

Supporting Information

Translating Solid State Organic Synthesis from a Mixer Mill to a Continuous Twin-Screw Extruder

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1 General Information

Unless otherwise stated, all reagents were purchased from commercial source and used without further purification.

^1H NMR spectra were recorded on a Bruker AVX400 (400 MHz) spectrometer at ambient temperature. ^{13}C NMR spectra were recorded on a Bruker AVX400 (100 MHz) spectrometer at ambient temperature. ^{19}F NMR were recorded on a Bruker AVX400 (376 MHz) spectrometer at ambient temperature. Mass spectra (ESI) data were analyzed using Waters LCT Premier TOF Mass spectrometer.

Extrusion reaction was carried out using a Three-Tec 12 mm, 40:1 L:D co-rotating twin screw extruder with six heating zones. Screw speeds were varied from 25 - 280 rpm and the temperature from ambient to 90 °C. Volumetric twin screw feeder (ZD 9 FB) is purchased from Three-Tec.

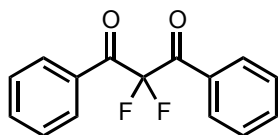
2 Experimental Procedures

General procedure for reaction optimization and analyzing fluorinated product using ^{19}F NMR

Each of the twin screw extruder six heating zones were heated to the desired temperature. Then a mixture of dibenzoylmethane (5 mmol, 1.12 g), Selectfluor (10 mmol, 3.54 g), NaCl and additive (either Na_2CO_3 or acetonitrile) were added to a 250 mL beaker. Then the mixture was mixed by hand using spatula. The premixed mixture was then fed manually to the extruder at desired screw speed.

The NMR yields of fluorinated products were determined by ^{19}F NMR using the internal standard method with trifluorotoluene as internal standard. After reaction mixture came out of twin screw extruder, about 2 g of reaction mixture was collect in a sample vial with ~ 0.1 g trifluorotoluene added as internal standard. Then 4 mL of CDCl_3 was added to the mixture and the vial was closed and shaken by hand for 30 s. About 1 mL reaction mixture was then passed through a pipette containing a small plug of cotton wool to filter out salts (unreacted/reacted Selectfluor salts and NaCl) and collected in a NMR tube for ^{19}F NMR analysis.

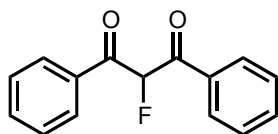
Continuous synthesis of 2,2-difluoro-1,3-diphenylpropane-1,3-dione using TSE with modified screw



A 90 g mixture of dibenzoylmethane (3.36 g, 15 mmol), Selectfluor (10.62 g, 30 mmol), Na_2CO_3 (45 mmol, 4.77 g), NaCl (71.3 g) was mixed by hand initially and poured into the volumetric twin screw feeder. The feed rate of volumetric feeder was set to 1.5% (solid adding speed about 3.75 g/min). The mixture was fed into the twin screw extruder at 280 rpm with the extruder barrel heated to 70 °C. The torque was maintained between 3-5 Nm and the material exited the barrel in 3 min as light beige color. After reaction was finished, 45 g of reaction material was collected in a 250 mL beaker, and 200 mL water was added to dissolve salts. After the mixture was stirred for 2 min, then the solid was filtered, collected and dried under high vacuum. Then recrystallization using cyclohexane gave 1.37 g 2,2-difluoro-1,3-diphenylpropane-1,3-dione (Yield = 70%).

^1H NMR (400 MHz, CDCl_3) δ 8.09 (d, 4H), 7.70 - 7.61 (m, 2H), 7.55 - 7.46 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ 187.5 (t, J = 27 Hz), 135.2, 131.8, 130.4 (t, J = 3 Hz), 129.1, 112.8 (t, J = 266 Hz). ^{19}F NMR (376 MHz, CDCl_3) δ - 102.66 (s). NMR data is in agreement with literature data.¹ HRMS (ESI) calcd for $[\text{M}+\text{NH}_4]^+$ $\text{C}_{15}\text{H}_{14}\text{NO}_2\text{F}_2$: 278.0993, found: 278.0983.

