

**Direct Access to Acyl Fluorides from Carboxylic Acids Using a Phosphine/Fluoride Deoxyfluorination
Reagent System**

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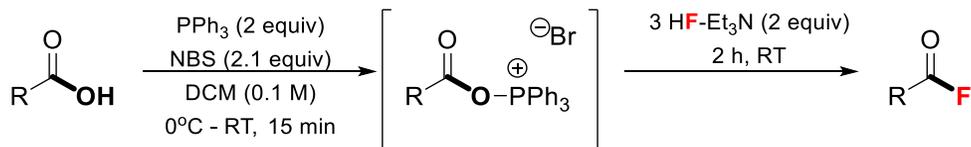
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General

Unless otherwise mentioned, all the chemicals were purchased from commercial sources and used without further purification. *N*-bromosuccinimide (NBS) was recrystallized from water and dried over P₂O₅ under high vacuum. Anhydrous dichloromethane (DCM) was purchased from EMD (drysol_v) and used as received. Polymer-bound PPh₃ (extent of labeling: 3 mmol/g) was purchased from Sigma-Aldrich (Catalog No. 93093) and used as received. In the cases indicated, flash column chromatography was performed to isolate products with suitable eluent as determined by TLC. ¹H, ¹³C, and ¹⁹F spectra were recorded on 400 MHz or 500 MHz Varian NMR spectrometers. ¹H NMR chemical shifts were determined relative to CDCl₃ as the internal standard at δ 7.26 ppm. ¹³C NMR shifts were determined relative to CDCl₃ at δ 77.16 ppm. ¹⁹F NMR chemical shifts were determined relative to CFC₃ at δ 0.00 ppm. Mass spectra were recorded on a high-resolution mass spectrometer, EI or ESI mode.

****Caution!** *Et₃N-3HF* must be handled only by trained personnel, using appropriate personal protection equipment in a well-ventilated hood. Contact with the skin must be avoided.

General procedure for the preparation of acyl fluorides and NMR yield determination



The following representative procedure for the synthesis of **2a** was used. On the bench-top, benzoic acid **1a** (0.25 mmol, 30.5 mg) and triphenylphosphine, PPh_3 (0.5 mmol, 131.2 mg) were charged into an oven-dried screw-cap vial equipped with a magnetic stir bar. After this, anhydrous dichloromethane, DCM (2.5 mL) was added, the vial was capped, and this mixture was then cooled to $0^\circ C$ using an ice-bath. Subsequently, *N*-bromosuccinimide, NBS (2.1 equiv, 0.525 mmol, 94 mg) was added as a solid in one portion, the vial was re-capped, and the mixture was kept in the ice-bath for two minutes. After this time, the ice-bath was removed, and this solution was further stirred for 15 min. Once this time concluded, the vial was opened and $3HF-Et_3N$ (2 equiv, 0.5 mmol, 82 μL) was added via micropipette. This mixture was stirred further for 2 h at room temperature. After this time internal standard, *p*-toluenesulfonyl fluoride (45 mg, 0.26 mmol, 104% of theoretical yield) dissolved in anhydrous DCM (1 mL) was added, the mixture was stirred for 2 min, then analyzed by ^{19}F NMR spectroscopy. The yield was determined by comparing the relative integration of internal standard (*p*-tolylsulfonyl fluoride, ^{19}F NMR δ 65.8) with the acyl fluoride.

General procedure for the preparation/purification of acyl fluorides using PPh_3 (Method A)

Unless otherwise stated, the following representative procedure was used for the synthesis and purification of acyl fluoride products **2**. On the bench-top, carboxylic acid derivative **1** (1 equiv, 0.5 mmol) and triphenylphosphine, PPh_3 (2 equiv, 1 mmol, 262.3 mg) and anhydrous DCM (5 mL) were charged into an oven-dried screw-cap vial equipped with a magnetic stir bar. The vial was capped, and this mixture was then cooled to $0^\circ C$ using an ice-bath. Subsequently, *N*-bromosuccinimide, NBS (2.1 equiv, 1.05 mmol, 187 mg) was added as a solid in one portion, the vial was re-capped, and the mixture was kept in the ice-bath for two minutes. After this time, the ice-bath was removed, and this solution was further stirred for 15 min. After this time, the vial was opened and $3HF-Et_3N$ (2 equiv, 1 mmol, 163 μL) was added via micropipette. This mixture was stirred further for 2 h at room temperature. After this time, the vial was opened, and the reaction mixture was diluted with hexanes (20 mL), and the mixture was stirred for 10 min. During this time, large amounts of succinimide and triphenylphosphine oxide precipitate, which are then removed by passing the mixture through a short pad of silica (2 cm thick x 3 cm diameter). Subsequently, the silica pad was further washed with hexanes or an appropriate mixture of solvent (*see below for each case*). The filtrate was then concentrated under reduced pressure to afford pure product without the need of further purification.

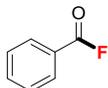
General procedure for the preparation/purification of acyl fluorides using polymer-bound PPh₃ (Method B)

For products **2h** and **2q** this method using polymer-bound triphenylphosphine was implemented. On the bench-top, carboxylic acid derivative **1** (1 equiv, 0.5 mmol) and commercially-available polymer-bound triphenylphosphine, PS-PPh₃ (extent of P-labeling = 3 mmol/g, 2 equiv, 1 mmol, 333 mg) and anhydrous DCM (5 mL) were charged into an oven-dried screw-cap vial equipped with a magnetic stir bar. The vial was capped, and this mixture was then cooled to 0 °C using an ice-bath. Subsequently, *N*-bromosuccinimide, NBS (2.1 equiv, 1.05 mmol, 187 mg) was added as a solid in one portion, the vial was re-capped, and the mixture was kept in the ice-bath for two minutes. After this time, the ice-bath was removed, and this solution was further stirred for 20 min. After this time, 3HF-Et₃N (2 equiv, 1 mmol, 163 μ L) was added via micropipette and the mixture was stirred further for 2 h at room temperature. After this time, the resin was removed by vacuum filtration and washed with DCM (2 mL) and hexanes (20 mL). Further addition of hexanes (10 mL) to this filtrate and stirring for 10 min, resulted in precipitation of succinimide, which was removed by filtration through a plug of celite, washing with hexanes (5 mL). Concentration of the filtrate under reduced pressure afforded the corresponding acyl fluoride without the need of further purification. If traces of succinimide are present in the product, they could be easily removed by washing a DCM or CHCl₃ solution with ice-cold water (5 mL x 2).

***Note: Slow hydrolysis to the carboxylic acid may occur if glassware/solvents are not properly dried. We recommend using oven-dried glassware for all manipulations. If trace amounts of starting materials are formed due to hydrolysis during work-up, they could be easily removed by dissolving the mixture in CHCl₃ and passing it through a short plug of silica.*

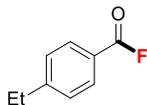
Synthesis and characterization data of products

Benzoyl fluoride (**2a**)¹



The title compound was obtained following the general Method A, using benzoic acid **1a** (0.5 mmol, 61 mg), PPh₃ (1 mmol, 262.3 mg), NBS (1.05 mmol, 187 mg) and 3HF-Et₃N (1 mmol, 163 μ L). Purified by filtration through a short plug of silica (2 cm thick x 3 cm diameter), washing the silica plug with hexanes (20 ml). Obtained as a clear oil in 65% isolated yield (40.5 mg) ¹H NMR (400 MHz, CDCl₃) δ 8.06 (dd, *J* = 8.6, 1.2 Hz, 2H), 7.68 (ddt, *J* = 7.9, 7.1, 1.3 Hz, 1H), 7.53 – 7.46 (m, 2H). ¹⁹F NMR (376 MHz, CDCl₃) δ 17.6 (s, 1F). These data match the previously reported structure.

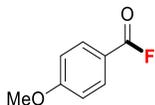
4-Ethylbenzoyl fluoride (**2b**)



The title compound was obtained following the general Method A, using 4-ethylbenzoic acid **1b** (0.5 mmol, 37.5 mg), PPh₃ (1 mmol, 262.3 mg), NBS (1.05 mmol, 187 mg) and 3HF-Et₃N (1 mmol, 163 μ L). Purified by filtration

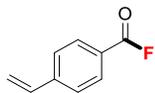
through a short plug of silica (2 cm thick x 3 cm diameter), washing the silica plug with a mixture of hexanes/EtOAc (15 ml; 5:1, v:v). Obtained as a clear oil in 71% isolated yield (54 mg). **¹H NMR** (400 MHz, CDCl₃) δ 7.96 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 7.7 Hz, 2H), 2.75 (q, *J* = 7.6 Hz, 2H), 1.28 (t, *J* = 7.6 Hz, 3H). **¹³C NMR** (126 MHz, CDCl₃) δ 157.7 (d, *J* = 342.8 Hz), 152.8, 131.8 (d, *J* = 4.2 Hz), 128.8, 122.5 (d, *J* = 60.9 Hz), 29.3, 15.2. **¹⁹F NMR** (376 MHz, CDCl₃) δ 17.0 (s, 1F). **HRMS-EI⁺** (M⁺) Calcd. for C₉H₉OF = 152.0637, found = 152.0636. **FT/IR** (ν_{max} (neat) **cm-1**): 2961 2361, 2339, 1682, 1320, 1294, 913, 745, 661, 506.

4-Methoxybenzoyl fluoride (2c)²



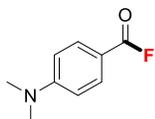
The title compound was obtained following the general Method A, using *p*-anisic acid **1c** (0.5 mmol, 76 mg), PPh₃ (1 mmol, 262.3 mg), NBS (1.05 mmol, 187 mg) and 3HF-Et₃N (1 mmol, 163 μL). Purified by filtration through a short plug of silica, washing the silica plug with a mixture of hexanes/EtOAc (15 ml; 20:1, v:v). Obtained as a clear oil in 80% isolated yield (62 mg). For a 10 mmol (1.521 g) scale reaction, the product was purified by filtration through a short plug of silica (2 cm thick x 3 cm diameter), washing with a mixture of hexanes/EtOAc (20 mL, 20:1, v:v, 2 times); the isolated yield was 70% (1.08 g). **¹H NMR** (400 MHz, CDCl₃) δ 7.99 (d, *J* = 8.9 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 3.90 (s, 3H). **¹⁹F NMR** (376 MHz, CDCl₃) δ 15.4 (s, 1F). These data match the previously reported structure .

4-Vinylbenzoyl fluoride (2d)



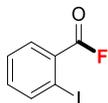
The title compound was obtained following the general Method A, using 4-vinylbenzoic acid **1d** (0.5 mmol, 74.1 mg), PPh₃ (1 mmol, 262.3 mg), NBS (1.05 mmol, 187 mg) and 3HF-Et₃N (1 mmol, 163 μL). Purified by filtration through a short plug of silica (2 cm thick x 3 cm diameter), washing the silica plug with hexanes (15 ml). Obtained as a yellow oil in 73% isolated yield (55 mg). **¹H NMR** (400 MHz, CDCl₃) δ 8.00 (d, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 7.3 Hz, 2H), 6.78 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.95 (dd, *J* = 17.6, 7.0 Hz, 1H), 5.50 (t, *J* = 10.2 Hz, 1H). **¹³C NMR** (101 MHz, CDCl₃) δ 157.4 (d, *J* = 343.0 Hz), 144.5, 135.7, 131.9 (t, *J* = 4.0 Hz), 126.8 (d, *J* = 12.1 Hz), 124.0 (d, *J* = 61.3 Hz), 119.0 – 117.4 (m). **¹⁹F NMR** (376 MHz, CDCl₃) δ 17.3 (s, 1F). **HRMS-EI⁺** (M⁺) Calcd. for C₉H₇OF = 150.04810, found = 150.04819. **FT/IR** (ν_{max} (neat) **cm-1**): 2924, 2852, 1801, 1764, 1604, 1403, 1252, 1177, 1034, 1004, 923, 856, 770, 724, 702.

4-(Dimethylamino)benzoyl fluoride (2e)³



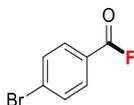
The title compound was prepared following the general Method A, using 4-(dimethylamino)benzoic acid **1e** (0.5 mmol, 82.6 mg), PPh₃ (1 mmol, 262.3 mg), NBS (1.05 mmol, 187 mg) and 3HF-Et₃N (1 mmol, 163 μL). Purified by filtration through a short plug of silica (2 cm thick x 3 cm diameter), washing the silica plug with a mixture of hexanes/DCM (15 ml; 1:1, v:v). Obtained as a white solid in 73% isolated yield (61 mg). ¹H NMR (400 MHz, CDCl₃) δ 7.86 (d, *J* = 9.1 Hz, 2H), 6.66 (d, *J* = 9.1 Hz, 2H), 3.09 (s, 6H). ¹⁹F NMR (376 MHz, CDCl₃) δ 11.8 (s, 1F). These spectra match the previously reported structure.

2-Iodobenzoyl fluoride (**2f**)⁴



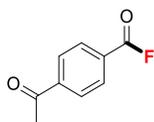
The title compound was prepared following the general Method A, using 2-iodobenzoic acid **1f** (0.5 mmol, 124 mg), PPh₃ (1 mmol, 262.3 mg), NBS (1.05 mmol, 187 mg) and 3HF-Et₃N (1 mmol, 163 μL). Purified by filtration through a short plug of silica (2 cm thick x 3 cm diameter), washing the silica plug with a hexanes (15 ml). Obtained as a white solid, 83% isolated yield (104 mg). ¹H NMR (400 MHz, CDCl₃) δ 8.14 – 8.10 (m, 1H), 8.02 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.50 (tdd, *J* = 7.4, 1.2, 0.4 Hz, 1H), 7.30 (ddd, *J* = 8.0, 7.4, 1.7 Hz, 1H). ¹⁹F NMR (376 MHz, CDCl₃) δ 28.7 (s, 1F). These spectra match the previously reported structure .

4-Bromobenzoyl fluoride (**2g**)



The title compound was prepared following the general Method A, using 4-bromobenzoic acid **1g** (0.5 mmol, 100.5 mg), PPh₃ (1 mmol, 262.3 mg), NBS (1.05 mmol, 187 mg) and 3HF-Et₃N (1 mmol, 163 μL). Purified by filtration through a short plug of silica (2 cm thick x 3 cm diameter), washing the silica plug with hexanes (20 mL). Obtained as a white solid in 67% isolated yield (68 mg). **Melting point:** 93-94 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.95 – 7.85 (m, 2H), 7.70 – 7.66 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 156.9 (d, *J* = 343.7 Hz), 132.8 (td, *J* = 5.8, 3.6 Hz), 132.7, 131.1, 124.0 (d, *J* = 62.5 Hz). ¹⁹F NMR (376 MHz, CDCl₃) δ 17.9 (s, 1F). **HRMS-ESI⁺** (M⁺) Calcd. for C₇H₄OBr = 201.9430, found = 201.9427. **FT/IR** (ν_{max} (neat) **cm⁻¹**): 2292, 2361, 1802, 1398, 1247, 1024, 1001, 914, 839, 744, 673.

