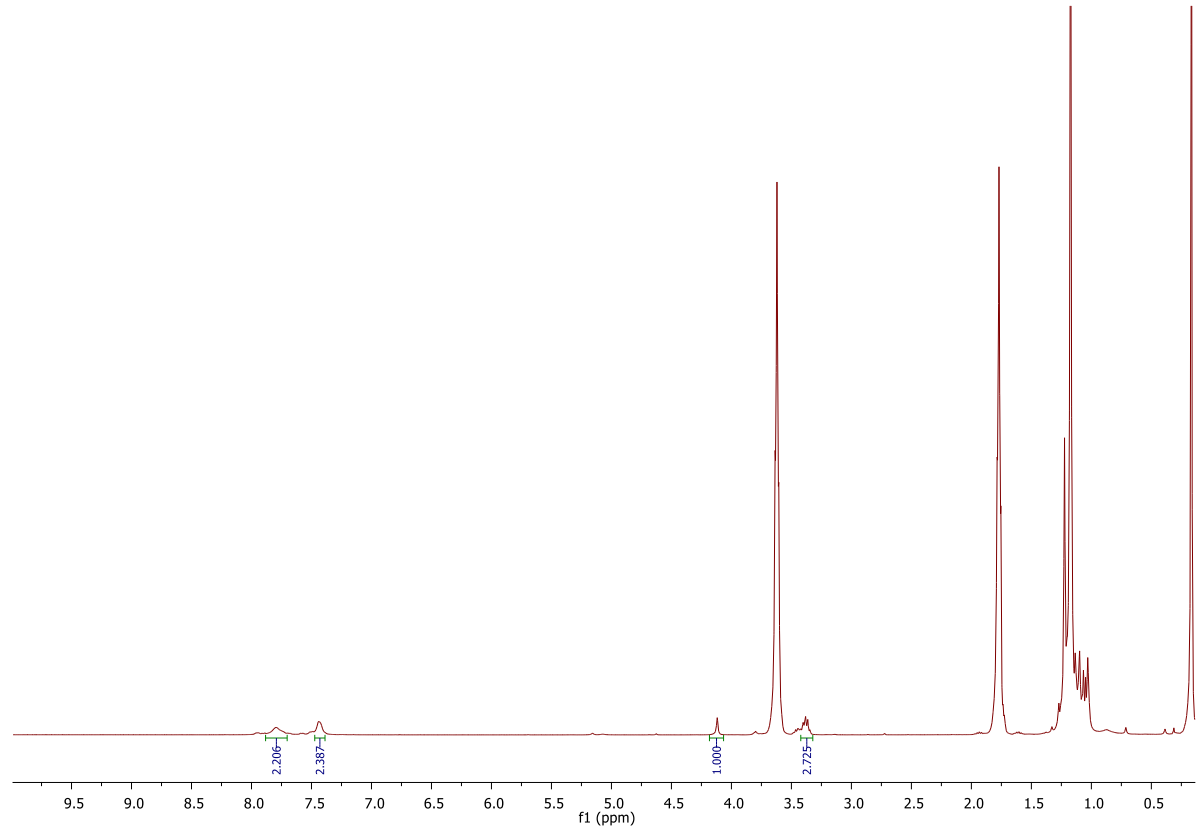


Methylation:

