Supporting Information

Metal- and base-free synthesis of functionalized α, α-difluoroimines via electrophilic fluorination of *N*-substituted enamines

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1. General Information

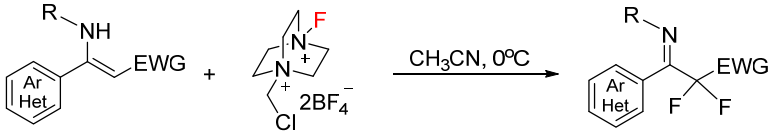
Unless otherwise stated, all commercial reagents were used as received. Reactions were conducted in dry glassware using anhydrous solvents (pass through activated alumina columns). Reaction temperatures were controlled using IKAmag temperature modulator, and unless stated otherwise, reactions were performed at room temperature (rt, approximately, 24 ^{o}C). Thin-layer chromatography (TLC) was conducted on plates (GF254) supplied by Yantai Chemicals (China) and visualized using a combination of UV, anisaldehyde, iodine, and potassium permanganate staining. Silica gel (200-300 mesh) supplied by Tsingdao Haiyang Chemicals (China) was used for flash column chromatography. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on Bruker spectrometers (400 MHz, 500 MHz). Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26), carbon (chloroform δ 77.16) or tetramethylsilane (TMS δ 0.00) was used as a reference. Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), bs (broad singlet). Coupling constants were reported in Hertz (Hz). All high resolution mass spectra were obtained from the Tianjin University Mass Spectrometry Facility.

2. Experimental procedure

(A) Materials

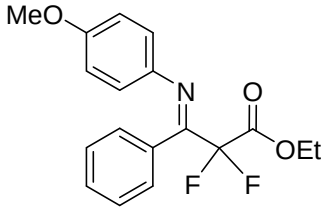
Substrates (Enamines) were prepared according to the known procedures.[1]

(B) Experimental procedure for functionalized α-fluoroinime synthesis

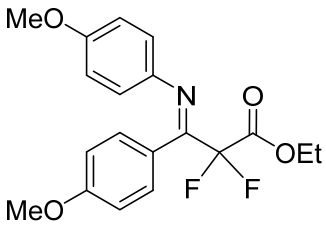


1 **Selectfluor** **2**

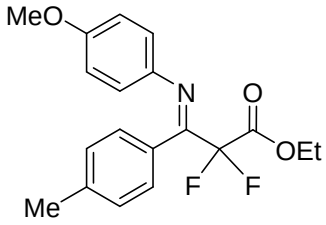
The stirred solution of enamine **1** (0.5 mmol) in CH_3CN (5 mL) was cooled to 0 ^oC, and Selectfluor (443 mg, 1.25 mmol) was added in portions. The resulting mixture was stirred at 0 ^oC till **1** was completely consumed (1h, monitored by TLC). After that, the reaction mixture was diluted with Et_2O and filtered through a pad of Celite. The combined organic mixture was concentrated in vacuo and purified by silica gel column chromatography (Hexane/EtOAc) to afford the desired product **2**.



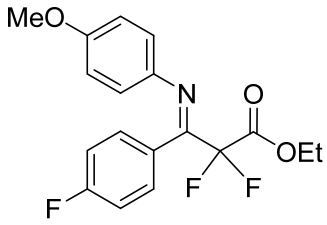
Ethyl (*E*)-2,2-difluoro-3-((4-methoxyphenyl)imino)-3-phenylpropanoate (2a): 158 mg, 95% yield; Yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.39 – 7.32 (m, 3H), 7.28 – 7.26 (m, 2H), 6.69 (s, 4H), 4.44 (q, *J* = 7 Hz, 2H), 3.73 (s, 3H), 1.40 (t, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 163.36 (t, *J* = 31 Hz), 159.81 (t, *J* = 30 Hz), 157.86, 140.02, 131.00, 130.04, 128.91, 128.72, 123.64, 114.01, 113.13 (t, *J* = 253 Hz), 63.07, 55.45, 14.19; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): – 105.11; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{18}H_{18}F_2NO_3$) requires *m/z* 334.1255, found *m/z* 334.1260



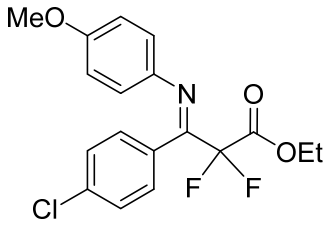
Ethyl (*E*)-2,2-difluoro-3-(4-methoxyphenyl)-3-((4-methoxyphenyl)imino)propanoate (2b): 162 mg, 89% yield; Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.23 (d, *J* = 9 Hz, 2H), 6.82 (d, *J* = 9 Hz, 2H), 6.71 (s, 4H), 4.43 (q, *J* = 7 Hz, 2H), 3.79 (s, 3H), 3.73 (s, 3H), 1.39 (t, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 163.45 (t, *J* = 31 Hz), 160.82, 159.45 (t, *J* = 30 Hz), 157.60, 140.42, 130.69, 123.28, 122.73, 114.11, 114.07, 113.35 (t, *J* = 253 Hz), 62.97, 55.41, 55.32, 14.14; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): – 104.80; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{19}H_{20}F_2NO_4$) requires *m/z* 364.1360, found *m/z* 364.1364



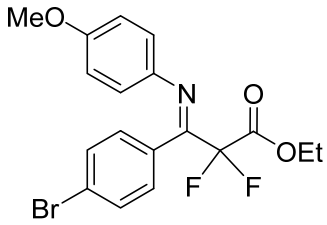
Ethyl (*E*)-2,2-difluoro-3-((4-methoxyphenyl)imino)-3-(p-tolyl)propanoate (2c): 153 mg, 88% yield; Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.17 (d, *J* = 8 Hz, 2H), 7.13 (d, *J* = 8 Hz, 2H), 6.70 (s, 4H), 4.43 (q, *J* = 7 Hz, 2H), 3.73 (s, 3H), 2.33 (s, 3H), 1.40 (t, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 163.45 (t, *J* = 31 Hz), 159.94 (t, *J* = 30 Hz), 157.72, 140.28, 140.26, 129.41, 128.87, 127.88, 123.48, 114.01, 113.23 (t, *J* = 253 Hz), 63.01, 55.44, 21.57, 14.18; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): – 105.05; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{19}H_{20}F_2NO_3$) requires *m/z* 348.1411, found *m/z* 348.11410



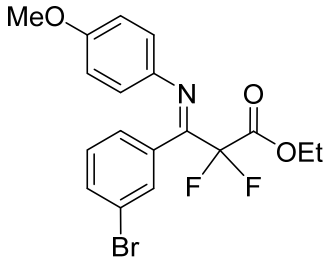
Ethyl (*E*)-2,2-difluoro-3-(4-fluorophenyl)-3-((4-methoxyphenyl)imino)propanoate (2d): 160 mg, 91% yield; Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.32 – 7.29 (m, 2H), 7.07 – 7.02 (m, 2H), 6.75 – 6.69 (m, 4H), 4.47 (q, *J* = 7 Hz, 2H), 3.76 (s, 3H), 1.42 (t, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 163.39 (d, *J* = 250 Hz), 163.07 (t, *J* = 31 Hz), 158.67 (t, *J* = 30 Hz), 157.82, 139.72, 131.09 (d, *J* = 9 Hz), 126.71 (d, *J* = 4 Hz), 123.33, 115.93 (d, *J* = 22 Hz), 114.02, 112.95 (t, *J* = 253 Hz), 63.02, 55.34, 14.05; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): –104.99, –109.24; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{18}H_{17}F_3NO_3$) requires *m/z* 352.1161, found *m/z* 352.1165;



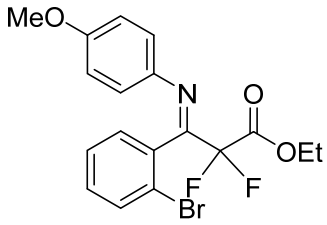
Ethyl (*E*)-3-(4-chlorophenyl)-2,2-difluoro-3-((4-methoxyphenyl)imino)propanoate (2e): 178 mg, 97% yield; Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.31 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 6.72 – 6.67 (m, 4H), 4.44 (q, *J* = 7 Hz, 2H), 3.72 (s, 3H), 1.39 (t, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 163.04 (t, *J* = 31 Hz), 158.57 (t, *J* = 30 Hz), 158.00, 139.65, 136.30, 130.36, 129.21, 129.09, 123.44, 114.12, 112.96 (t, *J* = 253 Hz), 63.12, 55.39, 14.11; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): – 104.95; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{18}H_{17}ClF_2NO_3$) requires *m/z* 368.0865, found *m/z* 368.0870



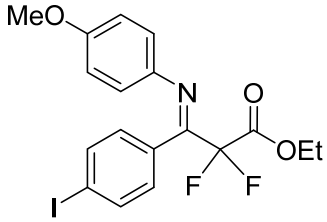
Ethyl (*E*)-3-(4-bromophenyl)-2,2-difluoro-3-((4-methoxyphenyl)imino)propanoate (2f): 196 mg, 95% yield; Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.47 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 6.73 – 6.67 (m, 4H), 4.44 (q, *J* = 7 Hz, 2H), 3.74 (s, 3H), 1.40 (t, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 163.09 (t, *J* = 31 Hz), 158.63 (t, *J* = 30 Hz), 158.05, 139.67, 132.09, 130.57, 129.72, 124.72, 123.50, 114.18, 112.95 (t, *J* = 253 Hz), 63.18, 55.47, 14.17; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): – 104.95; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{18}H_{17}BrF_2NO_3$) requires *m/z* 412.0360, found *m/z* 412.0363



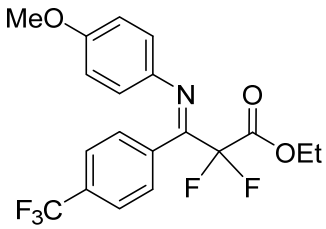
Ethyl (*E*)-3-(3-bromophenyl)-2,2-difluoro-3-((4-methoxyphenyl)imino)propanoate (2g): 190 mg, 92% yield; Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.51 (dt, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.47 (s, 1H), 7.21 – 7.16 (m, 2H), 6.70 (d, *J* = 2.5 Hz, 4H), 4.44 (q, *J* = 7 Hz, 2H), 3.72 (s, 3H), 1.40 (t, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 162.96 (t, *J* = 31 Hz), 158.17, 157.83 (t, *J* = 30 Hz), 139.35, 133.17, 132.90, 131.54, 130.29, 127.58, 123.68, 122.80, 114.12, 112.84 (t, *J* = 253 Hz), 63.15, 55.42, 14.12; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): – 104.98; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{18}H_{17}BrF_2NO_3$) requires *m/z* 412.0360, found *m/z* 412.0362



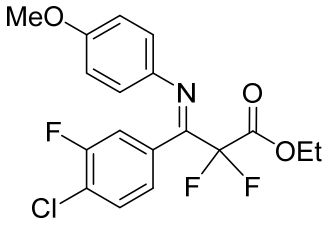
Ethyl (*E*)-3-(2-bromophenyl)-2,2-difluoro-3-((4-methoxyphenyl)imino)propanoate (2h): 177 mg, 86% yield; Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.56 (d, *J* = 8 Hz, 1H), 7.41 – 7.36 (m, 2H), 7.31 – 7.27 (m, 1H), 6.81 (d, *J* = 9 Hz, 2H), 6.71 (d, *J* = 9 Hz, 2H), 4.54 – 4.43 (m, 2H), 3.74 (s, 2H), 1.44 (t, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 163.09 (t, *J* = 31 Hz), 158.49, 157.49 (dd, *J* = 33 Hz, 29 Hz), 139.40, 133.33, 133.28, 131.27, 130.72, 127.47, 124.07, 121.61, 113.86, 112.44 (dd, *J* = 255 Hz, 251 Hz), 63.15, 55.40, 14.21; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): – 104.37 (d, *J* = 277 Hz), – 106.78, (d, *J* = 277 Hz) ; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{18}H_{17}BrF_2NO_3$) requires *m/z* 412.0360, found *m/z* 412.0364



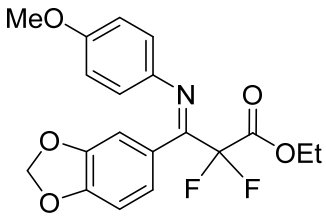
Ethyl (*E*)-2,2-difluoro-3-(4-iodophenyl)-3-((4-methoxyphenyl)imino)propanoate (4i): 220 mg, 96% yield; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.68 (d, *J* = 8 Hz, 2H), 7.01 (d, *J* = 8 Hz, 2H), 6.73 – 6.67 (m, 4H), 4.44 (q, *J* = 7 Hz, 2H), 3.73 (s, 3H), 1.39 (t, *J* = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.04 (t, *J* = 31 Hz), 158.67 (t, *J* = 30 Hz), 158.01, 139.61, 137.96, 130.49, 130.25, 123.48, 114.14, 112.89 (t, *J* = 253 Hz), 96.77, 63.14, 55.42, 14.14; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): – 104.93; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{18}H_{17}F_2INO_3$) requires *m/z* 460.0221, found *m/z* 460.0225



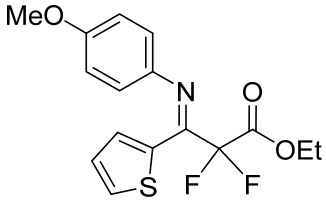
Ethyl (*E*)-2,2-difluoro-3-((4-methoxyphenyl)imino)-3-(4-(trifluoromethyl)phenyl)propanoate (2j): 199 mg, 99% yield; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.61 (d, *J* = 8 Hz, 2H), 7.41 (d, *J* = 8 Hz, 2H), 6.89 (q, *J* = 9 Hz, 4H), 4.46 (q, *J* = 7 Hz, 2H), 3.74 (s, 3H), 1.41 (t, *J* = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 162.83 (t, *J* = 31 Hz), 158.12, 158.11 (t, *J* = 31 Hz), 139.22, 134.51, 131.85 (q, *J* = 33 Hz), 129.35, 125.65 (q, *J* = 4 Hz), 123.59 (q, *J* = 271 Hz), 123.50, 114.09, 112.77 (t, *J* = 253 Hz), 63.16, 55.35, 14.05; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): – 63.07, – 104.94; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{19}H_{17}F_5NO_3$) requires *m/z* 402.1129, found *m/z* 402.1131



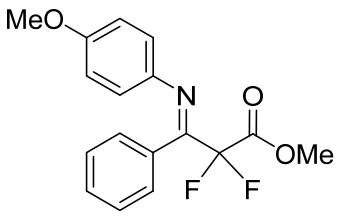
Ethyl (*E*)-3-(3-chloro-4-fluorophenyl)-2,2-difluoro-3-((4-methoxyphenyl)imino)propanoate (2k): 189 mg, 98% yield; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.40 – 7.38 (m, 1H), 7.15 – 7.07 (m, 2H), 6.74 – 6.67 (m, 4H), 4.44 (q, *J* = 7 Hz, 2H), 3.75 (s, 3H), 1.40 (t, *J* = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 162.91 (t, *J* = 31 Hz), 158.96 (d, *J* = 252 Hz), 158.23, 157.17 (t, *J* = 30 Hz), 139.31, 131.37, 129.34 (d, *J* = 8 Hz), 127.86 (d, *J* = 4 Hz), 123.52, 121.98 (d, *J* = 18 Hz), 117.22 (d, *J* = 21 Hz), 114.26, 112.87 (t, *J* = 253 Hz), 63.25, 55.48, 14.16; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): – 104.90, – 111.49; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{18}H_{16}ClF_3NO_3$) requires *m/z* 386.0771, found *m/z* 386.0773



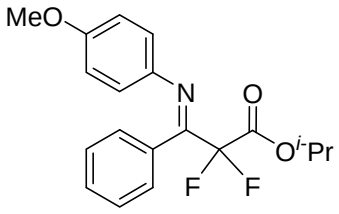
Ethyl (*E*)-3-(benzo[d][1,3]dioxol-5-yl)-2,2-difluoro-3-((4-methoxyphenyl)imino)propanoate (2l): 158 mg, 84% yield; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.80 – 6.72 (m, 7H), 5.96 (s, 2H), 4.43 (q, *J* = 7 Hz, 2H), 3.74 (s, 3H), 1.39 (t, *J* = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.36 (t, *J* = 31 Hz), 158.99 (t, *J* = 30 Hz), 157.80, 149.08, 147.90, 140.09, 124.10, 123.69, 123.41, 114.11, 113.19 (t, *J* = 253 Hz), 109.21, 108.73, 101.59, 63.04, 55.45, 14.17; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): – 104.83; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{19}H_{18}F_2NO_5$) requires *m/z* 378.1153, found *m/z* 378.1157



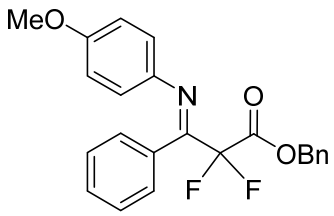
Ethyl (*Z*)-2,2-difluoro-3-((4-methoxyphenyl)imino)-3-(thiophen-2-yl)propanoate (2m): 132 mg, 78% yield; Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.57 – 7.56 (m, 1H), 7.42 (dd, *J* = 8 Hz, 1 Hz, 1H), 7.01 (dd, *J* = 5 Hz, 4 Hz, 1H), 6.88 (d, *J* = 9 Hz, 2H), 6.73 (d, *J* = 9 Hz, 2H), 4.41 (q, *J* = 7 Hz, 2H), 3.81 (s, 3H), 1.36 (t, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 163.01 (t, *J* = 31 Hz), 157.76, 153.44 (t, *J* = 30 Hz), 141.47, 133.12 (t, *J* = 4 Hz), 131.71, 129.47 (t, *J* = 3 Hz), 126.77, 120.71, 114.89, 113.74 (t, *J* = 256 Hz), 63.12, 55.58, 14.13; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): – 103.98; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{16}H_{16}F_2NO_3S$) requires *m/z* 340.0819, found *m/z* 340.0821



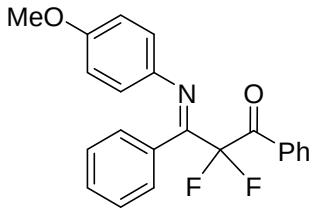
Methyl (*E*)-2,2-difluoro-3-((4-methoxyphenyl)imino)-3-phenylpropanoate (2n): 150 mg, 94% yield; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.42 – 7.29 (m, 5H), 6.72 (s, 4H), 3.99 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.88 (t, *J* = 31 Hz), 159.73 (t, *J* = 30 Hz), 157.88, 139.87, 130.86, 130.08, 128.87, 128.73, 123.70, 113.98, 113.43 (t, *J* = 253 Hz), 55.42, 53.55; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): –105.14; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{17}H_{16}F_2NO_3$) requires *m/z* 320.1098, found *m/z* 320.1093



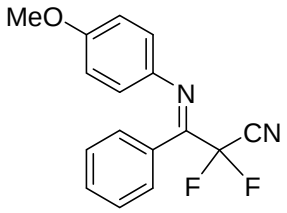
Isopropyl (*E*)-2,2-difluoro-3-((4-methoxyphenyl)imino)-3-phenylpropanoate (2o): 160 mg, 92% yield; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.41 – 7.28 (m, 5H), 6.71 (s, 4H), 5.34 – 5.28 (m, 1H), 3.75 (s, 3H), 1.41 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 162.88 (t, *J* = 31 Hz), 159.83 (t, *J* = 30 Hz), 157.81, 140.06, 131.04, 130.01, 128.91, 128.70, 123.59, 114.00, 112.88 (t, *J* = 253 Hz), 71.32, 55.44, 21.70; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): –104.96; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{19}H_{20}F_2NO_3$) requires *m/z* 348.1411, found *m/z* 348.1414



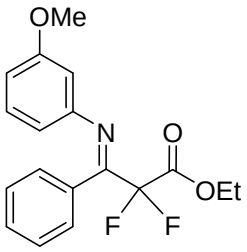
Benzyl (*E*)-2,2-difluoro-3-((4-methoxyphenyl)imino)-3-phenylpropanoate (2p): 178 mg, 90% yield; Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.49 – 7.48 (m, 2H), 7.43 – 7.38 (m, 4H), 7.35 (t, *J* = 8 Hz, 2H), 7.29 (d, *J* = 8 Hz, 2H), 6.71 (d, *J* = 9 Hz, 2H), 6.64 (d, *J* = 9 Hz, 2H), 5.45 (s, 2H), 3.75 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 163.27 (t, *J* = 32 Hz), 159.58 (t, *J* = 30 Hz), 157.86, 139.80, 134.76, 130.84, 130.04, 128.84, 128.74, 128.73, 128.70, 128.67, 123.68, 113.92, 113.28 (t, *J* = 254 Hz), 68.38, 55.38; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): – 104.67; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{23}H_{20}F_2NO_3$) requires *m/z* 396.1411, found *m/z* 396.1408



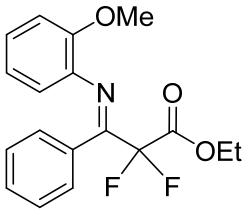
(*E*)-2,2-Difluoro-3-((4-methoxyphenyl)imino)-1,3-diphenylpropan-1-one (2q): 175 mg, 96% yield; Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.07 (d, *J* = 8 Hz, 2H), 7.62 (t, *J* = 8 Hz, 1H), 7.50 (t, *J* = 8 Hz, 2H), 7.43 – 7.34 (m, 5H), 6.64 (d, *J* = 9 Hz, 2H), 6.54 (d, *J* = 9 Hz, 2H), 3.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 188.48 (t, *J* = 27 Hz), 161.30 (t, *J* = 29 Hz), 157.89, 139.91, 133.85, 133.24, 131.05, 130.24, 130.13, 128.95, 128.87, 128.63, 123.38, 114.74 (t, *J* = 254 Hz), 113.99, 55.42; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): – 100.73; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{22}H_{18}F_2NO_3$) requires *m/z* 366.1306, found *m/z* 366.1310



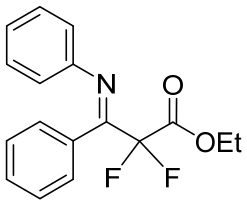
(*E*)-2,2-Difluoro-3-((4-methoxyphenyl)imino)-3-phenylpropanenitrile (2r): 142 mg, 99% yield; Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.47 (t, *J* = 8 Hz, 1H), 7.41 (t, *J* = 8 Hz, 2H), 7.28 (d, *J* = 7 Hz, 2H), 6.86 (d, *J* = 9 Hz, 2H), 6.76 (d, *J* = 9 Hz, 2H), 3.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 158.77, 156.06 (t, *J* = 30 Hz), 138.88, 130.74, 129.53, 129.17, 128.74, 124.62, 114.17, 111.52 (t, *J* = 44 Hz), 110.32 (t, *J* = 246 Hz), 55.48; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): – 87.19; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{16}H_{13}F_2N_2O$) requires *m/z* 287.0996, found *m/z* 287.0996



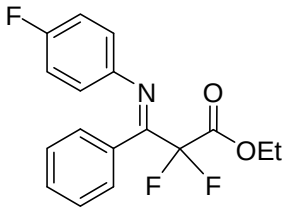
Ethyl (*E*)-2,2-difluoro-3-((3-methoxyphenyl)imino)-3-phenylpropanoate (2s): 157 mg, 94% yield; Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.37 – 7.27 (m, 5H), 7.05 (t, *J* = 9 Hz, 1H), 6.58 – 6.56 (m, 1H), 6.28 – 6.27 (m, 2H), 4.44 (q, *J* = 7 Hz, 2H), 3.79 (s, 3H), 3.65 (s, 3H), 1.39 (t, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 163.11 (t, *J* = 31 Hz), 161.62 (t, *J* = 30 Hz), 160.02, 148.62, 130.39, 130.20, 129.64, 128.92, 128.51, 113.18, 112.78 (t, *J* = 254 Hz), 111.20, 106.51, 63.20, 55.32, 14.16; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): – 105.30; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{18}H_{18}F_2NO_3$) requires *m/z* 334.1255, found *m/z* 334.1250



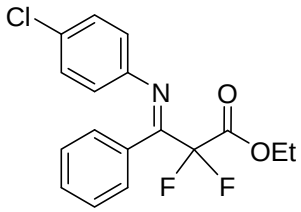
Ethyl (*E*)-2,2-difluoro-3-((2-methoxyphenyl)imino)-3-phenylpropanoate (2t): 155 mg, 93% yield; Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.35 – 7.26 (m, 5H), 7.01 (td, *J* = 8 Hz, 2 Hz, 1H), 6.79 (td, *J* = 8 Hz, 1 Hz, 1H), 6.76 (d, *J* = 8 Hz, 1H), 6.65 (dd, *J* = 8 Hz, 2 Hz, 1H), 4.46 (q, *J* = 7 Hz, 2H), 3.63 (s, 3H), 1.42 (t, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 163.14 (t, *J* = 31 Hz), 162.80 (t, *J* = 30 Hz), 148.87, 137.27, 131.22, 130.03, 128.20, 128.14, 126.02, 120.93, 120.64, 112.68 (t, *J* = 254 Hz), 111.79, 63.11, 55.44, 14.09; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): – 104.89; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{18}H_{18}F_2NO_3$) requires *m/z* 334.1255, found *m/z* 334.1258



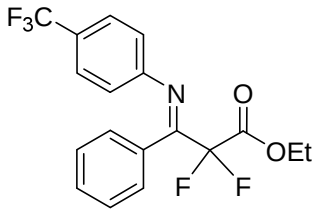
Ethyl (*E*)-2,2-difluoro-3-phenyl-3-(phenylimino)propanoate (2u): 141 mg, 93% yield; Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.36 – 7.25 (m, 5H), 7.17 (t, *J* = 8 Hz, 2H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.71 (d, *J* = 7.5 Hz, 2H), 4.45 (q, *J* = 7 Hz, 2H), 1.40 (t, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 163.14 (t, *J* = 31 Hz), 161.51 (t, *J* = 30 Hz), 147.39, 130.36, 130.15, 129.01, 128.80, 128.50, 125.33, 120.86, 112.82 (t, *J* = 254 Hz), 63.17, 14.16; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): –105.28; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{17}H_{16}F_2NO_2$) requires *m/z* 304.1149, found *m/z* 304.1150



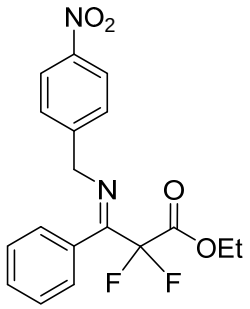
Ethyl (*E*)-2,2-difluoro-3-((4-fluorophenyl)imino)-3-phenylpropanoate (2v): 133 mg, 83% yield; Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.39 – 7.36 (m, 1H), 7.33 – 7.30 (m, 2H), 7.25 – 7.24 (m, 2H), 6.88 – 6.84 (m, 2H), 6.70 – 6.67 (m, 2H), 4.44 (q, *J* = 7 Hz, 2H), 1.40 (t, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 163.09 (t, *J* = 31 Hz), 161.88 (t, *J* = 31 Hz), 160.57 (d, *J* = 244 Hz), 143.26 (d, *J* = 3 Hz), 130.32, 128.92, 128.70, 122.95 (d, *J* = 8 Hz), 115.70 (d, *J* = 23 Hz), 112.76 (t, *J* = 254 Hz), 63.21, 14.17; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): – 105.31, – 117.18; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{17}H_{15}F_3NO_2$) requires *m/z* 322.1055, found *m/z* 322.1059



Ethyl (*E*)-3-((4-chlorophenyl)imino)-2,2-difluoro-3-phenylpropanoate (2w): 145 mg, 86% yield; Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.39 – 7.36 (m, 1H), 7.33 – 7.30 (m, 2H), 7.25 – 7.23 (m, 2H)，7.14 (d, *J* = 9 Hz, 2H), 6.65 (d, *J* = 9 Hz, 2H), 4.44 (q, *J* = 7 Hz, 2H), 1.39 (t, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 163.00 (t, *J* = 31 Hz), 162.30 (t, *J* = 30 Hz), 145.83, 130.99, 130.44, 130.05, 129.02, 128.93, 128.71, 122.41, 112.63 (t, *J* = 254 Hz), 63.27, 14.17; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): – 105.31; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{17}H_{15}ClF_2NO_2$) requires *m/z* 338.0759, found *m/z* 338.0763

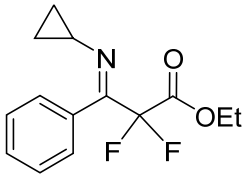


Ethyl (*E*)-2,2-difluoro-3-phenyl-3-((4-(trifluoromethyl)phenyl)imino)propanoate (2x). 167 mg, 90% yield; Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.47 (d, *J* = 8 Hz, 2H), 7.40 – 7.38 (m, 1H), 7.34 – 7.32 (m, 2H), 7.28 – 7.26 (m, 2H), 6.82 (d, *J* = 8 Hz, 2H), 4.47 (q, *J* = 7 Hz, 2H), 1.41 (t, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 163.12 (t, *J* = 30 Hz), 162.82 (t, *J* = 31 Hz), 150.55, 130.64, 129.66, 128.90, 128.69, 127.21 (q, *J* = 33 Hz), 126.16 (q, *J* = 4 Hz), 124.14 (q, *J* = 270 Hz), 120.61, 112.40 (t, *J* = 254 Hz), 63.36, 14.11; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): – 62.25, – 105.37; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{18}H_{15}F_5NO2$) requires *m/z* 372.1023, found *m/z* 372.1024

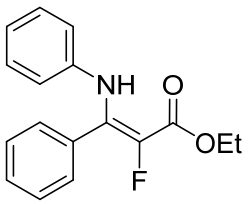


Ethyl (*E*)-2,2-difluoro-3-((4-nitrobenzyl)imino)-3-phenylpropanoate (2y): 125 mg, 69% yield; White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.17 (d, *J* = 9 Hz, 2H), 7.53 – 7.47 (m, 3H), 7.39 (d, *J* = 9 Hz, 2H), 7.31 – 7.29 (m, 2H), 4.65 (s, 2H), 4.41 (q, *J* = 7 Hz, 2H), 1.35 (t, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 164.91 (t, *J* = 30 Hz), 163.17 (t, *J* = 31 Hz), 147.18, 146.03, 130.54, 129.95, 129.06, 128.03, 127.79, 123.77, 112.58 (t, *J* = 253 Hz), 63.18, 55.69, 14.13; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): – 105.92; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{18}H_{17}F_2N_2O_4$)

requires *m/z* 363.1156, found *m/z* 363.1159



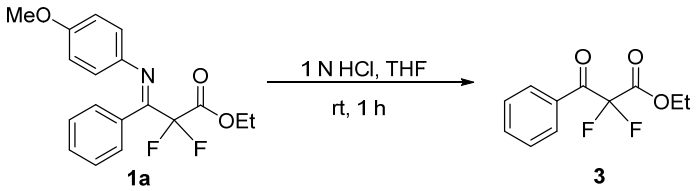
Ethyl (*E*)-3-(cyclopropylimino)-2,2-difluoro-3-phenylpropanoate (2z): 122 mg, 91% yield; Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.48 – 7.44 (m, 3H), 7.41 – 7.39 (m, 2H), 4.35 (q, *J* = 7 Hz, 2H), 2.92 – 2.88 (m, 1H), 1.33 (t, *J* = 7 Hz, 3H), 0.97 – 0.86 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 163.40 (t, *J* = 31 Hz), 159.65 (t, *J* = 30 Hz), 130.85, 129.81, 128.70, 128.50, 113.15 (t, *J* = 251 Hz), 62.68, 35.07, 14.02, 10.65; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): – 105.63; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{14}H_{16}F_2NO_2$) requires *m/z* 268.1149, found *m/z* 268.1150



Ethyl (*E*)-2-fluoro-3-phenyl-3-(phenylamino)acrylate (8): 109 mg, 44% yield; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.13 (brs, 1H), 7.45 – 7.43 (m, 2H), 7.36 – 7.32 (m, 3H), 7.05 (t, *J* = 8 Hz, 2H), 6.87 (t, *J* = 8 Hz, 1H), 6.62 (d, *J* = 8 Hz, 2H), 4.37 (q, *J* = 7 Hz, 2H), 1.40 (t, *J* = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 164.85 (d, *J* = 26 Hz), 143.56 (d, *J* = 24 Hz), 140.82, 132.34 (d, *J* = 230 Hz), 130.84, 129.79, 129.75, 128.84, 128.56, 122.59, 121.45, 60.93, 14.54; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): – 170.71; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{14}H_{16}F_2NO_2$) requires *m/z* 286.1243, found *m/z* 286.1234

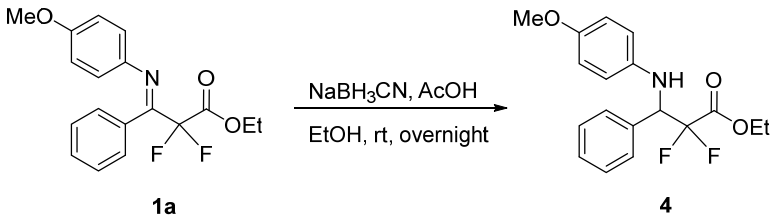
3. Late-stage Modification

a) Synthesis of compound 3 [2]



To a solution of **1a** (168 mg, 0.5 mmol) in THF (2 mL) was added 1 N HCl (2 mL) at 0 °C, and the resulting mixture was stirred at room temperature for 1h. Then the reaction mixture was extracted with Et_2O (3*5 mL), and the combined organic layer was washed with brine, dried with Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography (1:10, EA : Hexane) to afford **3** as colorless oil (95 mg, 83%). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.07 (d, *J* = 7.5 Hz, 2H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 2H), 6.71 (s, 4H), 4.38 (q, *J* = 7 Hz, 2H), 1.31 (t, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 185.58 (t, *J* = 27 Hz), 161.92 (t, *J* = 30 Hz), 135.20, 131.20, 130.02 (t, *J* = 2.6 Hz), 129.08, 109.91 (t, *J* = 253 Hz), 63.86, 13.91; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): – 107.64

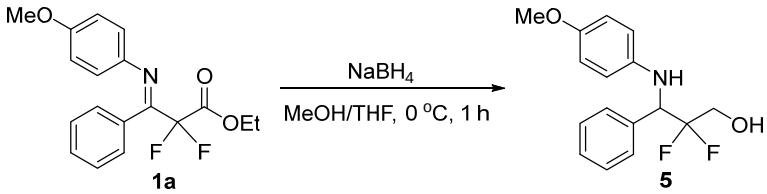
b) Synthesis of compound 4[3]



To a solution of **1a** (168 mg, 0.5 mmol) in EtOH (5 mL) was added $NaBH_3CN$ (130 mg, 2 mmol) and AcOH (120 mg, 2 mmol), the resulting mixture was stirred at room temperature overnight. After the reaction was finished, sat. $NaHCO_3$ was added and the aqueous was extracted with EA (3*5 mL). The combined organic layer was washed with brine, dried with Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography (1: 20, EA : Hexane) to afford **4** as white solid (151 mg, 90%). White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.42 – 7.32 (m, 5H), 6.73 – 6.70 (m, 2H), 6.62 – 6.60 (m, 2H), 5.03 (dd, *J* = 19.5 Hz, 7.5 Hz, 1H), 4.29 (q, *J* = 7 Hz, 2H), 4.17 (brs, 1H), 3.70 (s, 3H), 1.26 (t, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 163.75 (t, *J* = 31 Hz),

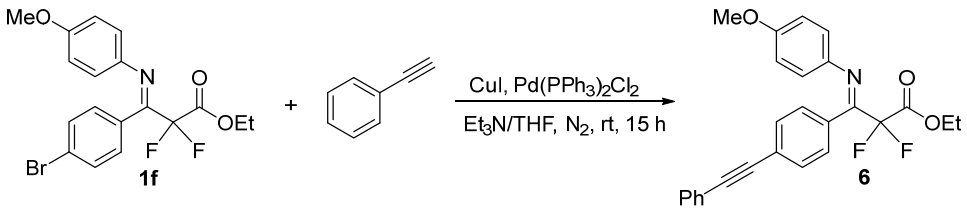
153.36, 139.43, 134.20, 128.89, 128.75, 128.47, 158.05, 139.67, 132.09, 130.57, 129.72, 124.72, 123.50, 114.18, 112.95 (t, J = 253 Hz), 63.18, 55.47, 14.17; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): – 108.84 (d, J = 257 Hz), – 119.81 (d, J = 257 Hz); HRMS (ESI) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{19}FO_2Na$) requires *m/z* 358.1231, found *m/z* 358.1233

c) Synthesis of compound 5[4]



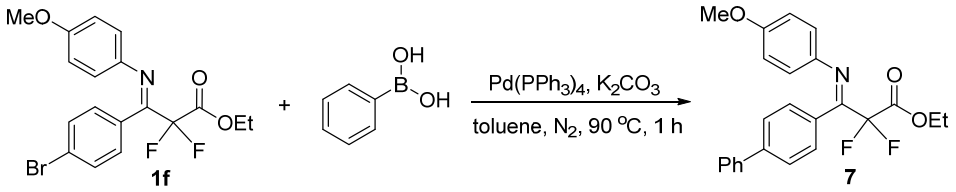
To a solution of **1a** (168 mg, 0.5 mmol) in MeOH/THF (*v*/*v* = 1/1, 4 mL) was added $NaBH_4$ (76 mg, 2 mmol) slowly at 0 °C, the reaction mixture was stirred at 0 °C for 1 h. TLC indicated the reaction was completion, sat. NH_4Cl was added to quench the reaction. The resulting mixture was extracted with EA (3*5 mL), the combined organic layers were washed with brine, dried with $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (1:2, EA : Hexane) to afford **5** as yellow solid (141 mg, 96%). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.43 – 7.31 (m, 5H), 6.71 (d, J = 9 Hz, 2H), 6.60 (d, J = 9 Hz, 2H), 4.88 – 4.83 (m, 1H), 4.30 (brs, 1H), 3.99 – 3.91 (m, 1H), 3.83 – 3.76 (m, 1H), 3.70 (s, 3H), 2.54 (brs, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 153.17, 140.00, 135.98, 128.76, 128.54, 128.38, 121.57 (t, J = 247 Hz), 116.00, 114.98, 63.01 (t, J = 31 Hz), 60.94 (dd, J = 26 Hz, 3 Hz), 55.80; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): – 113.97 (d, J = 256 Hz), – 117.86 (d, J = 256 Hz); HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{16}H_{18}F_2NO_2$) requires *m/z* 294.1306, found *m/z* 294.1308

d) Synthesis of compound 6



To a Sclenk tube was added **1f** (85 mg, 0.2 mmol), CuI (2 mg), $Pd(PPh_3)_2Cl_2$ (14 mg), Et_3N(1 mL) and THF (1 mL). Then the tube was charged with N_2, and was stirred at room temperature for 15 h until complete consumption of starting material as monitored by TLC. After the reaction was finished, the mixture was filtered through a pad of Celite, washed with EA. The combined organic mixture was concentrated in vacuo and purified by silica gel column chromatography (1:20, EA:Hexane) to afford compound **6** as yellow oil (73 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.56 – 7.50 (m, 4H), 7.39 – 7.37 (m, 3H), 7.31 – 7.28 (m, 2H), 6.73 (s, 4H), 4.47 (q, *J* = 7 Hz, 2H), 3.76 (s, 3H), 1.43 (t, *J* = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.23 (t, *J* = 31 Hz), 159.07 (t, *J* = 30 Hz), 158.01, 139.85, 131.85, 131.82, 130.55, 129.04, 128.80, 128.55, 125.24, 123.61, 122.89, 114.13, 113.08 (t, *J* = 253 Hz), 91.54, 88.64, 63.16, 55.47, 14.20; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): – 104.86; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{26}H_{22}F_2NO_3$) requires *m/z* 434.1568, found *m/z* 434.1571

e) Synthesis of compound 7[5]



Under N_2 atmosphere, to a solution of **1f** (103 mg, 0.25 mmol) and $Pd(PPh_3)_4$ (15 mg, 0.0125 mmol) in dry toluene (5 mL) was added K_2CO_3 (69 mg, 0.5 mmol), $Ph(OH)_2$ (61 mg, 0.5 mmol). The vigorously stirred mixture was heated to 90 °C for 1 h (monitored by TLC). After cooling, the mixture was filtered through a pad of Celite, the filter cake was washed with EA. The organic mixture was concentrated in vacuo and the residue was purified by column chromatography (1:20, EA : Hexane) to afford **7** as

yellow oil (81 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.59 – 7.56 (m, 4H), 7.44 (t, *J* = 8 Hz, 2H), 7.37 (d, *J* = 8 Hz, 3H), 6.78 – 6.71 (m, 4H), 4.47 (q, *J* = 7 Hz, 2H), 3.74 (s, 3H), 1.42 (t, *J* = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.37 (t, *J* = 31 Hz), 159.48 (d, *J* = 30 Hz), 157.86, 142.73, 140.09, 139.98, 129.60, 129.46, 129.01, 128.06, 127.29, 127.19, 123.57, 114.08, 113.24 (t, *J* = 253 Hz), 63.09, 55.43 14.19; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): –104.90; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{24}H_{22}F_2NO_3$) requires *m/z* 410.1568, found *m/z* 410.1571;

Reference:

[1] (a) C. A. Brandt, A. C. Silva, C. G. Pancote, C. L. Brito and M. Solveira, *Synthesis*, 2004, **10**, 1557. (b) W. Xie, J. Fang, J. Li and P. G. Wang, *Tetrahedron*, 1999, **55**, 12929. (c) W. Yu, Y. Du and K. Zhao, *Org. Lett.*, 2009, **11**, 2417. (d) A. V. Malkov, S. Stoncius, K. Vrankova, M. Arndt, *Chem, Eur. J.*, 2008, **14**, 8082.

[2] (a) W. Peng and J. M. Shreeve, *J. Org. Chem.*, 2005, **70**, 5760. (b) J. Xie, T. Zhang, F. Chen, N. Mehrkens, F. Rominger, M. Rudolph, A. S. K. Hashmi, *Angew. Chem. Int. Ed.*, 2016, **55**, 2934.

