Supporting Information

Direct Fluorination of Benzylic C-H Bonds with N-Fluorobenzenesulfonimide

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General Considerations

All reactions were carried out with commercial solvents and reagents that were used as received. For extended TBADT photochemical reactions, degassing of the solvent was carried out via several freeze/pump/thaw cycles. Flash chromatography was carried out with 230-400 mesh silica gel (SiliCycle, SiliaFlash® P60). Concentration and removal of trace solvents was done via a Büchi rotary evaporator using dry ice/acetone condenser, and vacuum applied from an aspirator or Büchi V-500 pump.All reagents and starting materials were purchased from Sigma Aldrich, Alfa Aesar, TCI America, and/or Strem, and were used without further purification. All solvents were purchased from Sigma Aldrich, EMD, Anachemia, Caledon, Fisher, or ACP and used without further purification, unless otherwise specified. Nuclear magnetic resonance (NMR) spectra were recorded using chloroform-d ($CDCl_3$) or acetonitrile-d_3). Signal positions (δ) are given in parts per million from tetramethylsilane (δ 0) and were measured relative to the signal of the solvent (^{1}H NMR: $CDCl_3$: δ 7.26, (CD_3CN: δ 1.94; ^{13}C NMR: $CDCl_3$: δ 77.16, CD_3CN: δ 118.26). ^{19}F NMR spectra were referenced to $CFCl_3$ (at 0.0 ppm) using an external standard 1,3,5-tris(trifluoromethyl)benzene in $CDCl_3$ set to -65.3 ppm[1] contained in a coaxial tube. Coupling constants (J values) are given in Hertz (Hz) and are reported to the nearest 0.1 Hz. 1H NMR spectral data are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet), coupling constants, number of protons. NMR spectra were recorded on a Bruker Avance 600 equipped with a QNP or TCI cryoprobe (600 MHz), Bruker 500 (500 MHz), or Bruker 400 (400 MHz). Assignments of ^{1}H and ^{13}C NMR spectra are based on analysis of ^{1}H-^{1}H COSY, HSQC, HMBC, TOCSY and 1D NOESY spectra, where applicable. Where necessary, 1,3,5-tris(trifluoromethyl)benzene was added to the crude reaction mixtures and used as an internal standard. Yields were then calculated following analysis of ^{1}H NMR spectra. Compounds that were not purified and whose yield was determined by NMR spectroscopic analysis of the crude reaction mixture with the addition of an internal standard were structurally identified by comparison of their spectral data to that reported previously: **22**[2], **23**[3] and **24**[4]. Volatile substrates **31**, **32**, **33**, **34**, **35** and **36** were partially purified by extraction of the crude reaction mixtures with pentane. Removal of the solvent via careful air-drying yielded mixtures of these compounds. No further purification was carried out to separate isomers of these compounds or to remove unreacted starting materials. High-resolution mass spectra were performed on an Agilent 6210 TOF LC/MS, Bruker MaXis Impact TOF LC/MS, or Bruker micrOTOF-II LC mass spectrometer. In the cases where complete separation of starting material and product was not possible, the product yield was calculated taking into account the amount of starting material remaining in the sample (as measured by ^{1}H NMR spectroscopy).

Method A: Photochemical reaction with TBADT

A suspension of substrate (1 eq), NFSI (3 eq), TBADT (2 mol %), and Li_2CO_3 or $NaHCO_3$ (1 eq) in CH_3CN (0.6-0.8 M substrate) was degassed via 3 x freeze/pump/thaw cycles. The reaction was irradiated with a black light (long-wave UV, ~365 nm) for 24-72 h, until reaction progress as analyzed by ^{1}H NMR spectroscopy indicated no additional reaction progress. The resulting suspension was concentrated to dryness, CH_2Cl_2 was added and the mixture was filtered through a pad of celite. The crude reaction product was then purified by column chromatography.

Reaction Method B: Thermal AIBN-initiated reaction

To a suspension of substrate (1 eq), NFSI (3 eq) and Li_2CO_3 (1 eq) was added AIBN (5 mol %, 250 mM solution in CH_3CN, 0.6-0.8 M substrate). The resulting reaction mixture was then heated to 75 °C for 16-20 h, cooled and filtered through a pad of celite. The crude reaction product was then purified by column chromatography.

Flow reactions

Substrate (1 eq), NFSI (3 eq) and TBADT (0.02 eq) were dissolved in a minimal amount of degassed CH_3CN. Li_2CO_3 (1 eq) was then added, and the resulting slurry was sonicated for 10 min to break up larger solid particles. This slurry was then pumped through a flow reaction tube (Scheme 4 and Supporting Figure S1) at the following rates:

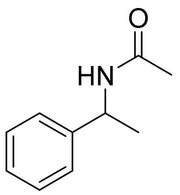
16: 0.33 mmol/h, 2 h residence time, 66 % isolated yield

17: 0.044 mmol/h, 16 h residence time, 34% isolated yield

20: 0.092 mmol/h, 5 h residence time, 70% isolated yield

The crude reaction products were then purified by column chromatography.

N-(1-phenylethyl)acetamide (12)



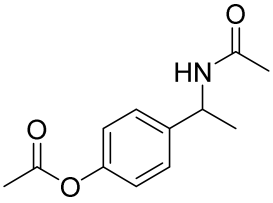
12

The spectral data derived for **12** was consistent with that reported by others. [5]

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.30 (m, 5H), 5.86 (br s, 1H), 5.12 (m, 1H), 1.48 (d, J = 6.9, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 169.3, 143.3, 128.8, 127.5, 126.3, 48.9, 23.6, 21.8

HRMS (EI^+) calcd for $C_{10}H_{13}NO^+$ 163.0997, found 163.0976

4-(1-acetamidoethyl)phenyl acetate (13)

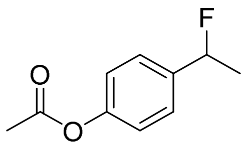


13

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.33 (d, J = 8.6 Hz, 2H), 7.05 (d, J = 8.6 Hz, 2H), 5.69 (br s, 1H), 5.13 (m, 1H), 2.29 (s, 3H), 1.97 (s, 3H), 1.48 (d, J = 6.9 Hz, 3H); **^{13}C-NMR** (125 MHz, $CDCl_3$): δ 169.7, 169.2, 150.0, 140.8, 127.6, 121.9, 48.4, 23.6, 21.6, 21.3

HRMS (ESI^+) calcd for $C_{12}H_{15}NO_3H^+$ 222.1125, found 222.1109

4-(1-fluoroethyl)phenyl acetate (16)



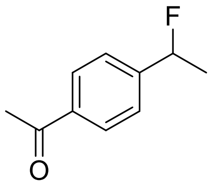
16

The spectral data derived for **16** was consistent with that reported by others.[4]

^{1}**H-NMR** (400 MHz, $CDCl_3$): δ 7.37 (d, J = 8.1 Hz, 2H), 7.10 (d, J = 8.2 Hz, 2H), 5.62 (dq, J = 47.6, 6.4 Hz, 1H), 2.31 (s, 3H), 1.64 (dd, J = 23.9, 6.5 Hz, 3H); ^{13}**C-NMR** (100 MHz, $CDCl_3$) δ 169.6, 150.6 (d, J = 2.3 Hz), 139.2 (d, J = 19.9 Hz), 126.6 (d, J = 6.7 Hz), 121.8, 90.6 (d, J = 168.1 Hz), 23.1 (d, J = 25.1 Hz), 21.3 ^{19}**F-NMR** (470 MHz, $CDCl_3$) δ –168.5

HRMS (EI$^+$) calcd for $C_{10}H_{11}FO_2Na^+$ 205.0635, found 205.0609

1-(4-(1-fluoroethyl)phenyl)ethan-1-one (17)



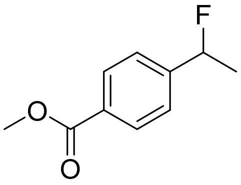
17

The spectral data derived for **15** was consistent with that reported by others.[4]

^{1}**H-NMR** (500 MHz, $CDCl_3$): δ 7.97 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H), 5.68 (dq, J = 47.6, 6.4 Hz, 1H), 2.60 (s, 3H), 1.64 (dd, J = 24.1, 6.5 Hz, 3H); ^{13}**C-NMR** (125 MHz, $CDCl_3$): δ 197.8, 146.8 (d, J = 19.6 Hz), 137.0 (d, J = 1.8 Hz), 128.7, 125.2 (d, J = 7.3 Hz), 90.4 (d, J = 169.8 Hz), 26.8, 23.1 (d, J = 24.6 Hz); ^{19}**F-NMR** (470 MHz, $CDCl_3$) δ –173.4

HRMS (EI$^+$) calcd for $C_{10}H_{11}FO_2^+$ 182.0743, found 182.0736

methyl 4-(1-fluoroethyl)benzoate (18)

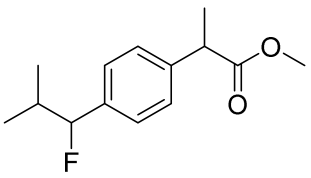


18

^{1}**H-NMR** (500 MHz, $CDCl_3$): δ 8.05 (d, J = 8.1 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 5.68 (dq, J = 47.6, 6.4 Hz, 1H), 3.92 (s, 3H), 1.65 (dd, J = 24.1, 6.5 Hz, 3H); ^{13}**C-NMR** (125 MHz, $CDCl_3$): δ 166.9, 146.7 (d, J = 19.7 Hz), 130.6, 130.0, 125.1 (d, J = 7.2 Hz), 90.5 (d, J = 169.6 Hz), 52.3, 23.1 (d, J = 24.8 Hz); ^{19}**F-NMR** (470 MHz, $CDCl_3$) δ –173.2

HRMS (EI$^+$) calcd for $C_{10}H_{11}FO_2^+$ 182.0743, found 182.0722

methyl 2-(4-(1-fluoro-2-methylpropyl)phenyl)propanoate, Fluoro-ibuprofen methyl ester (20)



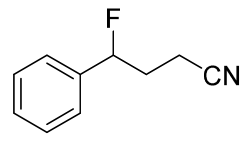
20

The spectral data derived for **20** was consistent with that reported by others.[3]

^{1}**H-NMR** (500 MHz, $CDCl_3$): δ 7.30 (d, J = 8.1 Hz, 2H), 7.25 (d, J = 8.1 Hz, 2H), 5.08 (dd, J = 46.9, 6.8 Hz, 1H), 3.74 (q, J = 7.1 Hz, 1H), 3.66 (s, 3H), 2.10 (m, 1H), 1.50 (d, J = 7.3 Hz, 3H) , 1.02 (d, J = 6.78 Hz, 3H) , 0.85 (d, J = 6.9 Hz, 3H); ^{13}**C-NMR** (150 MHz, $CDCl_3$) δ 175.1, 140.5, 138.4 (d, J = 20.8 Hz), 127.5, 126.6 (d, J = 7.1 Hz), 99.2 (d, J = 173.6 Hz), 52.2, 45.3, 34.4 (d, J = 22.7 Hz), 18.7, 18.5 (d, J = 5.8 Hz), 17.7(d, J = 5.1 Hz); ^{19}**F-NMR** (470 MHz, CD_3CN) δ –179.0

HRMS (EI$^+$) calcd for $C_{14}H_{19}FO_2H^+$ 239.1447, found 239.1454

4-fluoro-4-phenylbutanenitrile (21)



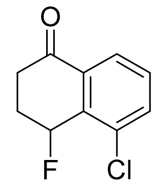
21

The spectral data derived for **21** was consistent with that reported by others. [6]