Continuous synthesis of 2-fluoro-1,3-diphenylpropane-1,3-dione using TSE with modified screw



A ~ 90 g mixture of dibenzoylmethane (3.36 g, 15 mmol), Selectfluor (10.62 g, 30 mmol), NaCl (75 g) was mixed with acetonitrile (6 mL) by hand initially and poured into the volumetric twin screw feeder. The feed rate of volumetric feeder was set to 8% with adding speed about 3.75 g/min. The mixture was fed into the twin screw extruder at 280 rpm with the extruder barrel heated to 60 °C. The torque was maintained around 3-5 and the material exited the barrel in 3 min as light beige color. After reaction was finished, 45 g of reaction material was collected in a 250 mL beaker, and 200 mL water was added to dissolve salts. After the mixture was stirred for 2 min, then the solid was filtered, collected and dried under high vacuum to give a mixture of product (1.79 g, 90% with diF: monoF = 1: 6).

¹H NMR (400 MHz, CDCl₃) δ 8.10 (d, *J* = 8.4 Hz, 4H), 7.65 - 7.59 (m, 2H), 7.53 - 7.45 (d, *J* = 11.0, 4.5 Hz, 4H), 6.54 (d, *J* = 49.2 Hz, 1H). **¹³C NMR** (100 MHz, CDCl₃) δ 191.3 (d, *J* = 20 Hz), 134.7, 133.7, 130.0 (d, *J* = 4 Hz), 128.9, 96.7 (d, *J* = 199 Hz). **¹⁹F NMR** (376 MHz, CDCl₃) δ - 186.79 (d, *J* = 49.2 Hz). NMR data is in agreement with literature data.¹ **HRMS** (ESI) calcd for [M+Na]⁺ C₁₅H₁₁O₂FNa: 265.0641, found: 265.0632.

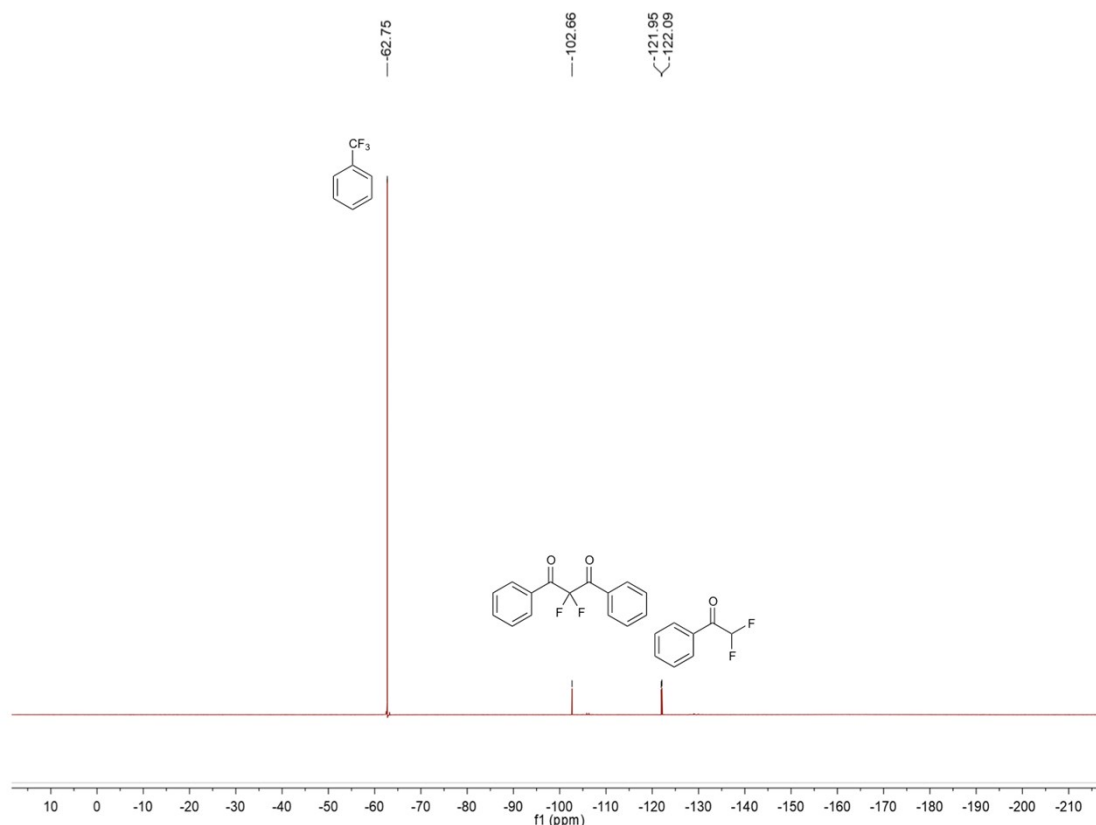
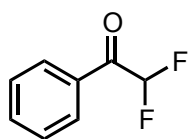


Figure S1: Crude ^{19}F NMR spectroscopy of reaction mixture after extrusion at 90 °C.