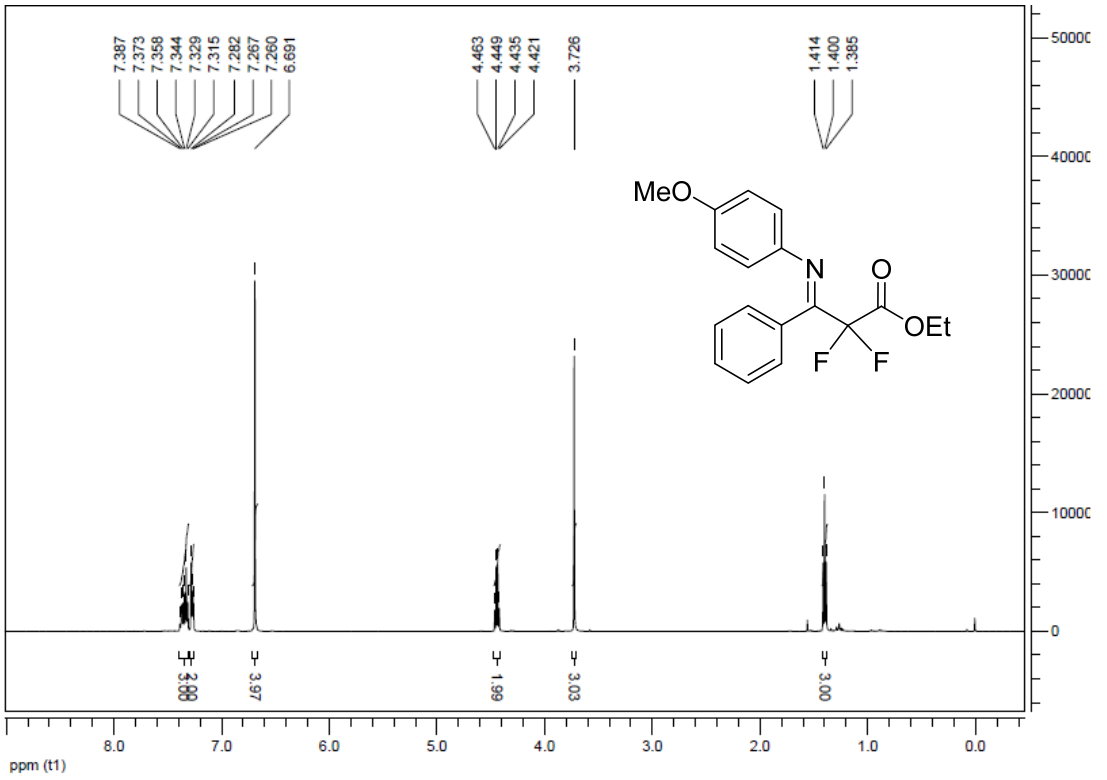
[3] (a) M. Z. Szewczyk, M. Rapp, D. Virieux, J.-L. Pirat and H. Koroniak. *New J. Chem.*, 2017, **41**, 6322. (b) M. Ke and Q. Song, *J. Org. Chem.*, 2016, **81**, 3654.

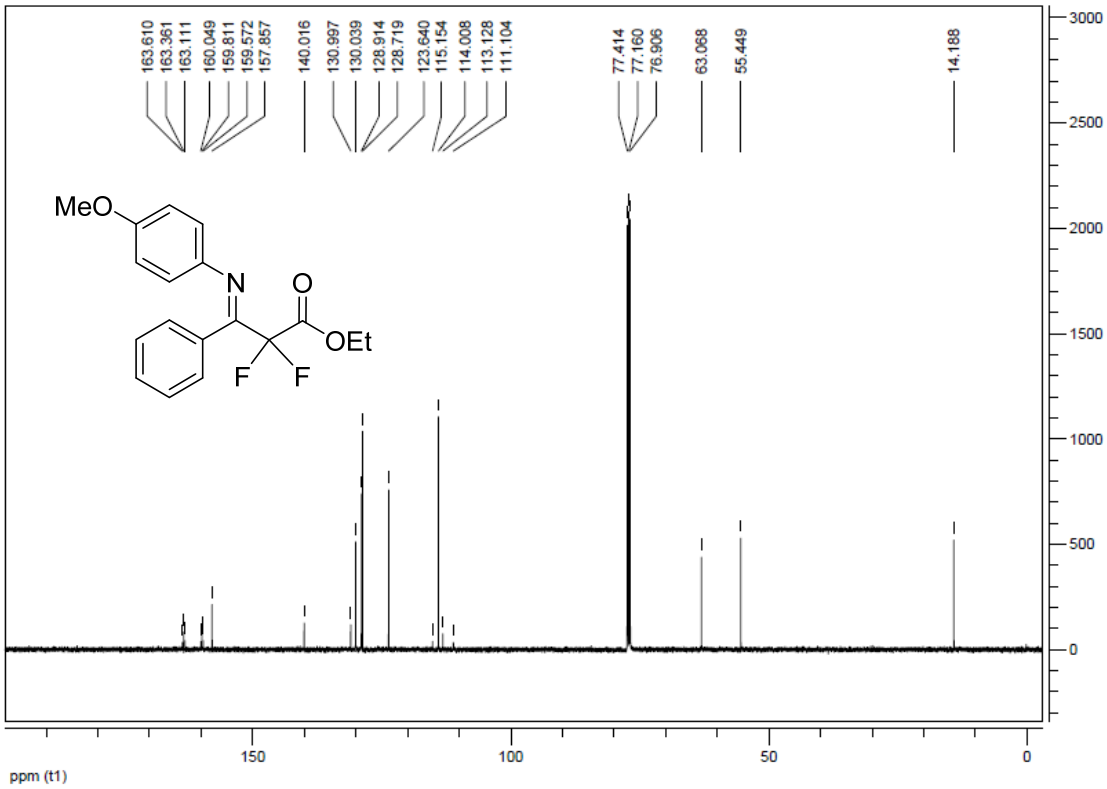
[4] A. Honraedt, A. Van Der Lee, J.-M. Campagne and E. Leclerc, *Adv. Synth. Catal.*, 2017, **359**, 2815.

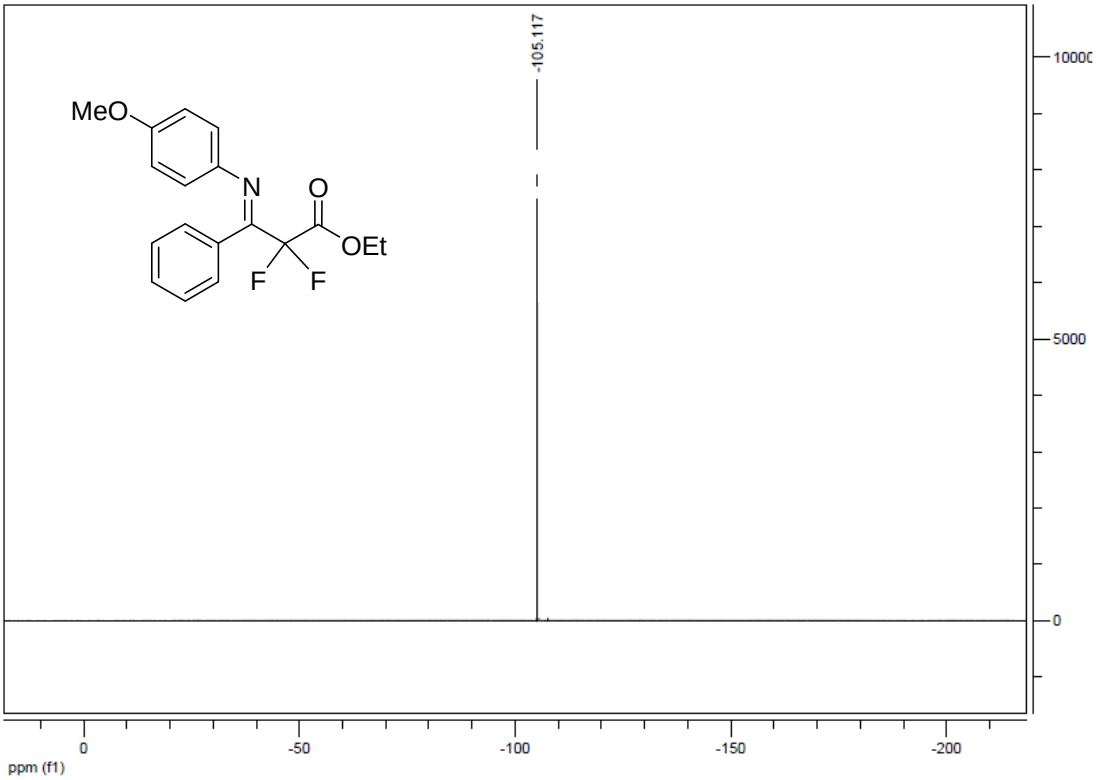
[5] F. Li, Z. Wu and J. Wang, *Angew. Chem. Int. Ed.*, 2015, 54, 656.

4. NMR Spectra

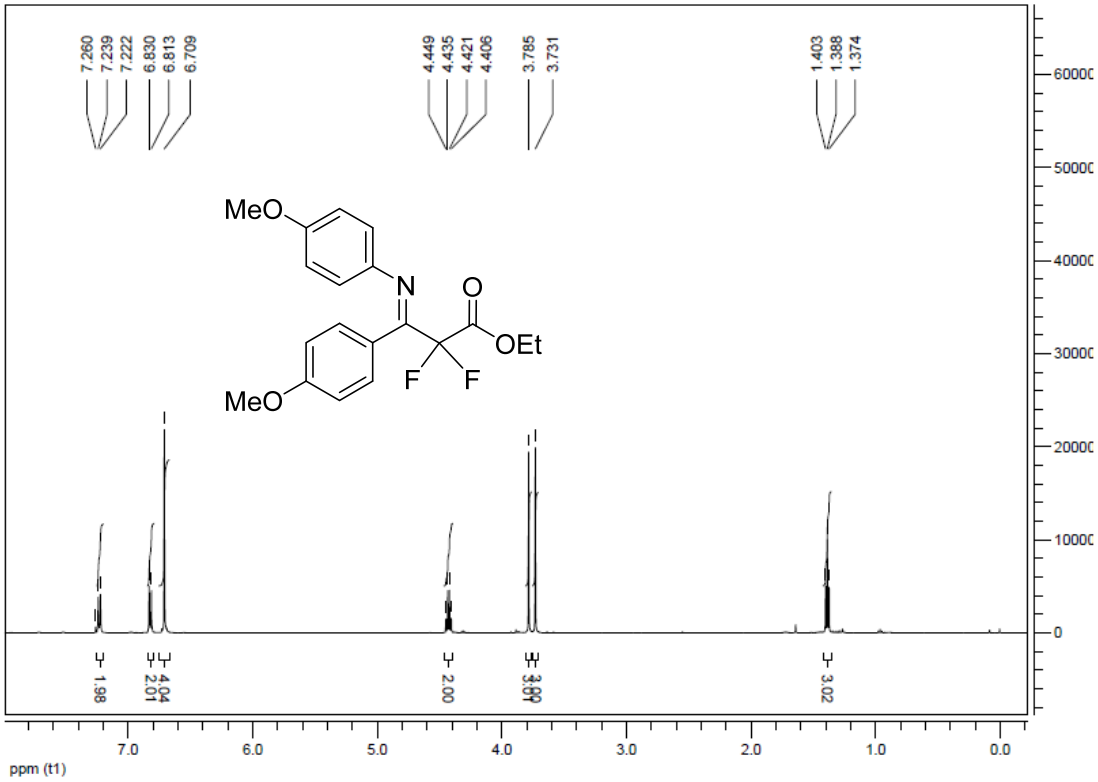
Ethyl (*E*)-2,2-difluoro-3-((4-methoxyphenyl)imino)-3-phenylpropanoate (2a)

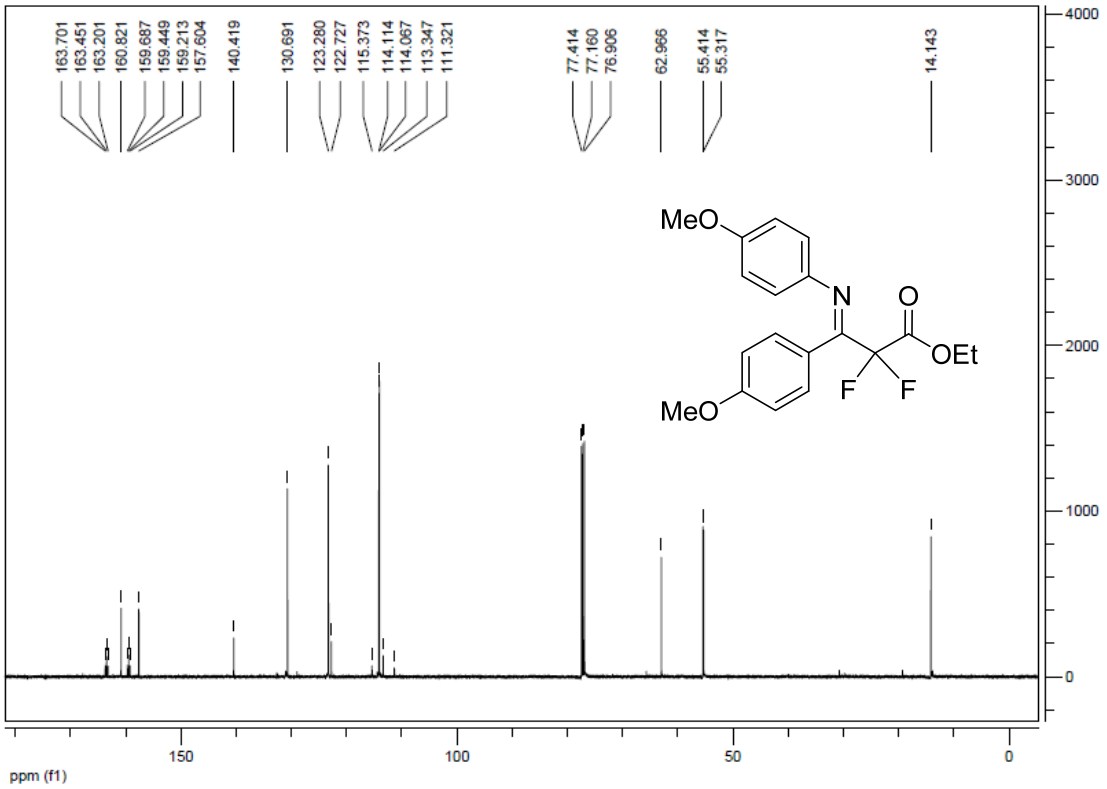






Ethyl (*E*)-2,2-difluoro-3-(4-methoxyphenyl)-3-((4-methoxyphenyl)imino)propanoate (2b)

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163.451
163.201
160.821
159.687
159.449
159.213
157.604
140.419
130.691
123.280
122.727
115.373
114.114
114.067
113.347
111.321
77.414
77.160
76.906
62.966
55.414
55.317
14.143
MeO
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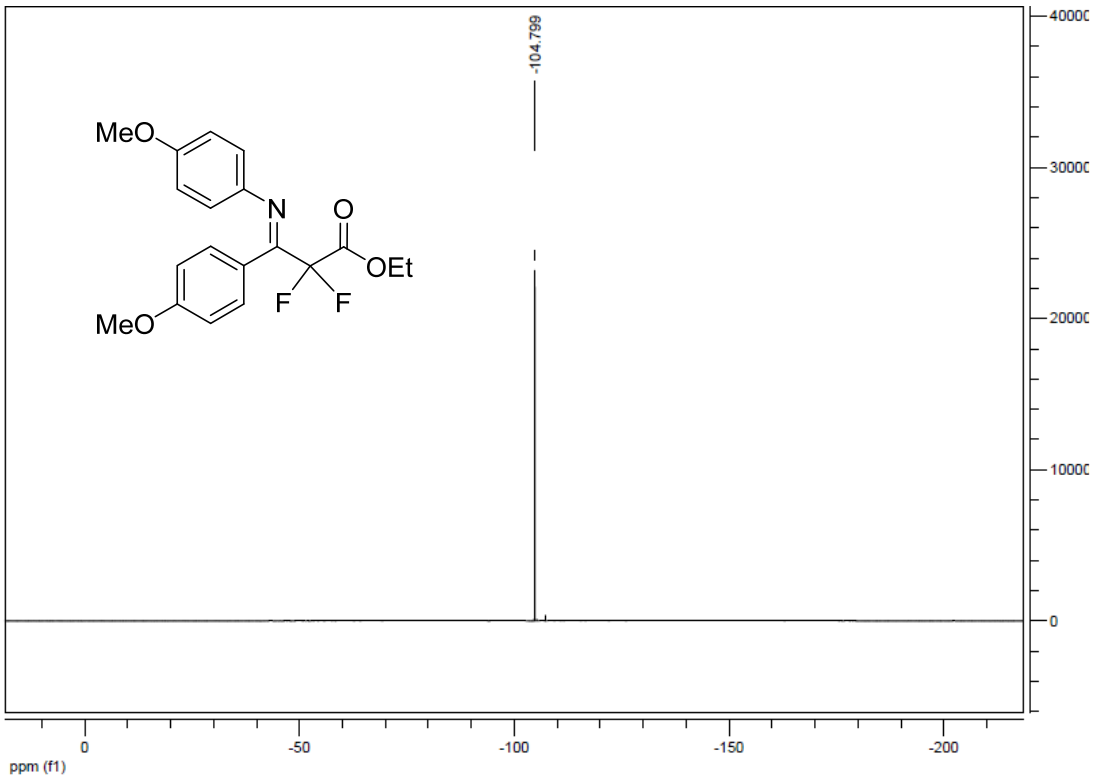
OEt
F
F
MeO
4000
3000
2000
1000
0
150
100
50
0
ppm (f1)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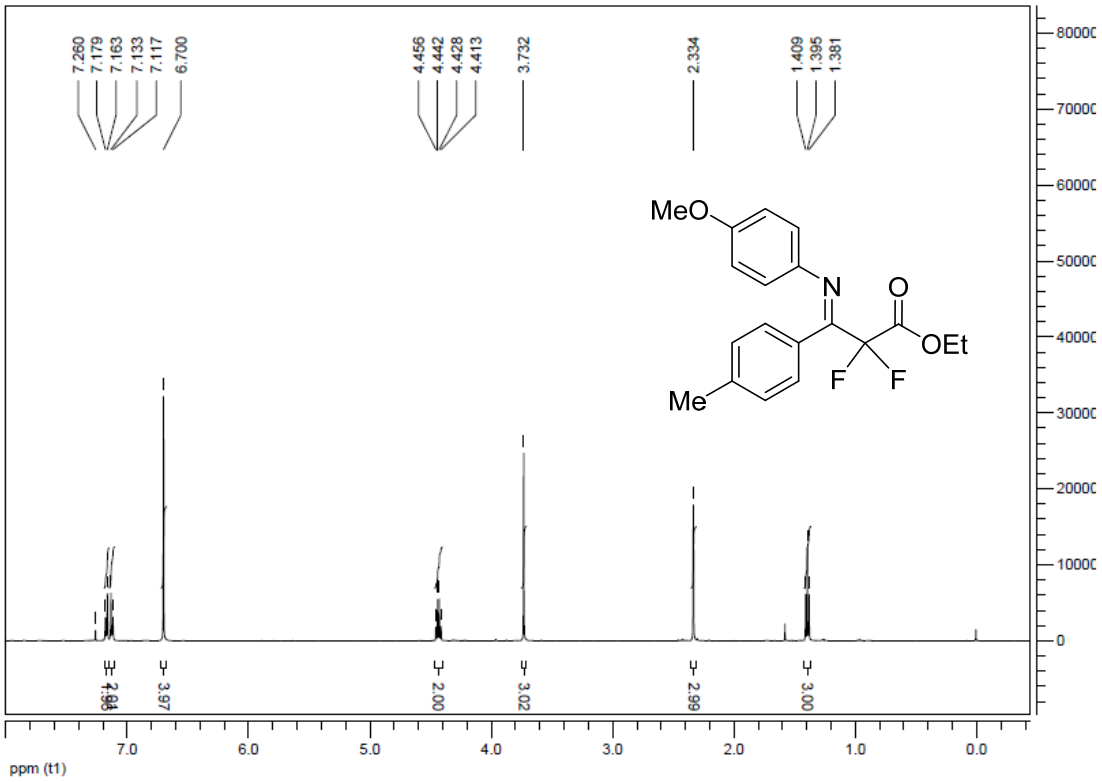
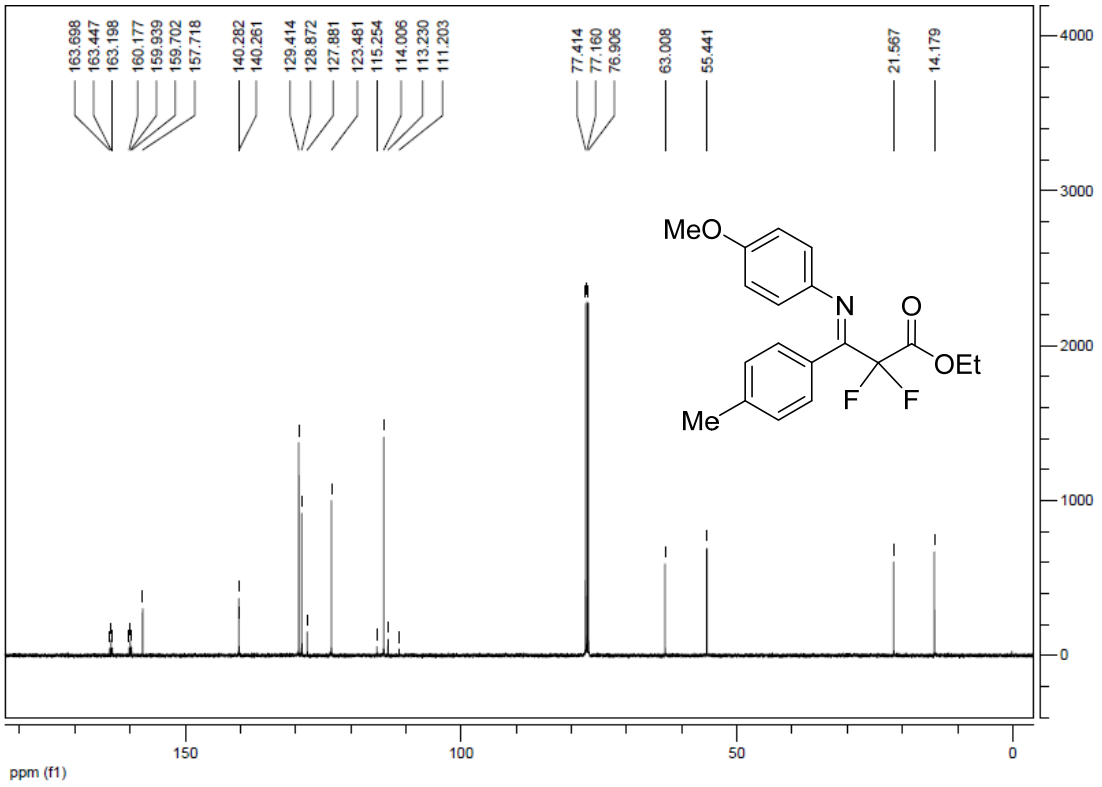
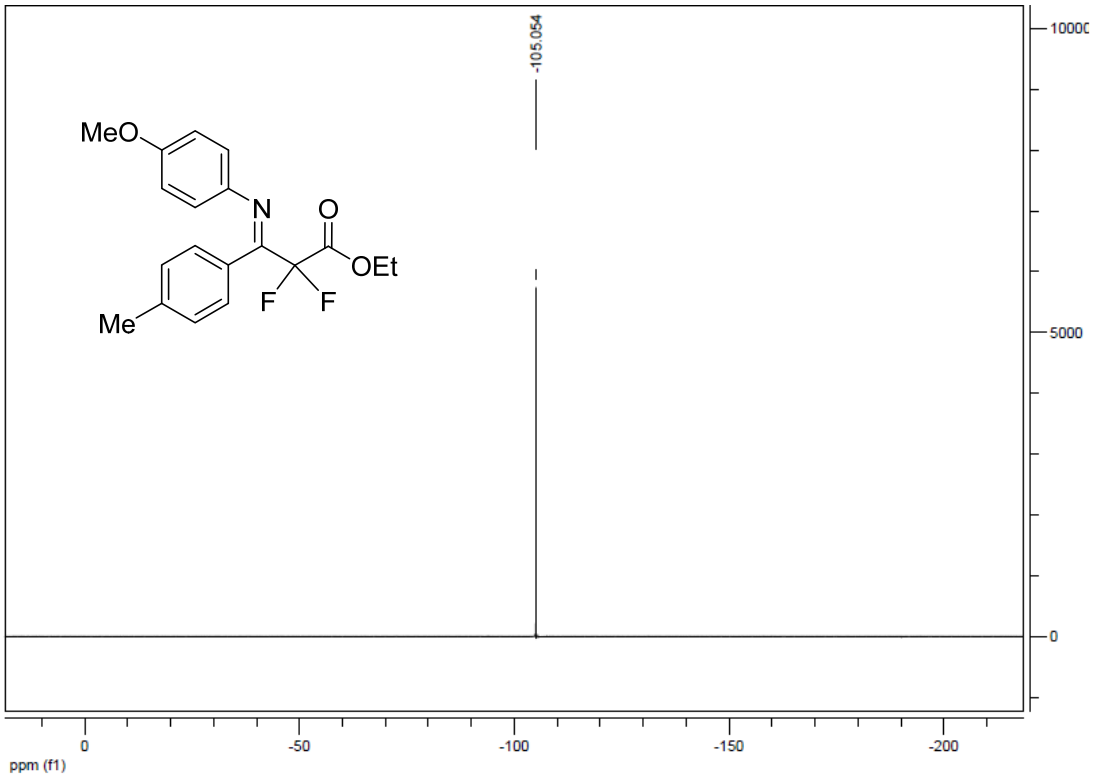
ppm (f1)

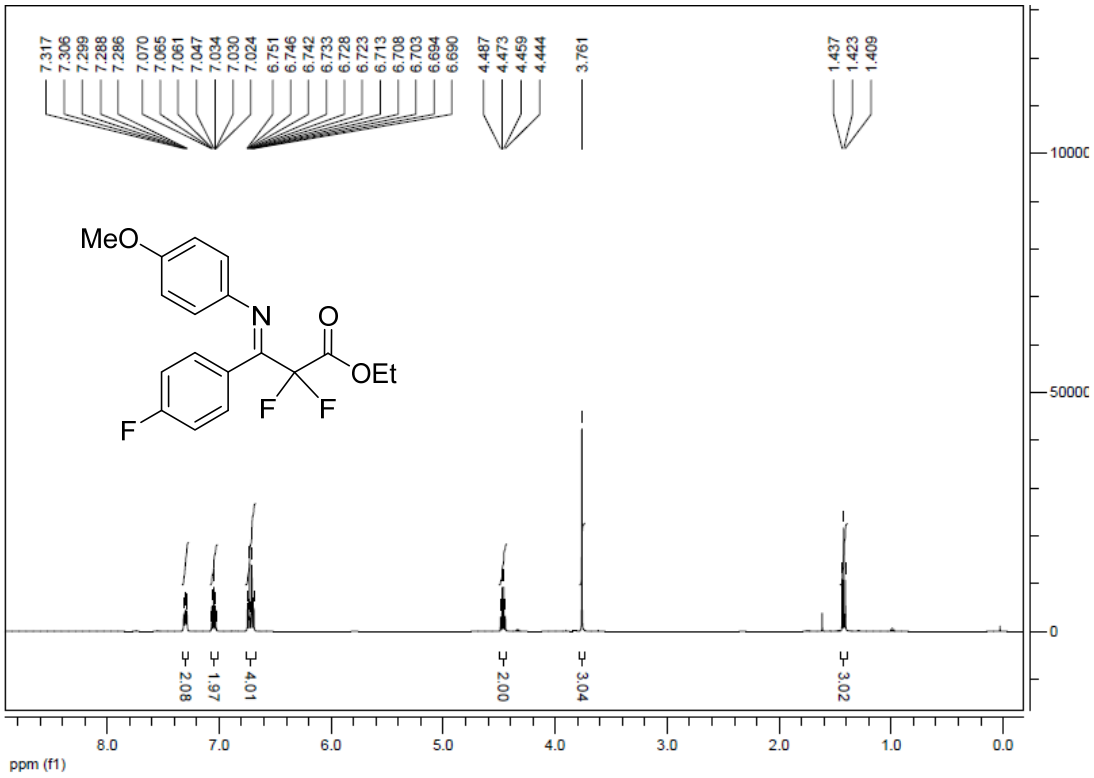
Ethyl (*E*)-2,2-difluoro-3-((4-methoxyphenyl)imino)-3-(p-tolyl)propanoate (2c)

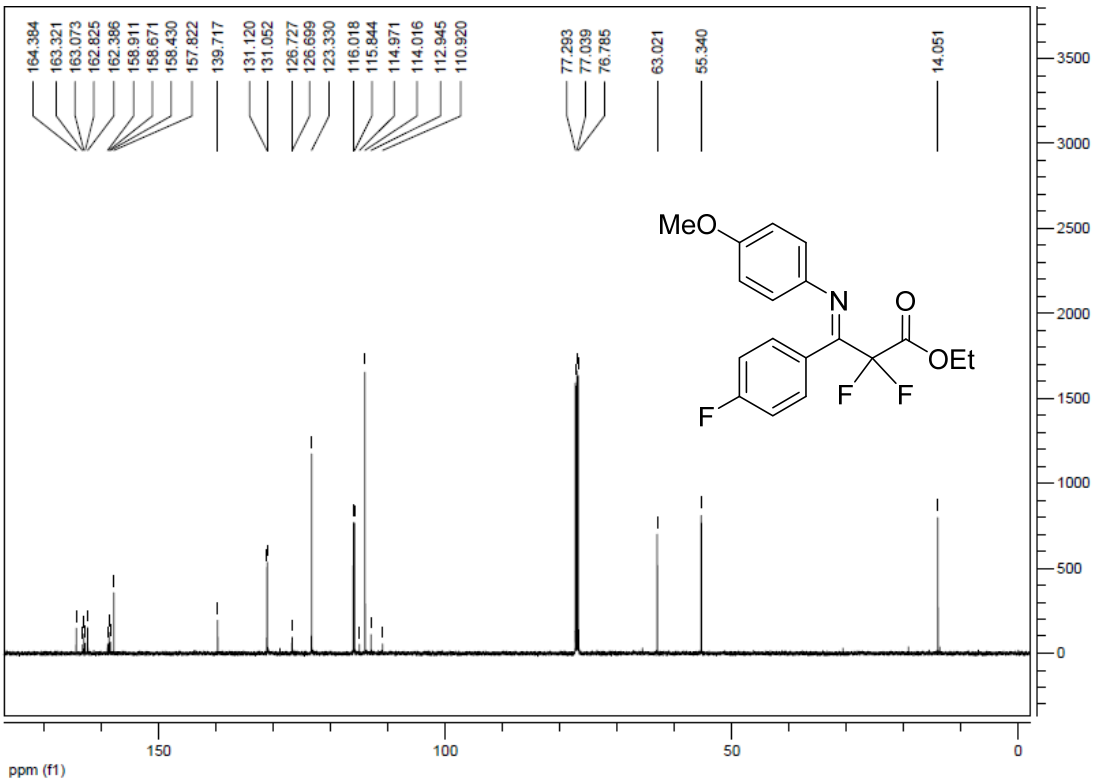






Ethyl (*E*)-2,2-difluoro-3-(4-fluorophenyl)-3-((4-methoxyphenyl)imino)propanoate (2d)

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158.430
157.822
139.717
131.120
131.052
126.727
126.699
123.330
116.018
115.844
114.971
114.016
112.945
110.920
77.293
77.039
76.785
63.021
55.340
14.051
MeO
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O
OEt
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F
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3000
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2000
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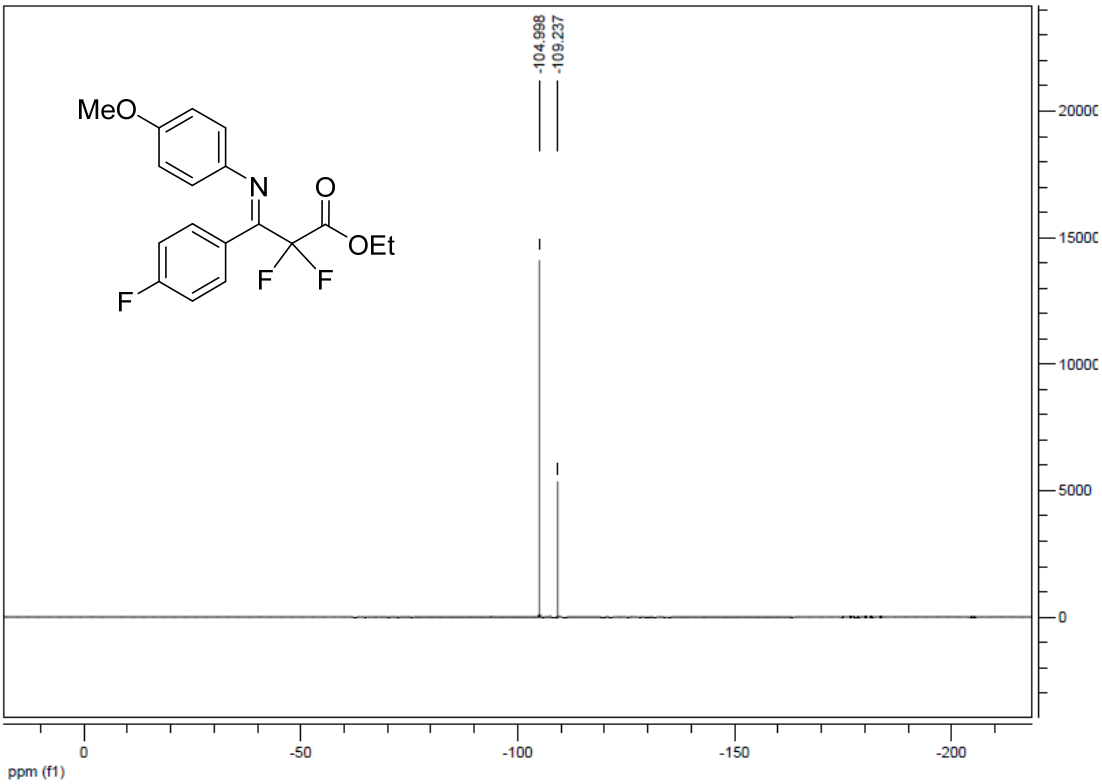
1000
500
0
150
100
50
0
ppm (f1)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OEt
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-100
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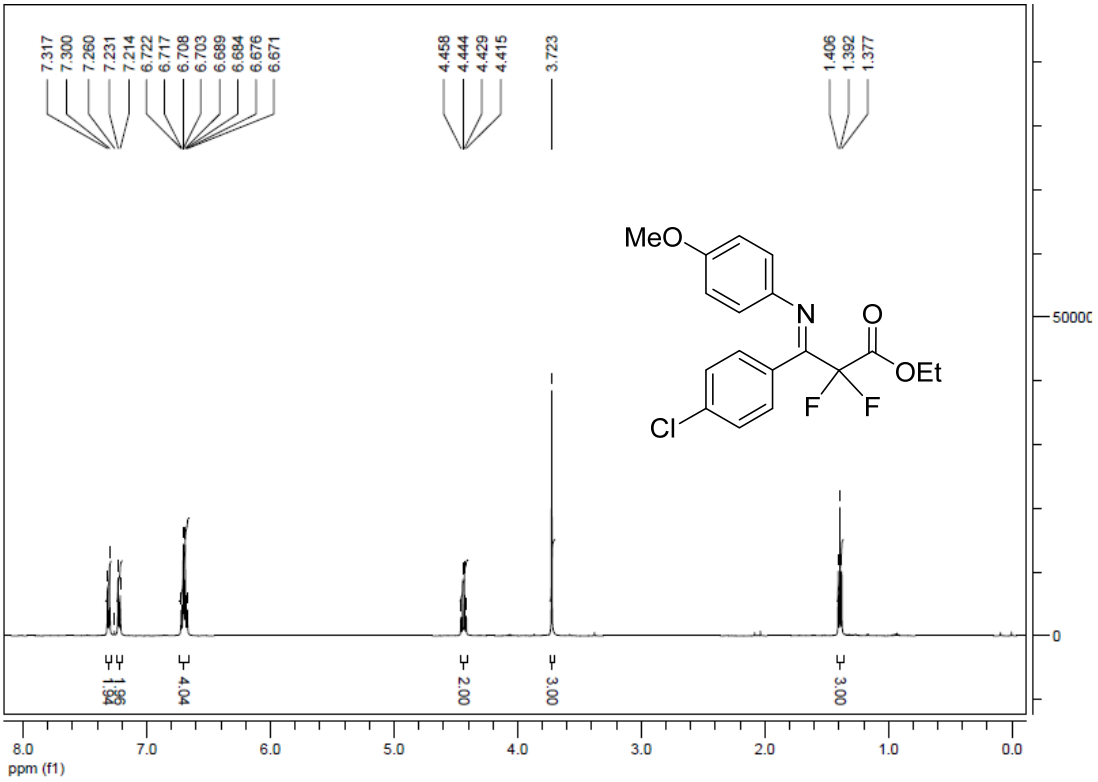
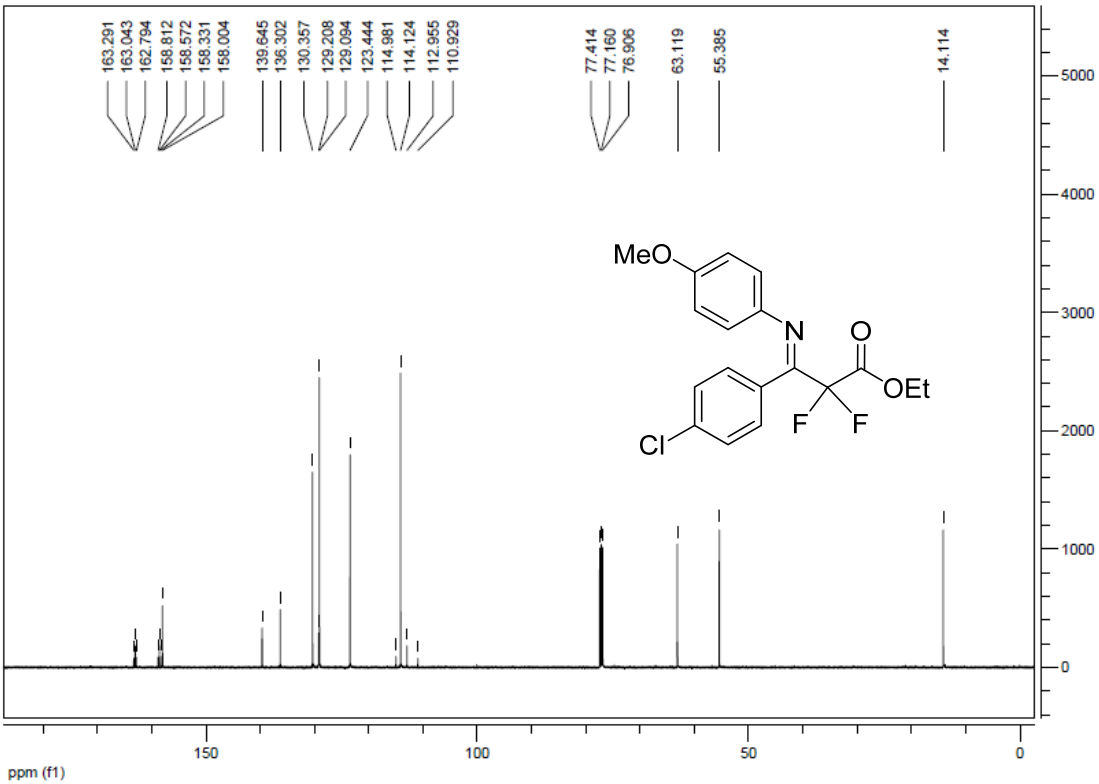
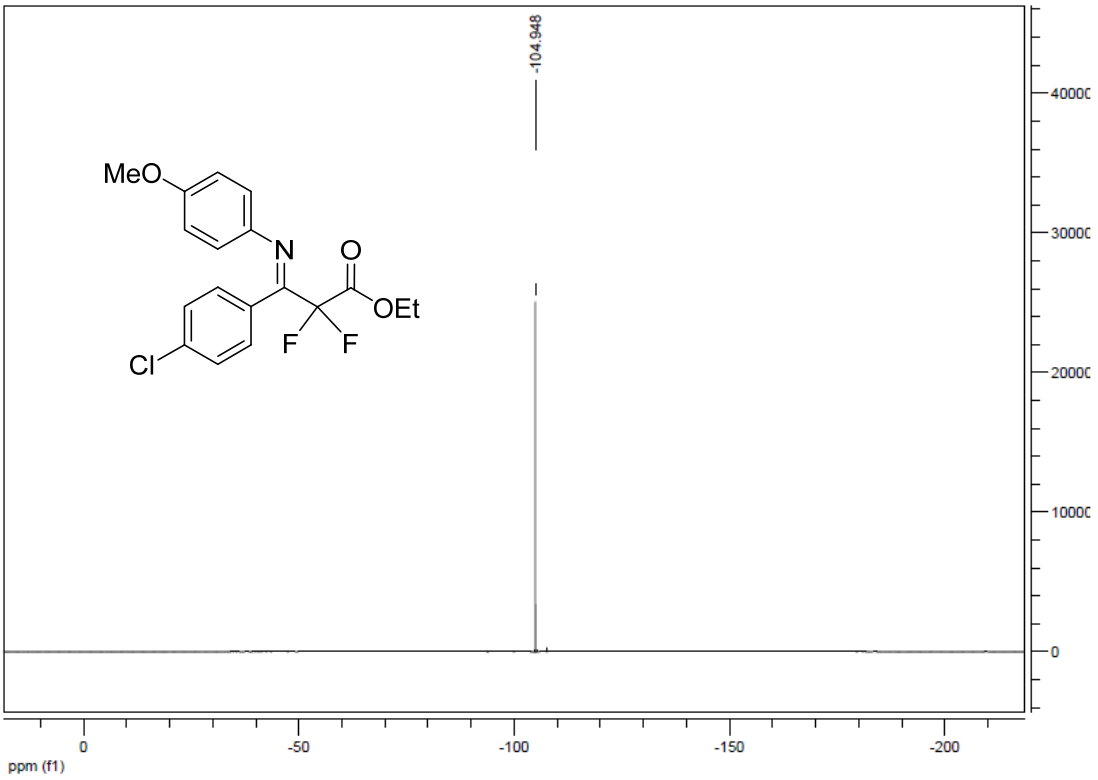
-200
ppm (f1)

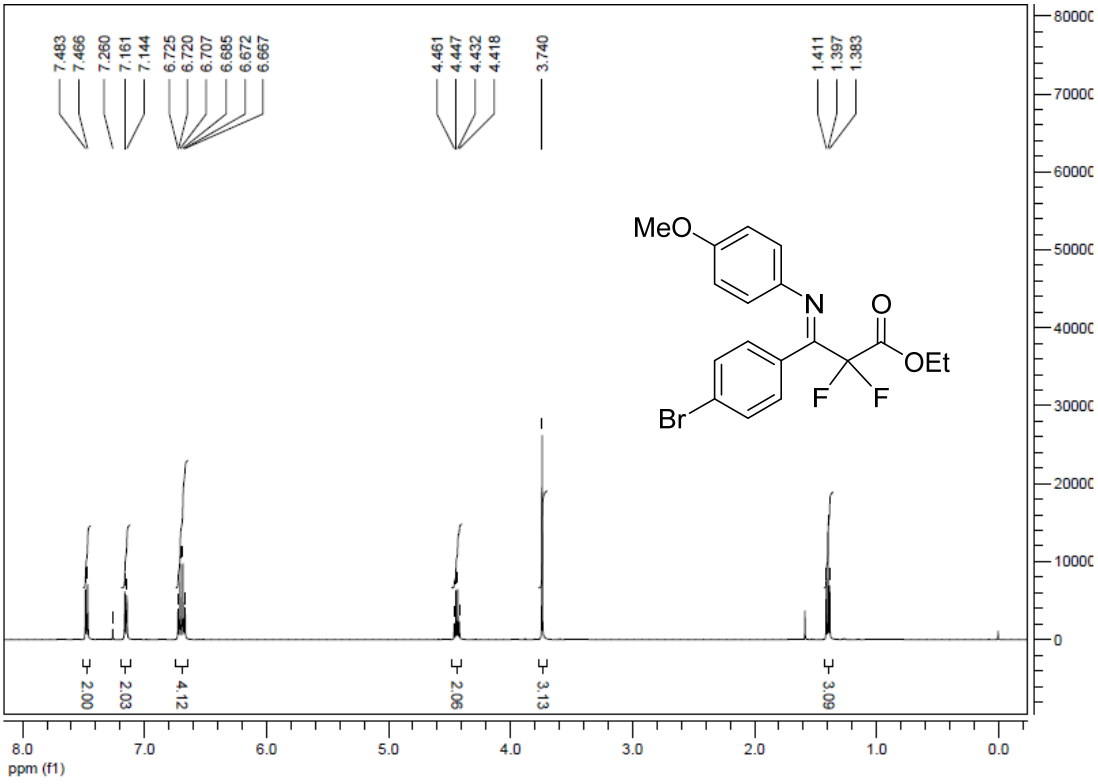
Ethyl (*E*)-3-(4-chlorophenyl)-2,2-difluoro-3-((4-methoxyphenyl)imino)propanoate (2e)