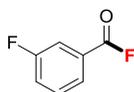
4-Acetylbenzoyl fluoride (**2h**)



The title compound was prepared in 99% yield as determined by ¹⁹F NMR following the general *Method A*, using 4-acetylbenzoic acid **1h** (0.5 mmol, 84 mg), PPh₃ (1 mmol, 262.3 mg), NBS (1.05 mmol, 187 mg) and 3HF-Et₃N (1 mmol, 163 μL). However, purification is best achieved by employing *Method B*. In this manner, the title compound

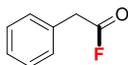
was prepared using 4-acetylbenzoic acid **1h** (0.25 mmol, 42 mg), polymer-bound PPh₃ (3 mmol/g, 166.5 mg), NBS (0.525 mmol, 94 mg) and 3HF-Et₃N (1 mmol, 82 μL). Purified by removing the resin by vacuum filtration, washed with DCM (2 mL) and hexanes (20 mL). Further addition of hexanes (10 mL) to this filtrate and stirring for 10 min, resulted in precipitation of succinimide, which was removed by filtration through a plug of celite, washing further with hexanes (5 mL). Concentration of the filtrate under reduced pressure gave **2h** as a white solid in 72% isolated yield (30 mg). **Melting point:** 201-202 °C **¹H NMR** (400 MHz, CDCl₃) δ 8.15 (d, *J* = 8.1 Hz, 2H), 8.08 (d, *J* = 8.2 Hz, 2H), 2.67 (s, 3H). **¹⁹F NMR** (376 MHz, CDCl₃) δ 19.7 (s, 1F). **¹³C NMR** (101 MHz, CDCl₃) δ 197.1, 156.6 (d, *J* = 345.6 Hz), 142.1, 131.8 (d, *J* = 3.8 Hz), 128.8, 128.7 (d, *J* = 61.8 Hz), 27.1 (d, *J* = 9.8 Hz). **HRMS-ES⁺** (M+H⁺) Calcd. for C₉H₈O₂F = 167.0508, found = 167.0508. **FT/IR** (ν_{max} (neat) **cm-1**): 2919.70, 2851.24, 2366.23, 1809.87, 1690.30, 1401.51, 1359.57, 1238.08, 1032.21, 1006.66, 754.995.

3-Fluorobenzoyl fluoride (**2i**)⁵



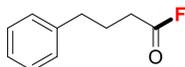
The title compound was prepared following the general Method A, using 3-fluorobenzoic acid **1i** (0.25 mmol, 35 mg), PPh₃ (0.5 mmol, 131.2 mg), NBS (0.525 mmol, 94 mg) and 3HF-Et₃N (0.5 mmol, 82 μL). The isolation of the compound was not successful due to instability to silica gel. Only yield as determined by ¹⁹F NMR is provided using *p*-tolyl-SO₂F (0.26 mmol, 45 mg) as internal standard (¹⁹F NMR: δ 65.7): **¹⁹F NMR** (376 MHz, CDCl₃) δ 18.6 (s, 1F) -111.5 (m, 1F). These spectra match the previously reported structure.

Phenylacetyl fluoride (**2j**)⁶



The title compound was prepared following the general Method A, using phenylacetic acid **1j** (0.5 mmol, 68 mg), PPh₃ (1 mmol, 262.3 mg), NBS (1.05 mmol, 187 mg) and 3HF-Et₃N (1 mmol, 163 μL). Purified by filtration through a short plug of silica (2 cm thick x 3 cm diameter), washing the silica plug with hexanes (20 mL). Obtained as a clear oil in 85% yield (58 mg). **¹H NMR** (399 MHz, CDCl₃) δ 7.41 – 7.33 (m, 3H), 7.32 – 7.27 (m, 2H), 3.82 (d, *J* = 2.5 Hz, 2H). **¹⁹F NMR** (376 MHz, CDCl₃) δ 44.4 (t, *J* = 2.4 Hz, 1F). These spectra match the previously reported structure.

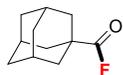
4-Phenylbutanoyl fluoride (**2k**)



The title compound was obtained following the general Method A, using phenyl butyric acid **1k** (0.5 mmol, 82.1 mg), PPh₃ (1 mmol, 262.3 mg), NBS (1.05 mmol, 187 mg) and 3HF-Et₃N (1 mmol, 163 μL). Purified by filtration through a short plug of silica (2 cm thick x 3 cm diameter), washing the silica plug with hexanes (20 mL). The filtrate was then concentrated under reduced pressure (not lower than 150 torr at 40°C) to afford a clear oil in 70% isolated

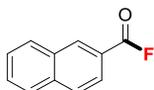
yield (58 mg). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.34 – 7.29 (m, 2H), 7.24 – 7.16 (m, 3H), 2.72 (t, $J = 7.5$ Hz, 2H), 2.52 (t, $J = 7.3$ Hz, 2H), 2.03 (p, $J = 7.4$ Hz, 2H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 163.5 (d, $J = 360.4$ Hz), 140.5, 128.7, 128.6, 126.5, 34.6, 31.4 (d, $J = 50.6$ Hz), 25.6 (d, $J = 2.0$ Hz). $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ 45.3 (s, 1F). **HRMS-EI⁺** (M^+) Calcd. for $\text{C}_{10}\text{H}_{11}\text{OF} = 166.0794$, found = 166.0795. **FT/IR** (ν_{max} (neat) **cm⁻¹**): 3030, 1836, 1707, 1490, 1457, 1217, 1094, 1024, 771, 698.

Adamantane-1-carbonyl fluoride (2l)⁷



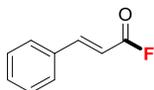
The title compound was obtained following the general Method A, using 1-adamantanecarboxylic acid **1l** (0.5 mmol, 91 mg), PPh_3 (1 mmol, 262.3 mg), NBS (1.05 mmol, 187 mg) and 3HF-Et₃N (1 mmol, 163 μL). Purified by filtration through a short plug of silica (2 cm thick x 3 cm diameter), washing the silica plug with hexanes (20 ml). Concentration of the filtrate under reduced pressure gave **2l** as a white low-melting solid in 81% isolated yield (74 mg). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 2.10 – 2.03 (m, 3H), 2.00 – 1.94 (m, 6H), 1.81 – 1.66 (m, 6H). $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ 23.4 (s, 1F). These spectra match the previously reported structure .

2-Naphthoyl fluoride (2m)⁵



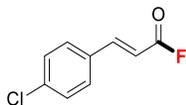
The title compound was obtained following the general procedure A, using 2-naphthoic acid **1m** (0.25 mmol, 43 mg), PPh_3 (0.5 mmol, 131.2 mg), NBS (0.525 mmol, 93.4 mg) and 3HF-Et₃N (0.5 mmol, 82 μL). Purified by filtration through a short plug of silica (2 cm thick x 3 cm diameter) washing with Hexanes (15 mL). White solid, 80% isolated yield (35.5 mg) $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.64 (s, 1H), 8.03 – 7.98 (m, 2H), 7.95 (d, $J = 11.0$ Hz, 1H), 7.93 – 7.88 (m, 1H), 7.69 (ddd, $J = 8.2, 6.8, 1.4$ Hz, 1H), 7.62 (ddd, $J = 8.2, 6.9, 1.3$ Hz, 1H). $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ 17.6 (s, 1F). These spectra match the previously reported structure.

Cinnamoyl fluoride (2n)⁸



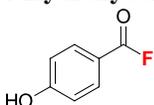
The title compound was obtained following the general Method A, using cinnamic acid **1n** (0.5 mmol, 74 mg), PPh_3 (1 mmol, 262.3 mg), NBS (1.05 mmol, 187 mg) and 3HF-Et₃N (1 mmol, 163 μL). Purified by filtration through a fritted funnel, washing the silica plug (2 cm thick x 3 cm diameter) with pentane (30 ml x2). The filtrate was then concentrated under reduced pressure (not lower than 150 torr at 40°C) to afford clear oil in 35% isolated yield (26 mg). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.84 (d, $J = 16.0$ Hz, 1H), 7.59 – 7.55 (m, 2H), 7.49 – 7.41 (m, 3H), 6.38 (dd, $J = 16.0, 7.3$ Hz, 1H). $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ 25.1 (d, $J = 7.3$ Hz, 1F). These spectra match the previously reported structure.

(E)-3-(4-Chlorophenyl)acryloyl fluoride (**2o**)



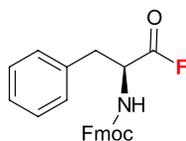
The title compound was obtained following the general Method A, using chlorocinnamic acid **1o** (0.5 mmol, 91.3 mg), PPh₃ (1 mmol, 262.3 mg), NBS (1.05 mmol, 187 mg) and 3HF-Et₃N (1 mmol, 163 μL). Purified by filtration through a short plug of silica (2 cm thick x 3 cm diameter), washing the silica plug with hexanes (20 ml). White solid, 55% isolated yield (50.1 mg). **Melting point:** 80-83 °C. **¹H NMR** (400 MHz, CDCl₃) δ 7.78 (d, *J* = 16.0 Hz, 1H), 7.53 – 7.47 (m, 2H), 7.44 – 7.37 (m, 2H), 6.34 (dd, *J* = 16.0, 7.1 Hz, 1H). **¹³C NMR** (126 MHz, CDCl₃) δ 156.9 (d, *J* = 338.7 Hz), 150.0 (d, *J* = 6.0 Hz), 138.1, 131.7, 130.0, 129.7, 112.8 (d, *J* = 67.8 Hz). **¹⁹F NMR** (376 MHz, CDCl₃) δ 25.5 (d, *J* = 7.1 Hz, 1F). **HRMS-EI⁺** (M⁺) Calcd. for C₉H₆OFCI = 184.0091, found = 184.0093. **FT/IR** (ν_{max} (neat) **cm**-1): 2963, 2923, 1786, 1630, 1592, 1491, 1408, 1306, 1178, 1086, 1012, 985, 816.

4-Hydroxybenzoyl fluoride (**2p**)⁹



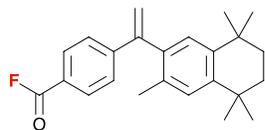
The title compound was obtained following the general Method A, using 4-hydroxybenzoic acid **1p** (0.5 mmol, 69 mg), PPh₃ (1 mmol, 262.3 mg), NBS (1.05 mmol, 187 mg) and 3HF-Et₃N (1 mmol, 163 μL). Purified by column chromatography using DCM (100%) as eluent. Obtained as a white solid in 52% isolated yield (36.4 mg). **¹H NMR** (400 MHz, CDCl₃) δ 7.97 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 7.5 Hz, 2H), 5.73 (s, 1H). **¹⁹F NMR** (376 MHz, CDCl₃) δ 15.7 (s, 1F). These spectra match the previously reported structure.

Fmoc-L-Phe-F (**2q**)¹⁰



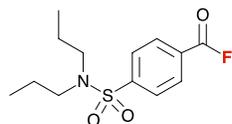
The title compound was prepared following the general Method B, using commercially available Fmoc-Phe-OH **1q** (0.5 mmol, 194 mg), polymer-bound PPh₃ (3 mmol/g, 1 mmol 333 mg), NBS (1.05 mmol, 187 mg) and 3HF-Et₃N (1 mmol, 163 μL). Purified by removing the resin by vacuum filtration, washed with DCM (2 mL) and hexanes (20 mL). Further addition of hexanes (10 mL) to this filtrate and stirring for 10 min, resulted in precipitation of succinimide, which was removed by filtration through a plug of celite, washing with hexanes (5 mL). Concentration of the filtrate under reduced pressure gave **2q** as a white solid in 50% isolated yield (97.3mg). **¹H NMR** (400 MHz, CDCl₃) δ 7.77 (d, *J* = 7.6 Hz, 2H), 7.54 (dd, *J* = 7.6, 3.4 Hz, 2H), 7.44 – 7.39 (m, 2H), 7.36 – 7.29 (m, 5H), 7.14 (d, *J* = 7.0 Hz, 2H), 5.07 (d, *J* = 8.4 Hz, 1H), 4.87 – 4.80 (m, 1H), 4.44 (qd, *J* = 10.7, 6.9 Hz, 2H), 4.21 (t, *J* = 6.7 Hz, 1H), 3.21 – 3.16 (m, 2H). **¹⁹F NMR** (376 MHz, CDCl₃) δ 30.3 (d, *J* = 2.8 Hz). The spectral data matches the previously

4-(1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)vinyl)benzoyl fluoride (Bexarotene fluoride) (2r)



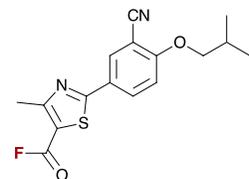
The title compound was obtained following the general Method A, using bexarotene **1r** (0.5 mmol, 174.24 mg), PPh₃ (1 mmol, 262.3 mg), NBS (1.05 mmol, 187 mg) and 3HF-Et₃N (1 mmol, 163 μL). Purified by filtration through a short plug of silica (2 cm thick x 3 cm diameter), washing the silica plug with a mixture of DCM/hexanes 1:1 (15 ml). White solid, 80% isolated yield (139.4 mg). **Melting point:** 90-94 °C. **¹H NMR** (400 MHz, CDCl₃) δ 7.99 (d, J = 8.7 Hz, 2H), 7.45 (d, J = 7.7 Hz, 2H), 7.15 (s, 1H), 7.12 (s, 1H), 5.89 (d, J = 1.2 Hz, 1H), 5.43 (d, J = 1.2 Hz, 1H), 1.97 (s, 3H), 1.73 (s, 4H), 1.34 (s, 6H), 1.31 (s, 6H). **¹³C NMR** (101 MHz, CDCl₃) δ 157.4 (d, J = 342.9 Hz), 148.9, 148.2, 144.8, 142.7, 137.6, 132.8, 131.7 (d, J = 3.7 Hz), 128.3, 128.2, 127.3, 123.7 (d, J = 61.2 Hz), 118.3, 35.3, 35.3, 34.2, 34.0, 32.1, 32.0, 20.1. **¹⁹F NMR** (376 MHz, CDCl₃) δ 17.4 (s, 1F). **HRMS-EI⁺ (M⁺)** Calcd. for C₂₄H₂₇OF = 350.2046, found = 350.2059. **FT/IR (ν_{max} (neat) cm⁻¹):** 2956, 2917, 2857, 1795, 1603, 1455, 1359, 1244, 1181, 1034, 1005, 922, 861, 774, 710

4-(N,N-dipropylsulfamoyl)benzoyl fluoride (Probenecid fluoride) (2s)



The title compound was obtained following the general Method A, using probenecid **1s** (0.5 mmol, 142.7 mg), PPh₃ (1 mmol, 262.3 mg), NBS (1.05 mmol, 187 mg) and 3HF-Et₃N (1 mmol, 163 μL). Purified by filtration through a short plug of silica (2 cm thick x 3 cm diameter), washing the silica plug with a mixture of DCM/hexanes 1:1 (10 ml). White solid, 73% isolated yield (105 mg). **Melting point:** 65-71 °C. **¹H NMR** (400 MHz, CDCl₃) δ 8.22 – 8.11 (m, 2H), 8.00 – 7.89 (m, 2H), 3.11 (t, J = 7.5 Hz, 4H), 1.55 (h, J = 7.5 Hz, 4H), 0.87 (t, J = 7.5 Hz, 6H). **¹³C NMR** (101 MHz, CDCl₃) δ 156.2 (d, J = 345.7 Hz), 146.9, 132.2 (d, J = 3.7 Hz), 128.3 (d, J = 62.5 Hz), 127.7 (d, J = 0.8 Hz), 50.1, 22.1, 11.3. **¹⁹F NMR** (376 MHz, CDCl₃) δ 19.7 (s, 1F). **HRMS-EI⁺ (M⁺)** Calcd. for C₁₃H₁₈NO₃FS = 287.099, found = 287.0995. **FT/IR (ν_{max} (neat) cm⁻¹):** 3095, 2971, 2936, 2874, 1804, 1594, 1464, 1343, 1238, 1159, 1088, 1033, 994, 859, 733, 684.