Note: The peak at 122.0 (d, $J = 53.5$ Hz) indicate that 2-difluoro-1-phenylethanone was formed as byproduct from 2,2-difluoro-1,3-diphenylpropane-1,3-dione during extrusion process at 90 °C under basic conditions, which agrees with results from the work by Pattison and coworkers.² ^{19}F NMR matching the isolated 2-difluoro-1-phenylethanone using solution method.

Synthesis of 2,2-difluoro-1-phenylethanone

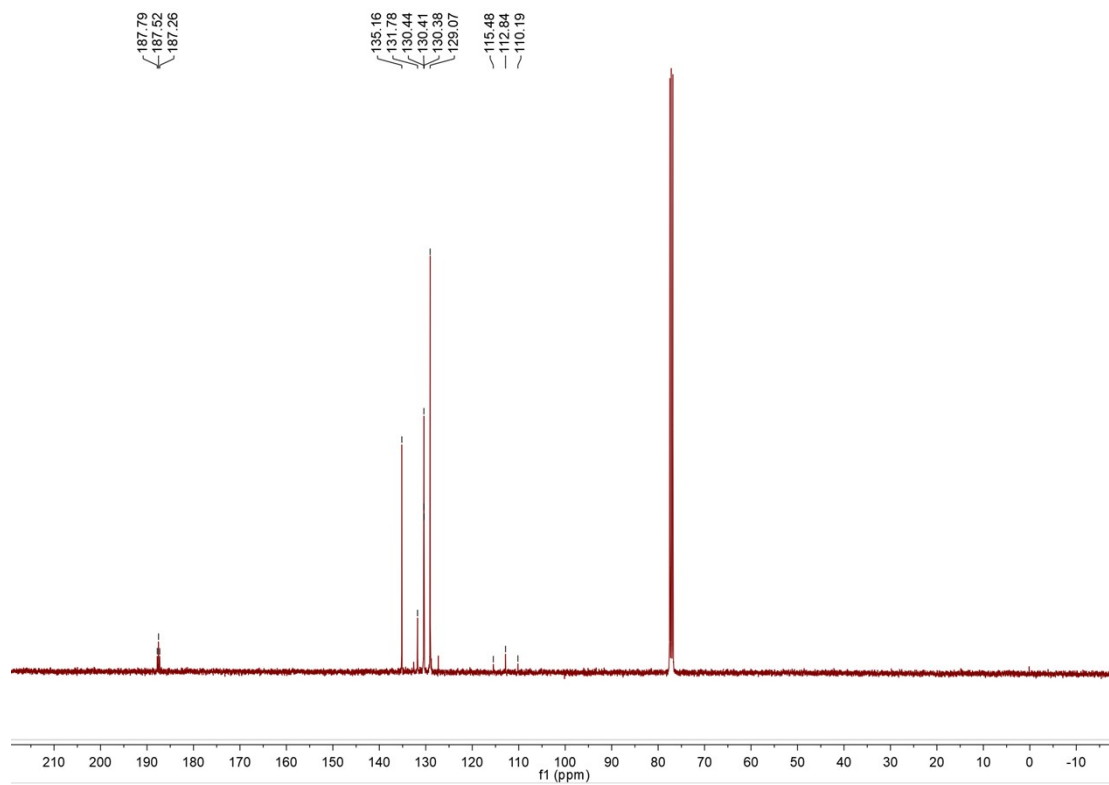
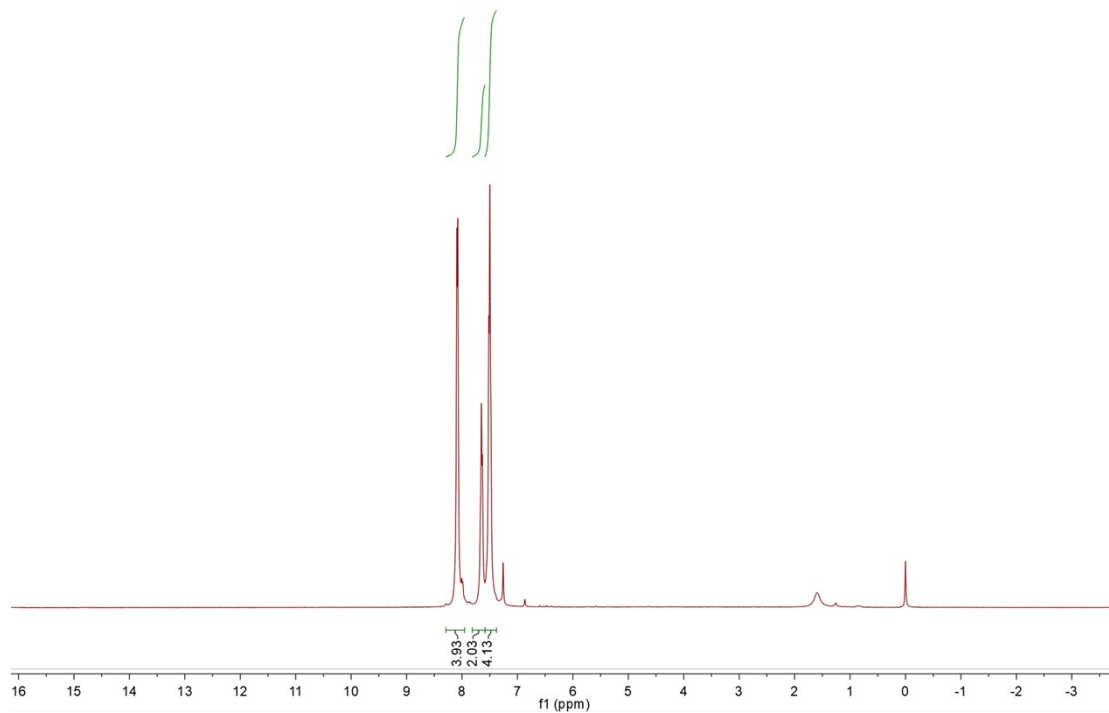
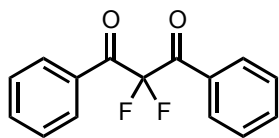


