Synthesis of Ketones and Mono-fluorinated Ketones via Boron Enolates Formed by Substitution of Esters with Benzylboronic Esters

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Contents

General Information	2
Optimization of Ketone Synthesis	3
General Synthesis 1: Synthesis of Ketones	4-12
Deuteration Experiment	13-15
Synthesis of mono-fluorinated ketones: Optimization of reaction conditions	16-17
General Synthesis 2: Synthesis of mono-fluorinated ketones	18-24
Spectroscopic data	25-56
Mechanism study	57-61
References	62

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. Other reagents were used as purchased. Reactions were performed under an atmosphere of dry nitrogen gas. Thin layer chromatography (TLC) was performed on Merck DFAlufoilien 60F254 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm, and subsequently developed using anisaldehyde or potassium permanganate staining solutions as appropriate. Flash column chromatography was carried out using CombiFlash Nextgen 300+. Melting points are uncorrected. NMR spectra were recorded on a 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), m (multiplet) and 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). 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). High resolution mass spectra were recorded using electrospray ionization (ESI) techniques on a Thermo Scientific Exactive Orbitrap instrument.

Optimization of Ketone Synthesis

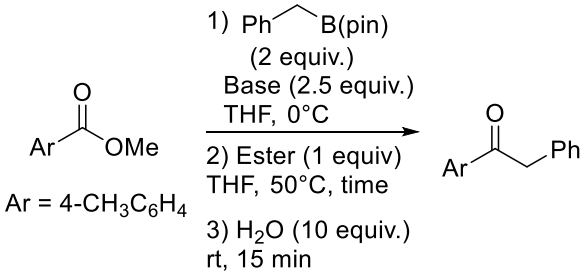
Method with NaHMDS

Under an atmosphere of nitrogen, 0.4 mmol of an ester, 0.8 mmol of the boron ester and 0.60 mmol (0.3 mL) of sodium bis(trimethylsilyl)amide (in 2M in THF) was added to 0.3 ml of THF. The solution was then heated to 50ºC for the time specified in the table, before cooling to room temperature. Once it had cooled to room temperature, water (0.07 ml, 4.0 mmol) was added dropwise, and stirred for 15 minutes. The solution was then eluted through a short column of celite and sodium sulfate and flushed through with diethyl ether then the solvent was removed under reduced pressure. A crude ^{1}H-NMR of the mixture was taken after addition of 10mg hexamethylbenzene as internal standard.

Method with LiTMP

Under an atmosphere of nitrogen, n-BuLi 2.5 M in hexanes (0.32 mL/0.8 mmol) was added to 2,2,6,6-tetramethylpiperidine (0.14 mL/ 0.80 mmol) in THF (1 mL) and was stirred at 0 °C for 15 minutes. Boron ester (0.80 mmol) was added to THF (0.5 mL) and added and stirred for an additional 15 minutes at 0 °C. 0.4 mmol of an ester was dissolved in THF (0.5 mL) and then heated to 50ºC for the time specified in the table. The solution was cooled to room temperature then water (0.07 ml, 4 mmol) was added to THF (1 mL) which was then added to the solution and stirred for 15 minutes at room temperature. The solution was then eluted through a short column of celite and sodium sulfate and flushed through with diethyl ether then the solvent was removed under reduced pressure. A crude ^{1}H-NMR of the mixture was taken after addition of 10mg hexamethylbenzene as internal standard.

Table S1: Optimization of ketone synthesis from esters and benzyl boronates



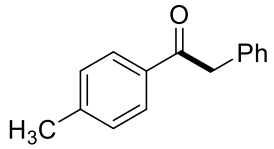
Entry	Base	Time	Yield / %[a]
1	NaHMDS	15 min	11
2	NaHMDS	1 hr	26
3	NaHMDS	2 hr	36
4	NaHMDS	4 hr	18
5	NaHMDS	24 hr	0
6	LiTMP	15 min	33
7	LiTMP	2 hr	89
8	LiTMP	4 hr	91

[(a)] yield determined by ^{1}H NMR using hexamethylbenzene as standard

General Synthesis 1: Synthesis of Ketones

Under an atmosphere of nitrogen, n-BuLi (2.5 M in hexanes, 0.4 mL, 1.0 mmol) was added to 2,2,6,6-tetramethylpiperidine (0.18 mL/ 1.0 mmol) in THF (1 mL) and was stirred at 0 °C for 15 minutes. Benzylboronic acid pinacol ester (0.18 mL, 0.8 mmol) was dissolved in THF (0.5 mL) then added to the LiTMP solution slowly and stirred for an additional 15 minutes at 0 °C. After this time, 0.4 mmol of an ester was dissolved in THF (0.5 mL) and then added to the reaction mixture which was then heated to 50 ºC for 2 hours. The solution was cooled to room temperature, then a mixture of H_2O (0.07 mL, 4 mmol) in THF (1 mL) was added to the solution and stirred for 15 minutes at room temperature. The reaction mixture was then eluted through a short column of celite and sodium sulfate and flushed through with diethyl ether. The filtrate was collected, and the solvent was removed under reduced pressure. The mixture was finally purified with an auto-column.

1-(4-methylphenyl)-2-phenylethan-1-one (2a)



2a

General synthesis 1 was followed, using 59.9 mg (0.4 mmol) of methyl 4-methylbenzoate, 0.4 mL (1 mmol) of n-BuLi and 0.18 mL (1 mmol) of TMP and heating the solution to 50ºC for 2 hours. This was purified using an autocolumn using a 5%-10% solvent gradient of diethyl ether and hexane. The ^{1}H-NMR and ^{13}C-NMR matched the literature.[2,4]

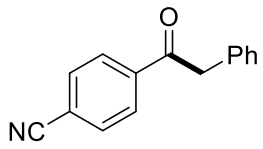
Yield = 52.8 mg (72%), White solid, R_f = 0.47 (5% ethyl acetate:hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.3 Hz, 2H), 7.34 - 7.19 (m, 7H), 4.24 (s, 2H), 2.38 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.4, 144.1, 134.9, 134.2, 129.5, 129.4, 128.8, 128.7, 126.9, 45.5, 21.7.

HRMS (ESI +): Exact mass calculated for $C_{15}H_{15}O$ $[M+H]^+$: 211.1123, found: 211.1133.

4-(2-phenylacetyl)benzonitrile (2b)



2b

General synthesis 1 was followed, using 64.2 mg (0.4 mmol) of methyl 4-cyanobenzoate, 0.4 mL (1 mmol) of n-BuLi and 0.18 mL (1 mmol) of TMP and heating the solution to 50ºC for 2 hours. The compound was purified was conducted using the autocolumn using an isocratic hold of 50% DCM with hexane. The ^{1}H-NMR of the pure product matched the literature value of the product found.[3]

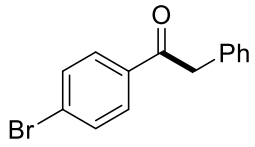
Yield = 21.1 mg (24%), White solid, R_f = 0.26 (10% ethyl acetate:hexanes).

^{1}H NMR (500 MHz, CDCl3) δ_H (ppm) = 8.07 (d, 2H, J = 8.45 Hz), 7.75 (d, 2H, J = 8.45 Hz), 7.32-7.35 (m, 2H), 7.23-7.25 (m, 3H), 4.29 (s, 2H)

^{13}C-NMR (126 MHz, CDCl3) δ_C (ppm) = 196.2, 139.4, 133.5, 132.5, 129.3, 129.0, 128.9, 127.3, 117.8, 116.4, 45.8.

HRMS (ESI +): Exact mass calculated for $C_{15}H_{11}NNaO$ $[M+Na]^+$: 244.0738, found: 244.0742.

1-(4-bromophenyl)-2-phenylethan-1-one (2c)



2c

General synthesis 1 was used, using 86 mg (0.4 mmol) of methyl 4-bromobenzoate, 0.4 mL (1 mmol) of n-BuLi and 0.18 mL (1 mmol) of TMP and heating the solution to 50ºC for 2 hours. A 5-10% diethyl ether and hexane gradient was used on the autocolumn to purify the product. The ^{1}H-NMR of the pure product matched the literature value of the product found.[2]

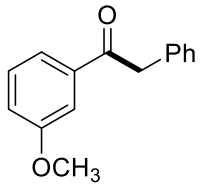
Yield = 72 mg (64%), White solid, R_f = 0.46 (5% ethyl acetate:hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm) = 7.87 (d, *J* = 8.7 Hz, 2H), 7.59 (d, *J* = 8.7 Hz, 2H), 7.36–7.30 (m, 2H), 7.29–7.23 (m, 3H), 4.25 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C (ppm) = 196.7, 135.4, 134.3, 132.1, 130.3, 129.5, 128.9, 128.5, 127.2, 45.7.

HRMS (ESI +): Exact mass calculated for $C_{14}H_{12}{}^{79}BrO$ $[M+H]^+$: 275.0072, found: 275.0079.

1-(3-methoxyphenyl)-2-phenylethane-1-one (2d)



2d

General synthesis 1 was used, using 0.06 mL (0.4 mmol) of methyl 3-methoxybenzoate, 0.4 mL (1 mmol) of n-BuLi and 0.18 mL (1 mmol) of TMP and heating the solution to 50ºC for 2 hours. The autocolumn was used for the purification, using a 5%-10% solvent gradient of diethyl ether and hexane. The ^{1}H-NMR and ^{13}C-NMR of the pure product matched the literature value of the product found.[4]

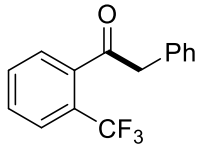
Yield = 61.7 mg (68%), Yellow solid, R_f = 0.47 (10% ethyl acetate:hexanes).

^{1}H NMR (500 MHz, CDCl3) δ_H (ppm) = 7.59 (d, J = 8.0 Hz, 1H), 7.52 (s, 1H), 7.36-7.29 (m, 3H), 7.27-7.22 (m, 3H), 7.08 (dd, J = 8.3, 2.6 Hz, 1H), 4.25 (s, 2H), 3.82 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 197.4, 159.8, 137.9, 134.5, 129.6, 129.4, 128.7, 126.9, 121.3, 119.6, 112.8, 55.4, 45.6.

HRMS (ESI +): Exact mass calculated for $C_{15}H_{15}O_2$ $[M+H]^+$: 227.1072, found: 227.1072.

2-phenyl-1-[2-(trifluoromethyl)phenyl]ethane-1-one (2e)



2e

General synthesis 1 was used, using 0.06 mL (0.4 mmol) of methyl 2-(trifluoromethyl)benzoate, 0.4 mL (1 mmol) of n-BuLi and 0.18 mL (1 mmol) of TMP and heating the solution to 50ºC for 2 hours. Two purifications using the autocolumn were needed,

the first at a set gradient of 5-10% ethyl acetate with hexane, then a more gradual gradient was made between 2.5-5% then ramping to 10% of ethyl acetate with hexane was used. There was no ^{1}H NMR or ^{13}C NMR reference literature for this molecule.

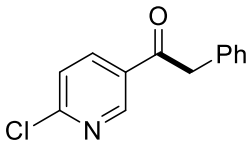
Yield = 86.4 mg (82%), Yellow solid, R_f = 0.39 (5% ethyl acetate:hexanes)

^{1}H NMR (500 MHz, CDCl3) δ_H (ppm) δ 7.72 – 7.66 (m, 1H), 7.54 (td, *J* = 7.2, 4.3 Hz, 2H), 7.36 – 7.29 (m, 2H), 7.27 (d, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 7.5 Hz, 2H), 4.15 (s, 2H).

^{13}C-NMR (126 MHz, CDCl3) δ_C (ppm) = 201.6, 139.8 (q, *J* = 2.2 Hz), 133.0, 131.7, 130.0, 129.7, 128.6, 127.18, 127.17, 127.0, 126.6 (q, *J* = 4.9 Hz), 123.6 (q, *J* = 273.7 Hz), 50.0 (q, *J* = 1.9 Hz).

HRMS (ESI +): Exact mass calculated for $C_{15}H_{12}F_3O$ $[M+H]^+$: 265.0840, found: 265.0842.

1-(6-chloropyridin-3-yl)-2-phenylethan-1-one (2f)



2f

General synthesis 1 was used, using 73.8 mg (0.4 mmol) of Ethyl 6-chloronicotinate, 0.4 mL (1 mmol) of n-BuLi and 0.18 mL (1 mmol) of TMP and heating the solution to 50ºC for 2 hours. The product was purified in the autocolumn using a gradient of 20-30% diethyl ether and hexane. There was no ^{1}H NMR or ^{13}C-NMR reference literature for this molecule.

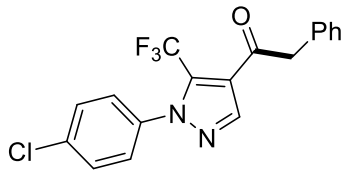
Yield = 38.1 mg (41%), Off-white solid, R_f = 0.29 (10% ethyl acetate:hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.99 (d, *J* = 1.9 Hz, 1H), 8.21 (dd, *J* = 8.3, 2.5 Hz, 1H), 7.42 (dd, *J* = 8.3, 0.6 Hz, 1H), 7.37 – 7.31 (m, 2H), 7.30 - 7.23 (m, 3H), 4.26 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 195.3, 155.8, 150.5, 138.7, 133.3, 130.8, 129.5, 129.1, 127.5, 124.8, 46.1.

HRMS (ESI +): Exact mass calculated for $C_{13}H_{11}{}^{35}ClNO$ $[M+H]^+$: 232.0529, found: 232.0530.

1-[1-(4-chlorophenyl)-4-(trifluoromethyl)-1H-pyrazol-3-yl]-2-phenylethane-1-one (2g)



2g

General synthesis 1 was used, using 72 mg (0.23 mmol) of ethyl 1-(4-chlorophenyl)-5-(Trifluoromethyl)-1H-pyrazole-4-carboxylate, 87 mg (0.4 mmol) benzylboronic acid pinacol ester (0.18 mL, 0.4 mmol), 0.16 mL (0.4 mmol) of n-BuLi and 0.068 mL (0.4 mmol) of TMP and heating the solution to 50ºC for 2 hours. Purification was by flash column chromatography using ethyl acetate and hexane as eluent (1:9)

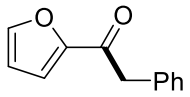
Yield = 35 mg (42%). White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.38 – 7.32 (m, 4H), 7.31 – 7.25 (m, 3H), 4.15 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 191.0, 141.3, 137.6, 136.1, 133.3, 132.0 (q, J = 40.6 Hz), 129.4, 129.4, 128.9, 127.3, 127.0 (q, *J* = 1.3 Hz), 124.1, 119.1 (q, J = 271.6 Hz), 48.9.

HRMS (ESI+): Exact mass calculated for $C_{18}H_{13}{}^{35}ClF_3N_2O$ $[M+H]^+$: 365.0669, found: 365.0661.

1-(furan-2-yl)-2-phenylethan-1-one (2h)



2h

General synthesis 1 was used, using 50 mg (0.4 mmol) of methyl 2-furoate, 175 mg (0.8 mmol) benzylboronic acid pinacol ester, 0.32 mL (0.8 mmol) of n-BuLi and 0.135 mL (0.8 mmol) of TMP and heating the solution to 50ºC for 2 hours. The mixture was purified by flash column chromatography using diethyl ether and hexane (5%). The ^{1}H-NMR and ^{13}C-NMR of the pure product matched the literature value of the product found.[5]

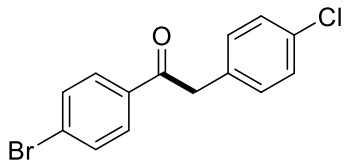
Yield = 74 mg (99%). Colourless oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 1.7, 0.7 Hz, 1H), 7.35 – 7.30 (m, 4H), 7.28 – 7.23 (m, 1H), 7.22 (dd, *J* = 3.6, 0.7 Hz, 1H), 6.52 (dd, *J* = 3.6, 1.7 Hz, 1H), 4.12 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 186.7, 152.5, 146.7, 134.2, 129.6, 128.7, 127.1, 118.0, 112.5, 45.5.

HRMS (ESI+): Exact mass calculated for $C_{12}H_{11}O_2$ $[M+H]^+$: 187.0759, found: 187.0751.

1-(4-bromophenyl)-2-(4-chlorophenyl)ethan-1-one (2i)



2i

General synthesis 1 was used, using 250 mg (1.0 mmol) of 2-(4-Chlorobenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 0.11 g (0.5 mmol) methyl 4-bromobenzoate, 0.5 mL (1 mmol) of n-BuLi and 0.23 mL (1 mmol) of TMP and heating the solution to 50ºC for 2 hours. The compound was purified using the auto column, using a gradient of 10-20% ethyl acetate with hexane. There was no ^{1}H NMR or ^{13}C NMR reference literature for this molecule.

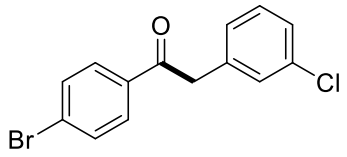
Yield = 120 mg (97%), White solid, R_f = 0.39 (5% ethyl acetate:hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.7 Hz, 2H), 7.61 (d, *J* = 8.7 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.6 Hz, 2H), 4.22 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 196.2, 135.2, 133.2, 132.6, 132.2, 130.9, 130.2, 129.0, 128.7, 44.8.

HRMS (ESI +): Exact mass calculated for $C_{14}H_{11}{}^{79}Br^{35}ClO$ $[M+H]^+$: 308.9682, found: 308.9677.

1-(4-bromophenyl)-2-(3-chlorophenyl)ethan-1-one (2j)



2j

General synthesis 1 was used, using 250 mg (1.0 mmol) of 2-(3-Chlorobenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 0.11 g (0.5 mmol) methyl 4-bromobenzoate, 0.5 mL (1 mmol) of n-BuLi and 0.23 mL (1 mmol) of TMP and heating the solution to 50°C for 2 hours. Using the autocolumn, a slow gradient from 0-20% over 60 CV using ethyl acetate and hexane allowed for a good separation of the product. There was no ^{1}H NMR or ^{13}C NMR reference literature for this molecule.

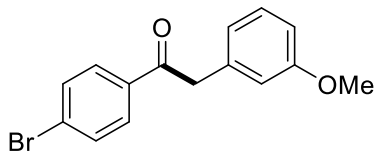
Yield = 84 mg (63%), White solid, R_f = 0.42 (5% ethyl acetate:hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.6 Hz, 2H), 7.62 (d, *J* = 8.6 Hz, 2H), 7.29 – 7.22 (m, 4H), 7.13 (dt, *J* = 6.5, 2.0 Hz, 1H), 4.22 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 195.8, 136.0, 135.0, 134.5, 132.1, 130.0, 129.9, 129.6, 128.7, 127.7, 127.3, 44.9.

HRMS (ESI +): Exact mass calculated for $C_{14}H_{11}{}^{79}Br^{35}ClO$ $[M+H]^+$: 308.9682, found: 308.9685.

1-(4-bromophenyl)-2-(3-methoxyphenyl)ethane-1-one (2k)



2k

General synthesis 1 was used, using 125 mg (0.5 mmol) of 2-(3-Methoxybenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 0.055 g (0.25 mmol) methyl 4-bromobenzoate, 0.25 mL (0.5 mmol) of n-BuLi and 0.12 mL (0.5 mmol) of TMP and heating the solution to 50ºC for 2 hours. The product was purified by autocolumn using an isocratic hold of 20% ethyl acetate with hexane. There was no ^{1}H NMR or ^{13}C NMR reference literature for this molecule.

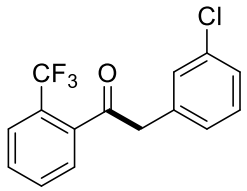
Yield = 81 mg (67%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.6 Hz, 2H), 7.58 (d, *J* = 8.6 Hz, 2H), 7.27 – 7.21 (m, 1H), 6.85 – 6.77 (m, 3H), 4.21 (s, 2H), 3.78 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.6, 159.9, 135.7, 135.3, 132.1, 130.3, 129.9, 128.5, 121.8, 115.2, 112.6, 55.3, 45.7.

HRMS (ESI +): Exact mass calculated for $C_{15}H_{14}{}^{79}BrO_2$ $[M+H]^+$: 305.0177, found: 305.0183.

2-(3-chlorophenyl)-1-(2-(trifluoromethyl)phenyl)ethan-1-one (2l)



2l

General synthesis 1 was used, using 126 mg (0.5 mmol) of 2-(3-Chlorobenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 51 mg (0.25 mmol) methyl 2-(trifluoromethyl)benzoate, 0.25 mL (0.5 mmol) of n-BuLi and 0.12 mL (0.5 mmol) of TMP and heating the solution to 50 ºC for 2 hours. Purification was by flash column chromatography using diethyl ether and hexane (5%) as eluent. There was no ^{1}H NMR or ^{13}C NMR reference literature for this molecule.

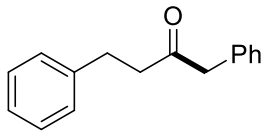
Yield = 93 mg (62%), Colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.69 (m, 1H), 7.63 – 7.53 (m, 2H), 7.40 – 7.33 (m, 1H), 7.30 – 7.21 (m, 3H), 7.15 – 7.07 (m, 1H), 4.12 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 201.0, 139.7 (q, *J* = 2.0 Hz), 135.0, 134.6, 132.0, 130.4, 130.02, 130.00, 128.1, 127.6, 127.2, 126.9 (q, *J* = 5.0 Hz), 123.7 (q, *J* = 273.6 Hz), 49.5 (q, *J* = 1.4 Hz). Aromatic C attached to CF_3 not visible

HRMS (ESI +): Exact mass calculated for $C_{15}H_{11}{}^{35}ClF_3O$ $[M+H]^+$: 299.0451, found: 299.0442

1,4-diphenylbutan-2-one (2m)



2m

General synthesis 1 was used, using 66 mg (0.4 mmol) of methyl hydrocinnamate, 175 mg (0.8 mmol) benzylboronic acid pinacol ester, 0.32 mL (0.8 mmol) of n-BuLi and 0.135 mL (0.8 mmol) of TMP and heating the solution to 50ºC for 2 hours. The mixture was purified by flash column chromatography using diethyl ether and hexane (2%).[6]

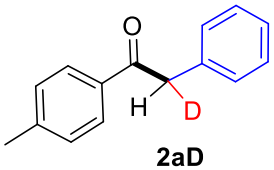
Yield = 70 mg (78%). Colourless oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 2H), 7.28 – 7.23 (m, 3H), 7.20 – 7.15 (m, 3H), 7.14 – 7.11 (m, 2H), 3.66 (s, 2H), 2.90 - 2.85 (m, 2H), 2.80 – 2.75 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 207.5, 141.0, 134.2, 129.5, 128.8, 128.6, 128.4, 127.1, 126.2, 50.5, 43.6, 29.9.

HRMS (ESI+): Exact mass calculated for $C_{16}H_{17}O$ $[M+H]^+$: 225.1279, found: 225.1272.

Deuteration Experiment



2aD

Procedure

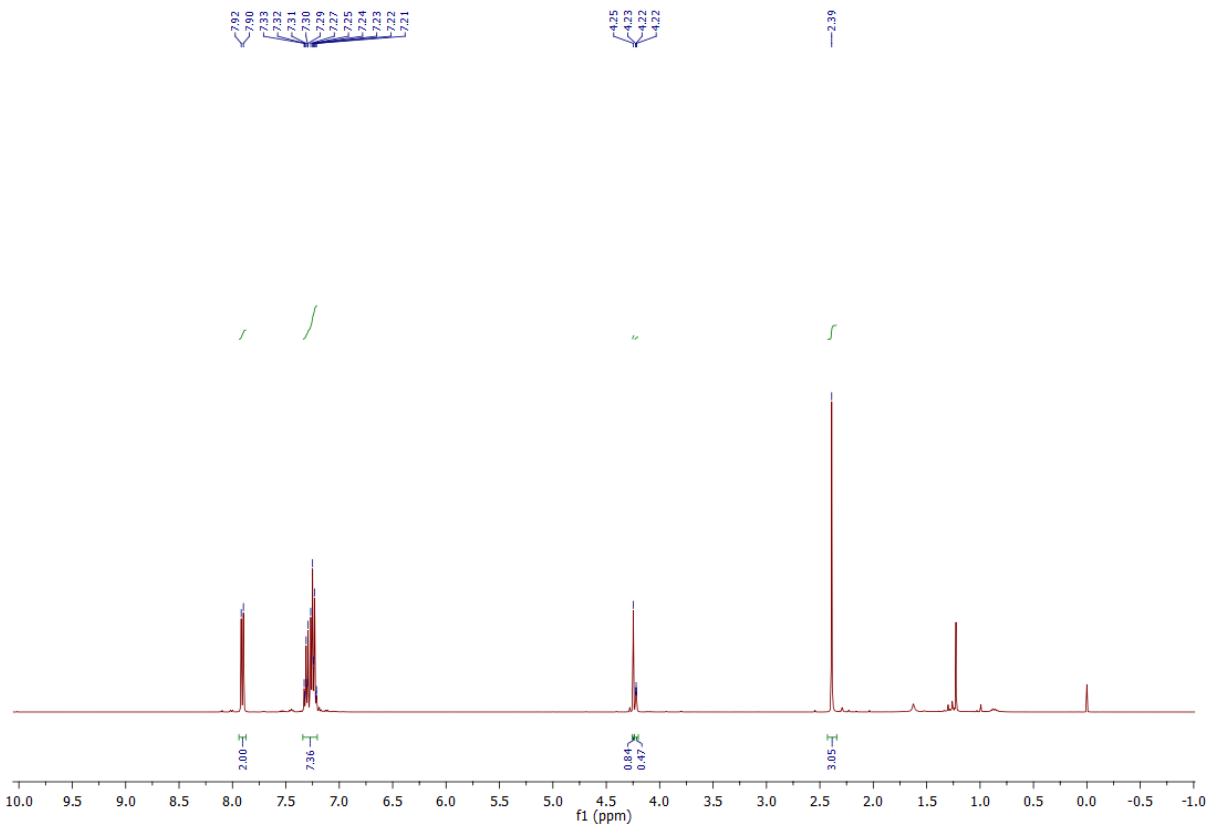
Under nitrogen atmosphere, *n*-BuLi (0.32 mL, 2.5 M in hexanes, 0.80 mmol) was added to 2,2,6,6-tetramethylpiperidine (0.136 mL, 0.80 mmol) in anhydrous THF (0.5 mL) and was stirred at 0 °C for 15 minutes. Benzylboronic acid pinacol ester was dissolved in 0.5 mL THF and then added to the LiTMP solution slowly. This mixture was stirred for an additional 15 minutes at 0 °C before a solution of methyl 4-methylbenzoate (0.050 g, 0.40 mmol) in 0.5 mL THF was added which was then heated to 50 °C for 15 minutes. The solution was cooled to room temperature and D_2O (0.072 mL, 4.00 mmol) was added to the solution was stirred for 15 minutes at room temperature. The reaction mixture was then eluted through a short column of celite and anhydrous sodium sulphate and flushed through with diethyl ether. The filtrate was collected, and the solvent was removed under reduced pressure. The product was then purified using flash column chromatography.

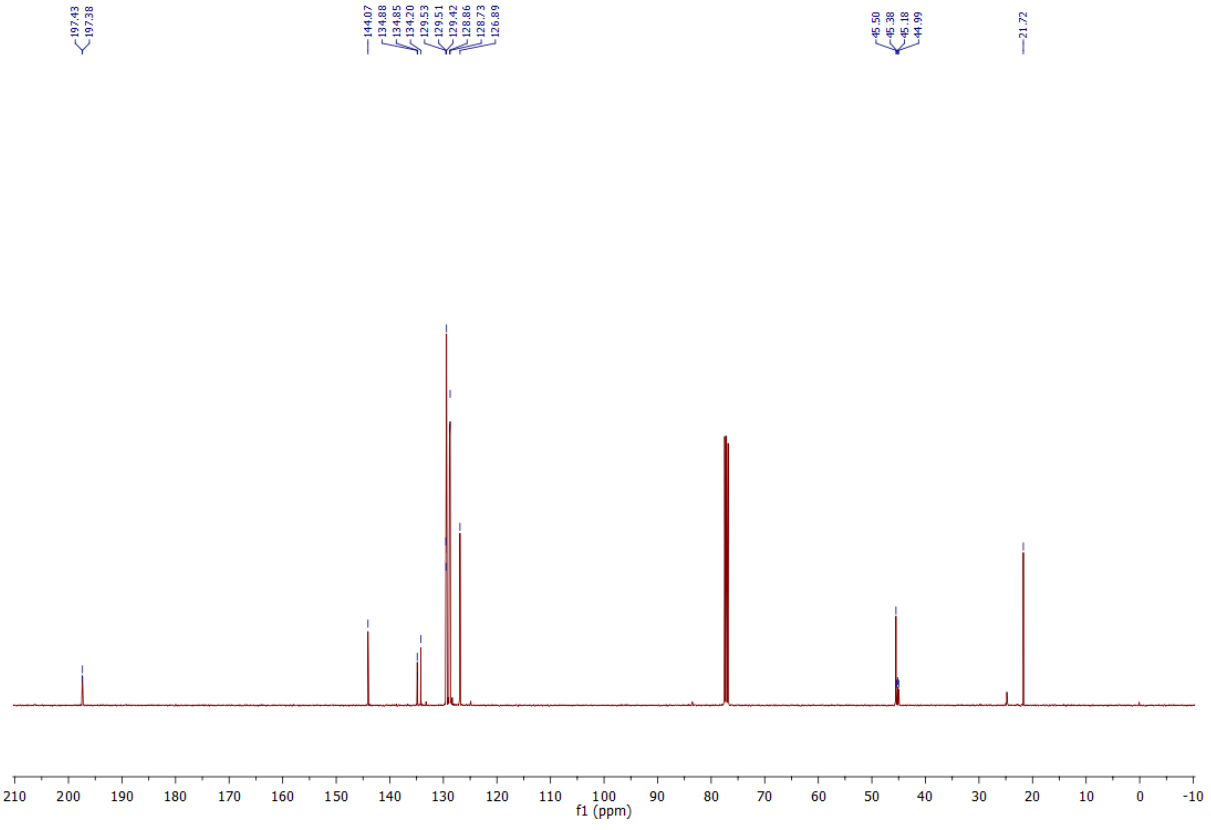
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.2 Hz, 2H), 7.34 – 7.20 (m, 7H), 4.25 (s, 0.84 H for CH_2), 4.22 (t, *J* = 1.8 Hz, 0.47H for CDH), 2.39 (s, 3H).

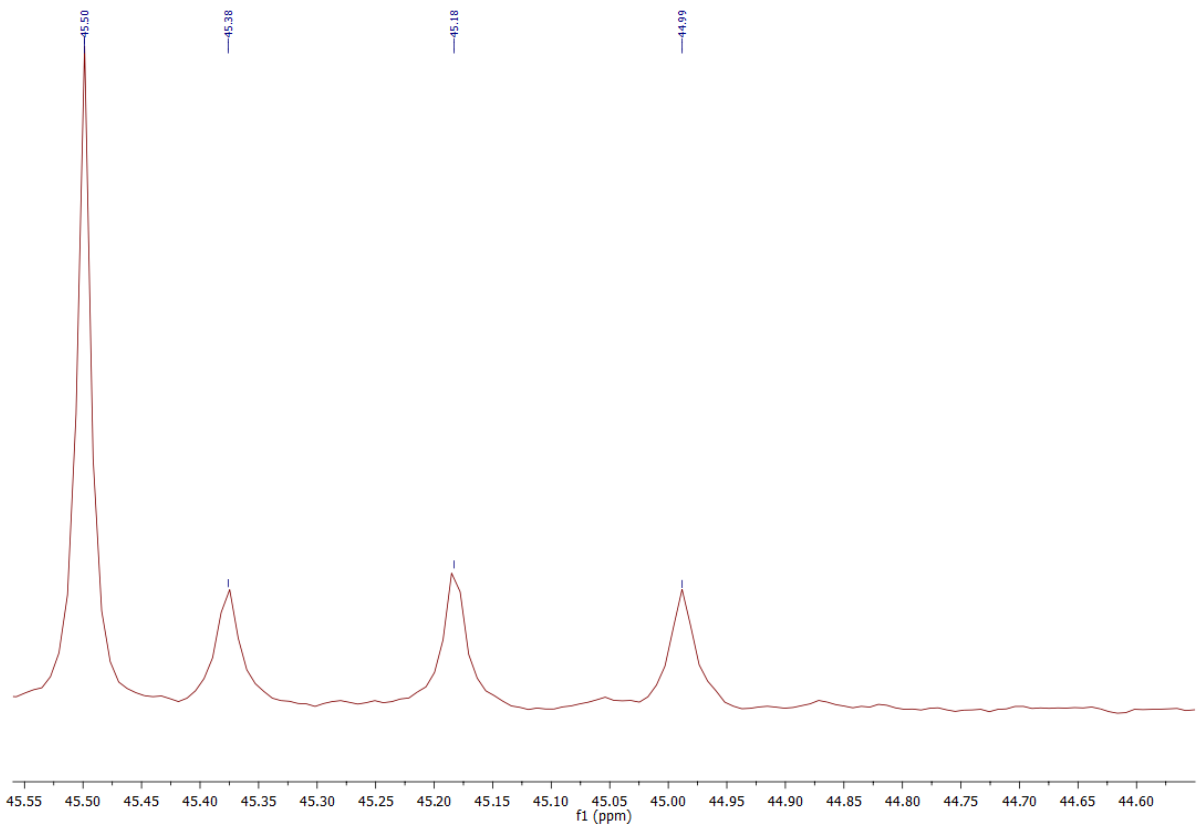
From ^{1}H NMR, the ratio of CH2 and CHD products was found to be 42 : 47.