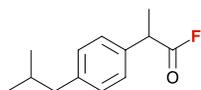
2-(3-cyano-4-isobutoxyphenyl)-4-methylthiazole-5-carbonyl fluoride (Febuxostat fluoride) (2t)



The title compound was obtained following the general Method A, using febuxostat **1t** (0.5 mmol, 158.2 mg), PPh₃ (1 mmol, 262.3 mg), NBS (1.05 mmol, 187 mg) and 3HF-Et₃N (1 mmol, 163 μL). Purified by filtration through a

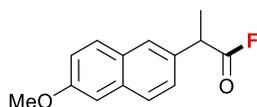
short plug of silica (2 cm thick x 3 cm diameter), washing the silica plug with a mixture of DCM/hexanes 1:1 (10 ml). White solid, 69% isolated yield (110 mg). **Melting point:** 145-150 °C. **¹H NMR** (400 MHz, CDCl₃) δ 8.18 (dd, J = 2.4, 0.9 Hz, 1H), 8.08 (dd, J = 8.8, 2.2 Hz, 1H), 7.03 (d, J = 8.9 Hz, 1H) 3.89 (d, J = 6.5 Hz, 2H), 2.75 (s, 3H), 2.18 (dt, J = 13.3, 6.6 Hz, 1H), 1.07 (d, J = 6.8 Hz, 6H). **¹³C NMR** (101 MHz, CDCl₃) δ 170.87, 166.79 (d, J = 6.7 Hz), 163.31, 152.12 (d, J = 329.4 Hz), 133.10, 132.64, 125.38, 115.98 (d, J = 70.0 Hz), 115.33, 112.96, 103.42, 76.01, 28.33, 19.22, 17.97 (d, J = 2.1 Hz). **¹⁹F NMR** (376 MHz, CDCl₃) δ 37.1 (s, 1F). **HRMS-EI⁺ (M⁺)** Calcd. for C₁₆H₁₅N₂O₂FS = 318.0838, found = 318.0847. **FT/IR (ν_{max} (neat) cm⁻¹):** 3015, 3013, 2955, 1974, 1621, 1602, 1533, 1479, 1383, 1370, 1346, 1217, 1214, 987, 771, 769.

2-(4-isobutylphenyl)propionyl fluoride (Ibuprofen fluoride) (2u)



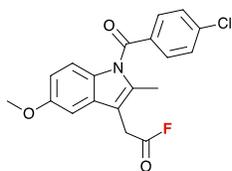
The title compound was obtained following the general Method A, using ibuprofen **1u** (0.5 mmol, 103.15 mg), PPh₃ (1 mmol, 262.3 mg), NBS (1.05 mmol, 187 mg) and 3HF-Et₃N (1 mmol, 163 μL). Diluted with pentane and purified by filtration through a short plug of silica (2 cm thick x 3 cm diameter), washing the silica plug with a mixture of DCM/hexanes 1:1 (10 ml). Concentrated under reduced pressure at 36°C, 200 torr (volatile). Light yellow oil, 91% isolated yield (95 mg). **¹H NMR** (400 MHz, CDCl₃) δ 7.23 (d, J = 8.2 Hz, 2H), 7.17 (d, J = 8.8 Hz, 2H), 3.86 (q, J = 7.2 Hz, 1H), 2.50 (d, J = 7.1 Hz, 2H), 1.96 – 1.82 (m, 1H), 1.60 (dd, J = 7.2, 0.9 Hz, 3H), 0.93 (d, J = 6.6 Hz, 6H). **¹³C NMR** (101 MHz, CDCl₃) δ 164.7 (d, J = 367.3 Hz), 141.9, 134.9 (d, J = 0.7 Hz), 130.0, 127.5, 45.2, 44.1 (d, J = 49.3 Hz), 30.4, 22.6, 18.3 (d, J = 1.4 Hz). **¹⁹F NMR** (376 MHz, CDCl₃) δ 38.7 (s, 1F). **HRMS-EI⁺ (M⁺)** Calcd. for C₁₃H₁₇OF = 208.1263, found = 208.1254. **FT/IR (ν_{max} (neat) cm⁻¹):** 3023, 2954, 2922, 1832, 1510, 1457, 1215, 1122, 1050, 923, 889, 769, 748, 667.

2-(6-methoxynaphthalen-2-yl)propionyl fluoride (Naproxen fluoride) (2v)



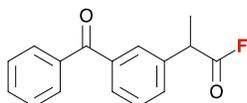
The title compound was obtained following the general Method A, using naproxen **1v** (0.5 mmol, 115.15 mg), PPh₃ (1 mmol, 262.3 mg), NBS (1.05 mmol, 187 mg) and 3HF-Et₃N (1 mmol, 163 μL). Purified by filtration through a short plug of silica (2 cm thick x 3 cm diameter), washing the silica plug with a mixture of DCM/hexanes 1:1 (20 ml). White solid, 69% isolated yield (80 mg). **Melting point:** 75-79 °C. **¹H NMR** (400 MHz, CDCl₃) δ 7.76 (d, J = 21.1 Hz, 1H), 7.74 (d, J = 3.6 Hz, 1H), 7.68 (d, J = 1.9 Hz, 1H), 7.37 (dd, J = 8.5, 1.9 Hz, 1H), 7.17 (dd, J = 8.9, 2.6 Hz, 1H), 7.13 (d, J = 2.6 Hz, 1H), 4.00 (q, J = 7.1 Hz, 1H), 3.93 (s, 3H), 1.67 (dd, J = 7.2, 0.9 Hz, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 164.6 (d, J = 367.3 Hz), 158.2, 134.3, 132.5 (d, J = 0.8 Hz), 129.5, 129.0, 127.9, 126.6, 125.9, 119.6, 105.8, 55.5, 44.4 (d, J = 49.5 Hz), 18.3. **¹⁹F NMR** (376 MHz, CDCl₃) δ 39.1 (s, 1F). **HRMS-EI⁺ (M⁺)** Calcd. for C₁₄H₁₃O₂F = 232.0900, found = 232.0909. **FT/IR (ν_{max} (neat) cm⁻¹):** 3019, 2987, 2941, 2849, 1822, 1602, 1388, 1265, 1226, 1127. 1059, 1024, 852, 823, 674.

2-[1-(4-chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]acetyl fluoride (Indomethacin fluoride) (2w)⁷



The title compound was obtained following the general Method A, using indomethacin **1w** (0.5 mmol, 178.90 mg), PPh₃ (1 mmol, 262.3 mg), NBS (1.05 mmol, 187 mg) and 3HF-Et₃N (1 mmol, 163 μ L). Purified by filtration through a short plug of silica (2 cm thick x 3 cm diameter), washing the silica plug with a mixture of EtOAc/hexanes 1:1 (10 ml). White solid, 61% isolated yield (108 mg). ¹H NMR (400 MHz, CDCl₃) δ 7.72 – 7.59 (m, 2H), 7.52 – 7.39 (m, 2H), 6.88 (d, J = 2.5 Hz, 1H), 6.84 (d, J = 9.1 Hz, 1H), 6.70 (dd, J = 9.0, 2.5, 1H), 3.87 (d, J = 2.6 Hz, 2H), 3.84 (s, 3H), 2.41 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 168.4, 160.7 (d, J = 363.9 Hz), 156.4, 139.8, 137.0, 133.7, 131.5, 130.9, 130.0, 129.4, 115.3, 112.3, 109.4 (d, J = 2.2 Hz), 100.9, 56.0, 28.5 (d, J = 58.0 Hz), 13.4. ¹⁹F NMR (376 MHz, CDCl₃) δ 43.9 (s, 1F). FT/IR (ν_{\max} (neat) **cm-1**): 3060, 2923, 1830, 1680, 1595, 1464, 1350, 1322, 1233, 1211, 1152, 1065, 1034, 1015, 908, 851, 754. The spectral data matches the previously reported product

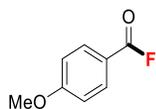
2-(3-benzoylphenyl)propionyl fluoride (Ketoprofen fluoride) (2x)



The title compound was obtained following the general Method A, using ketoprofen **1x** (0.5 mmol, 127.15 mg), PPh₃ (1 mmol, 262.3 mg), NBS (1.05 mmol, 187 mg) and 3HF-Et₃N (1 mmol, 163 μ L). Purified by filtration through a short plug of silica (2 cm thick x 3 cm diameter), washing the silica plug with a mixture of DCM/hexanes 1:1 (20 ml). Concentrated under reduced pressure at 36°C, 200 torr (volatile). Light yellow oil, 78% isolated yield (100 mg). ¹H NMR (399 MHz, CDCl₃) δ 7.82 – 7.78 (m, 2H), 7.76 (t, J = 1.9 Hz, 1H), 7.74 (dt, J = 7.2, 1.6 Hz, 1H), 7.64 – 7.59 (m, 1H), 7.56 – 7.47 (m, 4H), 3.96 (q, J = 7.2 Hz, 1H), 1.64 (dd, J = 7.2, 0.9 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 196.3, 164.0 (d, J = 367.2 Hz), 138.6, 138.0, 137.4, 132.9, 131.6, 130.3, 130.1, 129.4, 129.2, 128.6, 44.3 (d, J = 49.8 Hz), 18.2. ¹⁹F NMR (376 MHz, CDCl₃) δ 38.7 (s, 1F). HRMS-EI⁺ (M⁺) Calcd. for C₁₆H₁₃O₂F = 256.0900, found = 256.0910. FT/IR (ν_{\max} (neat) **cm-1**): 3259, 3058, 2978, 2934, 2877, 1834, 1736, 1704, 1656, 1596, 1579, 1447, 1315, 1281, 719, 700.

Scale-up procedure for the synthesis of 2c

4-Methoxybenzoyl fluoride (2c)¹¹

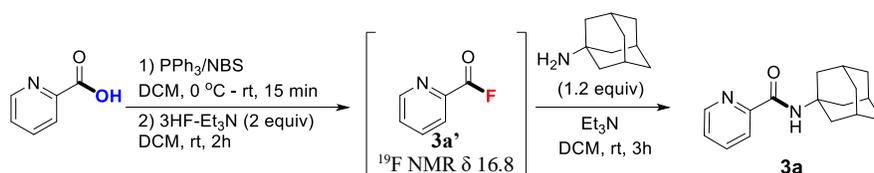


For a 10 mmol (1.521 g) scale reaction, the title compound was obtained following the general Method A, using *p*-anisic acid **1c** (10 mmol, 1.521 g), PPh₃ (20 mmol, 5.25 g), NBS (21 mmol, 3.74 g) and 3HF-Et₃N (20 mmol, 3.3 mL). The product was purified by filtration through a short plug of silica, washing with a mixture of

hexanes/EtOAc (20 mL, 20:1, v:v, 2 times); the isolated yield was 70% (1.08 g). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.99 (d, $J = 8.9$ Hz, 2H), 6.98 (d, $J = 8.8$ Hz, 2H), 3.90 (s, 3H). $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ 15.4 (s, 1F). These data match the previously reported structure .

Procedure for the tandem deoxofluorination/amide-bond formation sequence (Scheme 5)

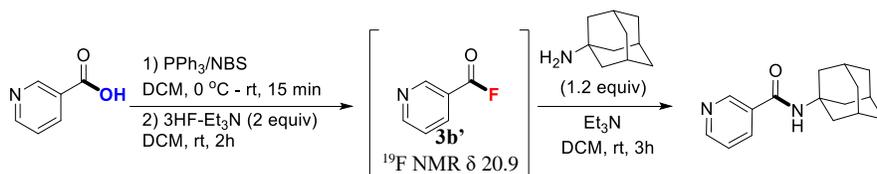
N-(Adamantan-1-yl)picolinamide (**3a**)¹²



On the bench-top, picolinic acid (1 equiv, 0.5 mmol, 61.5 mg) and triphenylphosphine, PPh_3 (2 equiv, 1 mmol, 262.3 mg) and anhydrous DCM (5 mL) were charged into an oven-dried screw-cap vial equipped with a magnetic stir bar. The vial was capped, and this mixture was then cooled to 0 °C using an ice-bath. Subsequently, *N*-bromosuccinimide, NBS (2.1 equiv, 1.05 mmol, 187 mg) was added as a solid in one portion, the vial was re-capped, and the mixture was kept in the ice-bath for two minutes. After this time, the ice-bath was removed, and this solution was further stirred for 15 min. After this time, 3HF- Et_3N (2 equiv, 1 mmol, 163 μL) was added via micropipette and the mixture was stirred further for 2 h at room temperature. After this time, the vial was opened, and a pre-mixed solution of adamantan-1-amine (1.2 equiv, 0.6 mmol, 91 mg) and Et_3N (10 equiv, 5 mmol, 697 μL) in anhydrous DCM (1 mL) was added at room temperature and the mixture was further stirred for 3h. After this time, the mixture was diluted with DCM and passed through a plug of celite. The filtrate was poured into H_2O (50 mL) and extracted with DCM (20 mL, 3 times). The aqueous layer was acidified (1N HCl) and extracted again with DCM (10 mL, 2 times). The organic layers were combined, washed with NaHCO_3 (aq. saturated), brine, dried over MgSO_4 and concentrated. The residue was purified by flash column chromatography using EtOAc in hexanes (gradient from 0% to 16%). *N*-(Adamantan-1-yl)picolinamide (**3a**) was obtained as a white solid in 91% yield (117 mg). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.91 – 8.90 (m, 1H), 8.71 – 8.69 (m, 1H), 8.09 – 8.01 (m, 1H), 7.39 – 7.34 (m, 1H), 5.78 (br. s, 1H), 2.14 (br. s, 6H), 1.73 (br. s, 6H), 1.58 (br. s, 3H). The spectral data matches the previously reported product.

***(3a') NMR Yield Determination:** In a separate experiment picolinoyl fluoride **3a'** was prepared in 95% as determined by $^{19}\text{F NMR}$ spectroscopy with *p*-Tolyl SO_2F (0.26 mmol) as internal standard, following general method A using picolinic acid (1 equiv, 0.25 mmol, 30.7 mg), triphenylphosphine, PPh_3 (2 equiv, 1 mmol, 131.2 mg), NBS (2.1 equiv, 1.05 mmol, 94 mg), anhydrous DCM (2.5 mL) and 3HF- Et_3N (2 equiv, 1 mmol, 82 μL). However, its isolation was unsuccessful due to instability $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ 16.8 (s, 1F).