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.38 (m, 5H), 5.58 (ddd, J = 47.6, 8.5, 4.0 Hz, 1H), 2.58 (dt, J = 17.0, 7.93 Hz, 1H), 2.48 (ddd, J = 17.0, 7.7, 5.7 Hz, 1H), 2.24 (m, 2H); **^{13}C-NMR** (150 MHz, $CDCl_3$) δ 138.4 (d, J = 19.7 Hz), 129.1 (d, J = 1.7 Hz), 129.0, 125.4 (d, J = 7.0 Hz), 118.9, 92.2 (d, J = 173.9 Hz), 33.1 (d, J = 24.8 Hz), 13.5 (d, J = 4.9 Hz); **^{19}F-NMR** (470 MHz, $CDCl_3$) δ –181.8

HRMS (EI$^+$) calcd for $C_{10}H_{10}FN^+$ 163.0797, found 163.0780

5-chloro-4-fluoro-3,4-dihydronaphthalen-1(2H)-one (25)

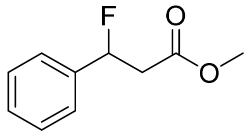


25

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.01 (d, J = 7.9 Hz, 1H), 7.67 (d, J = 7.9 Hz, 1H), 7.48 (dt, J = 7.9, 2.2 Hz, 1H), 6.11 (dt, J = 48.5, 2.6 Hz, 1H), 3.04 (m, 1H), 2.68 (m, 2H), 2.33 (m, 1H); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 196.0 (d, J = 1.8 Hz), 135.6 (d, J = 22.4 Hz), 135.5 (d, J = 10.2 Hz), 134.9 (d, J = 2.7 Hz), 133.9 (d, J = 2.4 Hz), 131.1 (d, J = 3.7 Hz), 125.8 (d, J = 2.7 Hz), 83.3 (d, J = 168.8 Hz), 32.1 (d, J = 2.7 Hz), 28.1 (d, J = 23.6 Hz) **^{19}F-NMR** (470 MHz, $CDCl_3$) δ –177.5

HRMS (ESI$^+$) calcd for $C_{10}H_8ClFONa^+$ 221.0140, found 221.0126

Methyl 3-fluoro-3-phenylpropanoate (26)



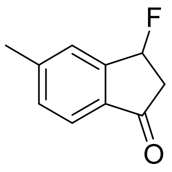
26

The spectral data derived for **26** was consistent with that reported by others.[4]

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.38 (m, 5H), 5.93 (ddd, J = 46.9, 9.1, 4.1 Hz, 1H), 3.74 (s, 3H), 3.04 (ddd, J = 16.0, 13.5, 9.1 Hz, 1H), 2.80 (ddd, J = 32.6, 16.0, 4.1 Hz, 1H); **^{13}C-NMR** (150 MHz, $CDCl_3$) δ 170.3 (d, J = 4.9 Hz), 138.8 (d, J = 19.5 Hz), 129.0 (d, J = 1.9 Hz), 128.8, 125.7 (d, J = 6.5 Hz), 90.8 (d, J = 172.6 Hz), 52.2, 42.4 (d, J = 27.2 Hz); **^{19}F-NMR** (470 MHz, $CDCl_3$) δ –175.3

HRMS (EI$^+$) calcd for $C_{10}H_{11}FO_2^+$ 182.0743, found 182.0756

3-fluoro-5-methyl-2,3-dihydro-1H-inden-1-one (27)



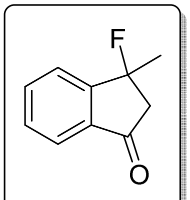
27

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.69 (d, J = 7.9 Hz, 1H), 7.54 (s, 1H), 7.39 (d, J = 7.9 Hz, 1H), 6.13 (ddd, J = 55.5, 6.6, 1.9 Hz, 1H), 3.11 (ddd, J = 19.0, 12.2, 6.6 Hz, 1H), 2.87 (ddd, J = 24.0, 19.0, 2.1, 1H), 2.50 (s, 3H); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 200.9, 150.9 (d, J = 17.0 Hz), 147.0 (d, J = 2.7 Hz), 135.0, 132.2 (d, J = 3.4 Hz), 127.1 (d, J = 1.8 Hz), 123.5, 88.2 (d, J = 177.2 Hz), 44.4 (d, J = 20.8 Hz), 22.3; **^{19}F-NMR** (470 MHz,

$CDCl_3$) δ –170.8

HRMS (EI$^+$) calcd for $C_{10}H_{10}FO^+$ 165.0710, found 165.0683

3-fluoro-3-methyl-2,3-dihydro-1H-inden-1-one (29)

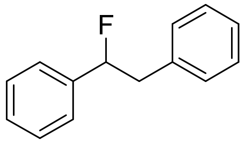


29

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.77 (d, J = 7.7 Hz, 1H), 7.73 (d, J = 4.1 Hz, 2H), 7.56 (m, 1H), 3.13 (dd, J = 20.5, 19.0 Hz, 1H), 2.88 (dd, J = 19.0, 11.7 Hz, 1H), 1.87 (d, J = 21.0 Hz, 3H); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 201.4 (d, J = 2.7 Hz), 153.8 (d, J = 20.2 Hz), 136.3 (d, J = 1.8 Hz), 135.6 (d, J = 2.3 Hz), 130.6 (d, J = 2.7 Hz), 124.3, 123.4, 95.5 (d, J = 176.1 Hz), 50.7 (d, J = 23.7 Hz), 25.9 (d, J = 29.8 Hz); **^{19}F-NMR** (470 MHz, $CDCl_3$) δ –-129.9

HRMS (EI$^+$) calcd for $C_{10}H_9FO^+$ 164.0637, found 164.0616

(1-fluoroethane-1,2-diyl)dibenzene (30)

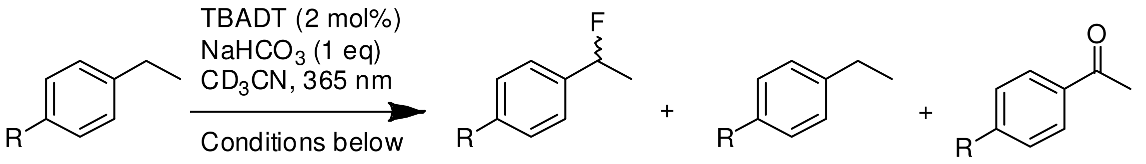


30

This compound was isolated as an inseparable mixture with the parent compound. The spectral data derived was consistent with that reported by others.[7]

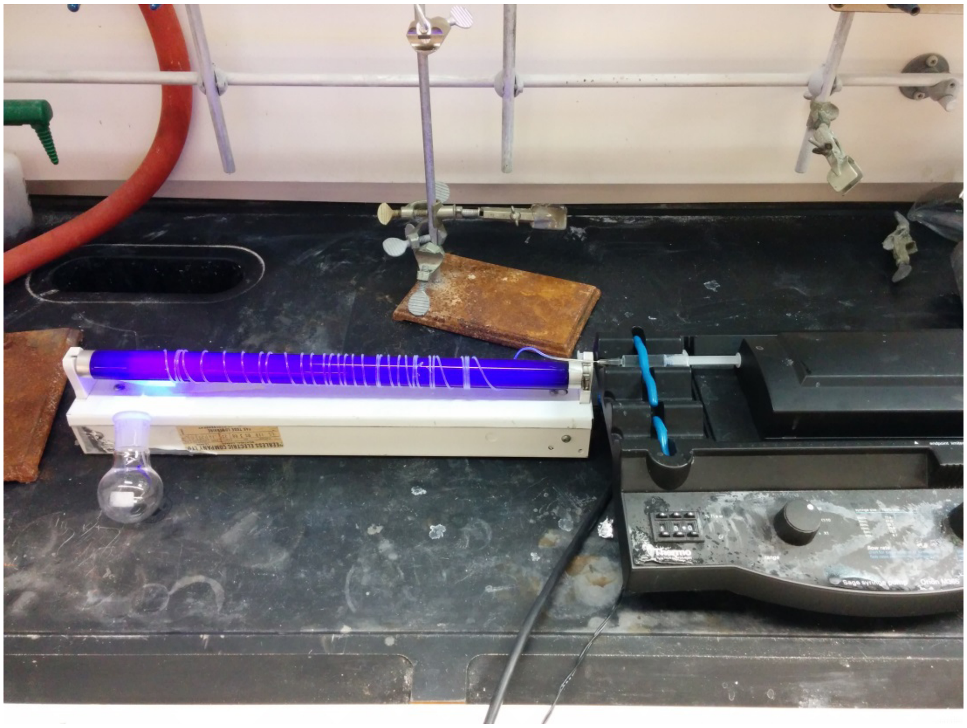
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.32 (m, 10H), 5.61 (ddd, J = 47.4, 8.1, 4.9 Hz, 1H), 3.27 (ddd, J = 17.4, 14.3, 8.1 Hz, 1H), 3.11 (ddd, J = 28.7, 14.3, 4.9 Hz, 1H)); **^{13}C-NMR** (150 MHz, $CDCl_3$) δ 139.9 (d, J = 19.9 Hz), 136.8 (d, J = 3.9 Hz), 129.7, 128.5, 128.5, 128.5, 126.9, 125.8 (d, J = 6.6 Hz), 95.0 (d, J = 174.1 Hz), 44.1(d, J = 24.6 Hz); **^{19}F-NMR** (470 MHz, $CDCl_3$) δ –175.3

HRMS (EI$^+$) calcd for $C_{14}H_{13}F^+$ 200.1001, found 200.1008



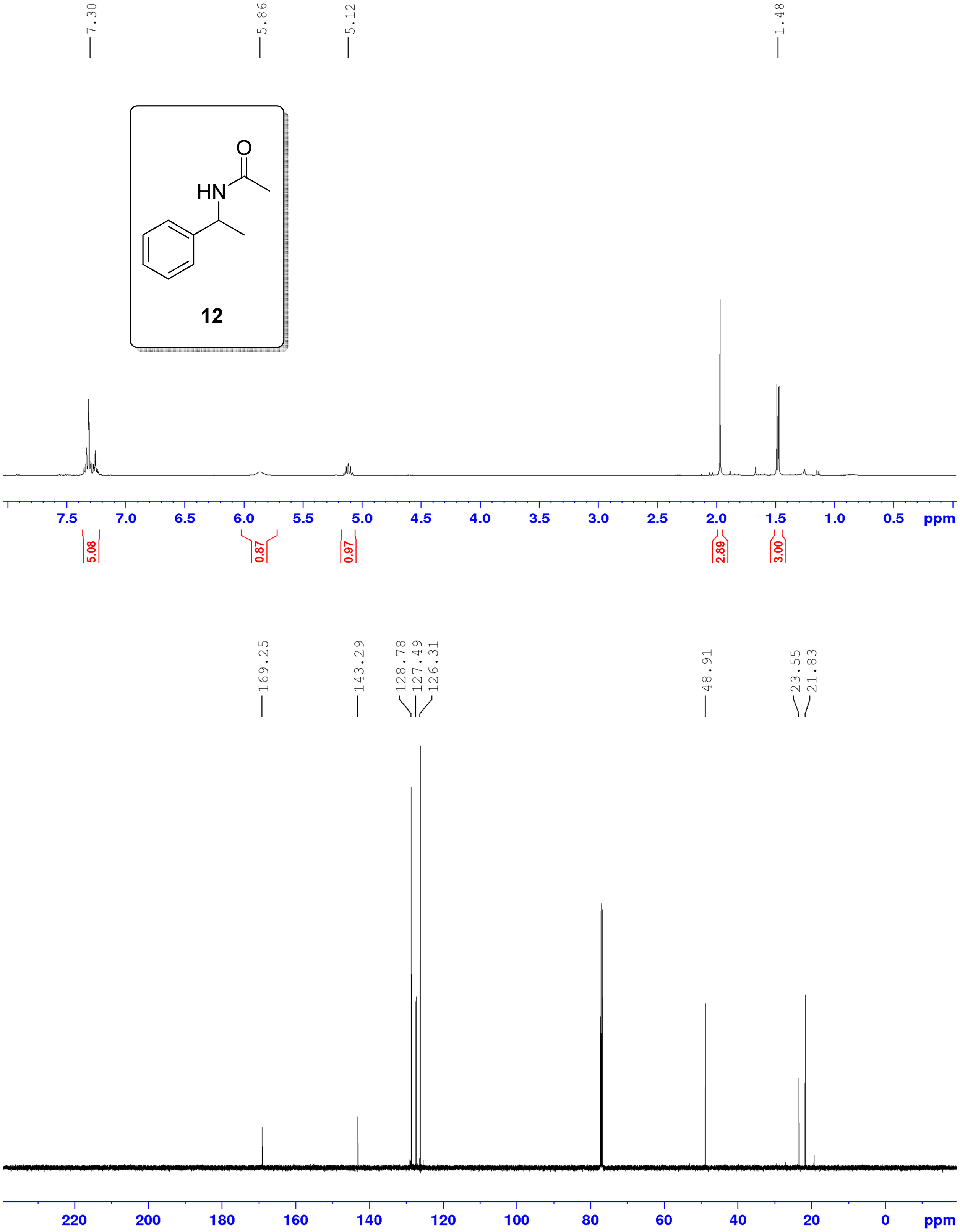
2 eq NFSI R = H	4 h	39 %	59 %	1 %
	24 h	76 %	19 %	5 %
	96h	78 %	8 %	14 %
24 h irradiation R = C(O)CH$_3$	1 eq NFSI	16 %	64 %	21 %
	2 eq NFSI	22 %	56 %	22 %
	3 eq NFSI	29 %	51 %	21 %
	4 eq NFSI	31 %	47 %	22 %
3 eq NFSI R = C(O)CH$_3$	24 h	32 %	48 %	21 %
	48 h	43 %	22 %	35 %
	72 h	47 %	16 %	37 %
	96 h	47 %	13 %	40 %
3 eq NFSI R = C(O)CH$_3$ Deoxygenated reaction mixture	24 h	47 %	41 %	12 %
	48 h	58 %	26 %	15 %
	120 h	60 %	20 %	20 %