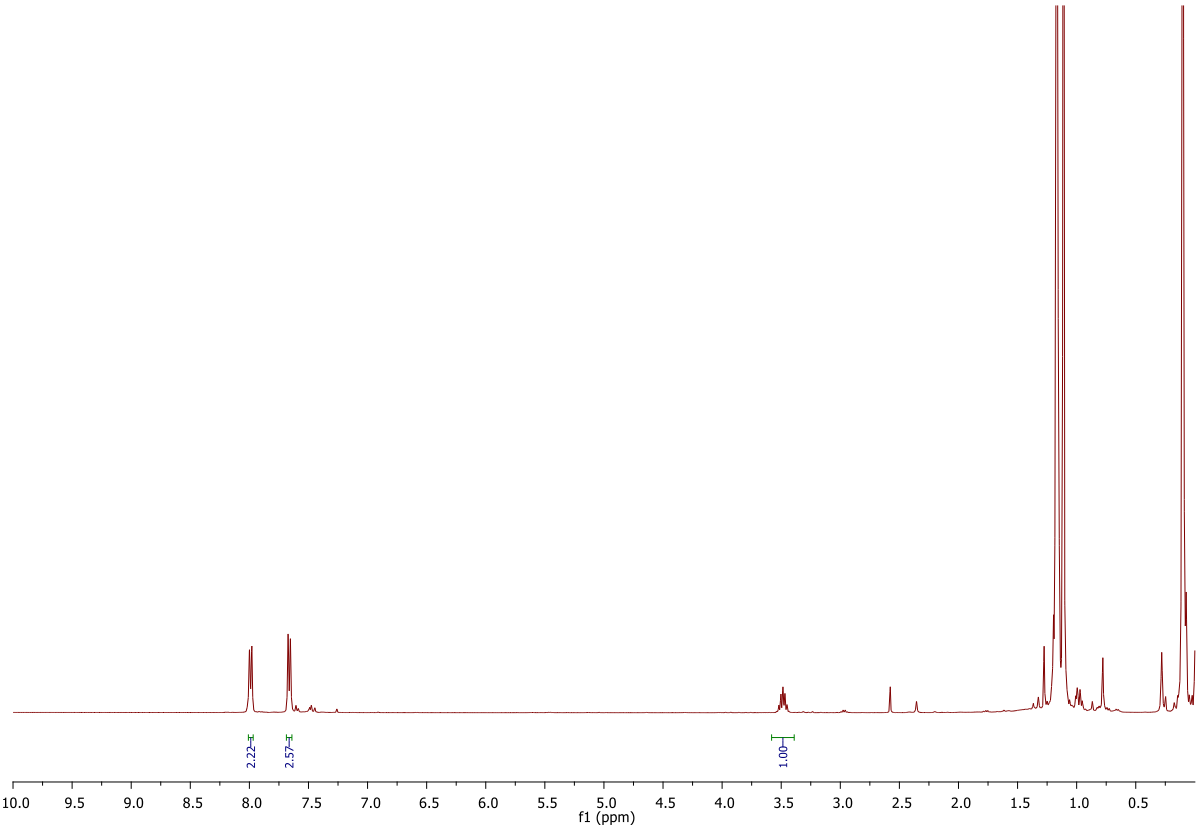


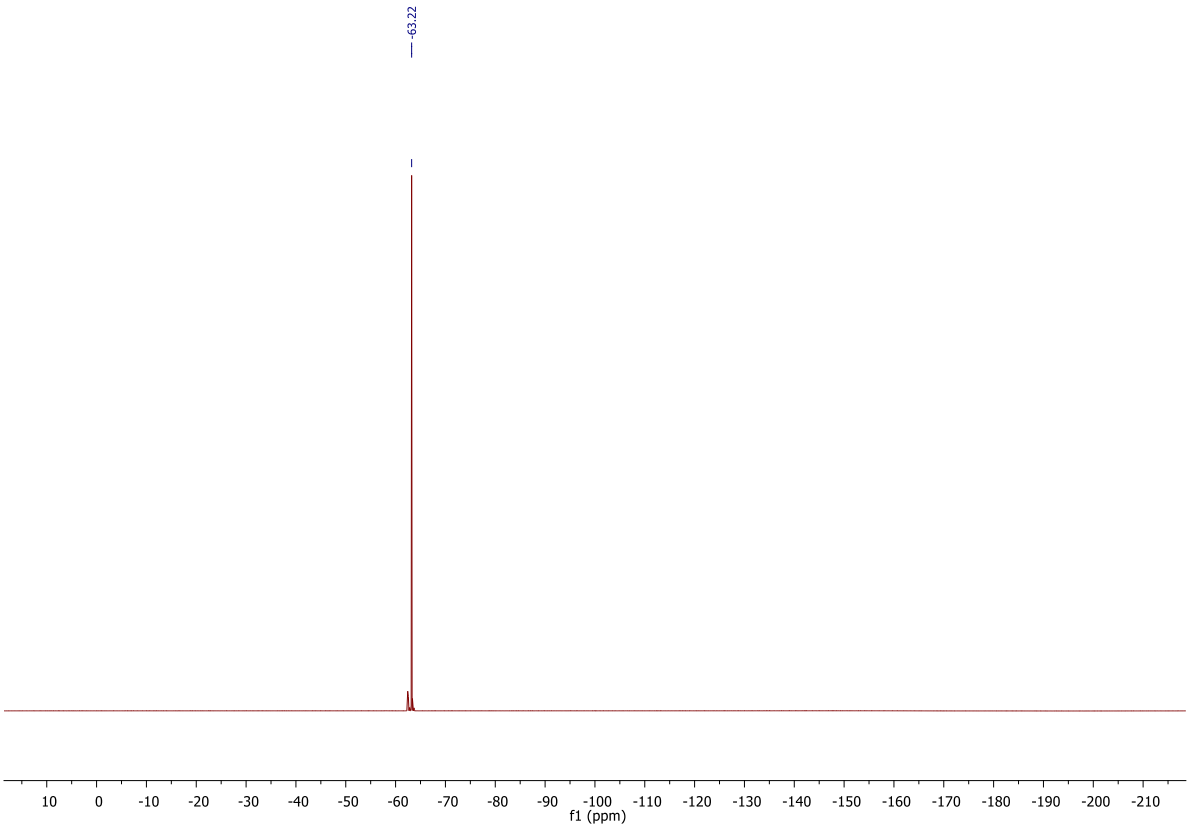
Ethyl 4-trifluoromethyl)benzoate (22 mg, 0.10 mmol) and bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (54 mg, 0.20 mmol) were dissolved in dry d^8-THF (0.5 mL) under nitrogen. Sodium bis(trimethylsilyl)amide (125 µL, 2M in THF, 0.25 mmol) was added and the mixture heated to 50 °C for 15 minutes. After this period the mixture was cooled and transferred using a dried syringe to an NMR tube sealed with parafilm under nitrogen. After an NMR spectrum was obtained to confirm the presence of the boron enolate, iodomethane (31 µL, 0.5 mmol) in THF (0.5 mL) was added and the mixture agitated over 15 minutes. The reaction mixture was then eluted (Et_2O) through a short plug of silica gel to remove solid materials before evaporation of solvent and dissolution in $CDCl_3$ to obtain an NMR spectrum. This confirmed the presence of *2-methyl-1-(4-(trifluoromethyl)phenyl)propan-1-one* **S12** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.8 Hz, 2H), 7.73 (d, *J* = 8.2 Hz, 2H), 3.54 (sept, *J* = 6.8 Hz, 1H), (1.23 (d, *J* = 6.8 Hz, 6H, obscured)). Data in agreement with the literature.[9]

Stage 1: Boron enolate



Stage 2: Dimethylation



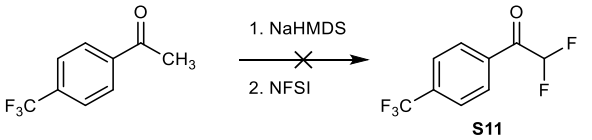

-63.22
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

Control Experiment: Attempted base-mediated fluorination / methylation of 4-(trifluoromethyl)acetophenone

A mechanistic possibility that we should rule out would be substitution of the ester with geminal bis(boron) species to give a boron enolate which could decompose by protodeboronation to yield a simple ketone. This ketone could then undergo deprotonation under the basic reaction conditions, to give an enolate which may then undergo fluorination or methylation.