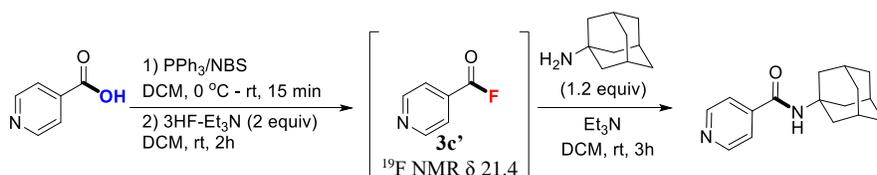
N-(Adamantan-1-yl)nicotinamide (**3b**)¹³ (Scheme 5)



On the bench-top, nicotinic acid (1 equiv, 0.5 mmol, 61.5 mg) and triphenylphosphine, PPh₃ (2 equiv, 1 mmol, 262.3 mg) and anhydrous DCM (5 mL) were charged into an oven-dried screw-cap vial equipped with a magnetic stir bar. The vial was capped, and this mixture was then cooled to 0 °C using an ice-bath. Subsequently, *N*-bromosuccinimide, NBS (2.1 equiv, 1.05 mmol, 187 mg) was added as a solid in one portion, the vial was re-capped, and the mixture was kept in the ice-bath for two minutes. After this time, the ice-bath was removed, and this solution was further stirred for 15 min. After this time, 3HF-Et₃N (2 equiv, 1 mmol, 163 uL) was added via micropipette and the mixture was stirred further for 2 h at room temperature. After this time, the vial was opened, and a pre-mixed solution of adamantan-1-amine (1.2 equiv, 0.6 mmol, 91 mg) and Et₃N (10 equiv, 5 mmol, 697 uL) in anhydrous DCM (1 mL) was added at room temperature and the mixture was further stirred for 3h. After this time, the mixture was diluted with DCM and passed through a plug of celite. The filtrate was poured into H₂O (50 mL) and extracted with DCM (20 mL, 3 times). The aqueous layer was acidified (1N HCl) and extracted again with DCM (10 mL, 2 times). The organic layers were combined, washed with NaHCO₃ (aq. saturated), brine, dried over MgSO₄ and concentrated. The residue was purified by flash column chromatography using EtOAc in hexanes (gradient from 0% to 16%). *N*-(Adamantan-1-yl)nicotinamide (**3b**) was obtained as a white solid in 83% yield (106.4 mg). ¹H NMR (400 MHz, CDCl₃) δ 8.50 (t, J = 5.0, 1.0 Hz, 1H), 8.16 (d, J = 7.8 Hz, 1H), 7.88 (br. s, 1H), 7.82 (td, J = 7.7, 1.7 Hz, 1H), 7.38 (ddd, J = 7.7, 4.7, 1.3 Hz, 1H), 2.15 (br. s, 6H), 2.12 (br. s, 3H), 1.73 (t, J = 15.0 Hz, 6H). The spectral data matches the previously reported product.

(3b') *NMR Yield Determination: In a separate experiment nicotinoyl fluoride **3b'** was prepared in 97% as determined by ¹⁹F NMR spectroscopy, with *p*-TolylSO₂F (0.26 mmol) as internal standard, following General Method A using nicotinic acid (1 equiv, 0.25 mmol, 30.7 mg), triphenylphosphine, PPh₃ (2 equiv, 1 mmol, 131.2 mg), NBS (2.1 equiv, 1.05 mmol, 94 mg), anhydrous DCM (2.5 mL) and 3HF-Et₃N (2 equiv, 1 mmol, 82 uL). However, its isolation was unsuccessful due to instability. ¹⁹F NMR (376 MHz, CDCl₃) δ 20.9 (s, 1F)

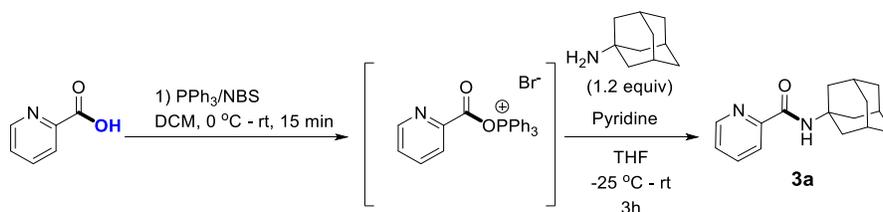
N-(Adamantan-1-yl)isonicotinamide (**3c**)¹⁴ (Scheme 5)



On the bench-top, isonicotinic acid (1 equiv, 0.5 mmol, 61.5 mg) and triphenylphosphine, PPh₃ (2 equiv, 1 mmol, 262.3 mg) and anhydrous DCM (5 mL) were charged into an oven-dried screw-cap vial equipped with a magnetic stir bar. The vial was capped, and this mixture was then cooled to 0 °C using an ice-bath. Subsequently, *N*-bromosuccinimide, NBS (2.1 equiv, 1.05 mmol, 187 mg) was added as a solid in one portion, the vial was re-capped, and the mixture was kept in the ice-bath for two minutes. After this time, the ice-bath was removed, and this solution was further stirred for 15 min. After this time, 3HF-Et₃N (2 equiv, 1 mmol, 163 uL) was added via micropipette and the mixture was stirred further for 2 h at room temperature. After this time, the vial was opened, and a pre-mixed solution of adamantan-1-amine (1.2 equiv, 0.6 mmol, 91 mg) and Et₃N (10 equiv, 5 mmol, 697 uL) in anhydrous DCM (1 mL) was added at room temperature and the mixture was further stirred for 3h. After this time, the mixture was diluted with DCM and passed through a plug of celite. The filtrate was poured into H₂O (50 mL) and extracted with DCM (20 mL, 3 times). The aqueous layer was acidified (1N HCl) and extracted again with DCM (10 mL, 2 times). The organic layers were combined, washed with NaHCO₃ (aq. saturated), brine, dried over MgSO₄ and concentrated. The residue was purified by flash column chromatography using EtOAc in hexanes (gradient from 0% to 16%). *N*-(Adamantan-1-yl)isonicotinamide (**3c**) was obtained as a white solid in 73% yield (94 mg). ¹H NMR (400 MHz, CDCl₃) δ 8.69 (d, J = 5.8 Hz, 2H), 7.53 (d, J = 5.7 Hz, 2H), 5.78 (br. s, 1H), 2.10 (br. s, 6H), 1.71 (br. s, 6H), 1.57 (s, 3H). The spectral data matches the previously reported product.

(3c') *NMR Yield Determination: In a separate experiment isonicotinoyl fluoride **3c'** was prepared in 94% as determined by ¹⁹F NMR spectroscopy, with *p*-TolylSO₂F (0.26 mmol) as internal standard, following General Method A using isonicotinic acid (1 equiv, 0.25 mmol, 30.7 mg), triphenylphosphine, PPh₃ (2 equiv, 1 mmol, 131.2 mg), NBS (2.1 equiv, 1.05 mmol, 94 mg), anhydrous DCM (2.5 mL) and 3HF-Et₃N (2 equiv, 1 mmol, 82 uL). However, its isolation was unsuccessful due to instability. ¹⁹F NMR (376 MHz, CDCl₃) δ 21.4 (s, 1F)

Preparation of *N*-(Adamantan-1-yl)picolinamide (**3a**) via acyloxyphosphonium ion (Scheme 5)



For comparison, the title compound was also prepared using the previously reported optimized reaction conditions¹⁵ for amide synthesis via acyloxyphosphonium ions. On the bench-top, picolinic acid (1 equiv, 0.5 mmol, 61.5 mg) and triphenylphosphine, PPh₃ (1 equiv, 0.5 mmol, 131.2 mg) and anhydrous DCM (2.5 mL) were charged into an oven-dried screw-cap vial equipped with a magnetic stir bar. The vial was capped, and this mixture was then cooled to 0 °C using an ice-bath. Subsequently, *N*-bromosuccinimide, NBS (1.1 equiv, 0.55 mmol, 98 mg) was added as a solid in one portion, the vial was re-capped, and the mixture was kept in the ice-bath for two minutes. After this time, the ice-bath was removed, and this solution was further stirred for 15 min. Subsequently, a pre-mixed solution of adamantan-1-amine (1.2 equiv, 0.6 mmol, 91 mg) and anhydrous pyridine (1.3 equiv, 0.65 mmol, 52 uL) in anhydrous THF (1 mL) was added dropwise at -25 °C. After addition was complete, the mixture was left stirring while slowly warmed to room temperature and further stirred for 3 h. After this time, the mixture was diluted with

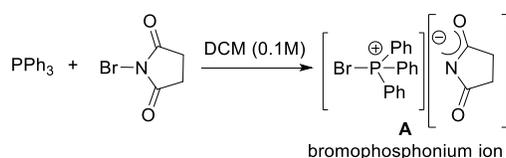
DCM (10 mL) and washed with H₂O (10 mL). The organic phase was separated, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by column chromatography to afford *N*-(Adamantan-1-yl)picolinamide (**3a**) as a white solid in 26% yield (33 mg). NMR spectroscopic data was identical to the product obtained by our method, using in situ formed acyl fluoride as acylating agent. This result demonstrates the superiority of acyl fluorides for amidation reactions using sterically encumbered amines.

Mechanistic Studies

Identification of reaction intermediates by NMR spectroscopic studies

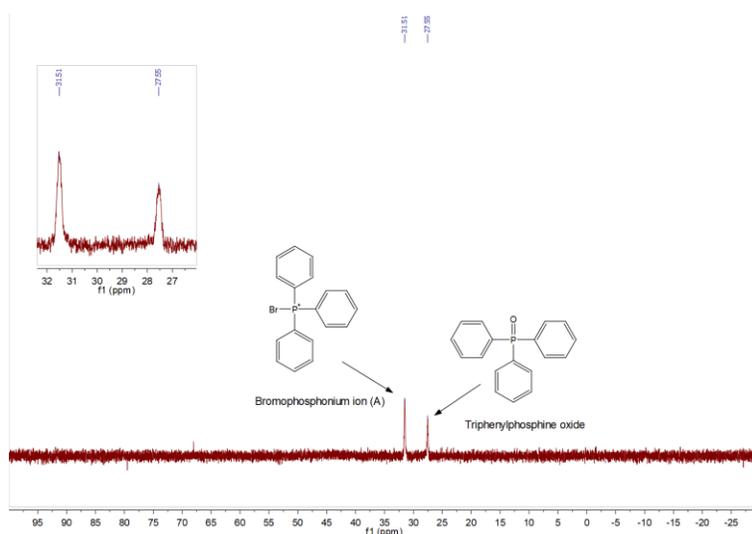
To gain insight into the mechanism of the present transformation, the following control experiments were conducted.

Control experiment 1

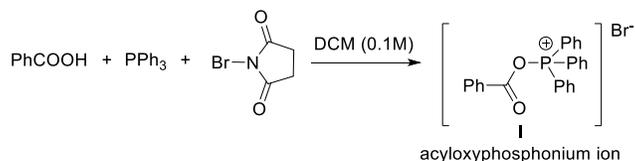


On the bench-top, triphenylphosphine, PPh₃ (0.5 mmol, 131.2 mg) was charged into an oven-dried crimp-top vial equipped with a magnetic stir bar. This vial was sealed with a septum, evacuated and backfilled with nitrogen 3 times. After this, anhydrous dichloromethane, DCM (2.5 mL) was added under a stream of nitrogen. This mixture was then cooled to 0 °C using an ice-bath. Subsequently, *N*-bromosuccinimide, NBS (2.1 equiv, 0.525 mmol, 94 mg) dissolved in anhydrous DCM (2.5 mL) was added via syringe at 0 °C. After stirring for 2 min an immediate color change was observed and an aliquot (1 mL) was taken for NMR analysis. The ³¹P NMR spectrum showed two new signals at δ 27.5 and δ 31.5, which were assigned to OPPh₃ and bromophosphonium ion **A**, respectively. In this case, we surmise that triphenyl phosphine oxide is formed due to hydrolysis of **A** by adventitious H₂O present in the system. (Figure S1).

Figure S1. ³¹P NMR spectrum after addition NBS to vial containing PPh₃.

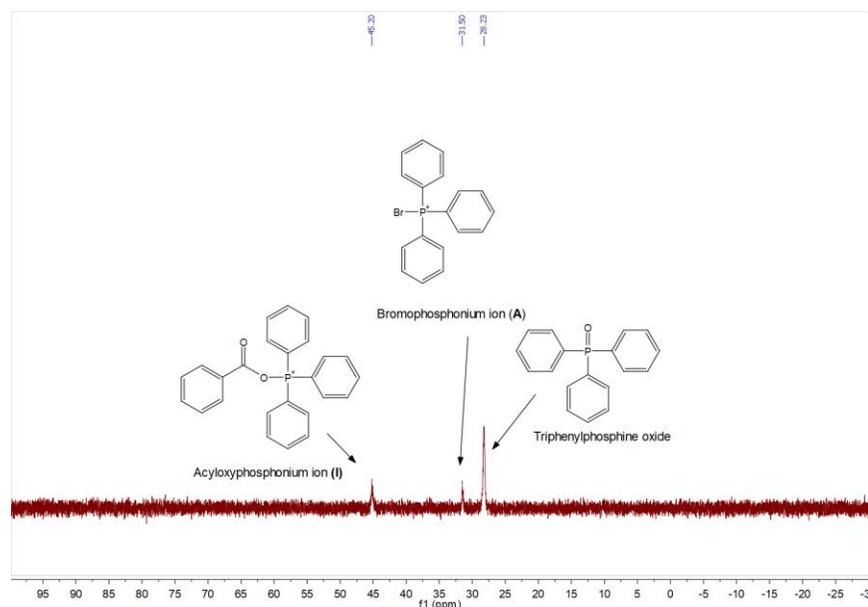


Control experiment 2



In a separate experiment, benzoic acid **1a** (0.25 mmol, 30.5 mg) and triphenylphosphine, PPh₃ (0.5 mmol, 131.2 mg) were charged into a crimp-top vial equipped with a magnetic stir bar. This vial was sealed with a septum, evacuated and backfilled with nitrogen 3 times. After this, anhydrous dichloromethane, DCM (2.5 mL) was added under a stream of nitrogen. This mixture was then cooled to 0 °C using an ice-bath. Subsequently, *N*-bromosuccinimide, NBS (2.1 equiv, 0.525 mmol, 94 mg) dissolved in anhydrous DCM (2.5 mL) was added via syringe at 0 °C. After stirring for 2 min an immediate color change was observed and an aliquot (1 mL) was taken for NMR analysis. The ³¹P NMR spectrum showed three signals at δ 28.2, δ 31.5 and δ 45.2 which were assigned to triphenylphosphine oxide, residual bromophosphonium ion **A** and acyloxyphosphonium ion **I**, respectively (Figure S2).

Figure S2. ³¹P NMR spectrum after addition of NBS to mixture of **1a** and PPh₃.



After this time, 3HF-Et₃N (2 equiv, 0.5 mmol, 82 μL) was added via syringe to the vial containing **I**. This mixture was stirred for 5 min, before taking a aliquot (1 mL) for NMR analysis. The ³¹P NMR spectrum showed a single peak at δ 29.2, corresponding to triphenylphosphine oxide (Figure S3A), while the ¹⁹F NMR spectrum showed three signals at δ 17.4, δ -39.6 (d, 660.8 Hz, P-F coupling) and δ -172.3, assigned as benzoyl fluoride **2a**, Ph₃PF₂ and residual HF (Figure S3B).

Figure S3A. ^{31}P NMR spectrum after addition of 3HF-Et $_3\text{N}$ to vial containing acyloxyphosphonium ion I.