Supporting Table S1: Optimization of TBADT-catalyzed benzylic fluorination



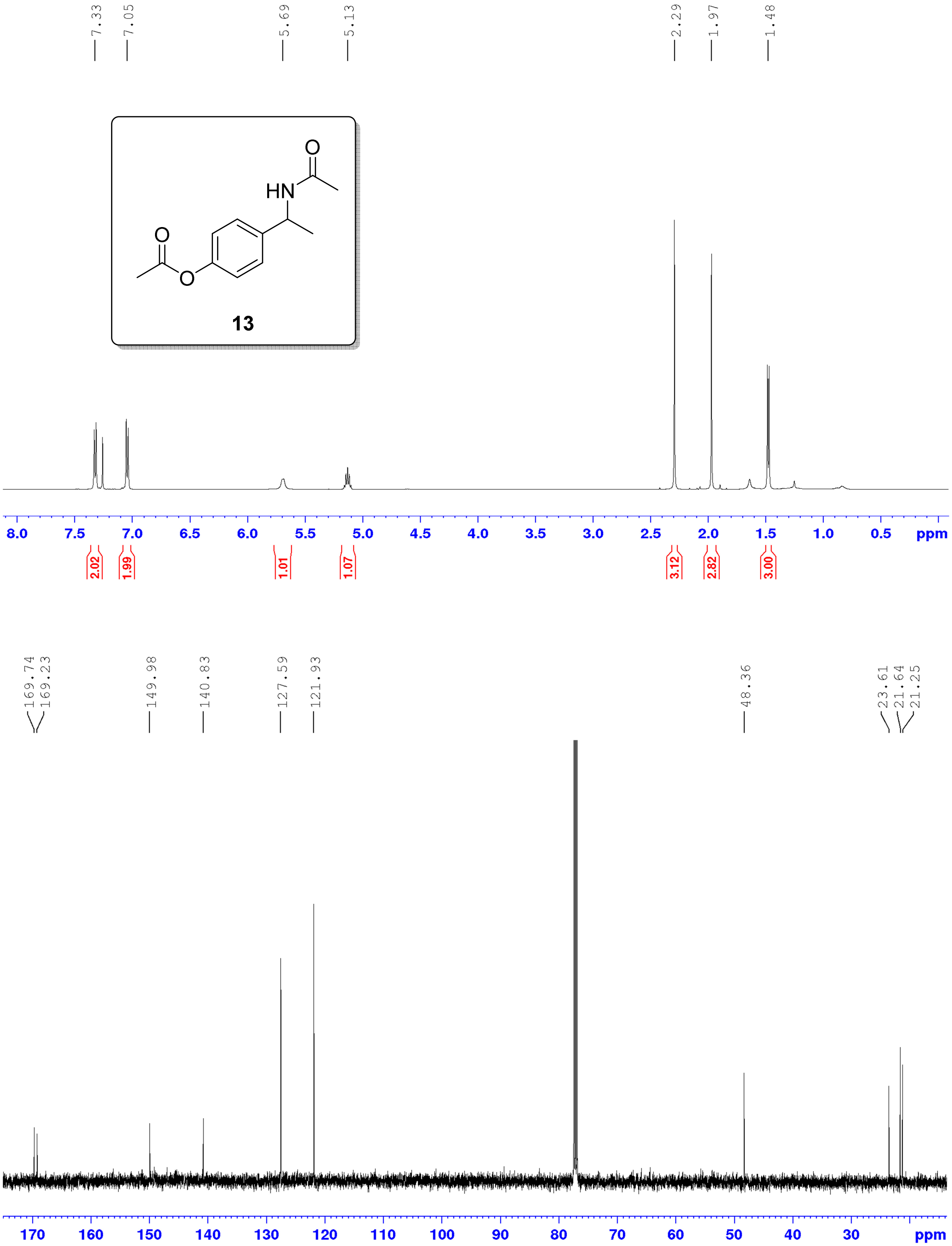
Supporting Figure S1: Flow apparatus for TBADT-catalyzed benzylic fluorination