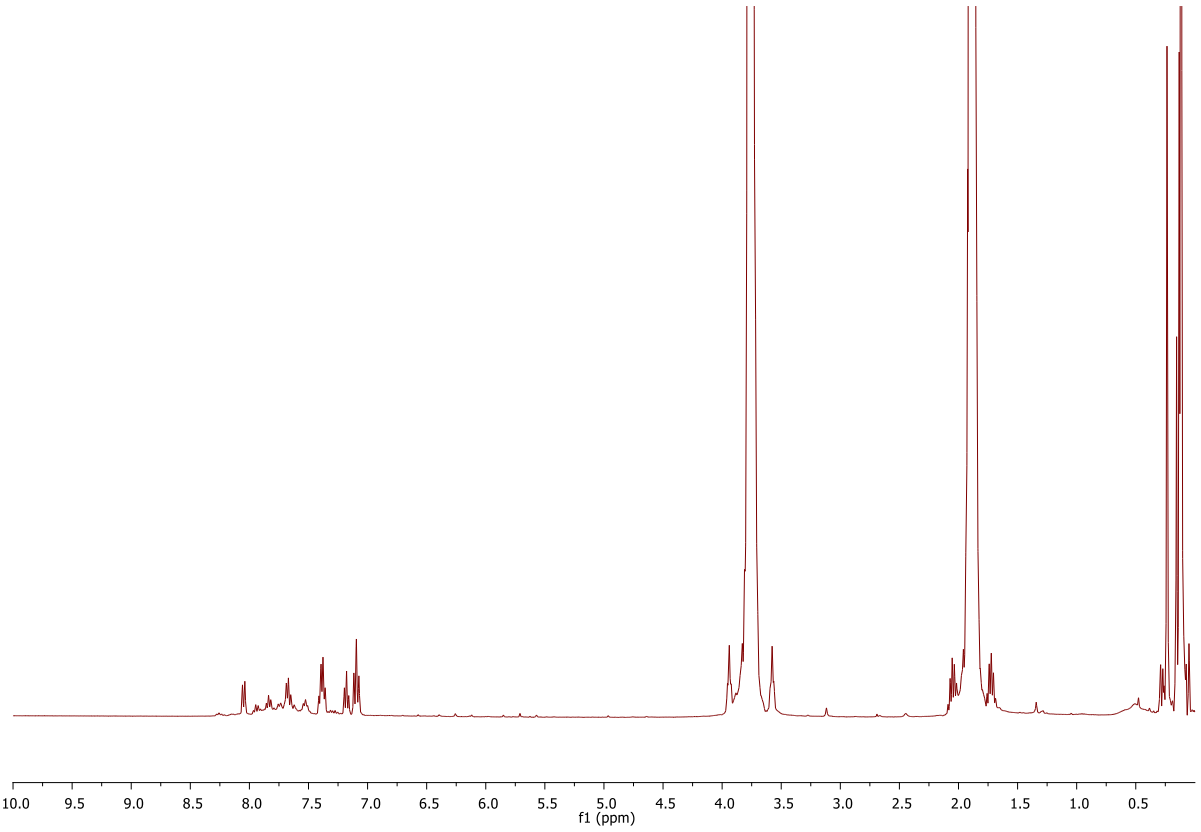
We have ruled this possibility out through reaction of a methyl ketone with NaHMDS to achieve deprotonation, followed by addition of NFSI or MeI solution. Addition of NFSI led to significant decomposition with starting ketone being returned and none of the expected difluoromethyl ketone being observed. Addition of MeI led to a mixture of di- and mono-methylated products as well as ketone starting material being returned, whilst the corresponding reaction using geminal bis(boron) addition to an ester gave exclusive dimethylation.