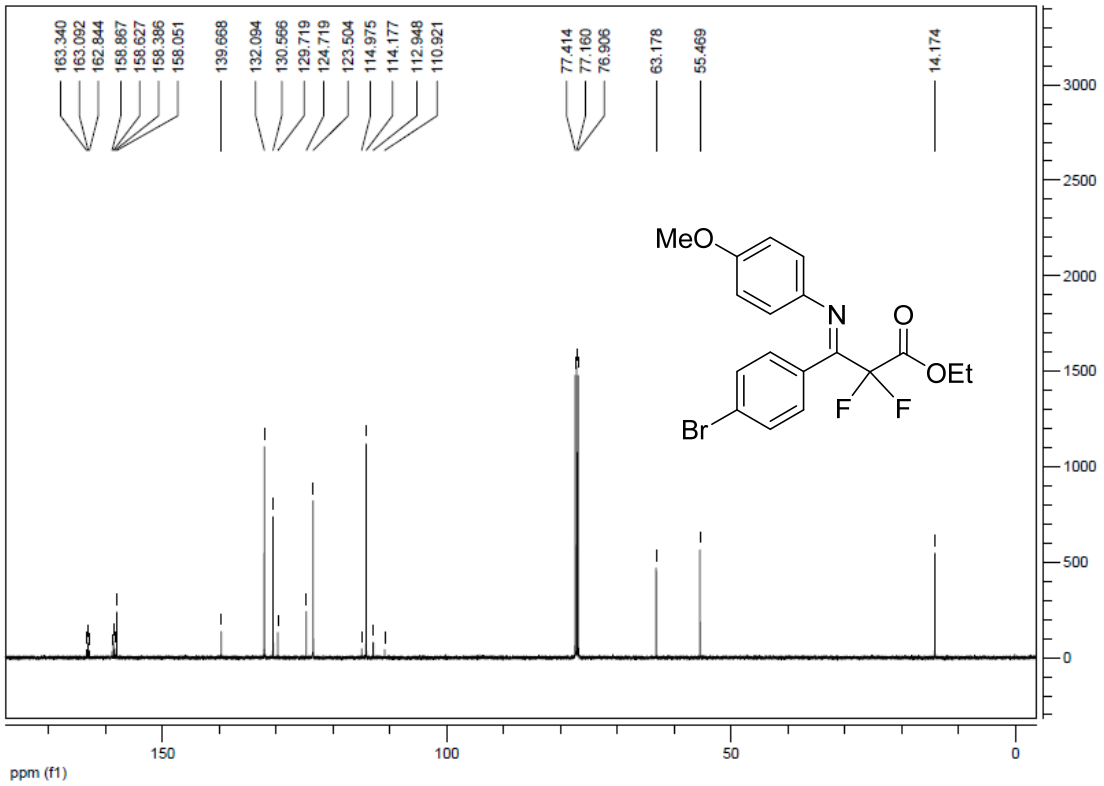






Ethyl (*E*)-3-(4-bromophenyl)-2,2-difluoro-3-((4-methoxyphenyl)imino)propanoate (2f)

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124.719
123.504
114.975
114.177
112.948
110.921
77.414
77.160
76.906
63.178
55.469
14.174
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F
Br
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2000
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500
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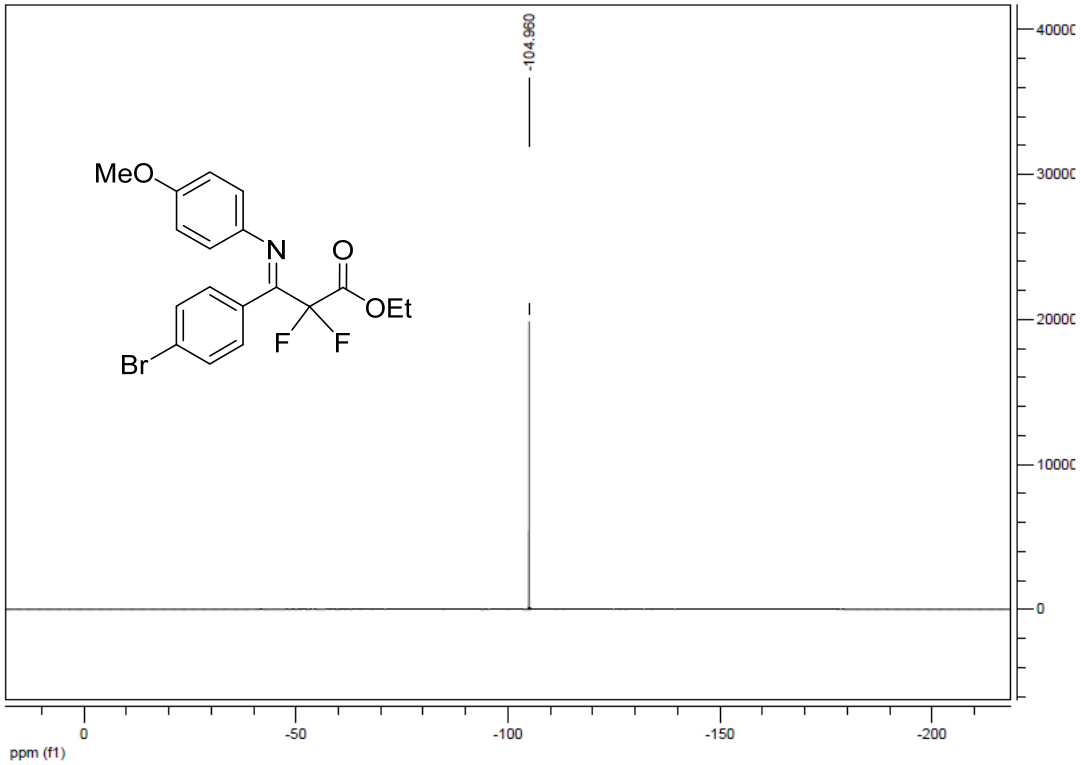
150
100
50
0
ppm (f1)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F
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20000
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-50
-100
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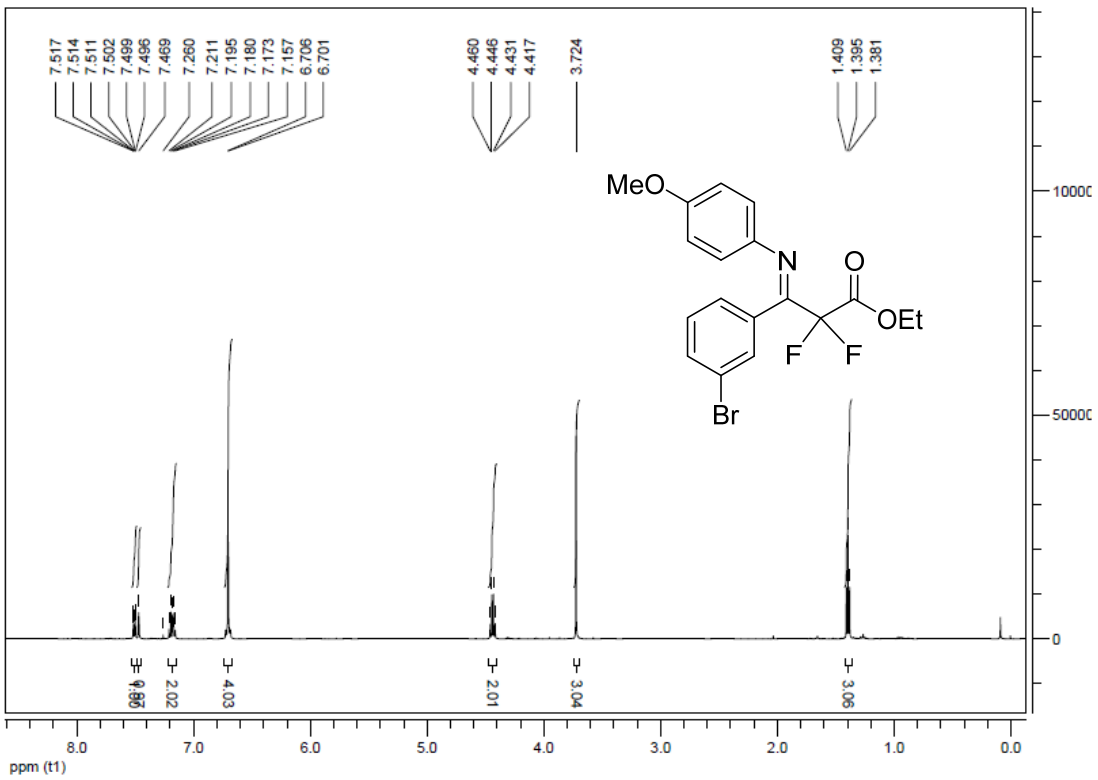
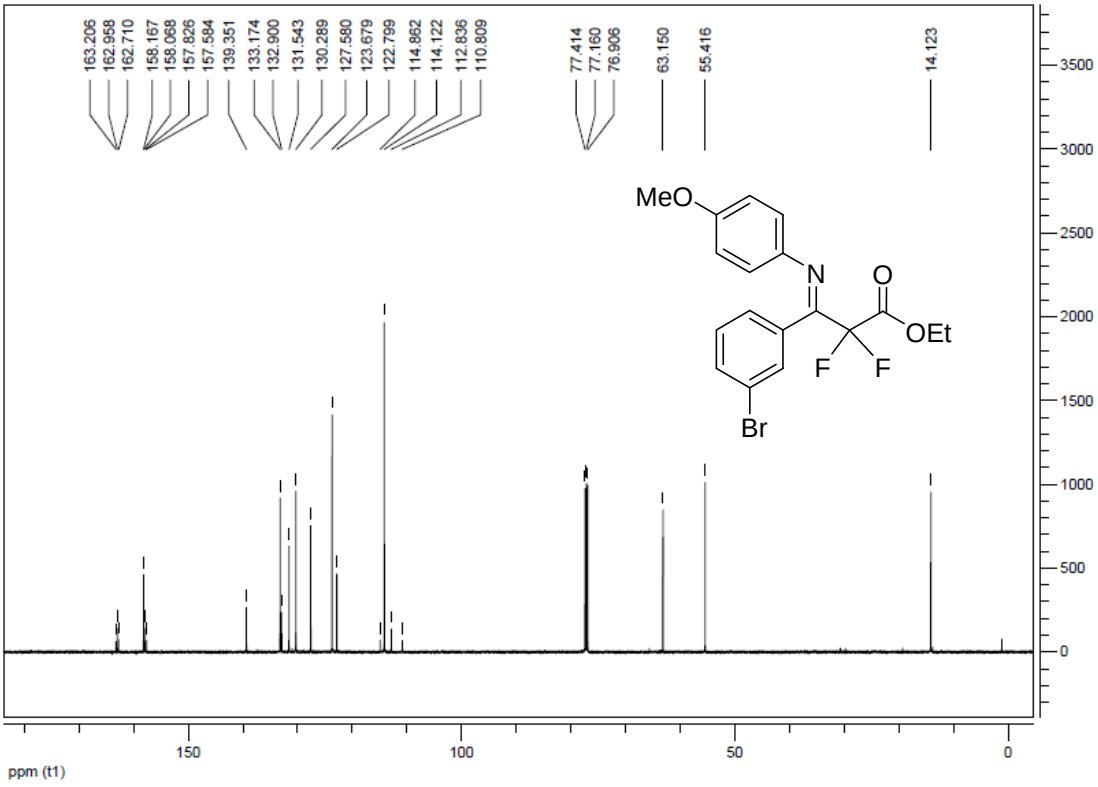
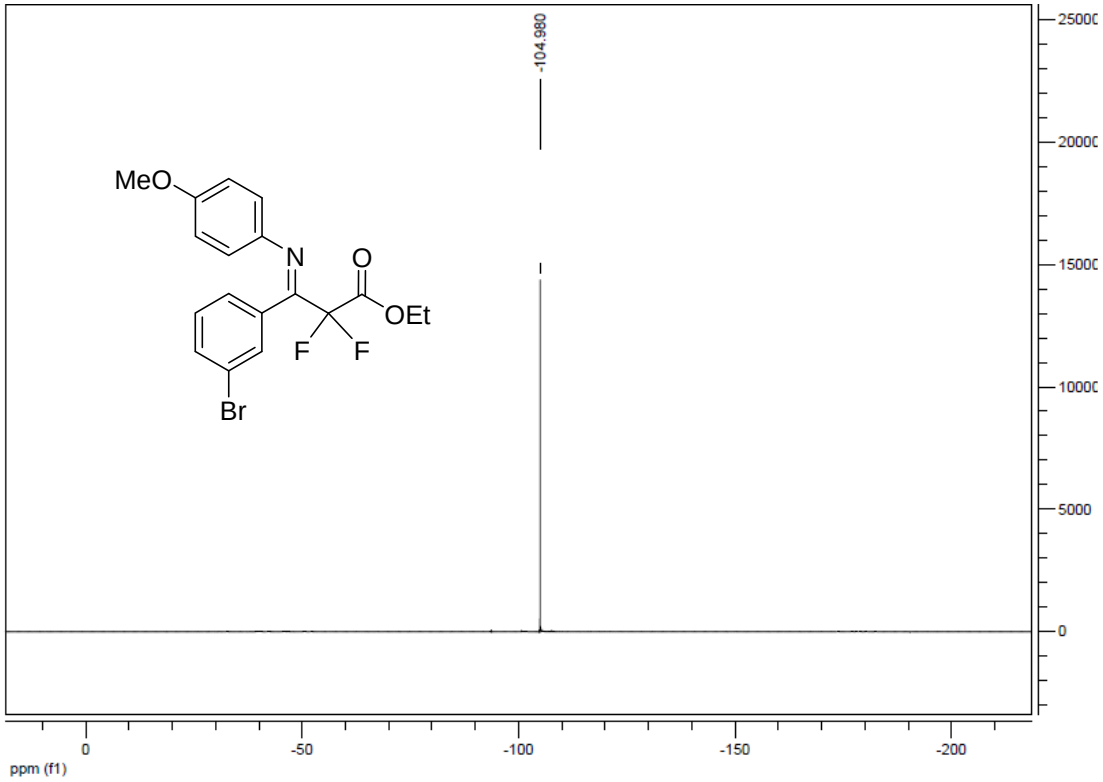
-200
ppm (f1)

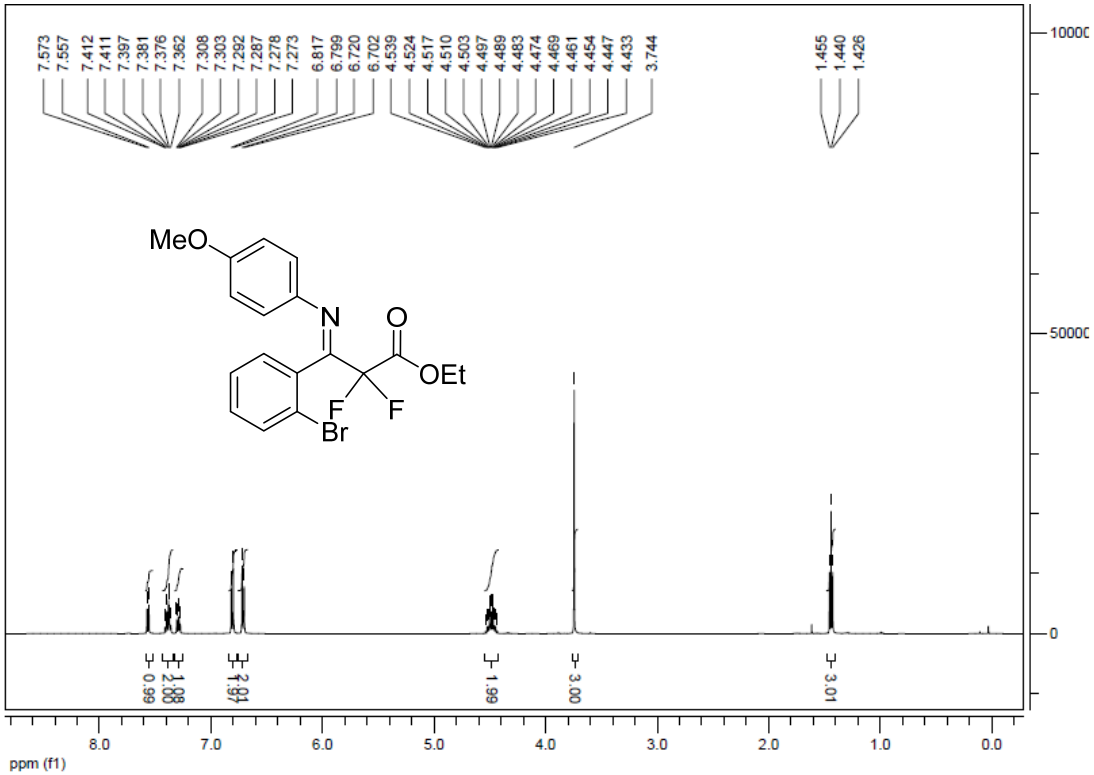
Ethyl (*E*)-3-(3-bromophenyl)-2,2-difluoro-3-((4-methoxyphenyl)imino)propanoate (2g)

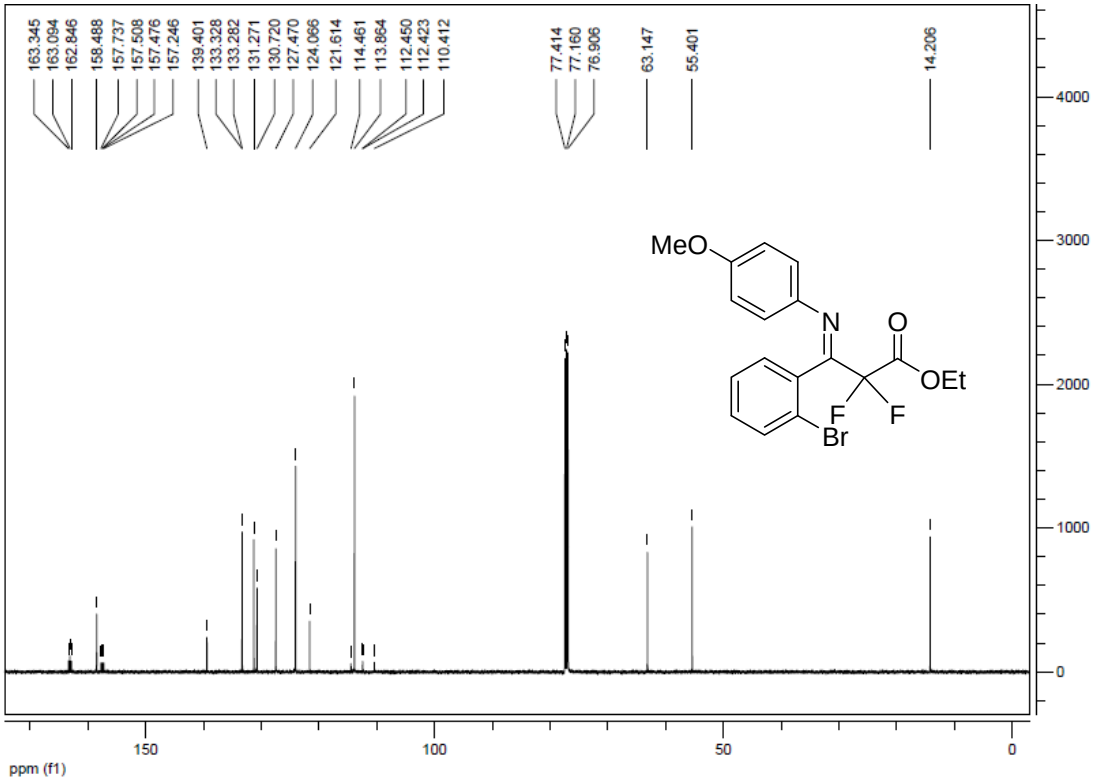






Ethyl (*E*)-3-(2-bromophenyl)-2,2-difluoro-3-((4-methoxyphenyl)imino)propanoate (2h)

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157.246
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127.470
124.066
121.614
114.461
113.864
112.450
112.423
110.412
77.414
77.160
76.906
63.147
55.401
14.206
MeO
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OEt
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F
Br
4000
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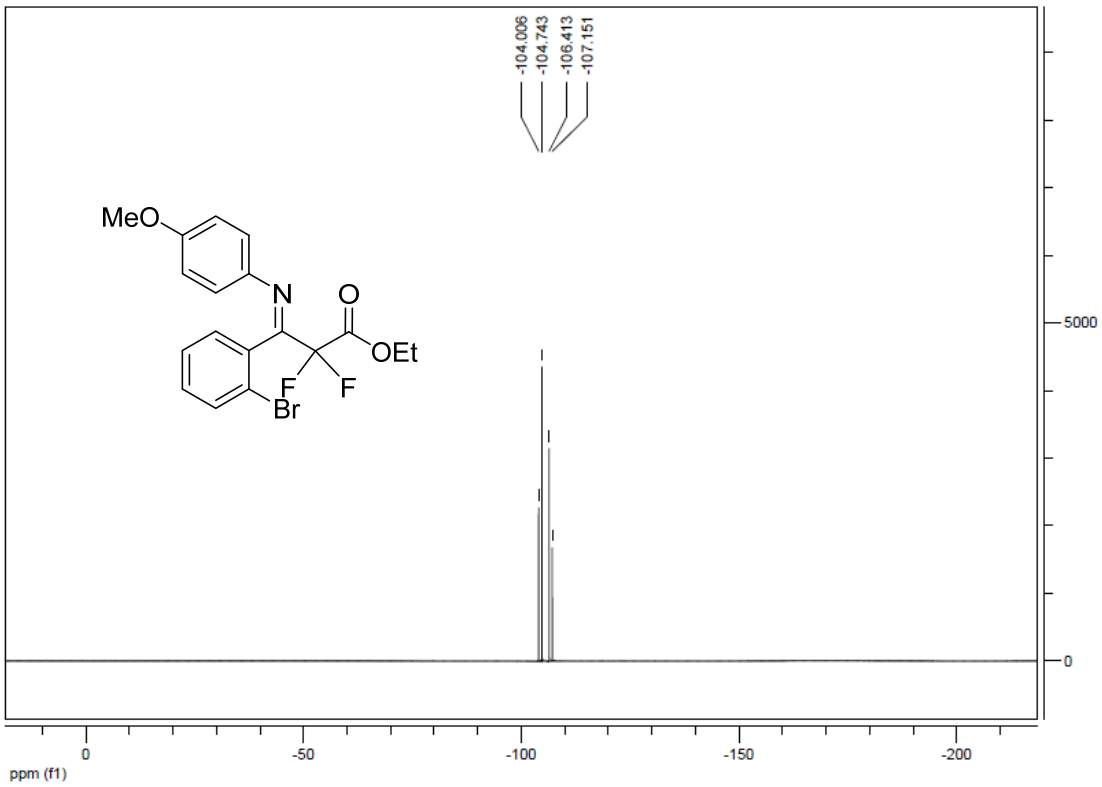
2000
1000
0
150
100
50
0
ppm (f1)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Br
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0
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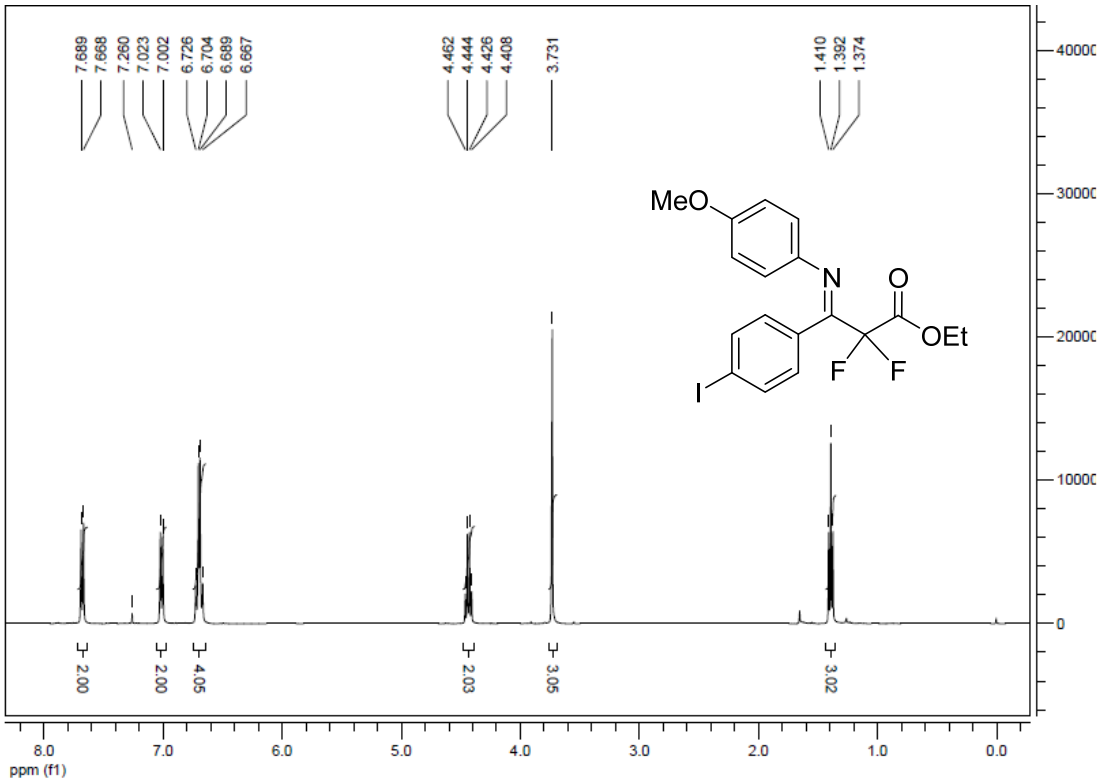
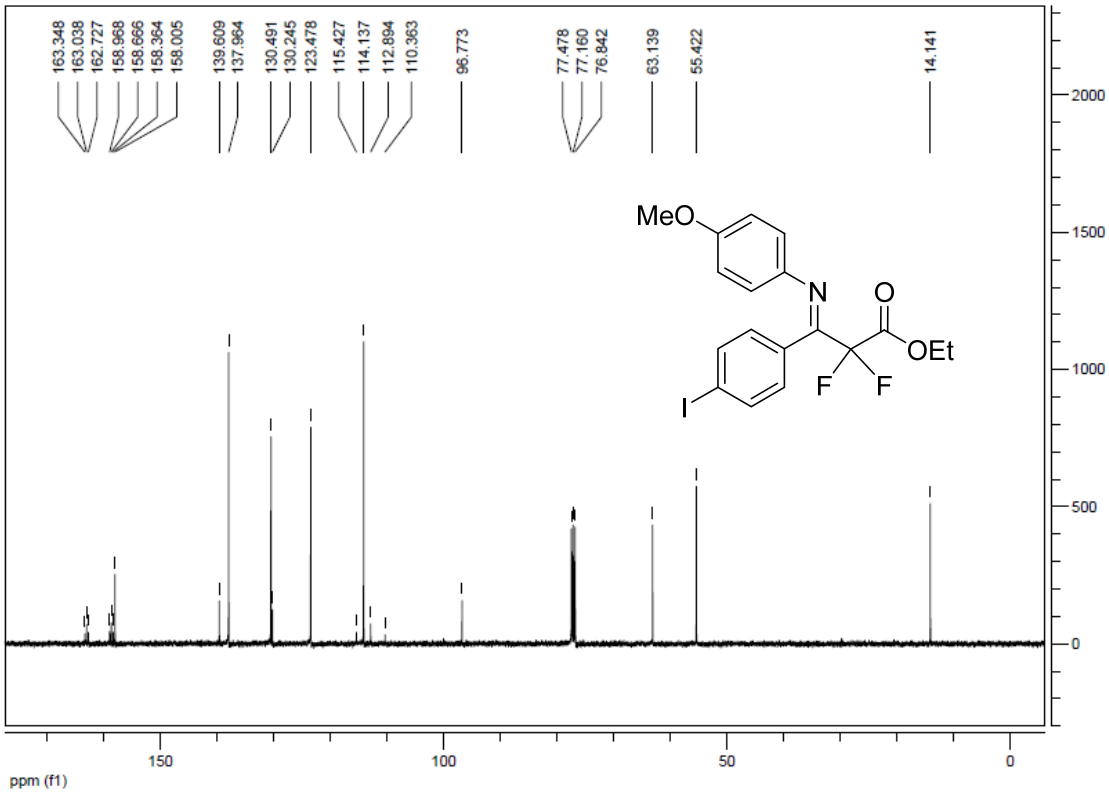
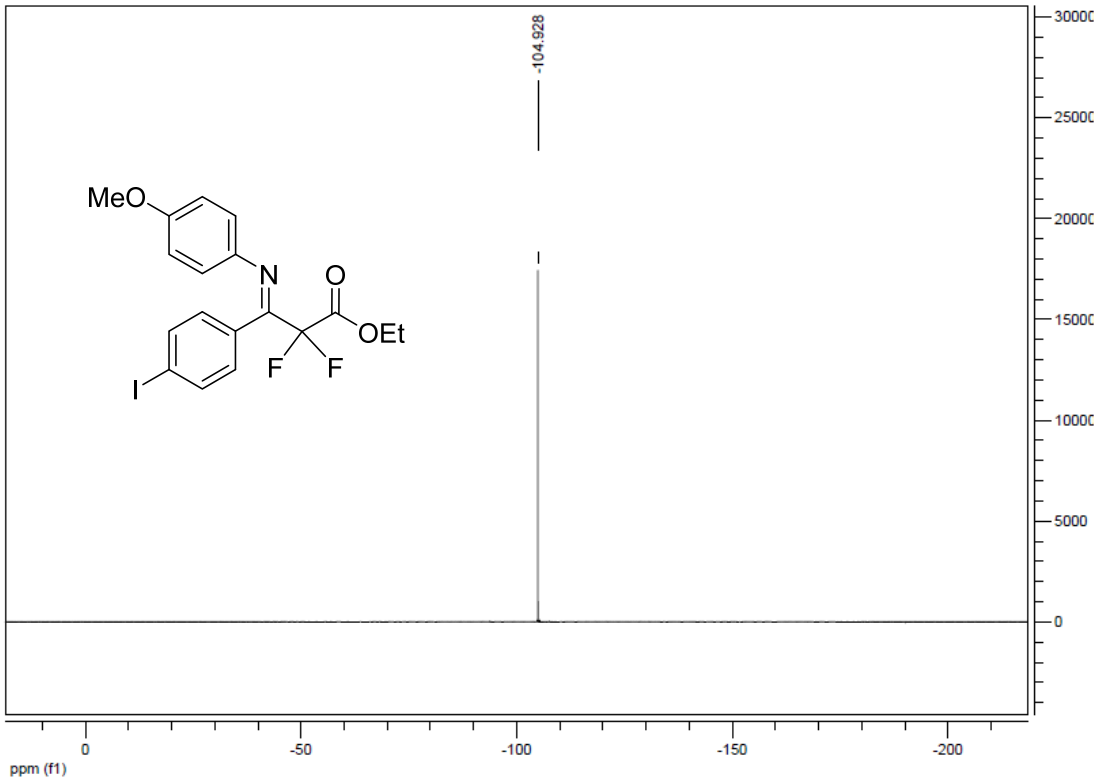
-100
-150
-200
ppm (f1)

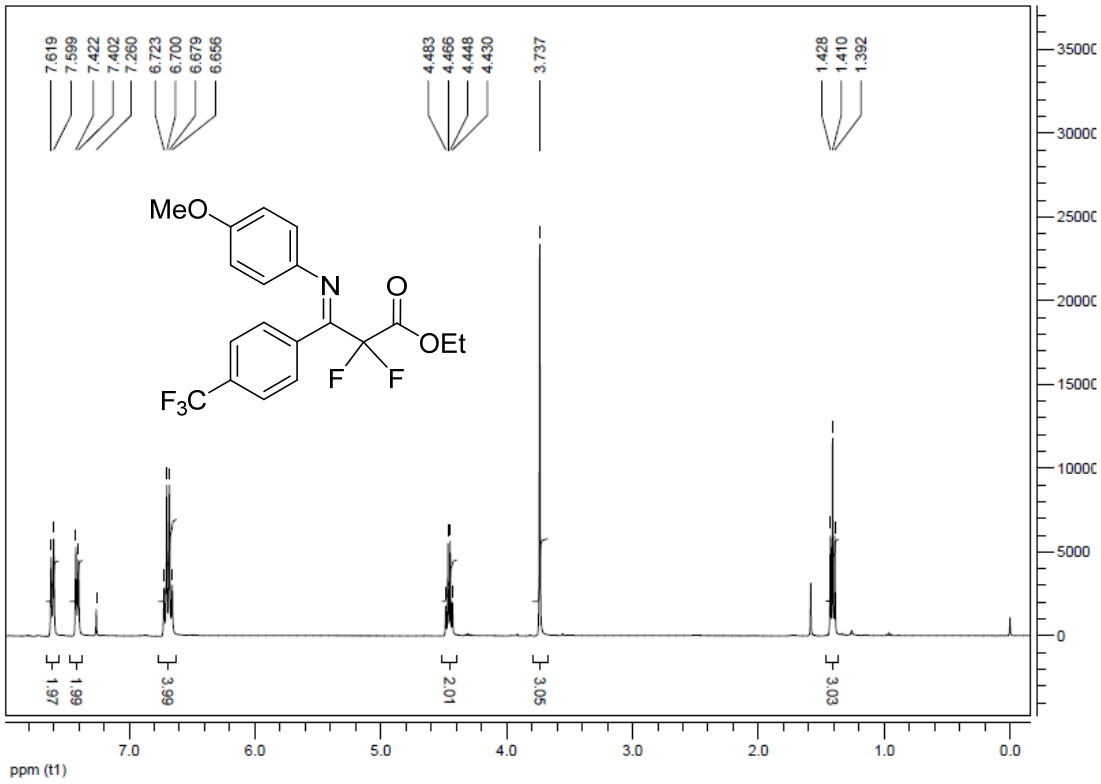
Ethyl (*E*)-2,2-difluoro-3-(4-iodophenyl)-3-((4-methoxyphenyl)imino)propanoate (2i)

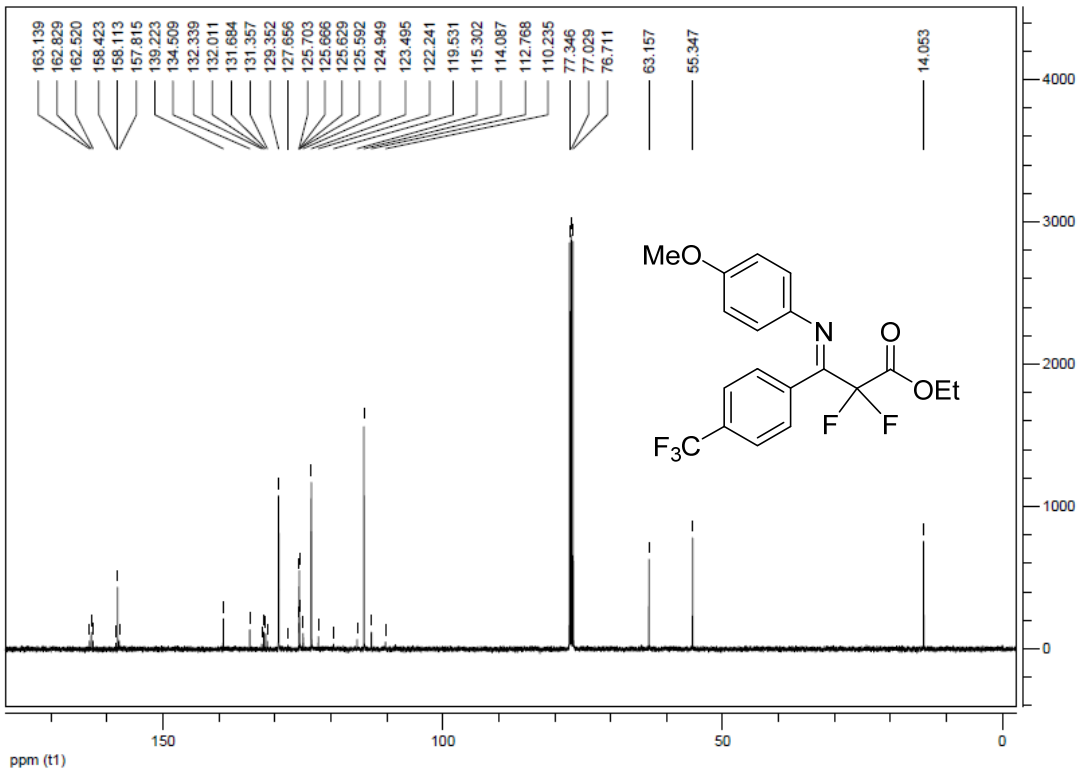






Ethyl (*E*)-2,2-difluoro-3-((4-methoxyphenyl)imino)-3-(4-(trifluoromethyl)phenyl)propanoate (2j)

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157.815
139.223
134.509
132.339
132.011
131.684
131.357
129.352
127.656
125.703
125.666
125.629
125.592
124.949
123.495
122.241
119.531
115.302
114.087
112.768
110.235
77.346
77.029
76.711
63.157
55.347
14.053
MeO
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O
OEt
F
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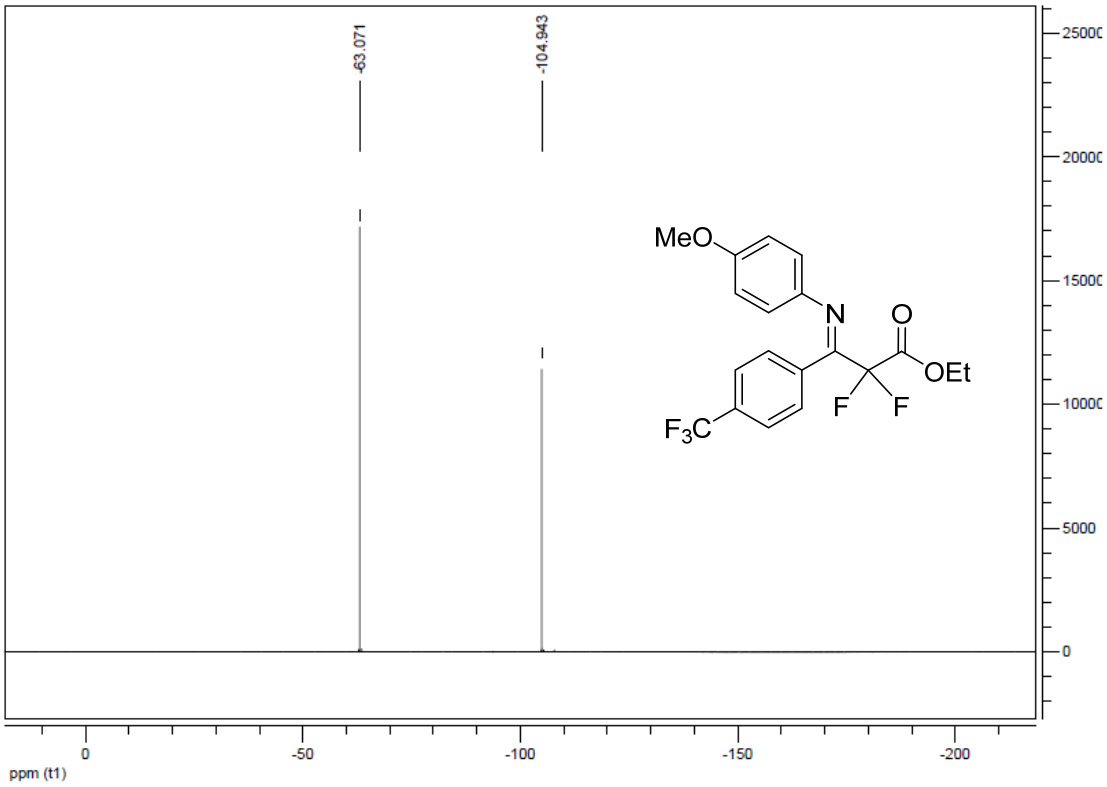
F3C
4000
3000
2000
1000
0
150
100
50
0
ppm (t1)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-104.943
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O
OEt
F
F
F3C
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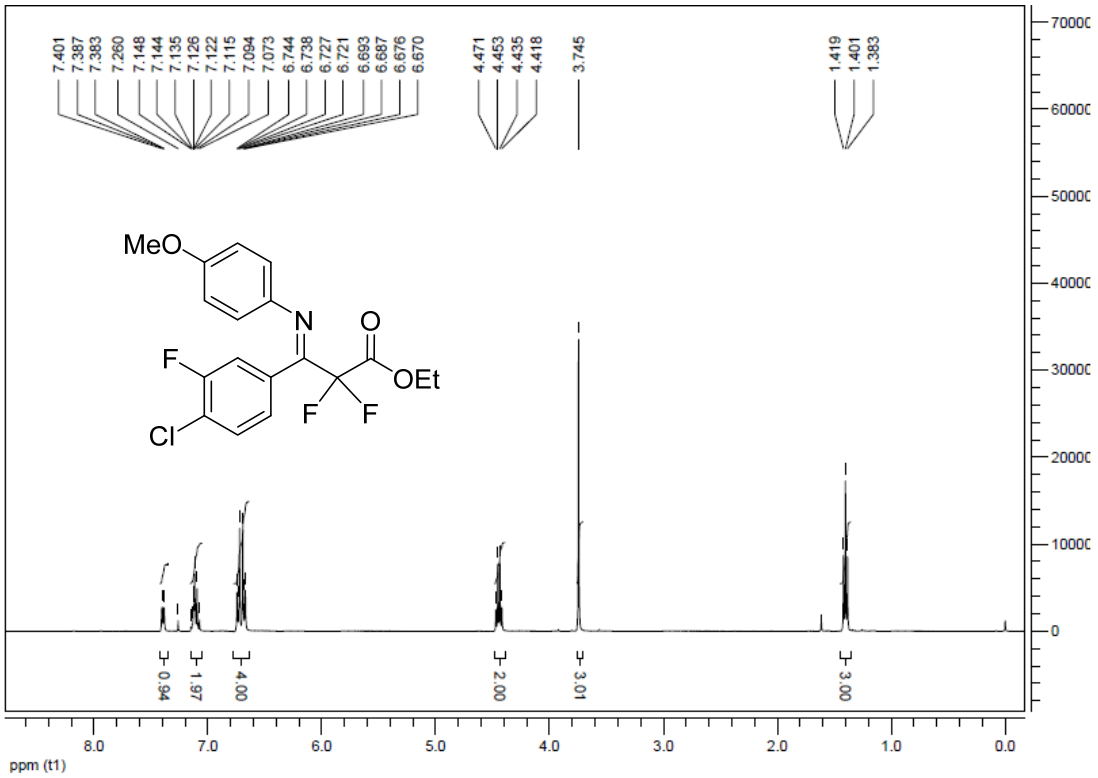
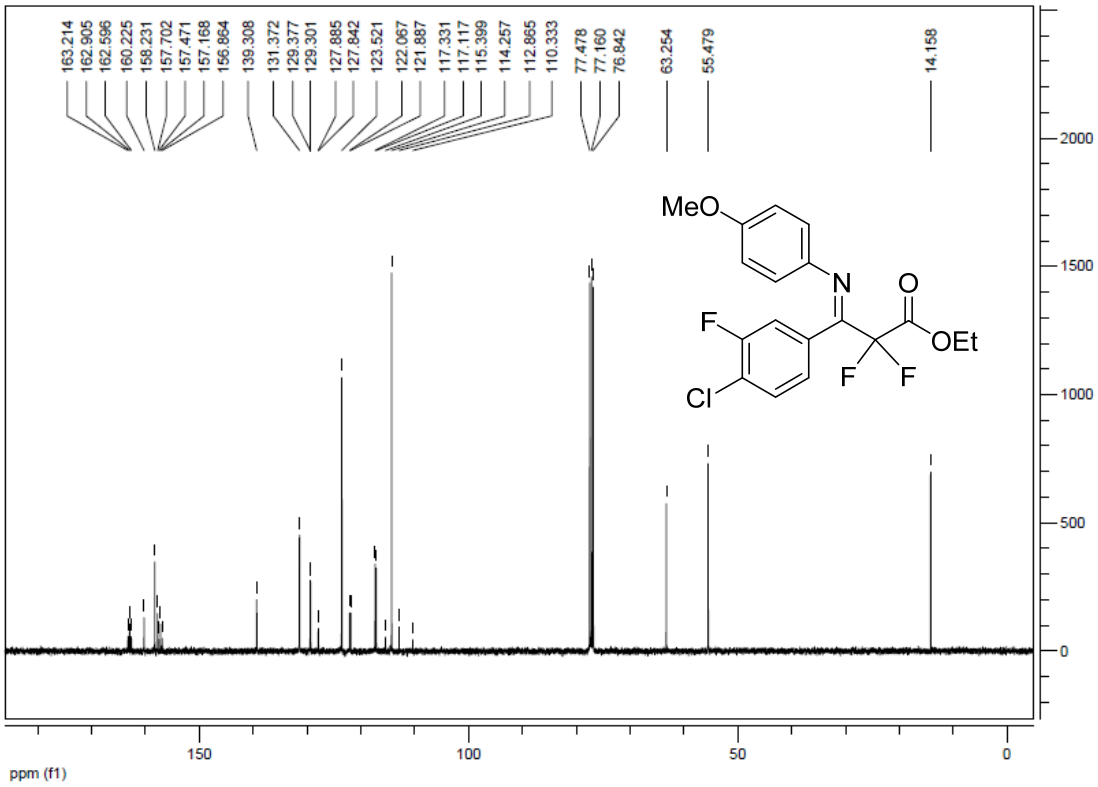
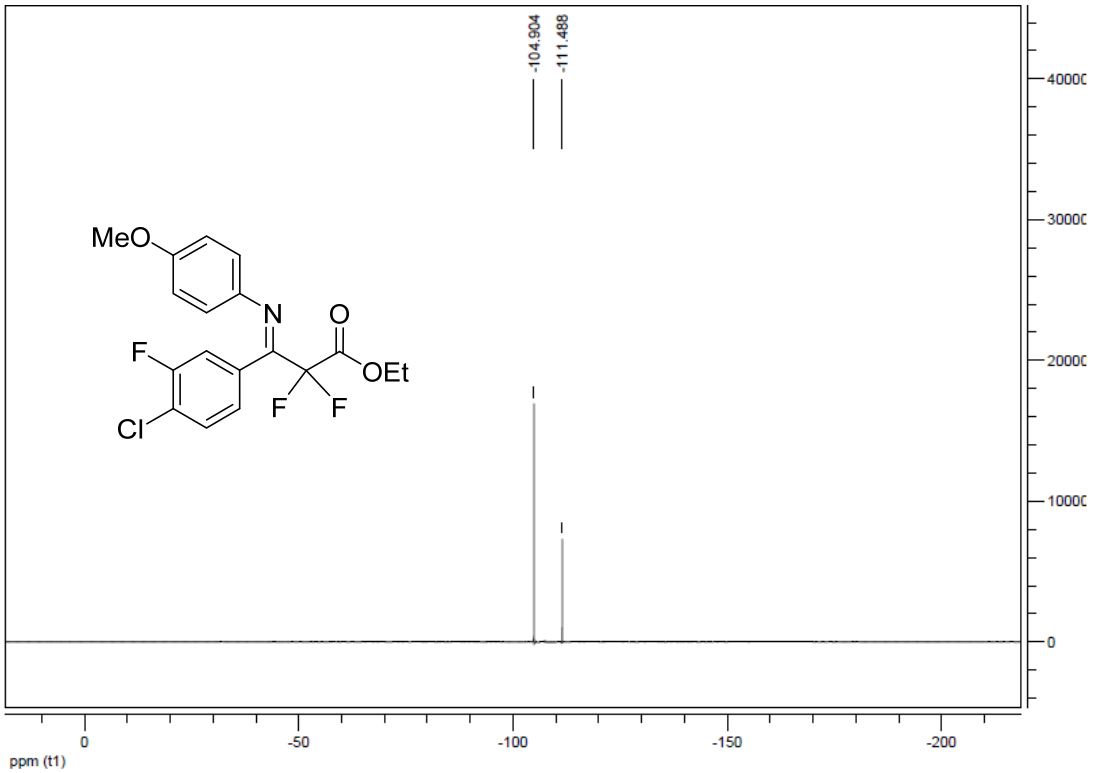
15000
10000
5000
0
0
-50
-100
-150
-200
ppm (t1)