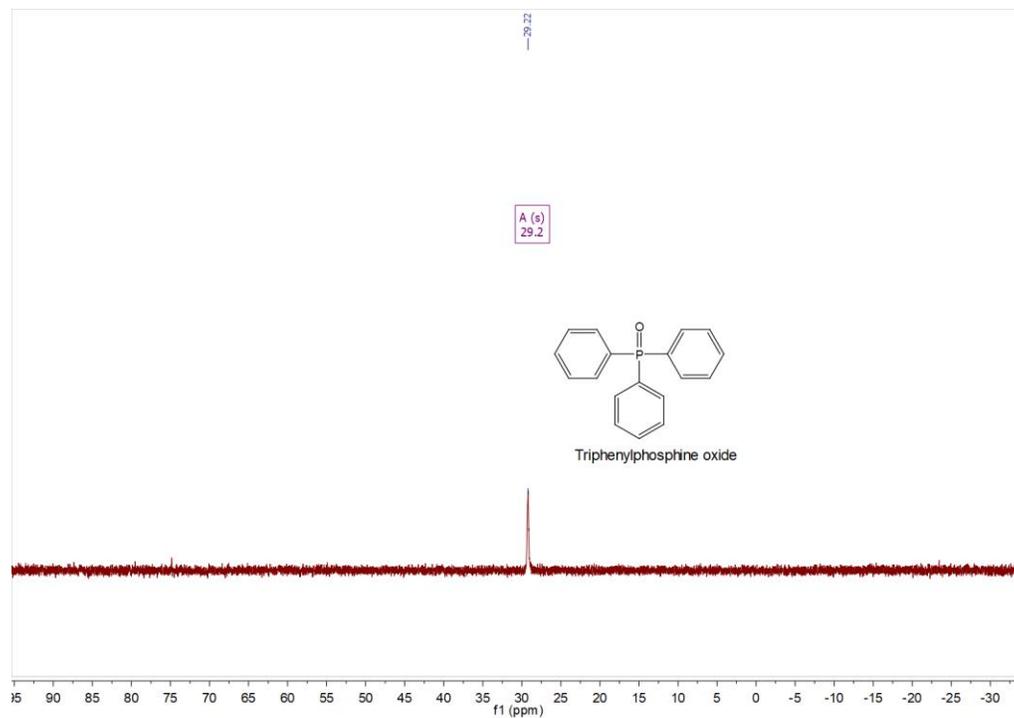
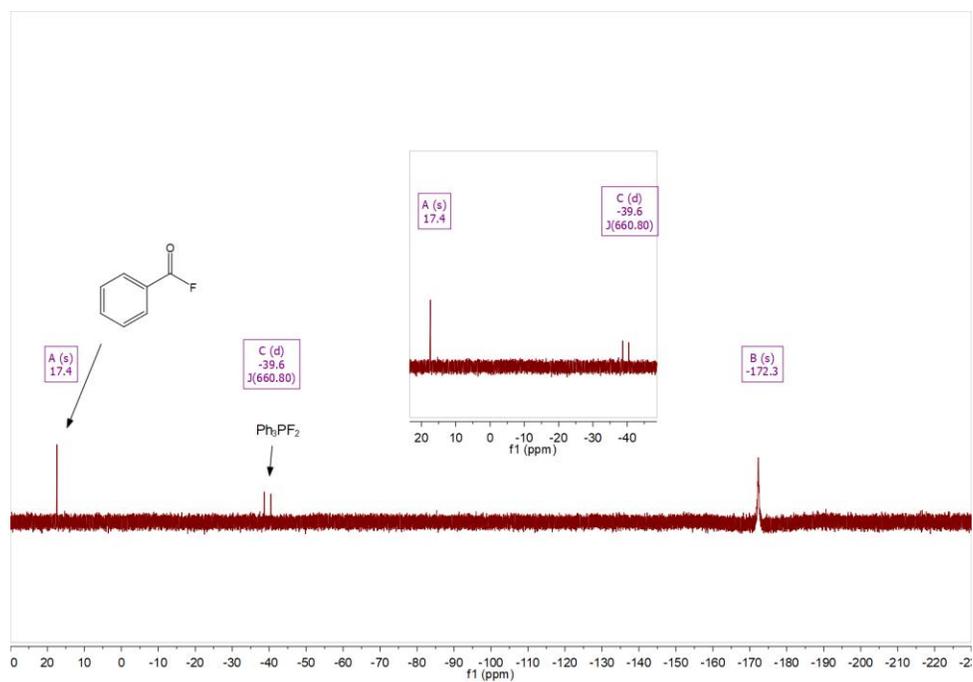
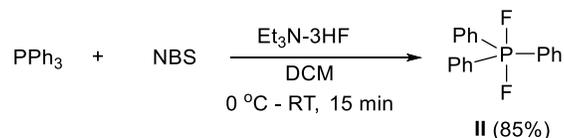


Figure S3B. ^{19}F NMR spectrum after addition of 3HF-Et $_3\text{N}$ to vial containing acyloxyphosphonium ion I.



Control Experiment 3



On the bench top, triphenylphosphine, PPh₃ (1 equiv, 0.5 mmol, 131.2 mg) was charged into a vial equipped with a magnetic stir bar. To this vial 3HF-Et₃N (0.5 mmol, 82 uL) was added via micropipette followed by anhydrous dichloromethane, DCM (2.5 mL). This mixture was then cooled to 0 °C using an ice-bath. Subsequently, *N*-bromosuccinimide, NBS (0.525 mmol, 94 mg) was added as a solid at 0 °C. This mixture was stirred and allowed to slowly warm up to room temperature over 15 min. After this time internal standard, *p*-toluenesulfonyl fluoride (87 mg, 0.5 mmol, 1 equiv) dissolved in anhydrous DCM (1 mL) was added and the mixture was stirred for 2 min. After this time, an aliquot (1 mL) was taken and ¹⁹F NMR (Figure S4A) and ³¹P NMR (Figure S4B) spectroscopic analysis. Triphenyldifluorophosphorane **II** formed in 85% yield, as determined by ¹⁹F NMR. The ³¹P NMR spectrum showed two signals at δ 31.7 (s) and at -57.5 (t, J = 659.0 Hz), which were assigned to triphenylphosphine oxide and Ph₃PF₂ **II**, respectively.

Figure S4A. ¹⁹F NMR spectrum after formation of species **II**

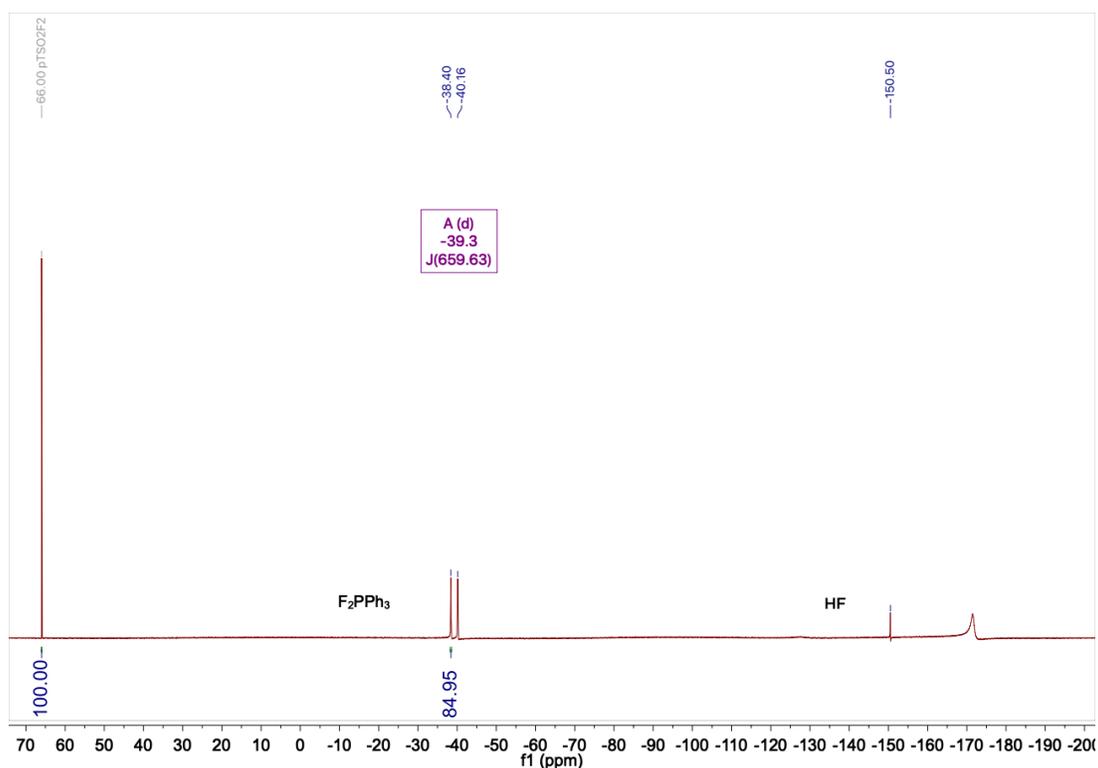
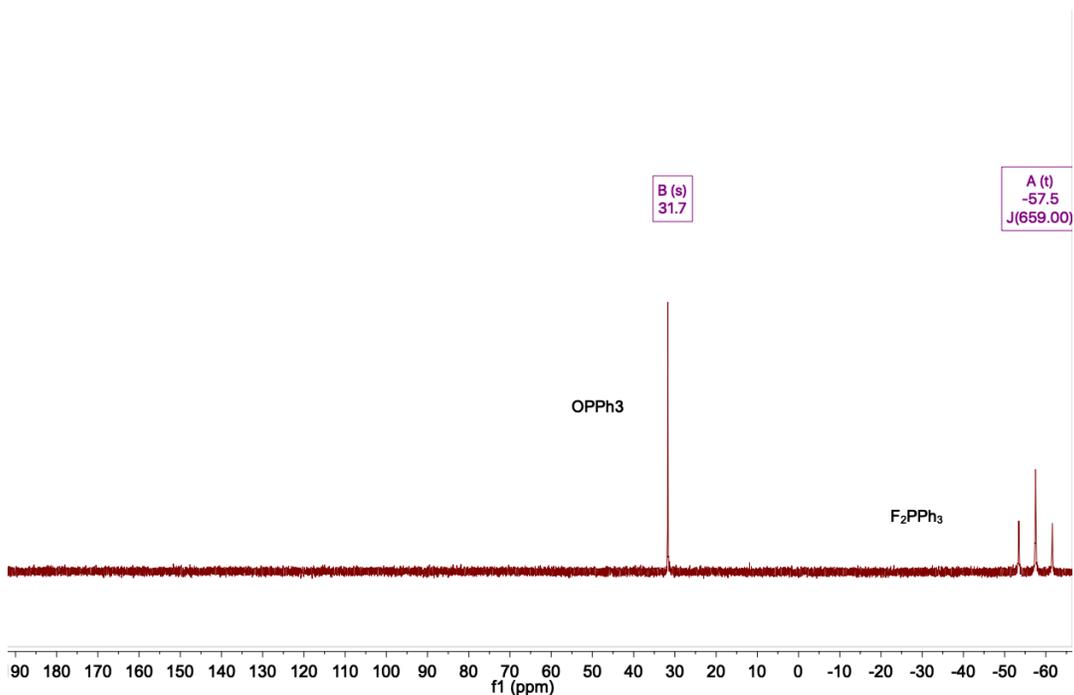
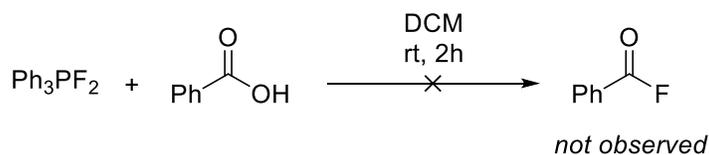


Figure S4B. ^{31}P NMR spectrum after formation of species **II**



Control Experiment 4



To Ph_3PF_2 , **II** generated exactly as in control experiment 3, benzoic acid **1a** (0.25 mmol, 30.5 mg) was added and this mixture was stirred further for 2 h at room temperature. After this time, internal standard, *p*-toluenesulfonyl fluoride (87 mg, 0.5 mmol) dissolved in anhydrous DCM (1 mL) was added and the mixture was stirred for 2 min. After this time, an aliquot (1 mL) was taken for ^{19}F NMR (Figure S5A) and ^{31}P NMR (Figure S5B) spectroscopic analysis. ^{19}F NMR spectrum showed no signal of the acyl fluoride or the intermediate **II**. The ^{31}P NMR spectrum only shows one signal at δ 31.9 representing triphenylphosphine oxide. This experiment showed that Ph_3PF_2 , **II** is not the species responsible for the observed deoxyfluorination, further lending support to the proposed mechanistic hypothesis via acyloxyphosphonium ion **I**. We surmised that Ph_3PF_2 **II** generated in this way, could be hydrolyzed to OPPh_3 by adventitious water present in the system. Ph_3PF_2 is known to be a highly moisture sensitive species.¹⁶

Figure S5A. ^{19}F NMR spectrum after addition of benzoic acid (**1a**)

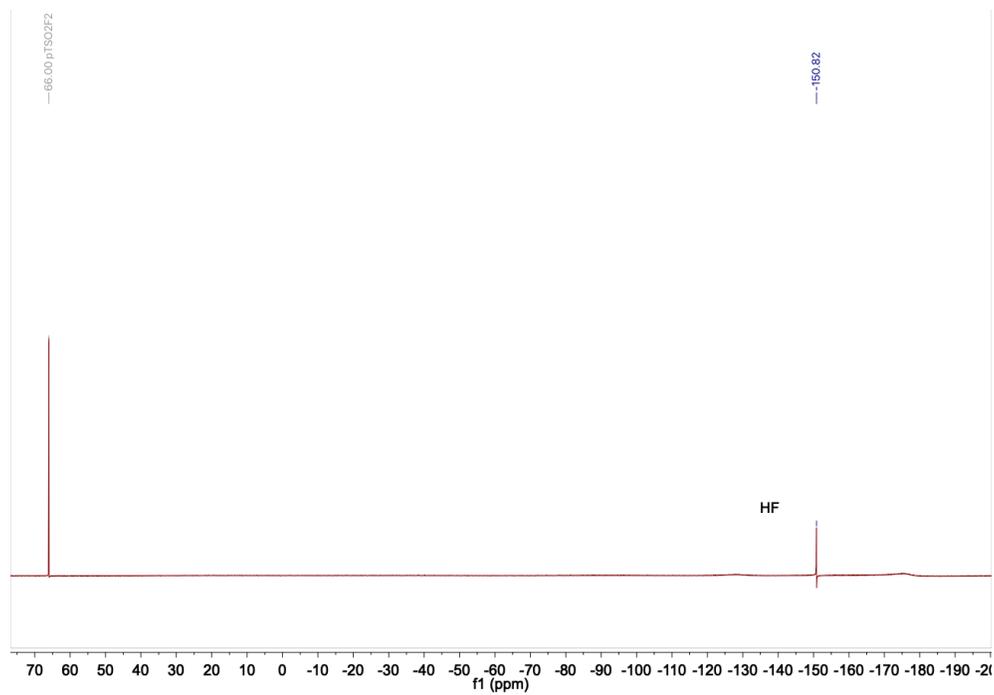
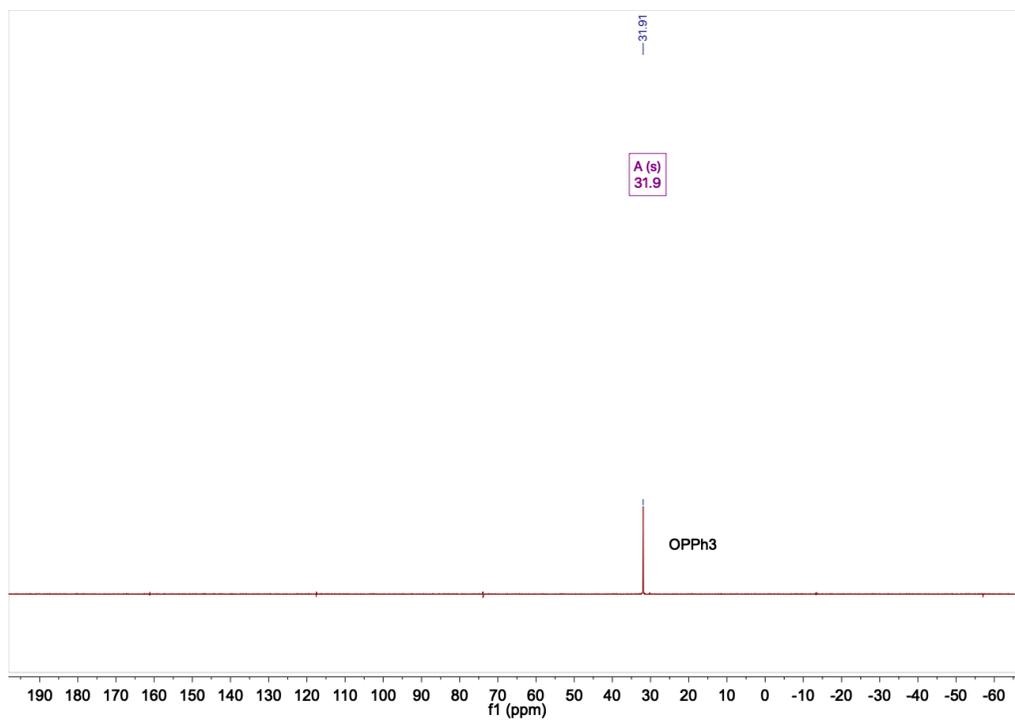