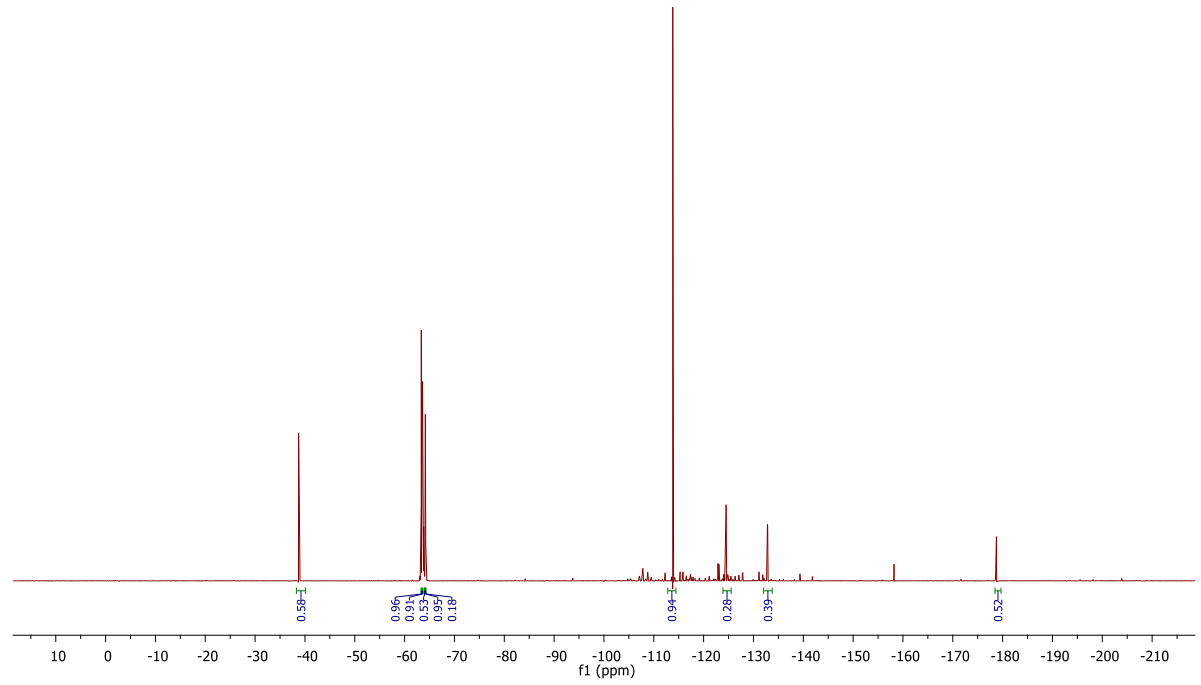
1) Fluorination



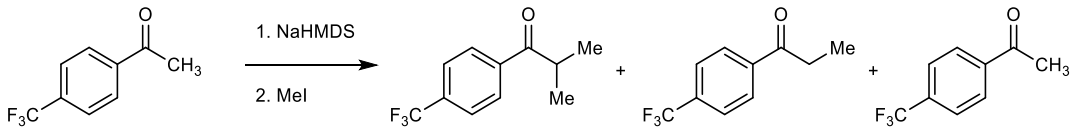
S11
- starting material returned
- significant decomposition

To a solution of 4-(trifluoromethyl)acetophenone (75.3 mg, 0.4 mmol) in dry THF was added a solution of sodium bis(trimethylsilyl)amide (0.5 mL, 2M in THF, 1.0 mmol) and the mixture heated to 50 °C for 15 minutes. After this period, this was cooled to room temperature and a solution of and a solution of *N*-fluorobenzenesulfonimide (378 mg, 1.2 mmol) in THF (1 mL) was added. After stirring for 15 minutes at room temperature the mixture was eluted through a short pad of silica (Et_2O) and concentrated. The difluorinated product was not observed among a range of unidentified decomposition products (see above compound **S11** for NMR of difluorinated product which is not in agreement).