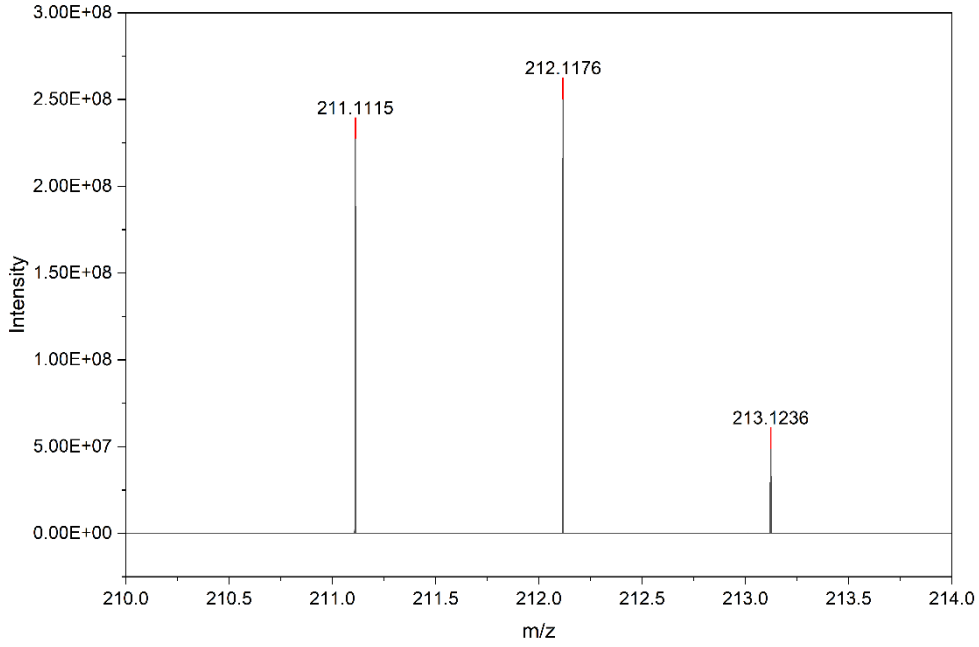
^{13}C NMR (101 MHz, $CDCl_3$) δ 197.4, 197.4, 144.1, 134.9, 134.8, 134.2, 129.5, 129.5, 129.4, 128.9, 128.7, 126.9, 45.5, 45.2 (t, *J* = 19.5 Hz, C-D), 21.7.

HRMS (ESI +): Exact mass calculated for $C_{15}H_{14}DO$ $[M+H]^+$: 212.1186, found: 212.1176. For protonated product, exact mass calculated for $C_{15}H_{15}O$ $[M+H]^+$: 211.1123, found: 211.1115.


7.92
7.90
7.33
7.32
7.31
7.30
7.29
7.27
7.25
7.24
7.23
7.22
7.21
4.25
4.23
4.22
4.22
2.39
2.00
7.36
0.84
0.47
3.05
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 -1.0
f1 (ppm)


197.43
197.38
144.07
134.88
134.85
134.20
129.53
129.51
129.42
128.86
128.73
126.89
45.50
45.38
45.18
44.99
21.72
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)





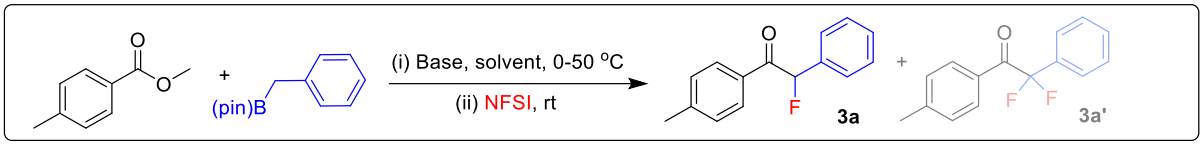
Peak	Peak Area	% Peak area
211.1115	3.304×10^5	42.4
212.1176	3.685×10^5	47.3
213.1236	7.966×10^4	10.2

Synthesis of mono-fluorinated ketones

Optimization of reaction conditions

Methyl 4-methylbenzoate (0.060 g, 0.40 mmol) was initially used to optimize conditions for mono-fluorination. Solutions of benzylboronic acid pinacol ester (1 equiv.) and freshly prepared lithium tetramethylpiperidide (LiTMP, 2.5 equiv.) in anhydrous THF were used to generate the boron enolate which was then trapped with *N*-Fluorobenzenesulfonimide (NFSI, 2 equiv.). NMR yields were calculated with respect to fluorobenzene as standard in ^{19}F NMR. These reaction conditions produced 26% of the expected mono-fluorinated ketone **3a** along with 16% of di-fluorinated ketone **3a′** (Table 1, entry 2). The di-fluorinated side product is believed to form *via* a second fluorination of the mono-fluorinated product in the presence of residual base and excess NFSI. Changes in the amount of NFSI did not result in any significant improvements on the yields (entry 1-4). Reducing the amount of LiTMP had a positive effect on both the yield of mono-fluorinated product and the mono- to di-fluorinated product ratio (entry 5-8). After the addition of ester, reaction time at 50 °C was also elongated to see how it affects the yields, but it did not result in any improvements (entry 9-10). A few changes in the amounts of LiTMP, ester and the boron reagent (entry 11-14) helped us optimize the reaction yields to 62% of the mono-fluorinated ketone **3a** with negligible di-fluorinated product (entry 11). As substitutes to LiTMP, NaHMDS and LiHMDS were also tried as preferred base to carry out the designed coupling which resulted in highly deteriorated yields of **3a** (entry 15-16).

Table S2: Optimization of mono-fluorination.



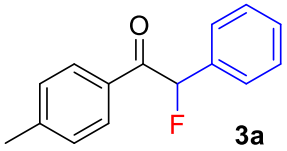
Entry No.	Changes to Reaction Conditions	% 3a, % 3a′
1	1.0 equiv. NFSI	15, 6
2	2.0 equiv. NFSI	26, 16
3	3.0 equiv. NFSI	24, 21
4	4.0 equiv. NFSI	27, 23
5	2.0 equiv. LiTMP	33, 14
6	3.0 equiv. LiTMP	6, 2
7	1.5 equiv. LiTMP	37, 10
8	1.0 equiv. LiTMP	51, 3
9	Heated for 30 minutes after addition of ester, 1 equiv. LiTMP	51, 7
10	Heated for 60 minutes after addition of ester, 1 equiv. LiTMP	-
11	1 equiv. LiTMP, 1.5 equiv. benzylboronic acid pinacol ester	62, <1
12	1 equiv. LiTMP, 1.5 equiv. ester	40, 2
13	1.5 equiv. LiTMP, 1.5 equiv. benzylboronic acid pinacol ester	55, 16
14	1.5 equiv. LiTMP, 2.0 equiv. benzylboronic acid pinacol ester	14, 0.7
15	1.5 equiv. benzylboronic acid pinacol ester, 1.0 equiv. NaHMDS instead of LiTMP	25, 3
16	1.5 equiv. benzylboronic acid pinacol ester, 1.0 equiv. LiHMDS instead of LiTMP	6, 20

Unless otherwise stated, reactions were performed in anhydrous THF by addition of benzylboronic acid pinacol ester (1 equiv.) to freshly prepared lithium tetramethylpiperidide (LiTMP, 2.5 equiv.) at 0 °C, followed by addition of methyl 4-methylbenzoate (0.060 g, 0.40 mmol) and then heating the solution to 50 °C. This was followed by addition of NFSI (2 equiv.) at room temperature. % NMR yields are reported.

General Synthesis 2: Synthesis of mono-fluorinated ketones

A solution of LiTMP (0.4 mmol, 1equiv.) was prepared by adding *n*-BuLi to 2,2,6,6-tetramethylpiperidine in anhydrous THF (0.5 mL) and stirring at 0 °C for 15 minutes. A solution of benzylboronic acid pinacol ester derivative (0.6 mmol, 1.5 equiv.) in THF (0.5 mL) was added and the mixture was stirred at 0 °C. After 15 minutes, THF (0.5 mL) solution of ester (0.4 mmol, 1 equiv.) was added and the reaction mixture was heated to 50 °C for 15 minutes, followed by cooling it to room temperature before a THF (1 mL) solution of NFSI (0.8 mmol, 2 equiv.) was added. After stirring for 15 minutes at room temperature, the mixture was eluted through a short pad of silica (Et_2O) and concentrated *in vacuo*. The product was then purified using flash column chromatography.

2-Fluoro-2-phenyl-1-(*p*-tolyl)ethan-1-one (3a)



3a

This compound was prepared using General Synthesis 2 using methyl 4-methylbenzoate (0.060 g, 0.40 mmol), benzylboronic acid pinacol ester (0.130 g, 0.60 mmol), 2,2,6,6-tetramethylpiperidine (0.057 g, 0.068 mL, 0.40 mmol), *n*-BuLi (0.16 mL, 0.40 mmol, 2.5 M in hexanes), N-fluorobenzenesulfonimide (0.252 g, 0.8 mmol) in THF (2.5 mL total). The compound was purified by flash column chromatography using acetone/hexane (1%) as eluent.[7]

Yield = 0.051 g, 56% (62% NMR yield); yellow liquid; R_f = 0.43 (acetone/hexane (5%)).

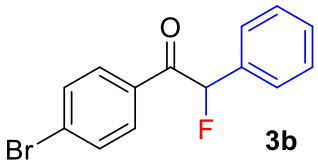
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.3 Hz, 2H), 7.49 (dd, *J* = 7.8, 1.4 Hz, 2H), 7.42 – 7.34 (m, 3H), 7.22 (d, *J* = 8.1 Hz, 2H), 6.51 (d, *J* = 48.7 Hz, 1H), 2.37 (s, 1H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 193.9 (d, *J* = 21.2 Hz), 144.9, 134.6 (d, *J* = 19.9 Hz), 131.6, 129.7 (d, *J* = 2.7 Hz), 129.5, 129.3 (d, *J* = 2.7 Hz), 129.2, 127.5 (d, *J* = 5.5 Hz), 93.9 (d, *J* = 185.3 Hz), 21.8.

^{19}F NMR (471 MHz, $CDCl_3$) δ -175.67 (d, *J* = 48.8 Hz).

HRMS (ESI+): Exact mass calculated for $C_{15}H_{14}FO$ $[M+H]^+$: 229.1029, found: 229.1030.

1-(4-bromophenyl)-2-fluoro-2-phenylethan-1-one (3b)



3b

This compound was prepared using General Synthesis 2 using methyl 4-bromobenzoate (0.086 g, 0.40 mmol), benzylboronic acid pinacol ester (0.130 g, 0.60 mmol), 2,2,6,6-tetramethylpiperidine (0.057 g, 0.068 mL, 0.40 mmol), *n*-BuLi (0.16 mL, 0.40 mmol, 2.5 M in hexanes), N-fluorobenzenesulfonimide (0.252 g, 0.8 mmol) in THF (2.5 mL total). The compound was purified by flash column chromatography using diethyl ether/hexane (0.5%) as eluent.[7]

Yield = 0.091 g, 78% (86.5% NMR yield); white solid, Melting point = 89-92 °C; R_f = 0.47 (Et_2O/ hexane (5%)).

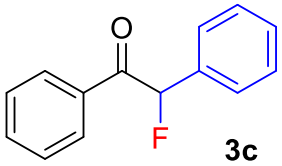
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 8.7 Hz, 2H), 7.49 – 7.44 (m, 2H), 7.43 – 7.36 (m, 3H), 6.44 (d, *J* = 48.6 Hz, 1H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 193.6 (d, *J* = 21.9 Hz), 134.1 (d, *J* = 20.0 Hz), 132.8 (d, *J* = 0.8 Hz), 132.2, 130.7 (d, *J* = 3.2 Hz), 129.9 (d, *J* = 2.6 Hz), 129.3, 129.3, 127.3 (d, *J* = 5.7 Hz), 94.3 (d, *J* = 186.6 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) δ -176.26 (d, *J* = 48.7 Hz).

HRMS (ESI+): Exact mass calculated for $C_{14}H_{10}{}^{79}BrFNaO$ $[M+Na]^+$: 314.9797, found: 314.9798.

2-Fluoro-1,2-diphenylethan-1-one (3c)



3c

This compound was prepared using General Synthesis 2 using ethyl benzoate (0.060 g, 0.40 mmol), benzylboronic acid pinacol ester (0.130 g, 0.60 mmol), 2,2,6,6-tetramethylpiperidine (0.057 g, 0.068 mL, 0.40 mmol), *n*-BuLi (0.16 mL, 0.40 mmol, 2.5 M in hexanes), N-fluorobenzenesulfonimide (0.252 g, 0.8 mol) in THF (2.5 mL total). The compound was purified by flash column chromatography using diethyl ether/hexane (1%) as eluent.[7]

Yield = 0.063 g, 73% (80.4% NMR yield); white solid, Melting point = 55-58 °C; R_f = 0.39 (Et_2O/ hexane (5%)).

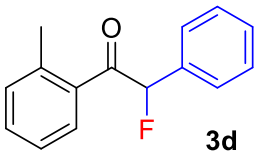
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 8.3, 0.9 Hz, 2H), 7.58 – 7.52 (m, 1H), 7.52 – 7.46 (m, 2H), 7.46 – 7.35 (m, 5H), 6.51 (d, *J* = 48.6 Hz, 1H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 194.4 (d, *J* = 21.4 Hz), 134.4 (d, *J* = 19.9 Hz), 134.2, 133.9, 129.8 (d, *J* = 2.6 Hz), 129.2, 128.8, 127.5 (d, *J* = 5.5 Hz), 94.1 (d, *J* = 185.7 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) δ -175.89 (d, *J* = 48.8 Hz).

HRMS (ESI+): Exact mass calculated for $C_{14}H_{11}FNaO$ $[M+Na]^+$: 237.0692, found: 237.0688.

2-Fluoro-2-phenyl-1-(*o*-tolyl)ethan-1-one (3d)



3d

This compound was prepared using General Synthesis 2 using methyl *o*-toluate (0.060 g, 0.40 mmol), benzylboronic acid pinacol ester (0.130 g, 0.60 mmol), 2,2,6,6-tetramethylpiperidine (0.057 g, 0.068 mL, 0.40 mmol), *n*-BuLi (0.16 mL, 0.40 mmol, 2.5 M in hexanes), N-fluorobenzenesulfonimide (0.252 g, 0.8 mol) in THF (2.5 mL total). The compound was purified by flash column chromatography using diethyl ether/hexane (1%) as eluent.[8]

Yield = 0.052 g, 57% (64% NMR yield); white solid, Melting point = 49-52 °C; R_f = 0.44 (Et_2O/ hexane (5%)).

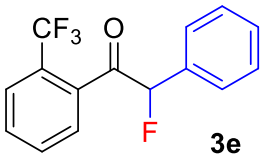
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.0 Hz, 1H), 7.43 – 7.32 (m, 6H), 7.24 – 7.18 (m, 2H), 6.39 (d, *J* = 48.4 Hz, 1H), 2.32 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 198.3 (d, *J* = 22.4 Hz), 138.9 (d, *J* = 0.7 Hz), 135.1, 134.0 (d, *J* = 20.5 Hz), 131.9 (d, *J* = 12.7 Hz), 129.5 (d, *J* = 2.2 Hz), 129.0, 128.5 (d, *J* = 2.9 Hz), 127.1 (d, *J* = 5.9 Hz), 125.6, 94.4 (d, *J* = 187.9 Hz), 20.6.

^{19}F NMR (471 MHz, $CDCl_3$) δ -177.49 (d, *J* = 48.6 Hz).

HRMS (ESI+): Exact mass calculated for $C_{15}H_{14}FO$ $[M+H]^+$: 229.1029, found: 229.1028.

2-Fluoro-2-phenyl-1-(2-(trifluoromethyl)phenyl)ethan-1-one (3e)



3e

This compound was prepared using General Synthesis 2 using methyl 2-(trifluoromethyl)benzoate (0.082 g, 0.40 mmol), benzylboronic acid pinacol ester (0.130 g, 0.60 mmol), 2,2,6,6-tetramethylpiperidine (0.057 g, 0.068 mL, 0.40 mmol), *n*-BuLi (0.16 mL, 0.40 mmol, 2.5 M in hexanes), N-fluorobenzenesulfonimide (0.252 g, 0.8 mol) in THF (2.5 mL total). The compound was purified by flash column chromatography using acetone/hexane (1%) as eluent

Yield = 0.045 g, 40% (62% NMR yield); colourless viscous liquid; R_f = 0.35 (acetone/hexane (5%)).

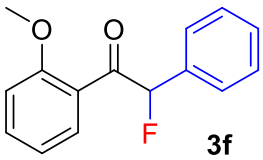
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.8 Hz, 1H), 7.58 (t, *J* = 7.7 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.40 (s, 5H), 7.12 (d, *J* = 7.6 Hz, 1H), 6.20 (d, *J* = 47.5 Hz, 1H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 199.9 (d, *J* = 28.3 Hz), 136.0 – 135.9 (m), 133.6 (d, *J* = 20.8 Hz), 131.6 (d, *J* = 0.6 Hz), 130.8, 129.7 (d, *J* = 1.7 Hz), 129.0, 127.9 (d, *J* = 2.3 Hz), 127.4 (d, *J* = 2.6 Hz), 126.9 (q, *J* = 4.6 Hz), 126.6 (d, *J* = 6.7 Hz), 95.2 (dq, *J* = 189.6, 1.4 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) δ -58.07 (d, *J* = 3.0 Hz), -181.86 (dq, *J* = 47.6, 3.0 Hz).

HRMS (ESI+): Exact mass calculated for $C_{15}H_{10}F_4NaO$ $[M+Na]^+$: 305.0565, found: 305.0564.

2-fluoro-1-(2-methoxyphenyl)-2-phenylethan-1-one (3f)



3f

This compound was prepared using General Synthesis 2 using methyl 2-methoxybenzoate (0.066 g, 0.40 mmol), benzylboronic acid pinacol ester (0.130 g, 0.60 mmol), 2,2,6,6-tetramethylpiperidine (0.057 g, 0.068 mL, 0.40 mmol), *n*-BuLi (0.16 mL, 0.40 mmol, 2.5 M in hexanes), N-fluorobenzenesulfonimide (0.252 g, 0.8 mol) in THF (2.5 mL total). The compound was purified by flash column chromatography using acetone/hexane (4%) as eluent.

Yield = 0.048 g, 49% (70% NMR yield); off-white solid, Melting point = 36-39 °C; R_f = 0.22 (acetone/hexane (5%)).

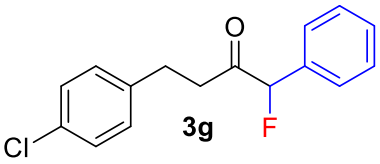
^{1}H NMR (500 MHz, $CDCl_3$) 7.73 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.47 – 7.42 (m, 1H), 7.40 – 7.36 (m, 2H), 7.35 – 7.30 (m, 3H), 7.00 – 6.95 (m, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.70 (d, *J* = 48.8 Hz, 1H), 3.84 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 195.9 (d, *J* = 20.8 Hz), 158.3, 134.6, 134.5 (d, *J* = 19.6 Hz), 131.3 (d, *J* = 2.1 Hz), 129.4 (d, *J* = 2.9 Hz), 128.8 (d, *J* = 1.2 Hz), 128.2 (d, *J* = 5.0 Hz), 125.3, 121.2, 111.6, 95.6 (d, *J* = 181.7 Hz), 55.4.

^{19}F NMR (471 MHz, $CDCl_3$) δ -172.69 (d, *J* = 48.9 Hz).

HRMS (ESI+): Exact mass calculated for $C_{15}H_{14}FO_2$ $[M+H]^+$: 245.0978, found: 245.0974.

4-(4-Chlorophenyl)-1-fluoro-1-phenylbutan-2-one (3g)



3g

This compound was prepared using General Synthesis 2 using methyl 3-(4-chlorophenyl)propanoate (0.079 g, 0.40 mmol), benzylboronic acid pinacol ester (0.130 g, 0.60 mmol), 2,2,6,6-tetramethylpiperidine (0.057 g, 0.068 mL, 0.40 mmol), *n*-BuLi (0.16 mL, 0.40 mmol, 2.5 M in hexanes), N-fluorobenzenesulfonimide (0.252 g, 0.8 mol) in THF (2.5 mL total). The compound was purified by flash column chromatography using diethyl ether/hexane (1%) as eluent.

Yield = 0.042 g, 38% (46% NMR yield); colourless viscous liquid, R_f = 0.42 (Et_2O/ hexane (5%)).

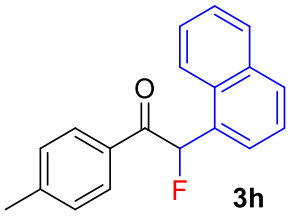
^{1}H NMR (500 MHz, $CDCl_3$) 7.41 – 7.35 (m, 3H), 7.35 – 7.31 (m, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 5.68 (d, *J* = 48.5 Hz, 1H), 2.97 – 2.78 (m, 4H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 205.5 (d, *J* = 25.9 Hz), 139.0, 133.9 (d, *J* = 20.4 Hz), 132.1, 129.8, 129.5 (d, *J* = 1.8 Hz), 129.0, 128.7, 126.0 (d, *J* = 7.1 Hz), 95.9 (d, *J* = 187.9 Hz), 38.9, 28.3 (d, *J* = 1.7 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) δ -185.23 (d, *J* = 48.6 Hz).

HRMS (ESI+): Exact mass calculated for $C_{16}H_{14}{}^{35}ClFNaO$ $[M+Na]^+$: 299.0615, found: 299.0614.

2-fluoro-2-(naphthalen-1-yl)-1-(*p*-tolyl)ethan-1-one (3h)



3h

This compound was prepared using General Synthesis 2 using methyl 4-methylbenzoate (0.060 g, 0.40 mmol), (1-naphthylmethyl)boronic acid pinacol ester (0.160 g, 0.60 mmol), 2,2,6,6-tetramethylpiperidine (0.057 g, 0.068 mL, 0.40 mmol), *n*-BuLi (0.16 mL, 0.40 mmol, 2.5 M in hexanes), N-fluorobenzenesulfonimide (0.252 g, 0.8 mmol) in THF (2.5 mL total). The compound was purified by flash column chromatography using acetone/hexane (1%) as eluent.[7]

Yield = 0.030 g, 27% (33% NMR yield); white solid, Melting point = 125-128 °C; R_f = 0.35 (acetone/hexane (5%)).

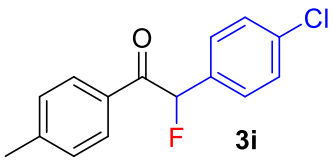
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 2H), 7.82 (d, *J* = 8.3 Hz, 2H), 7.66 – 7.60 (m, 1H), 7.58 – 7.51 (m, 2H), 7.45 – 7.40 (m, 1H), 7.18 (d, *J* = 48.2 Hz, 1H), 7.17 (d, *J* = 8.1 Hz, 2H), 2.35 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 194.4 (d, *J* = 20.7 Hz), 144.9, 134.2 (d, *J* = 1.7 Hz), 131.9, 131.4 (d, *J* = 1.6 Hz), 130.9 (d, *J* = 3.4 Hz), 130.6 (d, *J* = 18.1 Hz), 129.5, 129.2 (d, *J* = 2.2 Hz), 129.1, 127.9 (d, *J* = 6.4 Hz), 127.5 (d, *J* = 0.6 Hz), 126.5, 125.3 (d, *J* = 2.1 Hz), 123.6, 91.9 (d, *J* = 184.4 Hz), 21.8.

^{19}F NMR (471 MHz, $CDCl_3$) δ -174.04 (d, *J* = 48.6 Hz).

HRMS (ESI+): Exact mass calculated for $C_{19}H_{15}FNaO$ $[M+Na]^+$: 301.1005, found: 301.1007.

2-(4-Chlorophenyl)-2-fluoro-1-(*p*-tolyl)ethan-1-one (3i)



3i

This compound was prepared using General Synthesis 2 using methyl 4-methylbenzoate (0.060 g, 0.40 mmol), 4-chlorobenzylboronic acid pinacol ester (0.152 g, 0.60 mmol), 2,2,6,6-tetramethylpiperidine (0.057 g, 0.068 mL, 0.40 mmol), *n*-BuLi (0.16 mL, 0.40 mmol, 2.5 M in hexanes), N-fluorobenzenesulfonimide (0.252 g, 0.8 mmol) in THF (2.5 mL total). The

compound was purified by flash column chromatography using diethyl ether/hexane (0.5%) as eluent.[7]

Yield = 0.024 g, 23% (28% NMR yield); colourless viscous liquid, R_f = 0.39 (Et_2O/ hexane (5%)).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.2 Hz, 2H), 7.42 (dd, *J* = 8.4, 1.1 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 6.46 (d, *J* = 48.5 Hz, 1H), 2.39 (s, 3H).

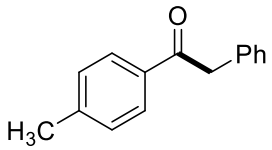
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 193.6 (d, *J* = 21.2 Hz), 145.2, 133.1 (d, *J* = 20.4 Hz), 131.4 (d, *J* = 0.6 Hz), 129.6, 129.4, 129.3 (d, *J* = 3.0 Hz), 128.8 (d, *J* = 5.6 Hz), 93.3 (d, *J* = 186.3 Hz), 21.9.

^{19}F NMR (471 MHz, $CDCl_3$) δ -176.55 (d, *J* = 48.7 Hz).

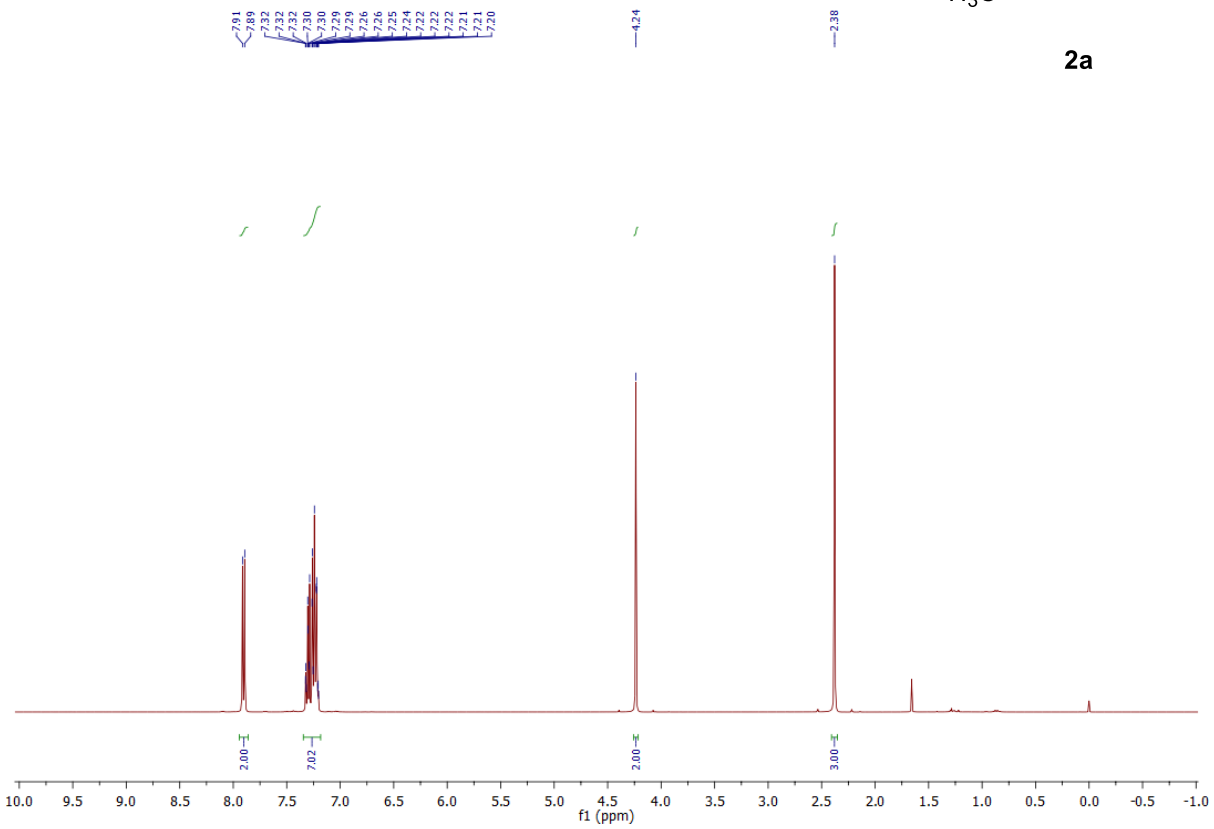
HRMS (ESI+): Exact mass calculated for $C_{15}H_{12}{}^{35}ClFNaO$ $[M+Na]^+$: 285.0458, found: 285.0456.