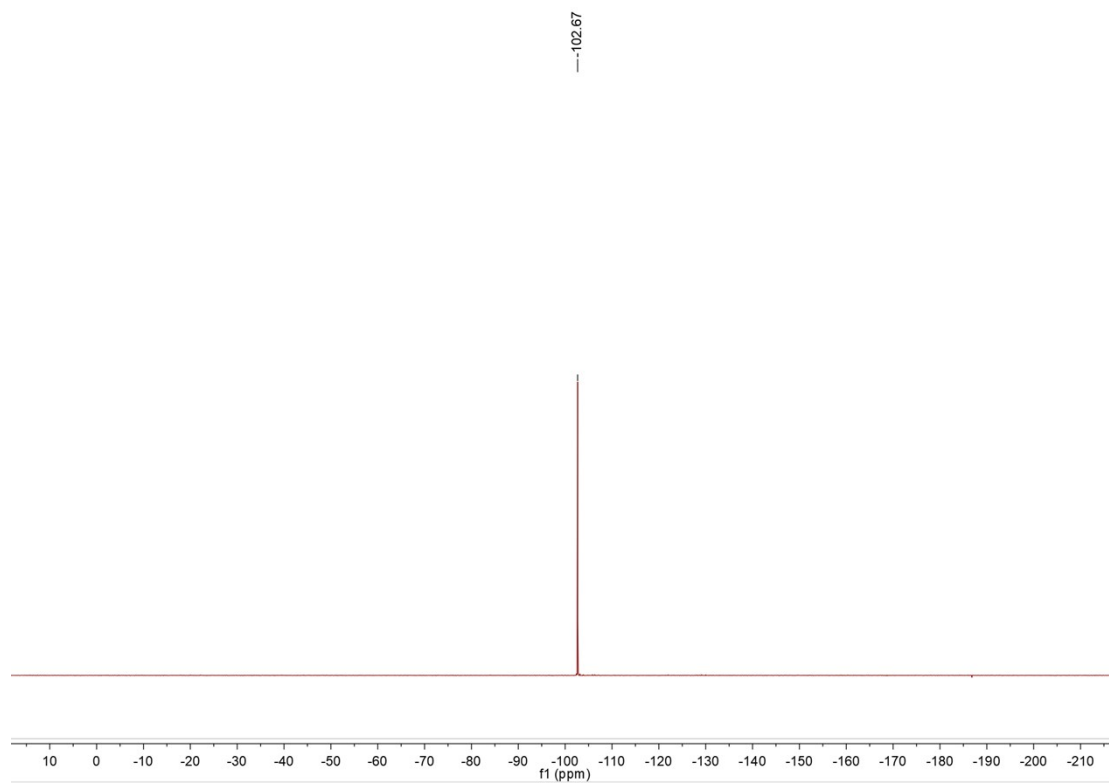
The synthesis of the titled compound was prepared using a method modified from the literature.³ Ethylbenzoylacetate (4.3 mL) was stirred in aqueous NaOH (1 M, 25 mL) at room temperature for 20 hours. The reaction mixture was transferred to a separating funnel and DCM (10 mL) was added. The aqueous phase was then further washed with DCM (2 x 10 mL) to remove any unreacted ester. The aqueous phase was acidified to pH 1 with 1 M HCl and the precipitate filtered, washing on the filter with water, and dried on the filter then under vacuum overnight to yield the beta keto acid as a white solid. To this acid (2.545 g, 15.5 mmol.) was added Selectfluor (13.718 g, 2.5 equiv.) and acetonitrile (100 mL). A reflux