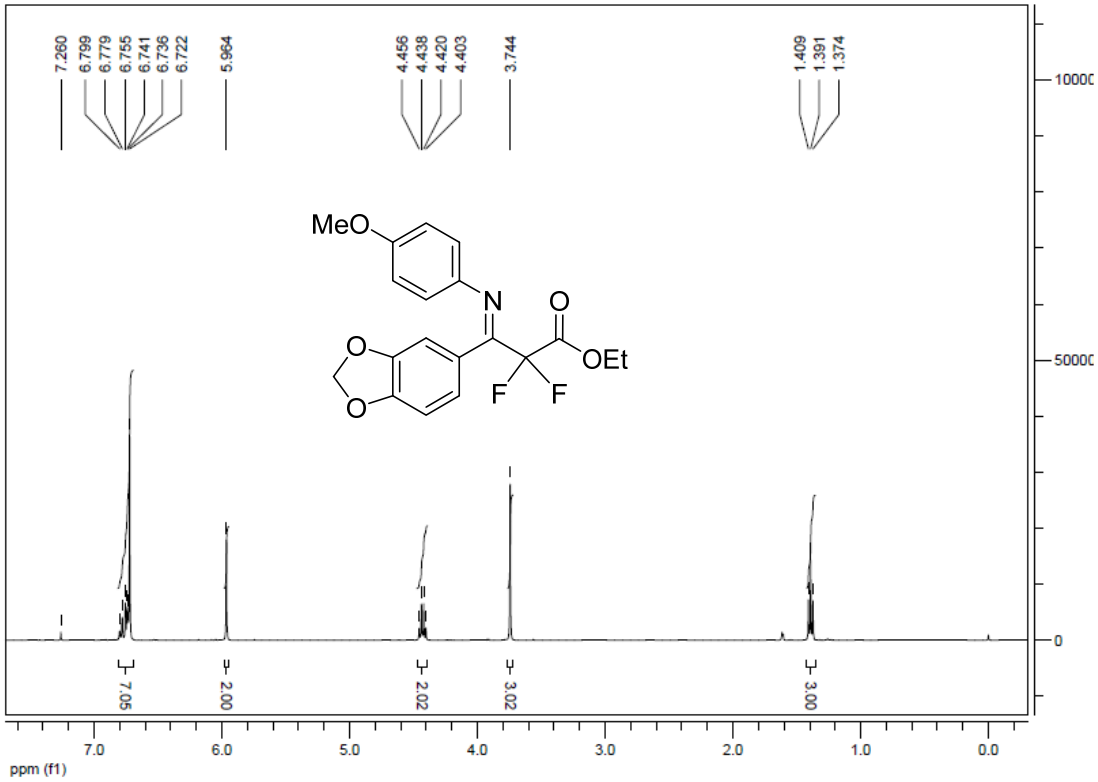
Ethyl (*E*)-3-(3-chloro-4-fluorophenyl)-2,2-difluoro-3-((4-methoxyphenyl)imino)propanoate (2k)

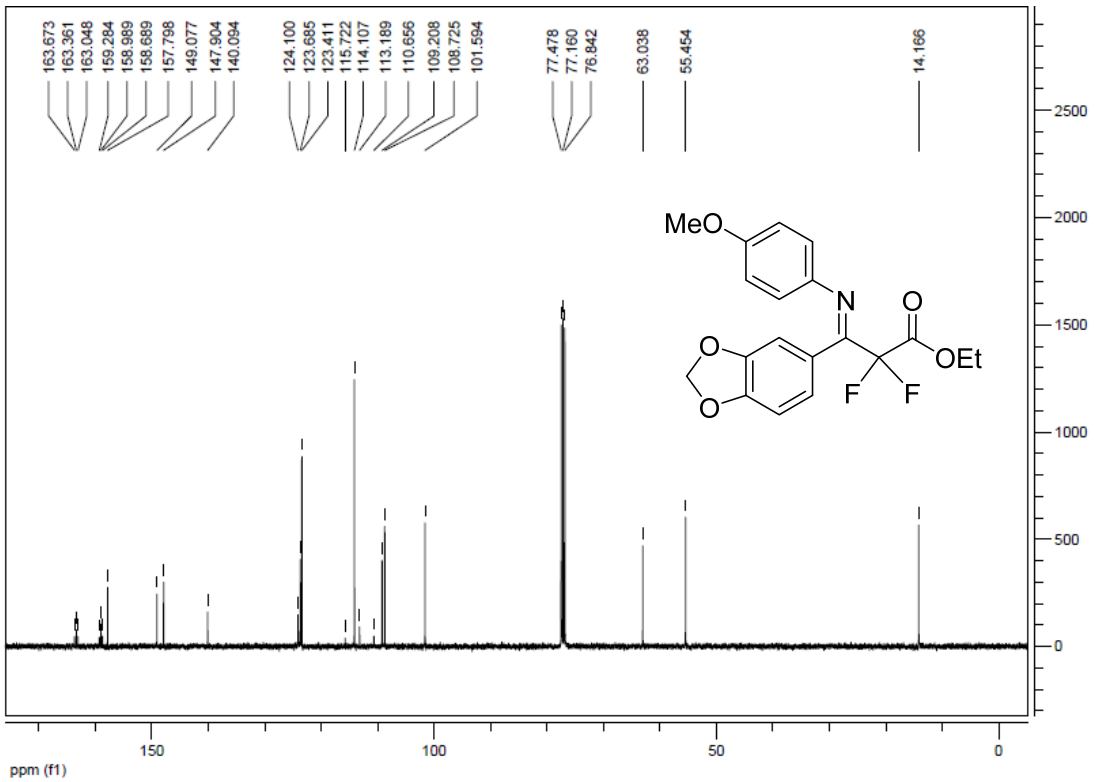


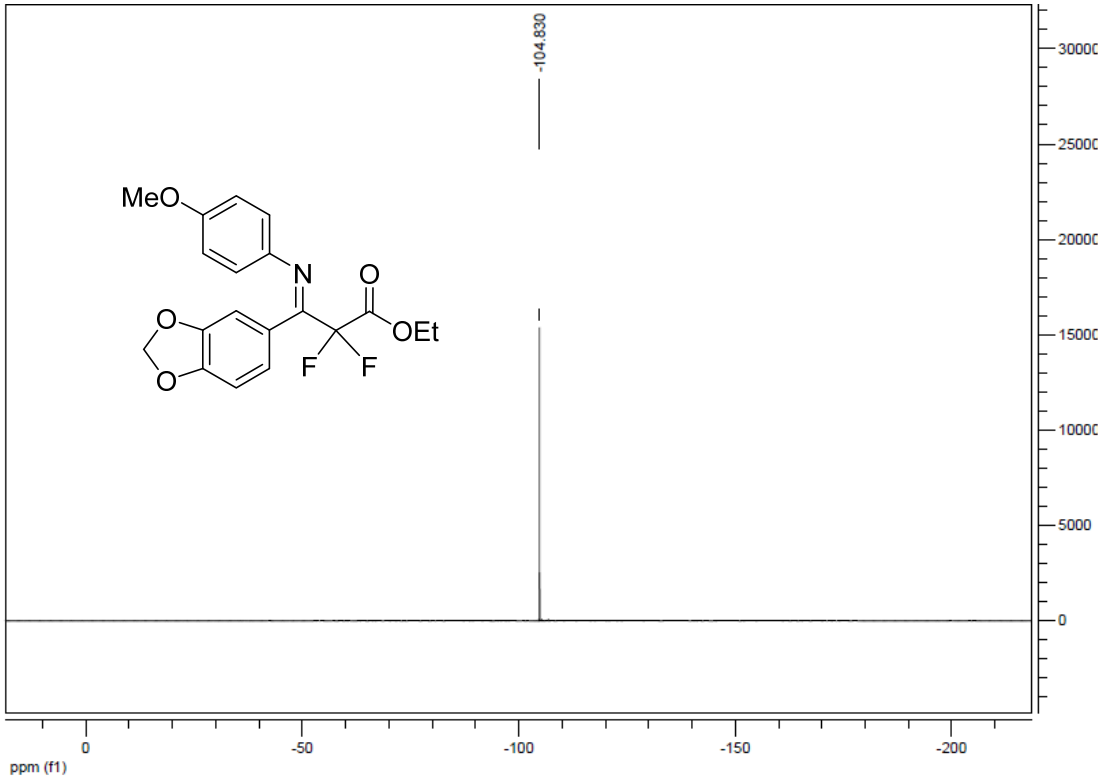




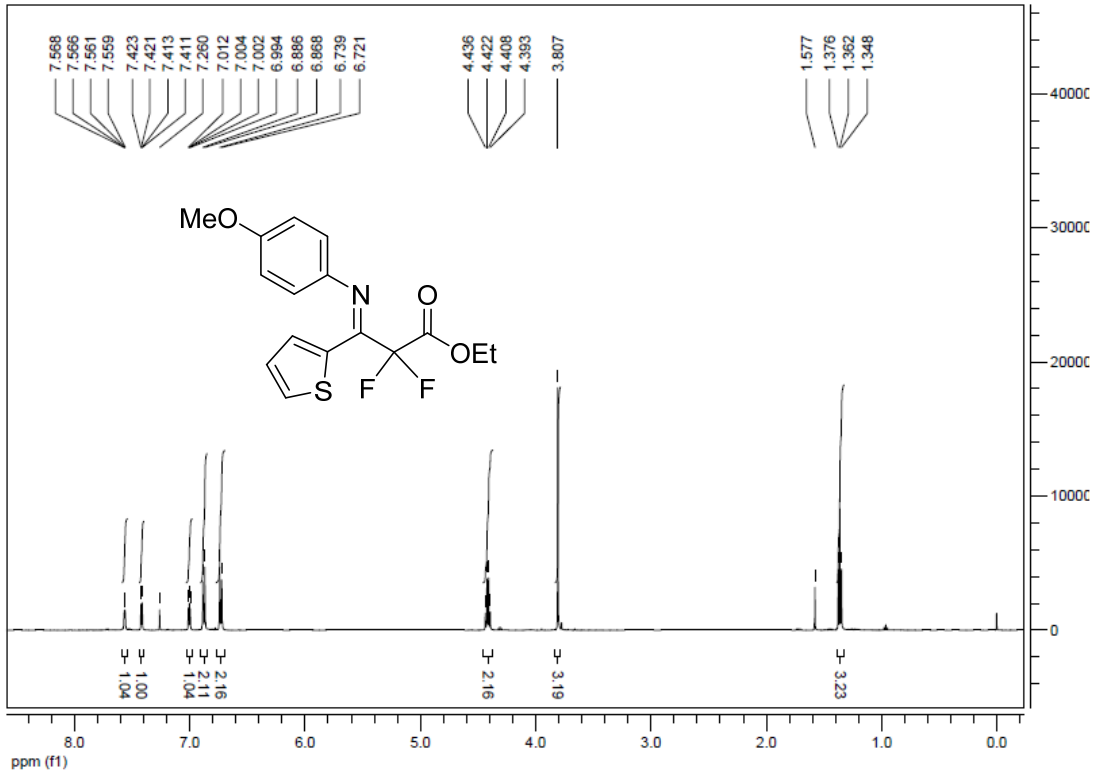
Ethyl (*E*)-3-(benzo[d][1,3]dioxol-5-yl)-2,2-difluoro-3-((4-methoxyphenyl)imino)propanoate (2l)

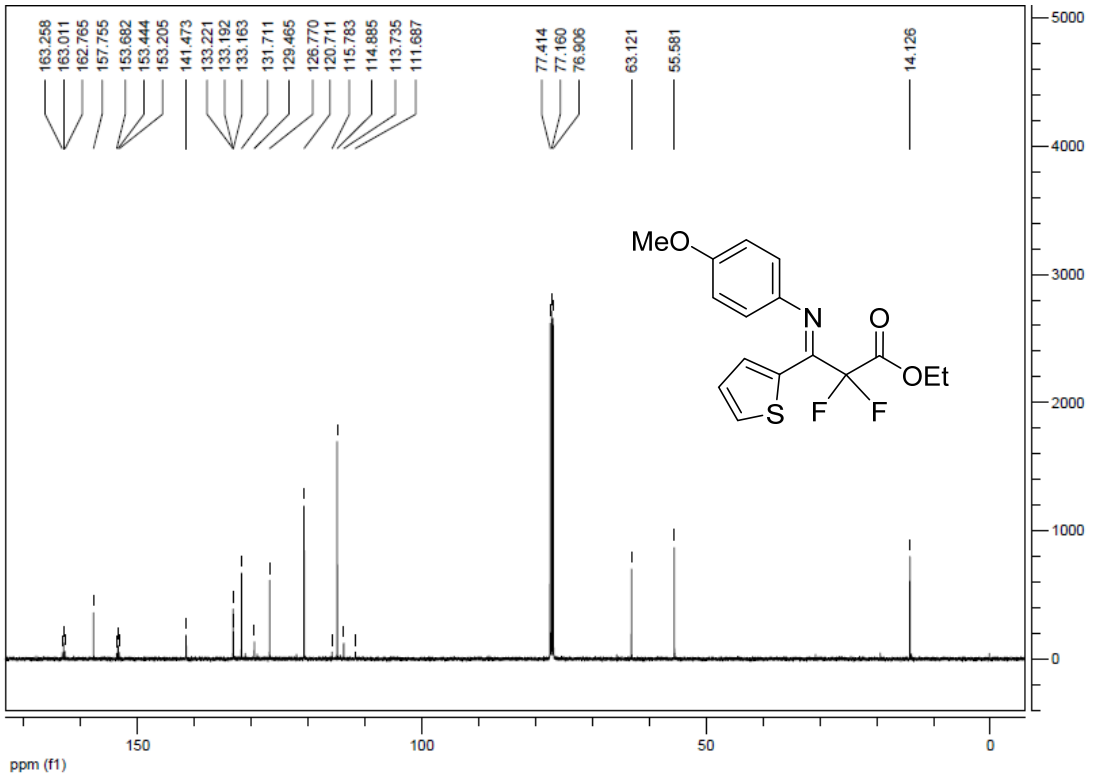


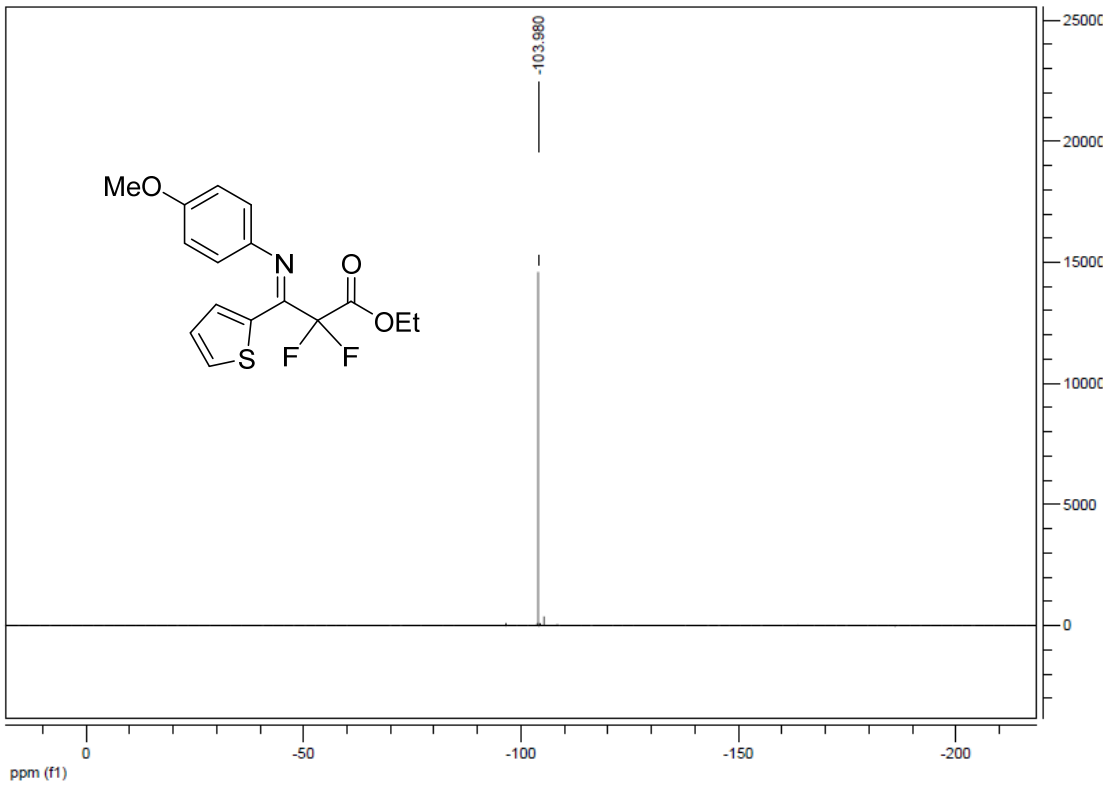

163.673
163.361
163.048
159.284
158.989
158.689
157.798
149.077
147.904
140.094
124.100
123.685
123.411
115.722
114.107
113.189
110.656
109.208
108.725
101.594
77.478
77.160
76.842
63.038
55.454
14.166
MeO
N
O
OEt
O
O
F
F
2500
2000
1500
1000
500
0
150
100
50
0
ppm (f1)


-104.830
MeO
N
O
OEt
O
O
F
F
30000
25000
20000
15000
10000
5000
0
0
-50
-100
-150
-200
ppm (f1)

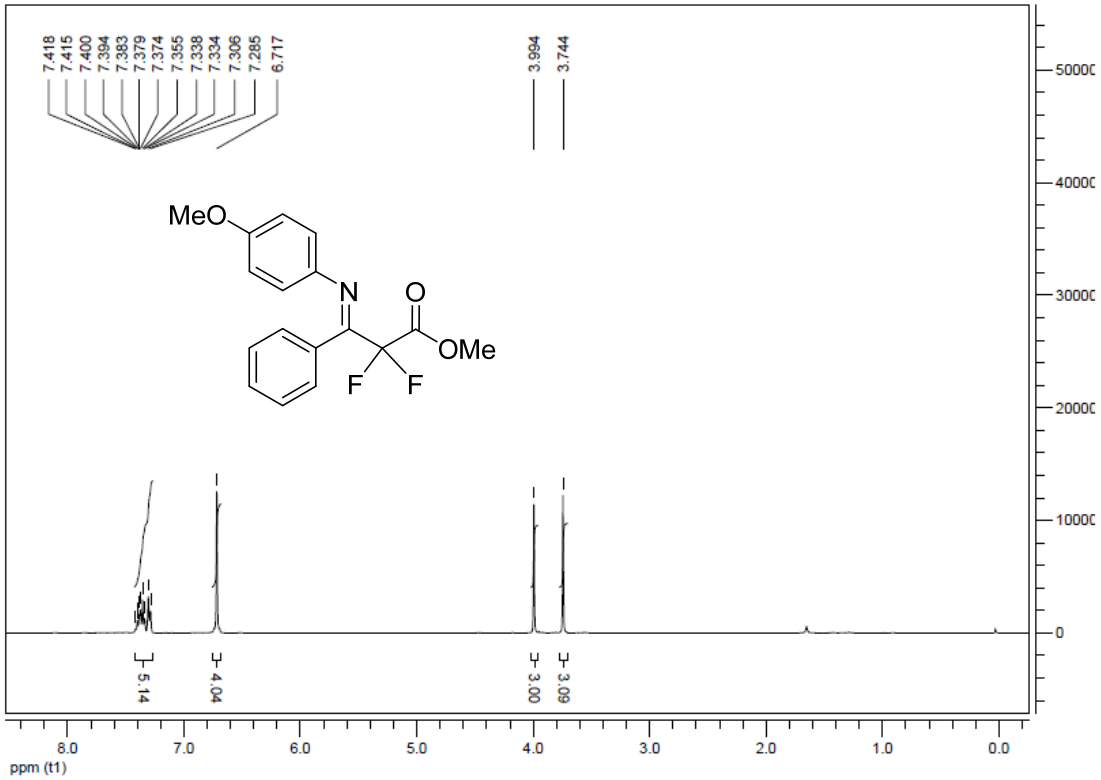
Ethyl (*Z*)-2,2-difluoro-3-((4-methoxyphenyl)imino)-3-(thiophen-2-yl)propanoate (2m)

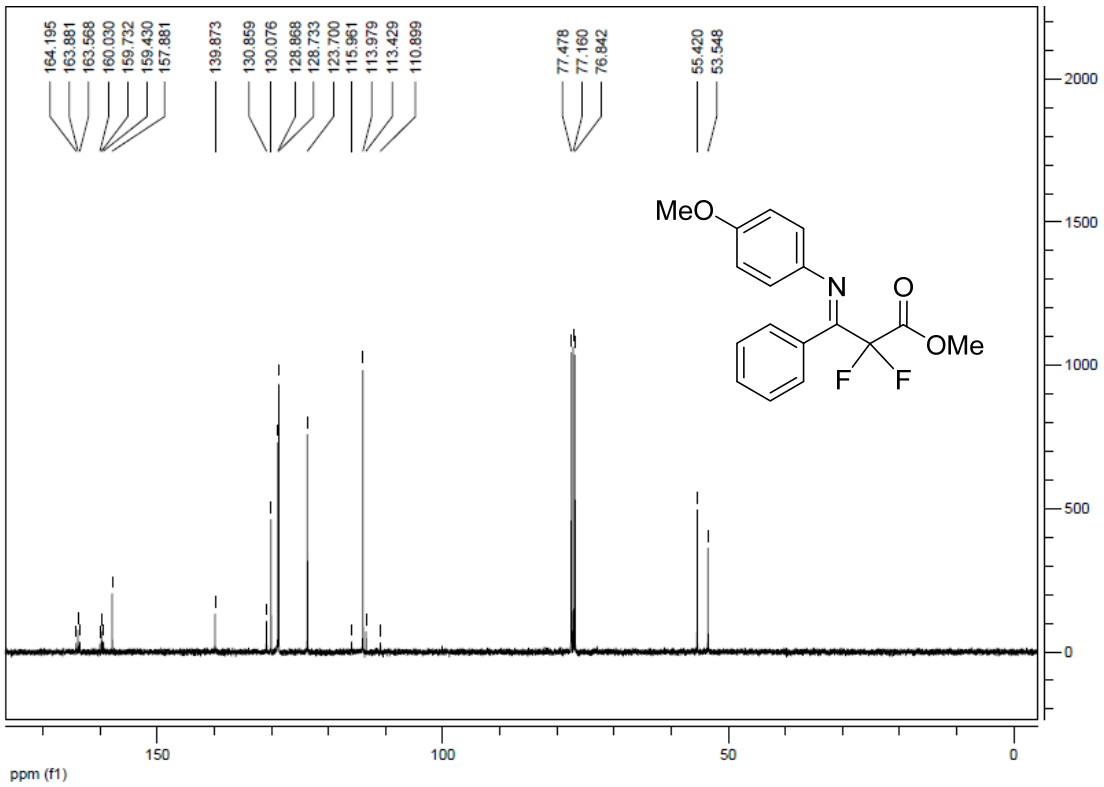


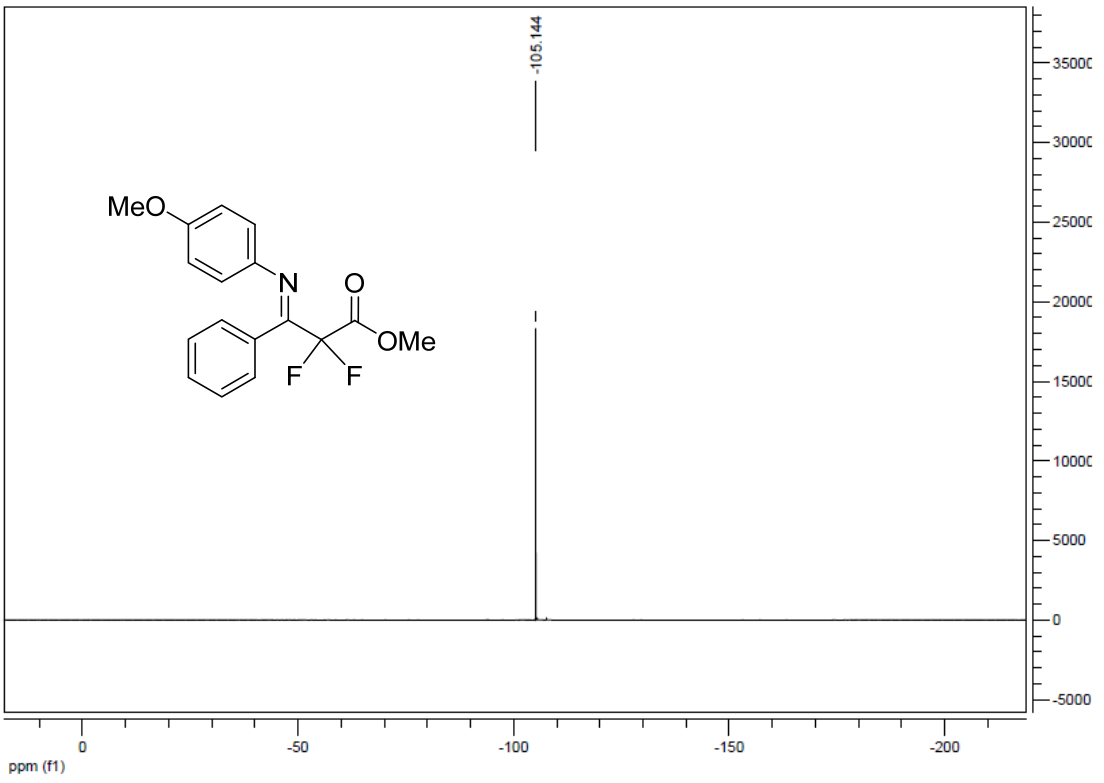




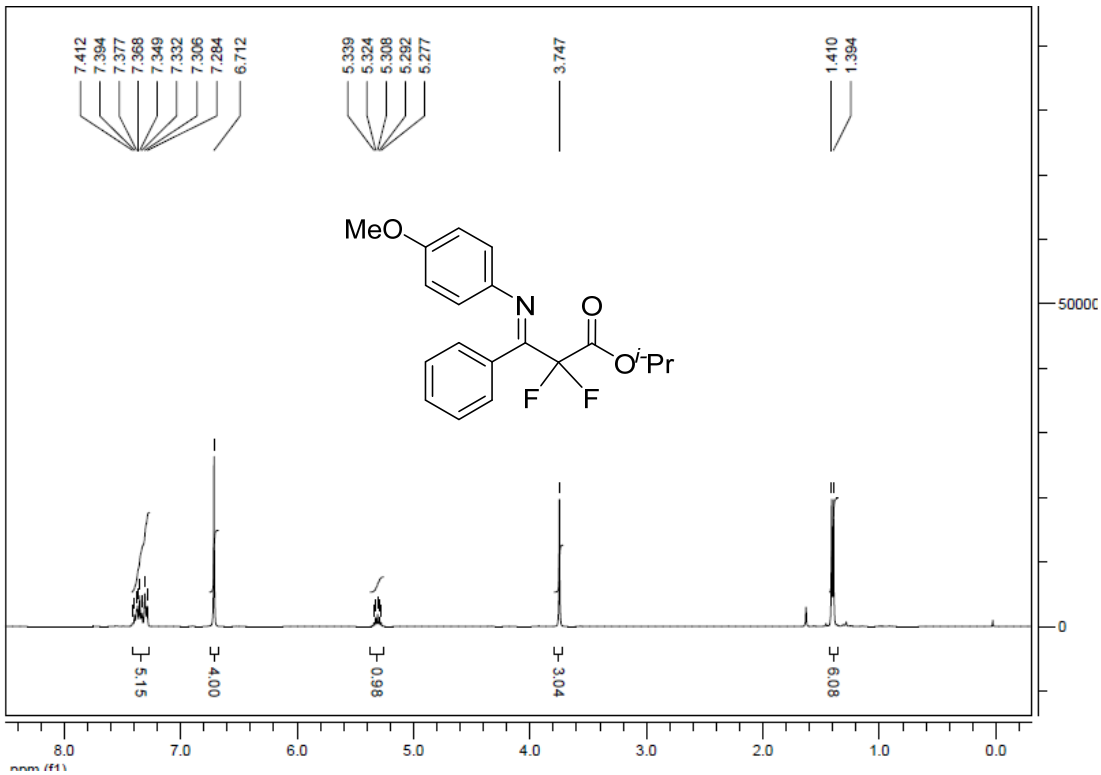
Methyl (*E*)-2,2-difluoro-3-((4-methoxyphenyl)imino)-3-phenylpropanoate (2n)

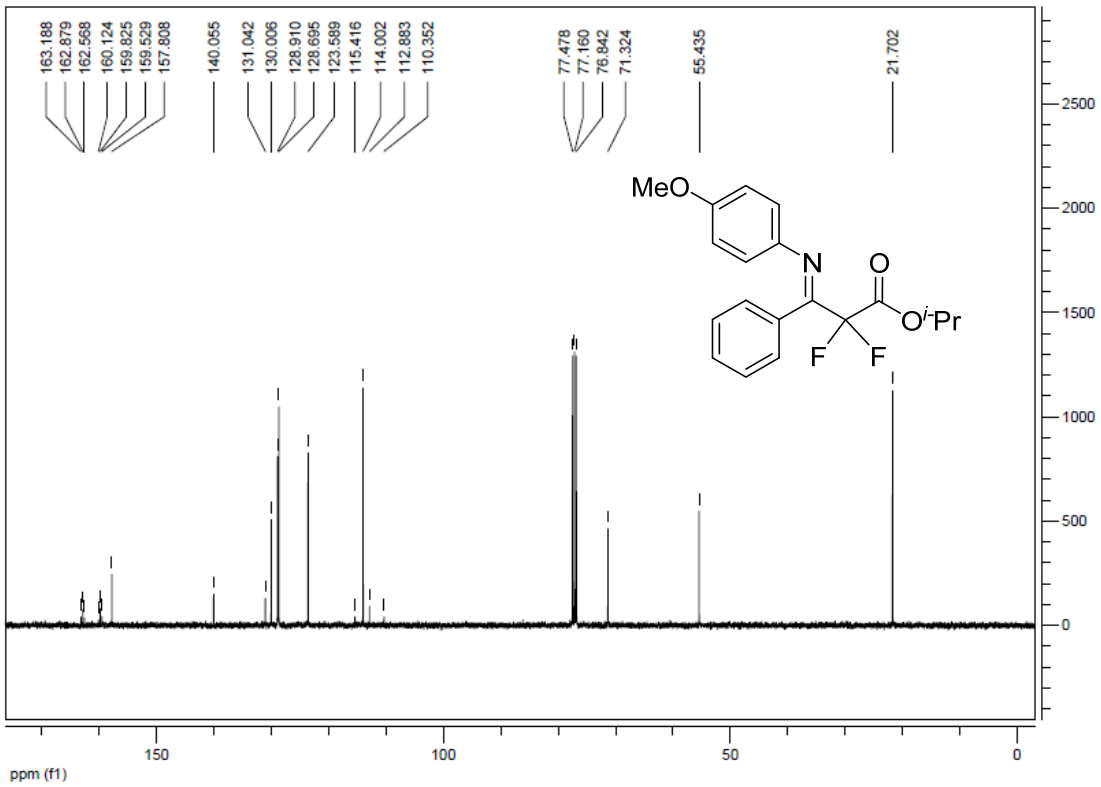


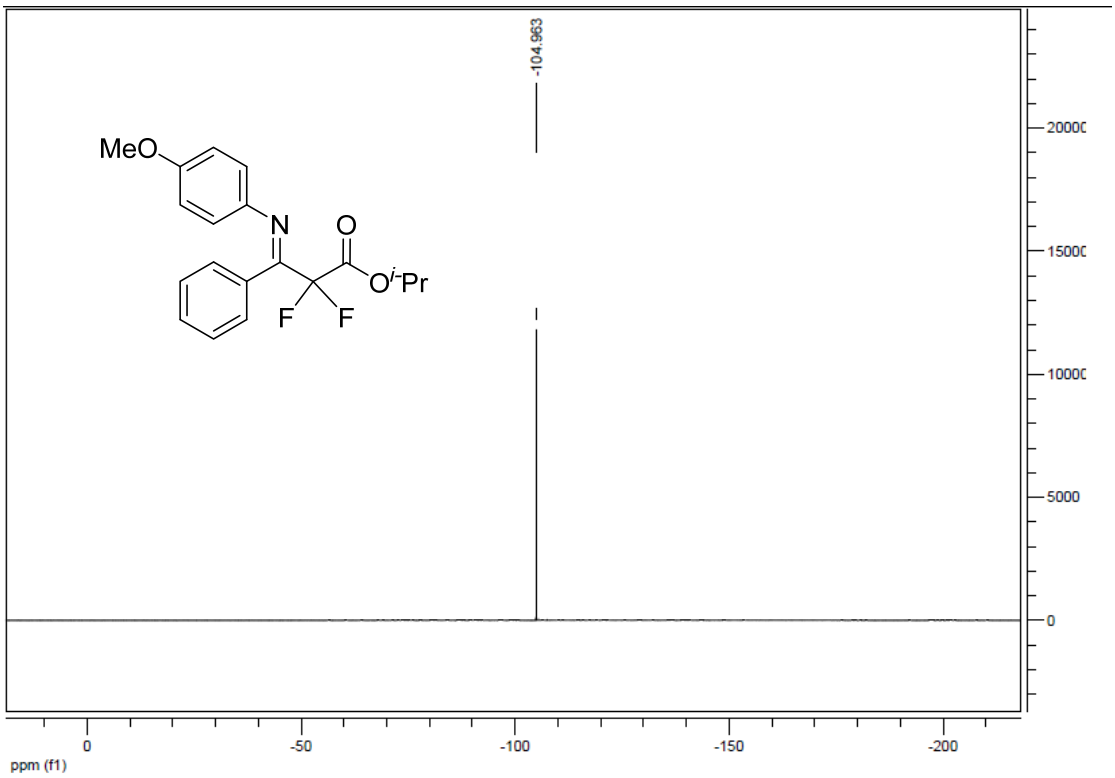

164.195
163.881
163.568
160.030
159.732
159.430
157.881
139.873
130.859
130.076
128.868
128.733
123.700
115.961
113.979
113.429
110.899
77.478
77.160
76.842
55.420
53.548
MeO
N
O
OMe
F
F
2000
1500
1000
500
0
150
100
50
0
ppm (f1)


-105.144
MeO
N
O
OMe
F
F
35000
30000
25000
20000
15000
10000
5000
0
-5000
0
-50
-100
-150
-200
ppm (f1)

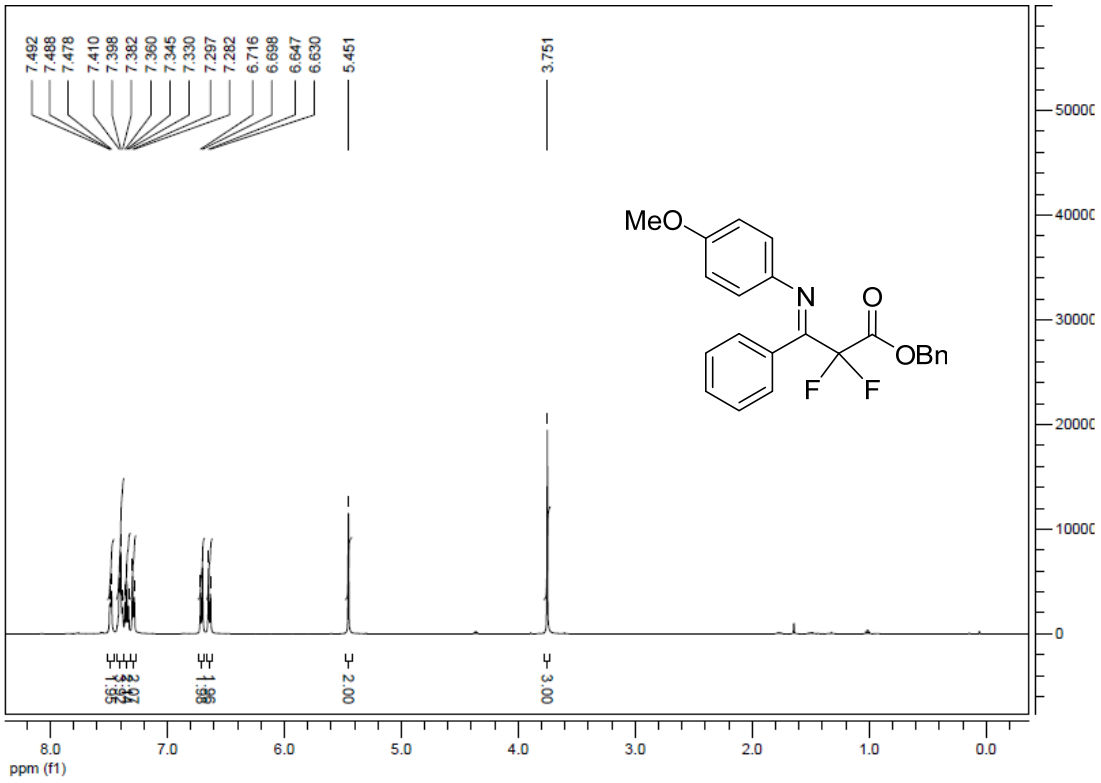
Isopropyl (*E*)-2,2-difluoro-3-((4-methoxyphenyl)imino)-3-phenylpropanoate (2o)