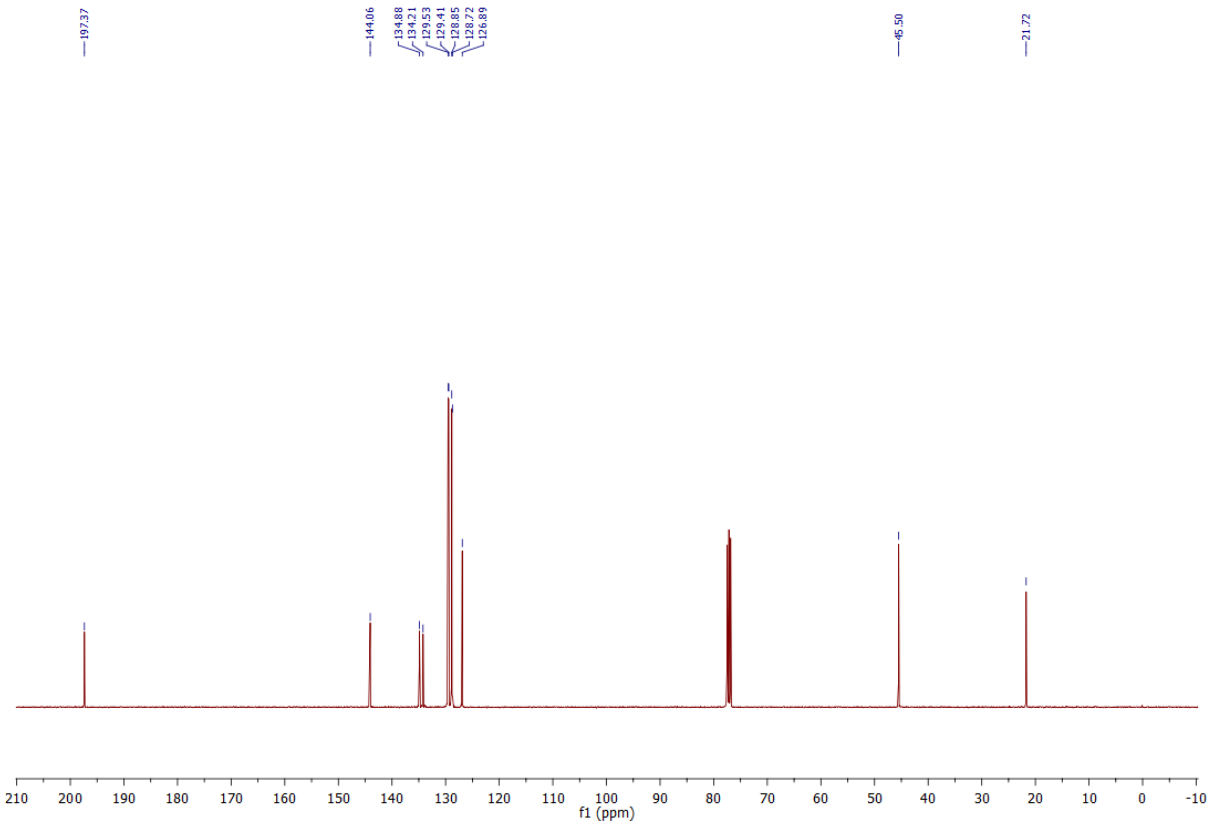
Spectroscopic data

1-(4-methylphenyl)-2-phenylethan-1-one (2a)

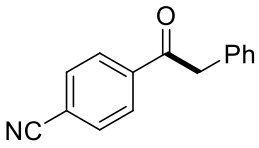


2a

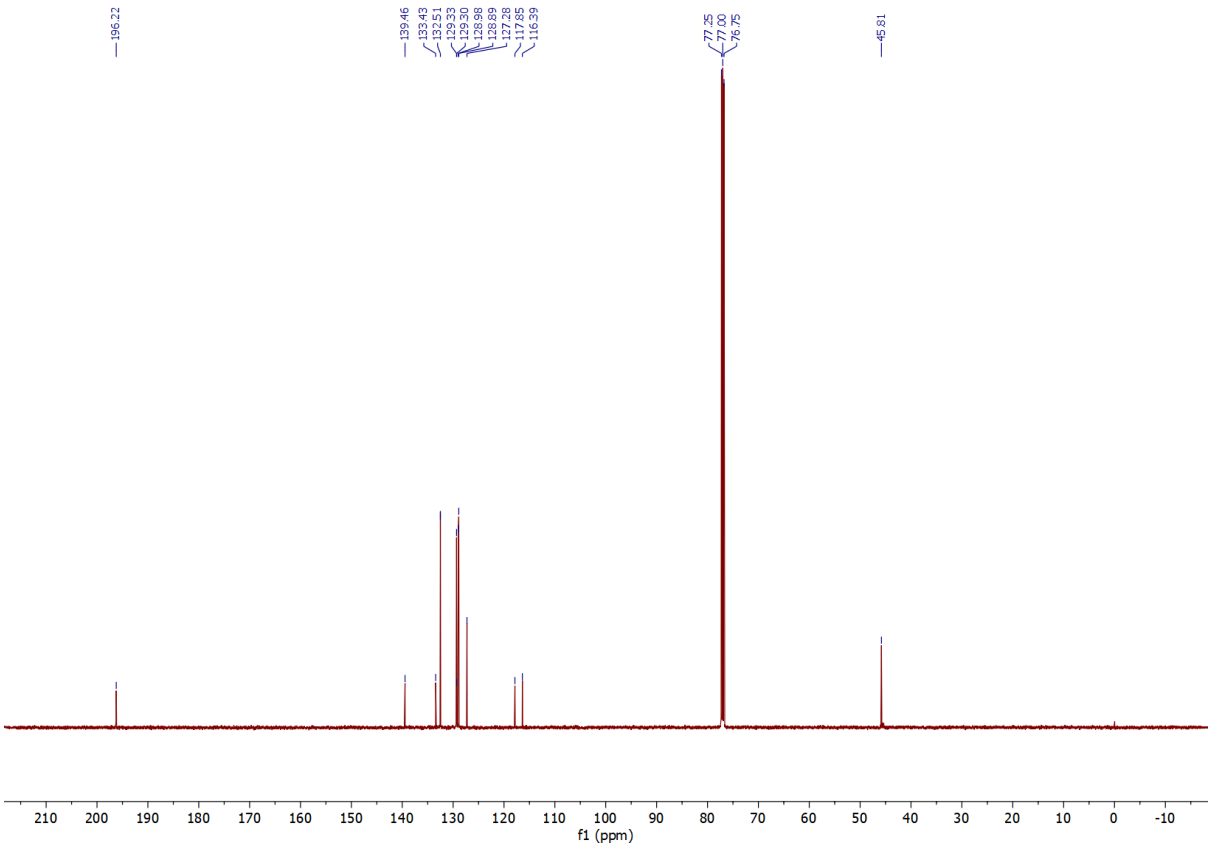




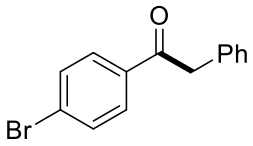
4-(2-phenylacetyl)benzonitrile (2b)



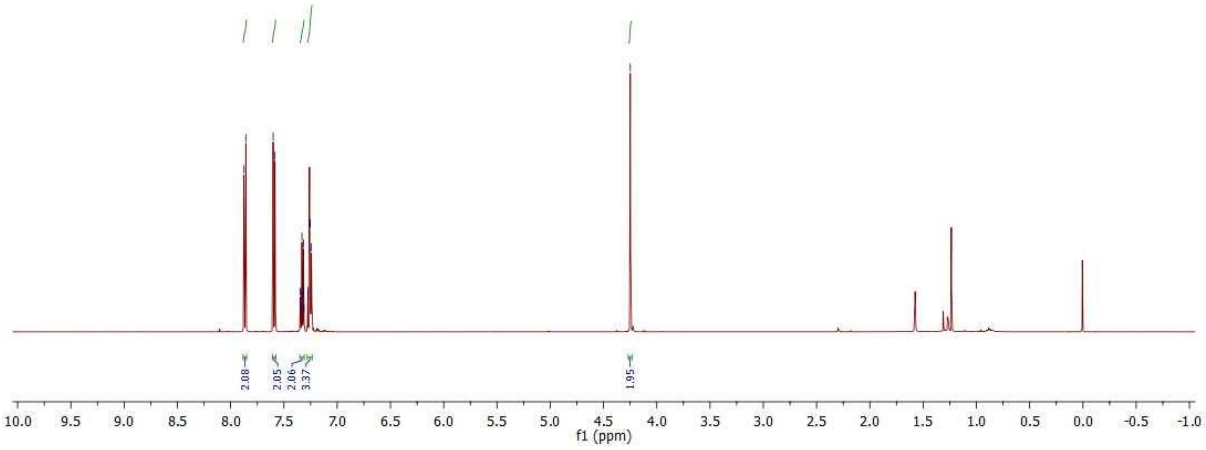
2b

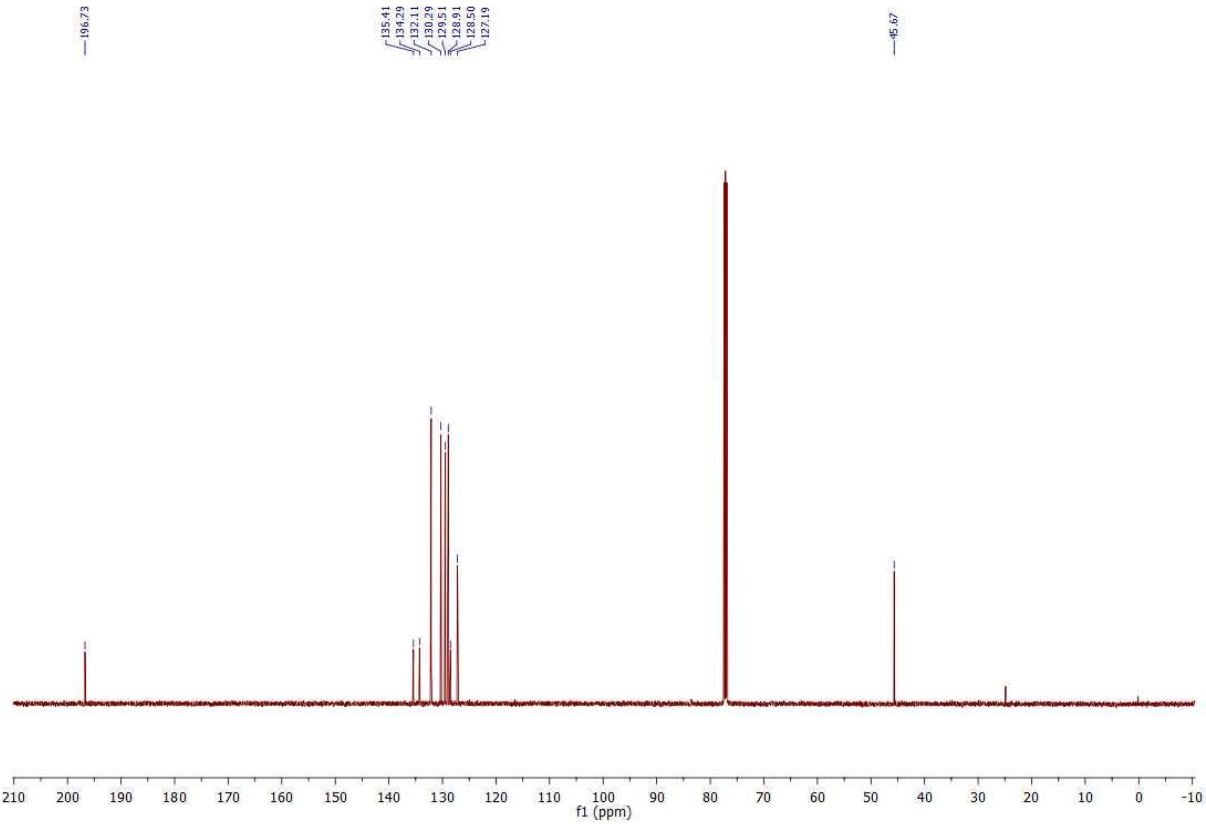


1-(4-bromophenyl)-2-phenylethan-1-one (2c)

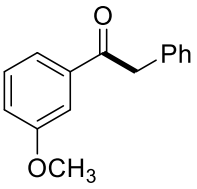


2c

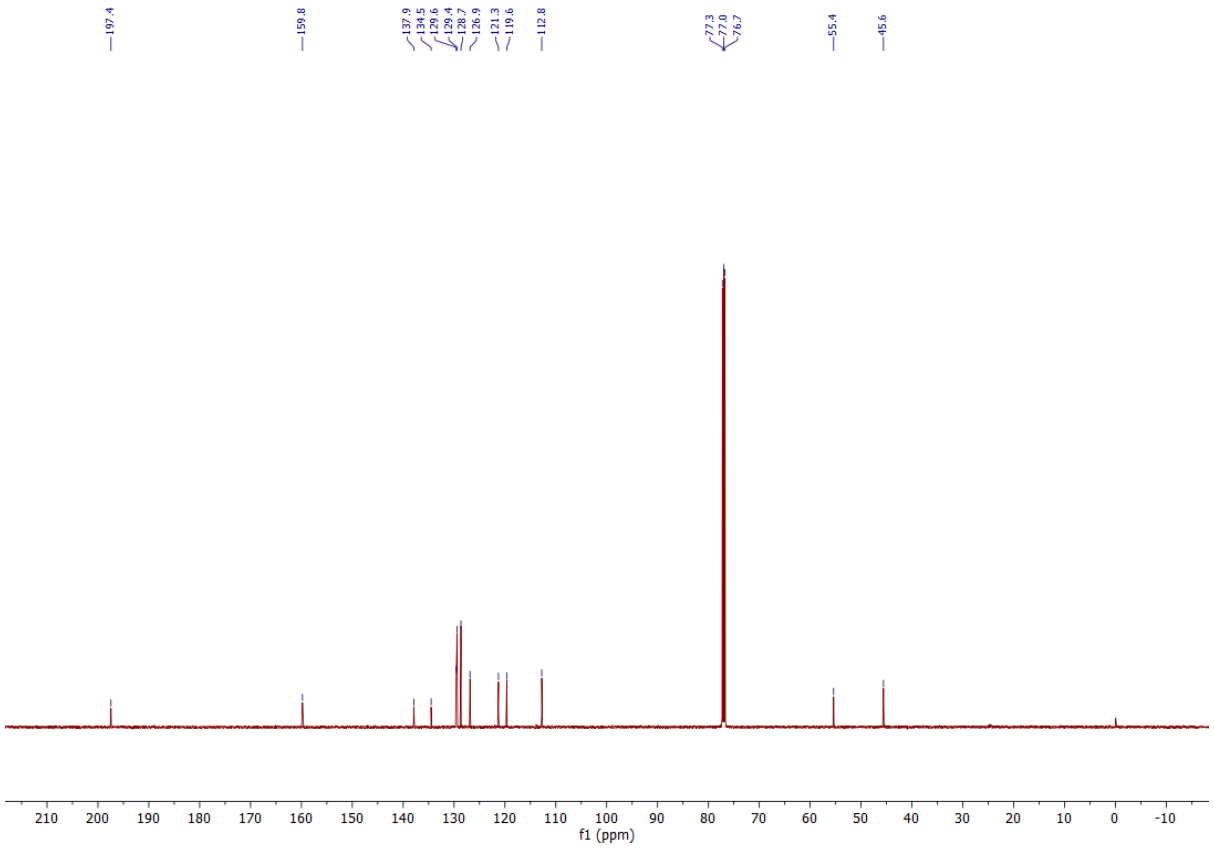




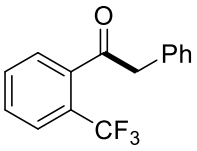
1-(3-methoxyphenyl)-2-phenylethane-1-one (2d)



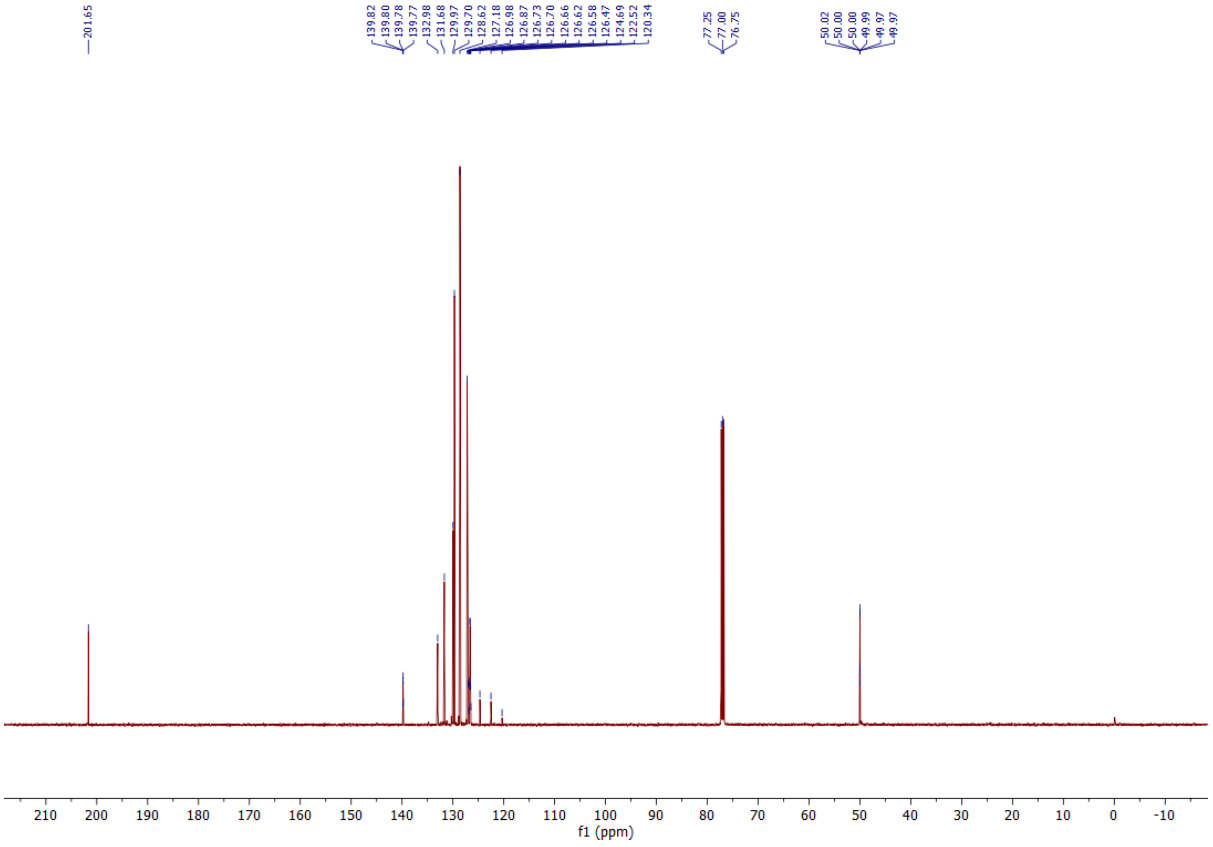
2d



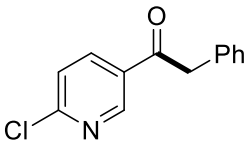
2-phenyl-1-[2-(trifluoromethyl)phenyl]ethane-1-one (2e)



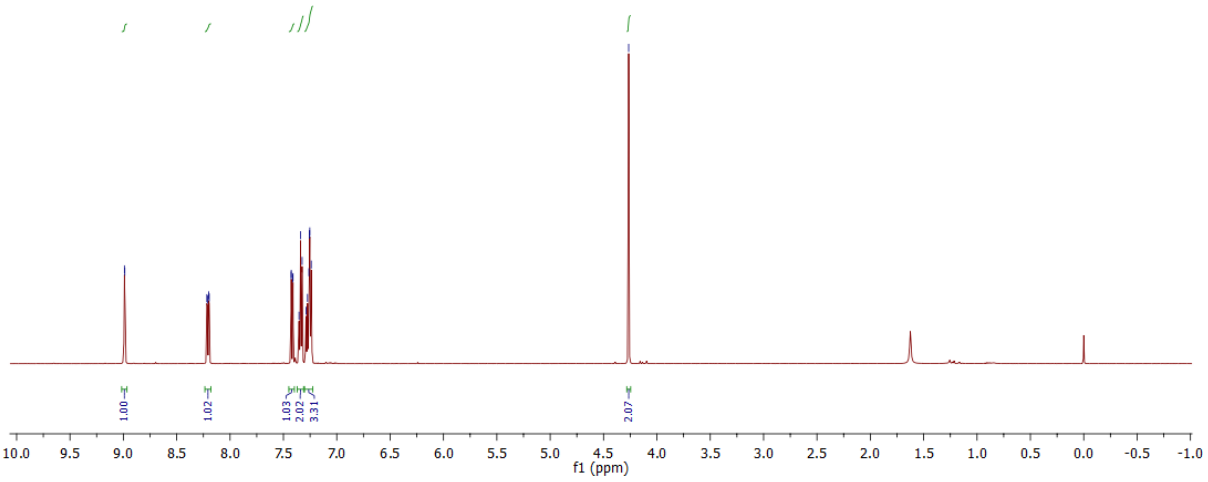
2e

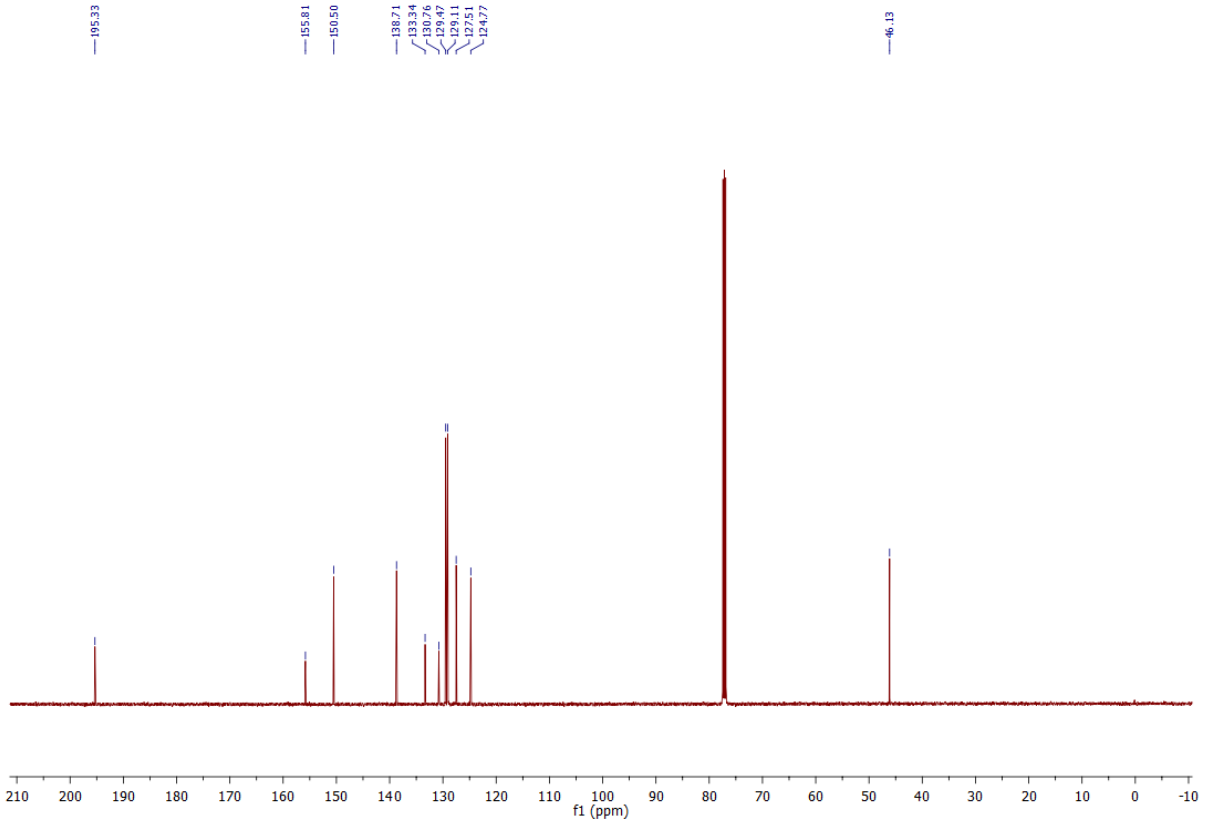


1-(6-chloropyridin-3-yl)-2-phenylethan-1-one (2f)

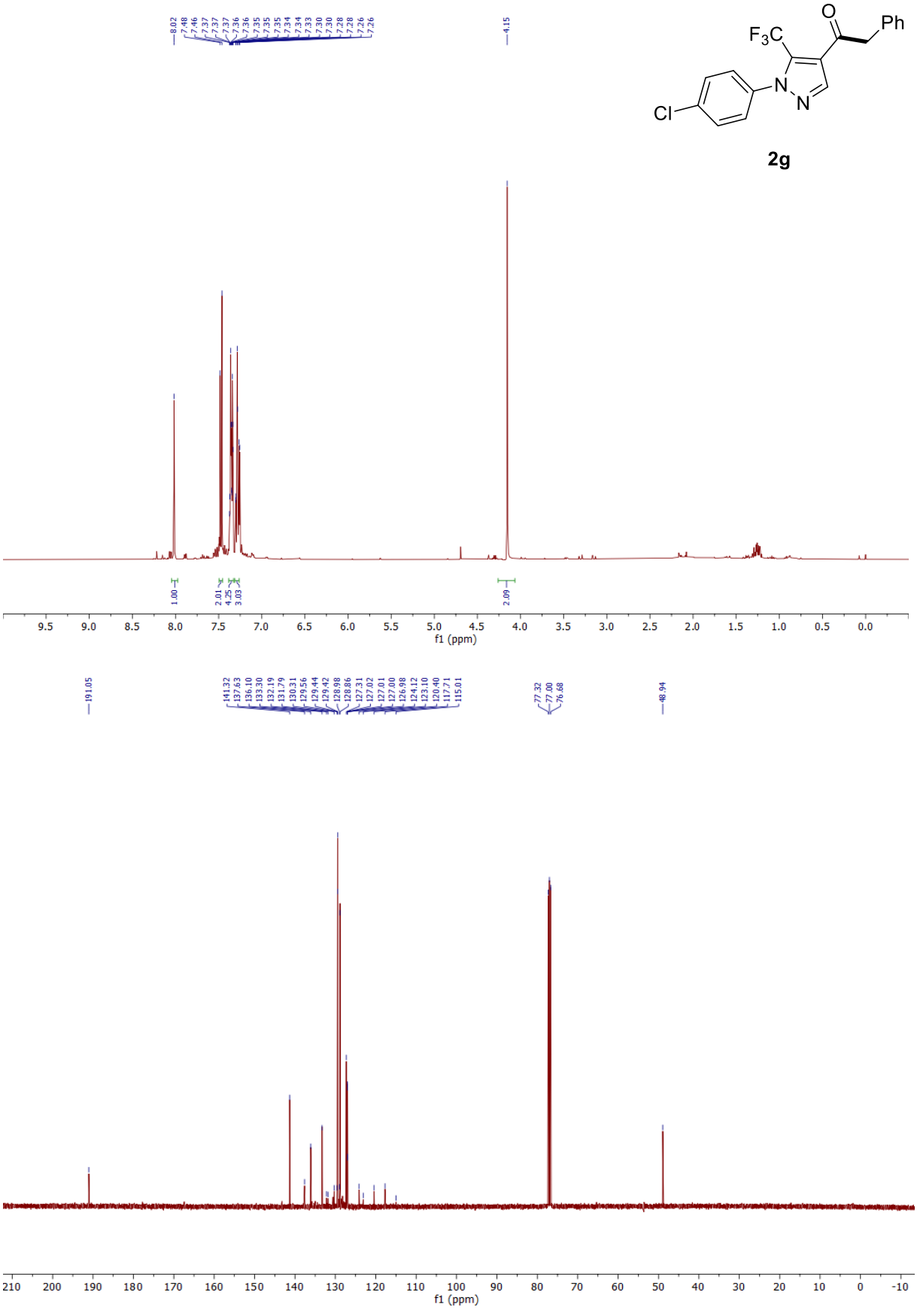


2f



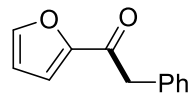


1-[1-(4-chlorophenyl)-4-(trifluoromethyl)-1H-pyrazol-3-yl]-2-phenylethane-1-one (2g)

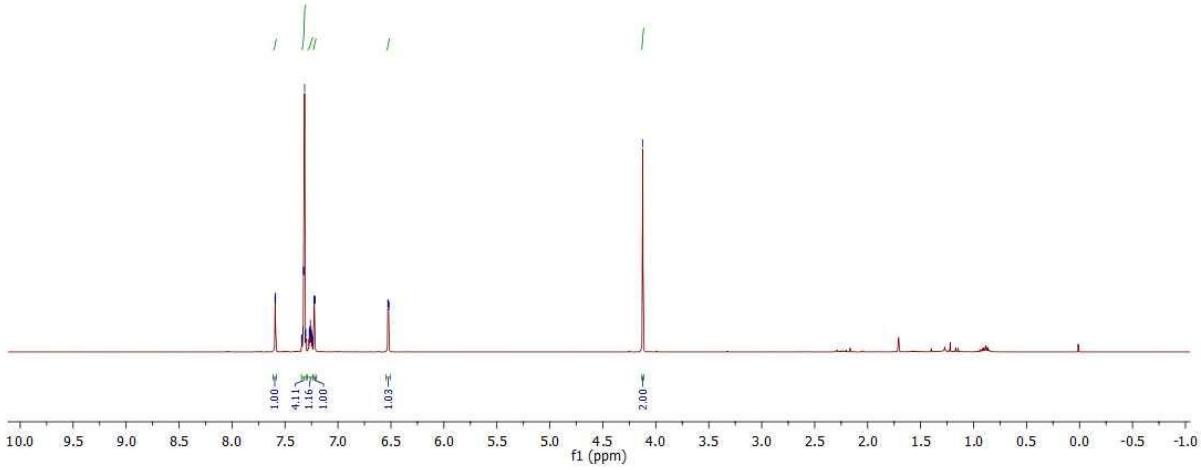


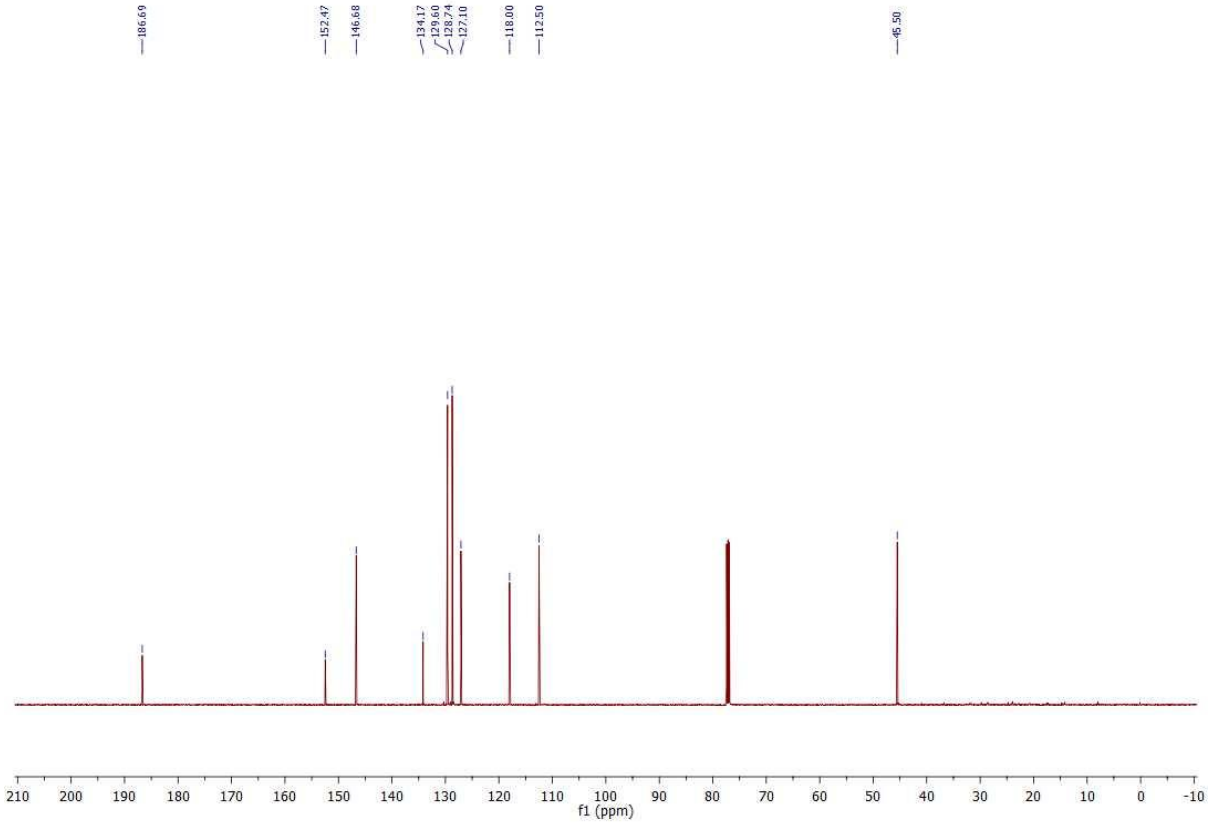
2g

1-(furan-2-yl)-2-phenylethan-1-one (2h)