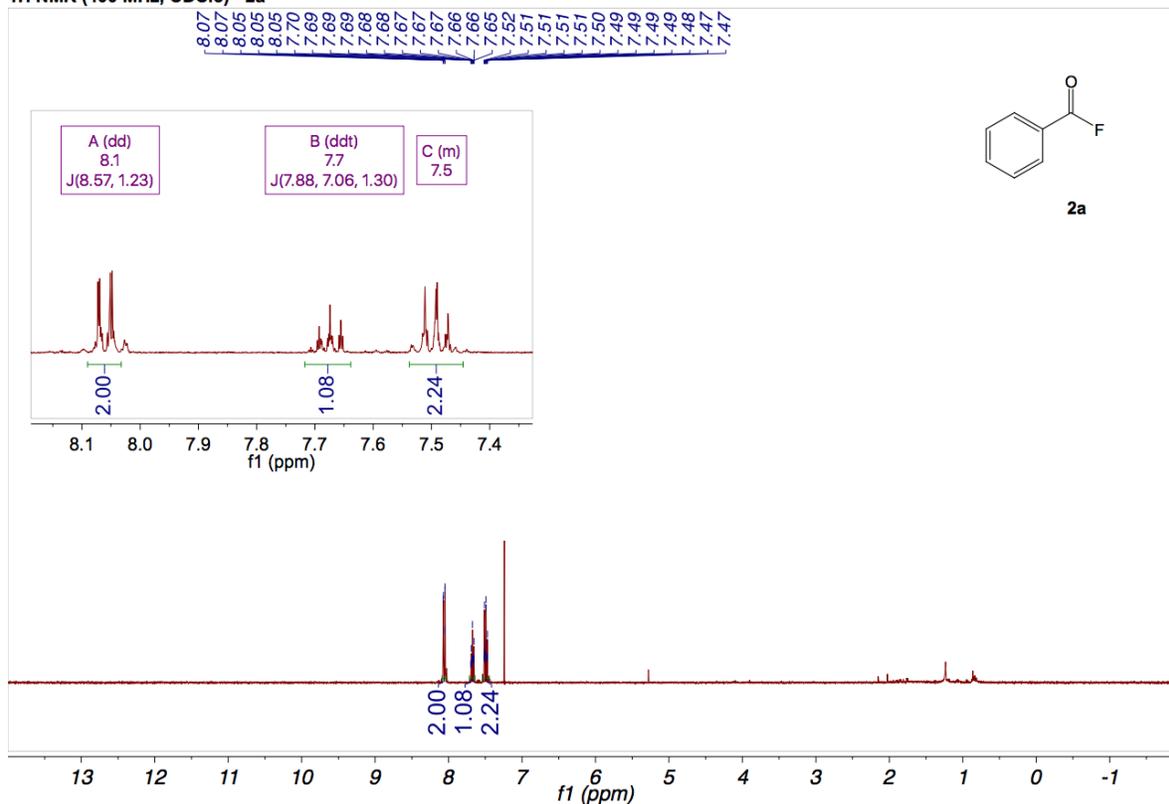
Figure S5B. ^{31}P NMR spectrum after addition of benzoic acid (**1a**)