12



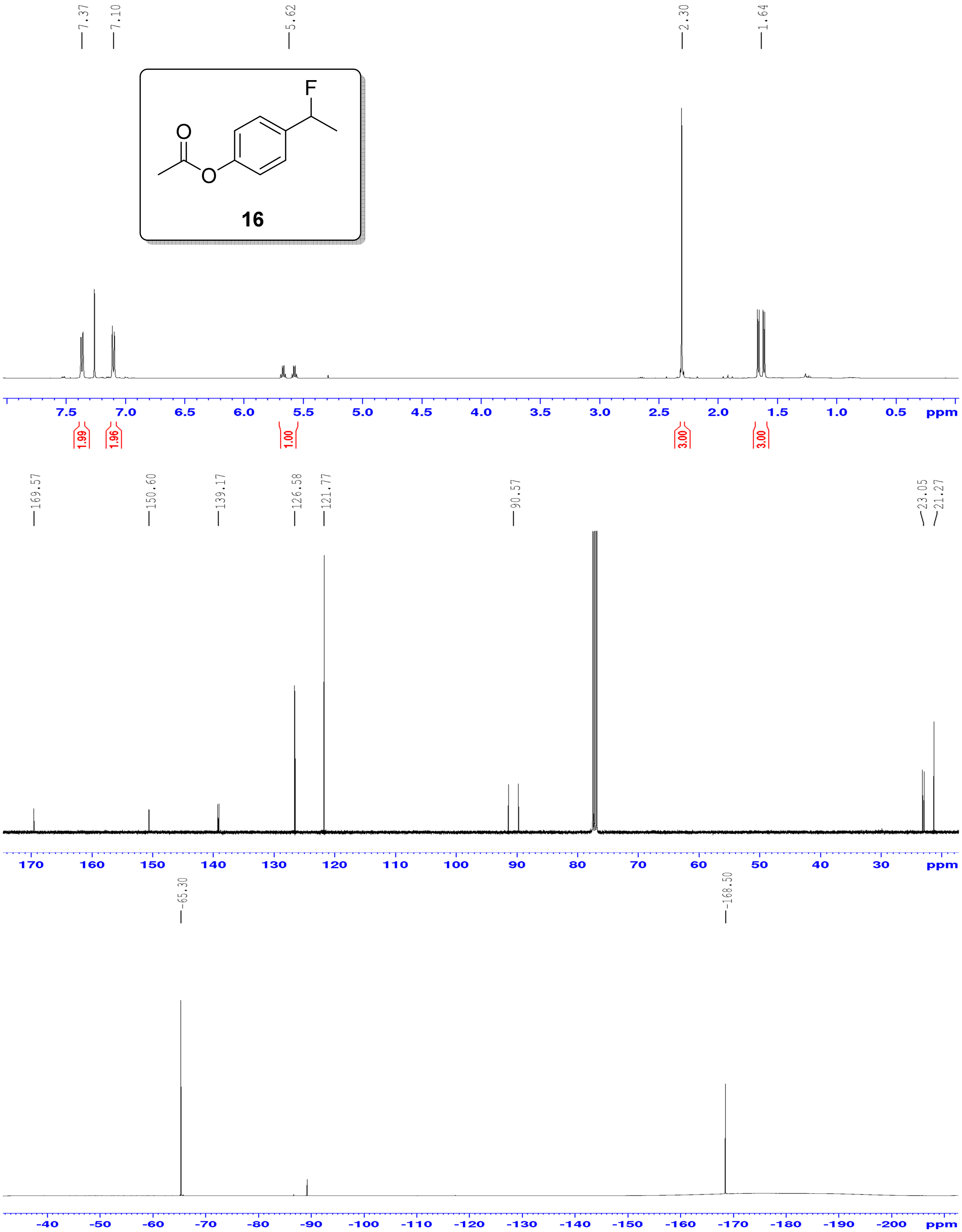
^{1}H and ^{13}C NMR spectra of **12**

13



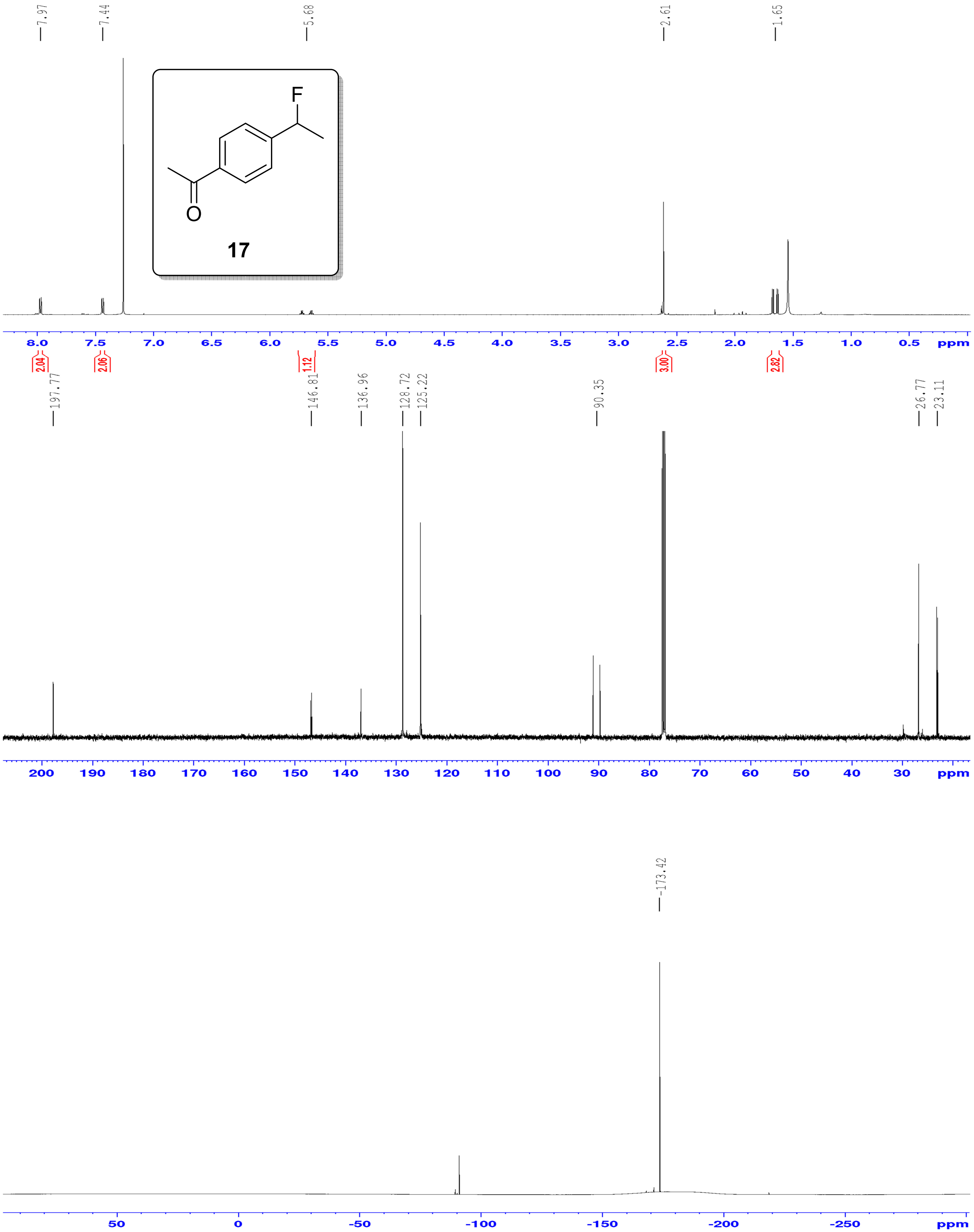
^{1}H and ^{13}C NMR spectra of **13**

16



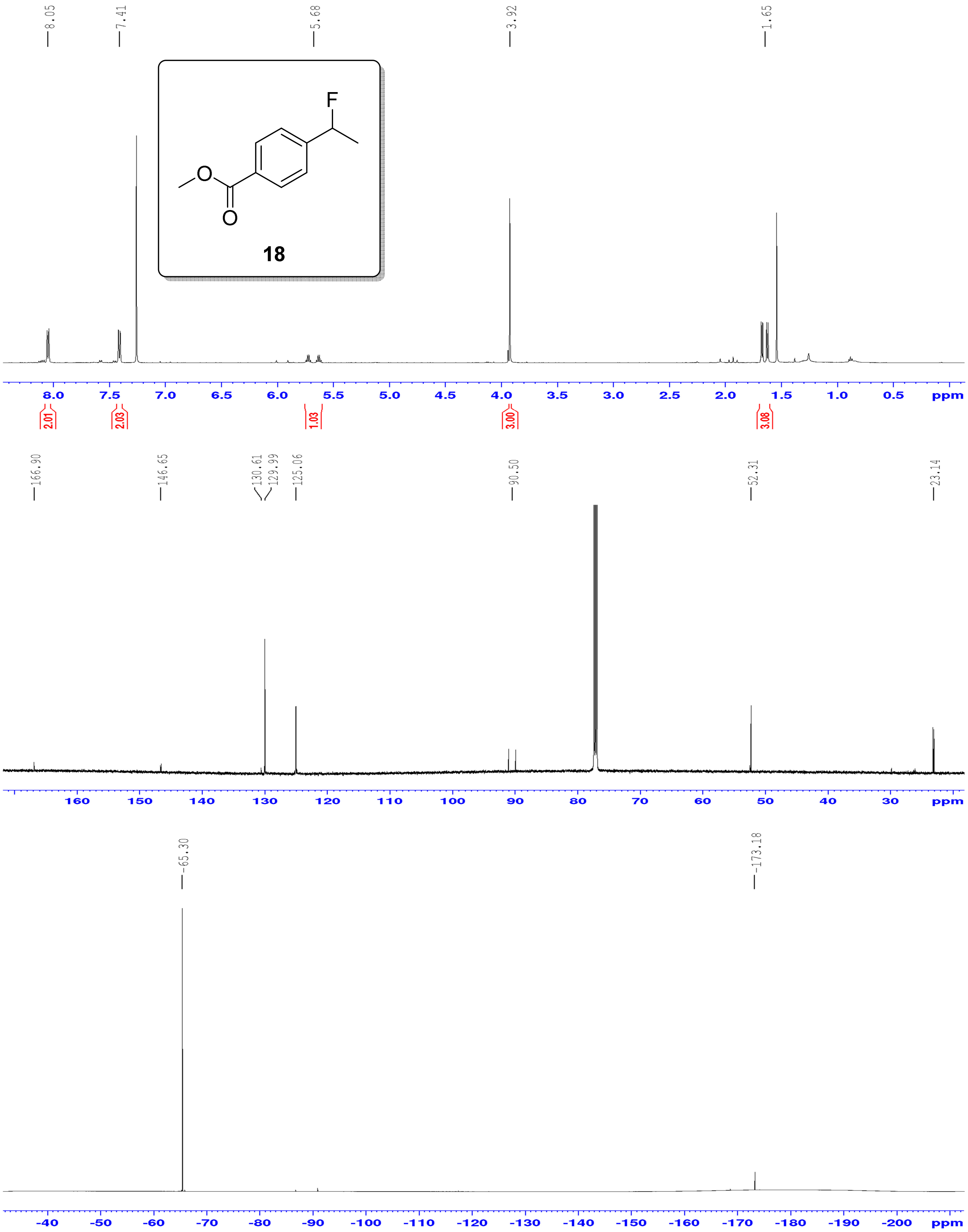
^{1}H, ^{13}C and ^{19}F NMR spectra of **16**

17



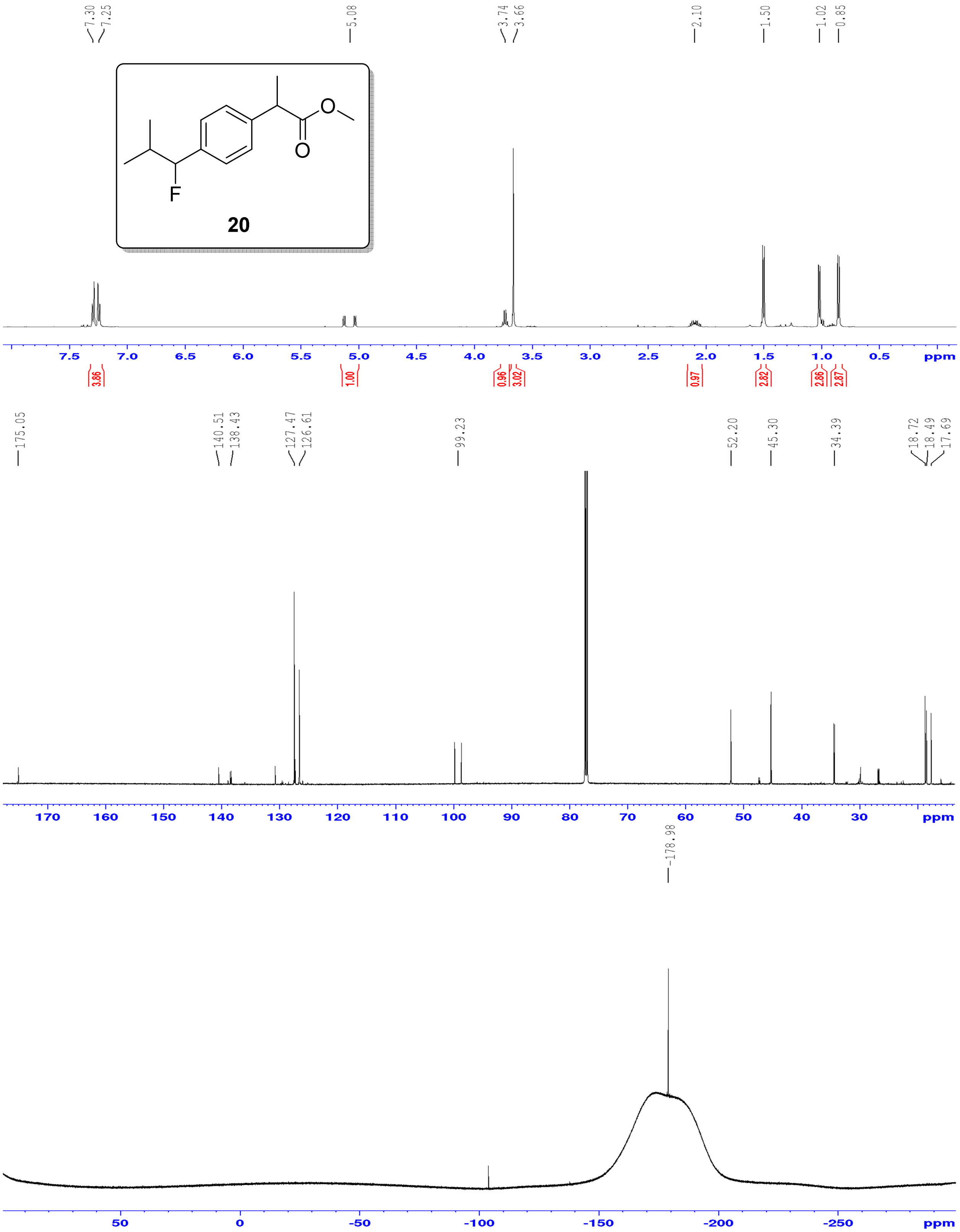
^{1}H, ^{13}C and ^{19}F NMR spectra of **17**