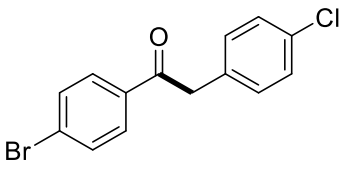


2h

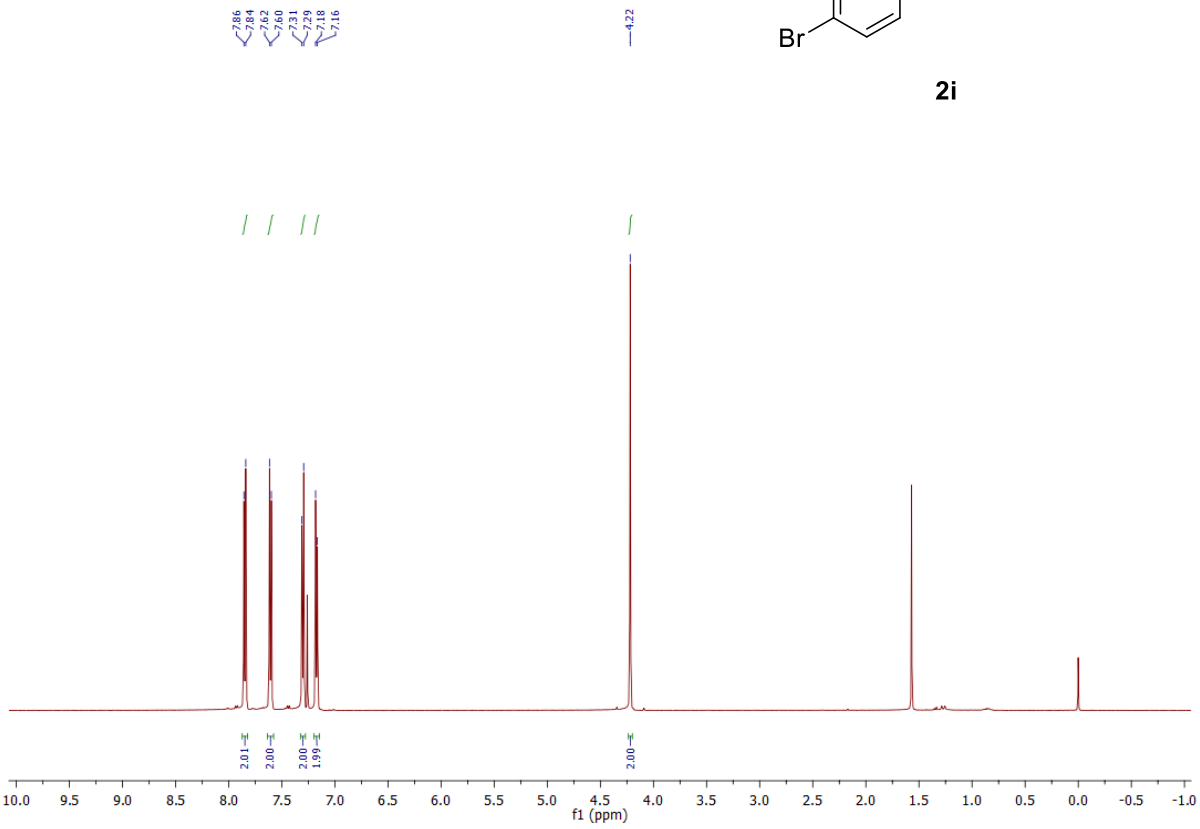


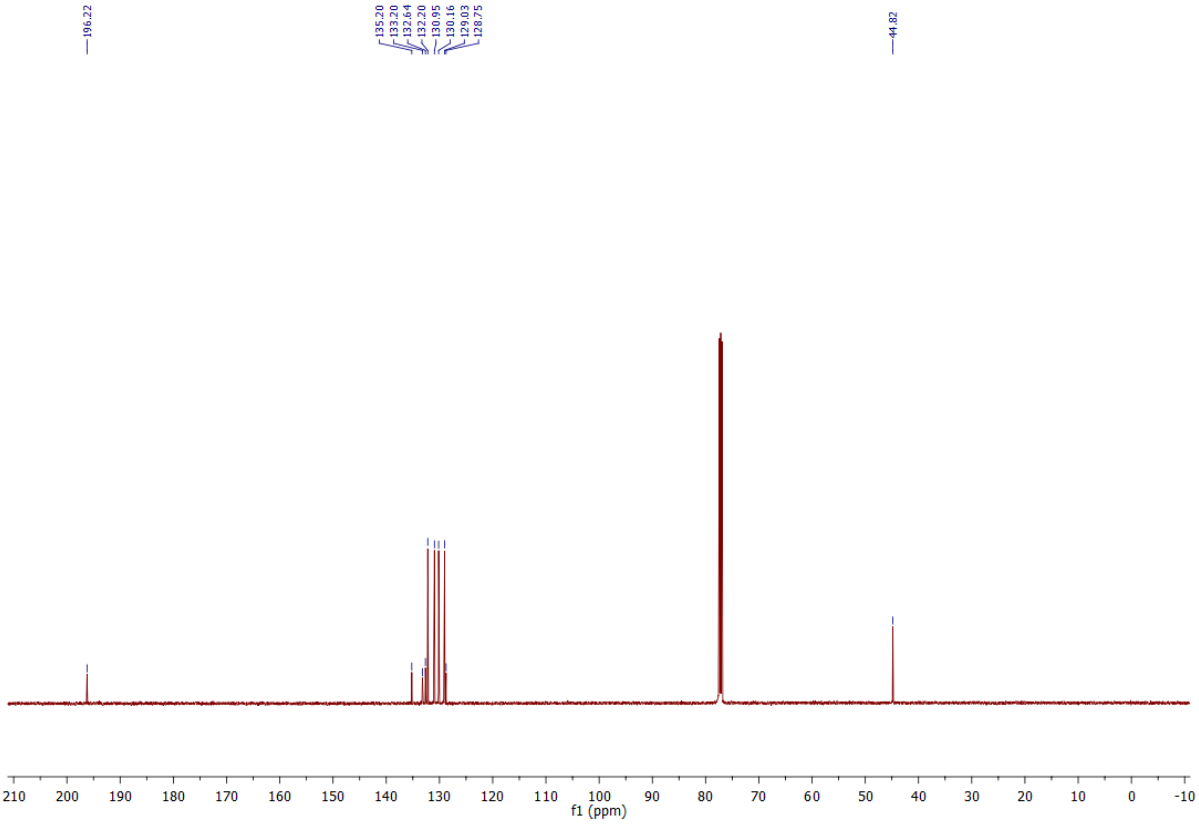


1-(4-bromophenyl)-2-(4-chlorophenyl)ethan-1-one (2i)

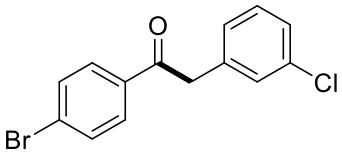


2i

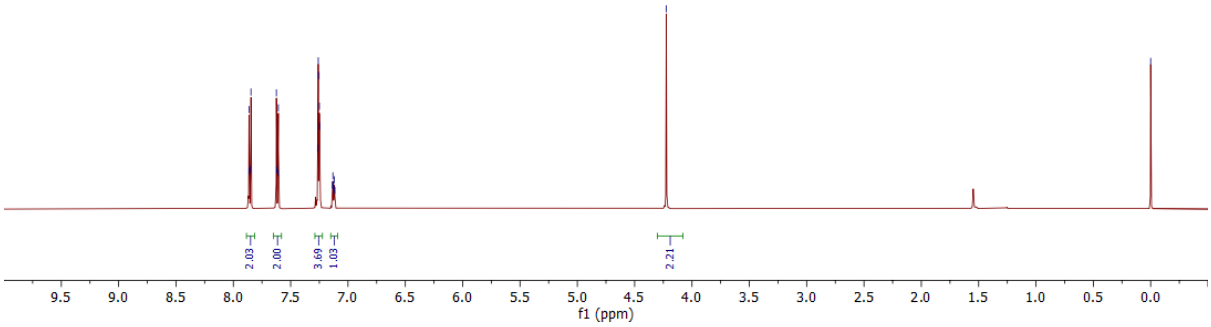


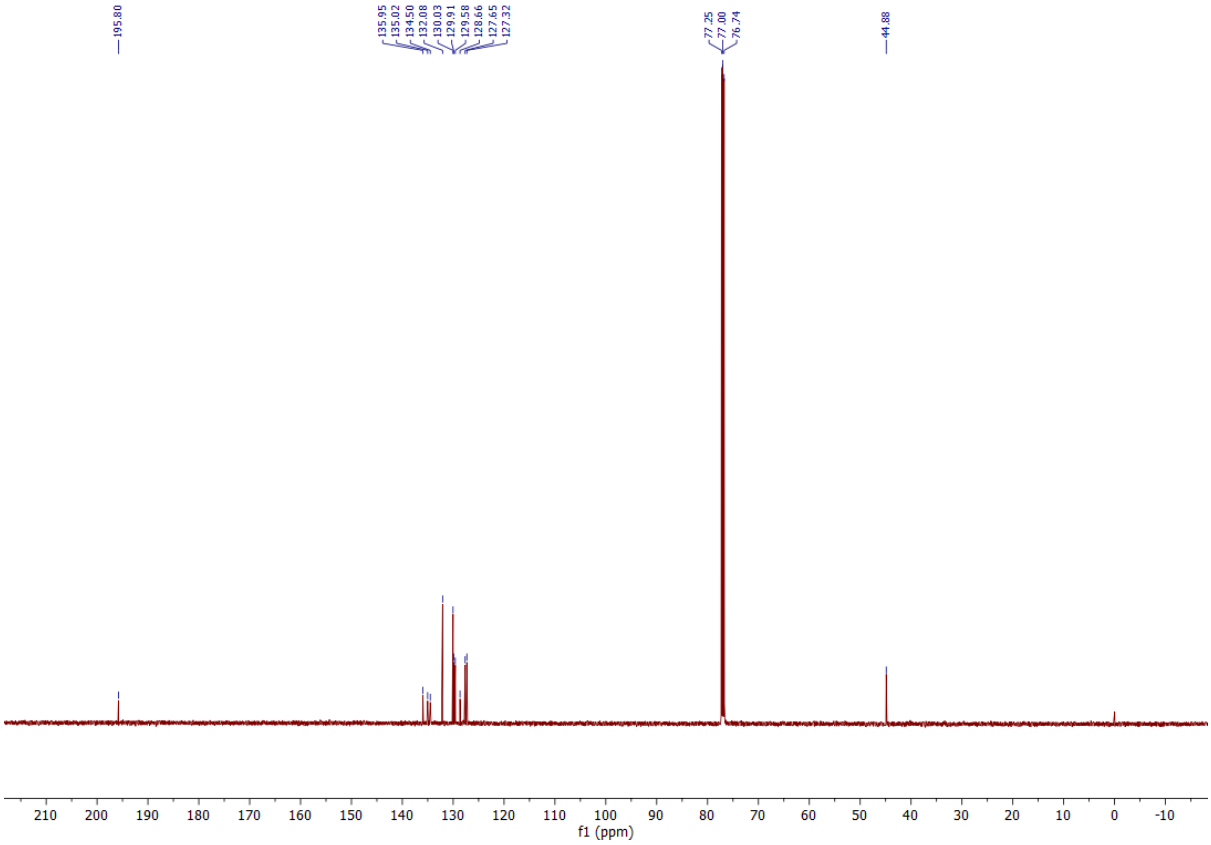


1-(4-bromophenyl)-2-(3-chlorophenyl)ethan-1-one (2j)

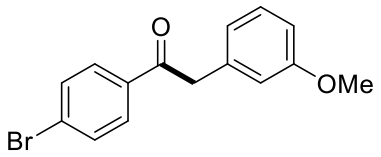


2j

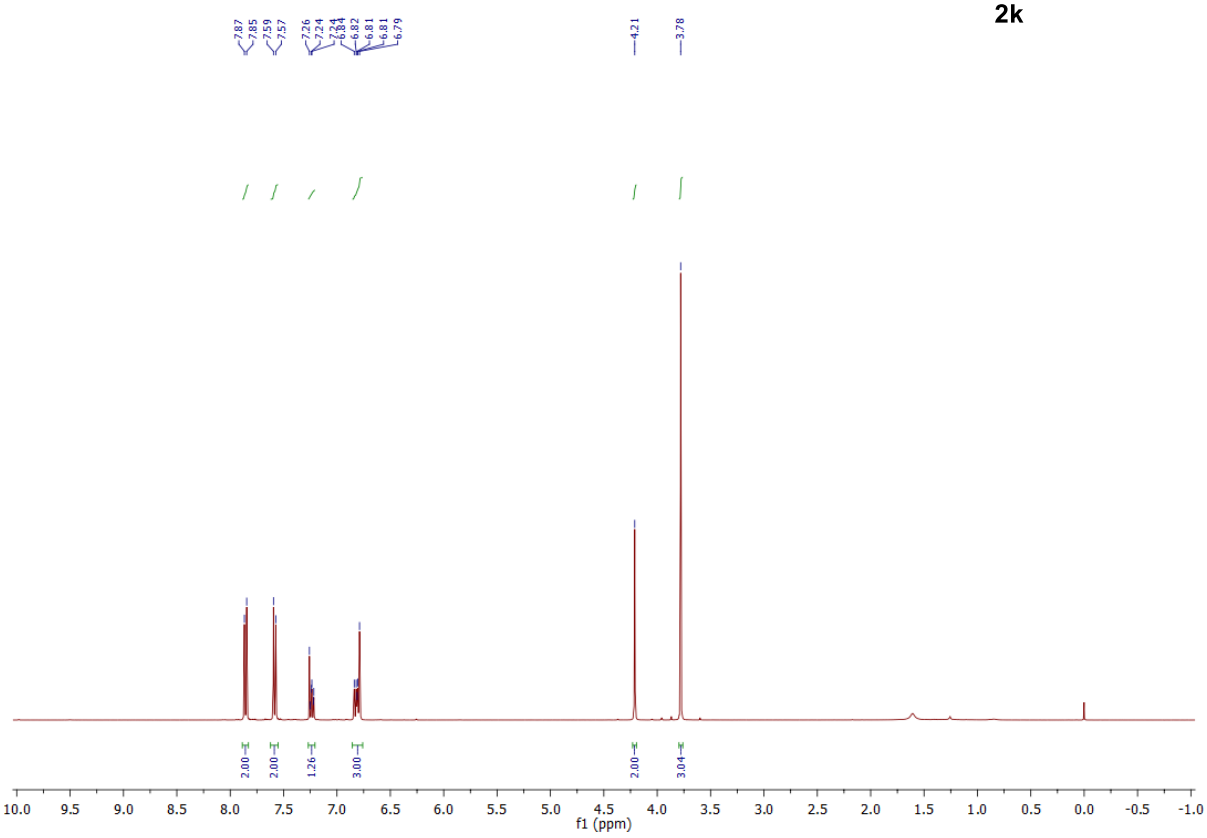


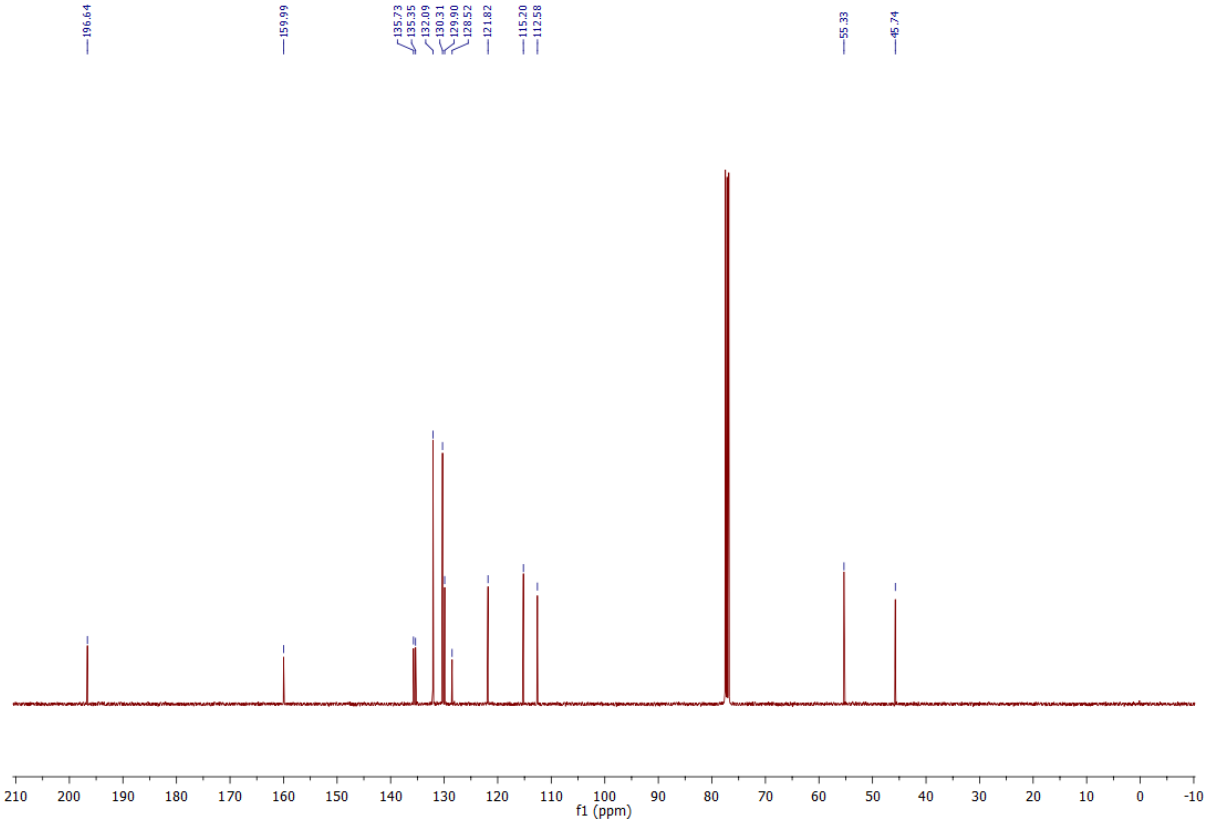


1-(4-bromophenyl)-2-(3-methoxyphenyl)ethane-1-one (2k)

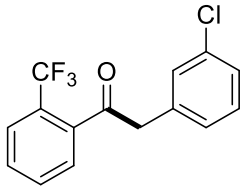


2k

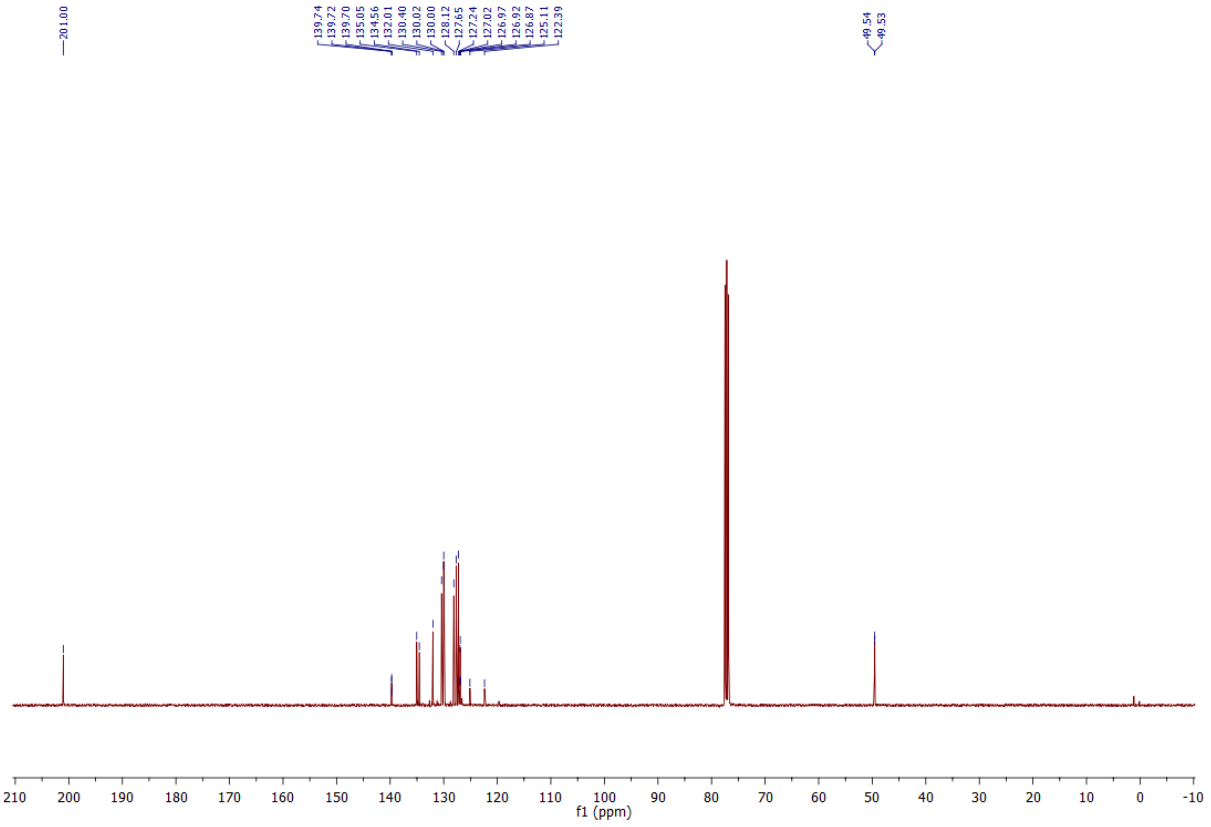




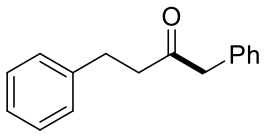
2-(3-chlorophenyl)-1-(2-(trifluoromethyl)phenyl)ethan-1-one (2l)



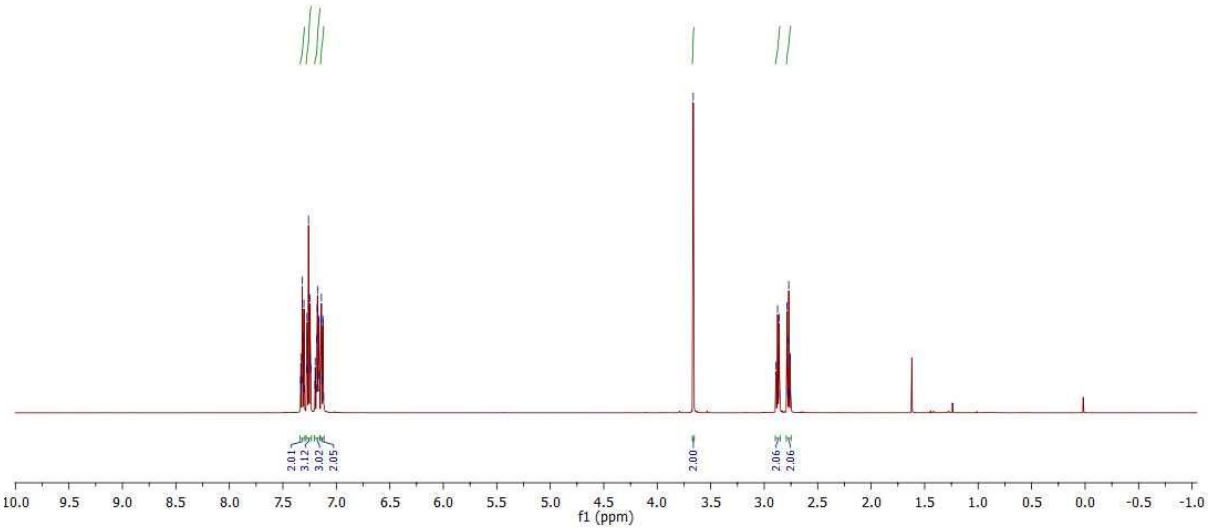
2l

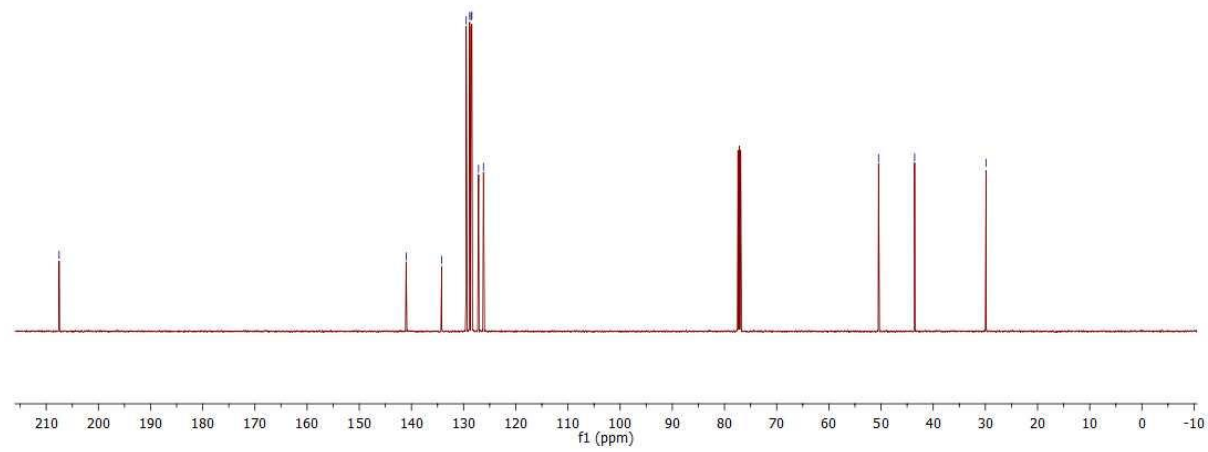


1,4-diphenylbutan-2-one (2m)

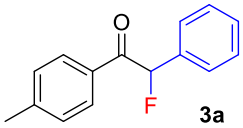


2m

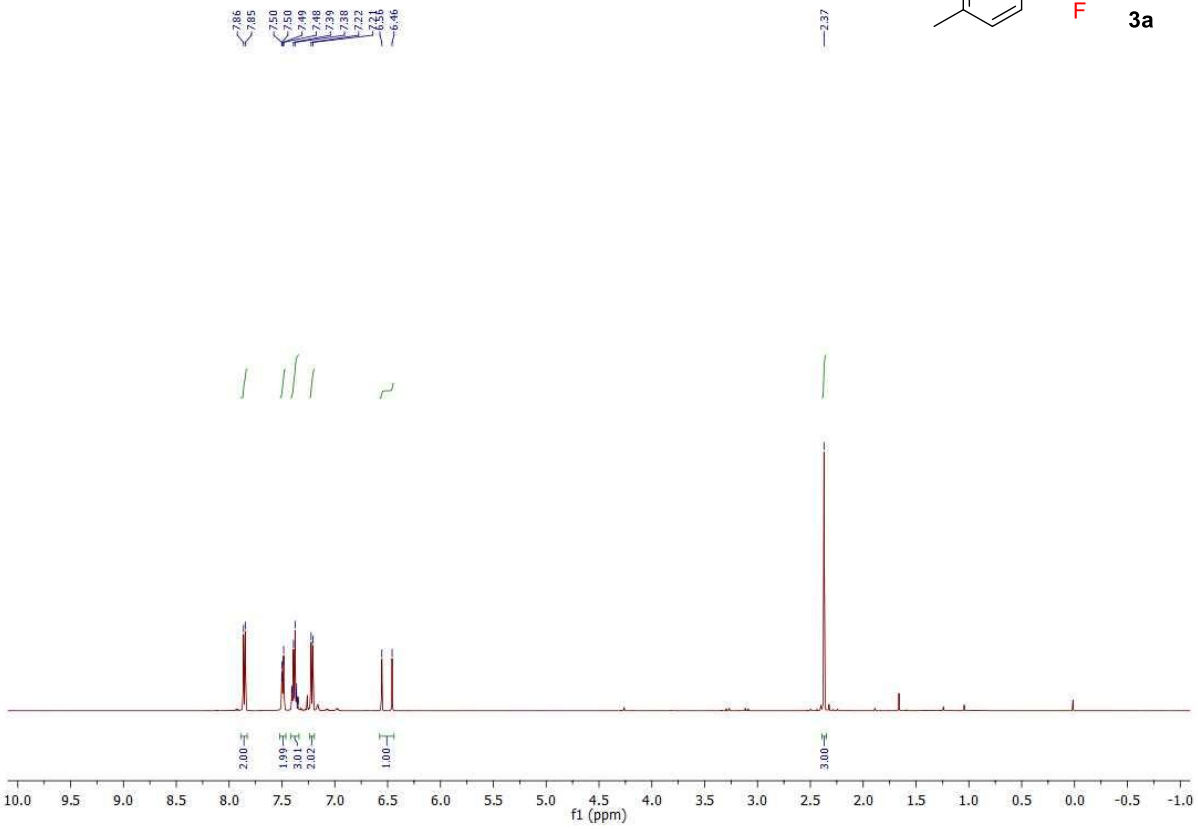


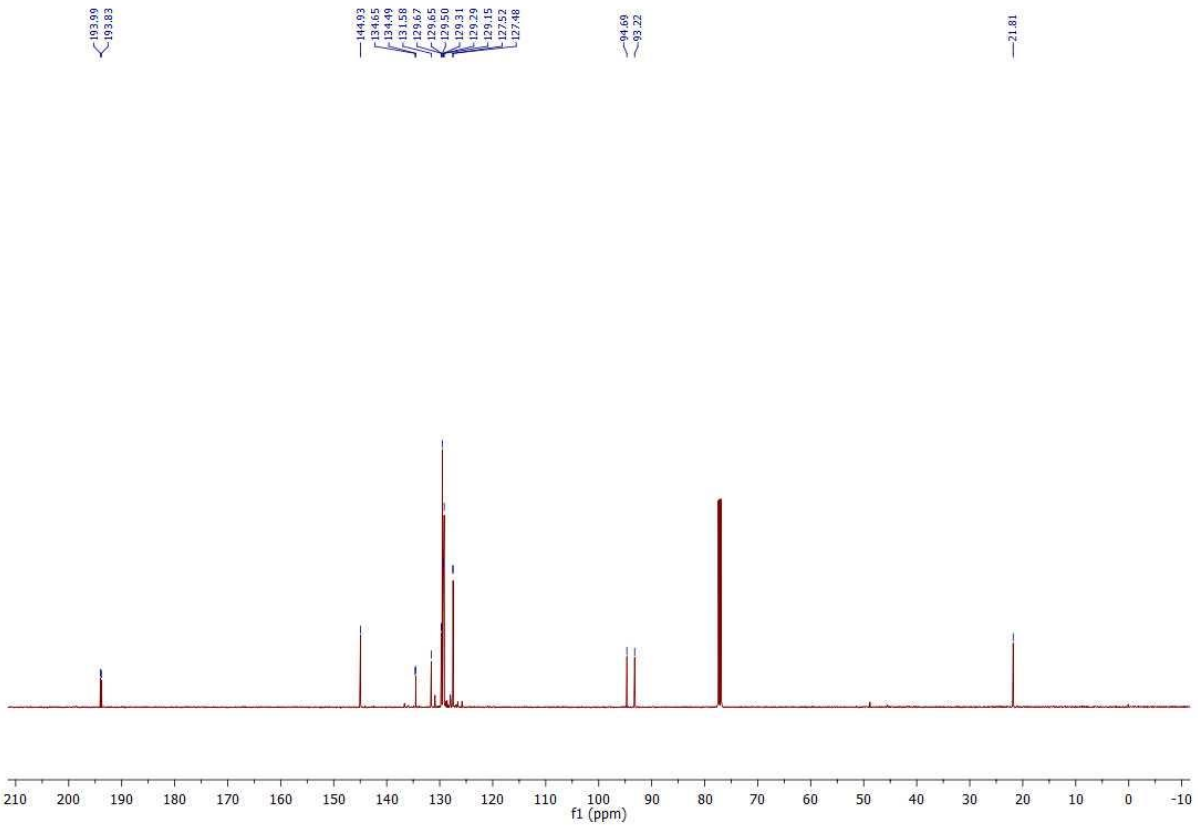


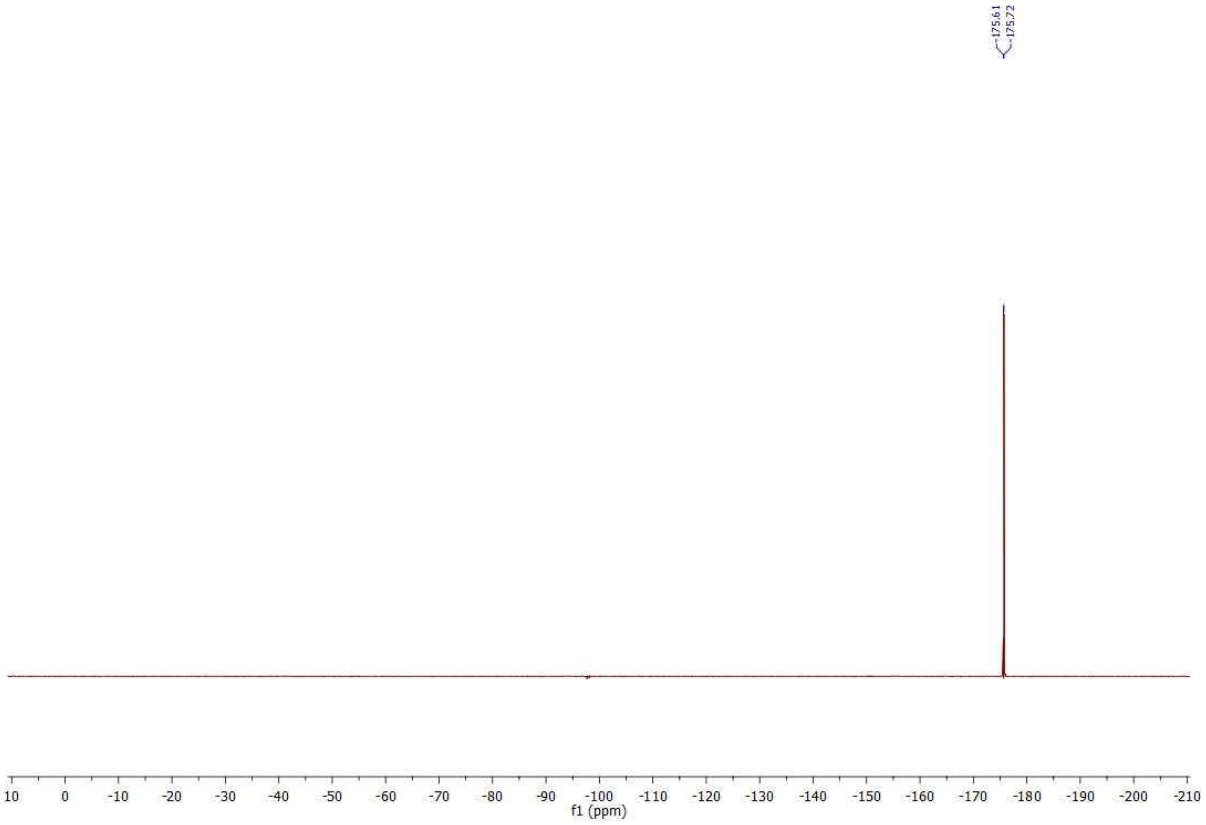
2-Fluoro-2-phenyl-1-(*p*-tolyl)ethan-1-one (3a)