10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


0.58
0.96
0.91
0.53
0.95
0.18
0.94
0.28
0.39
0.52
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

2) Methylation



S12 : **S13** : **S14**

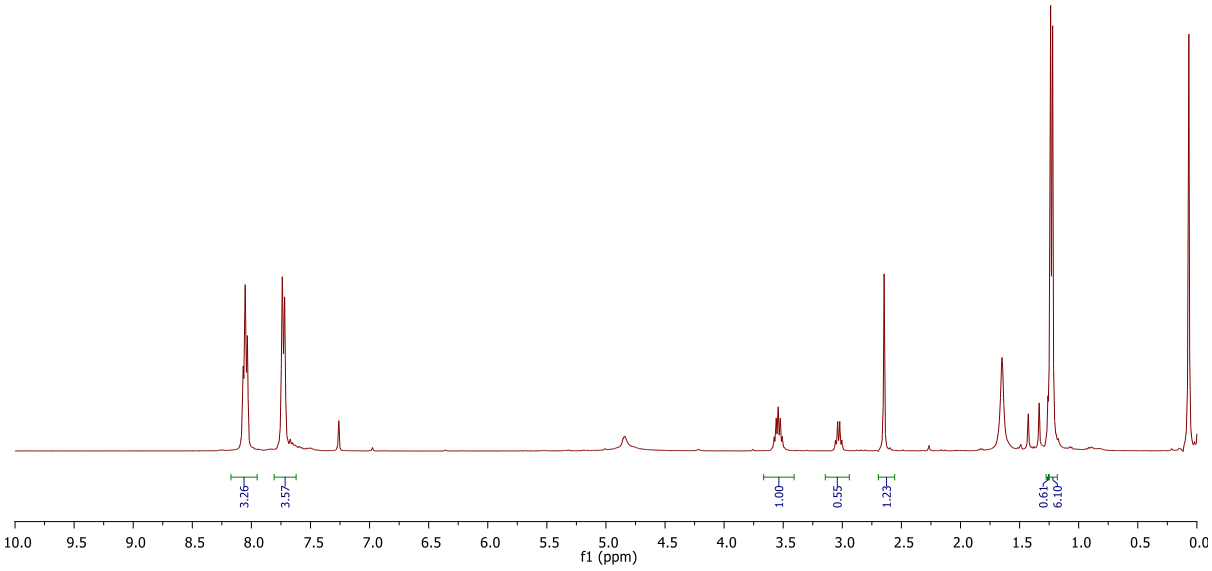
59 : 17 : 24

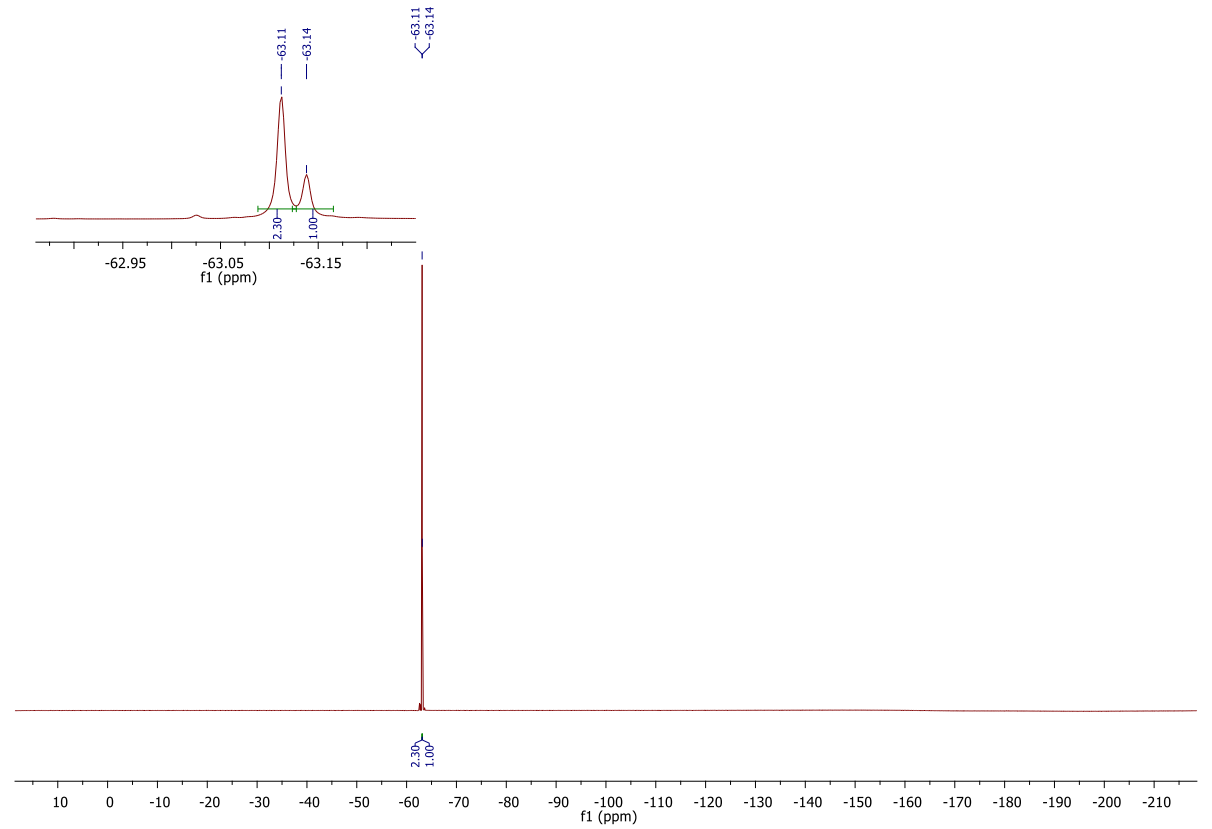
To a solution of 4-(trifluoromethyl)acetophenone (75.3 mg, 0.4 mmol) in dry THF was added a solution of sodium bis(trimethylsilyl)amide (0.5 mL, 2M in THF, 1.0 mmol) and the mixture heated to 50 °C for 15 minutes. After this period, this was cooled to room temperature and a solution of and a solution of iodomethane (125 µL, 2.0 mmol) in THF (1 mL) was added. After stirring for 15 minutes at room temperature the mixture was eluted through a short pad of silica (Et_2O) and concentrated. This resulted in a mixture of dimethylated and monomethylated products, as well as unreacted ketone starting material in a ratio of 59 : 17 : 24 respectively.

2-methyl-1-(4-(trifluoromethyl)phenyl)propan-1-one **S12** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.8 Hz, 2H), 7.73 (d, *J* = 8.2 Hz, 2H), 3.54 (sept, *J* = 6.8 Hz, 1H), 1.23 (d, *J* = 6.8 Hz, 6H). Data in agreement with the literature.[9]

1-(4-(trifluoromethyl)phenyl)propan-1-one **S13** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 7.8 Hz, 2H), 7.73 (d, J = 7.8 Hz, 2H), 3.03 (q, J = 7.2 Hz, 2H), (obscured, 1.24 (t, J = 7.2 Hz, 3H)); Data in agreement with the literature.[10]

1-(4-(trifluoromethyl)phenyl)ethan-1-one **S14** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 7.8 Hz, 2H), 7.73 (d, J = 7.8 Hz, 2H), 2.65 (s, 3H). Data in agreement with the literature.[11]


3.26
3.57
1.00
0.55
1.23
0.61
6.10
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


-63.11
-63.14
-63.11
-63.14
2.30
1.00
-62.95
-63.05
-63.15
f1 (ppm)
2.30
1.00
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

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