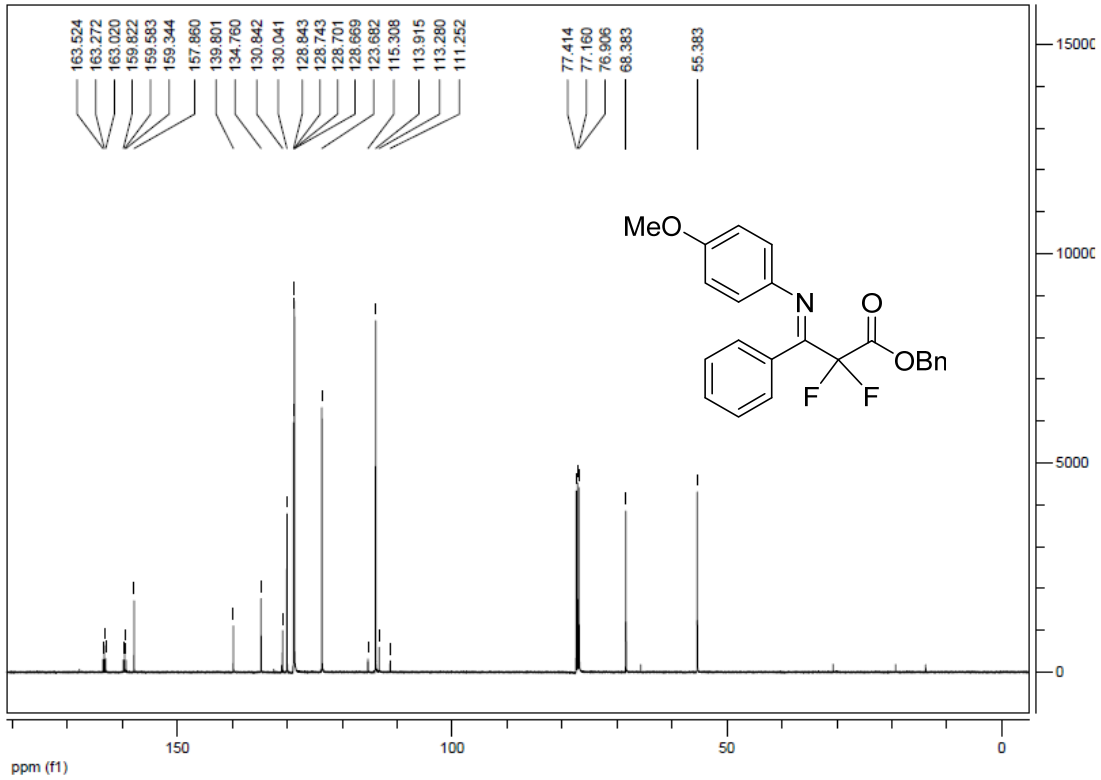


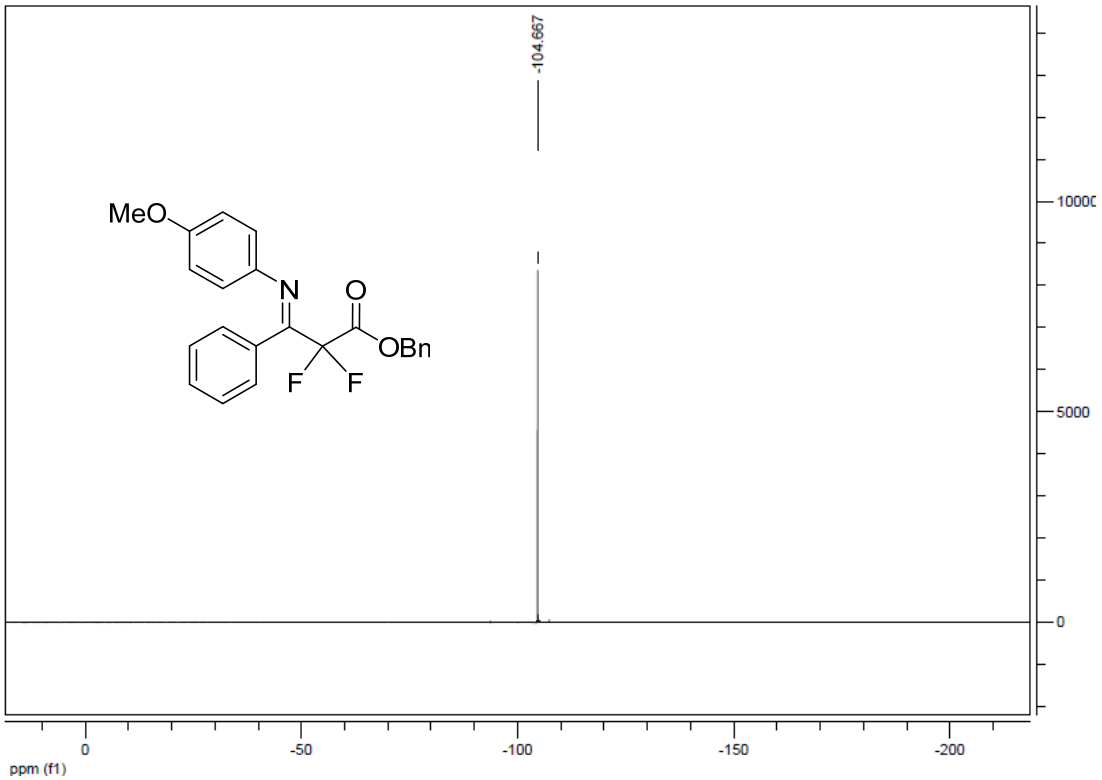




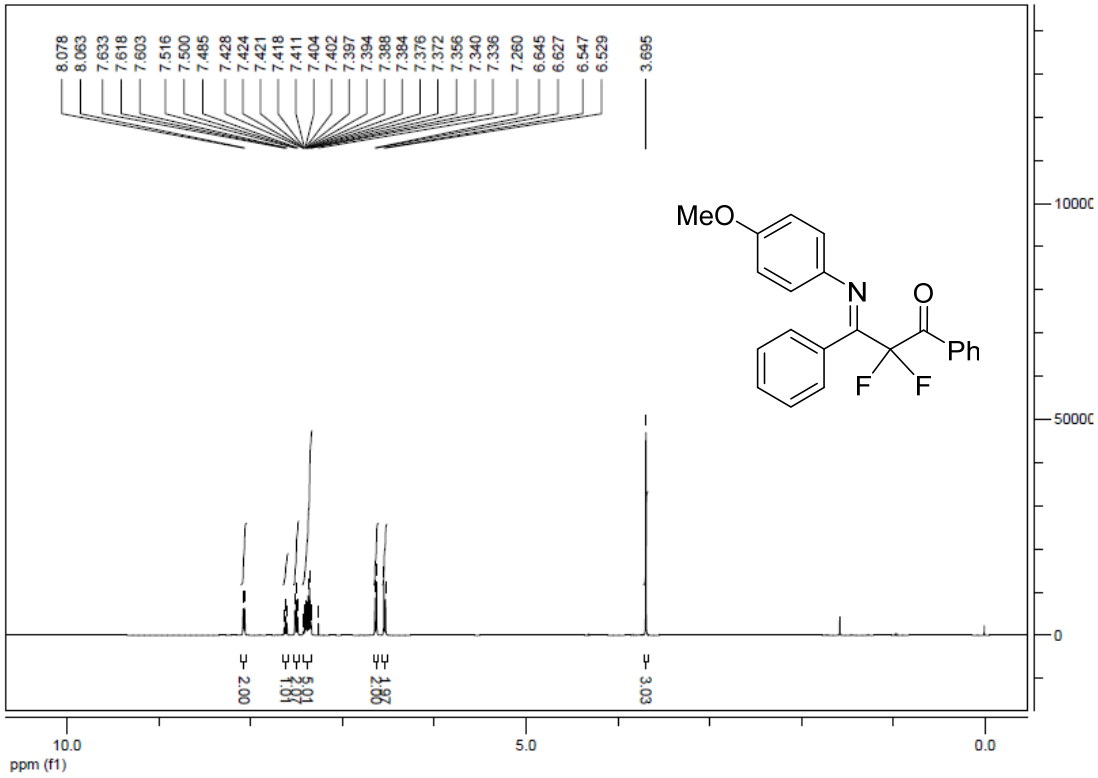
Benzyl (*E*)-2,2-difluoro-3-((4-methoxyphenyl)imino)-3-phenylpropanoate (2p)

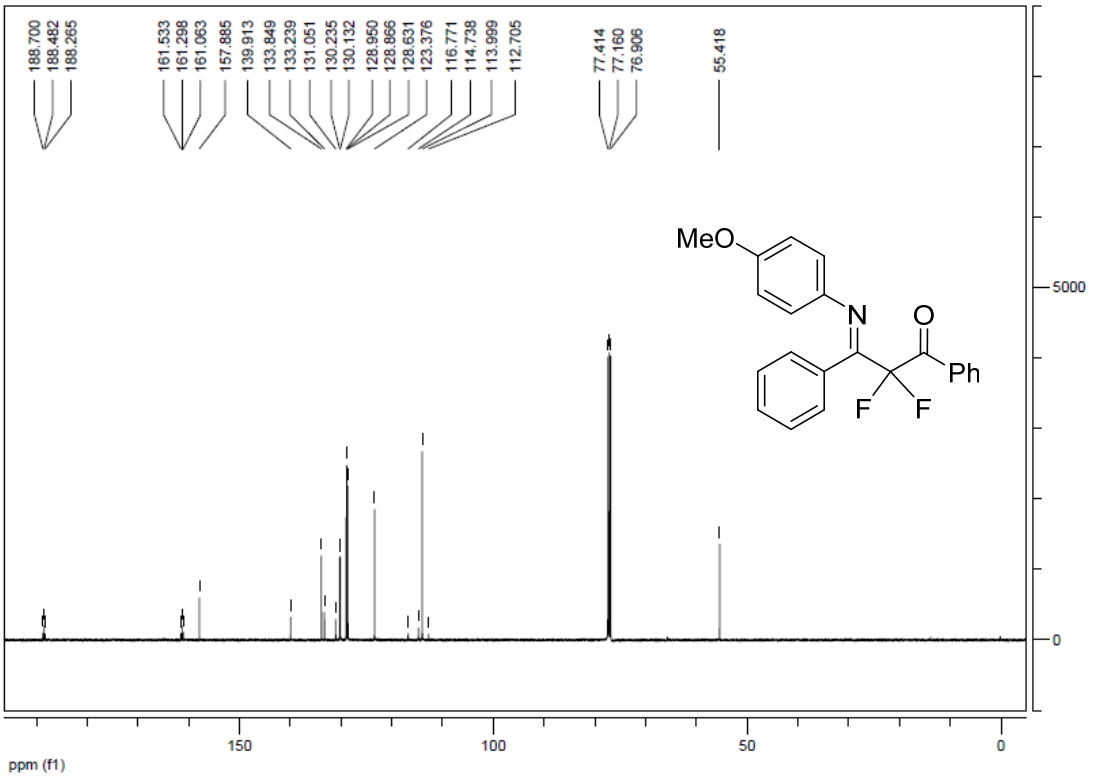


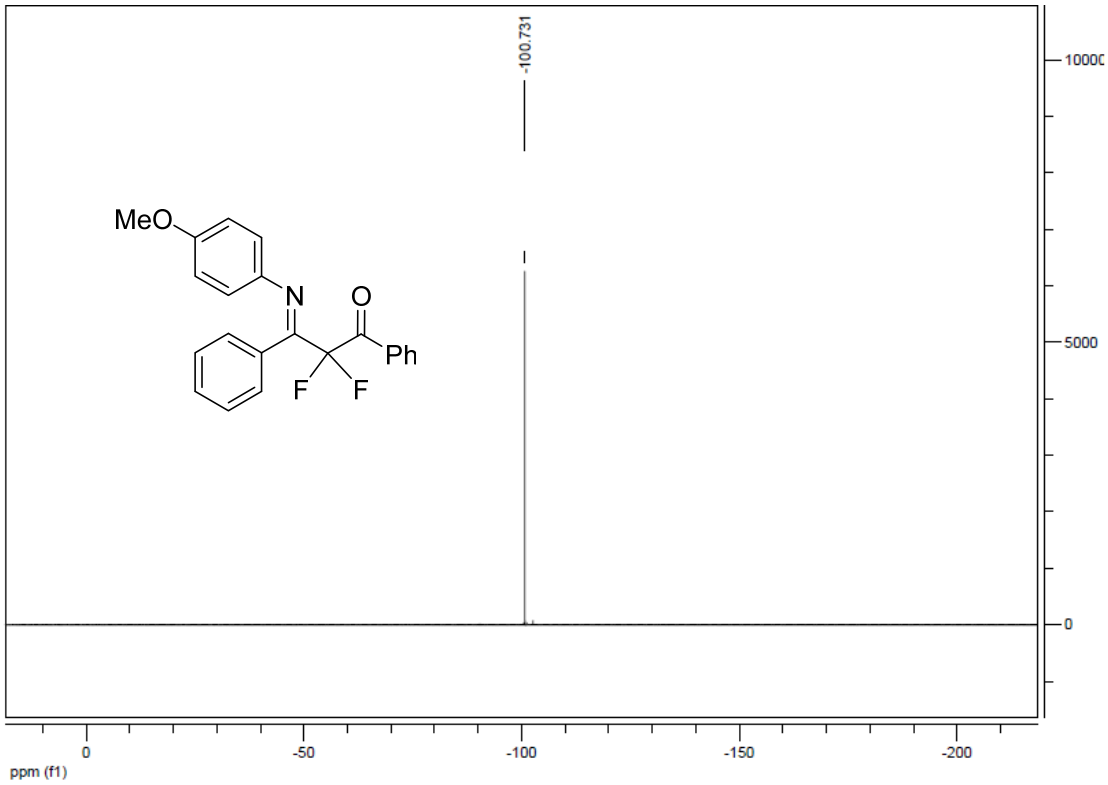

163.524
163.272
163.020
159.822
159.583
159.344
157.860
139.801
134.760
130.842
130.041
128.843
128.743
128.701
128.669
123.682
115.308
113.915
113.280
111.252
77.414
77.160
76.906
68.383
55.383
MeO
N
O
OBn
F
F
150000
100000
50000
0
150
100
50
0
ppm (f1)


-104.667
MeO
N
O
OBn
F
F
100000
50000
0
0
-50
-100
-150
-200
ppm (f1)

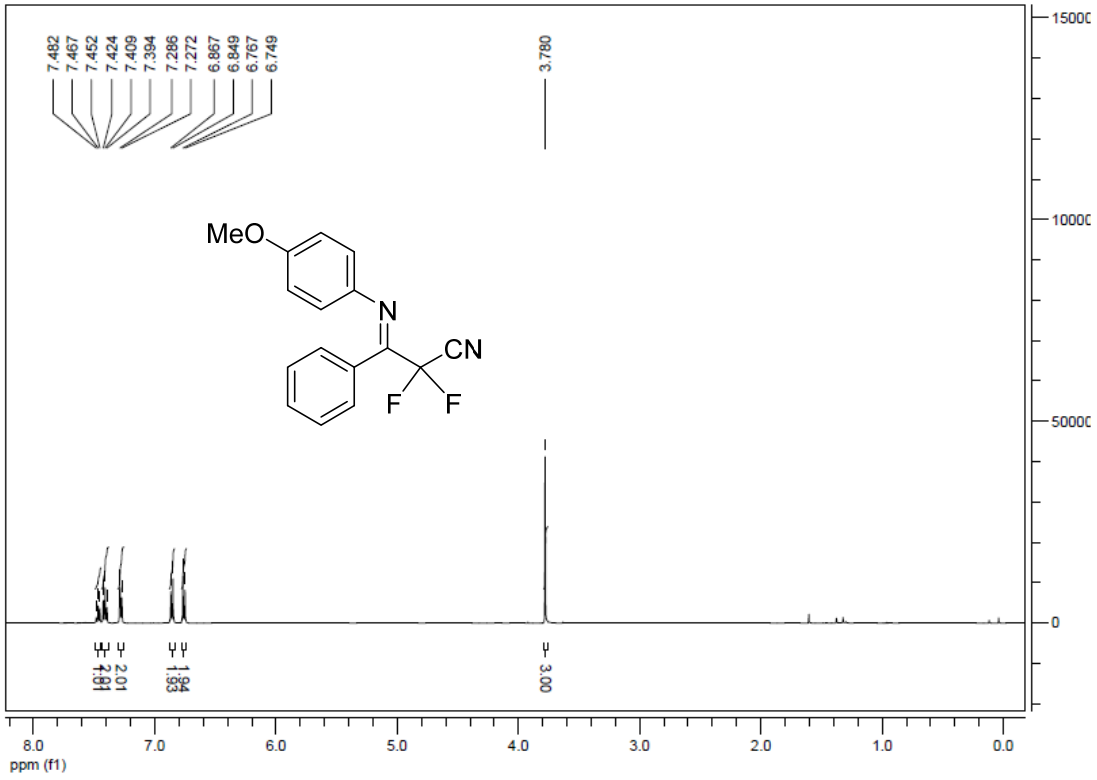
(*E*)-2,2-difluoro-3-((4-methoxyphenyl)imino)-1,3-diphenylpropan-1-one (2q)

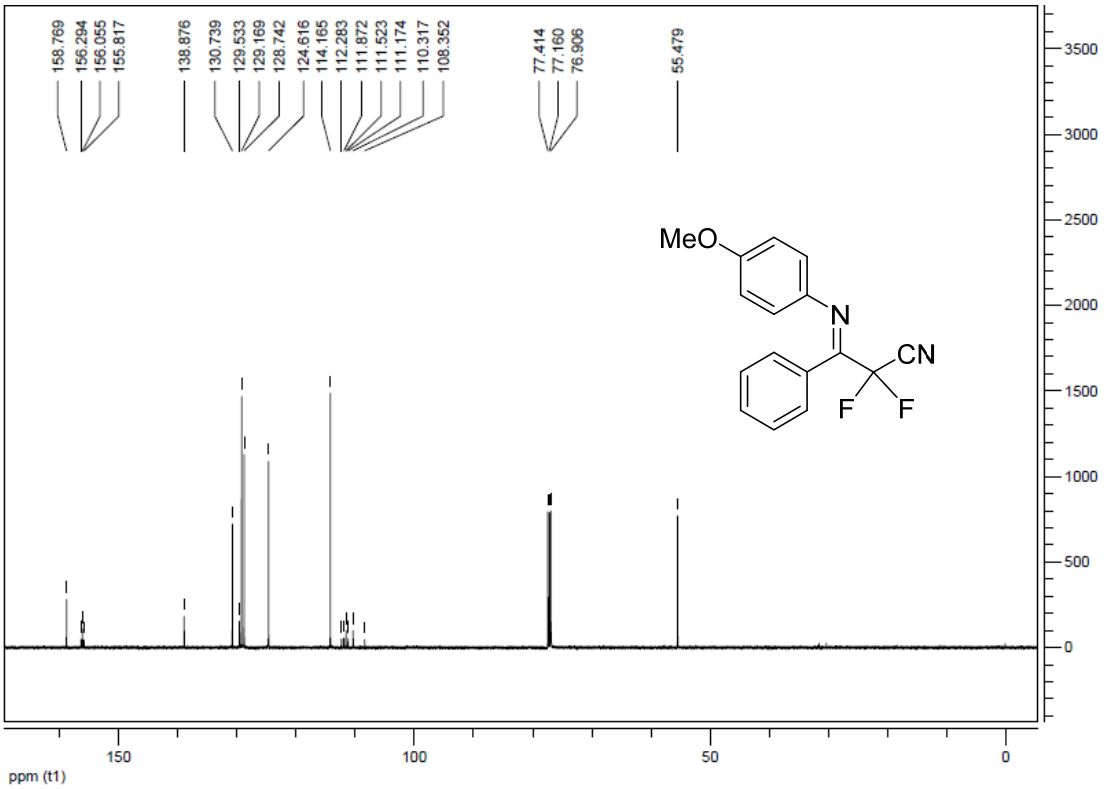


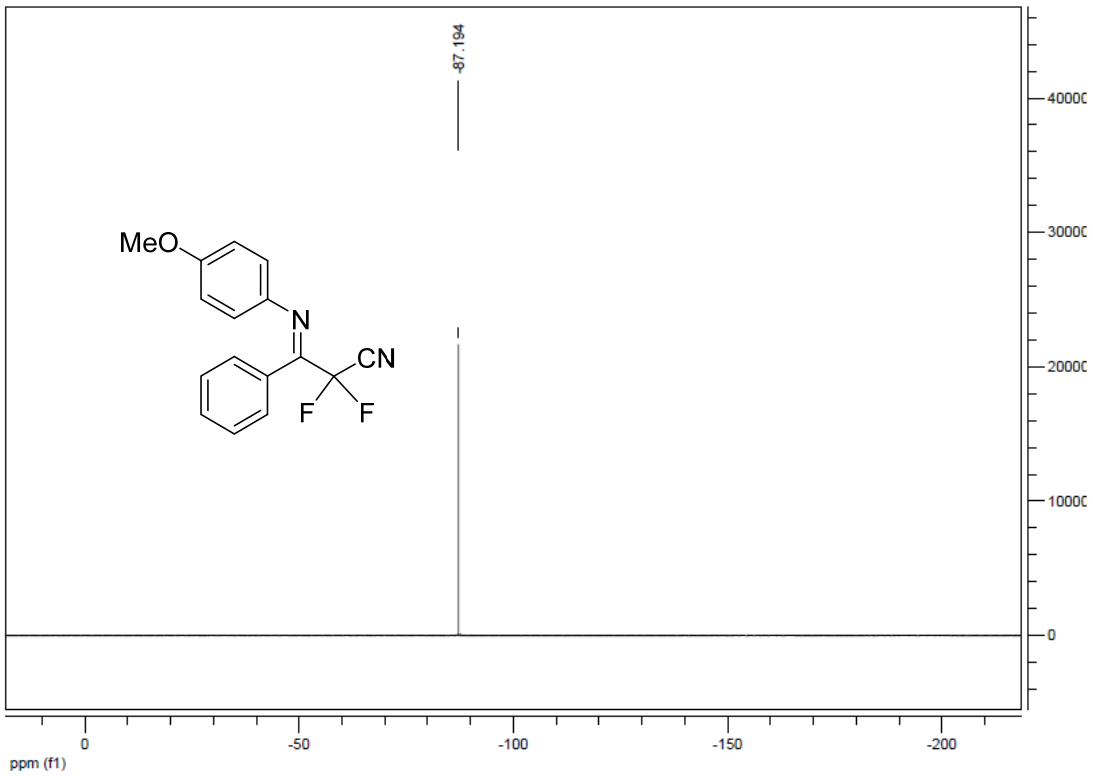




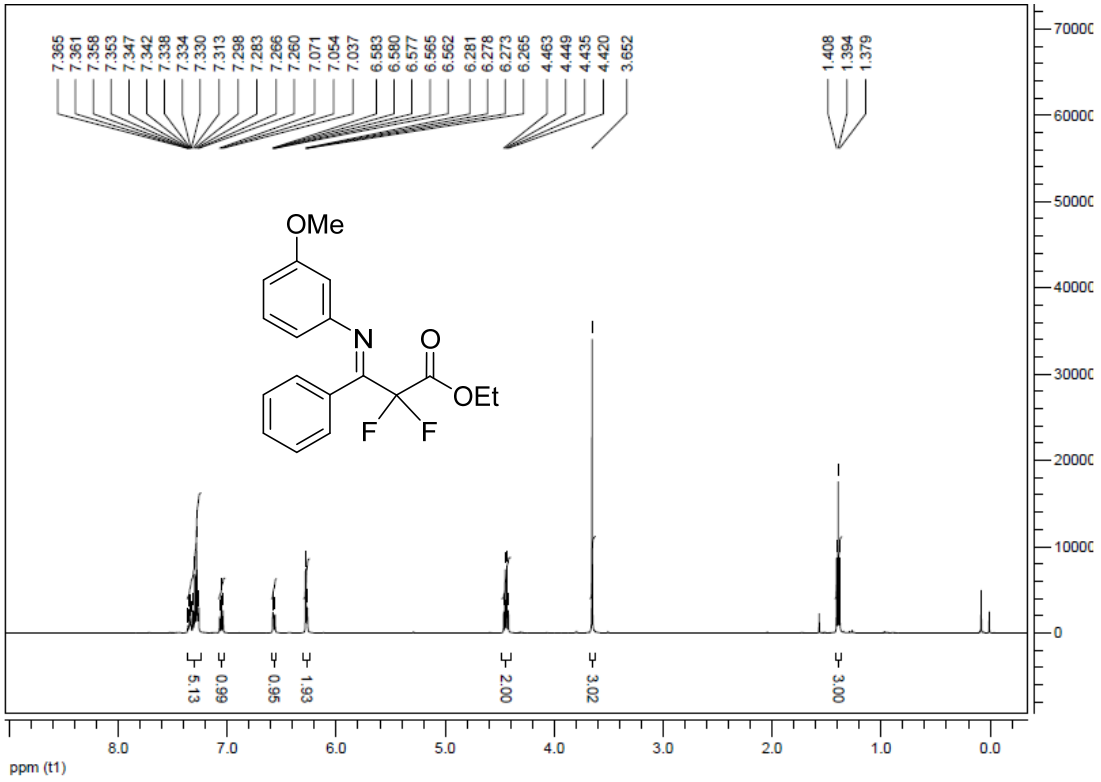
(*E*)-2,2-difluoro-3-((4-methoxyphenyl)imino)-3-phenylpropanenitrile (2r)

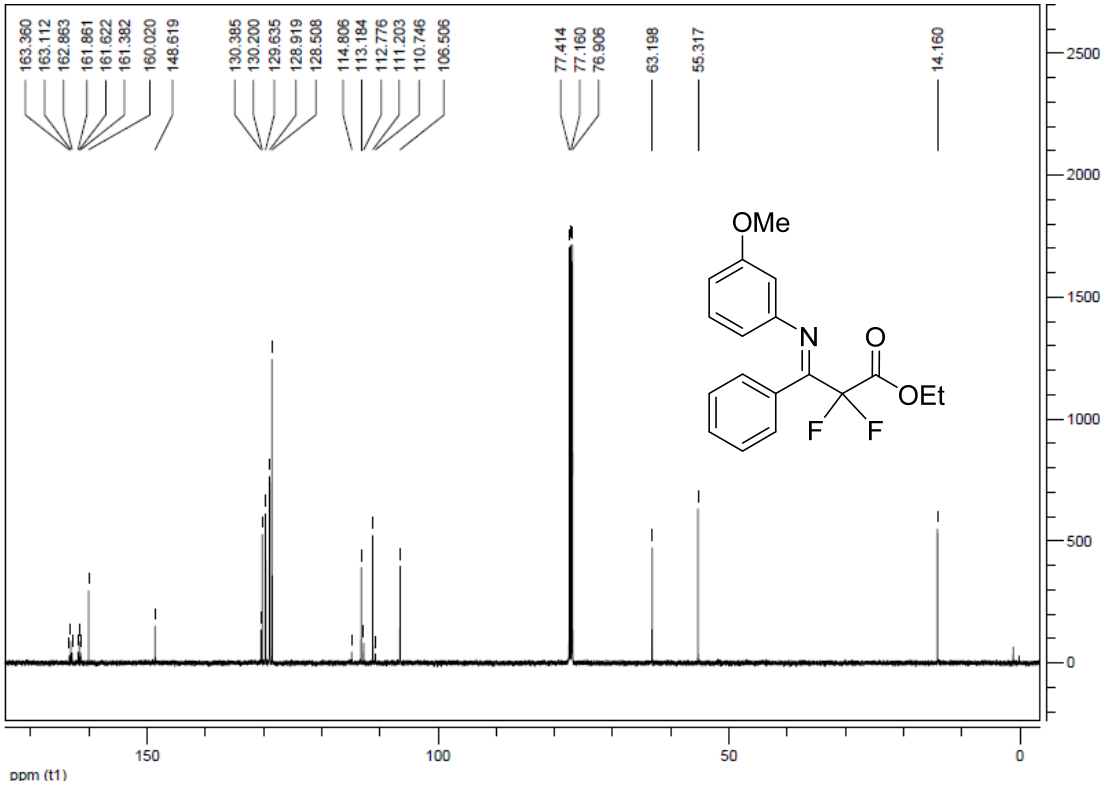


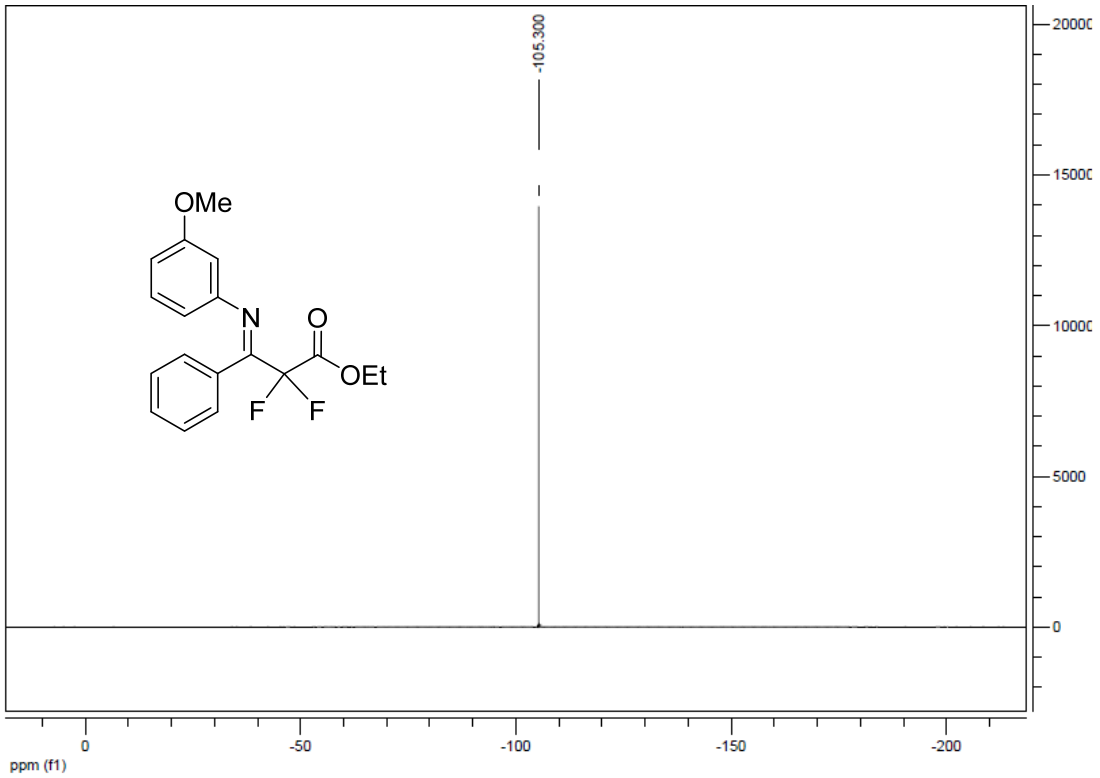

158.769
156.294
156.055
155.817
138.876
130.739
129.533
129.169
128.742
124.616
114.165
112.283
111.872
111.523
111.174
110.317
108.352
77.414
77.160
76.906
55.479
MeO
N
CN
F
F
3500
3000
2500
2000
1500
1000
500
0
150
100
50
0
ppm (t1)


-87.194
MeO
N
CN
F
F
40000
30000
20000
10000
0
0
-50
-100
-150
-200
ppm (f1)

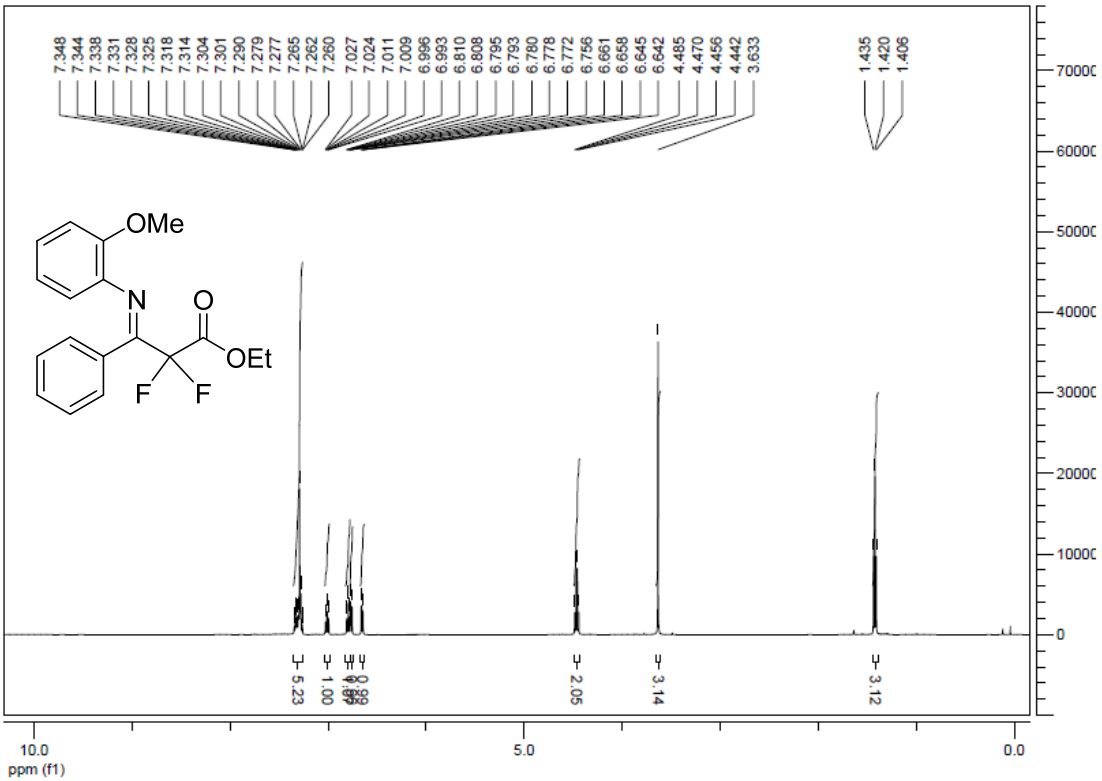
Ethyl (*E*)-2,2-difluoro-3-((3-methoxyphenyl)imino)-3-phenylpropanoate (2s)

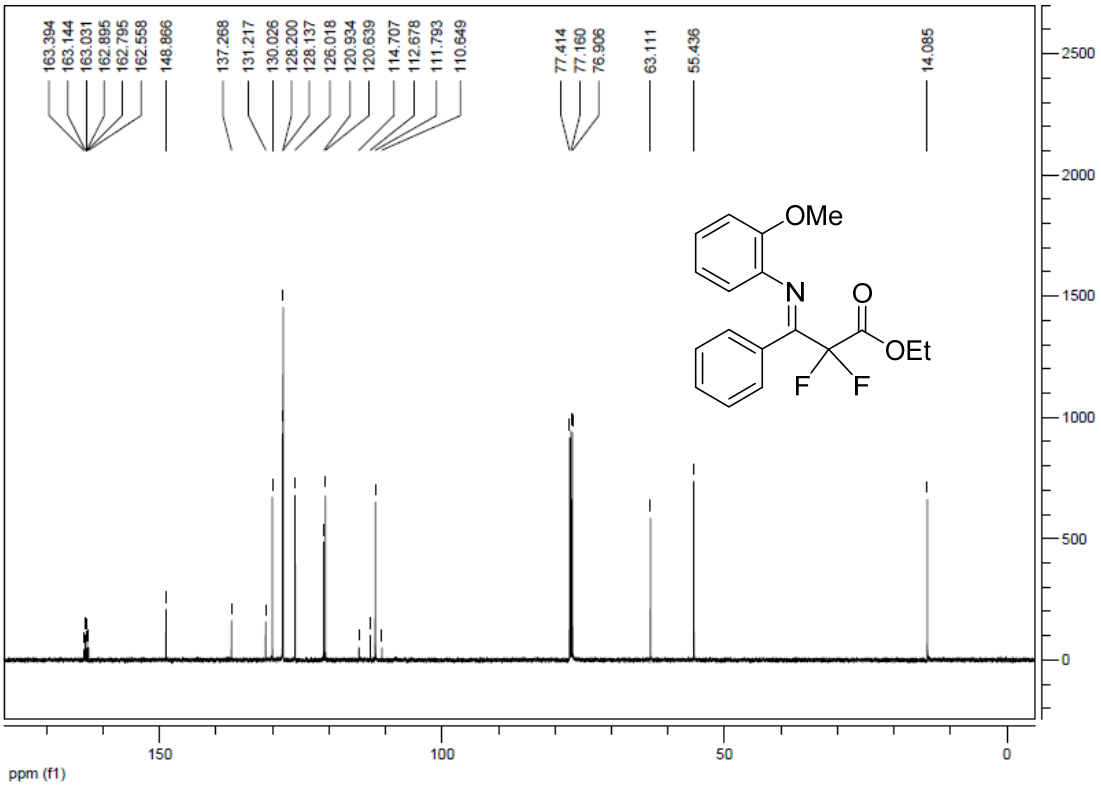


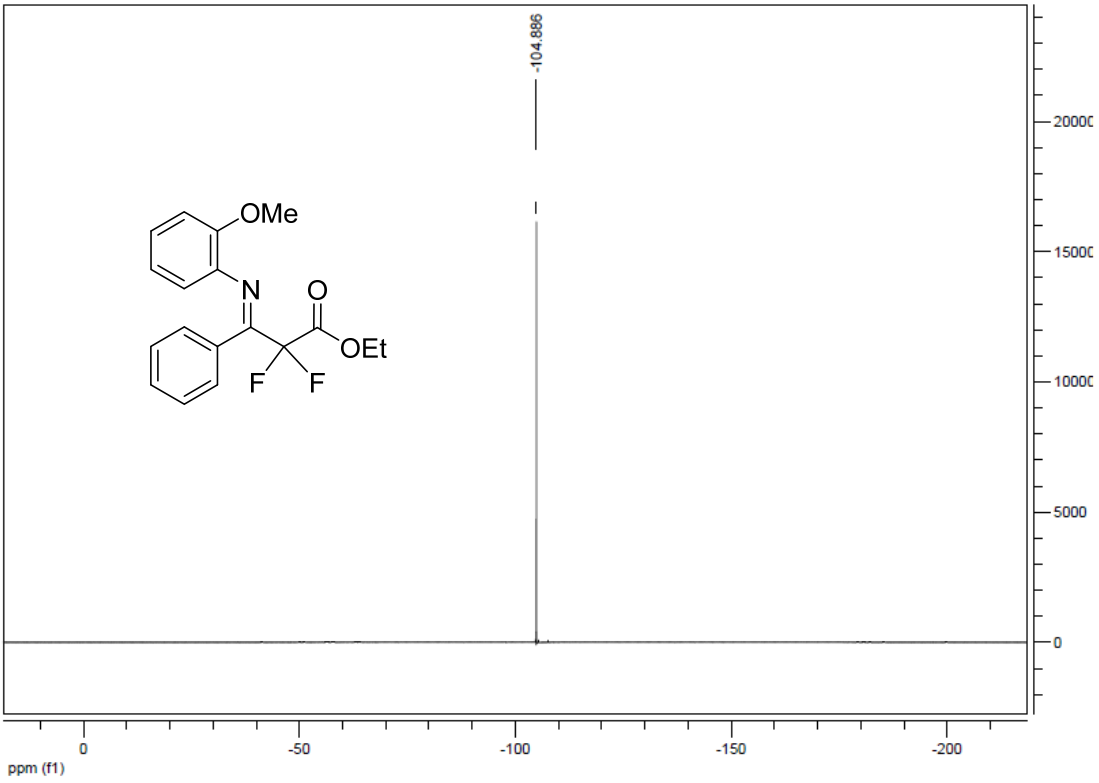




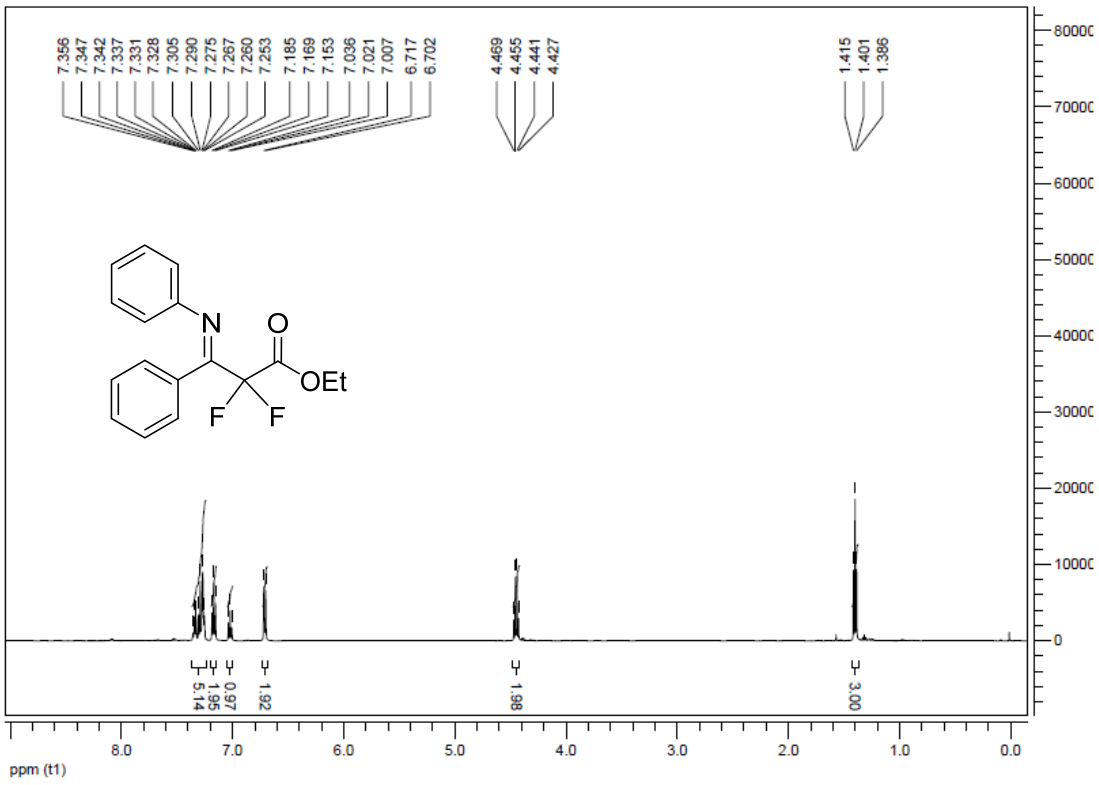
Ethyl (*E*)-2,2-difluoro-3-((2-methoxyphenyl)imino)-3-phenylpropanoate (2t)