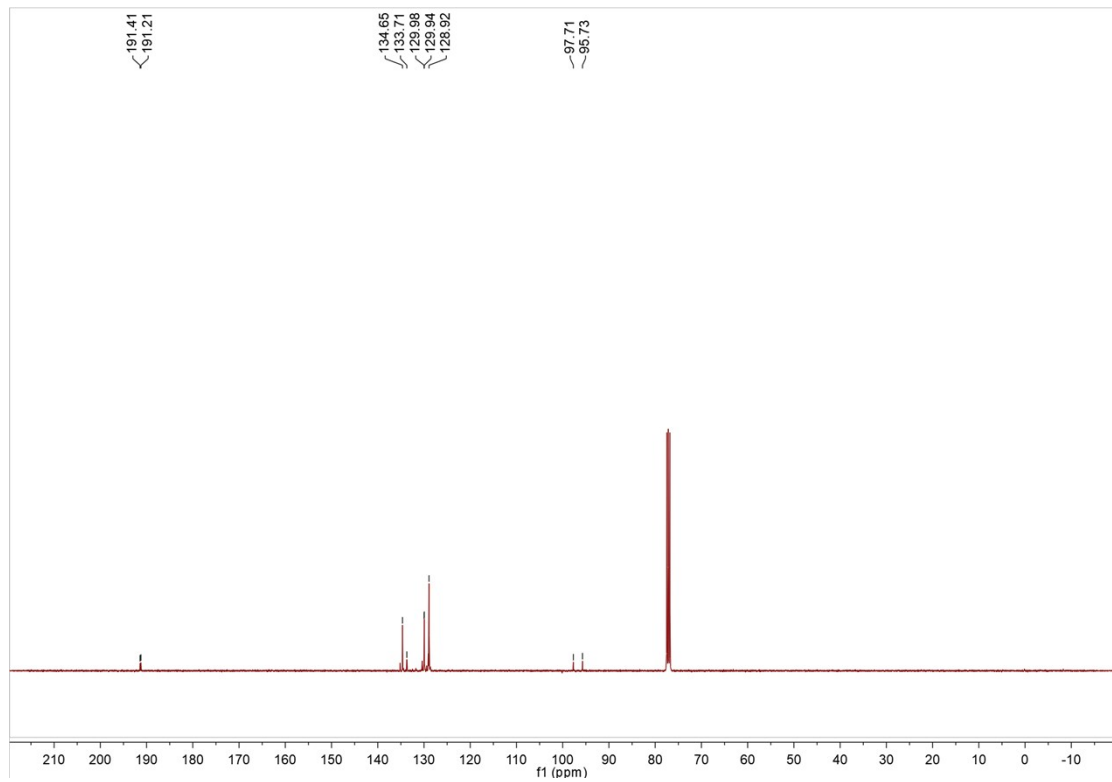
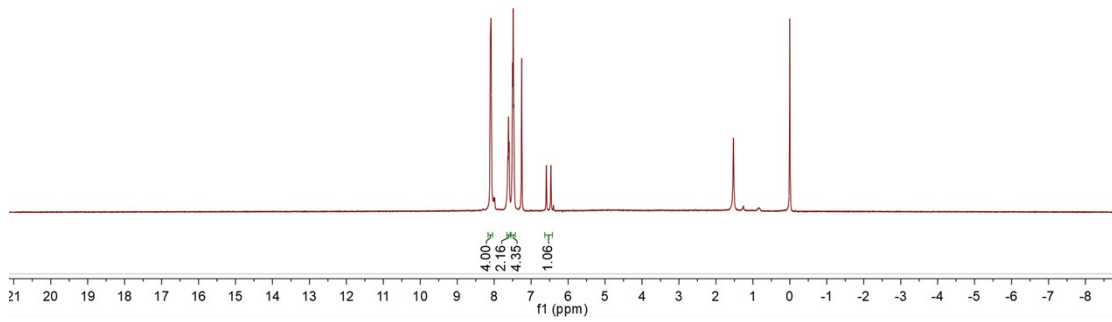
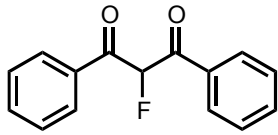
condenser was fitted and the mixture was heated to 60 °C for 3 days. The solvent was removed by rotary evaporation and to this residue was added water (50 mL) and DCM (50 mL) and the mixture transferred to a separating funnel. The aqueous phase was further extracted with DCM (2 x 50 mL), and the combined organic phase dried (MgSO₄), filtered and solvent removed. The product was isolated by flash column chromatography by gradient elution (0-10% EtOAc in petroleum ether), yielding the desired product as a colourless oil (47%, 1.146 g).