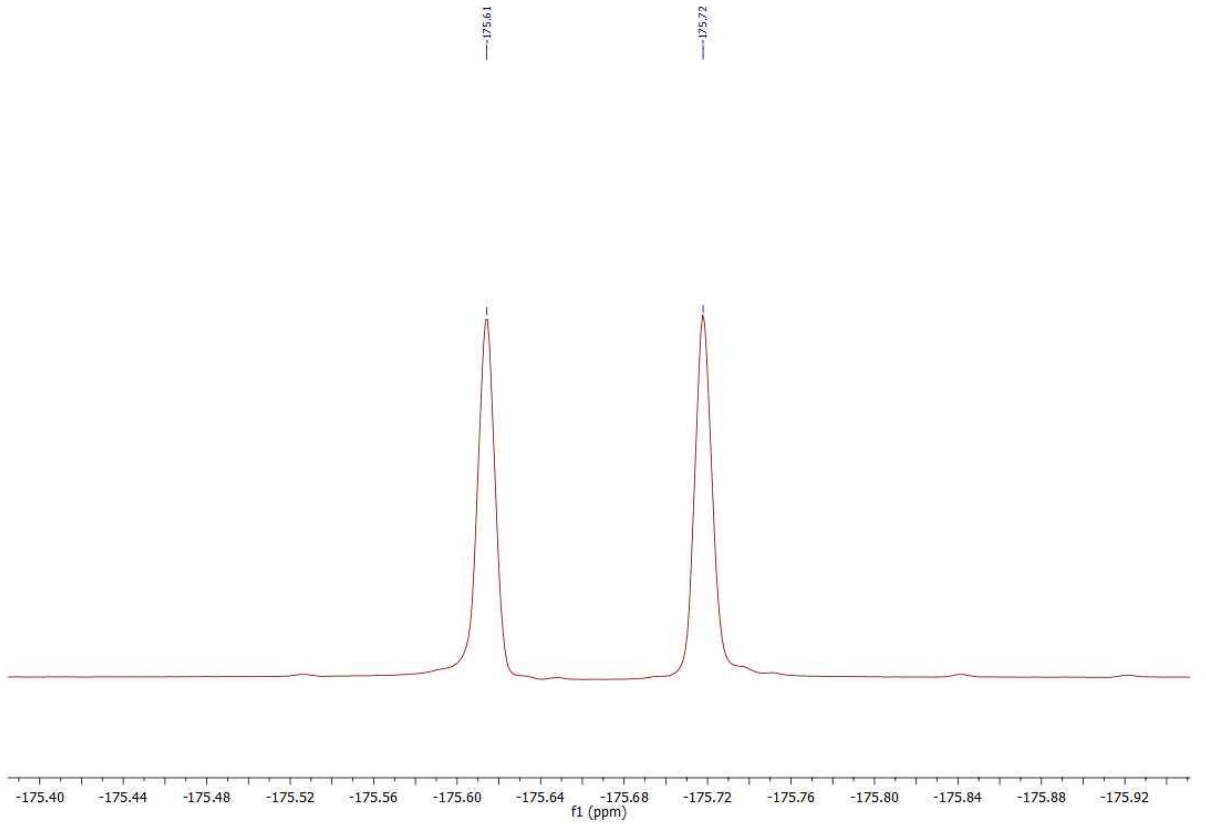


3a

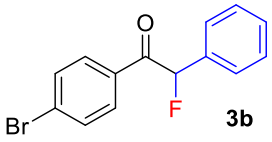




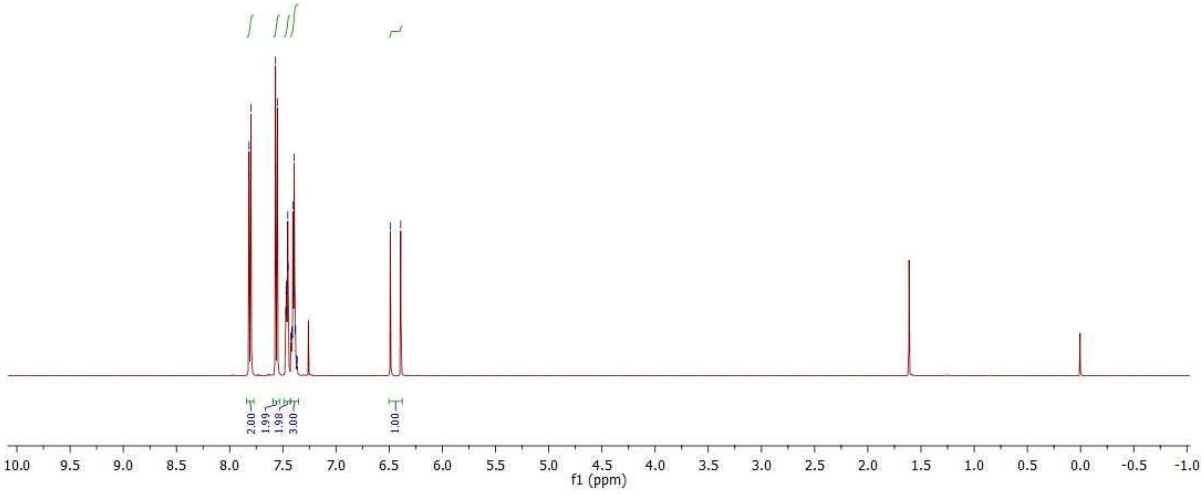

-175.61
-175.72
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

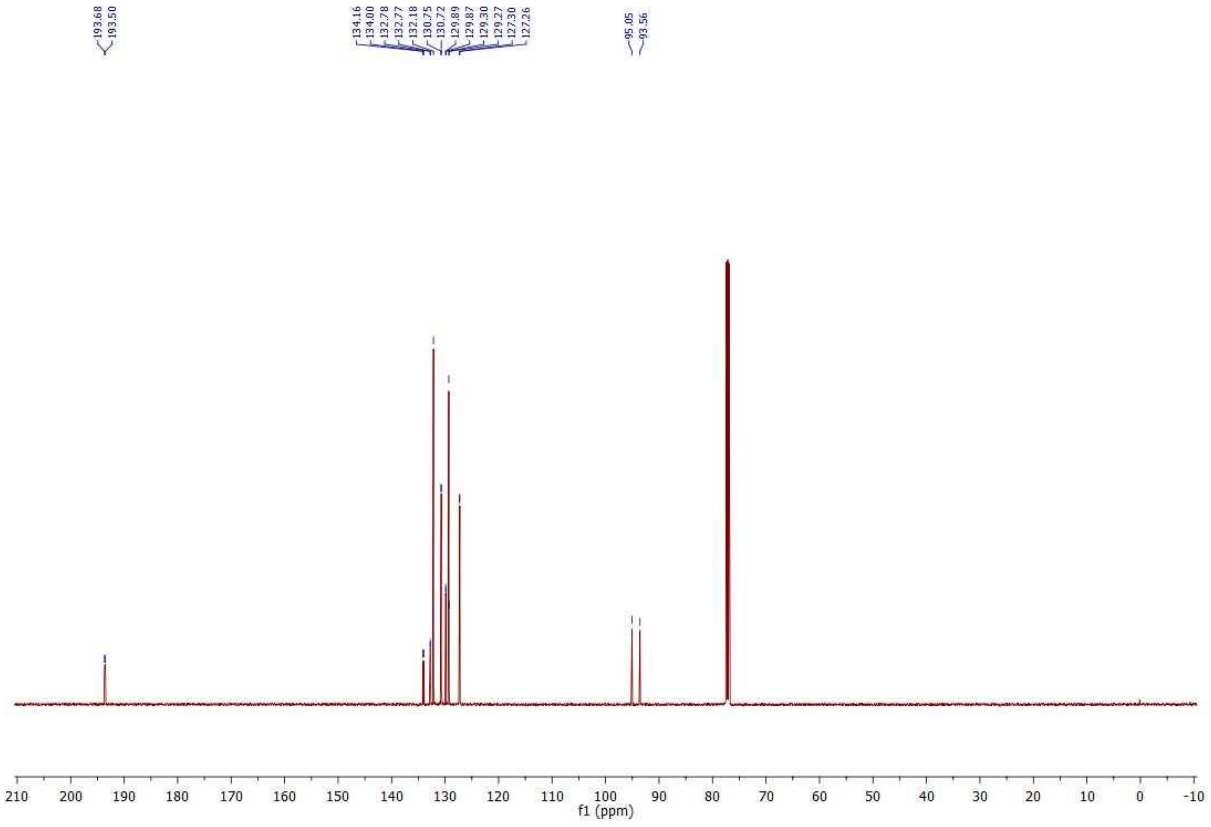

-175.61
-175.72
-175.40 -175.44 -175.48 -175.52 -175.56 -175.60 -175.64 -175.68 -175.72 -175.76 -175.80 -175.84 -175.88 -175.92
f1 (ppm)

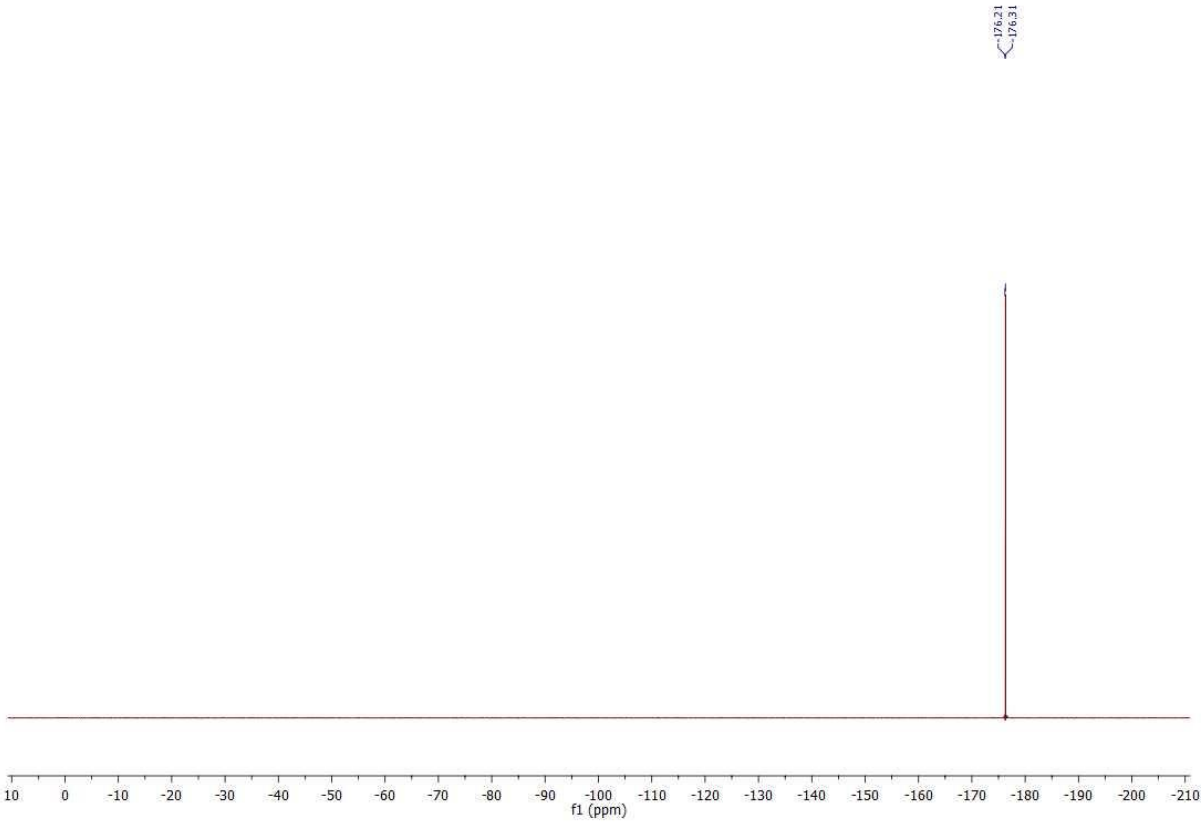
1-(4-bromophenyl)-2-fluoro-2-phenylethan-1-one (3b)

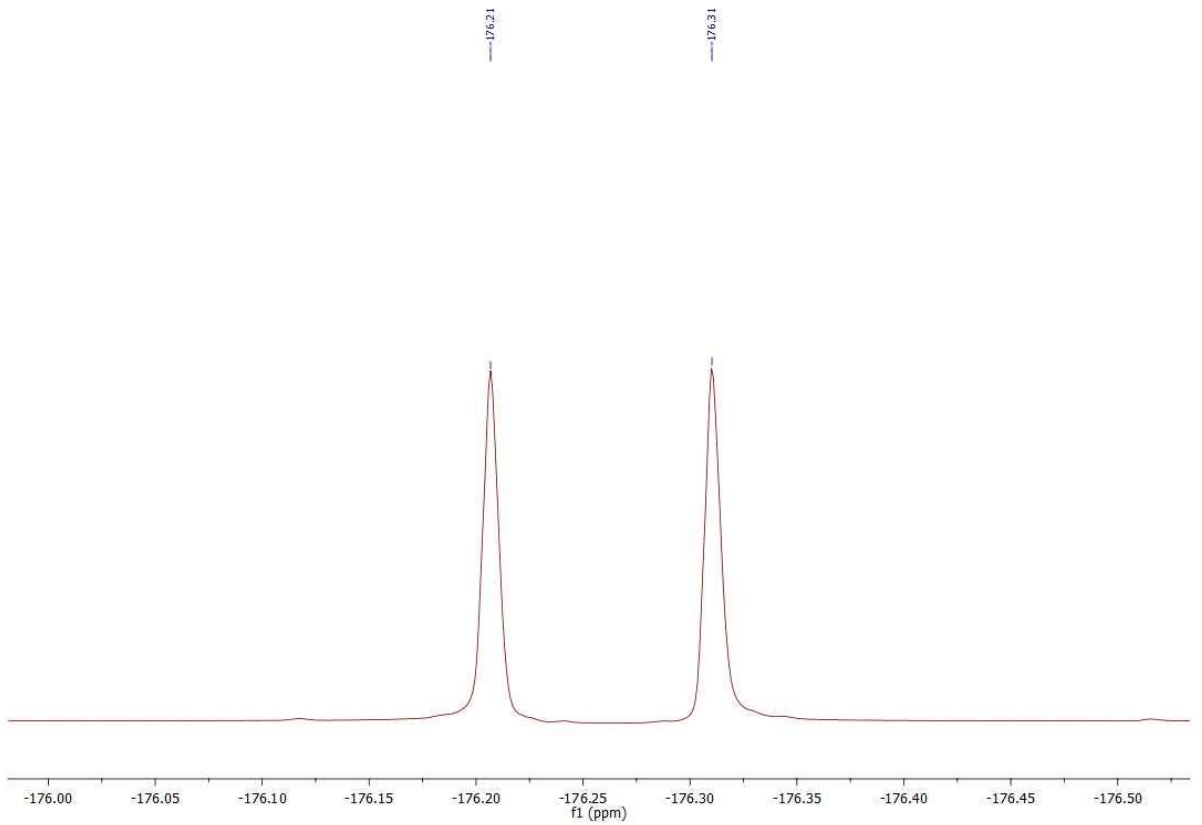


3b

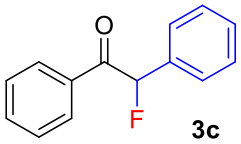




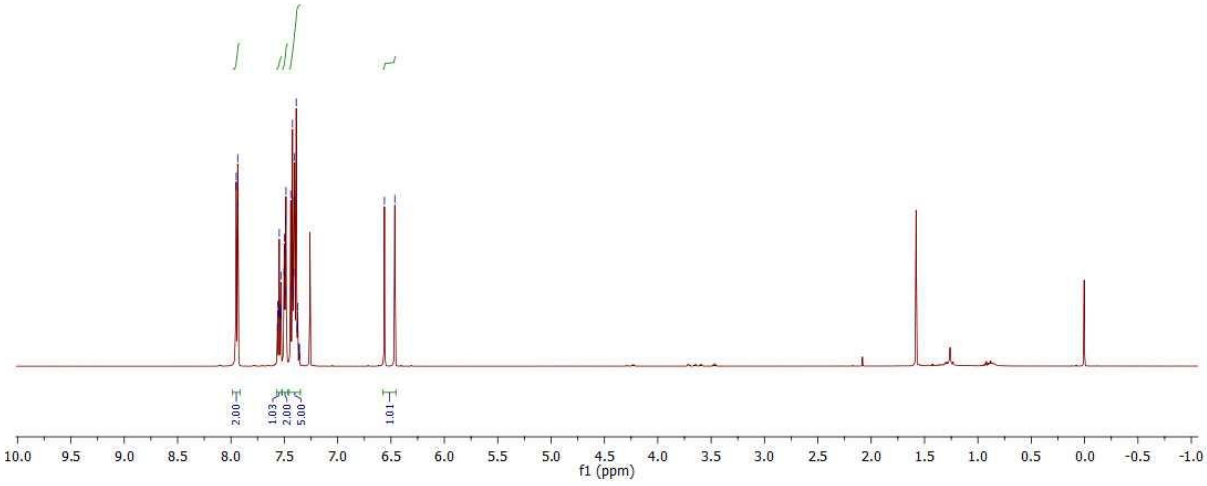

-176.21
-176.31
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

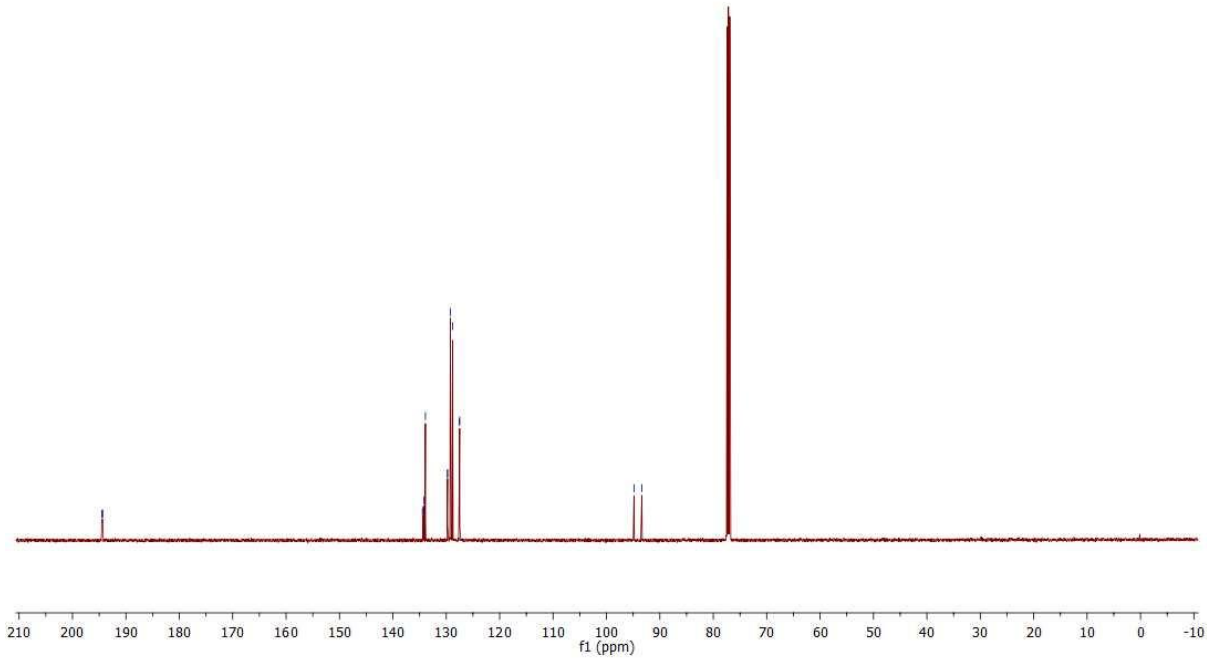

-176.21
-176.31
-176.00 -176.05 -176.10 -176.15 -176.20 -176.25 -176.30 -176.35 -176.40 -176.45 -176.50
f1 (ppm)

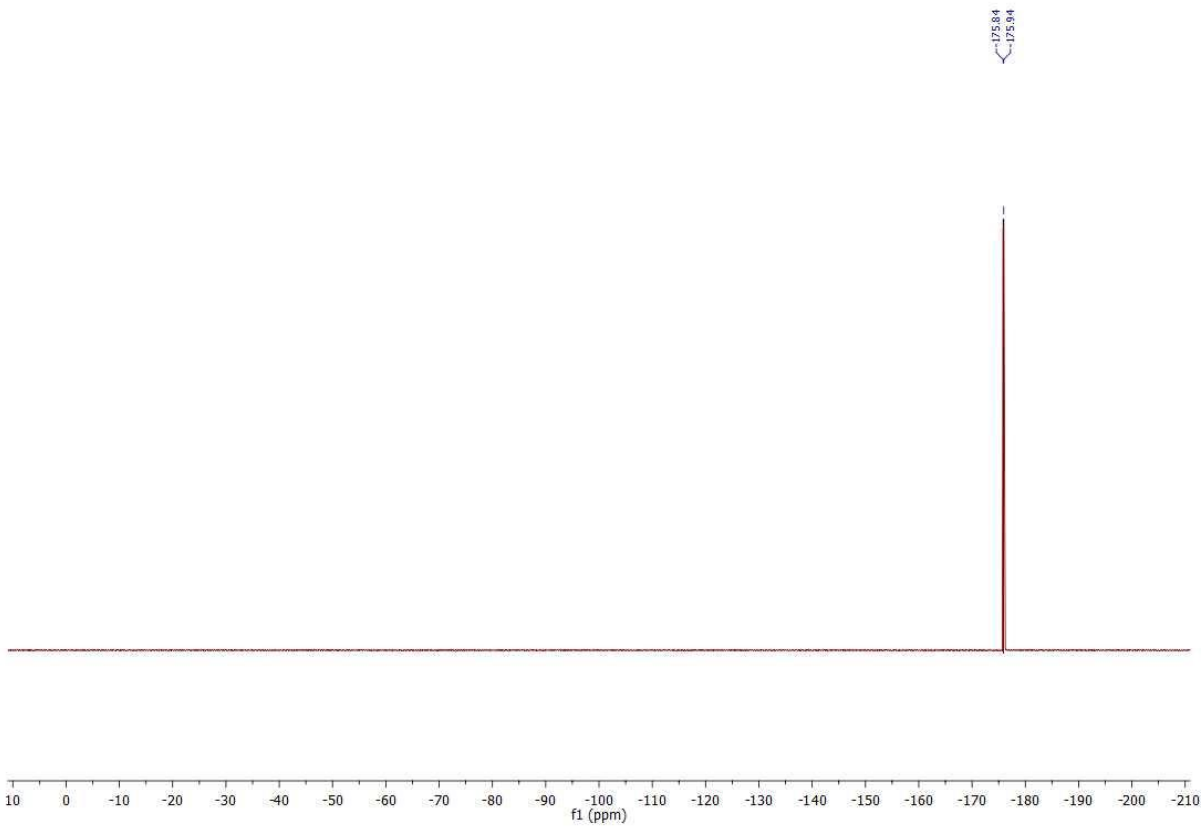
2-Fluoro-1,2-diphenylethan-1-one (3c)

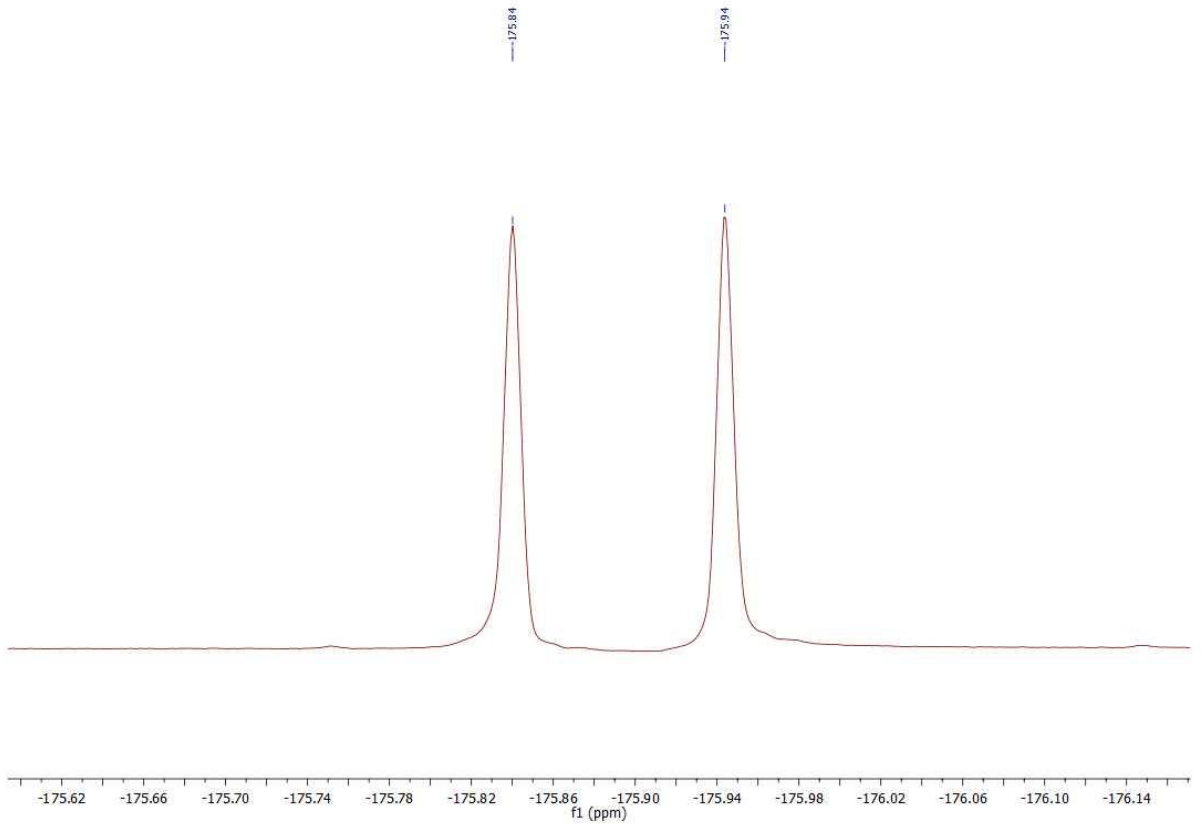


3c

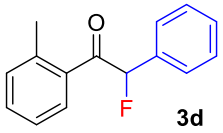




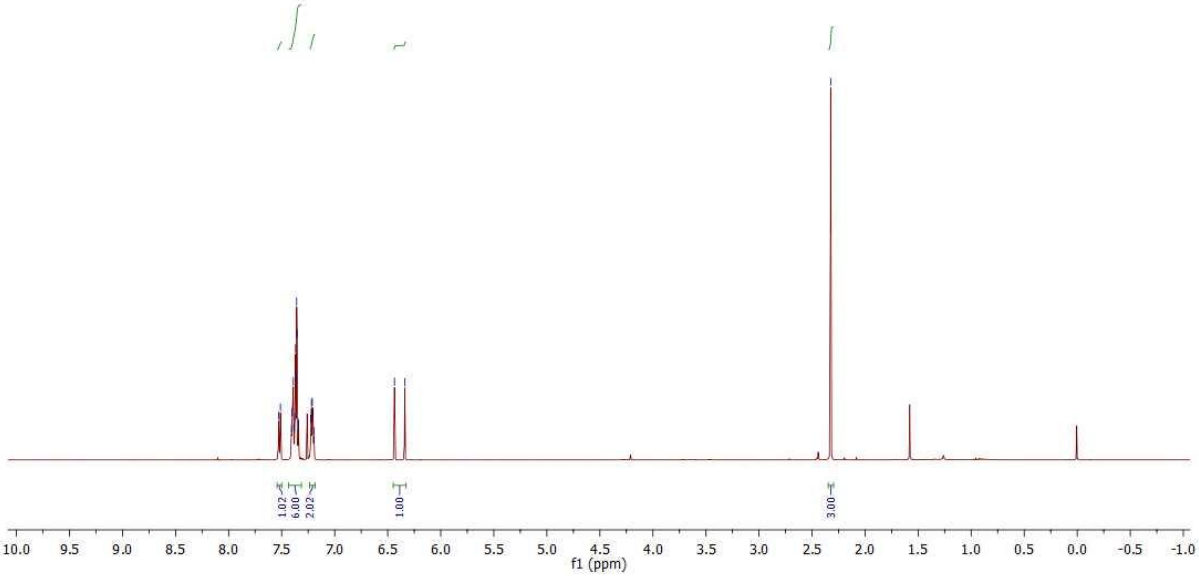

175.84
175.94
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

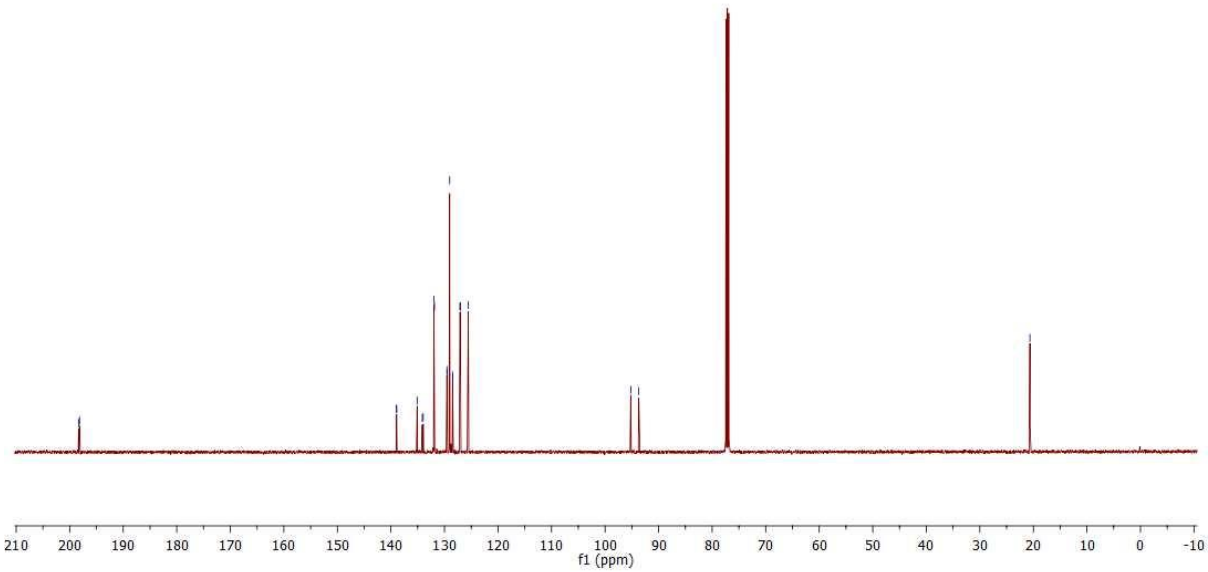

175.84
175.94
-175.62 -175.66 -175.70 -175.74 -175.78 -175.82 -175.86 -175.90 -175.94 -175.98 -176.02 -176.06 -176.10 -176.14
f1 (ppm)