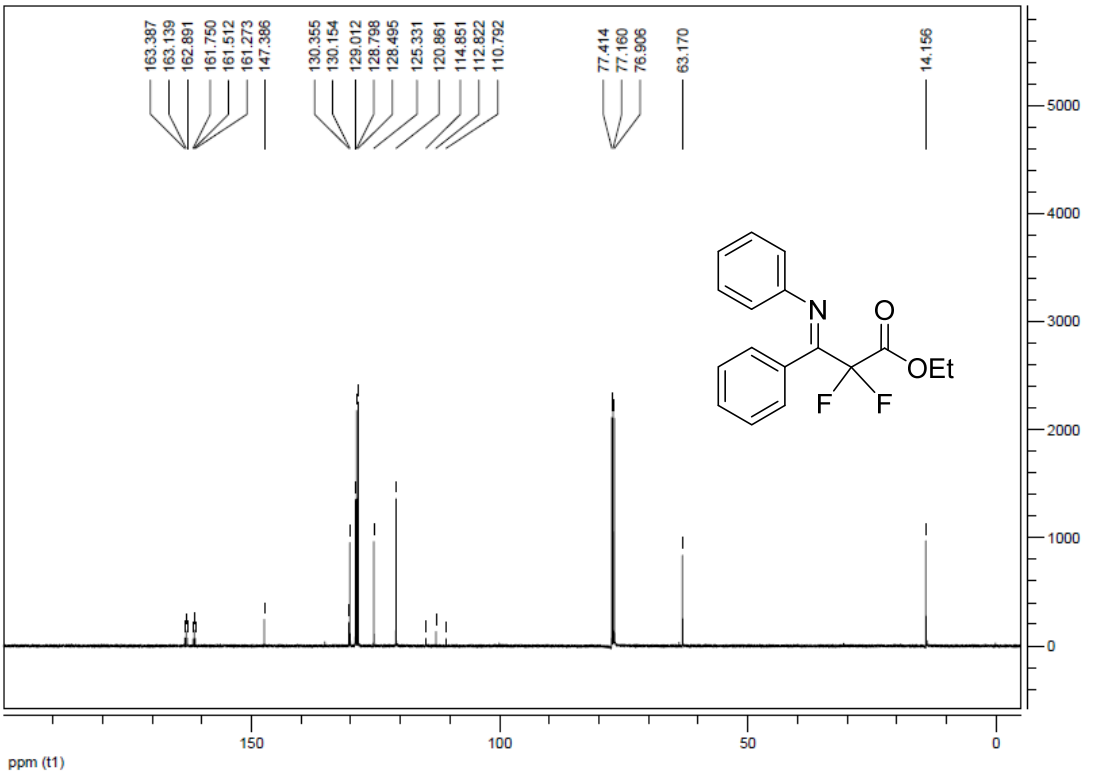


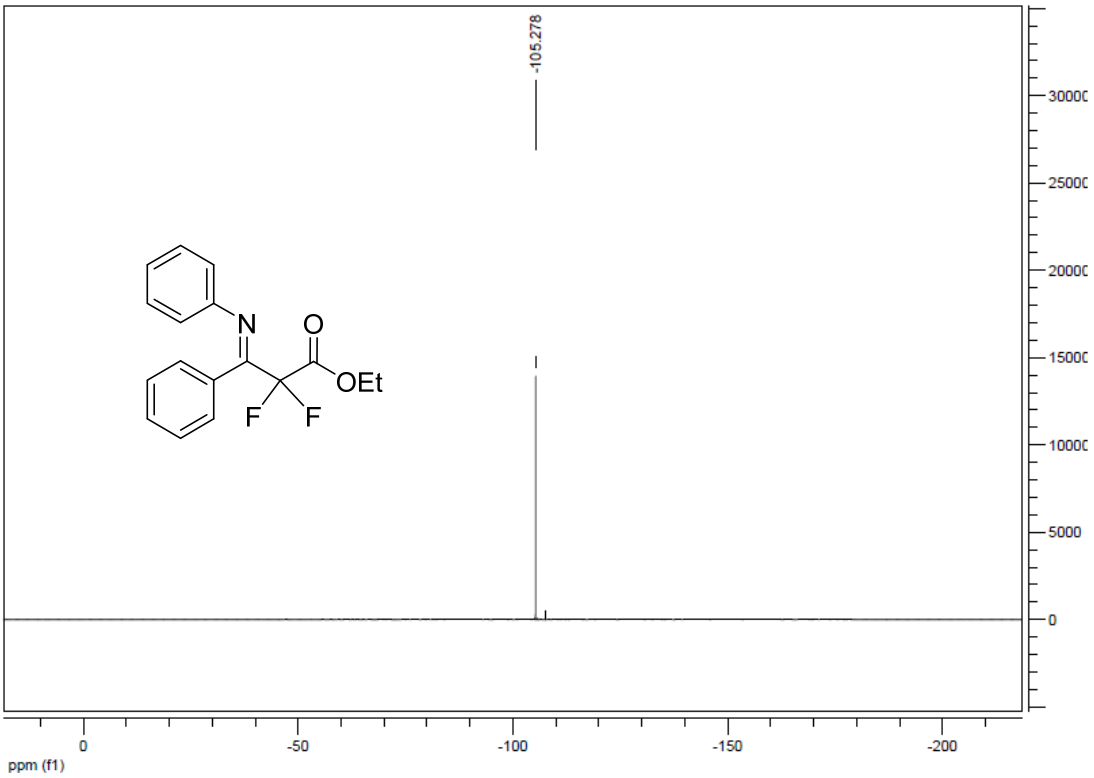

163.394
163.144
163.031
162.895
162.795
162.558
148.866
137.268
131.217
130.026
128.200
128.137
126.018
120.934
120.639
114.707
112.678
111.793
110.649
77.414
77.160
76.906
63.111
55.436
14.085
OMe
N
O
OEt
F
F
2500
2000
1500
1000
500
0
150
100
50
0
ppm (f1)


-104.886
OMe
N
O
OEt
F
F
2000
1500
1000
5000
0
0
-50
-100
-150
-200
ppm (f1)

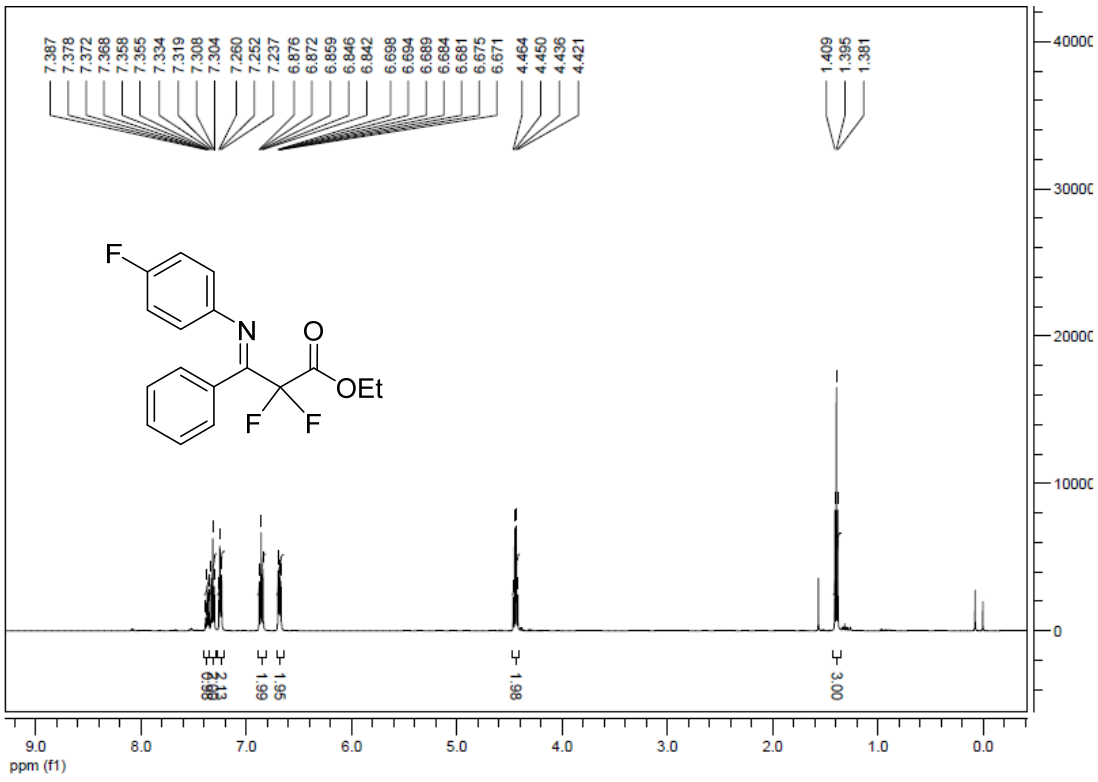
Ethyl (*E*)-2,2-difluoro-3-phenyl-3-(phenylimino)propanoate (2u)

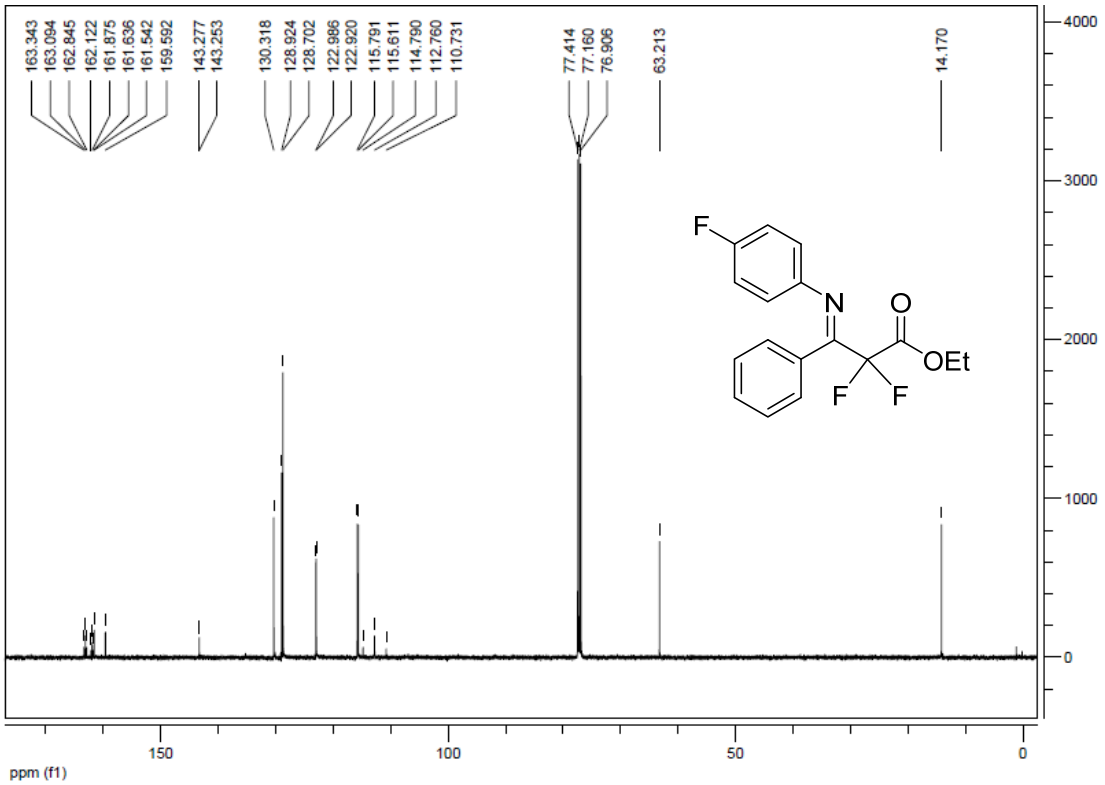






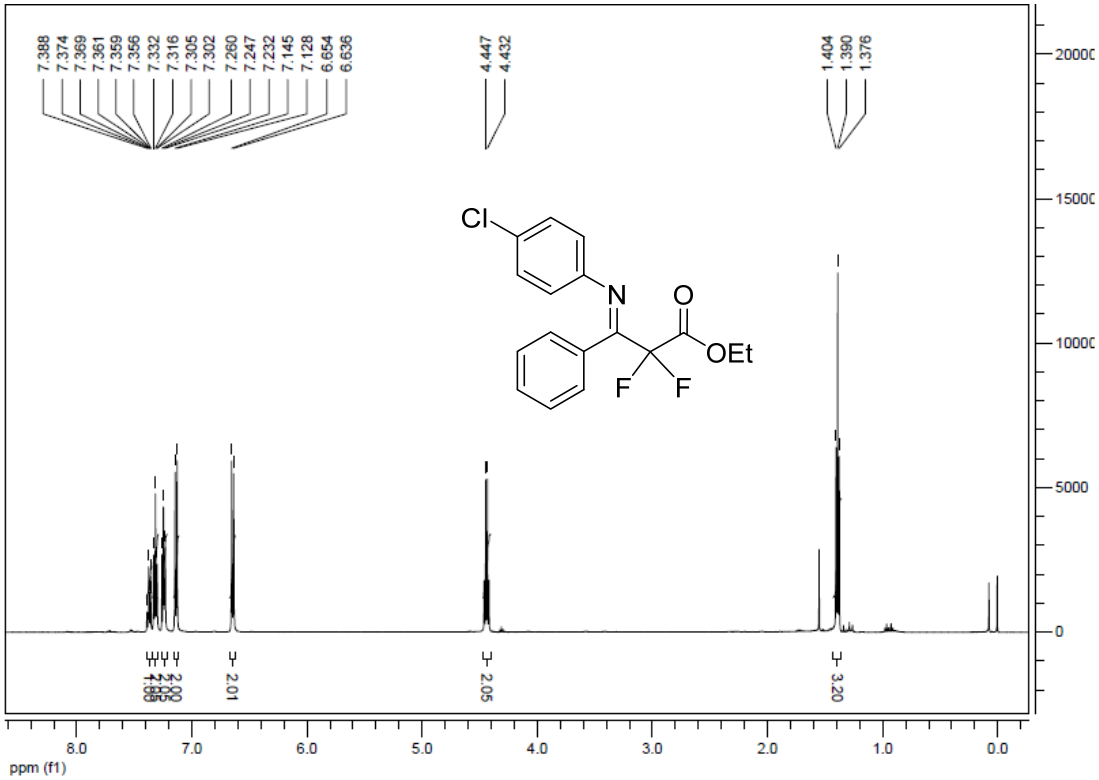
Ethyl (*E*)-2,2-difluoro-3-((4-fluorophenyl)imino)-3-phenylpropanoate (2v)

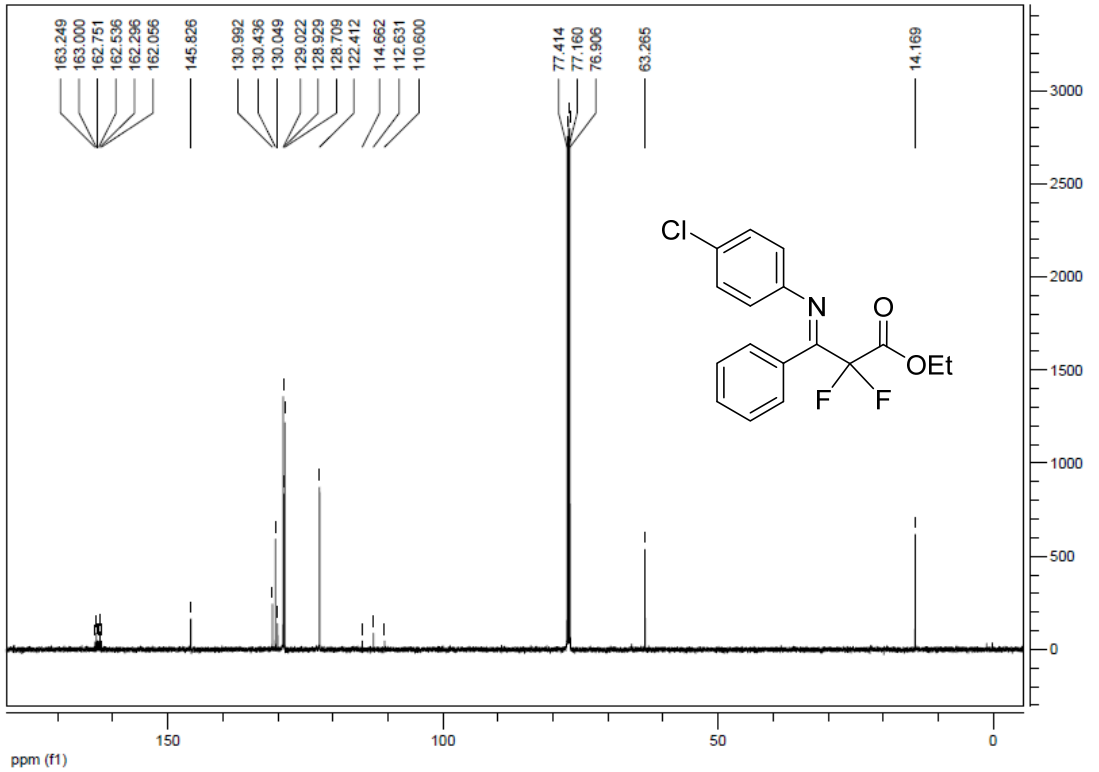


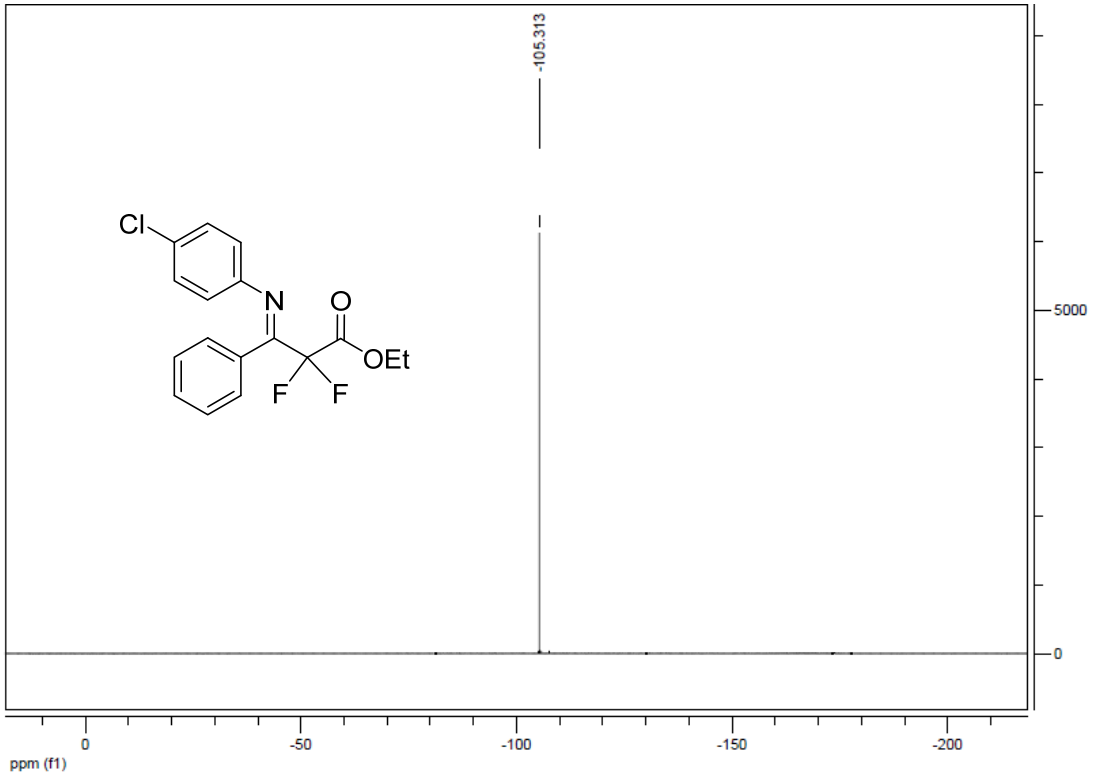

163.343
163.094
162.845
162.122
161.875
161.636
161.542
159.592
143.277
143.253
130.318
128.924
128.702
122.986
122.920
115.791
115.611
114.790
112.760
110.731
77.414
77.160
76.906
63.213
14.170
F
N
O
OEt
F
F
4000
3000
2000
1000
0
150
100
50
0
ppm (f1)


-105.306
-117.184
F
N
O
OEt
F
F
10000
5000
0
0
-50
-100
-150
-200
ppm (f1)

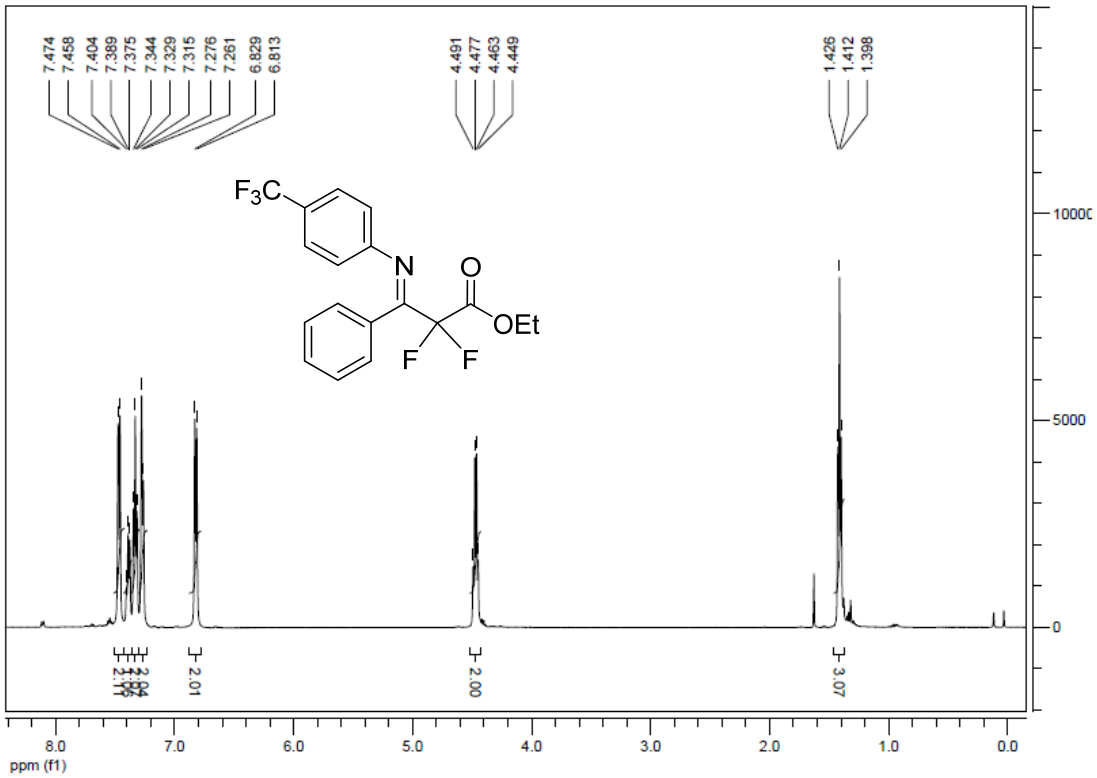
Ethyl (*E*)-3-((4-chlorophenyl)imino)-2,2-difluoro-3-phenylpropanoate (2w)

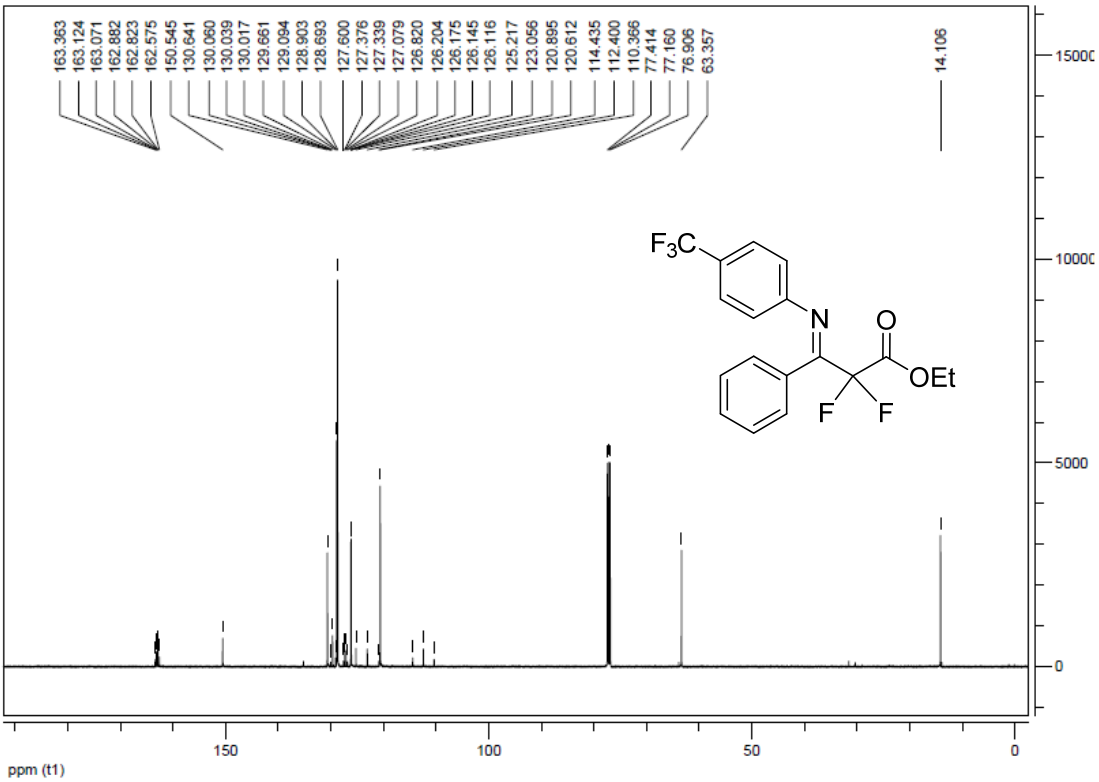


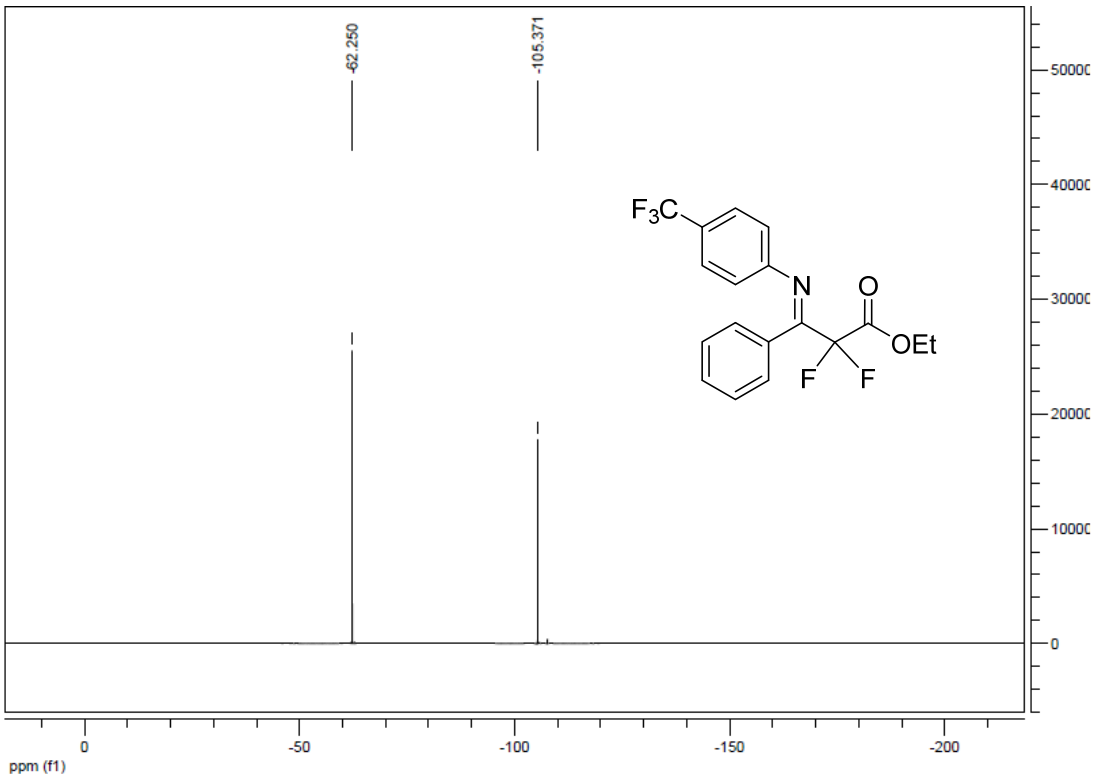




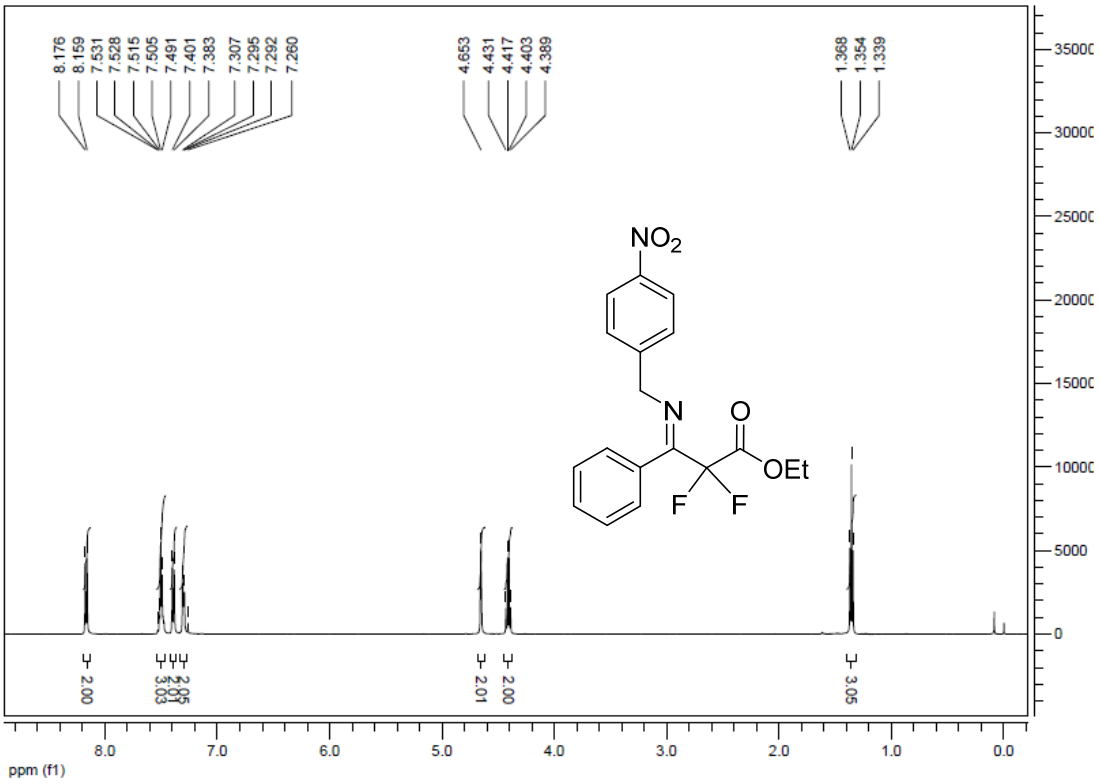
Ethyl (*E*)-2,2-difluoro-3-phenyl-3-((4-(trifluoromethyl)phenyl)imino)propanoate (2x)

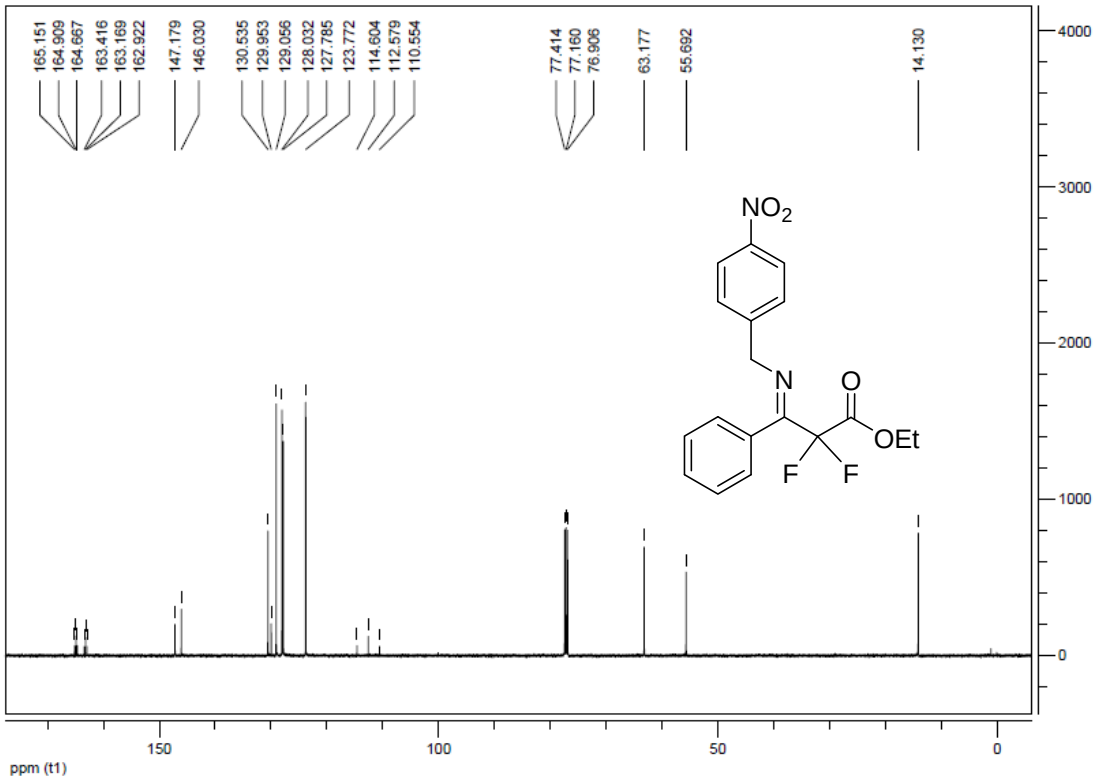


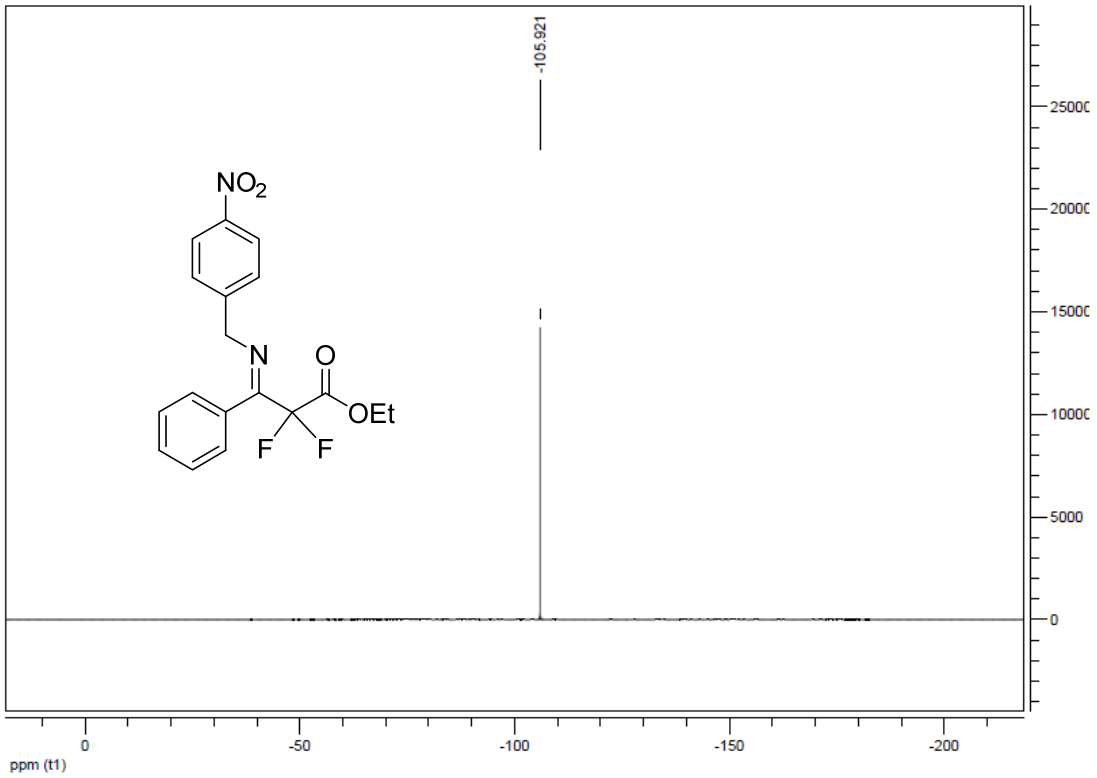

163.363
163.124
163.071
162.882
162.823
162.575
150.545
130.641
130.060
130.039
130.017
129.661
129.094
128.903
128.693
127.600
127.376
127.339
127.079
126.820
126.204
126.175
126.145
126.116
125.217
123.056
120.895
120.612
114.435
112.400
110.366
77.414
77.160
76.906
63.357
14.106
F3C
N
O
OEt
F
F
150
100
50
0
ppm (t1)


-62.250
-105.371
F3C
N
O
OEt
F
F
0
-50
-100
-150
-200
ppm (f1)

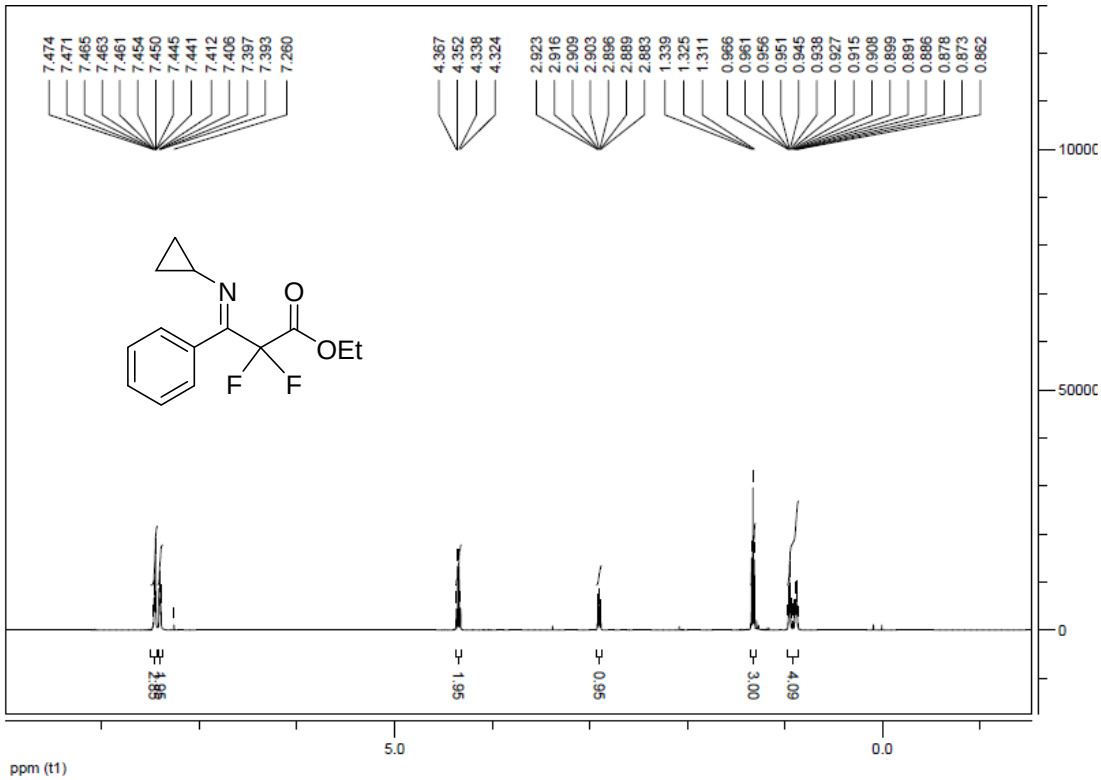
Ethyl (*E*)-2,2-difluoro-3-((4-nitrobenzyl)imino)-3-phenylpropanoate (2y)

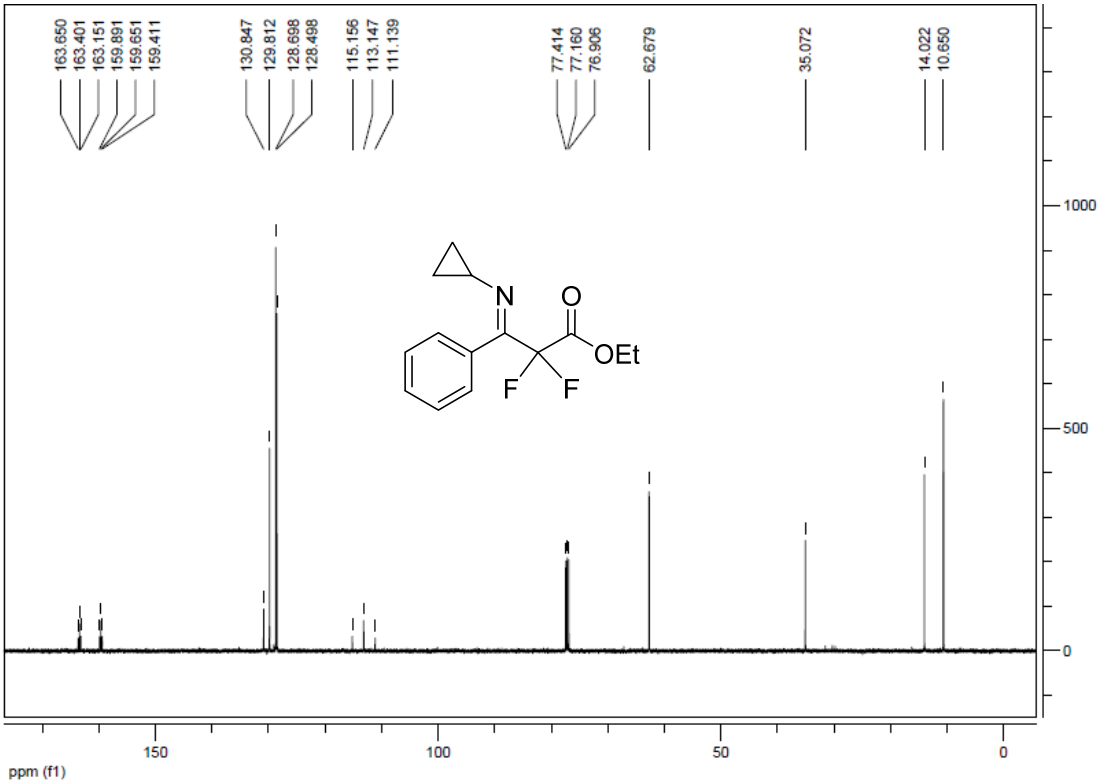


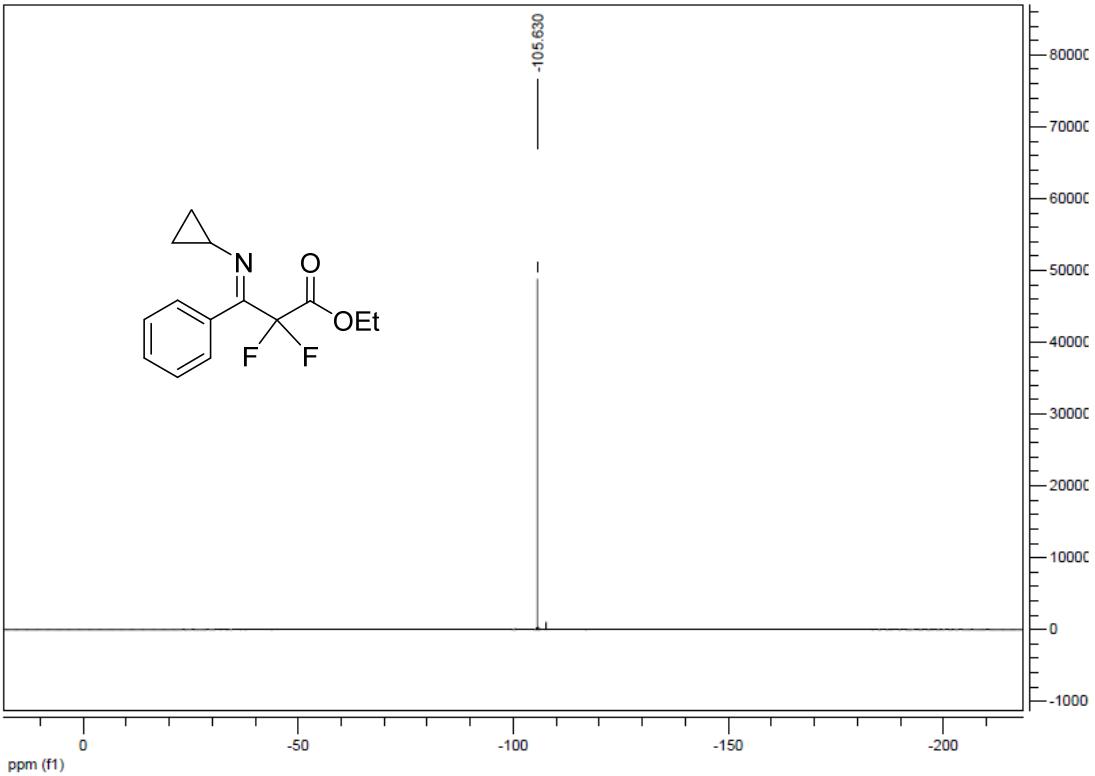




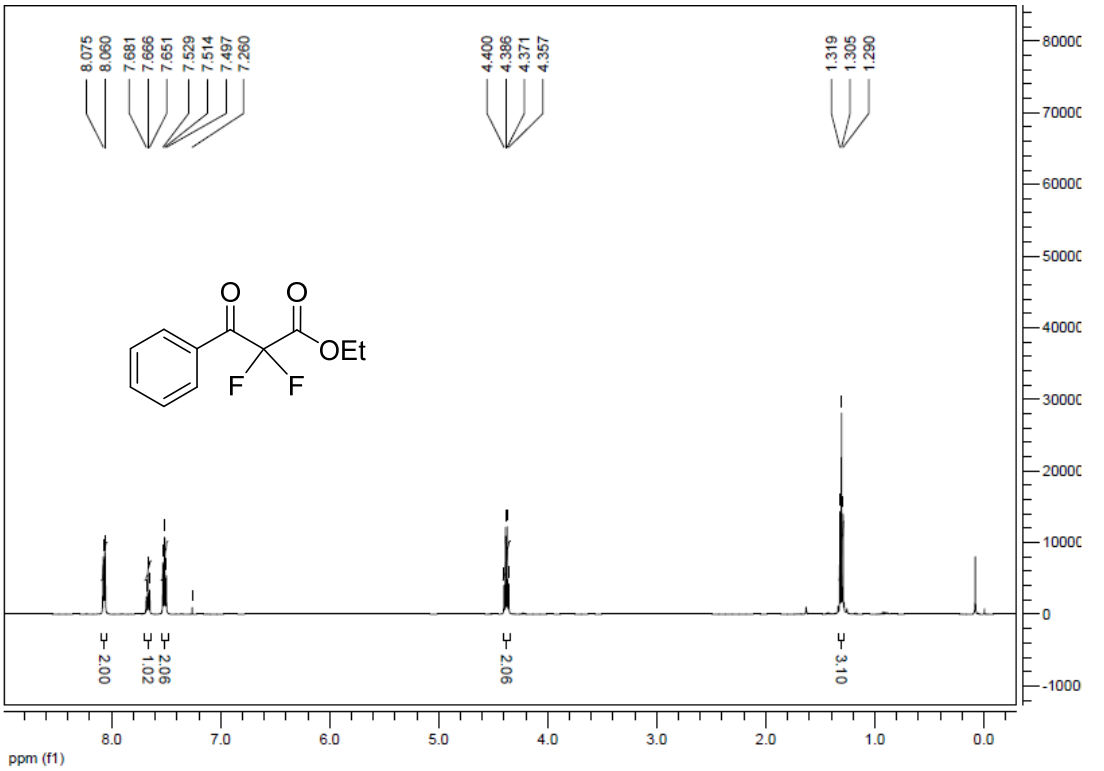
Ethyl (*E*)-3-(cyclopropylimino)-2,2-difluoro-3-phenylpropanoate (2z)