18



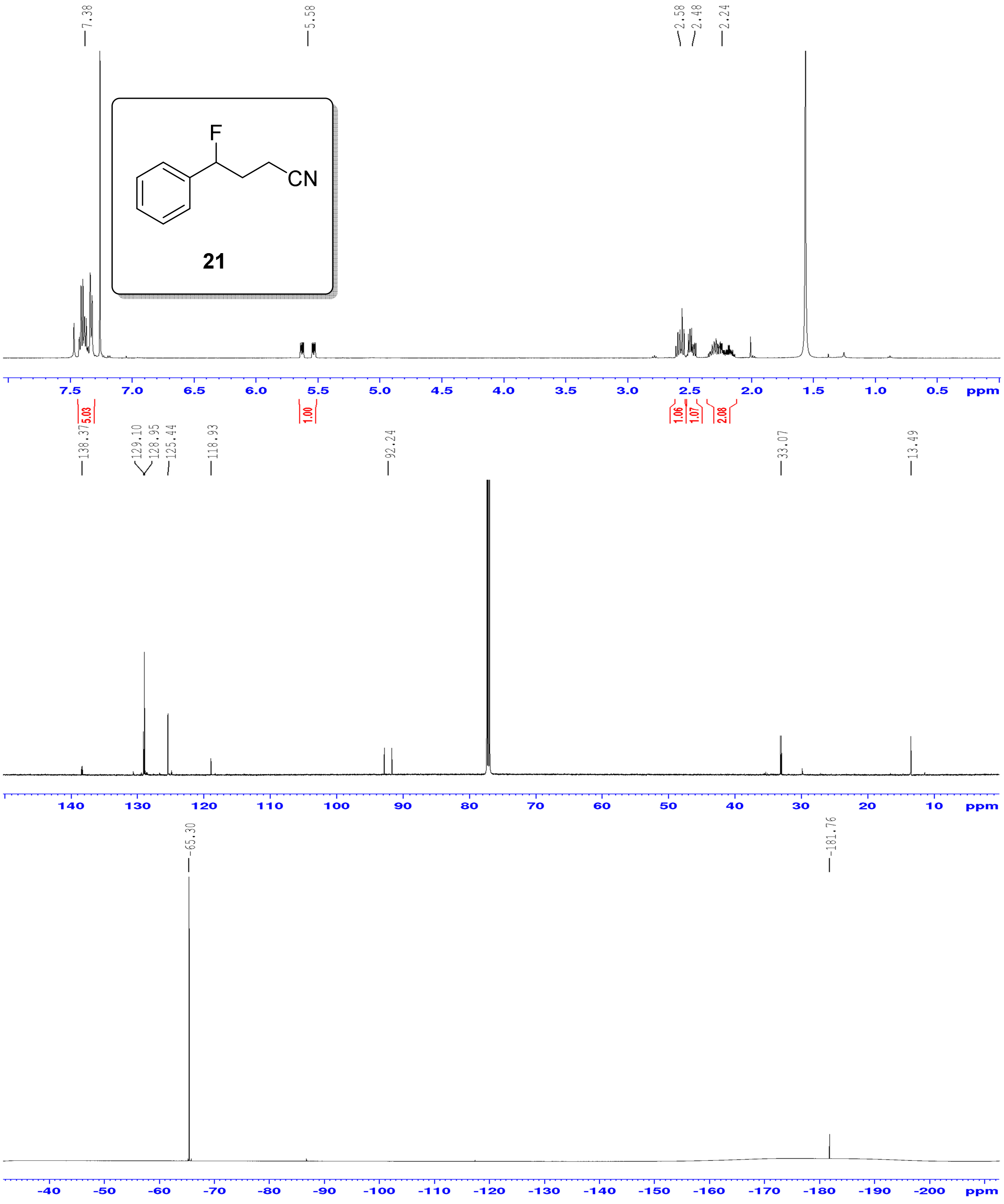
^{1}H, ^{13}C and ^{19}F NMR spectra of **18**

20



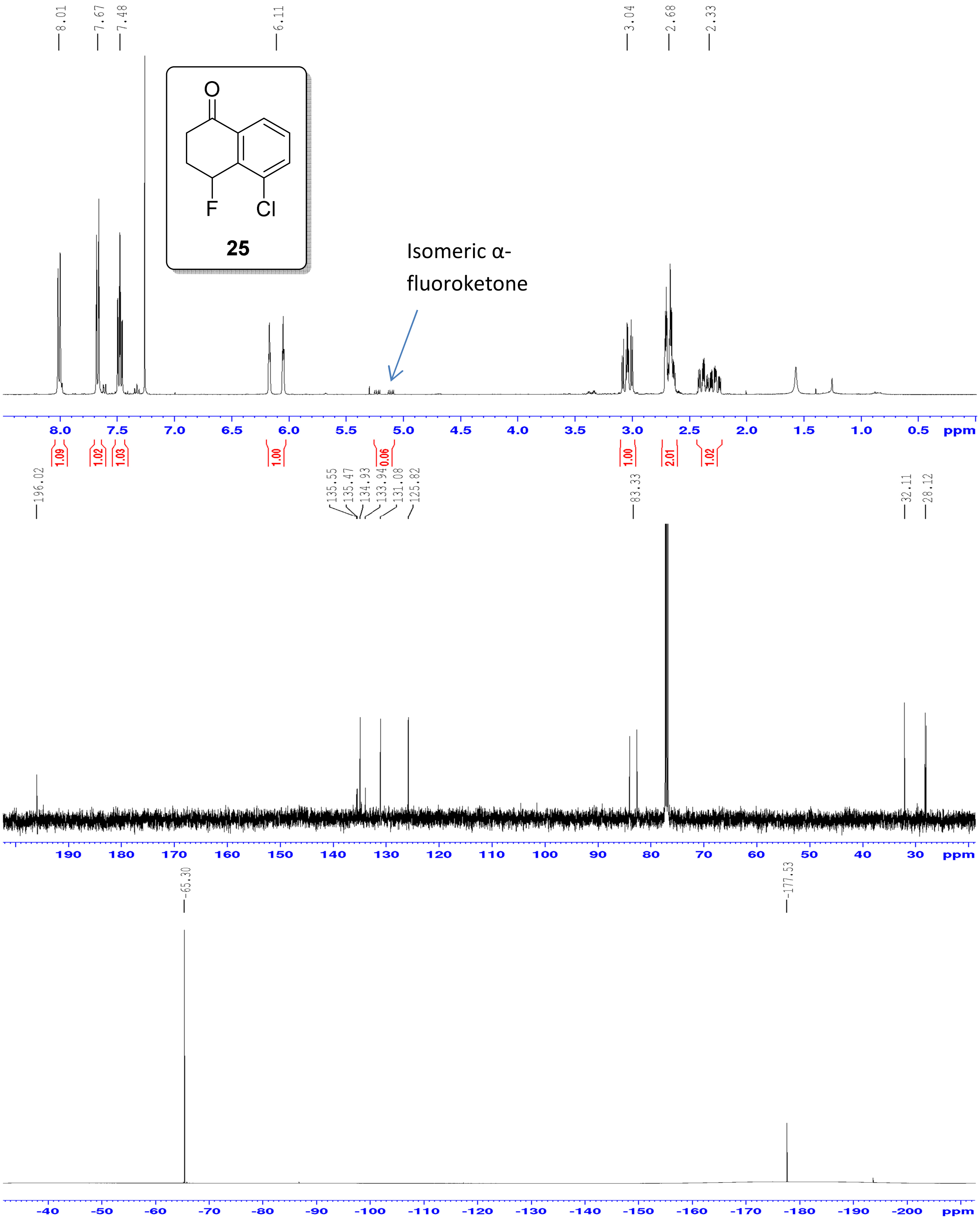
^{1}H, ^{13}C and ^{19}F NMR spectra of **20**

21

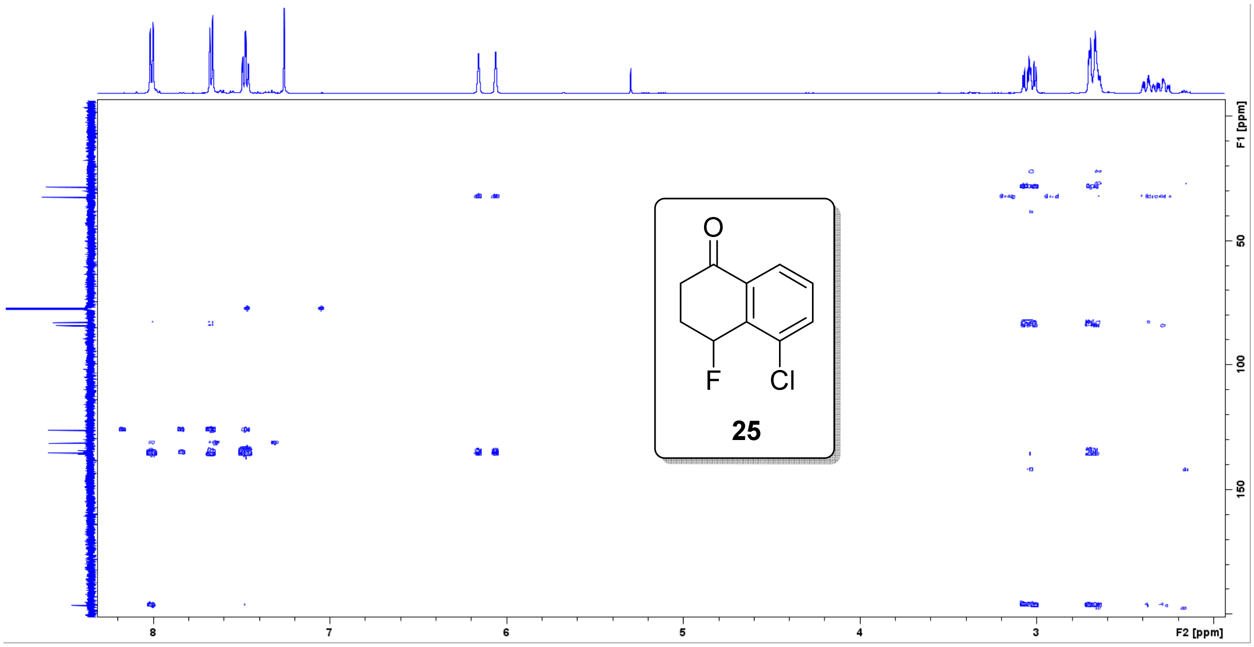


^{1}H, ^{13}C and ^{19}F NMR spectra of **21**

25

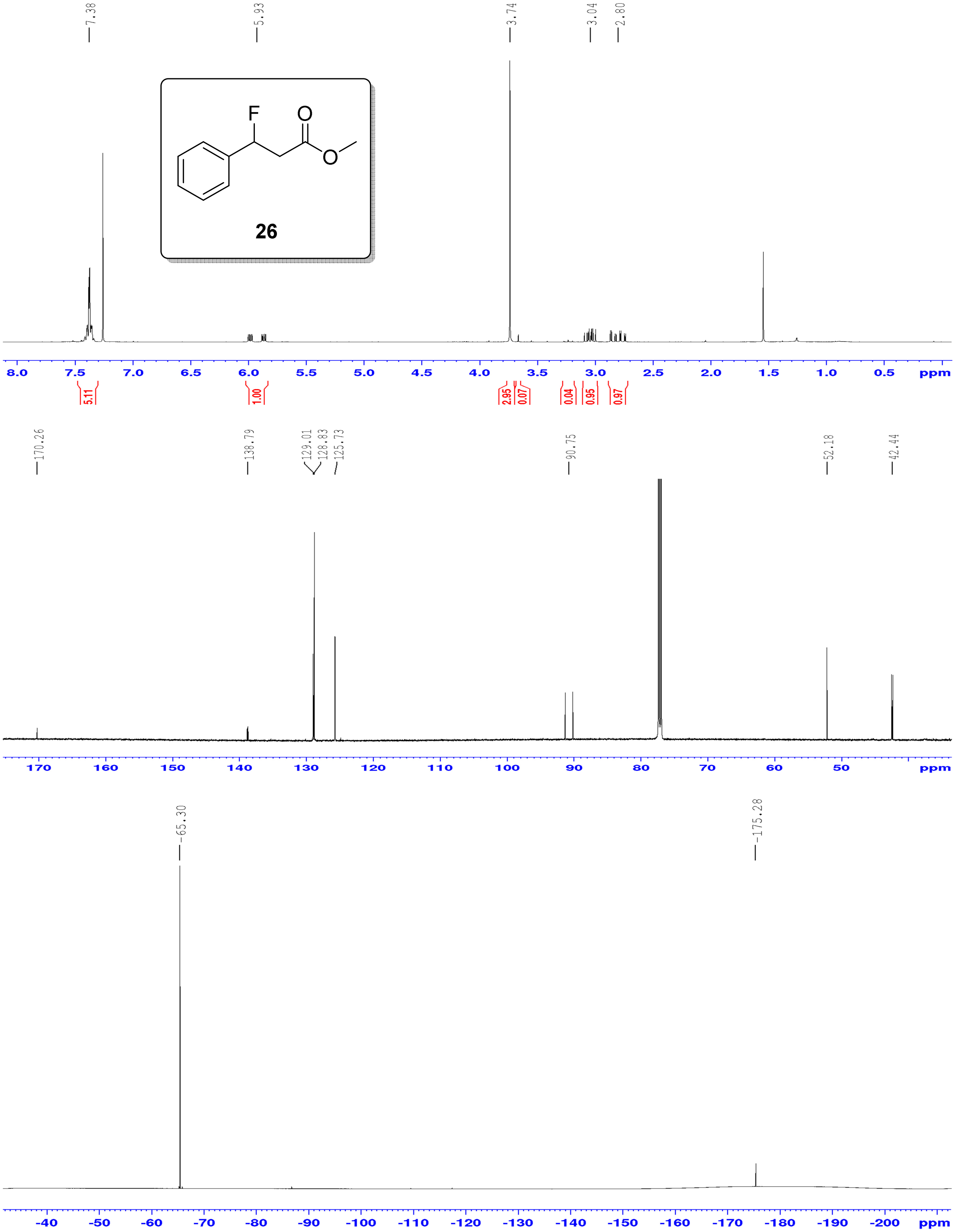


^{1}H, ^{13}C and ^{19}F NMR spectra of **25** containing 6% of isomeric α-fluoroketone