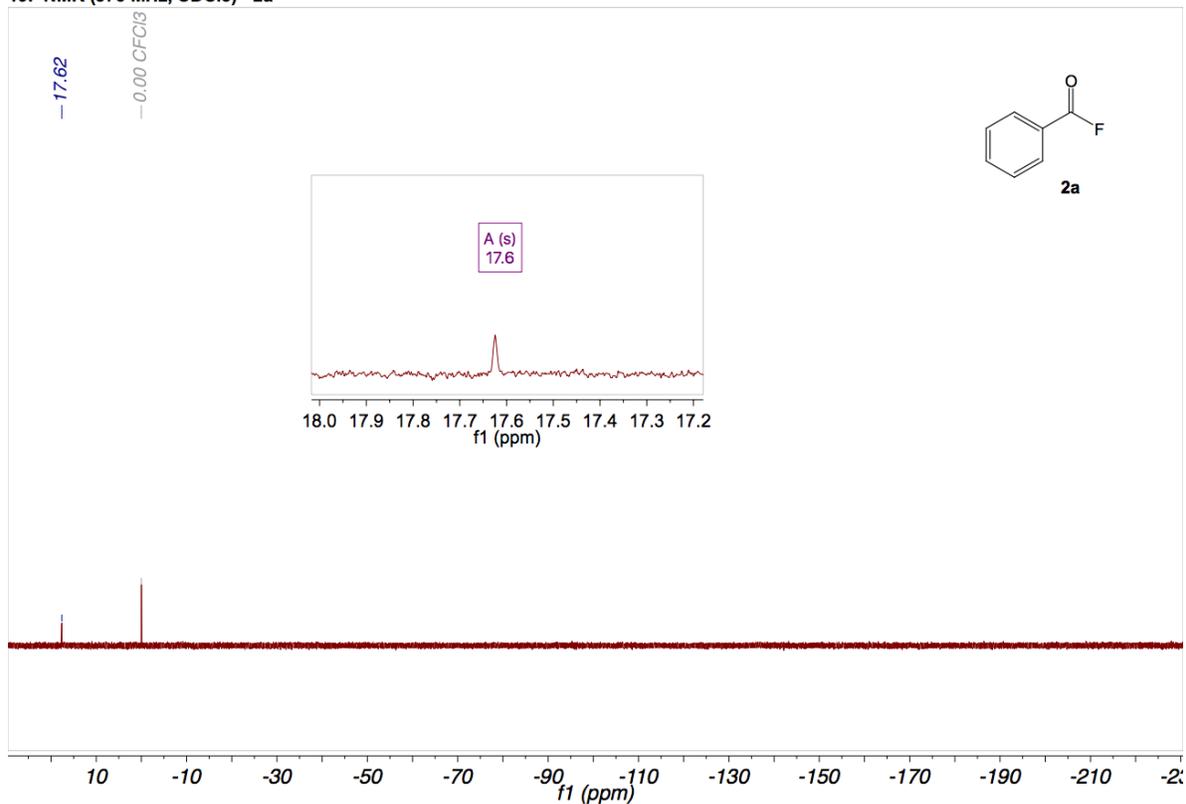
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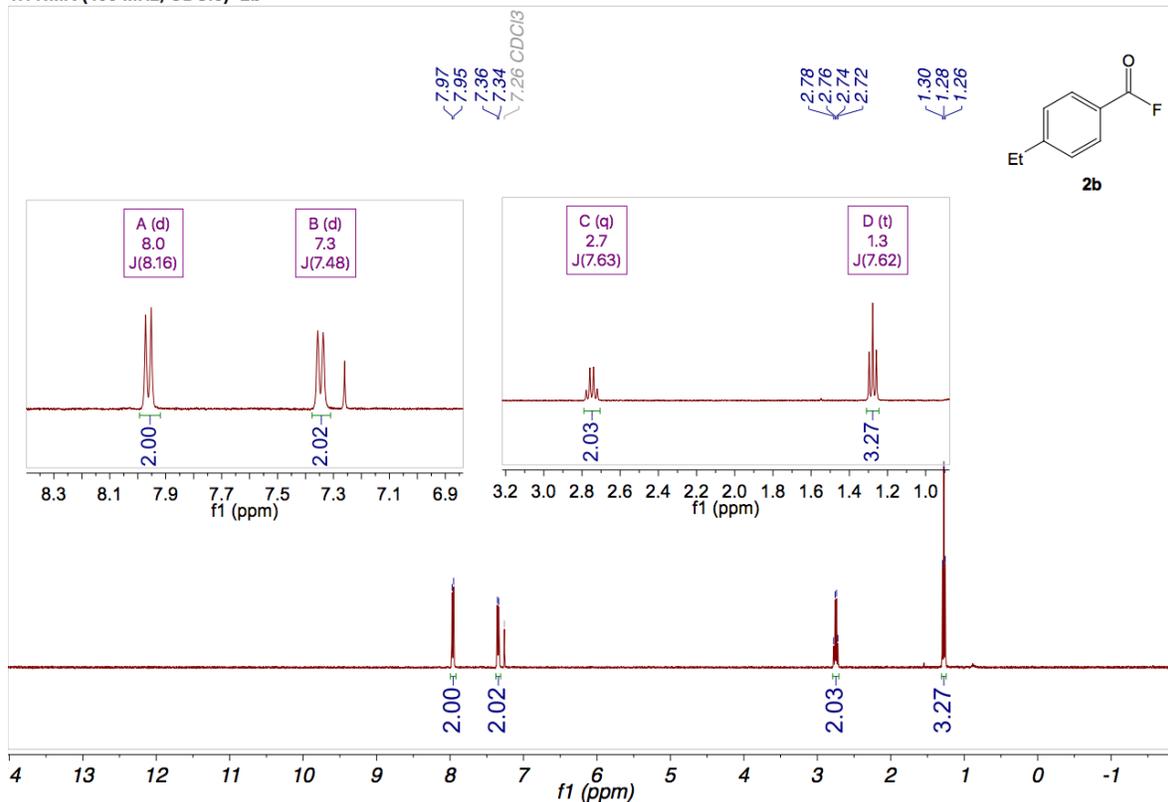
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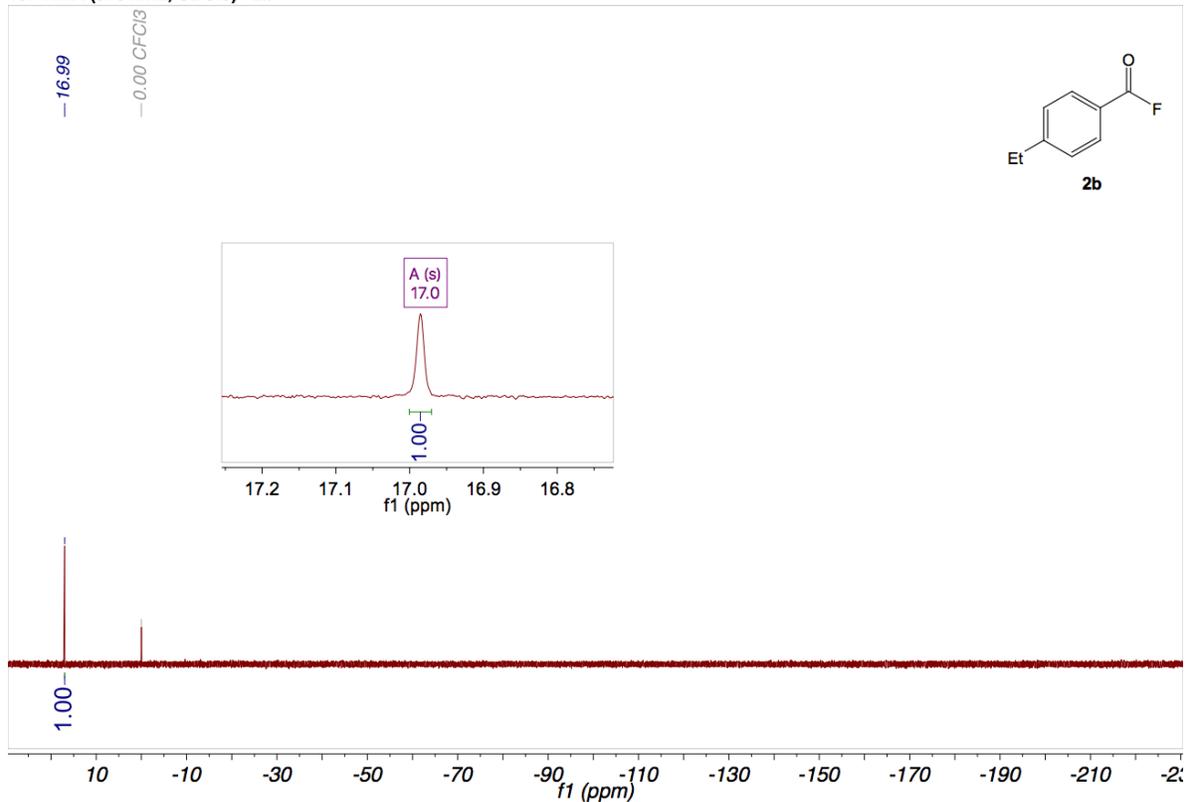
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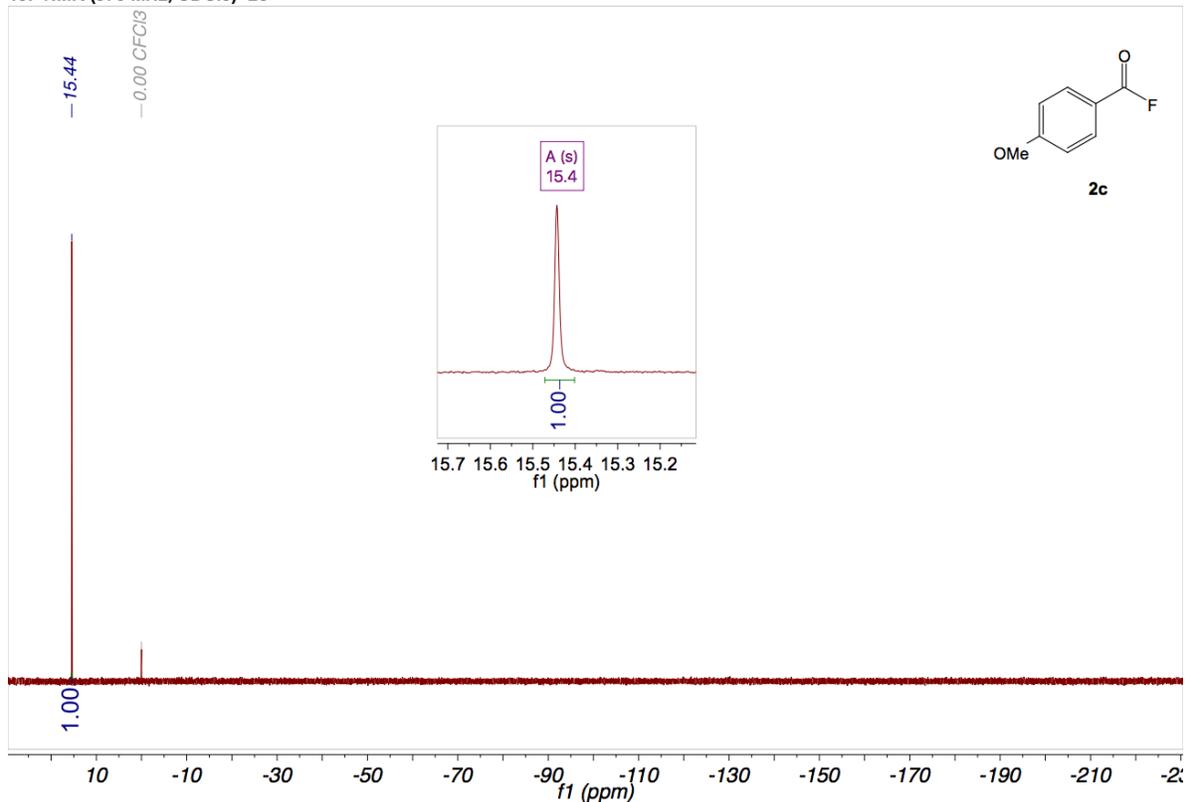
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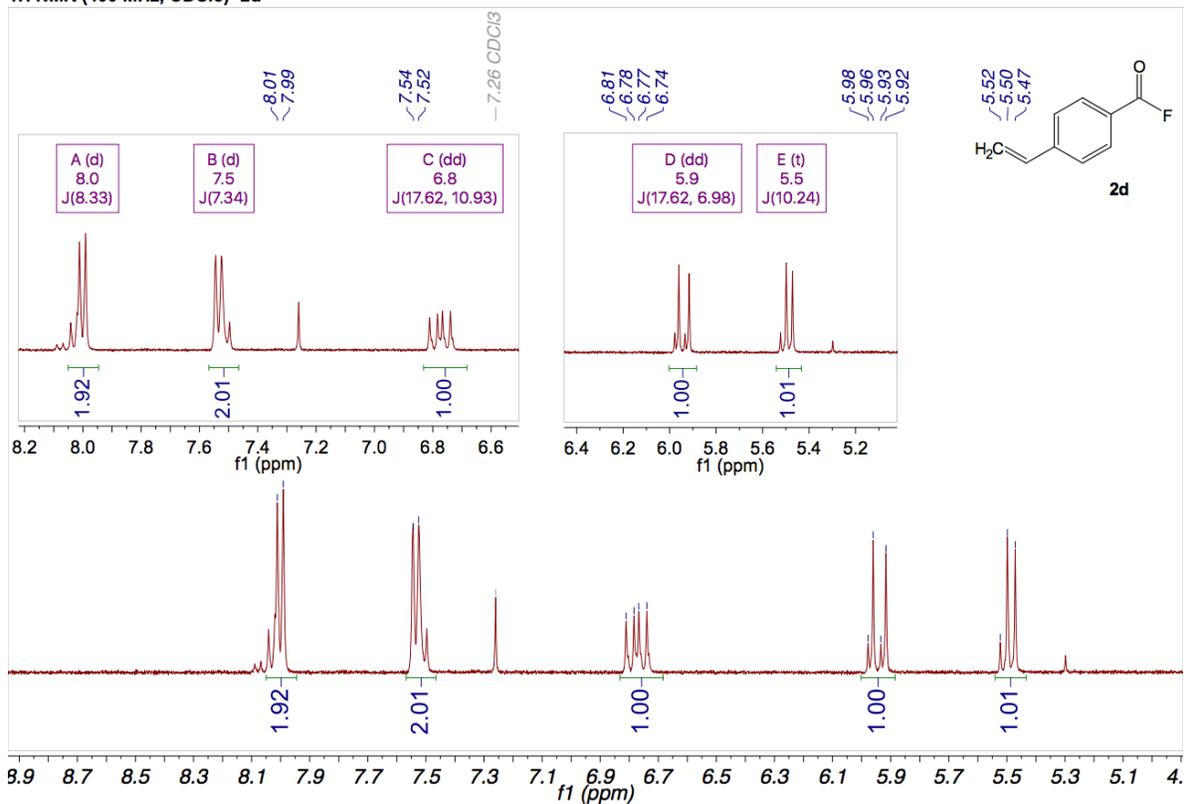
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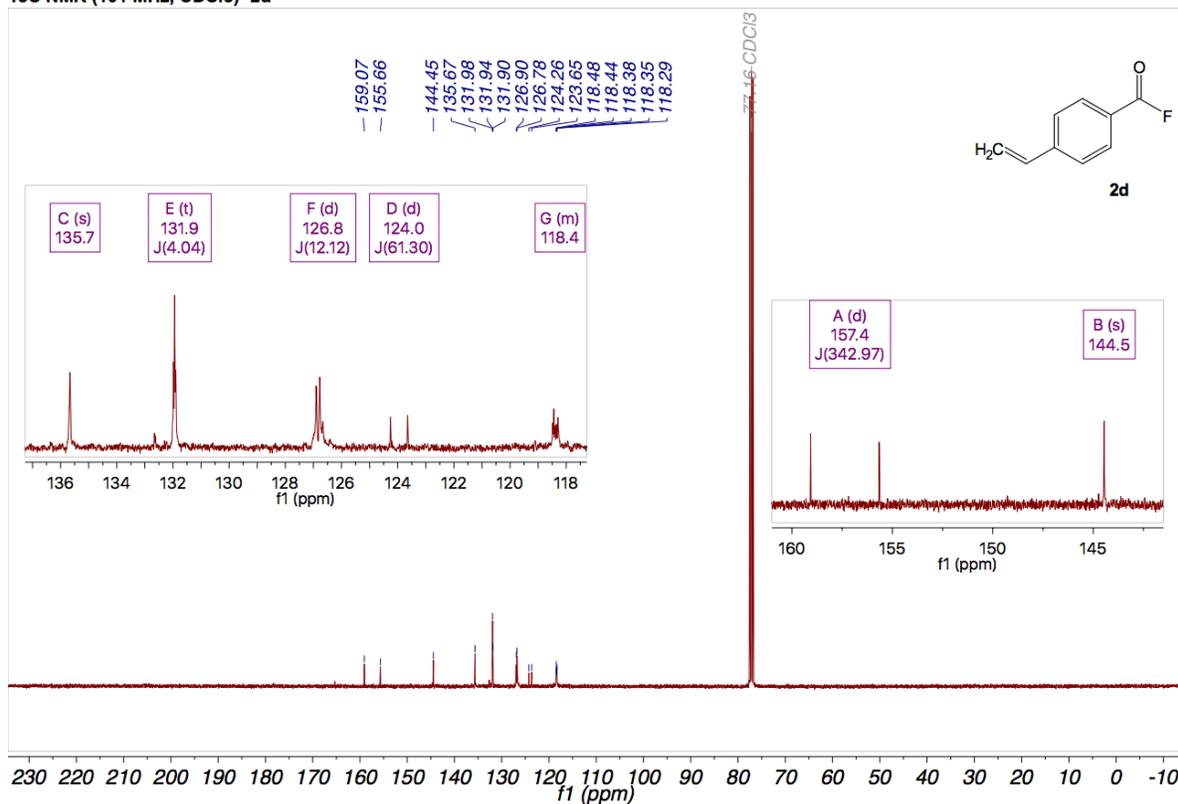
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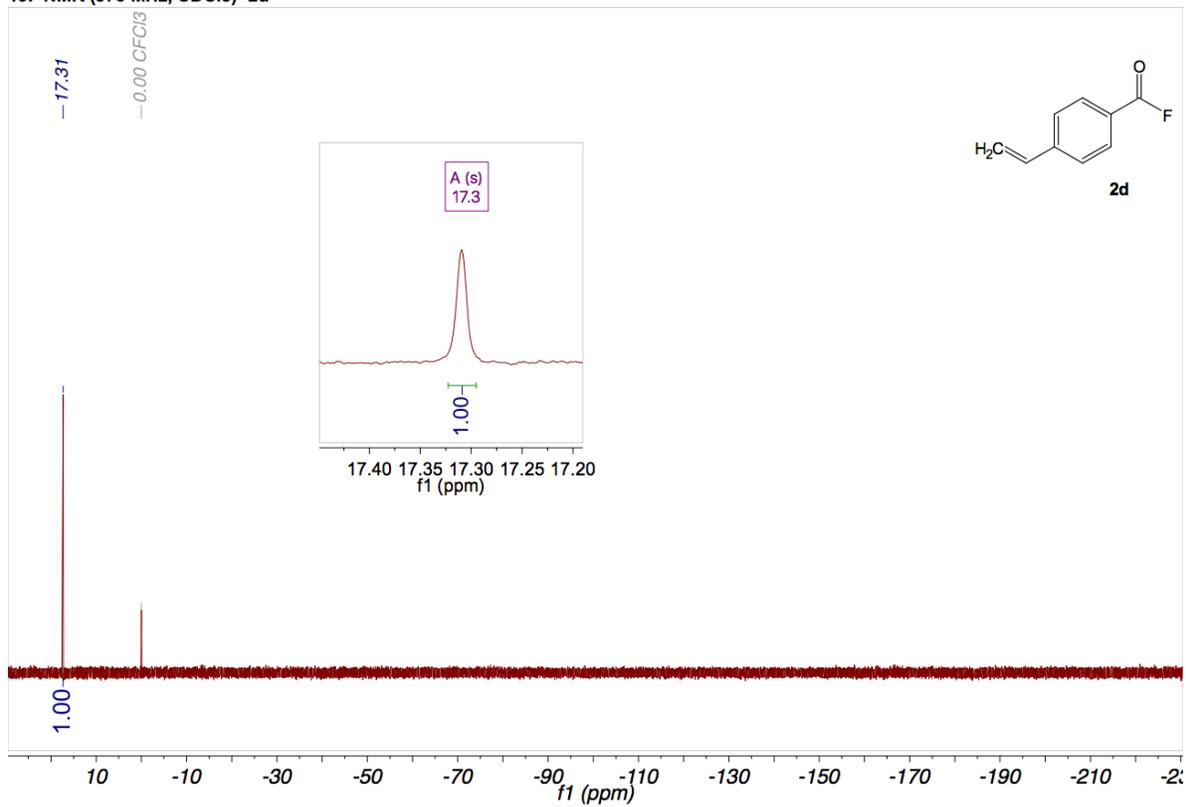
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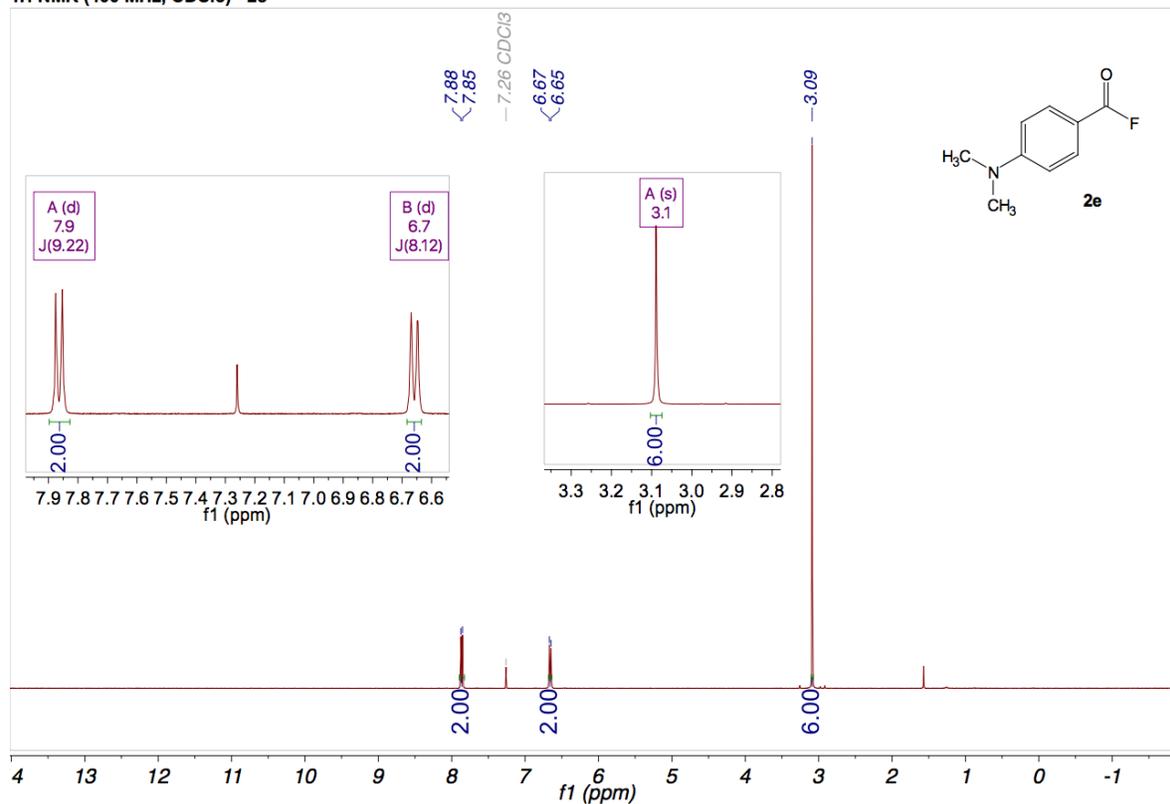