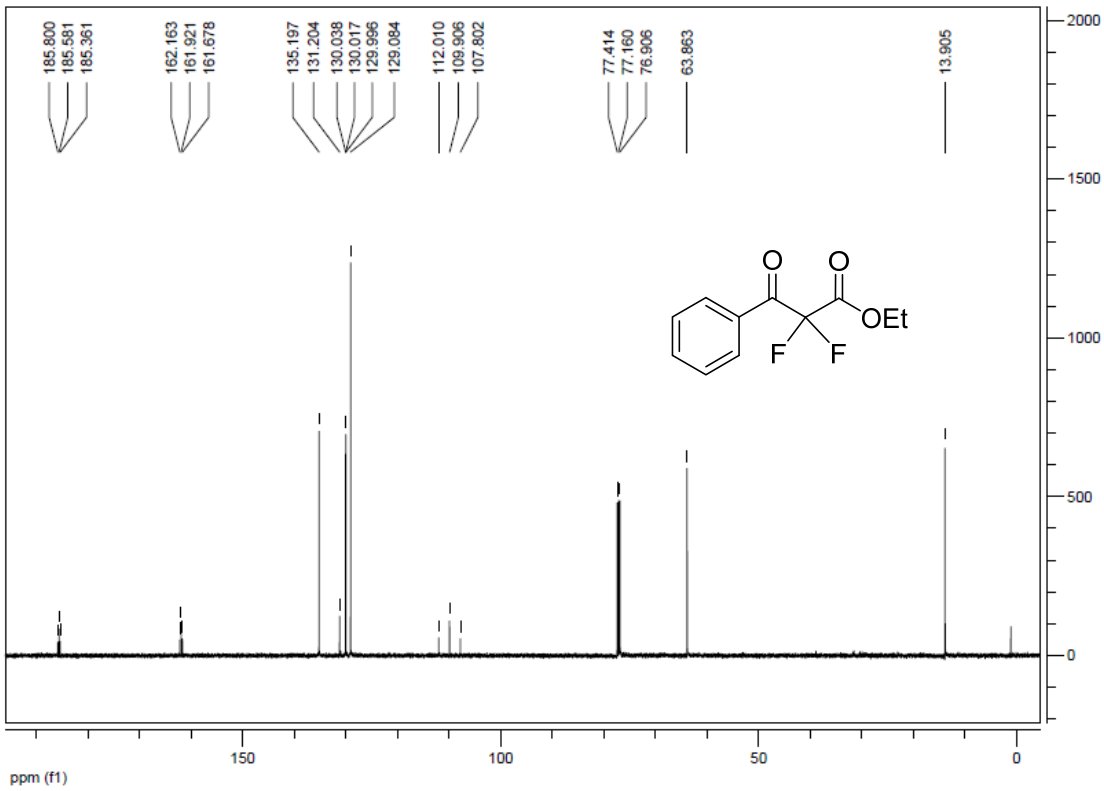


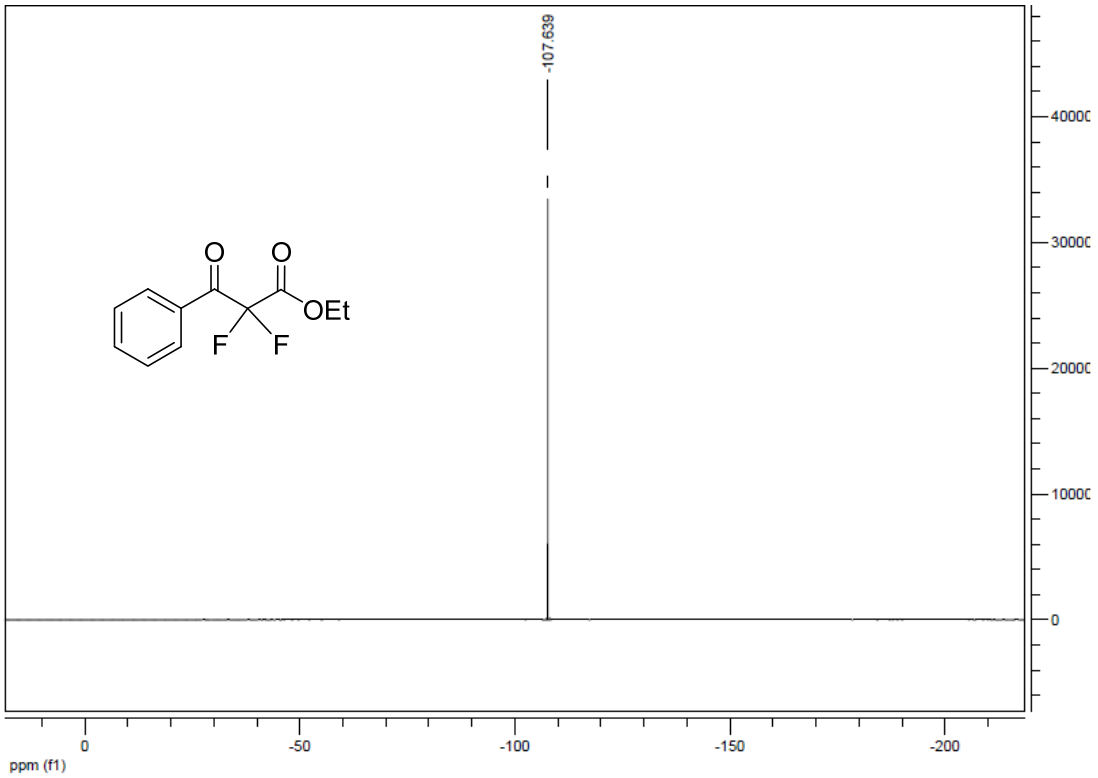

163.650
163.401
163.151
159.891
159.651
159.411
130.847
129.812
128.698
128.498
115.156
113.147
111.139
77.414
77.160
76.906
62.679
35.072
14.022
10.650
N
O
OEt
F
F
1000
500
0
150
100
50
0
ppm (f1)


-105.630
N
O
OEt
F
F
80000
70000
60000
50000
40000
30000
20000
10000
0
-1000
0
-50
-100
-150
-200
ppm (f1)

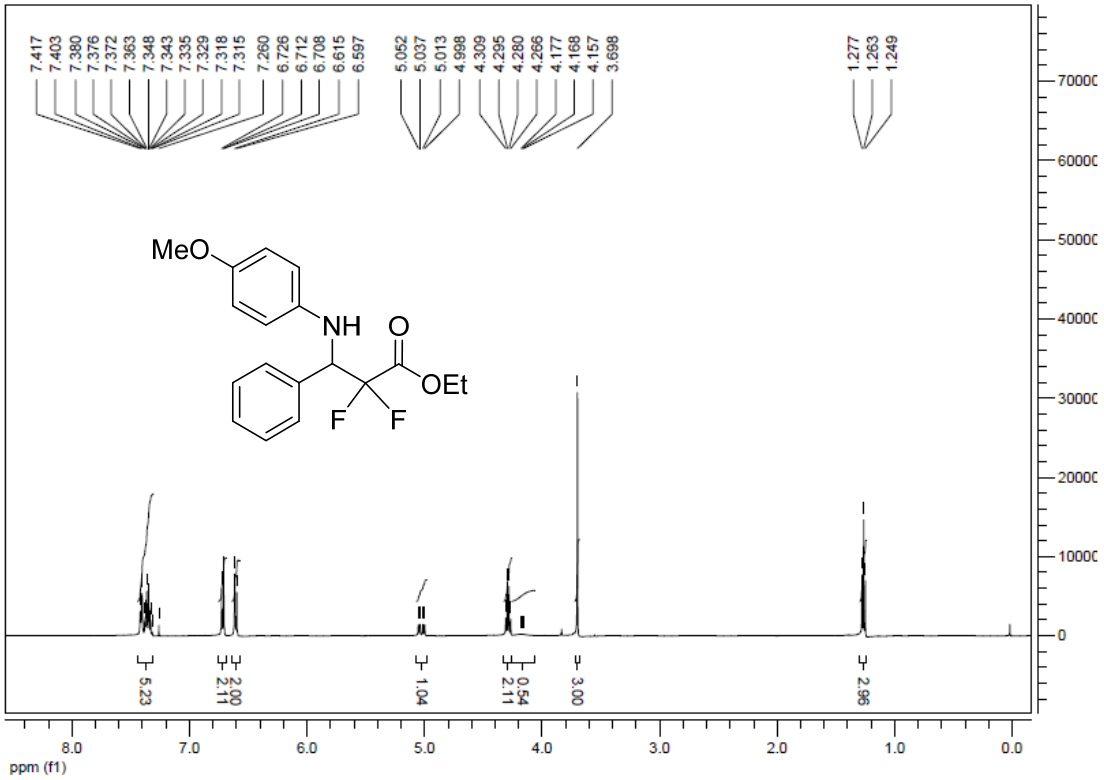
Ethyl 2,2-difluoro-3-oxo-3-phenylpropanoate (3)

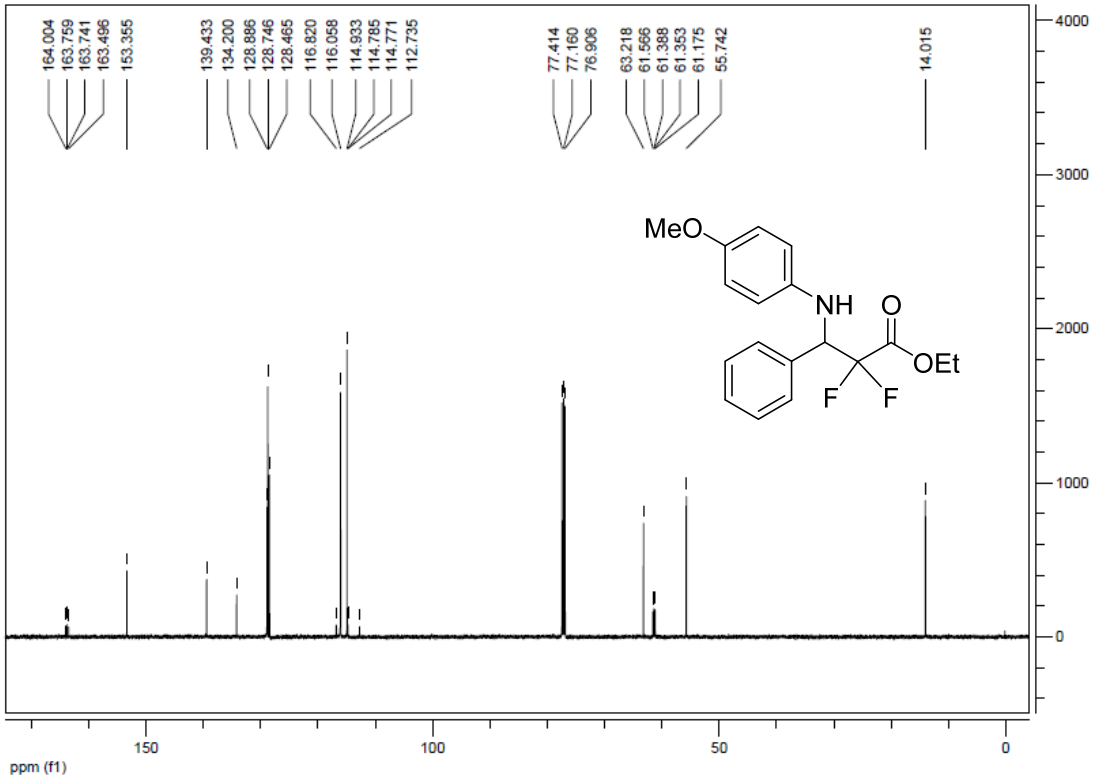






Ethyl 2,2-difluoro-3-((4-methoxyphenyl)amino)-3-phenylpropanoate (4)

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163.759
163.741
163.496
153.355
139.433
134.200
128.886
128.746
128.465
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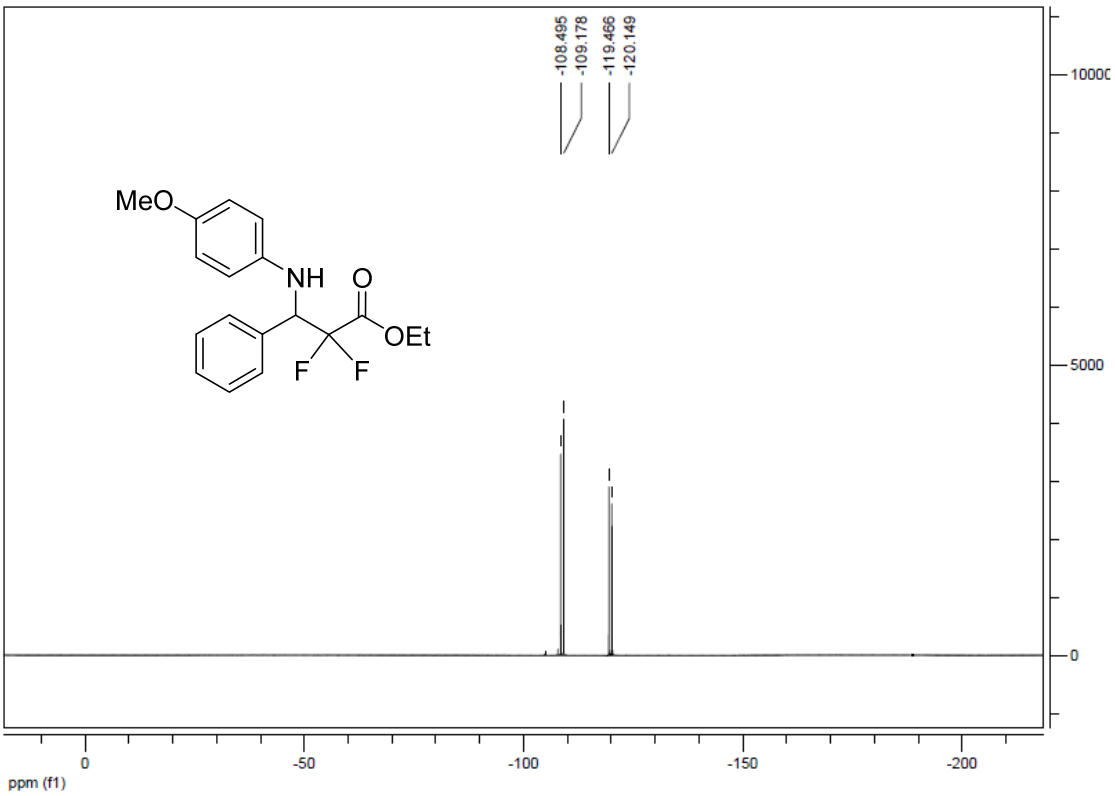
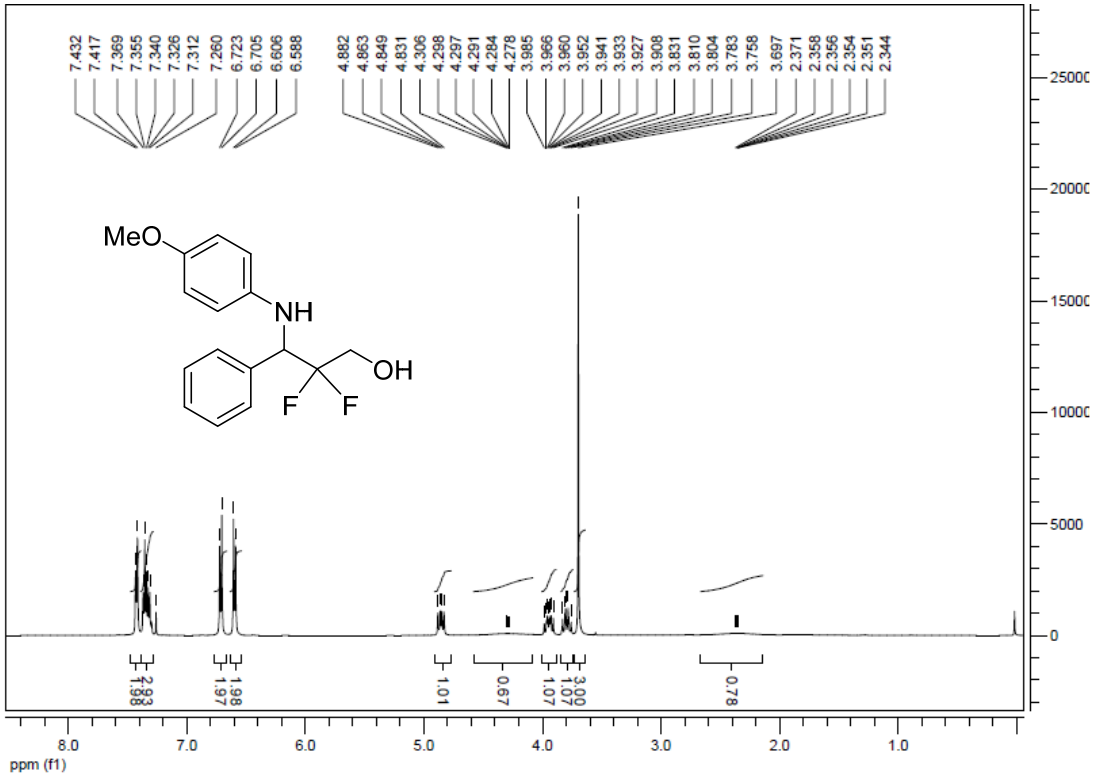
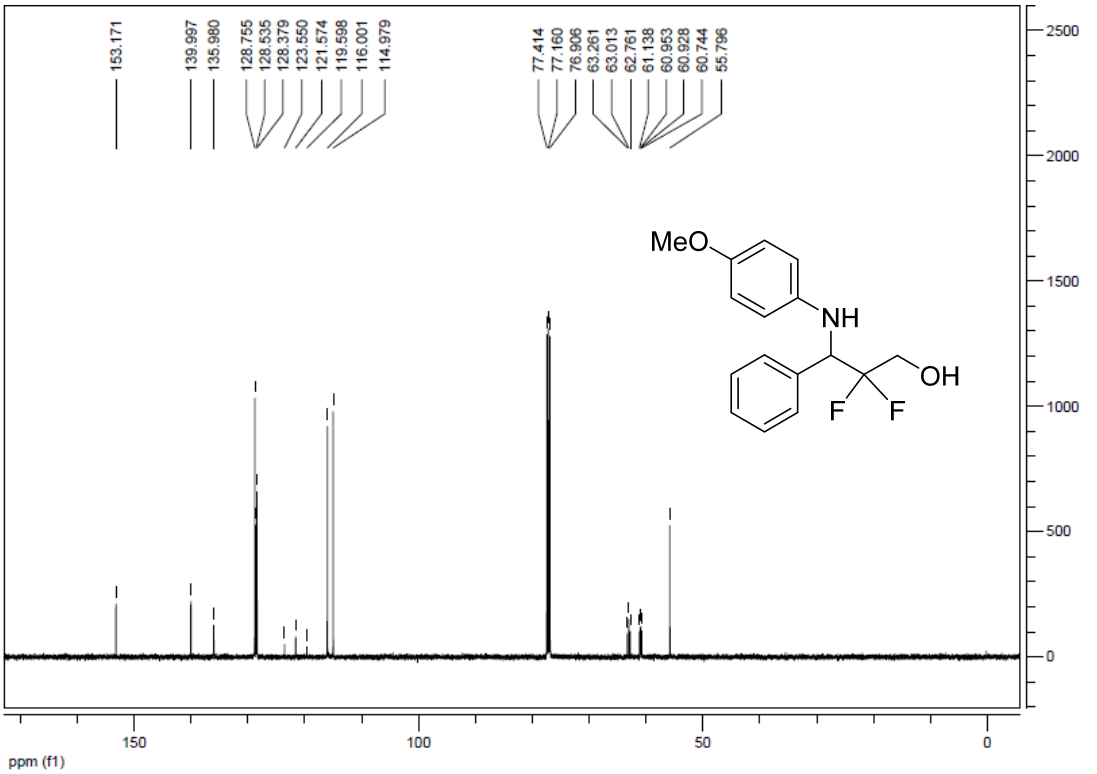
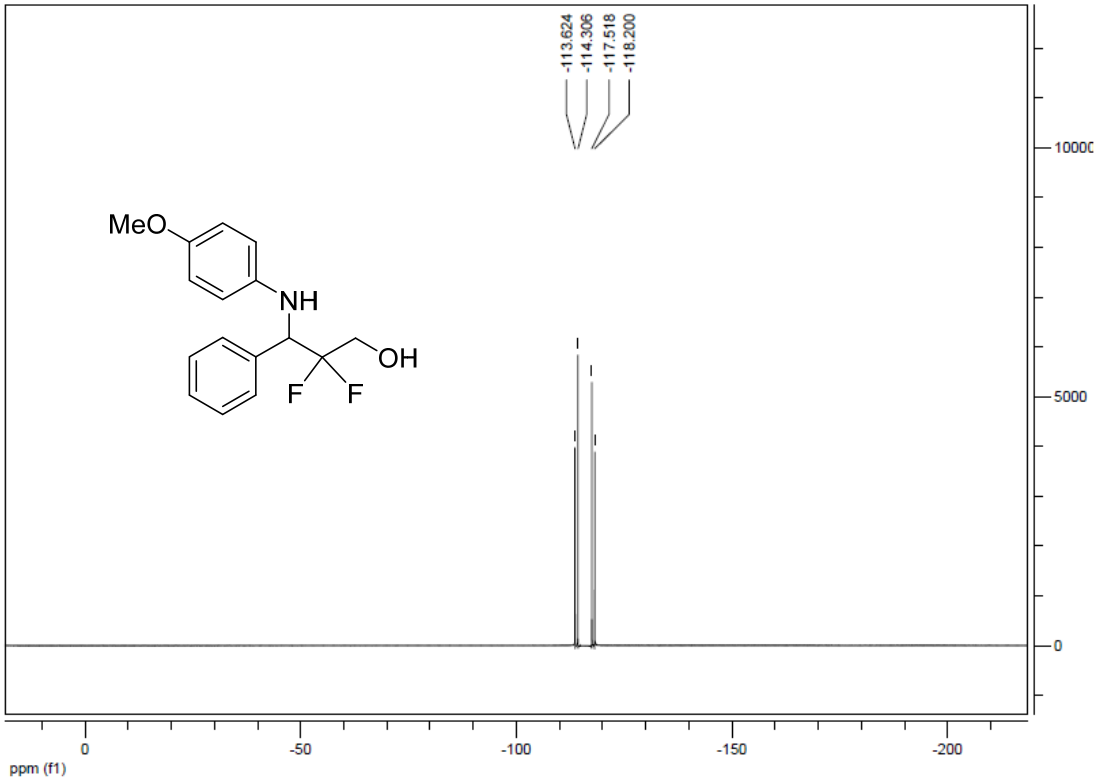
114.933
114.785
114.771
112.735
77.414
77.160
76.906
63.218
61.566
61.388
61.353
61.175
55.742
14.015
MeO
NH
O
OEt
F
F
4000
3000
2000
1000
0
150
100
50
0
ppm (f1)


-108.495
-109.178
-119.466
-120.149
MeO
NH
O
OEt
F
F
10000
5000
0
0
-50
-100
-150
-200
ppm (f1)

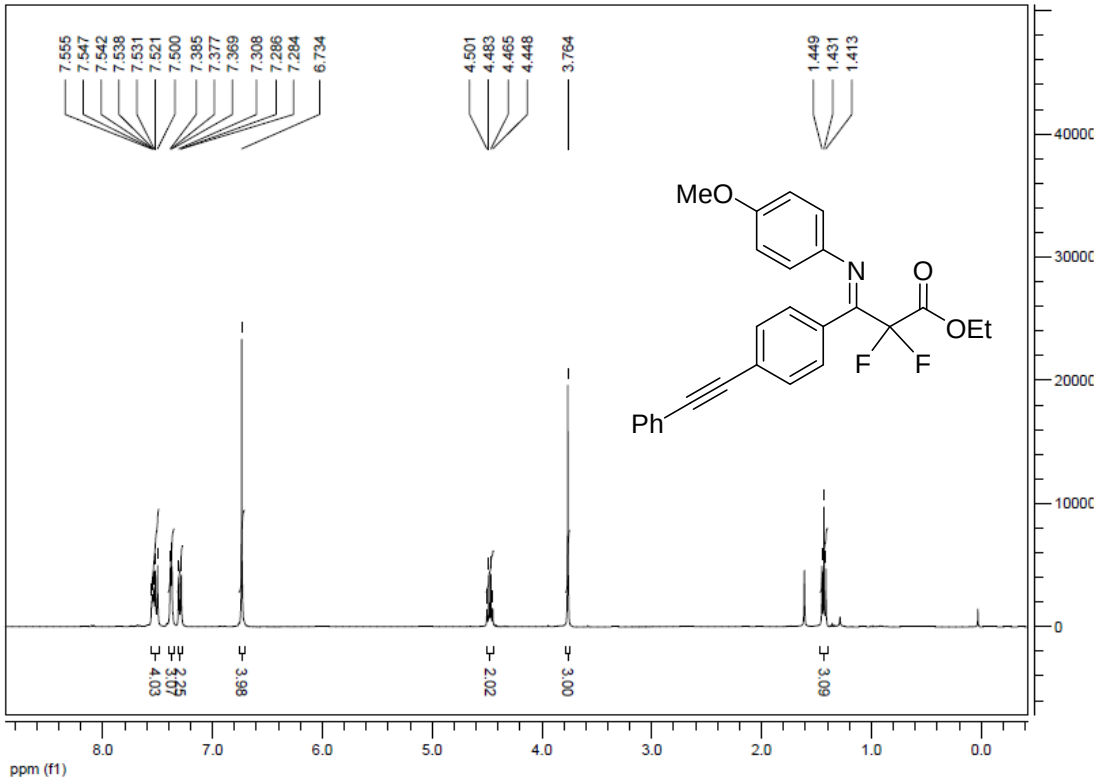
2,2-Difluoro-3-((4-methoxyphenyl)amino)-3-phenylpropan-1-ol (5)

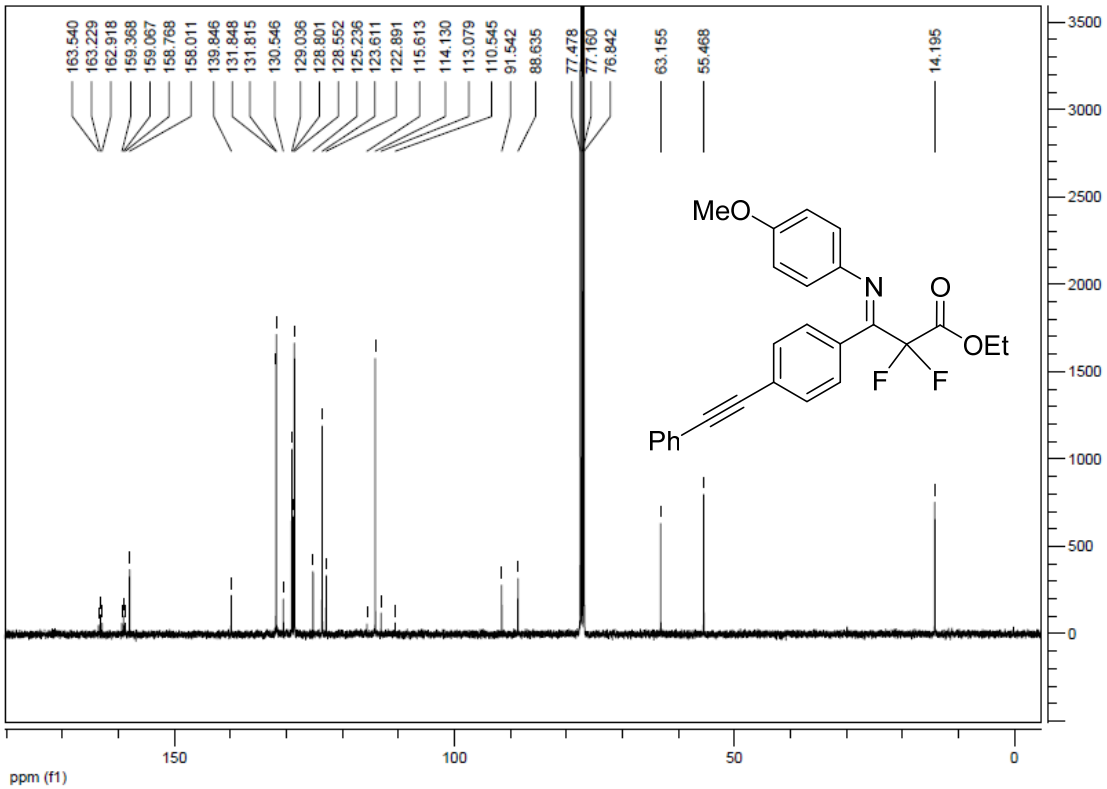






Ethyl (*E*)-2,2-difluoro-3-((4-methoxyphenyl)imino)-3-(4-(phenylethynyl)phenyl)propanoate (6)

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159.368
159.067
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158.011
139.846
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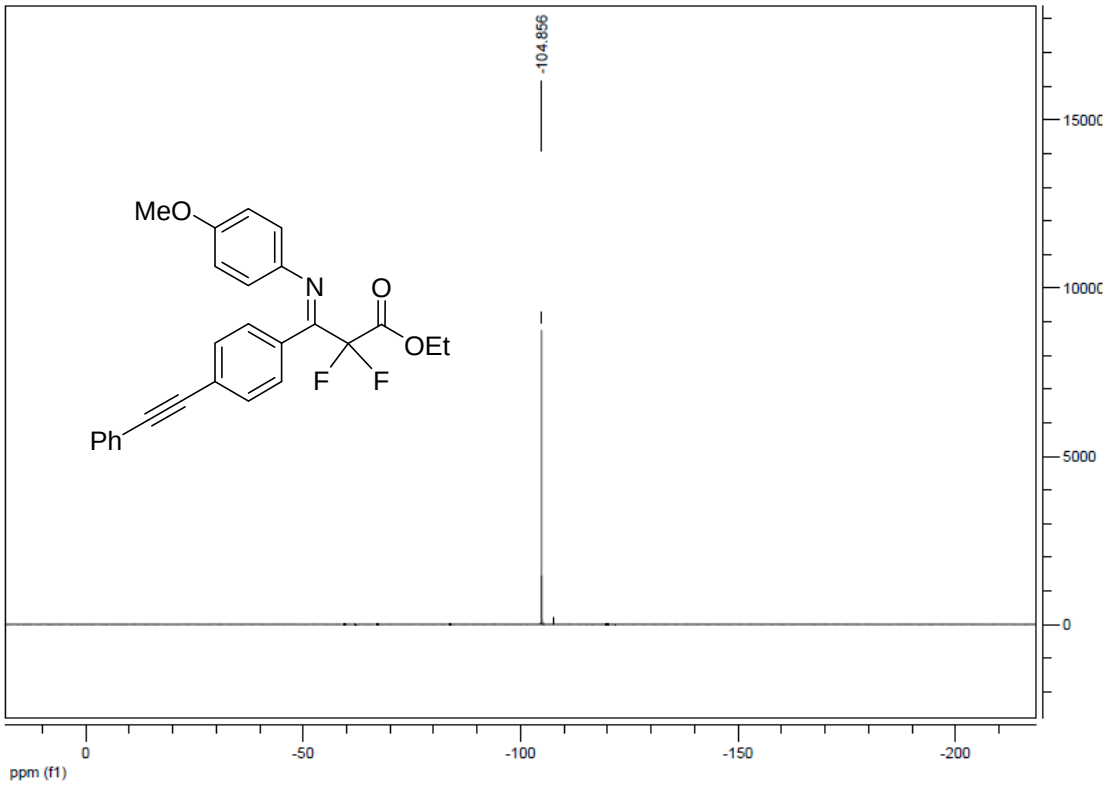
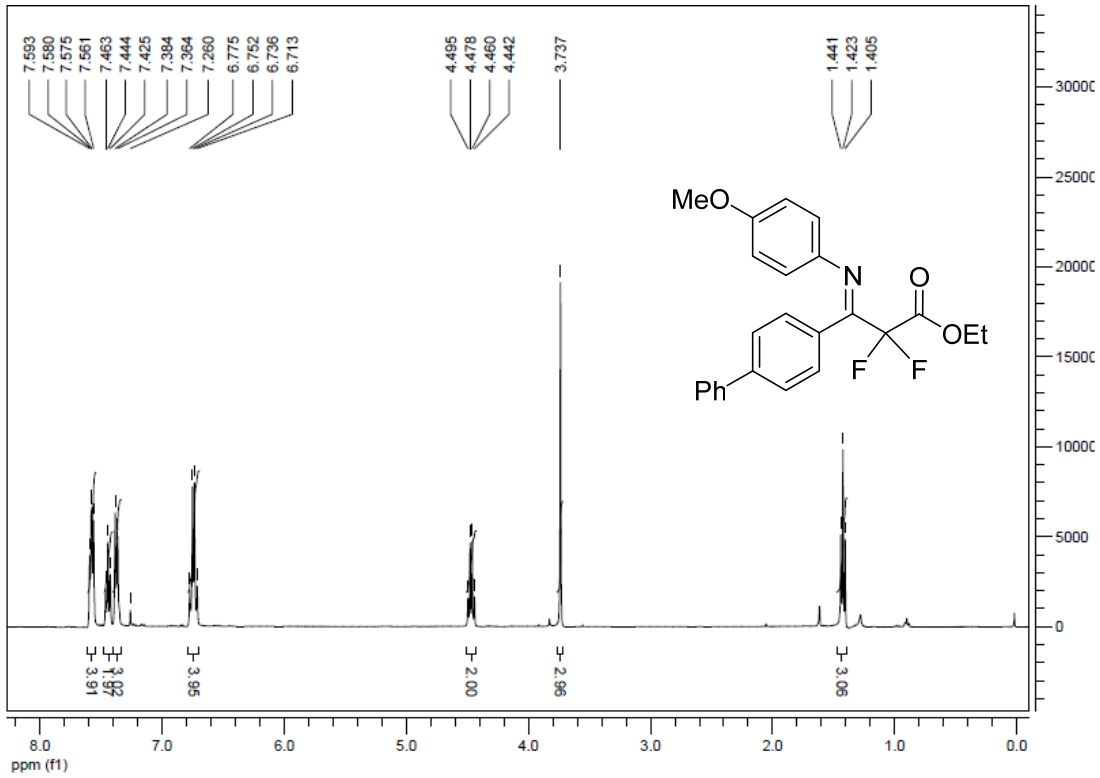
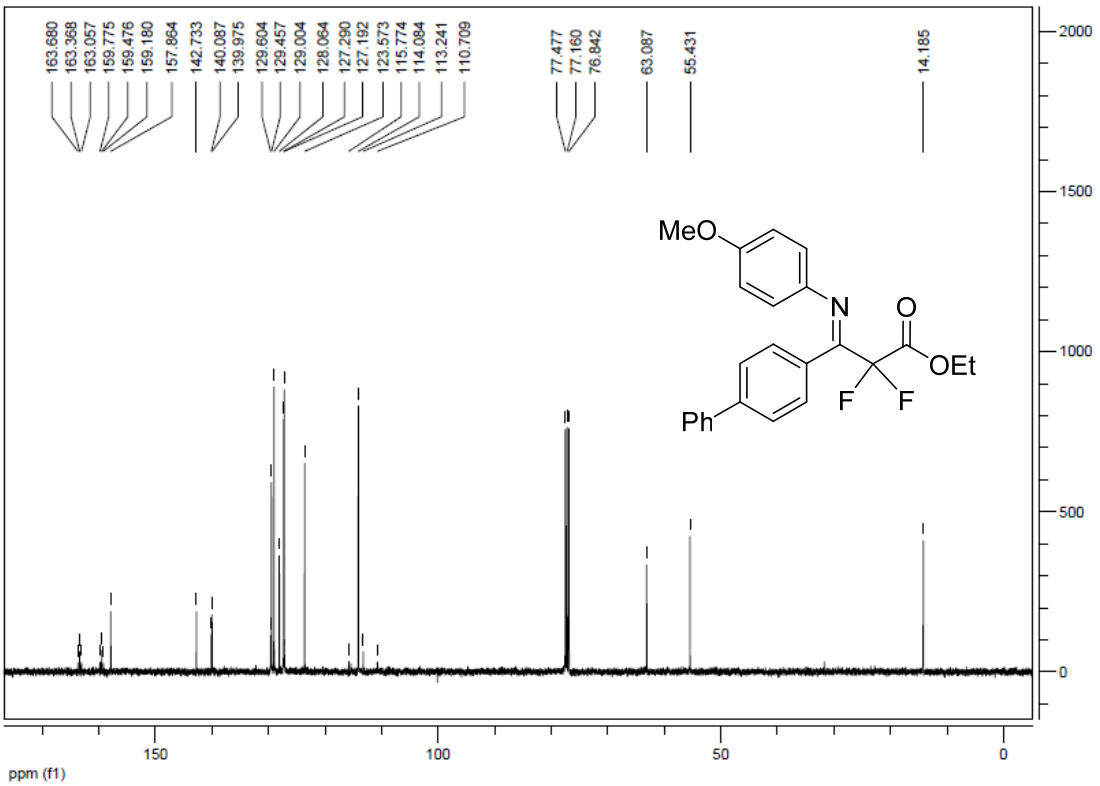
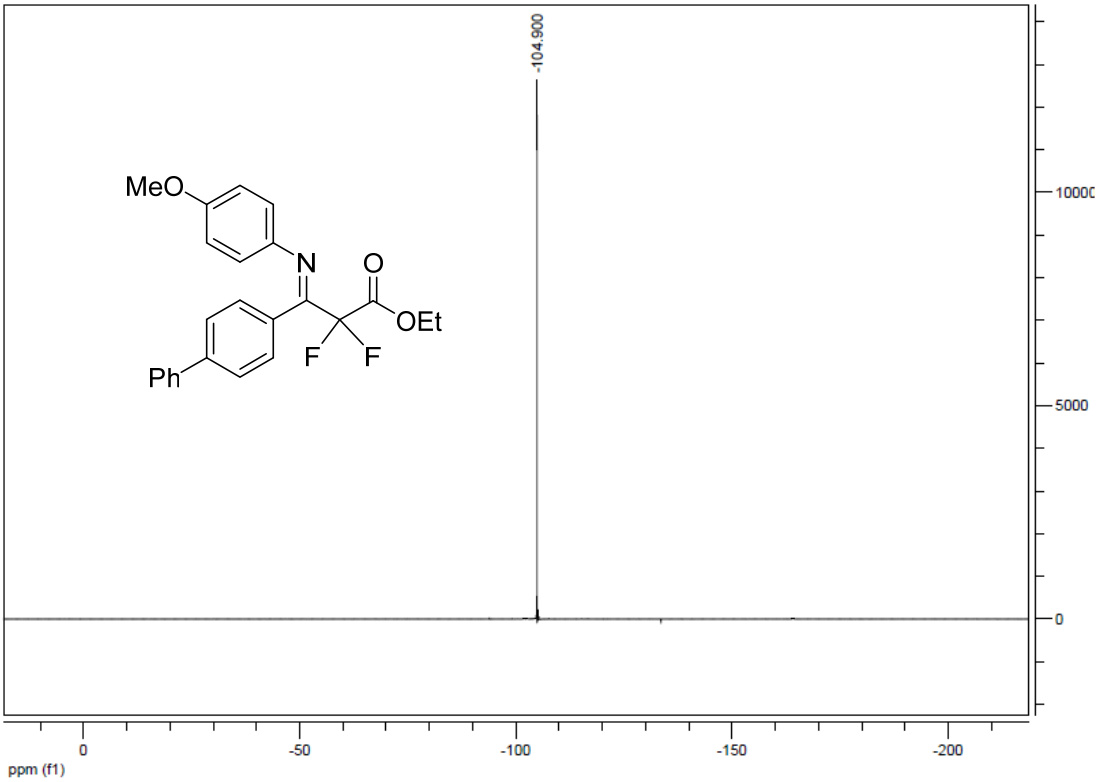
131.815
130.546
129.036
128.801
128.552
125.236
123.611
122.891
115.613
114.130
113.079
110.545
91.542
88.635
77.478
77.160
76.842
63.155
55.468
14.195
MeO
N
O
OEt
F
F
Ph
3500
3000
2500
2000
1500
1000
500
0
150
100
50
0
ppm (f1)