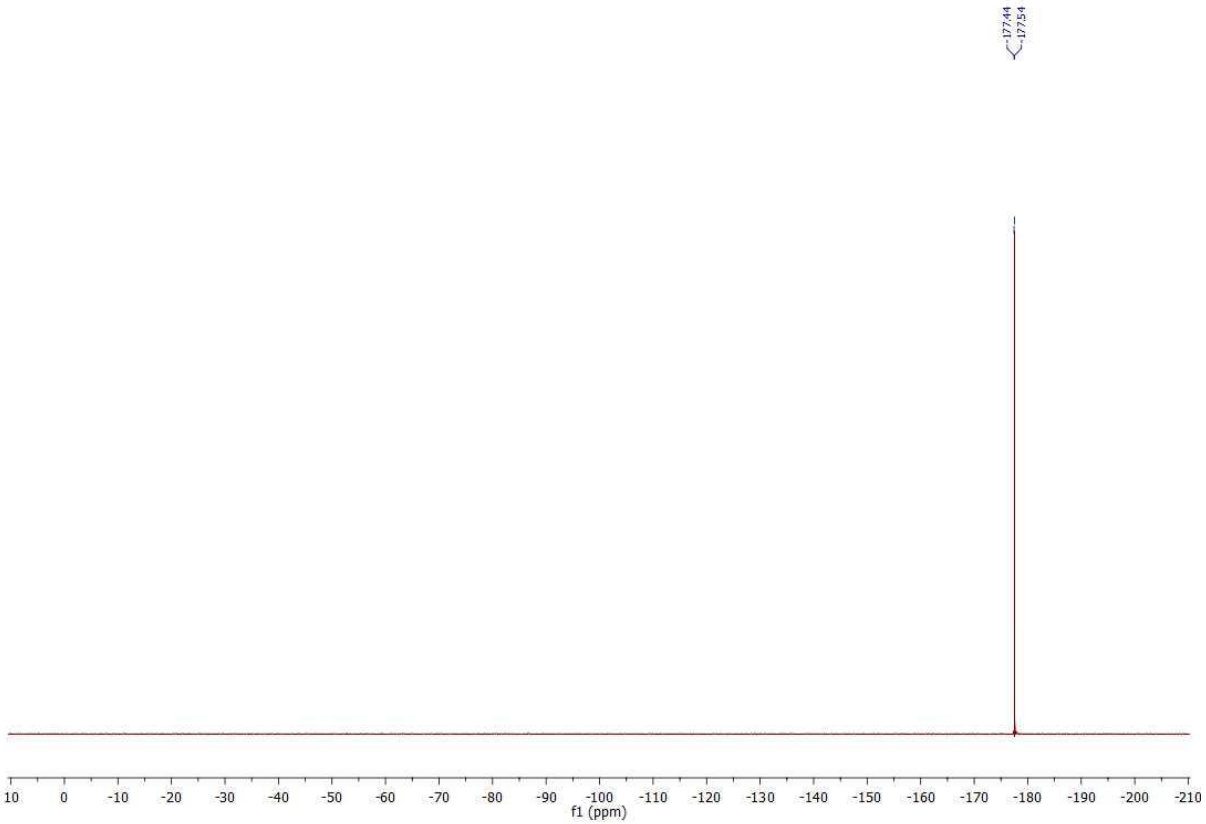
2-Fluoro-2-phenyl-1-(*o*-tolyl)ethan-1-one (3d)

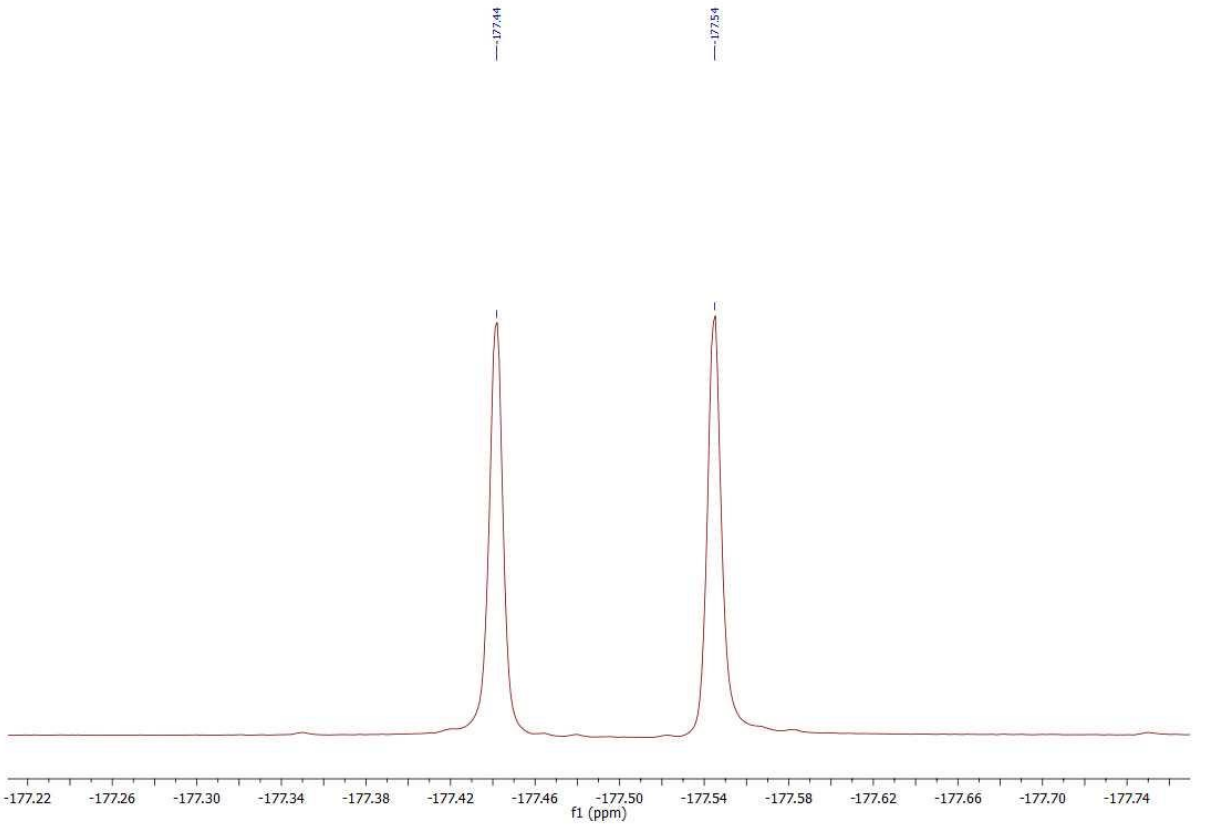


3d

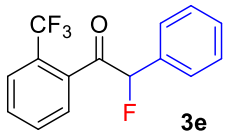





-177.44
-177.54
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

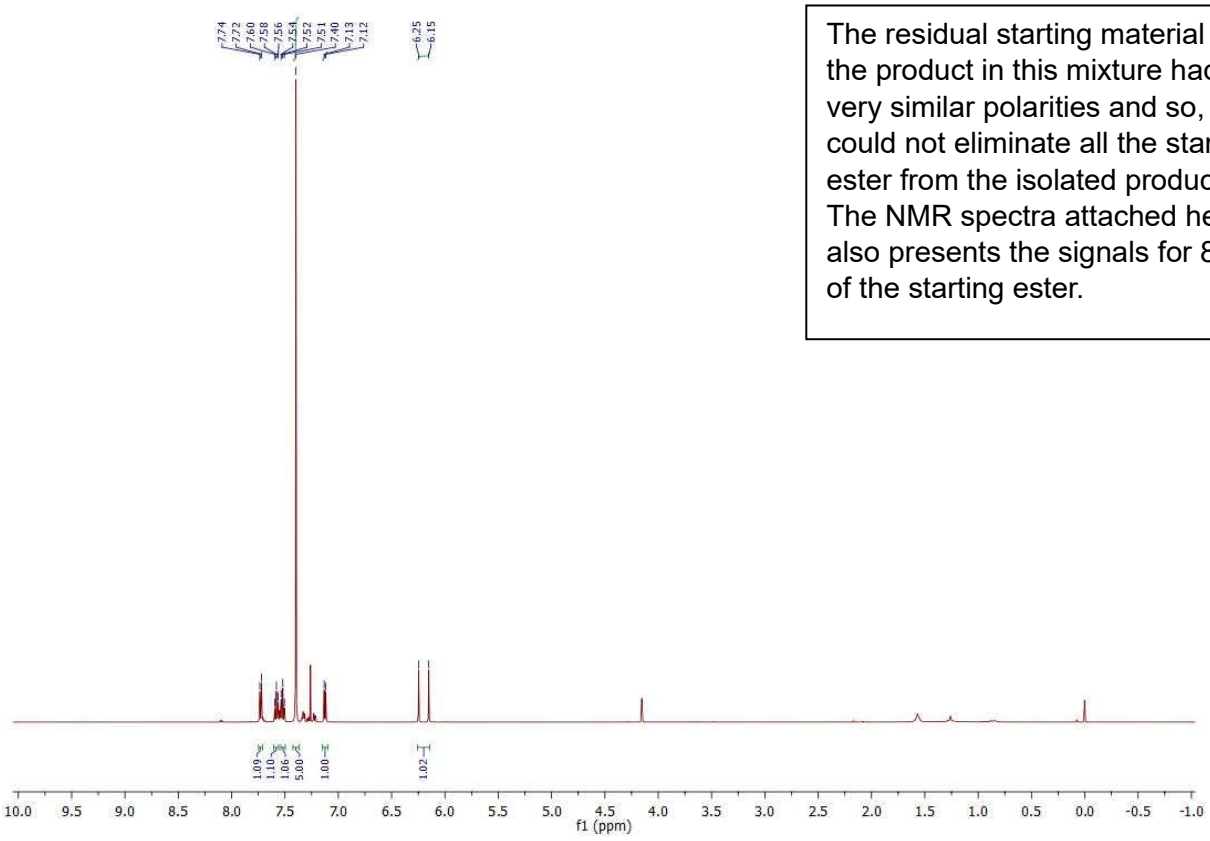

-177.44
-177.54
-177.22 -177.26 -177.30 -177.34 -177.38 -177.42 -177.46 -177.50 -177.54 -177.58 -177.62 -177.66 -177.70 -177.74
f1 (ppm)

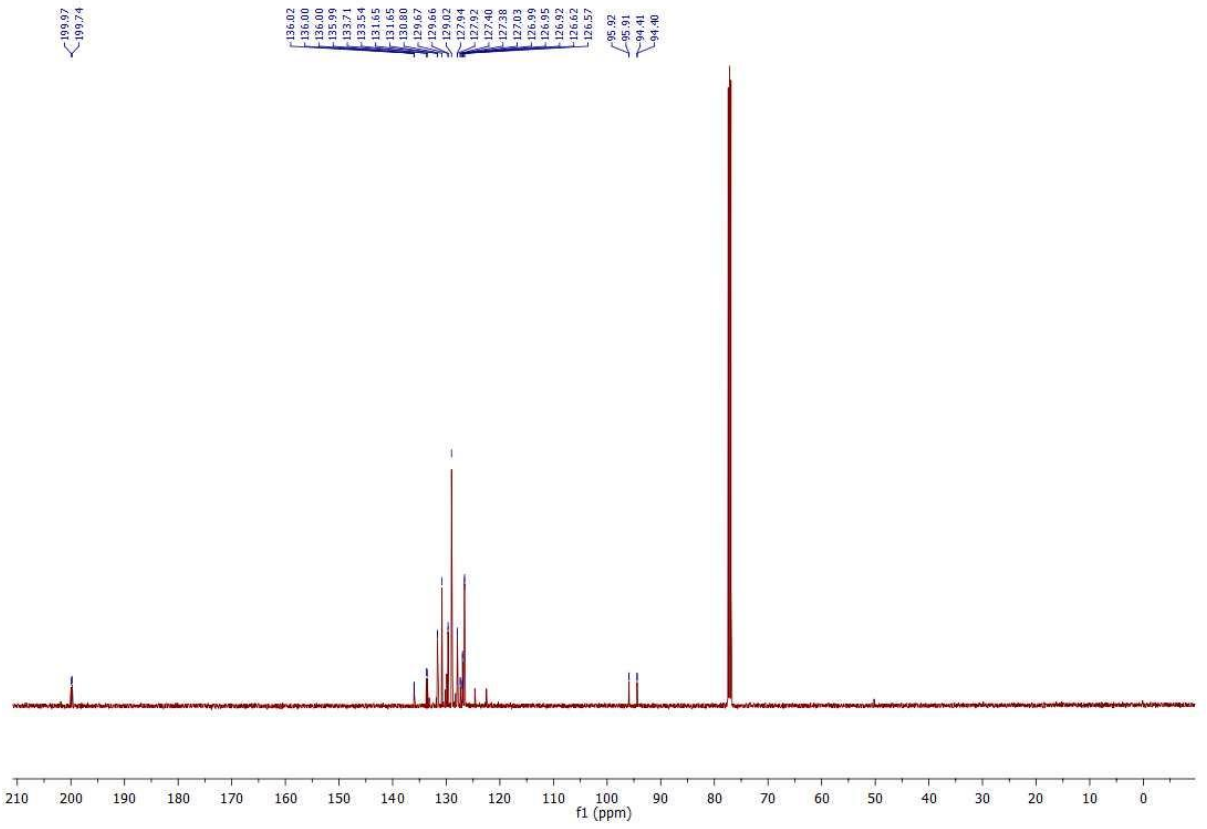
2-Fluoro-2-phenyl-1-(2-(trifluoromethyl)phenyl)ethan-1-one (3e)

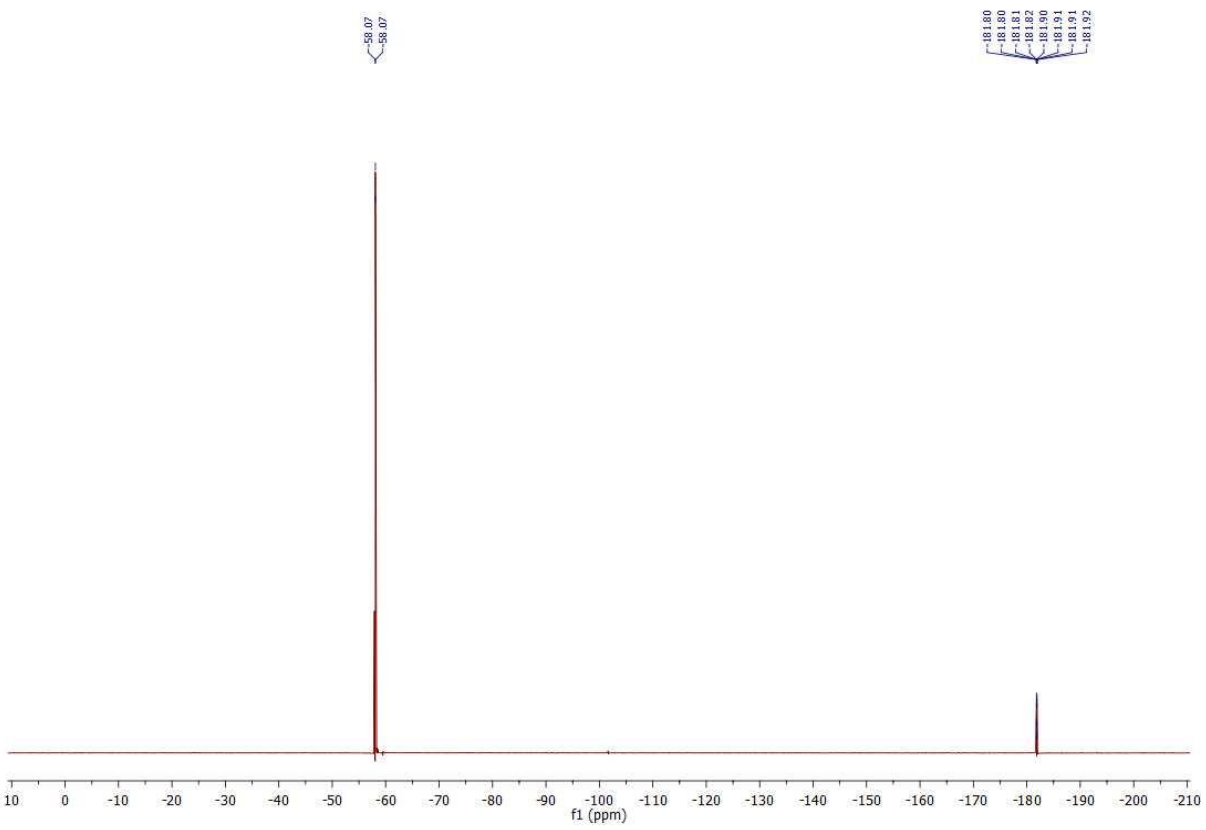


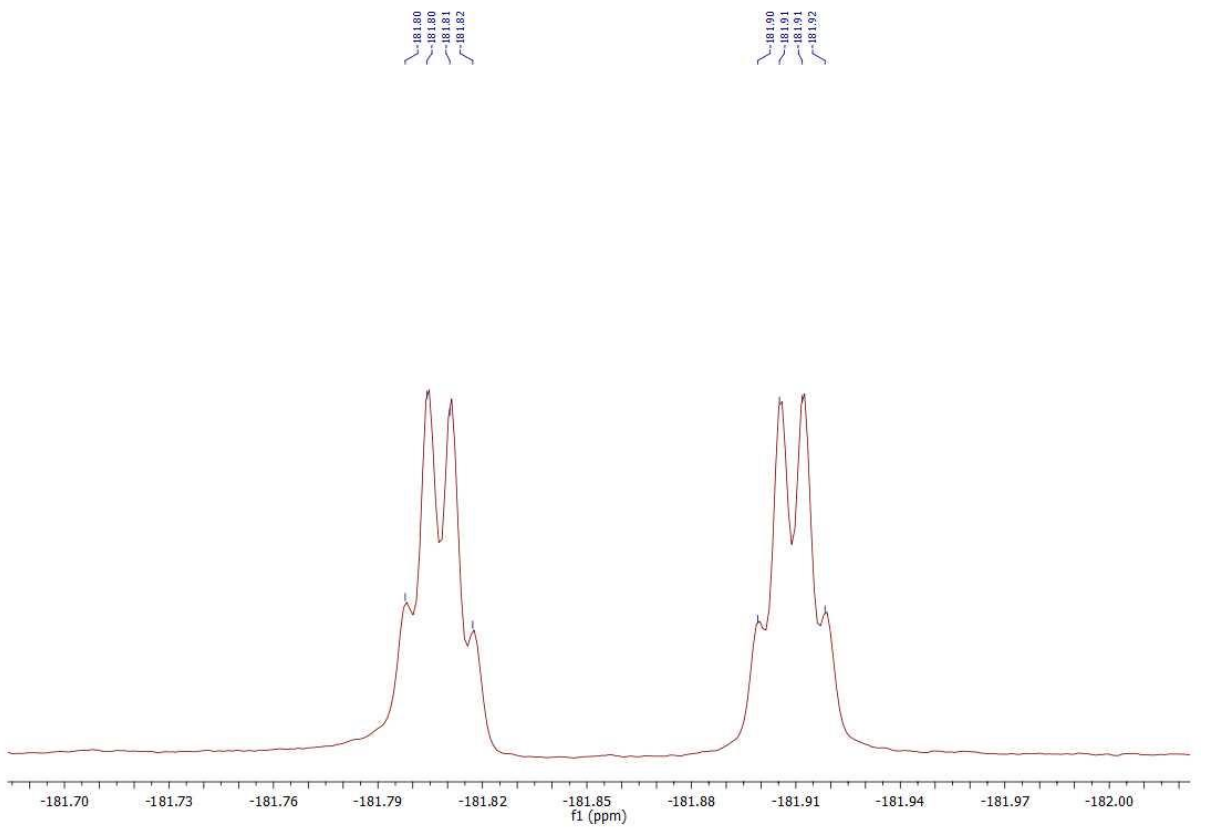
3e

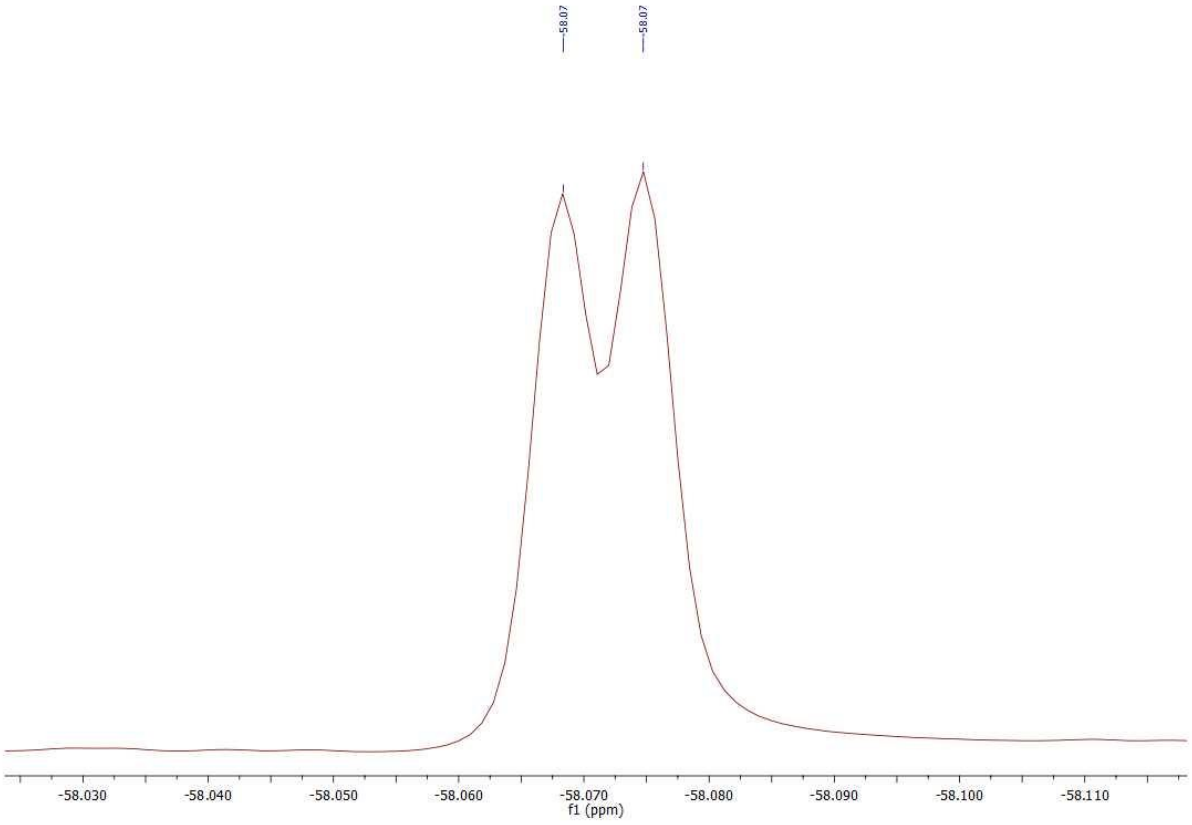
The residual starting material and the product in this mixture had very similar polarities and so, we could not eliminate all the starting ester from the isolated product. The NMR spectra attached here also presents the signals for 8% of the starting ester.



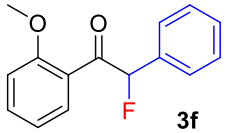



-58.07
-58.07
-181.80
-181.80
-181.81
-181.82
-181.90
-181.91
-181.91
-181.92
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

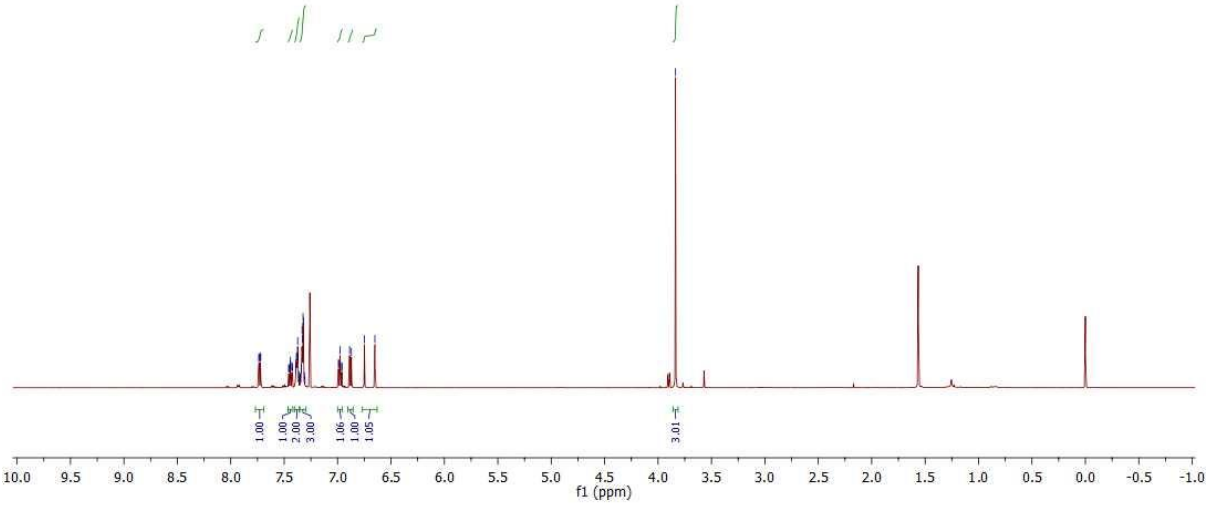

-181.80
-181.80
-181.81
-181.82
-181.90
-181.91
-181.91
-181.92
-181.70 -181.73 -181.76 -181.79 -181.82 -181.85 -181.88 -181.91 -181.94 -181.97 -182.00
f1 (ppm)

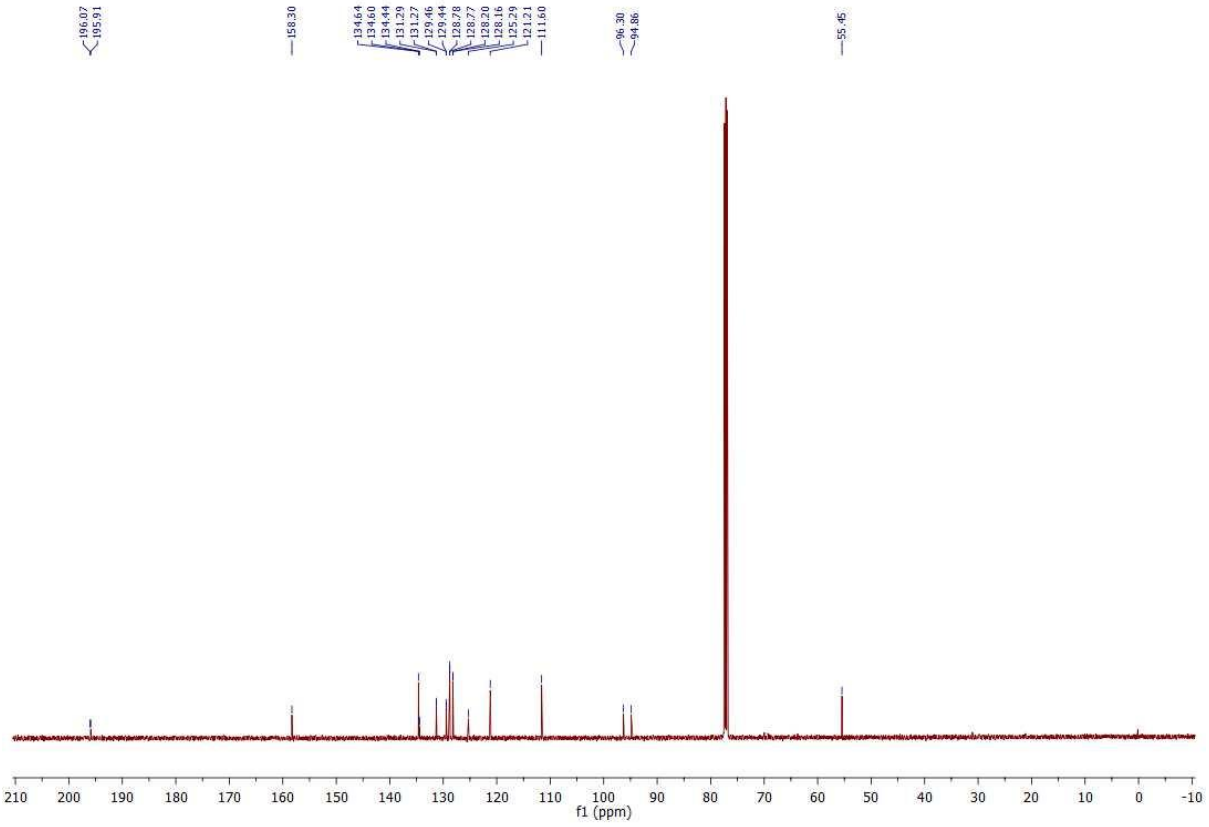

-58.07
-58.07
-58.030
-58.040
-58.050
-58.060
-58.070
-58.080
-58.090
-58.100
-58.110
f1 (ppm)

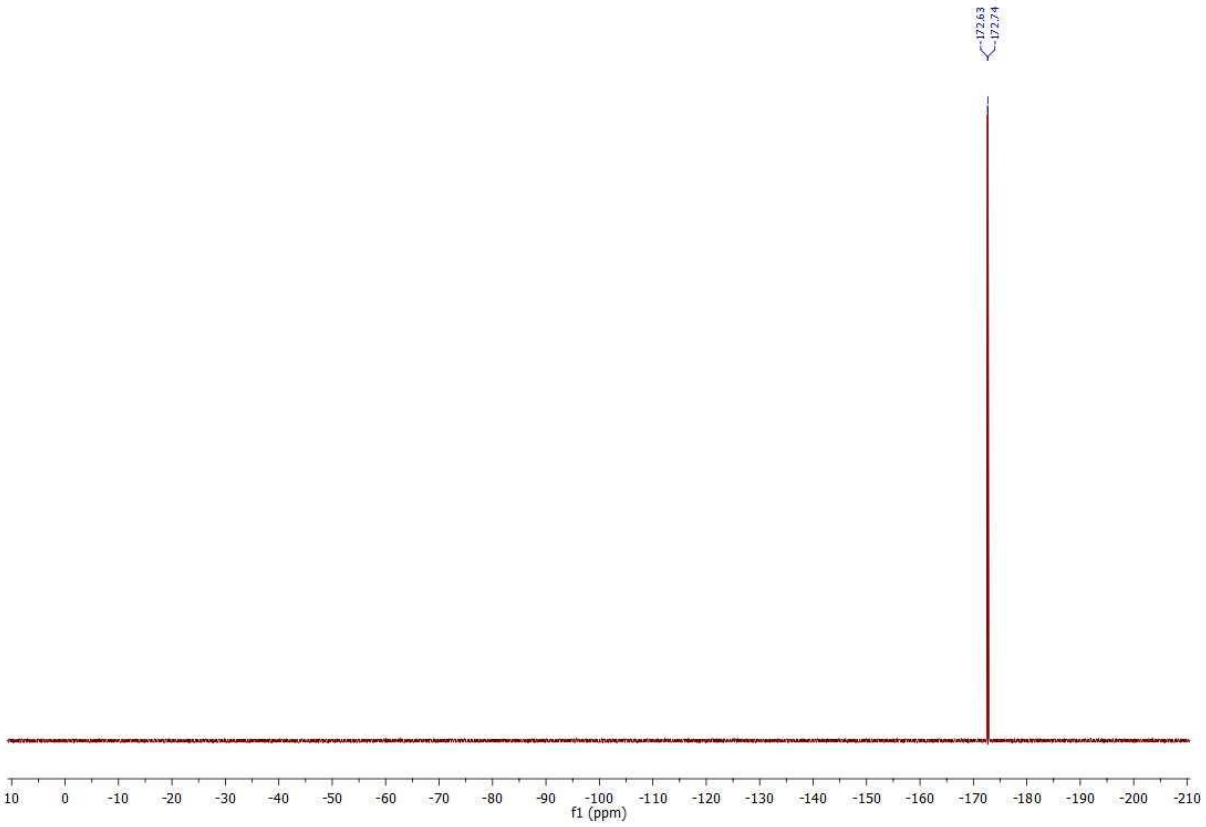
2-fluoro-1-(2-methoxyphenyl)-2-phenylethan-1-one (3f)