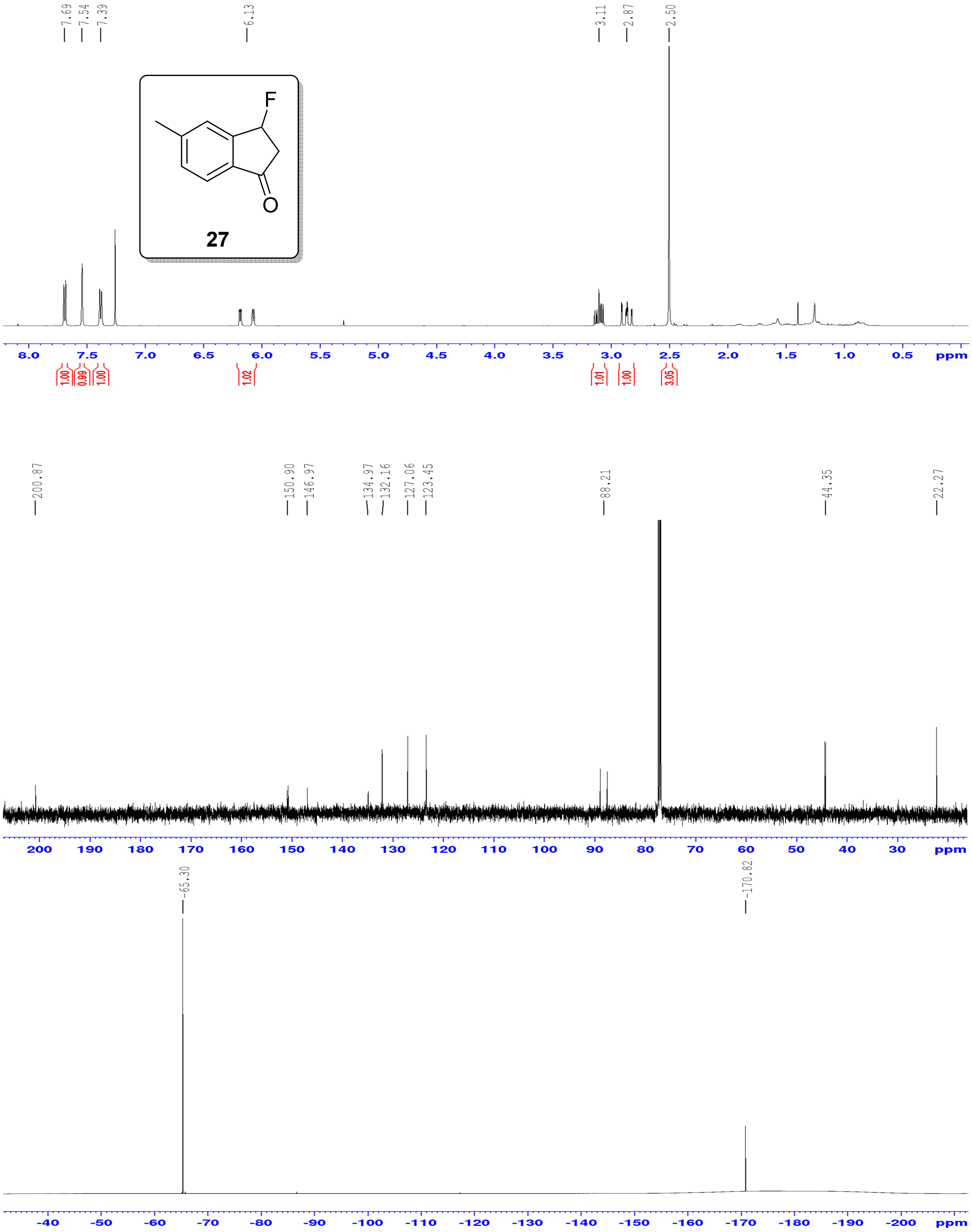
HMBC spectrum of compound **25**

26

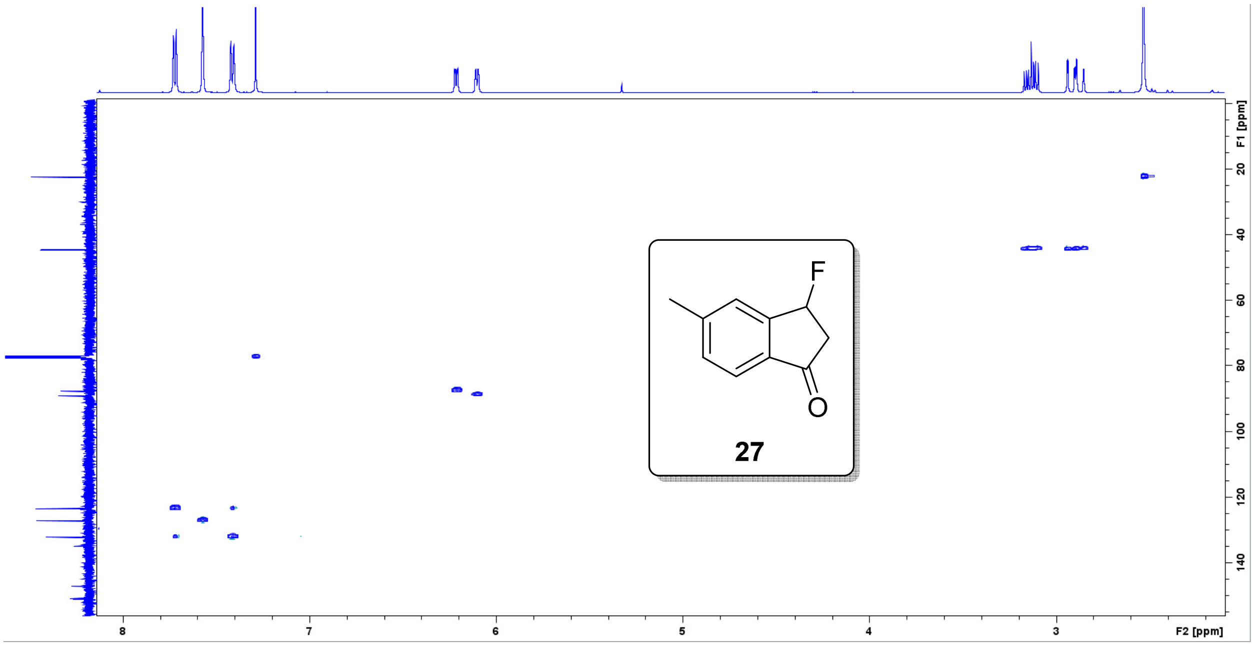


^{1}H, ^{13}C and ^{19}F NMR spectra of **26**

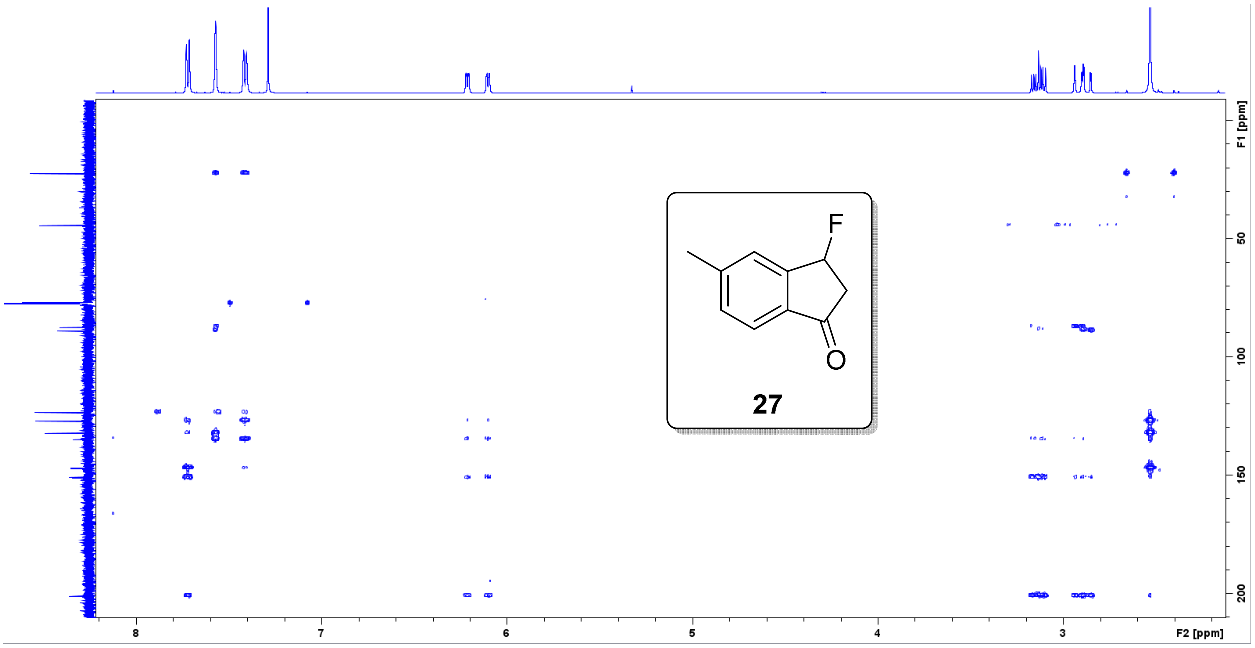
27



^{1}H, ^{13}C and ^{19}F NMR spectra of **27**

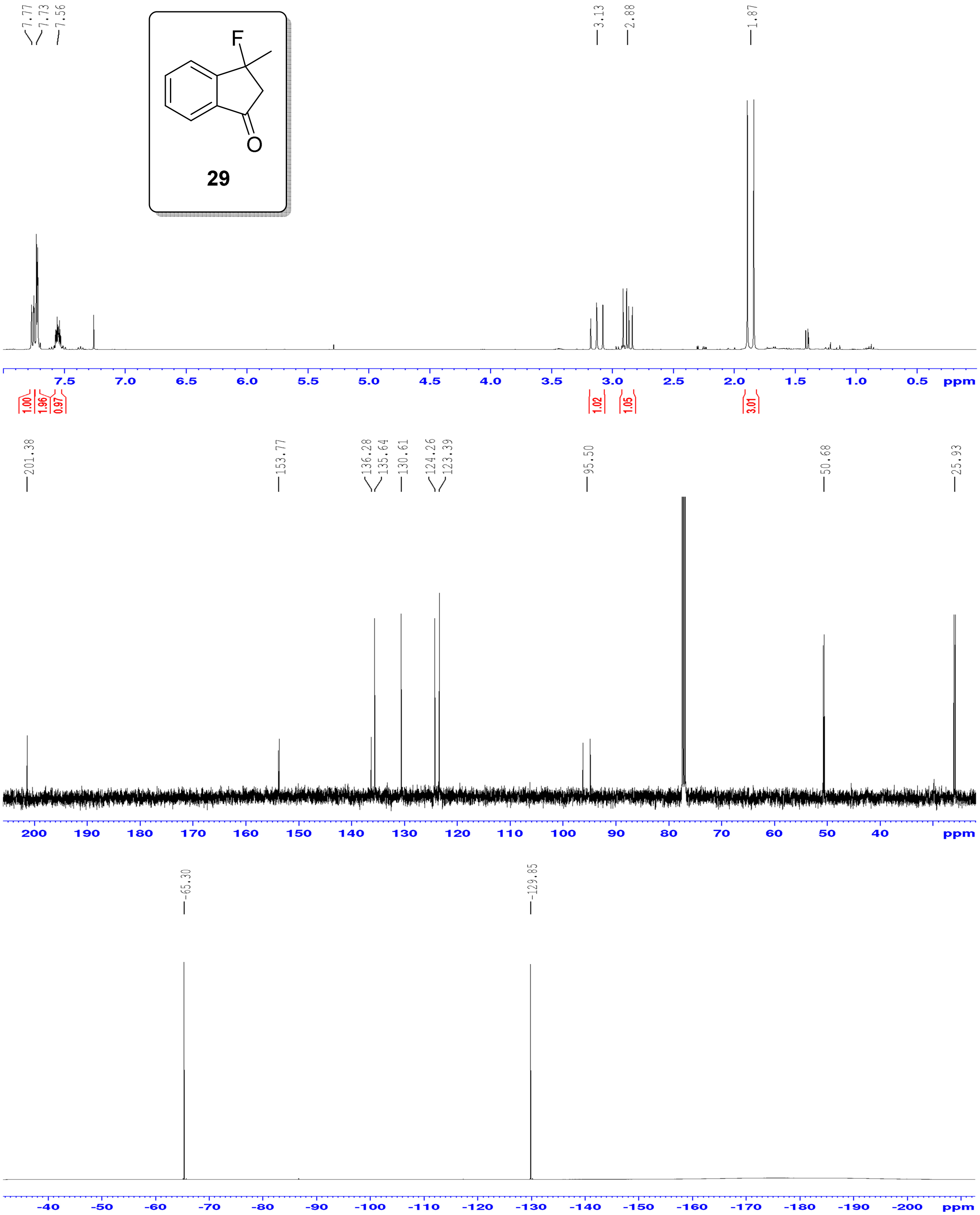