-104.856
MeO
N
O
OEt
F
F
Ph
15000
10000
5000
0
0
-50
-100
-150
-200
ppm (f1)

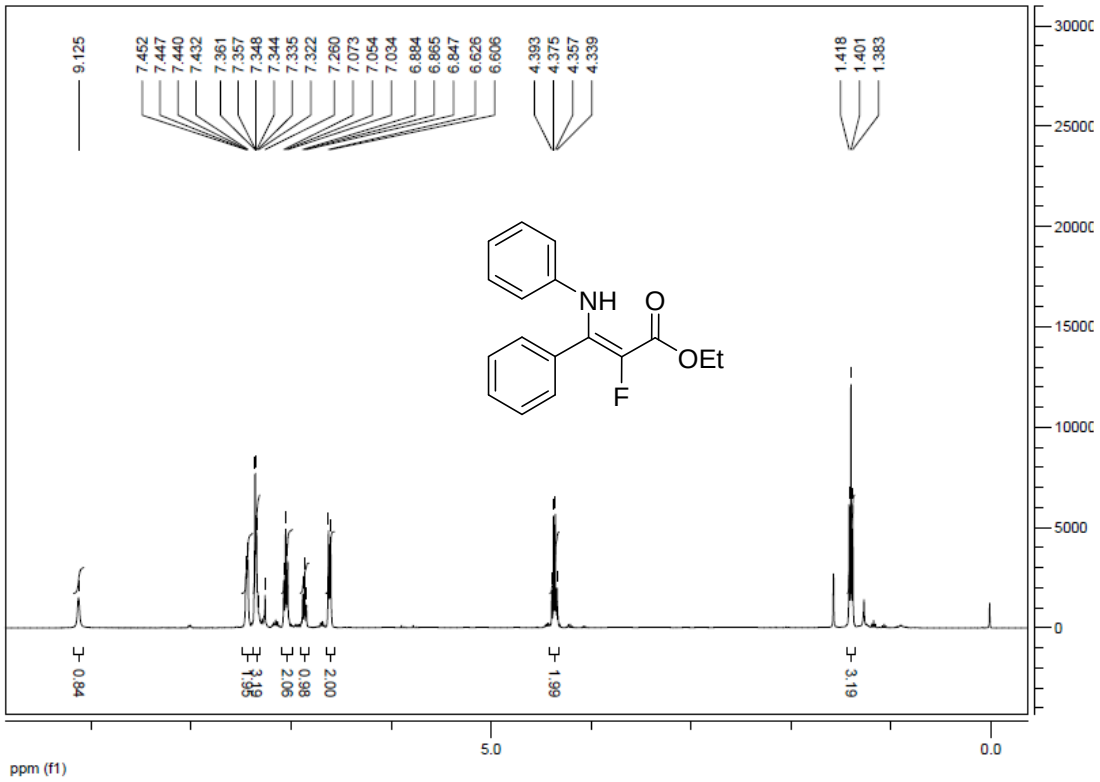
Ethyl (*E*)-3-([1,1'-biphenyl]-4-yl)-2,2-difluoro-3-((4-methoxyphenyl)imino)propanoate (7)

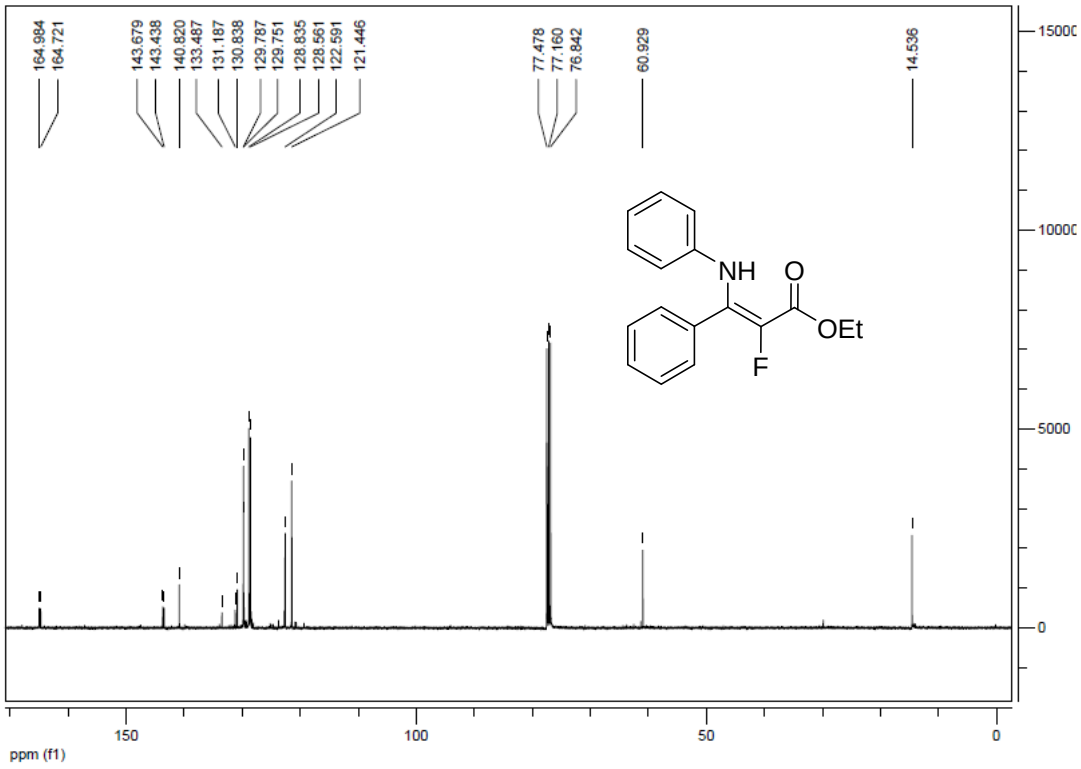






Ethyl (*E*)-2-fluoro-3-((4-methoxyphenyl)amino)-3-phenylacrylate (8)

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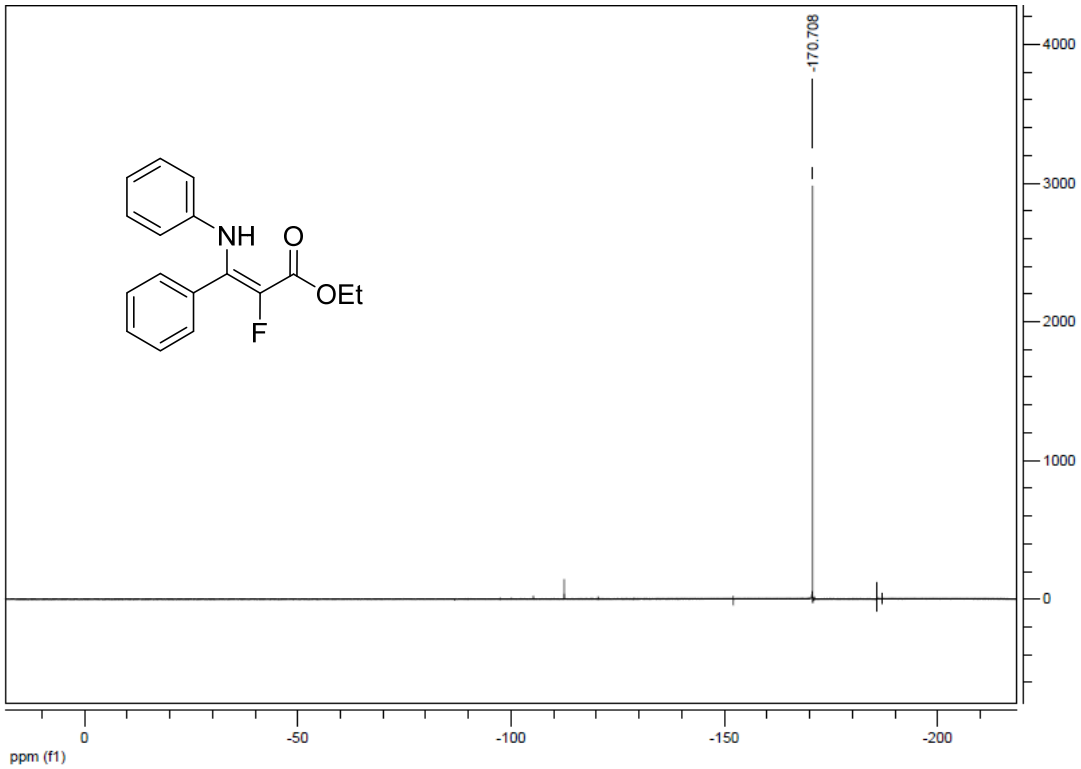
164.721
143.679
143.438
140.820
133.487
131.187
130.838
129.787
129.751
128.835
128.561
122.591
121.446
77.478
77.160
76.842
60.929
14.536
NH
O
OEt
F
15000
10000
5000
0
150
100
50
0
ppm (f1)


-170.708
NH
O
OEt
F
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3000
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1000
0
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-50
-100
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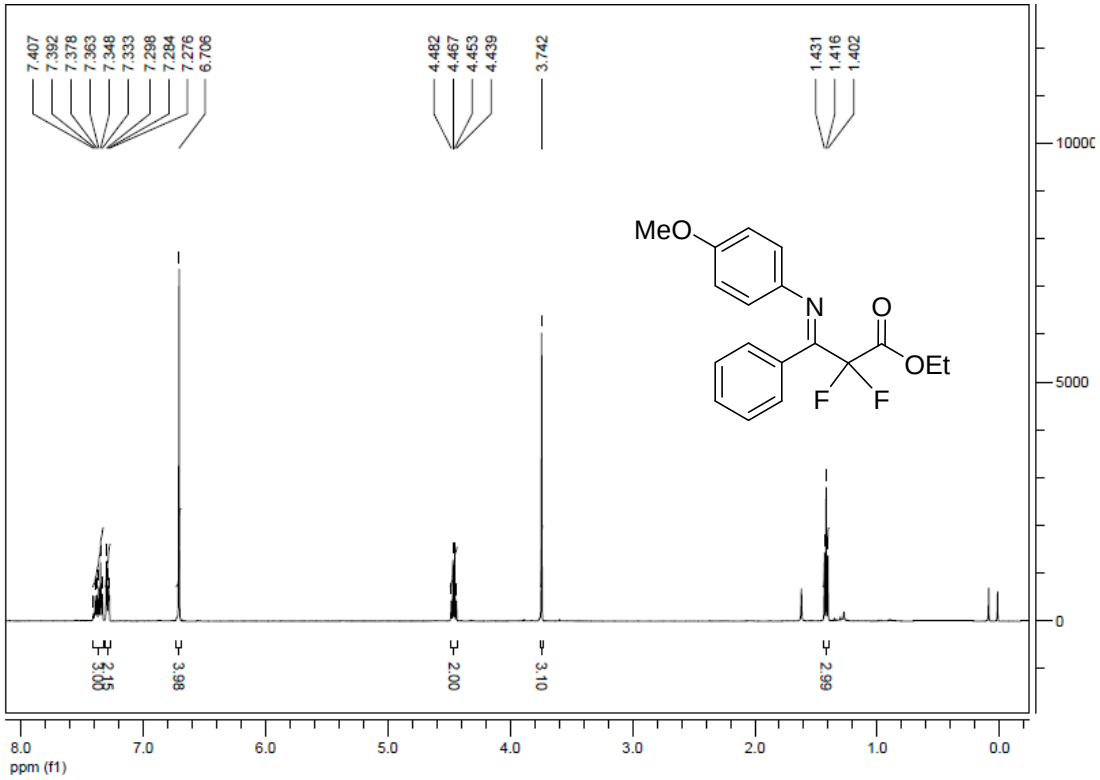
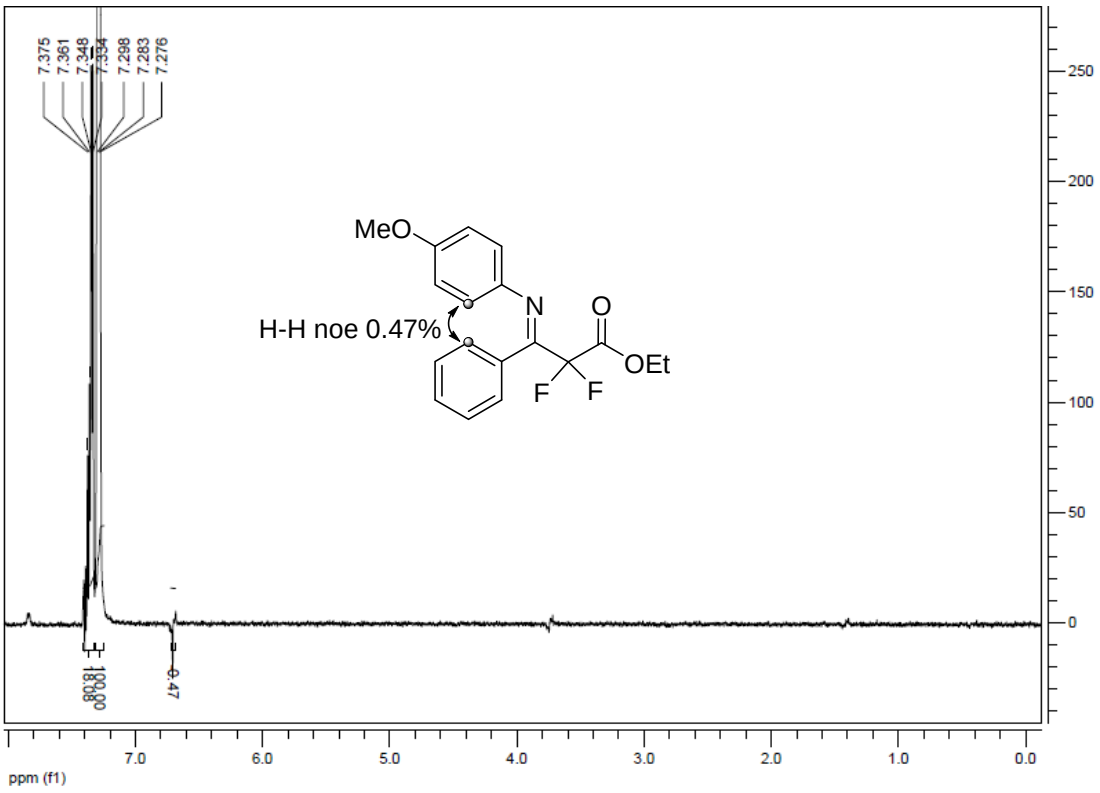
-200
ppm (f1)

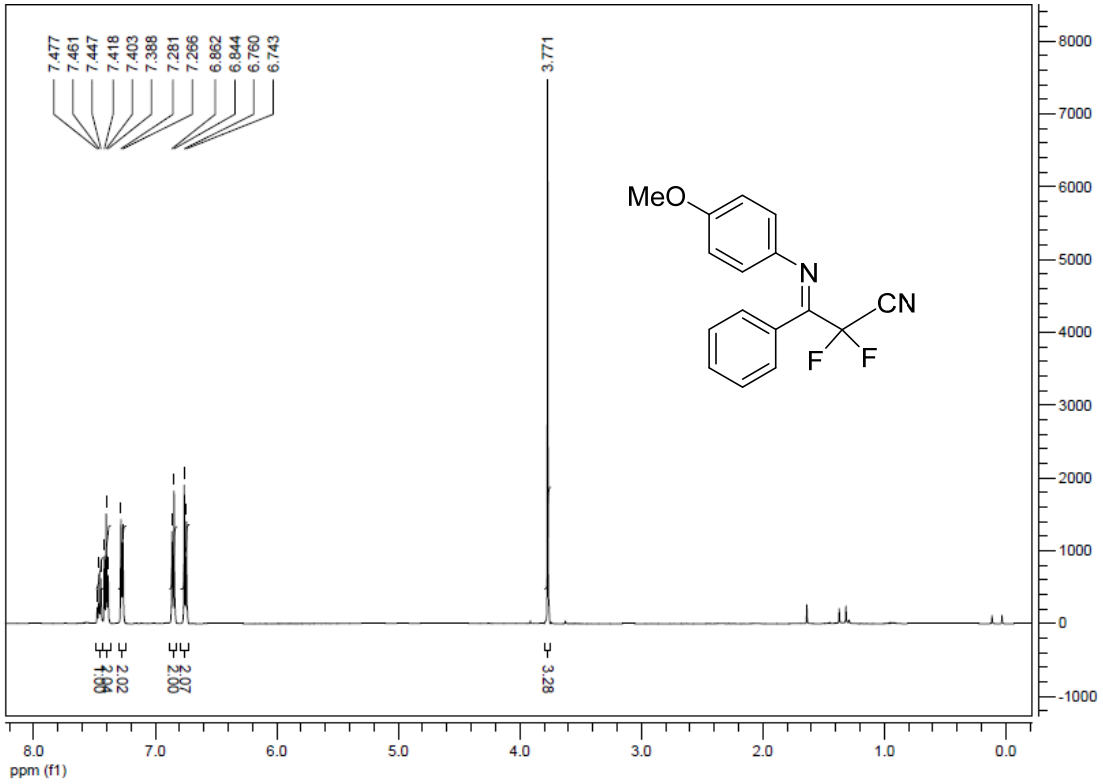
5. Determination of the configuration of the imine C=N bond

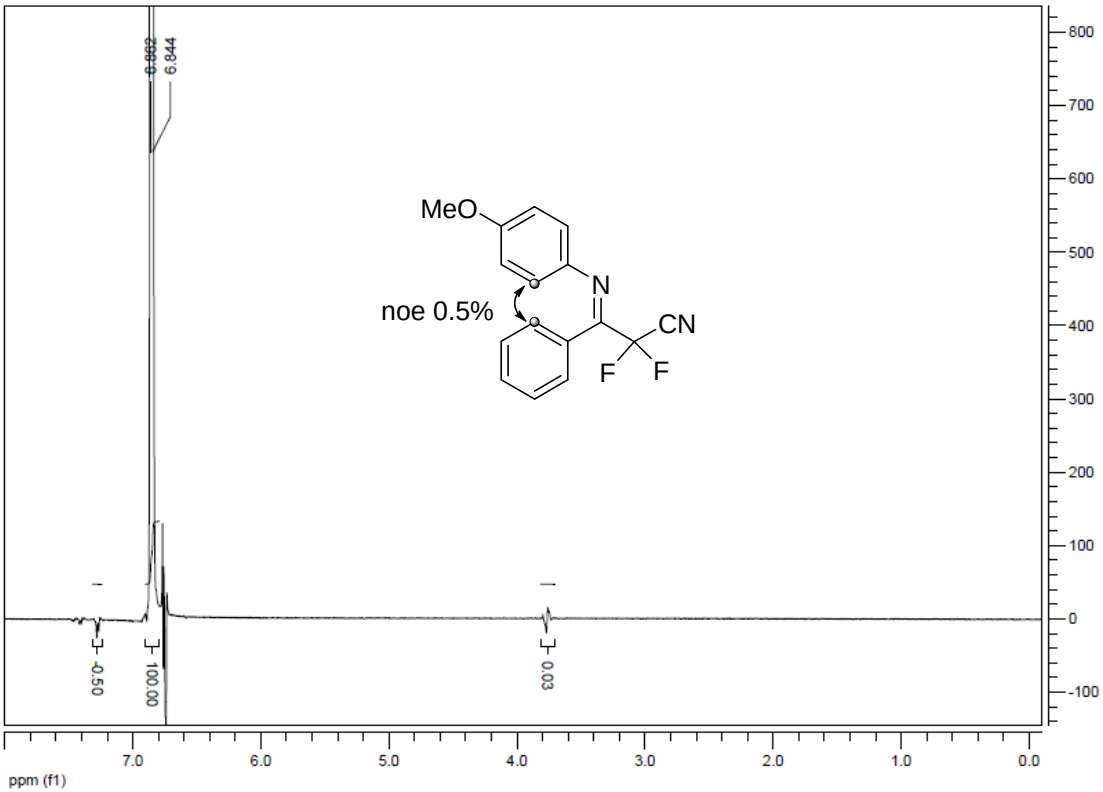
NOESY experiment of **2a**



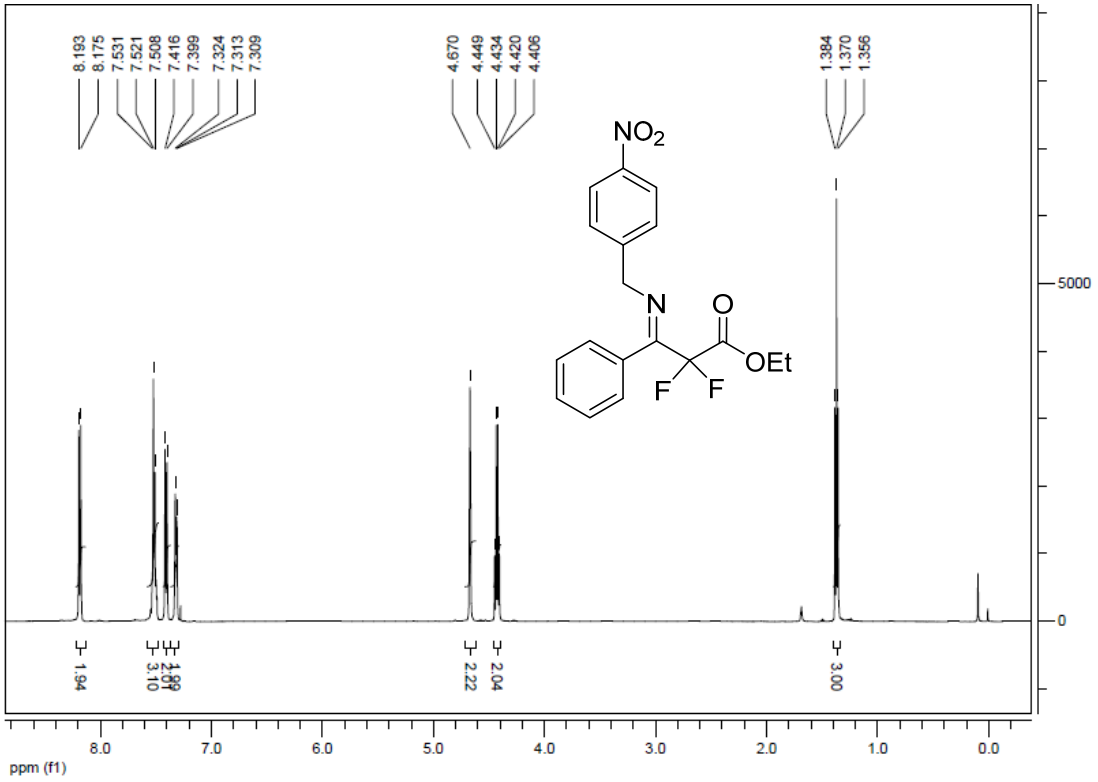


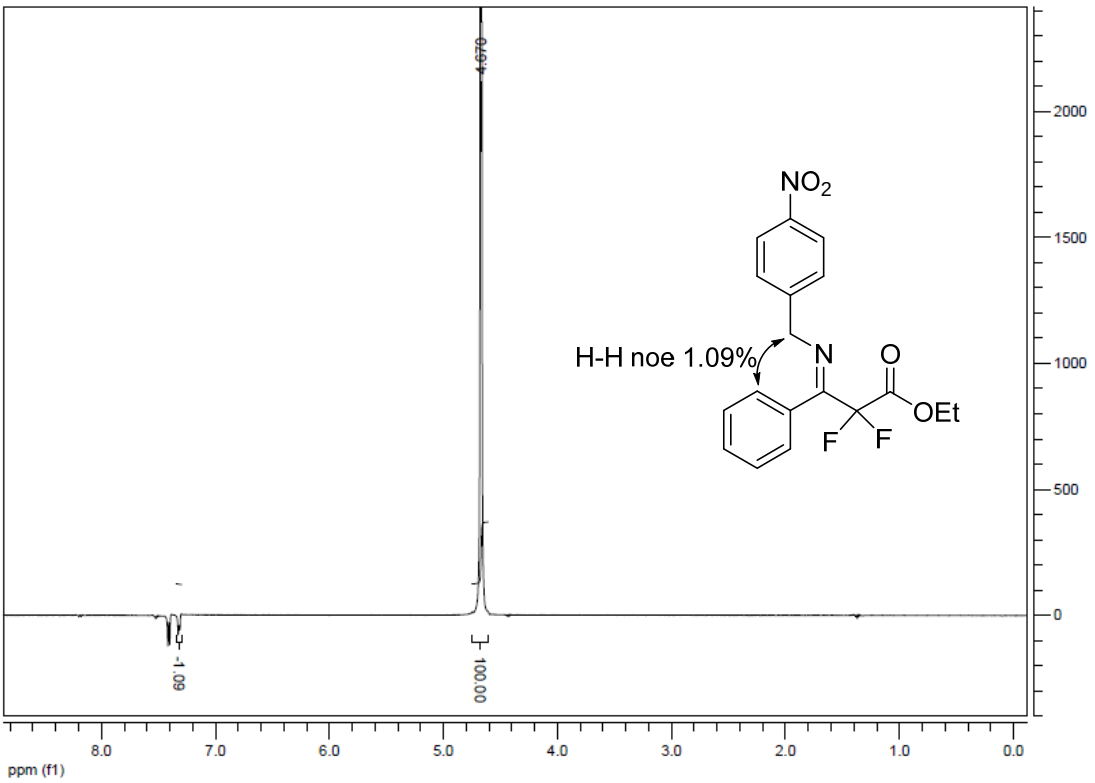
NOESY experiment of **2r**



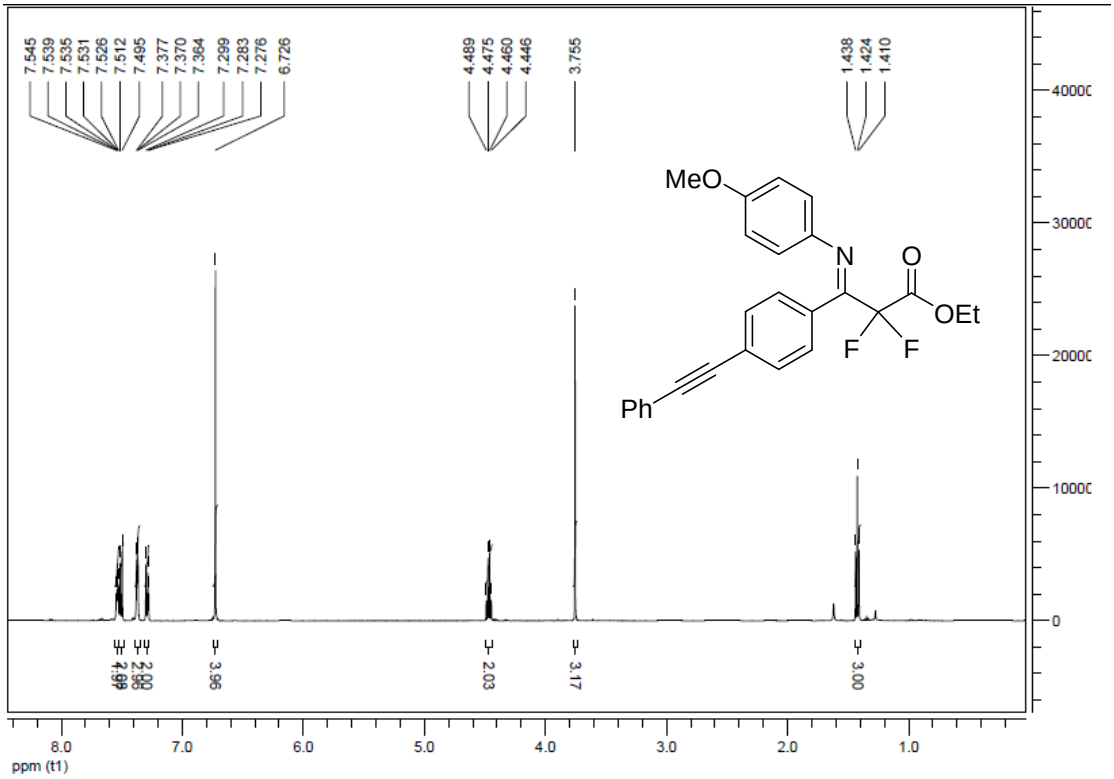


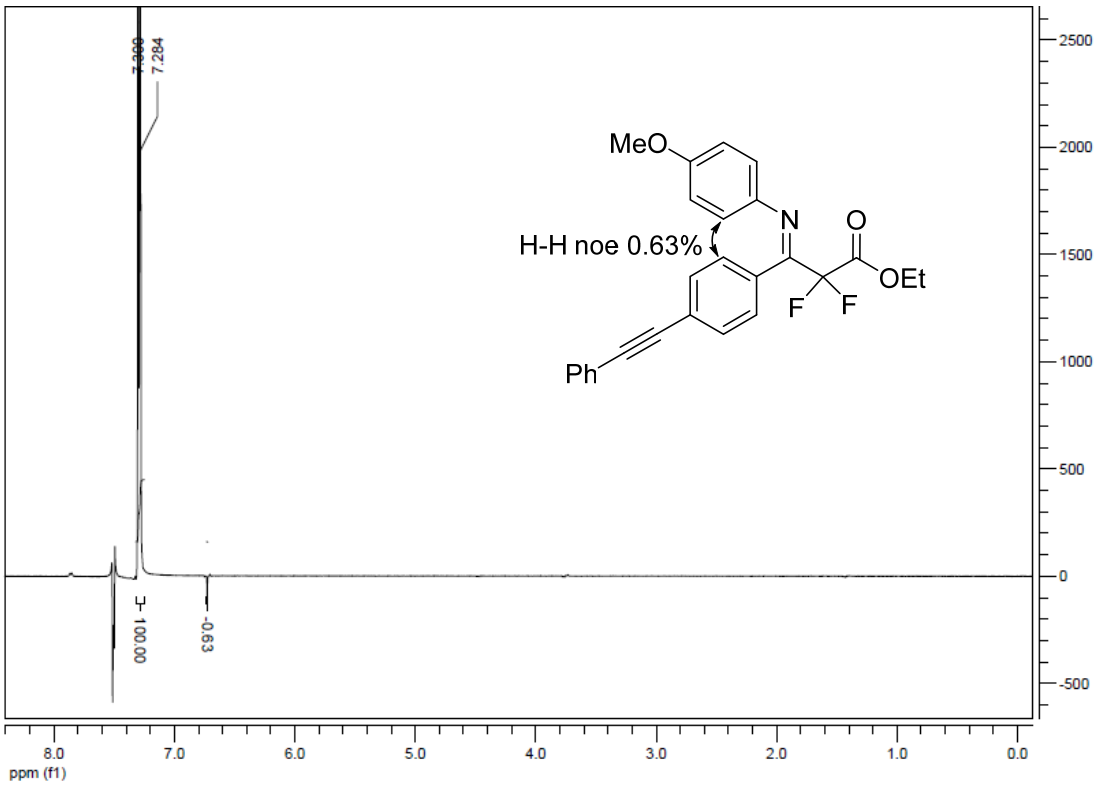
NOESY experiment of **2y**



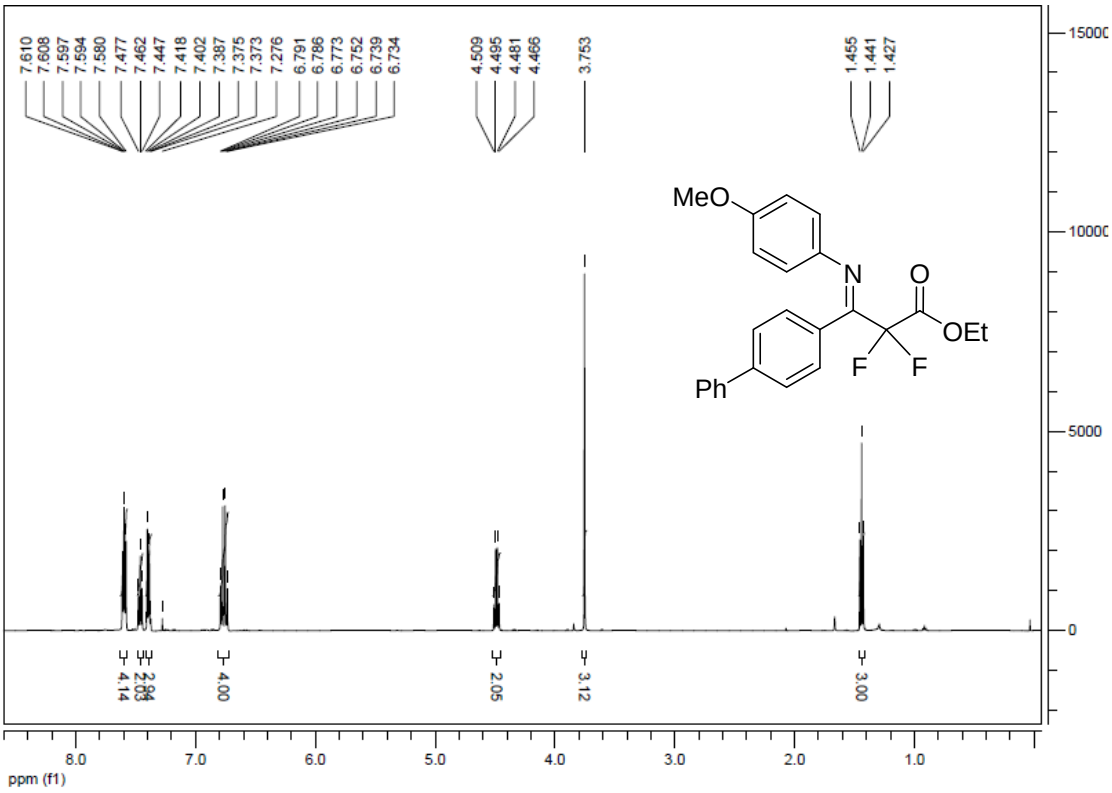


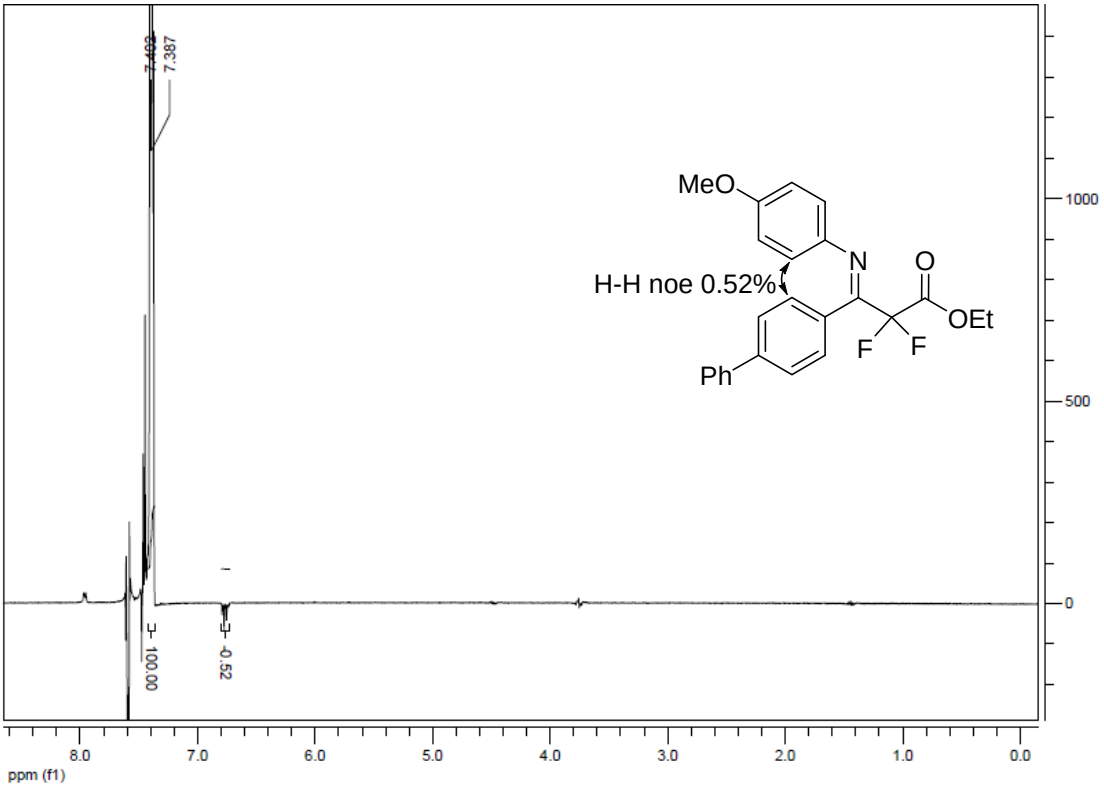
NOESY experiment of compound **6**





NOESY experiment of compound **7**





6. HRMS spectrum of the reaction solution of Scheme 4b

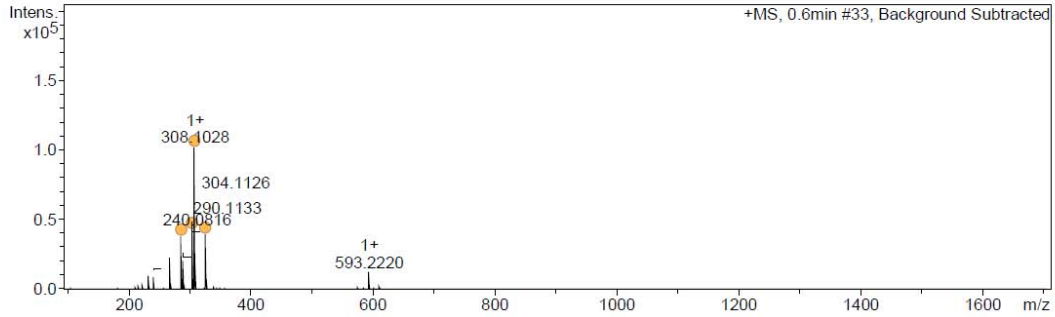
Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name	D:\Data\YSY\DATA\20180830\ZHONGYIYAO-LI-27_P1-A-4_01_9536.d	Acquisition Date	8/30/2018 3:23:42 PM
Method	20180427_test_sm-20180628-pos.m	Operator	bruker
Sample Name	ZHONGYIYAO-LI-27	Instrument	microtof Q II 228888.10387
Comment			

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.8 Bar
Focus	Active	Set Capillary	4500 V	Set Dry Heater	180 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	1700 m/z	Set Collision Cell RF	150.0 Vpp	Set Divert Valve	Source



Meas. m/z	#	Ion Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e¯ Conf	N-Rule	Adduct
286.122366	1	C17H17FNO2	100.00	286.123783	-1.4	-5.0	1.3	9.5	even	ok	M
	2	C13H13FN7	89.73	286.121098	-1.3	-4.4	12.7	10.5	even	ok	M
	3	C12H17FN3O4	25.16	286.119761	2.6	9.1	25.4	5.5	even	ok	M
	1	C17H17FNO2	100.00	286.123783	-1.4	-5.0	1.3	9.5	even	ok	M+H
	2	C13H13FN7	89.73	286.121098	-1.3	-4.4	12.7	10.5	even	ok	M+H
	3	C12H17FN3O4	25.16	286.119761	2.6	9.1	25.4	5.5	even	ok	M+H
	1	C15H18FNNaO2	100.00	286.121378	1.0	3.5	11.4	6.5	even	ok	M+Na
	2	C11H14FN7Na	8.01	286.118692	-3.7	-12.8	25.1	7.5	even	ok	M+Na
304.112637	1	C13H12F2N7	100.00	304.111676	1.0	3.2	4.4	10.5	even	ok	M
	2	C17H16F2NO2	55.93	304.114362	-1.7	-5.7	9.8	9.5	even	ok	M
	3	C12H16F2N3O4	31.41	304.110339	2.3	7.6	16.9	5.5	even	ok	M
	1	C13H12F2N7	100.00	304.111676	1.0	3.2	4.4	10.5	even	ok	M+H
	2	C17H16F2NO2	55.93	304.114362	-1.7	-5.7	9.8	9.5	even	ok	M+H
	3	C12H16F2N3O4	31.41	304.110339	2.3	7.6	16.9	5.5	even	ok	M+H
	1	C15H17F2NNaO2	100.00	304.111956	0.7	2.2	2.8	6.5	even	ok	M+Na
	2	C11H13F2N7Na	9.77	304.109271	3.4	11.1	16.5	7.5	even	ok	M+Na
308.102809	1	C17H16FNNaO2	17.05	308.105728	-2.9	-9.5	5.0	9.5	even	ok	M
	2	C13H12FN7Na	100.00	308.103042	-0.2	-0.8	8.8	10.5	even	ok	M
	3	C12H16FN3NaO4	49.20	308.101705	-1.1	-3.6	21.9	5.5	even	ok	M
	1	C17H16FNNaO2	17.05	308.105728	-2.9	-9.5	5.0	9.5	even	ok	M+H
	2	C13H12FN7Na	100.00	308.103042	-0.2	-0.8	8.8	10.5	even	ok	M+H
	3	C12H16FN3NaO4	49.20	308.101705	-1.1	-3.6	21.9	5.5	even	ok	M+H
	1	C15H17FNNa2O2	100.00	308.103322	0.5	1.7	7.8	6.5	even	ok	M+Na
	2	C11H13FN7Na2	26.58	308.100637	2.2	7.1	21.3	7.5	even	ok	M+Na
326.094800	1	C17H15F2NNaO2	100.00	326.096306	1.5	4.6	7.5	9.5	even	ok	M
	2	C13H11F2N7Na	93.76	326.093621	1.2	3.6	21.2	10.5	even	ok	M
	3	C12H15F2N3NaO4	25.91	326.092283	-2.5	-7.7	34.1	5.5	even	ok	M
	1	C17H15F2NNaO2	100.00	326.096306	1.5	4.6	7.5	9.5	even	ok	M+H
	2	C13H11F2N7Na	93.76	326.093621	1.2	3.6	21.2	10.5	even	ok	M+H
	3	C12H15F2N3NaO4	25.91	326.092283	-2.5	-7.7	34.1	5.5	even	ok	M+H
	1	C15H16F2NNa2O2	100.00	326.093900	0.9	2.8	20.1	6.5	even	ok	M+Na

Bruker Compass DataAnalysis 4.1 printed: 8/30/2018 3:49:06 PM by: bruker Page 1 of 1

Display Report

Analysis Info

Analysis Name	D:\Data\YSY\DATA\20180830\ZHONGYIYAO-LI-27_P1-A-4_01_9536.d	Acquisition Date	8/30/2018 3:23:42 PM
Method	20180427_test_sm-20180628-pos.m	Operator	bruker
Sample Name	ZHONGYIYAO-LI-27	Instrument	microtof Q II 228888.10387
Comment			

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.8 Bar
Focus	Active	Set Capillary	4500 V	Set Dry Heater	180 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	1700 m/z	Set Collision Cell RF	150.0 Vpp	Set Divert Valve	Source