¹H NMR (400 MHz, CDCl₃) δ 8.08 (d, *J* = 7.7 Hz, 2H), 7.76 - 7.59 (m, 1H), 7.59 - 7.41 (m, 2H), 6.30 (t, *J* = 53.5 Hz, 1H). **¹³C NMR** (100 MHz, CDCl₃) δ 188.0 (t, *J* = 26 Hz), 135.3, 131.9 (t, *J* = 2 Hz), (t, *J* = 2 Hz), 130.0 (t, *J* = 2 Hz), 111.6 (t, *J* = 254 Hz). **¹⁹F NMR** (376 MHz, CDCl₃) δ - 122.0 (d, *J* = 53.8 Hz). NMR data is in agreement with literature data.³ **HRMS** (ESI) calcd for [M+H]⁺ C₈H₇OF₂: 157.0465, found: 154.0461.

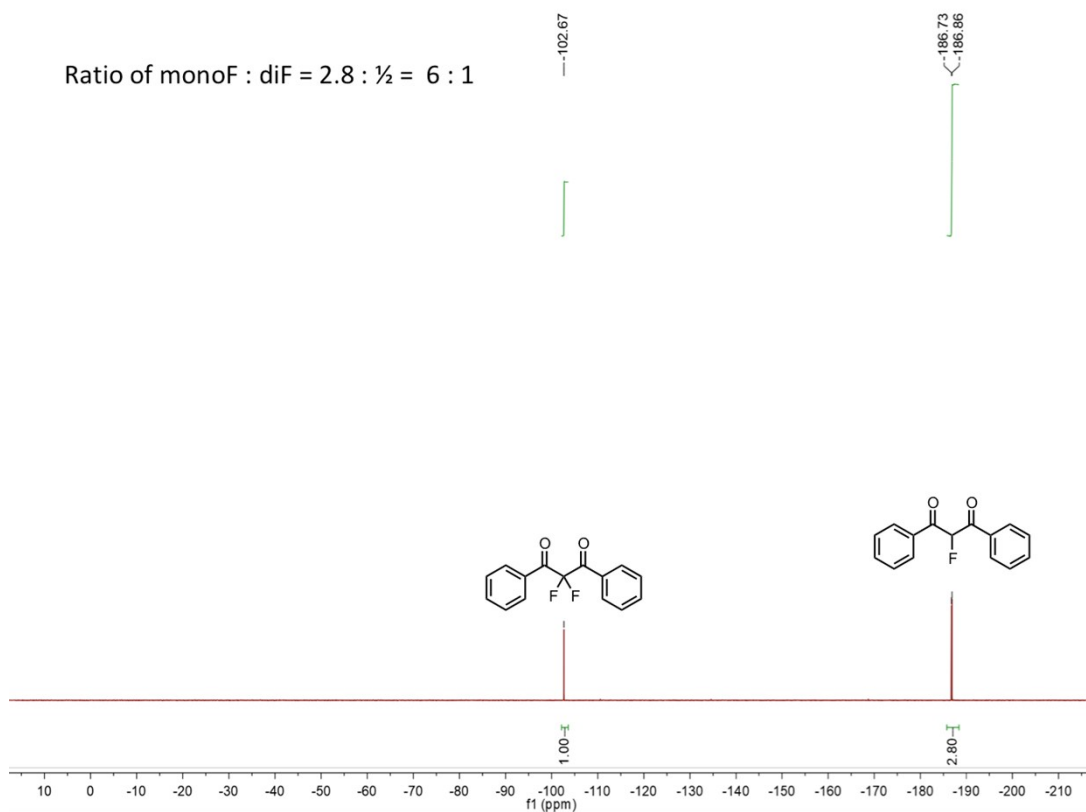
3 NMR Data

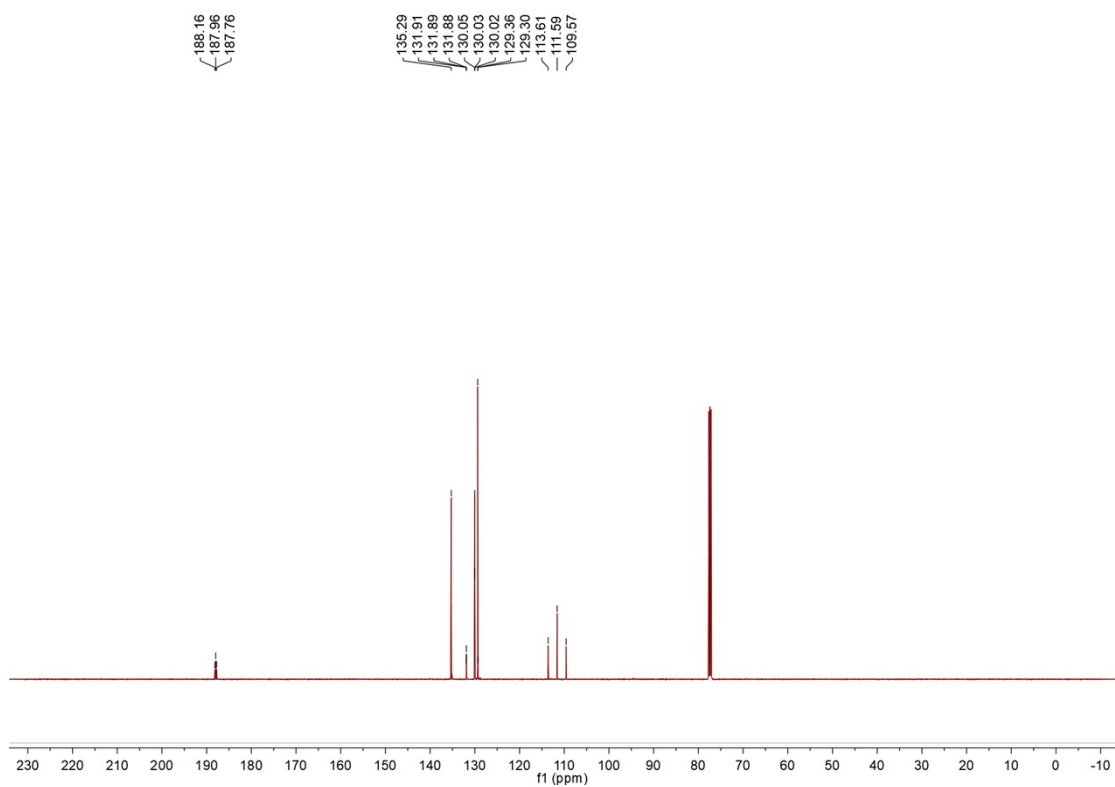
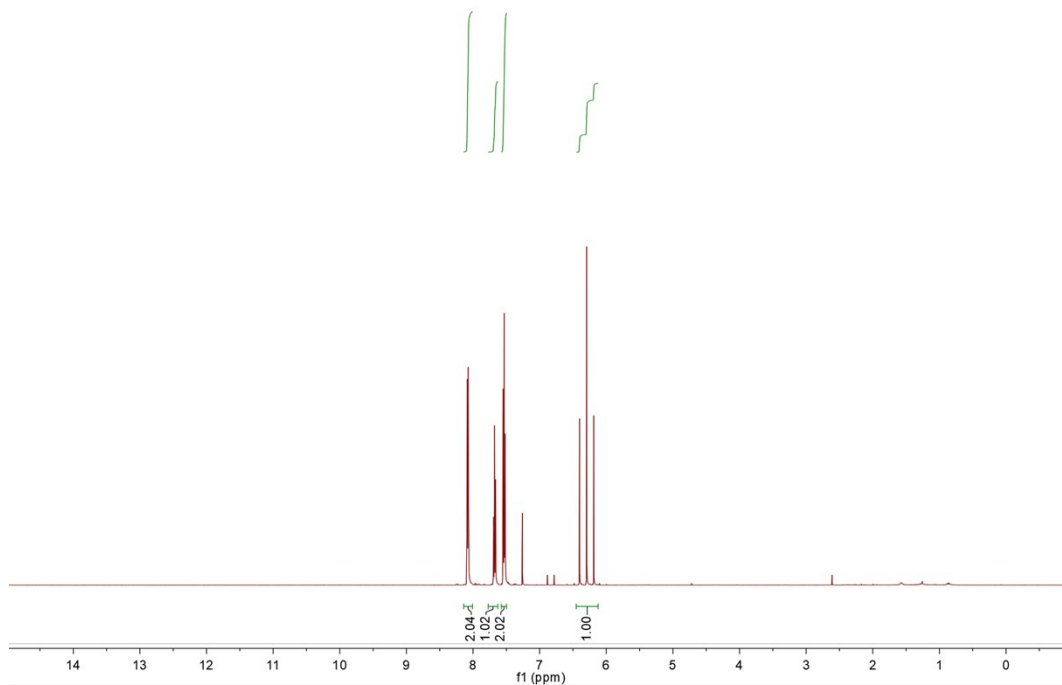
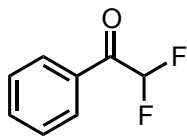