HSQC spectrum of compound **27**



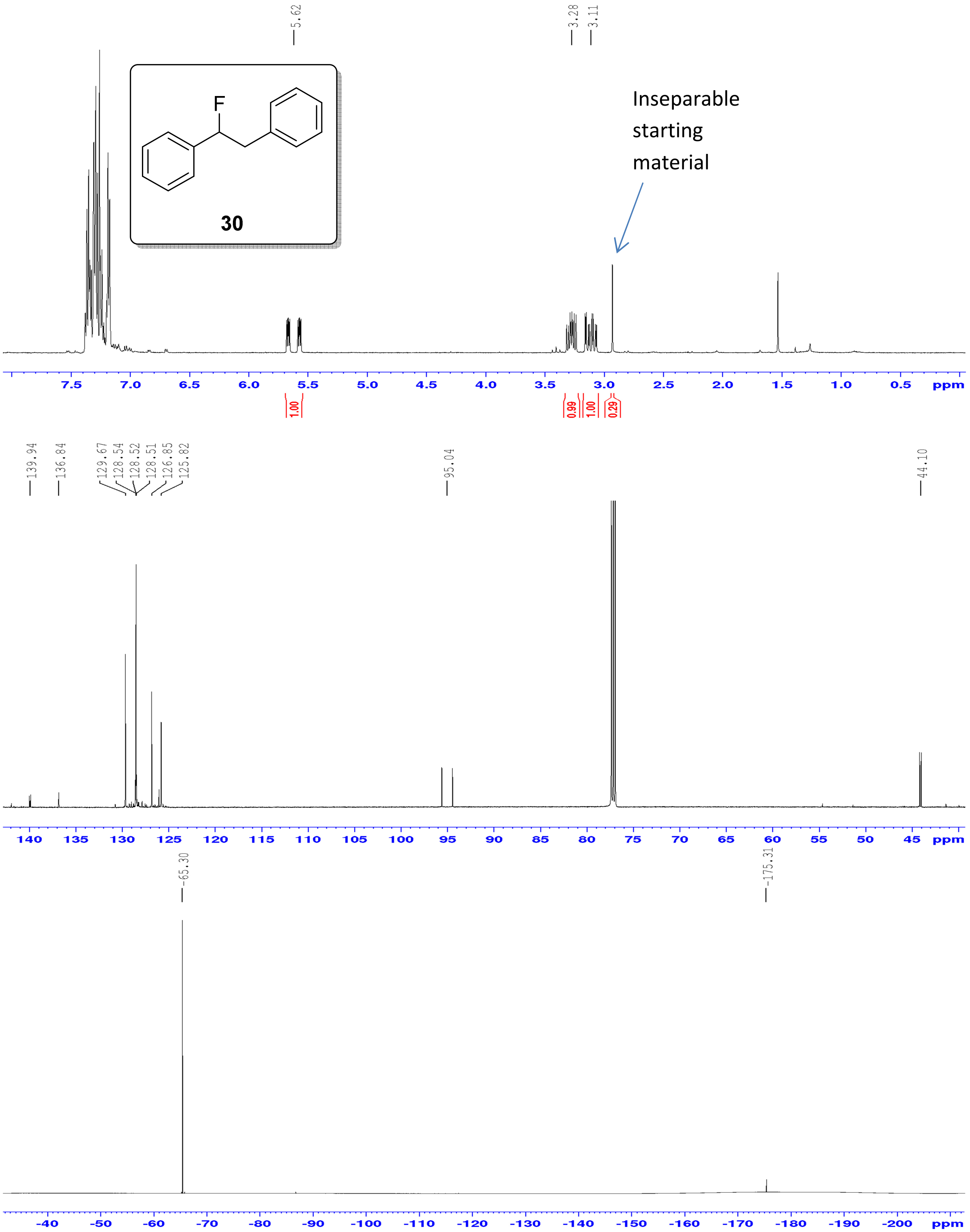
HMBC spectrum of compound **27**

29

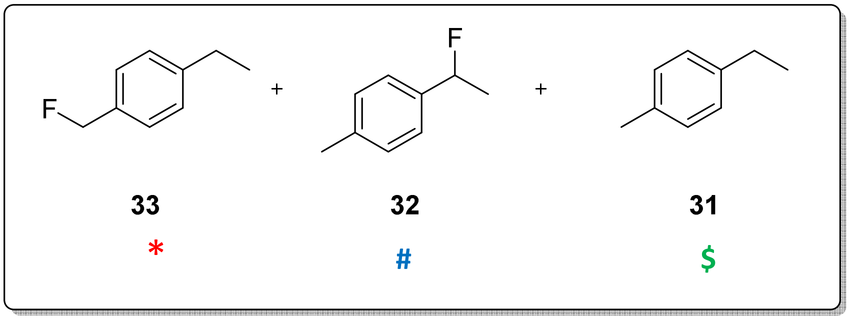


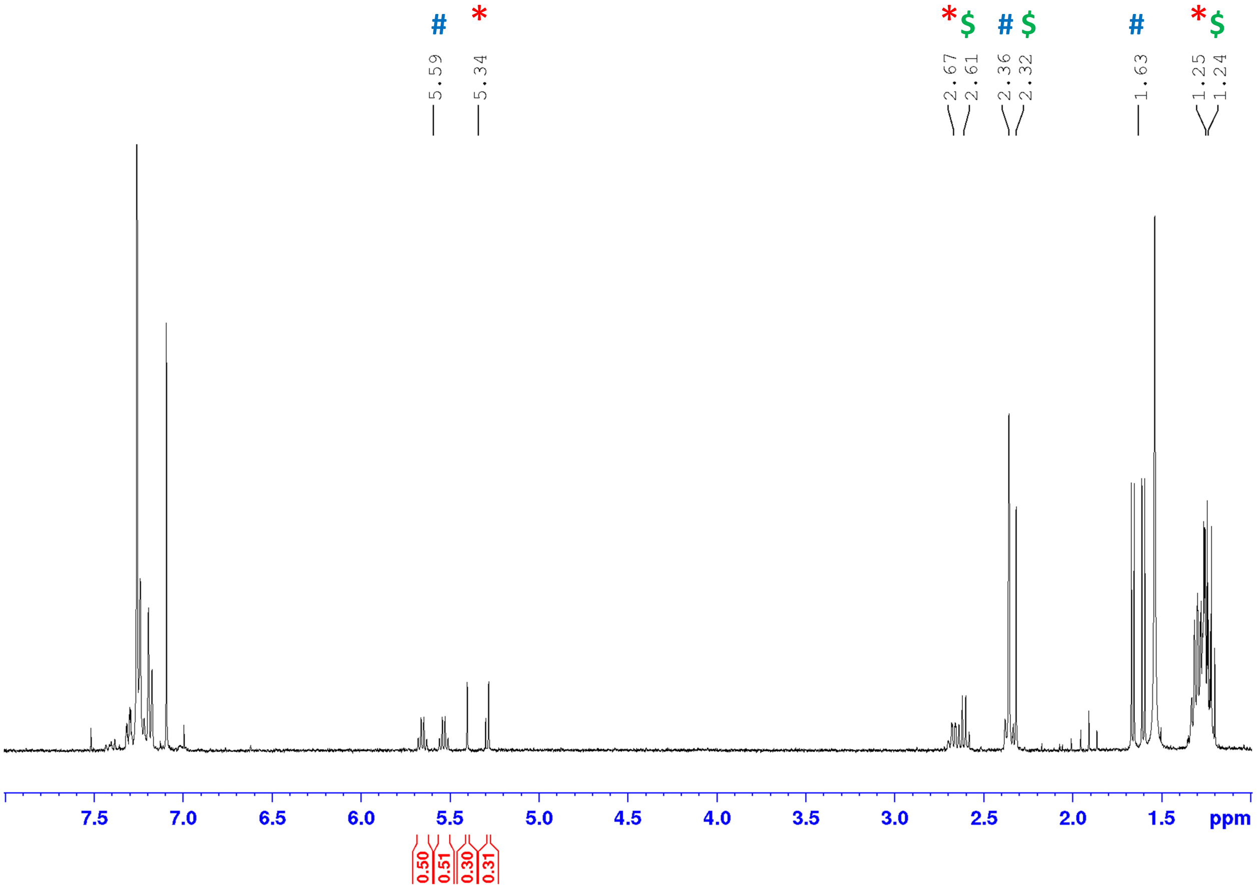
^{1}H, ^{13}C, ^{19}F NMR spectra of **29** containing 4% starting material