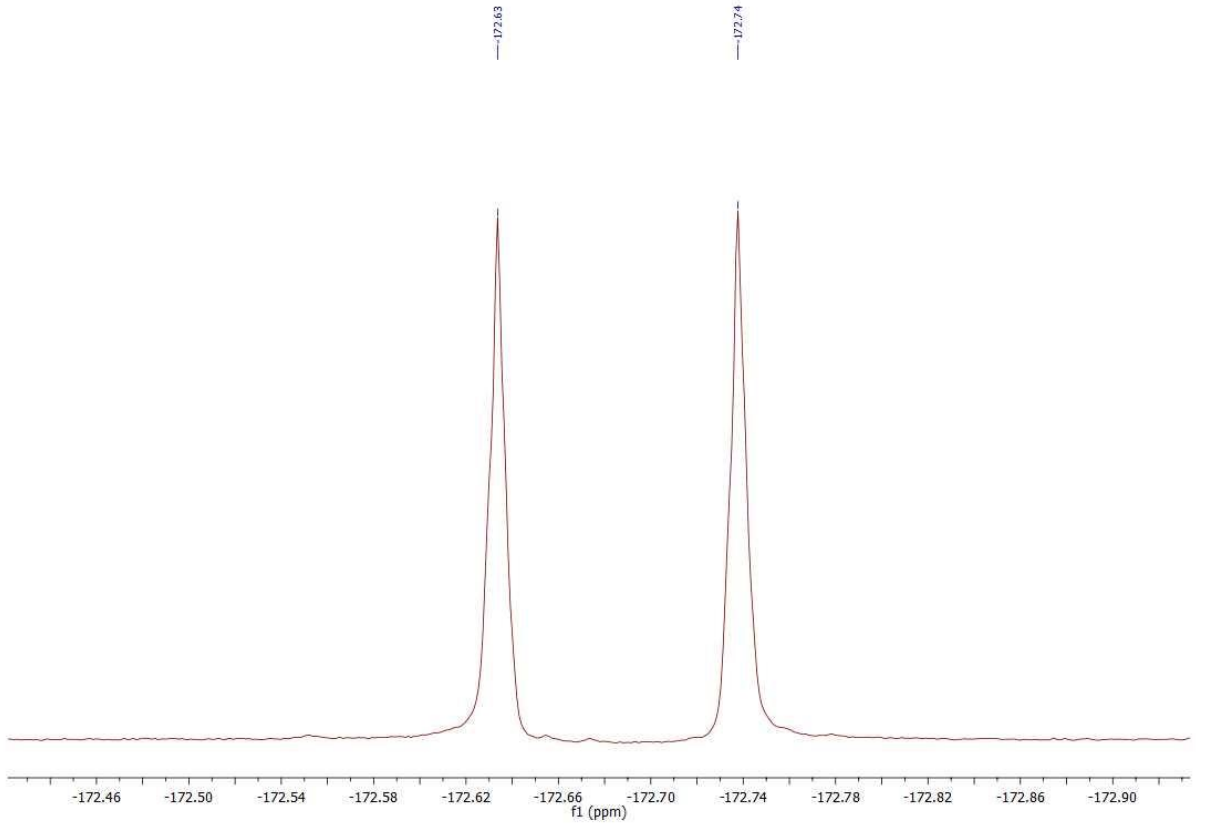


3f

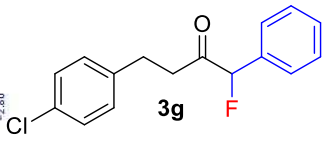


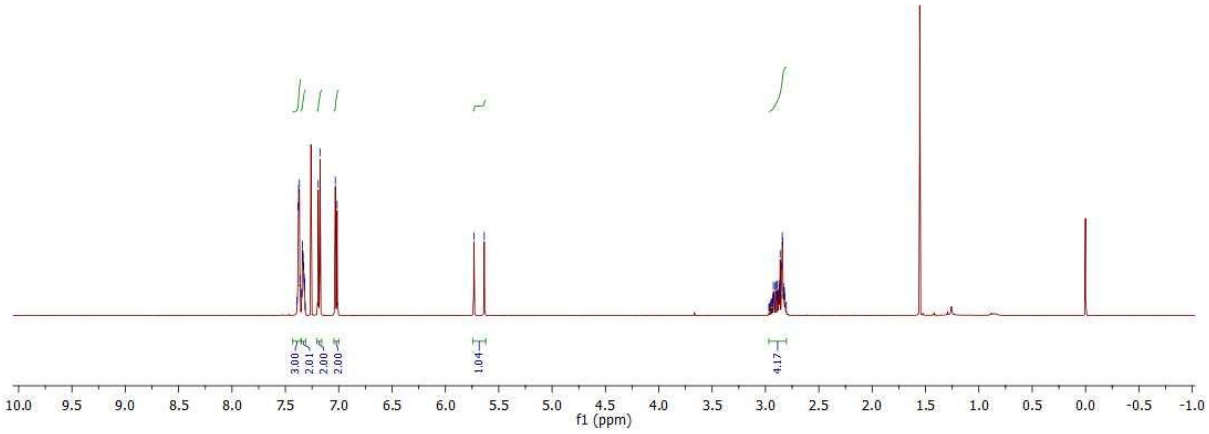


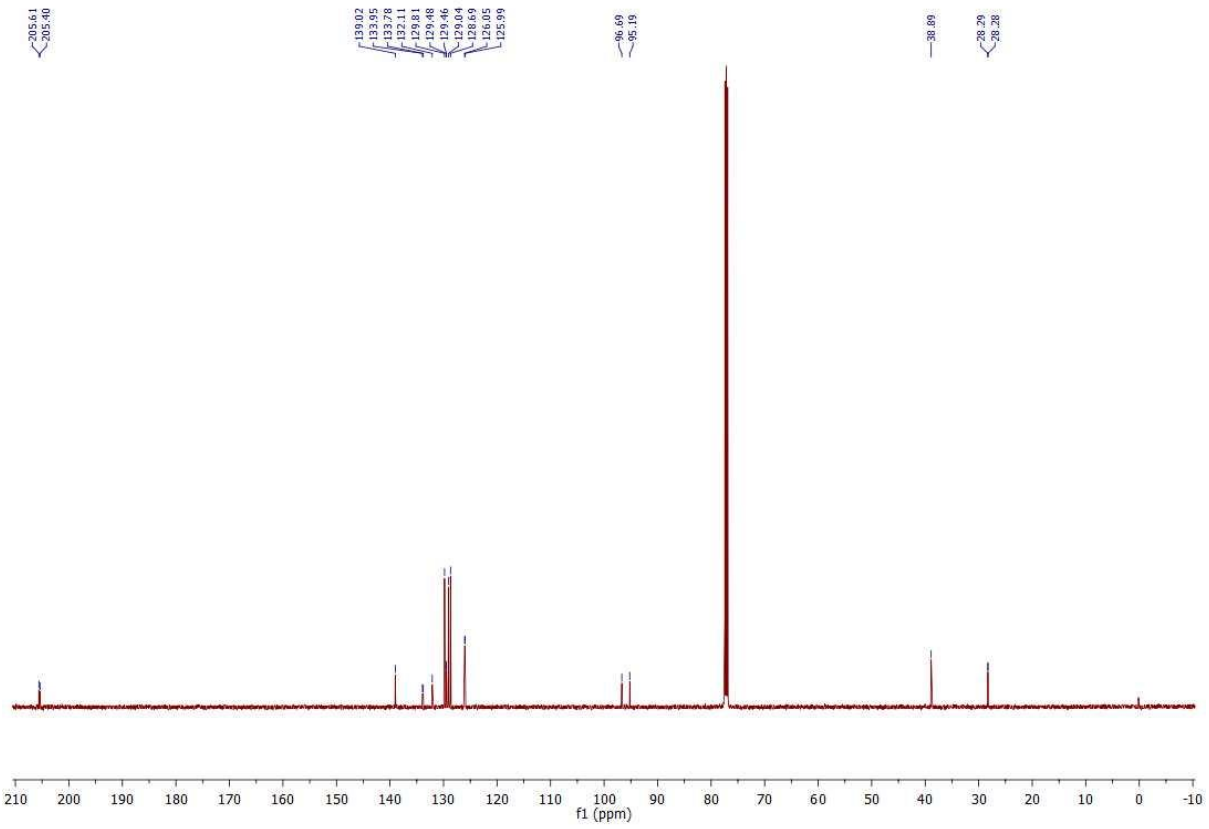

-172.63
-172.74
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

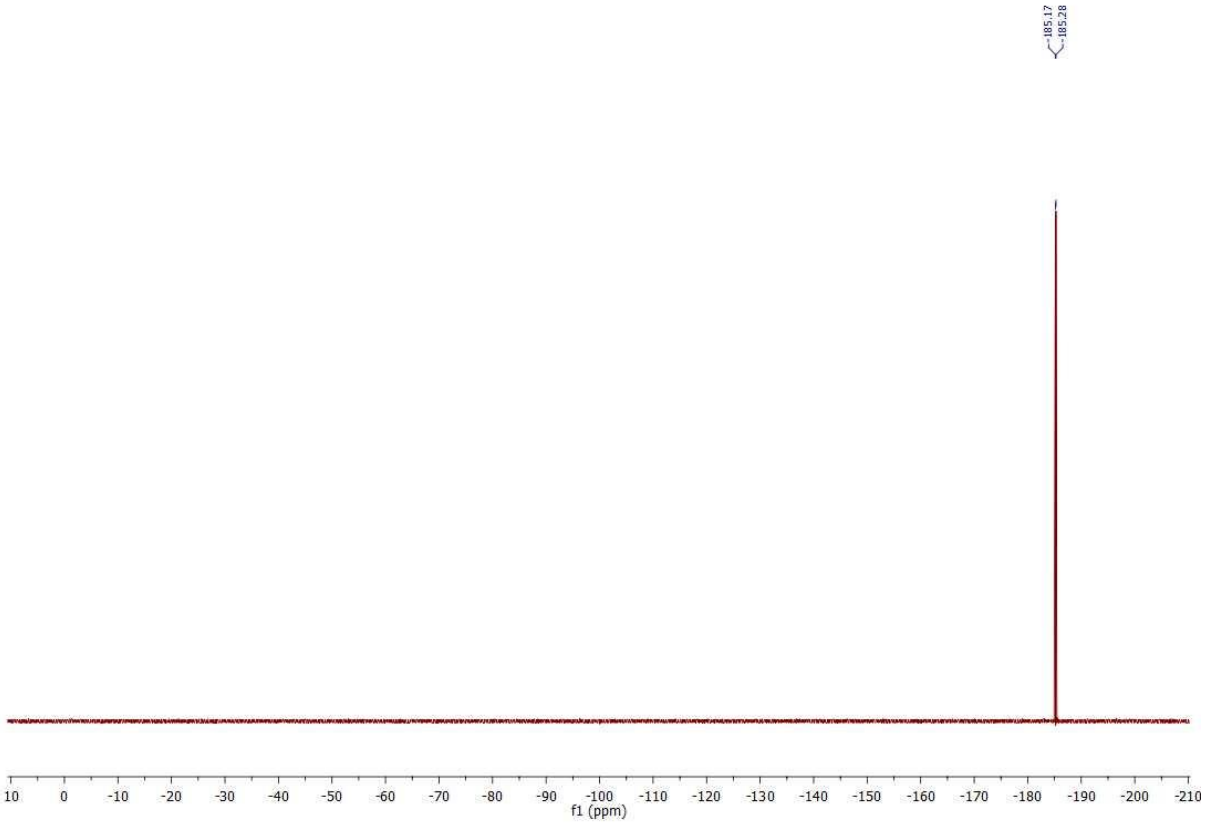

-172.63
-172.74
-172.46 -172.50 -172.54 -172.58 -172.62 -172.66 -172.70 -172.74 -172.78 -172.82 -172.86 -172.90
f1 (ppm)

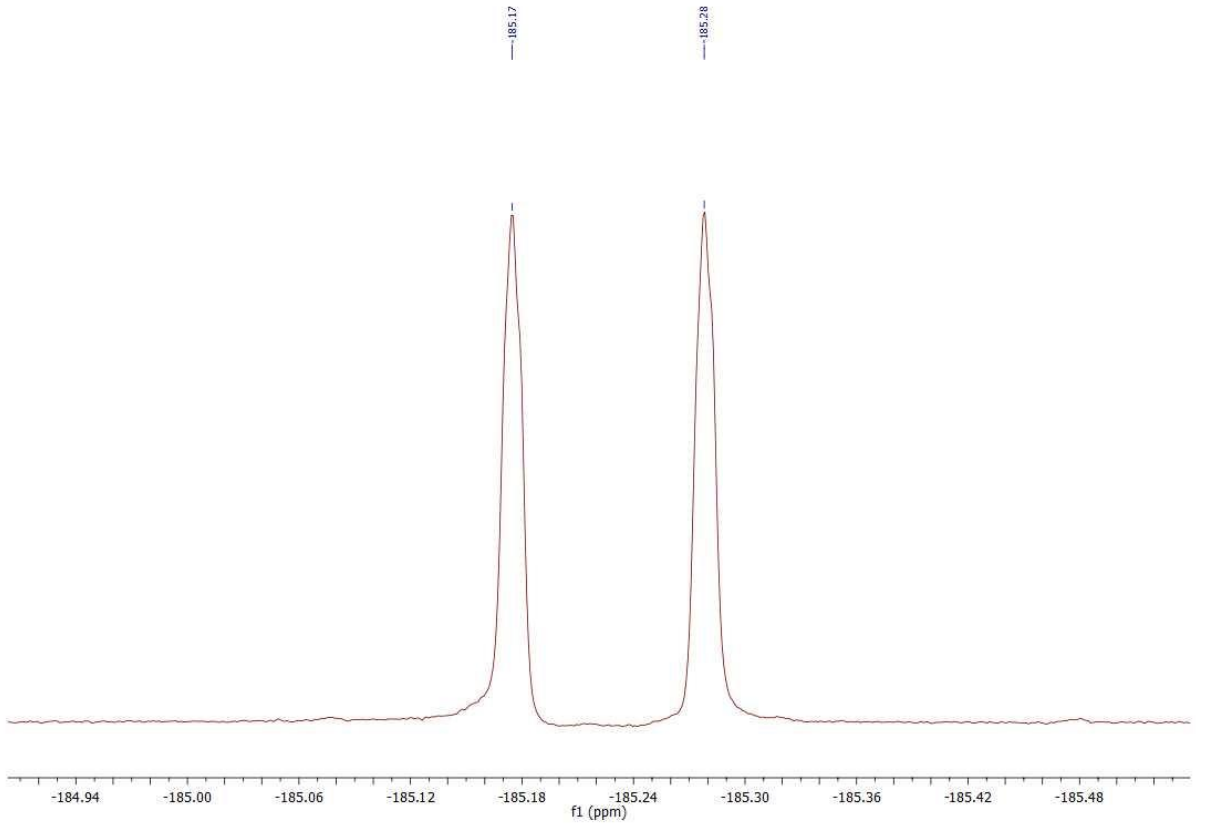
4-(4-Chlorophenyl)-1-fluoro-1-phenylbutan-2-one (3g)



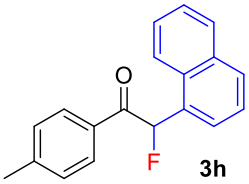


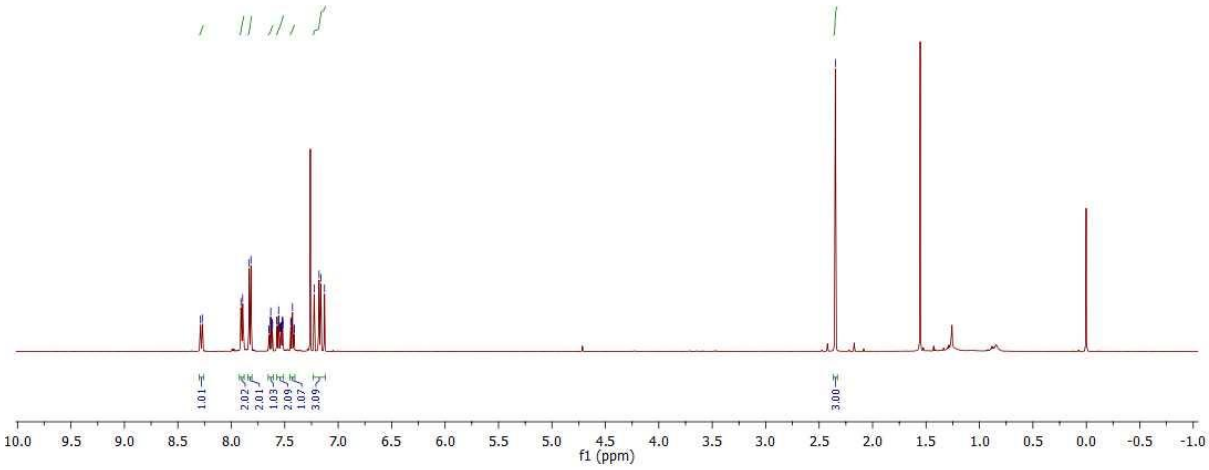


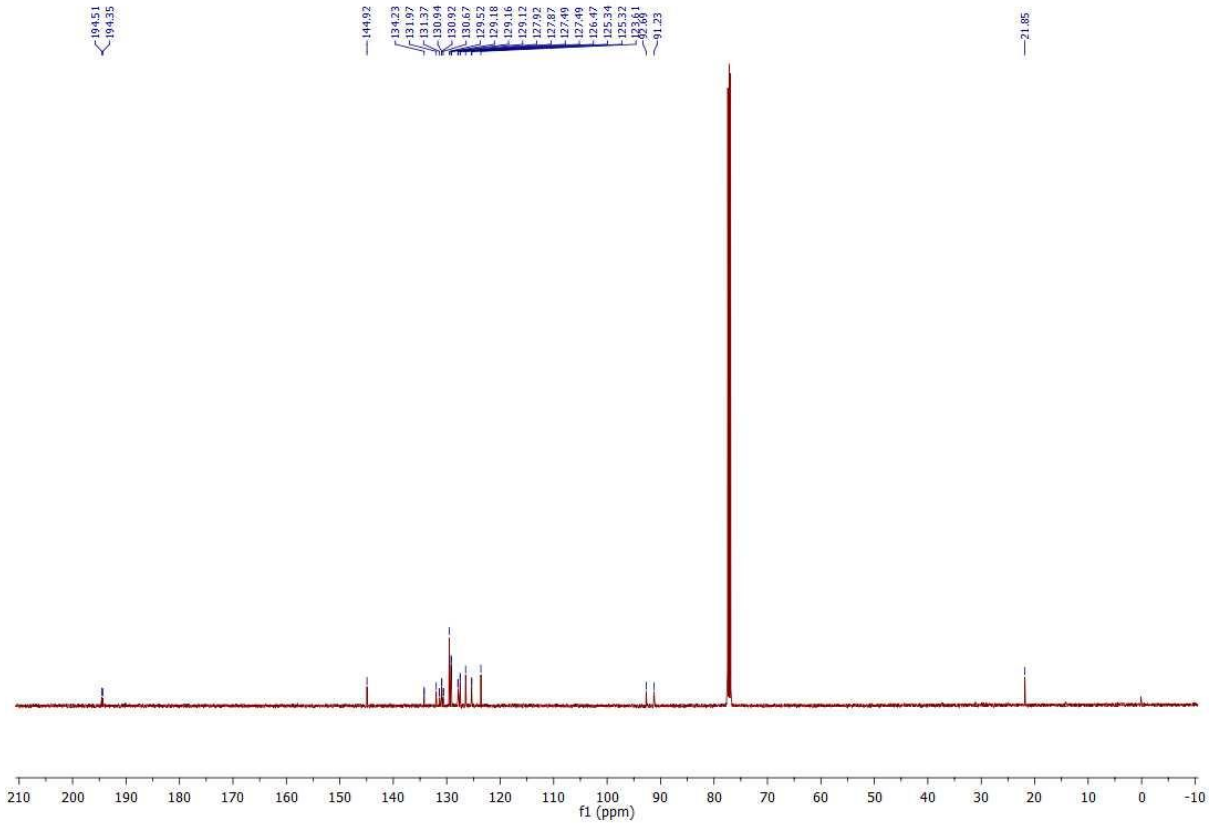

-185.17
-185.28
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

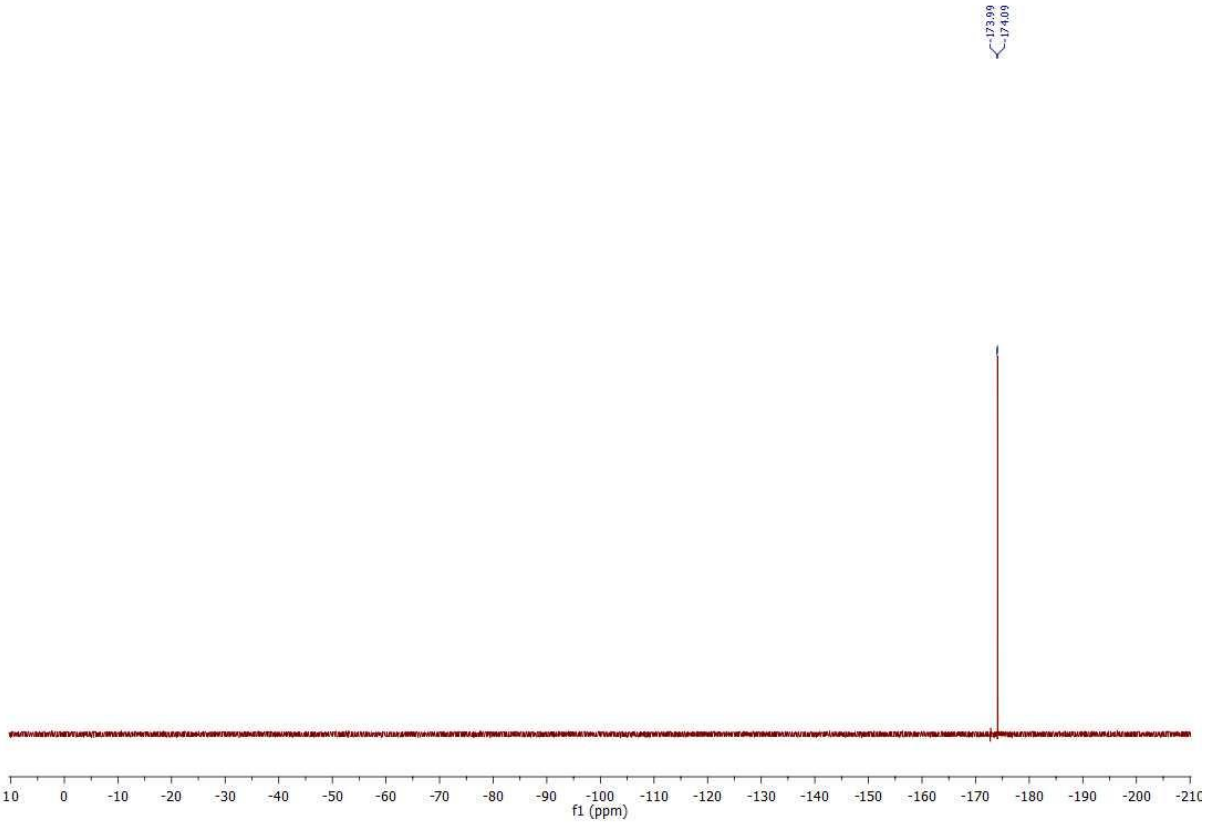

-185.17
-185.28
-184.94 -185.00 -185.06 -185.12 -185.18 -185.24 -185.30 -185.36 -185.42 -185.48
f1 (ppm)

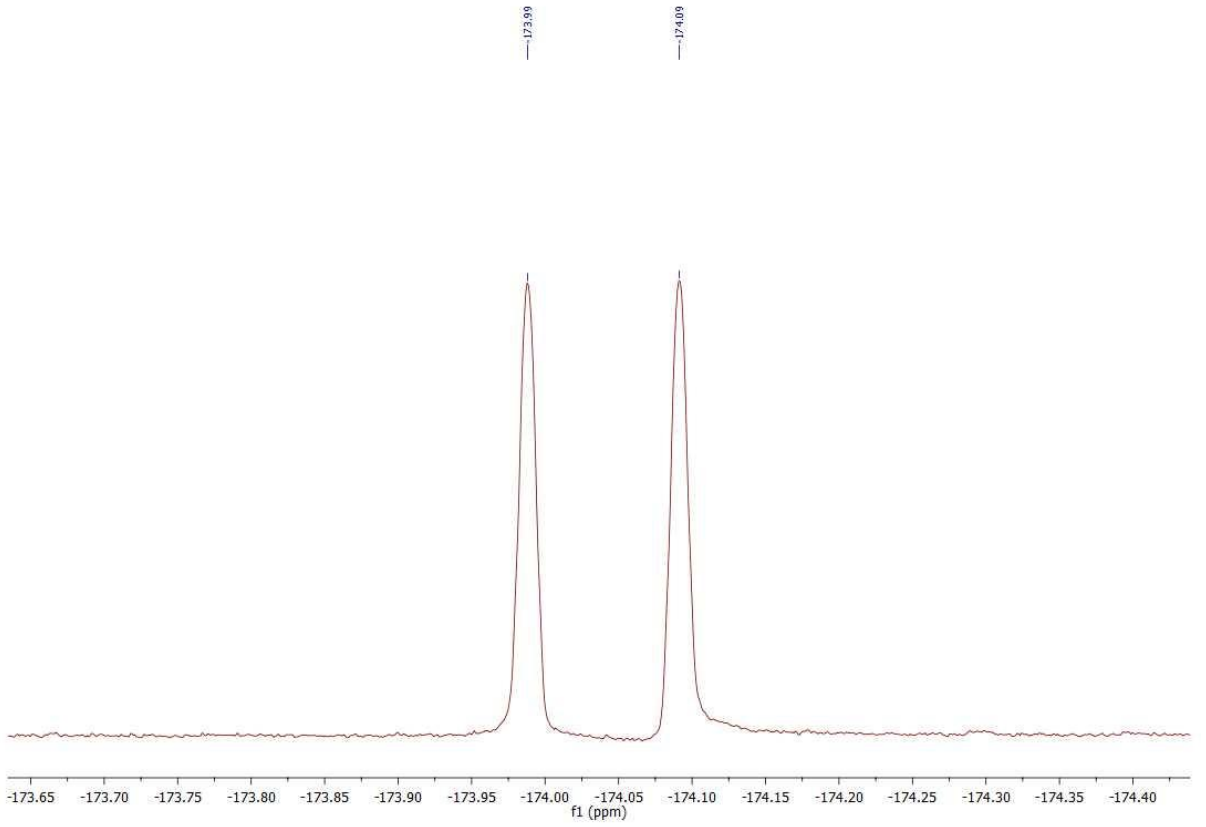
2-fluoro-2-(naphthalen-1-yl)-1-(*p*-tolyl)ethan-1-one (3h)



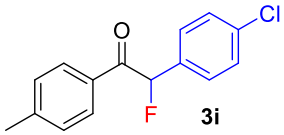




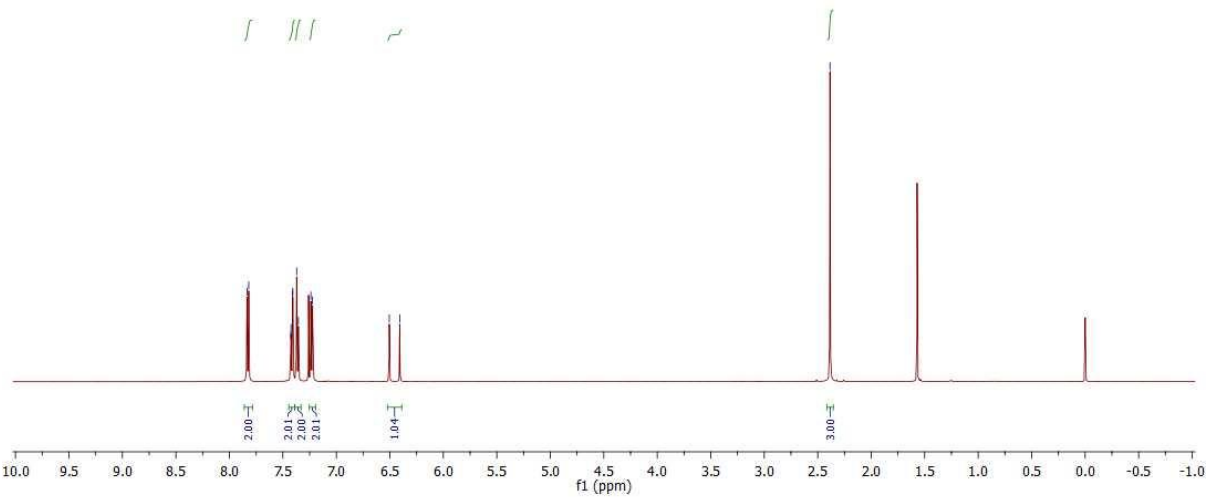

-173.99
-174.09
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

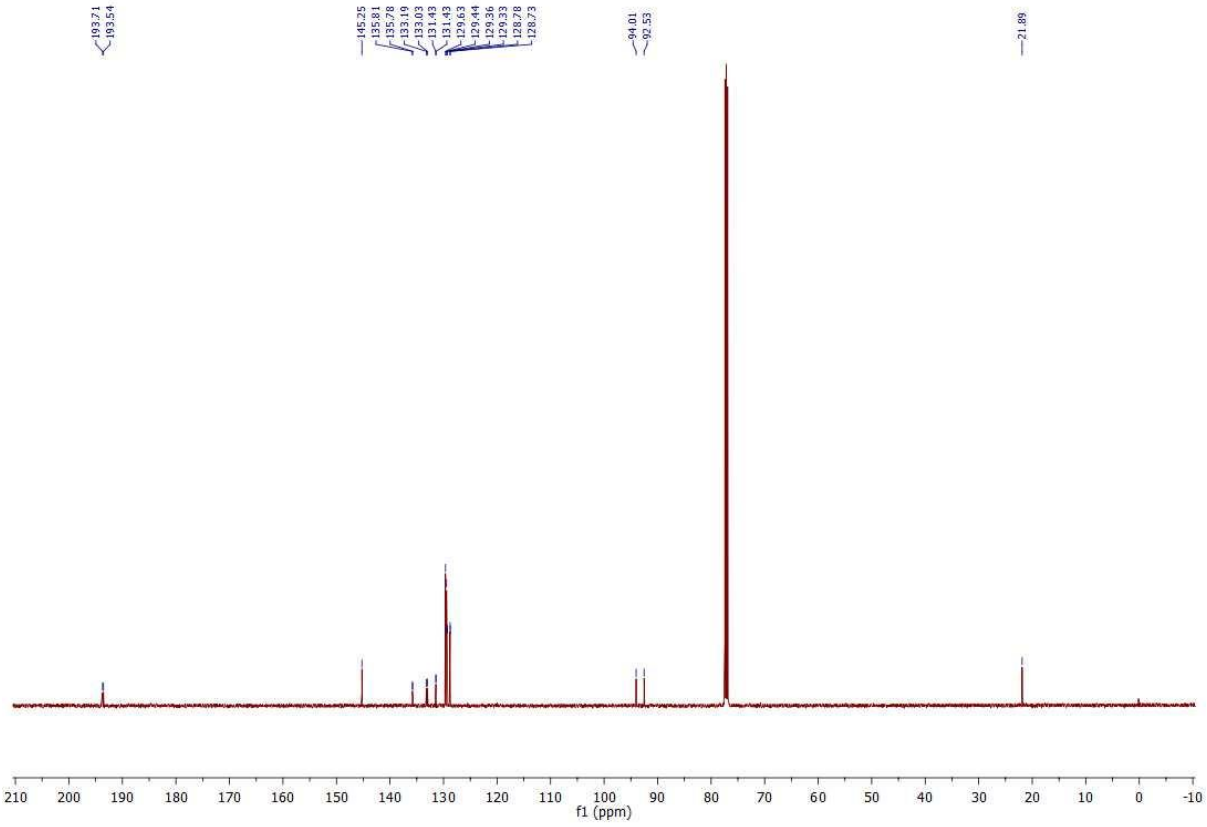

-173.99
-174.09
-173.65 -173.70 -173.75 -173.80 -173.85 -173.90 -173.95 -174.00 -174.05 -174.10 -174.15 -174.20 -174.25 -174.30 -174.35 -174.40
f1 (ppm)