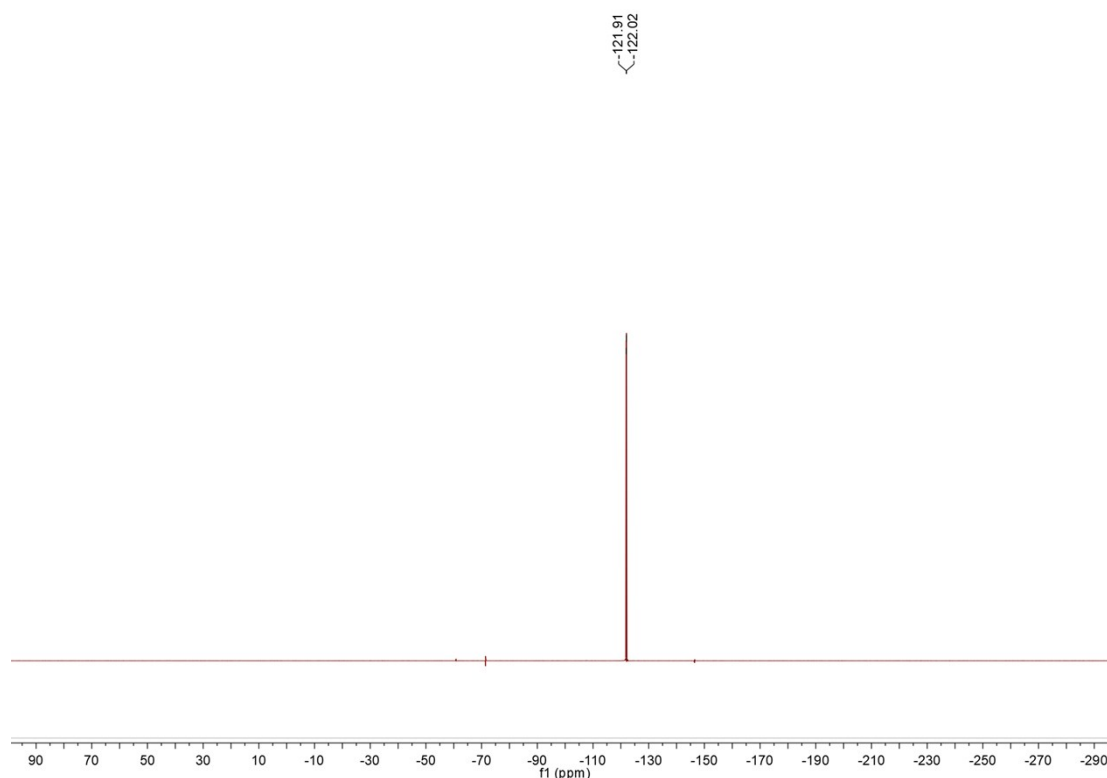




Ratio of monoF : diF = 2.8 : ½ = 6 : 1







4 References

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 - ² Leng, D. J.; Black, C. M.; Pattison, G. One-pot synthesis of difluoromethyl ketones by a difluorination/fragmentation process. *Org. Biomol. Chem.* **2016**, *14*, 1531.
 - ³ Li, Y.-L.; Li, J.; Deng, J. Practical Access to Difluoromethyl Ketones *via* Straightforward Decarboxylative Difluorination of β -Ketoacids. *Adv. Synth. Catal.* **2017**, *359*, 1407.