30

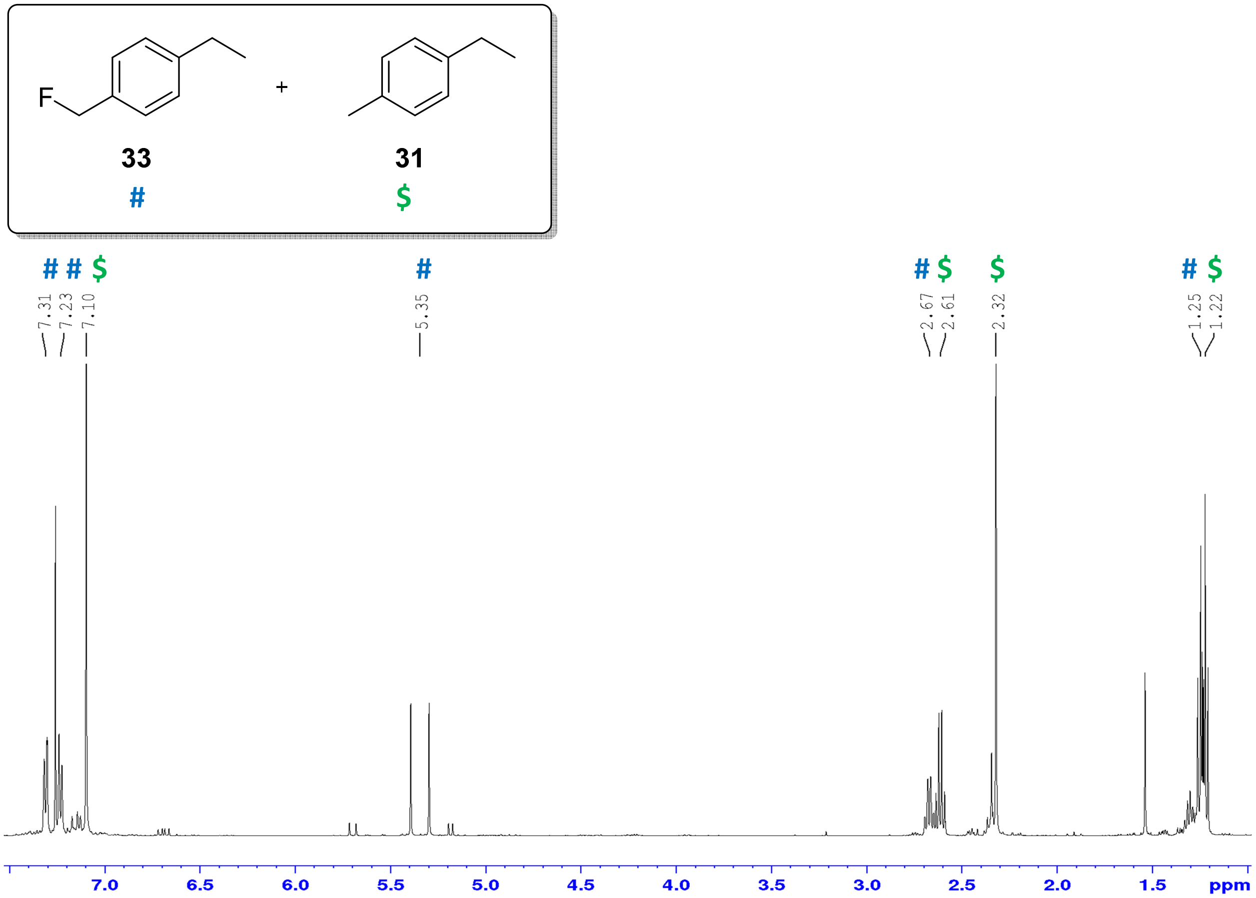


^{1}H, ^{13}C and ^{19}F NMR spectra of **30** containing 7% of the starting material as an inseparable impurity

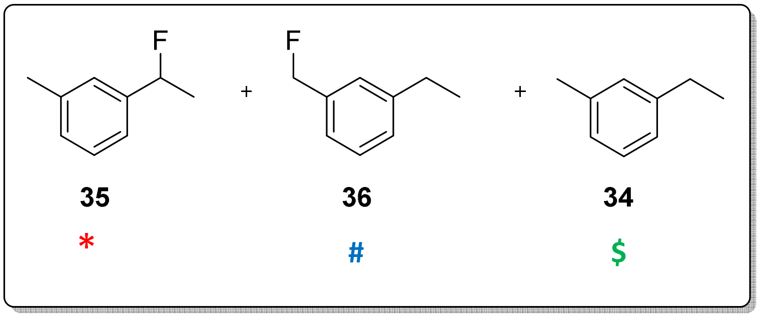


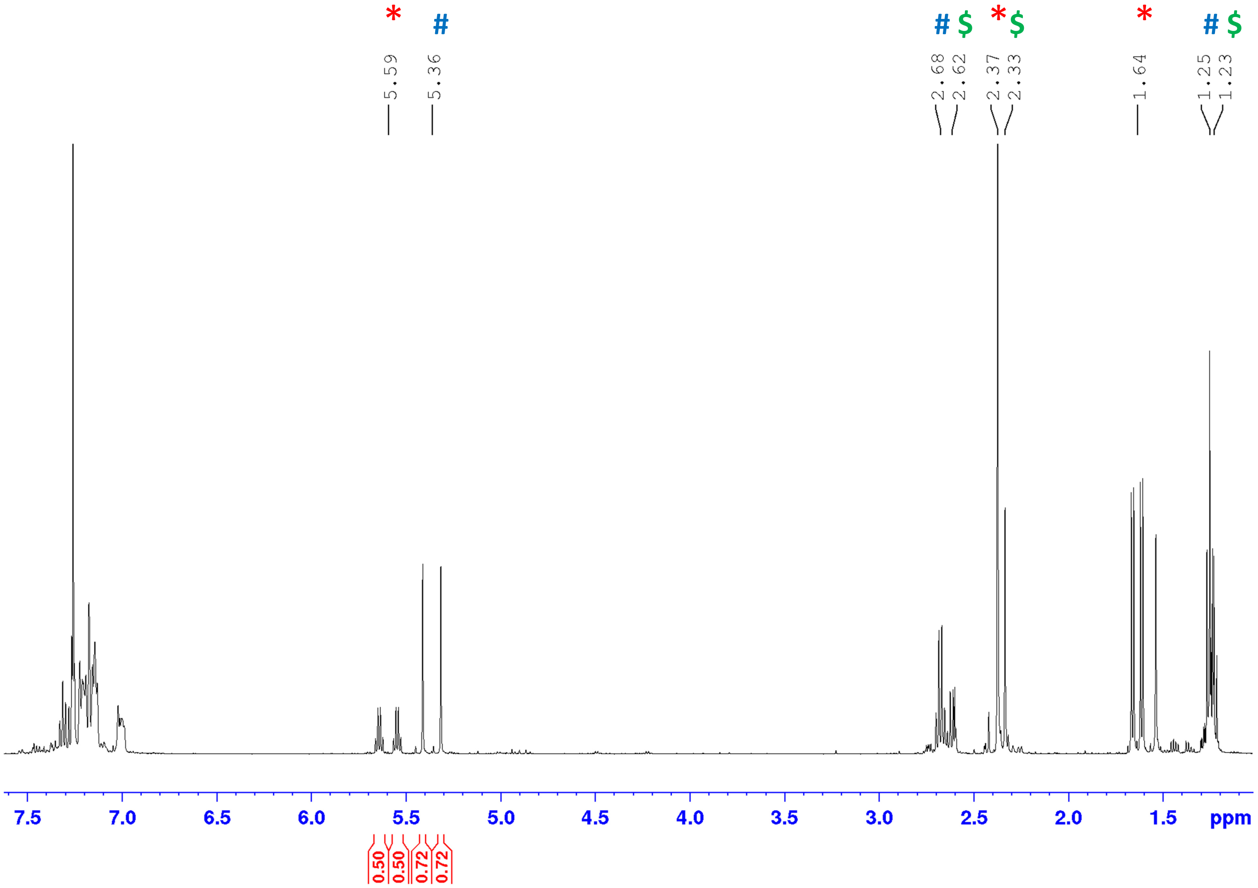


^{1}H NMR spectrum of a partially purified mixture of **31**, **32** and **33** produced using conditions A (Scheme 3)

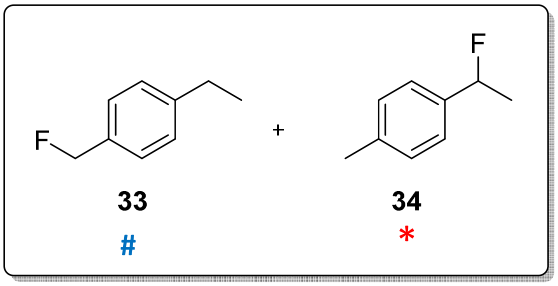


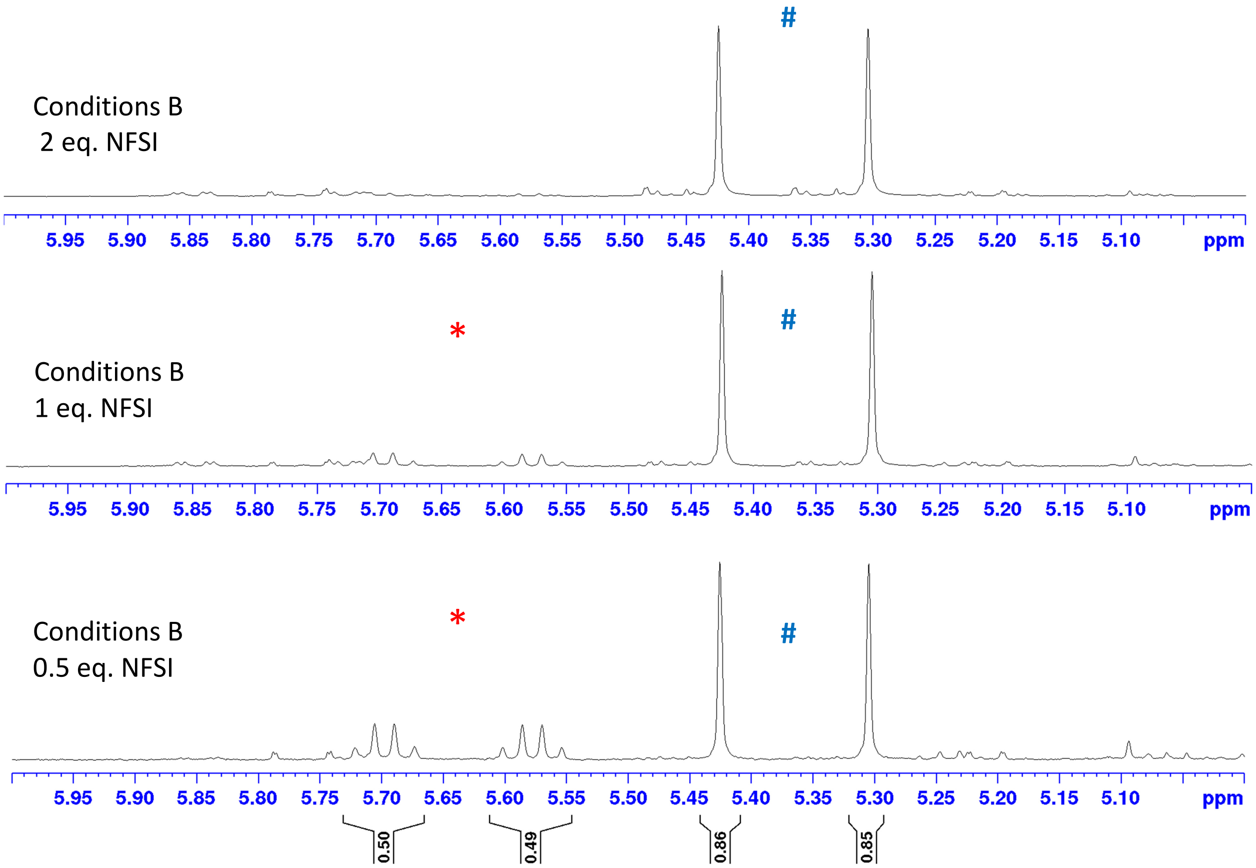
^{1}H NMR spectrum of a partially purified mixture of **31** and **33** produced using conditions B (Scheme 3)





^{1}H NMR spectrum of a partially purified mixture of **34**, **35** and **36** produced using conditions B (Scheme 3)





^{1}H NMR spectra of the AIBN-initiated fluorination of **31** with 2, 1 and 0.5 eq. NFSI

Supplementary references:

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