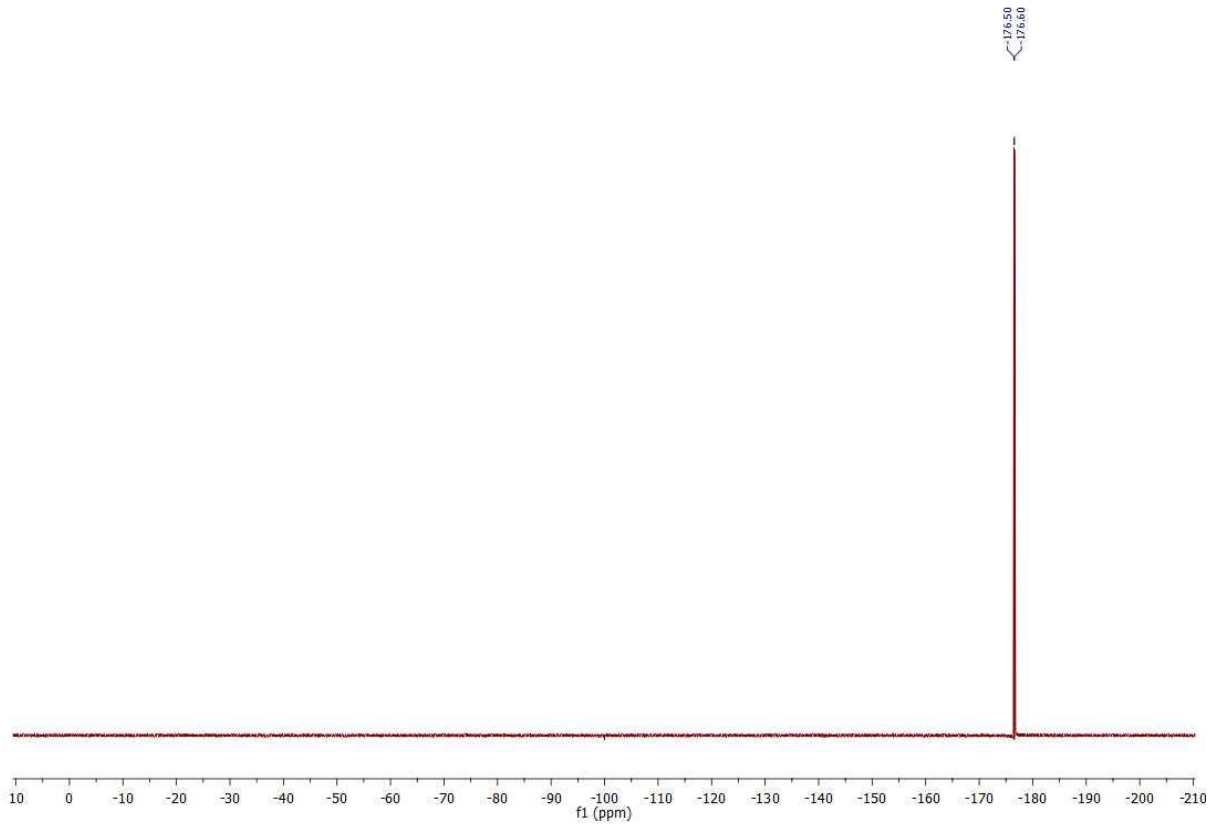
2-(4-Chlorophenyl)-2-fluoro-1-(*p*-tolyl)ethan-1-one (3i)

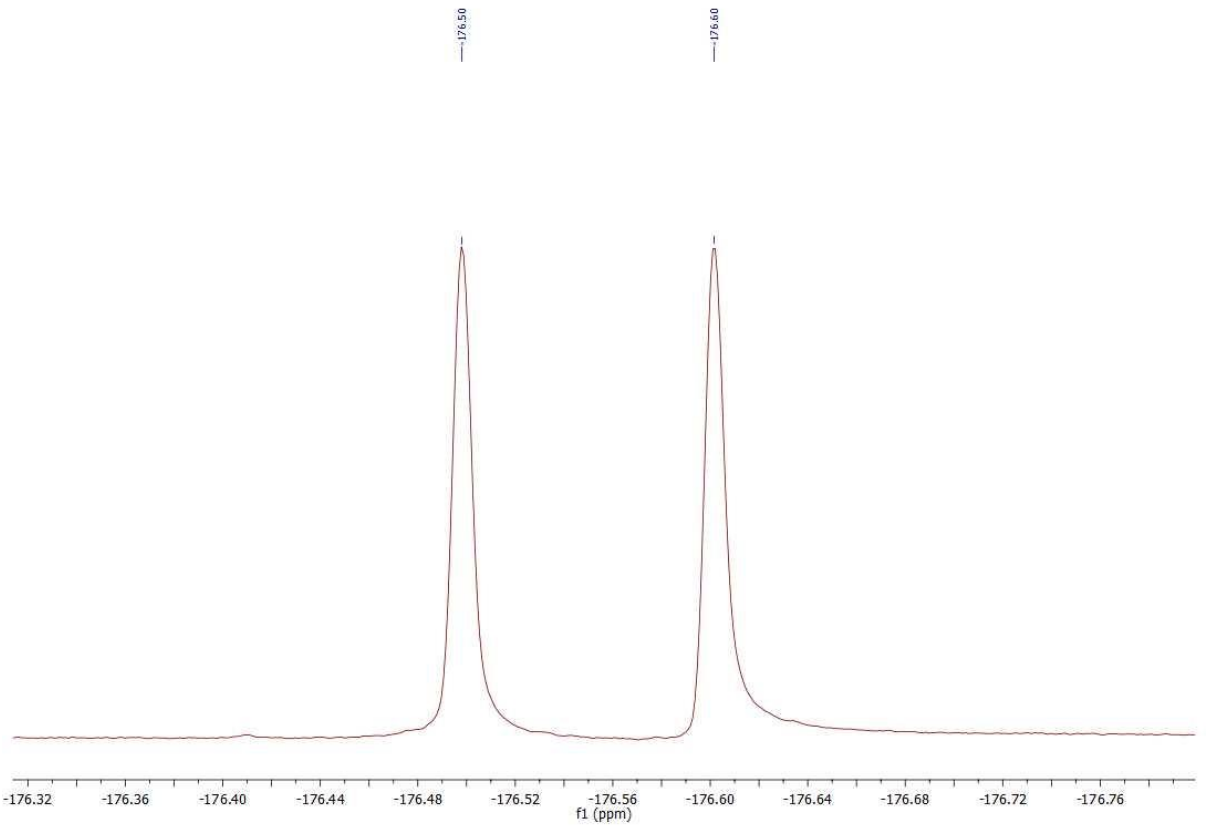


3i



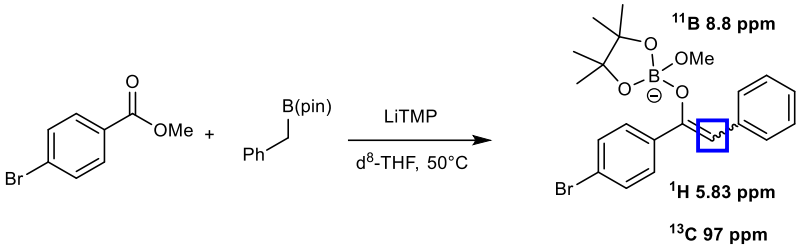



-176.50
-176.60
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)


-176.50
-176.60
-176.32 -176.36 -176.40 -176.44 -176.48 -176.52 -176.56 -176.60 -176.64 -176.68 -176.72 -176.76
f1 (ppm)

Mechanism study

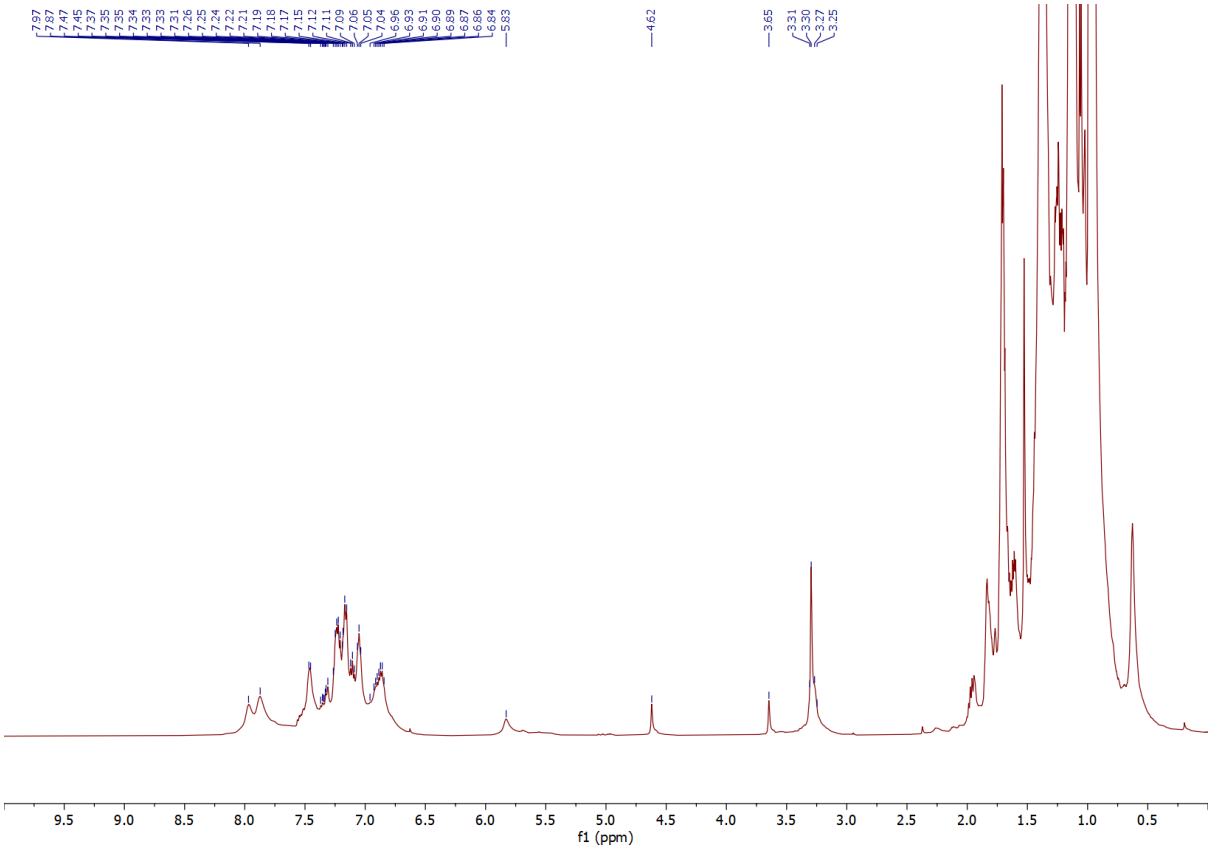
The main aim of the mechanism study was to prove the formation of the boron-enolate intermediate, by deprotonating $PhCH_2B(pin)$ with LiTMP and then reacting it with an ester, and observing the boron enolate by NMR. Then in a second step water was added to see if the boron-enolate reacts to trap an electrophile to form the desired ketone.

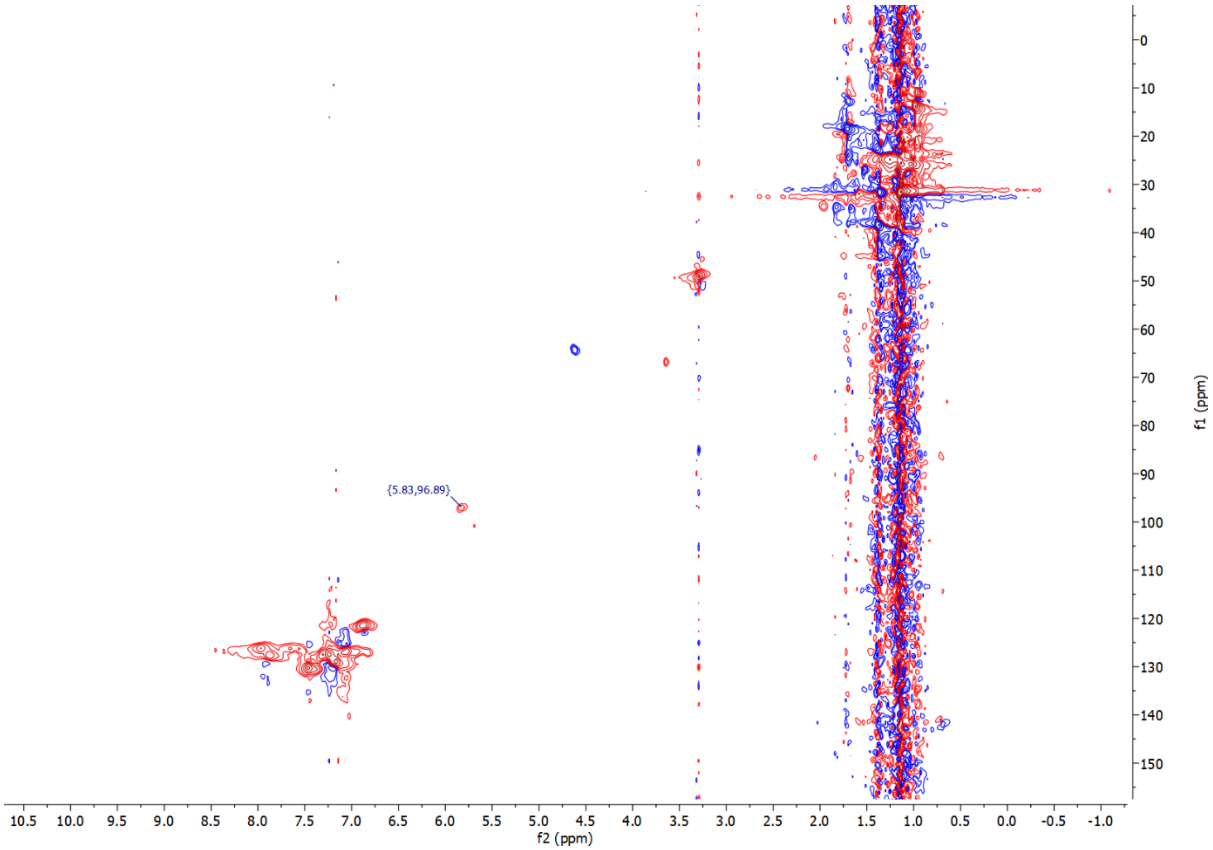


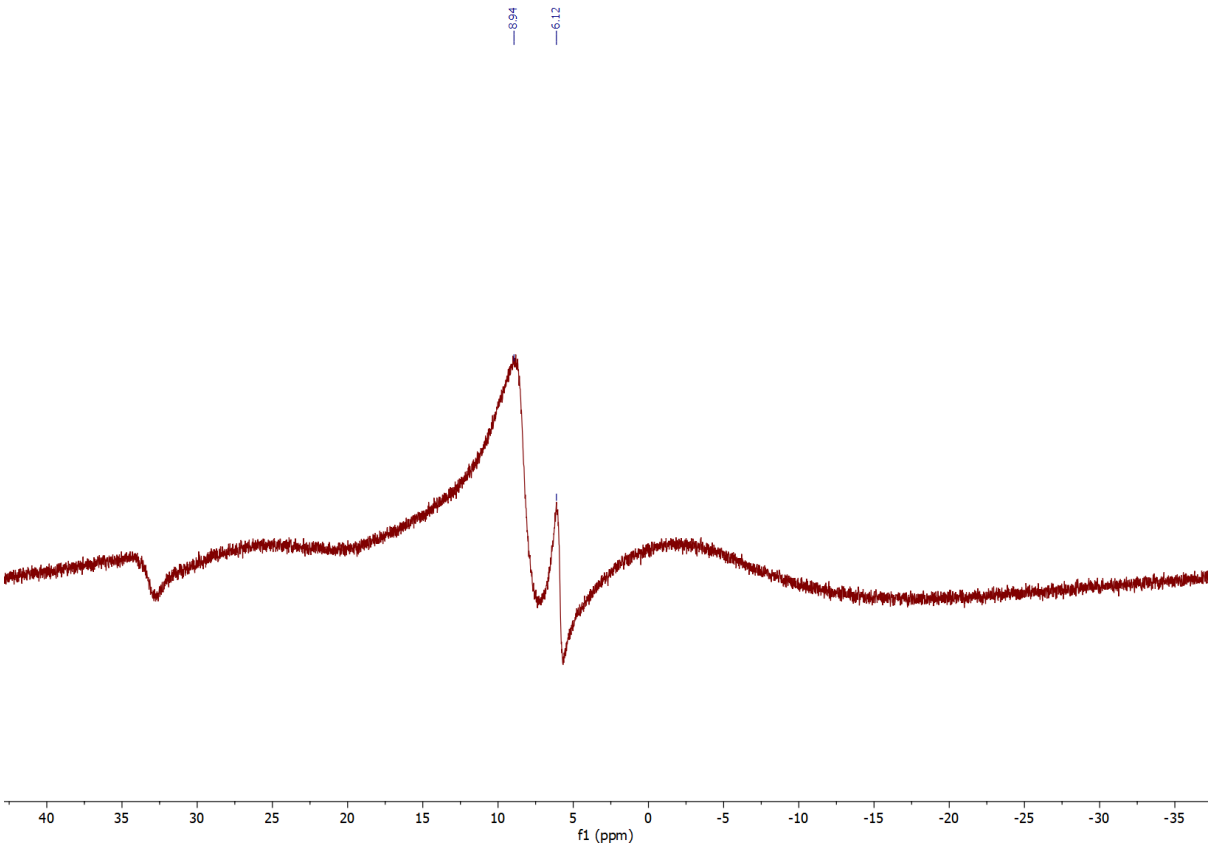
0.4 mL (1 mmol) of n-BuLi was added to 0.18 mL (1 mmol) of TMP and dried d^8-THF (0.5 mL) under nitrogen, the mixture was cooled to 0ºC for 15 minutes. After this period of time, 0.18 mL (0.8 mmol) of benzylboronic acid pinacol ester was added, with 0.2mL of dried d^8-THF, and the mixture was left to react for 15 minutes at 0ºC. After this period of time, 86 mg (0.4 mmol) of methyl 4-bromobenzoate was dissolved in 0.3 mL of d-THF and was added to the mixture. The mixture was then heated to 50ºC for 2 hours. After this period the mixture was cooled, and 0.88 mL of the mixture was transferred to an NMR tube using a dried syringe and then sealed with parafilm under nitrogen and spectra obtained.

Mixing methyl 4-bromobenzoate with benzylboronic pinacol ester in the presence of LiTMP in d8-THF gave a species that was shown to have a 1H signal at 5.83 ppm that showed a HSQC correlation to a 13C signal at 97 ppm. This is very indicative of an electron-rich enol-like alkene.

The O-bound nature of the boron enolate was further confirmed by 11B NMR, which showed a peak at 8.8 ppm which is indicative of quaternary species bound to oxygen and suggestive that the methoxide leaving group was involved in coordination to boron.

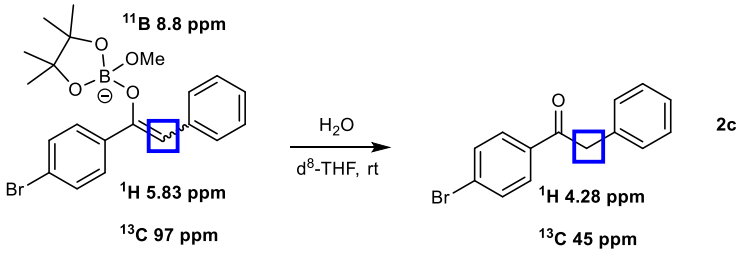

7.97
7.97
7.47
7.45
7.37
7.35
7.34
7.33
7.31
7.26
7.25
7.24
7.22
7.21
7.19
7.18
7.17
7.15
7.12
7.11
7.09
7.06
7.05
7.04
6.96
6.93
6.91
6.90
6.89
6.87
6.86
6.84
5.83
4.62
3.65
3.31
3.30
3.27
3.25
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


{5.83,96.89}
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150
f1 (ppm)
10.5 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 -1.0
f2 (ppm)



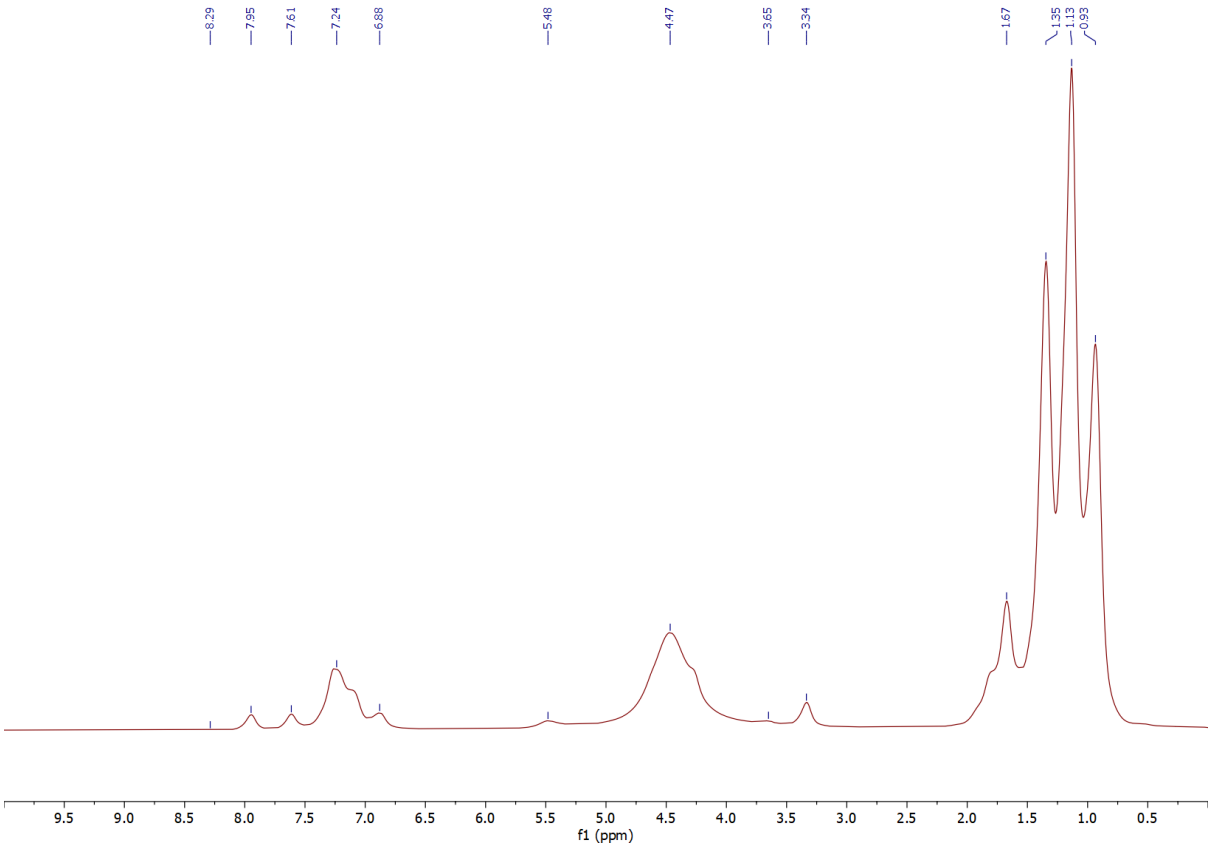
Control experiments to confirm reaction of boron enolate with H_2O

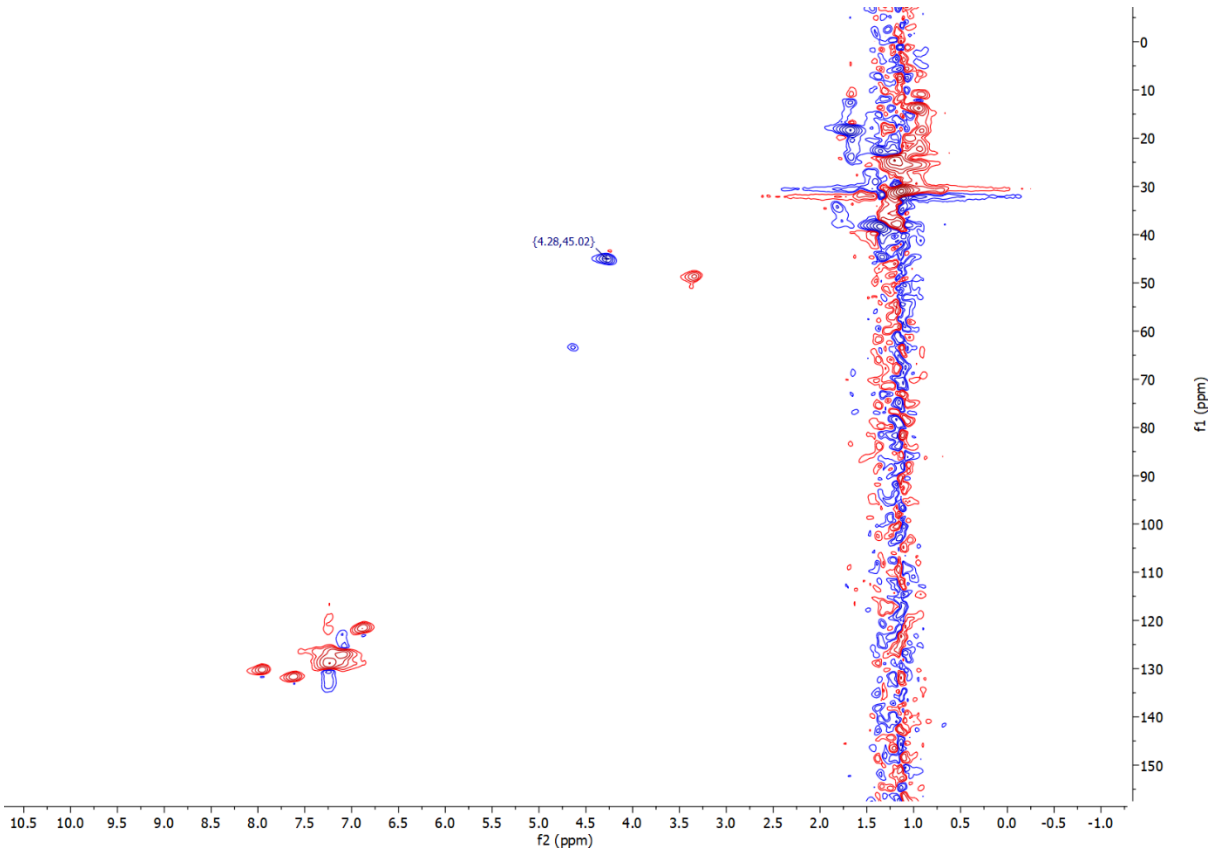
The second experiment investigated whether the boron-enolate did undergo electrophilic trapping with H_2O. The solution of the boron enolate was prepared as above and observed by NMR to ensure it matched the above data. H_2O was then added to confirm that there was a complete conversion to the protonated product, with no boron-enolate left unreacted.

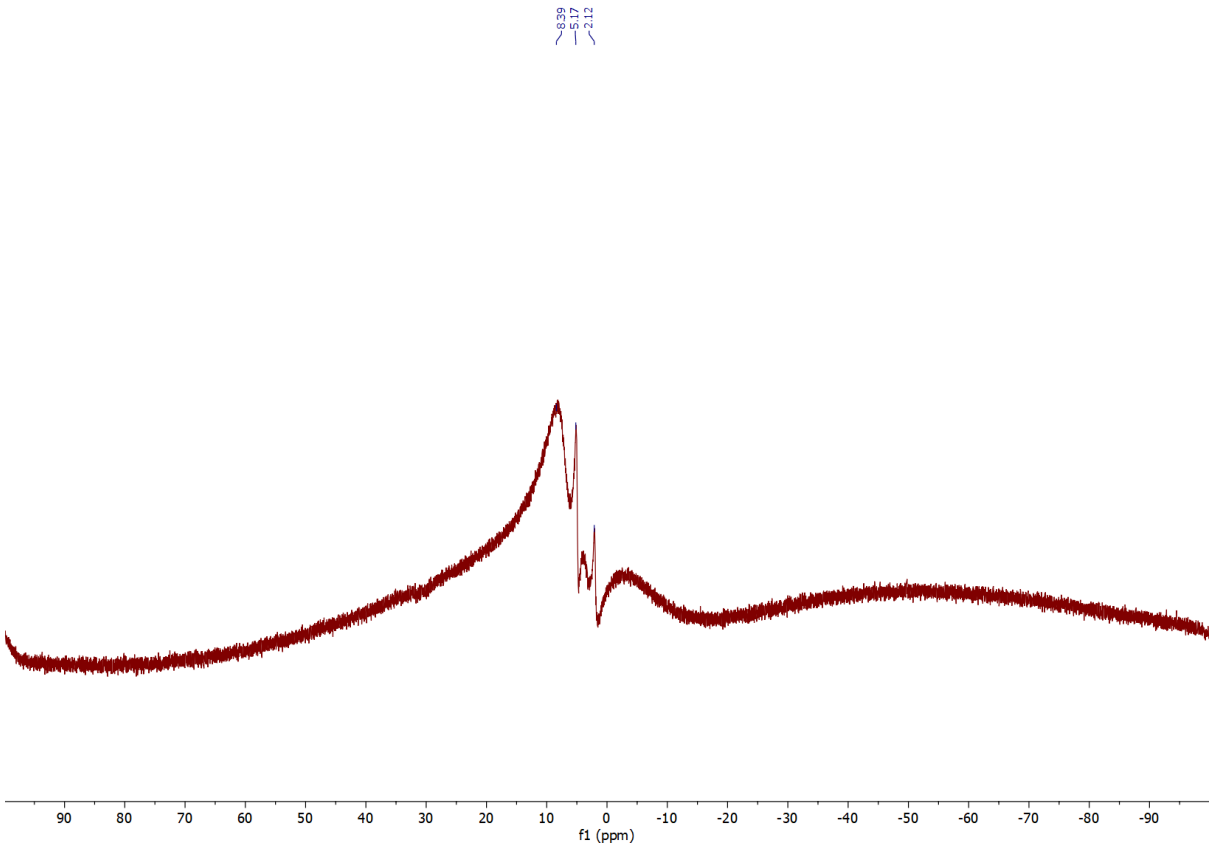


0.05 mL (2 mmol) of water was added to the rest of the boron-enolate solution made previously and was left for 15 minutes at room temperature. After this period the mixture was transferred to an NMR tube using a dried syringe and then sealed with parafilm under nitrogen and spectra obtained

The signal due to boron enolate disappeared and was replaced by a new signal ^{1}H 4.28 ppm, ^{13}C 45 ppm) that corresponded to the CH_2 group of compound **2c**


8.29
7.95
7.61
7.24
6.88
5.48
4.47
3.65
3.34
1.67
1.35
1.13
0.93
f1 (ppm)


{4.28,45.02}
f2 (ppm)
f1 (ppm)


8.39
5.17
2.12
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
f1 (ppm)

References

[1] D. Bradley, G. Williams, M. Lawton*, J. Org. Chem.* **2010**, *75*, 8351-8354.

[2] J.-W. Yu, S. Mao, Y.-Q. Wang, *Tetrahedron Lett.*, **2015**, *56*, 1575-1580.

[3] A. Takemiya, J. F. Hartwig, *J. Am. Chem. Soc.*, **2006**, *128*, 14800-14801.

[4] L. J. Gooßen, P. Mamone, C. Oppel, *Adv. Synth. Catal.*, **2011**, *353*, 57-63.

[5] B. Lee, P. J. Chirik, *J. Am. Chem. Soc.*, **2020**, *142*, 2429-2437.

[6] M. Yamashita, Y. Tanaka, A. Arita, M. Nishida, *J. Org. Chem.*, **1994**, *59*, 3500-3502.

[7] S. Dutta, A. Maity, S. Yang, R. K. Mallick, M. P. Gogoi, V. Gandon, A. K. Sahoo, *Org. Lett.*, **2025**, *27*, 808-813.

[8] J. Zhou, X. Fang, T. Shao, X. Yang, F. Wu, *J. Fluorine Chem.*, **2016**, *191*, 54-62.