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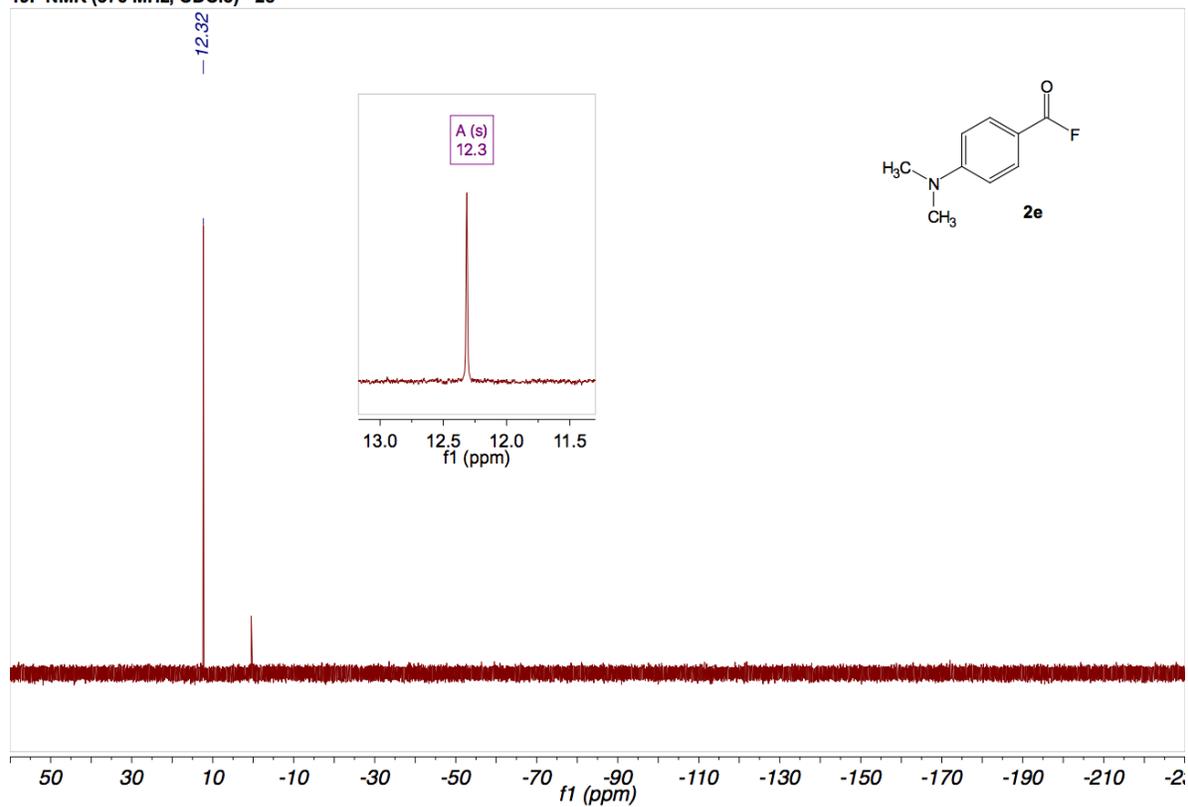
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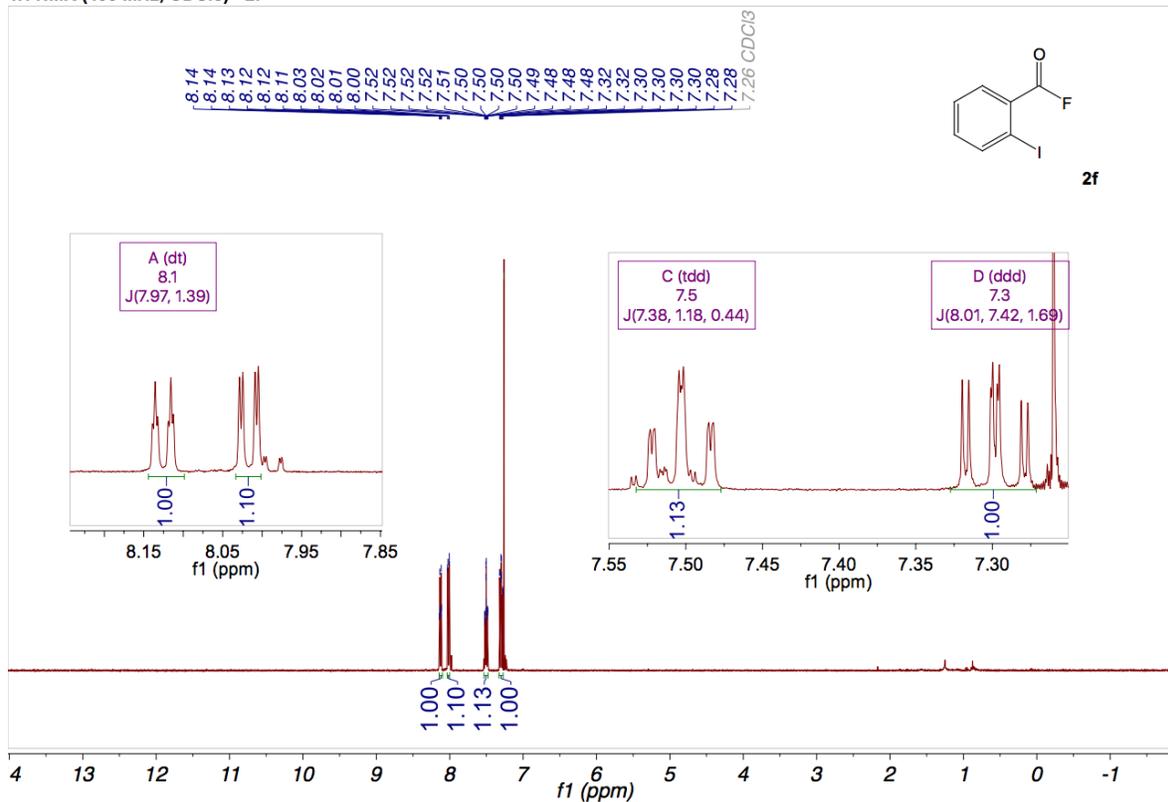
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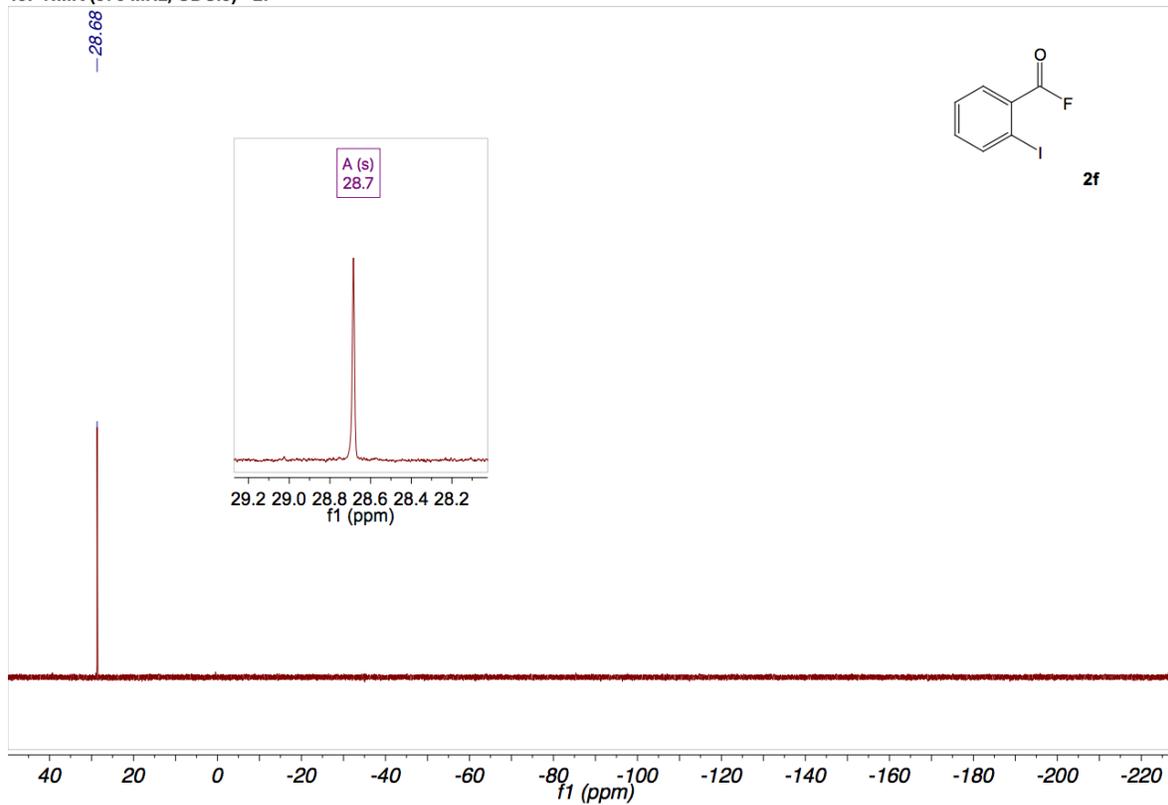
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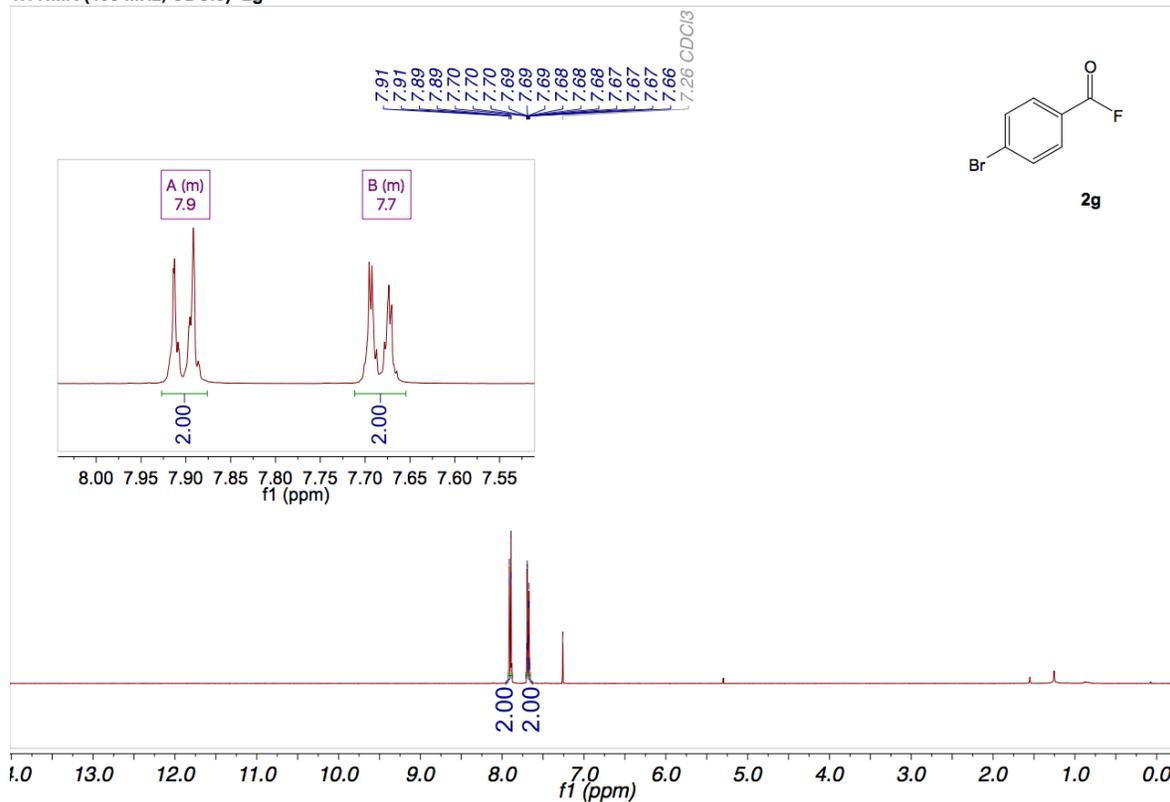
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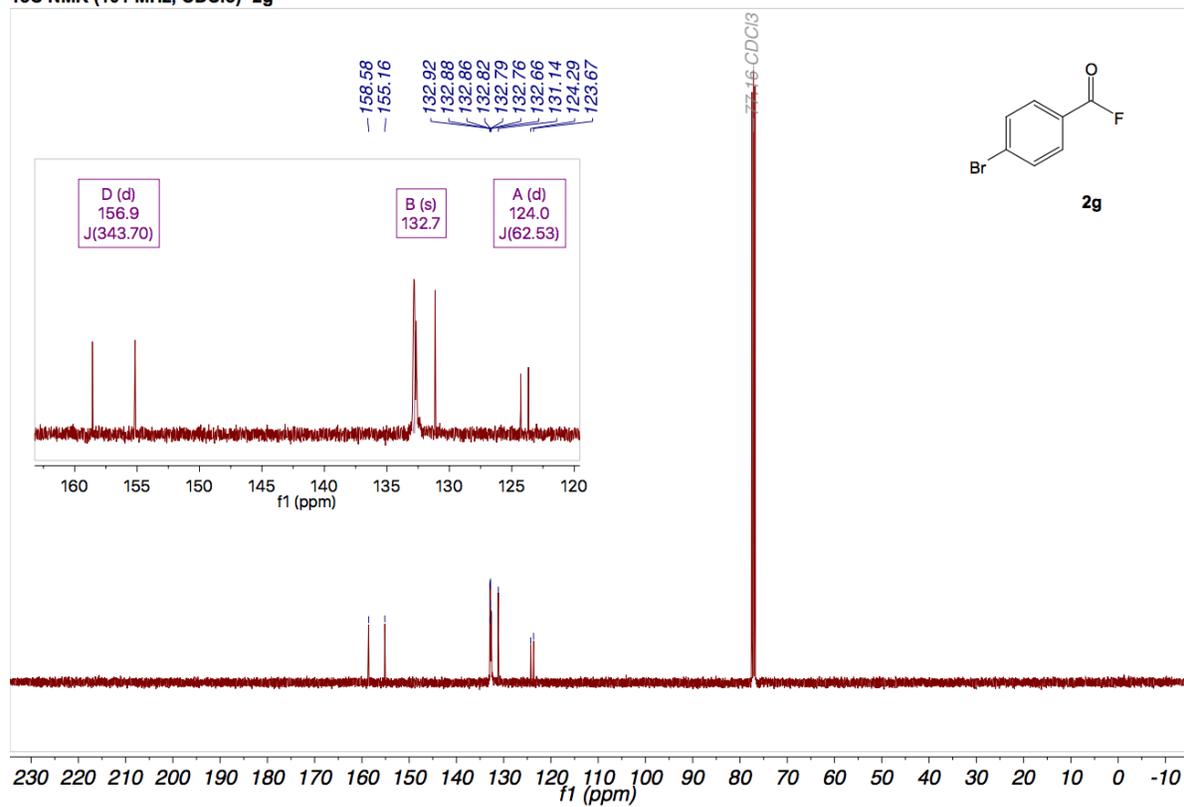
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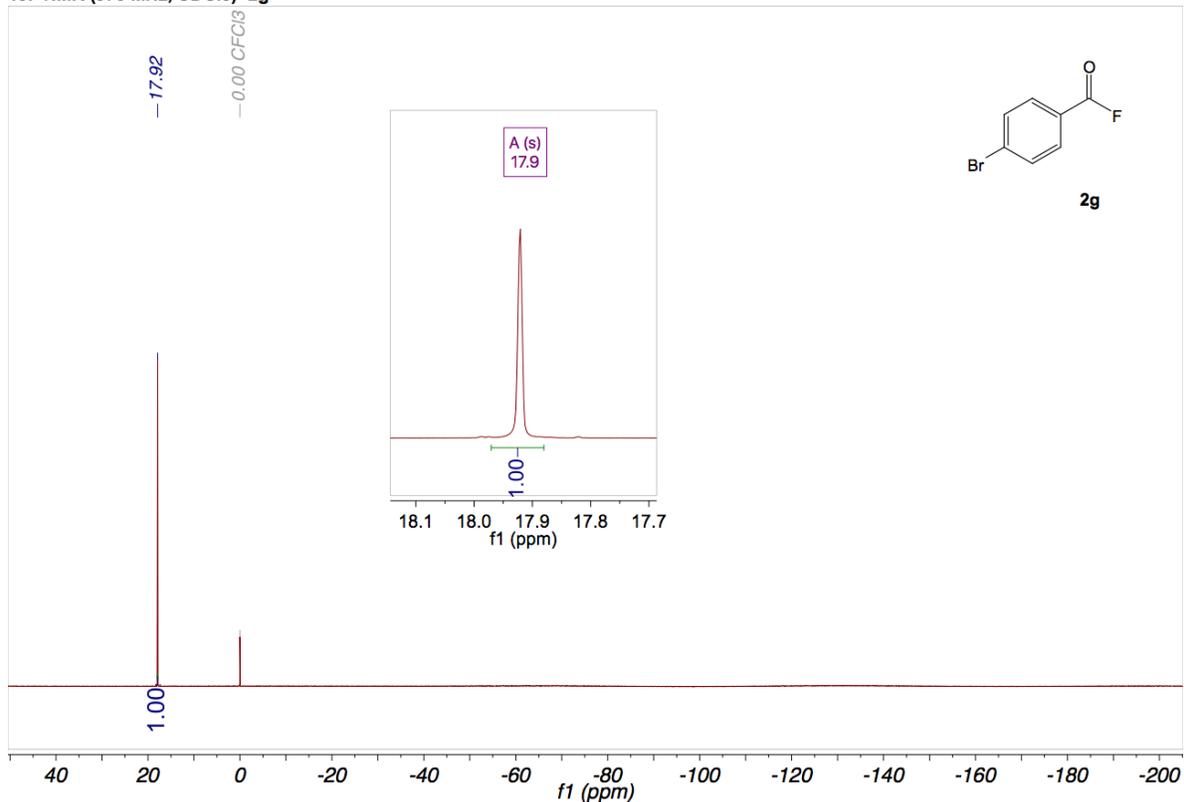
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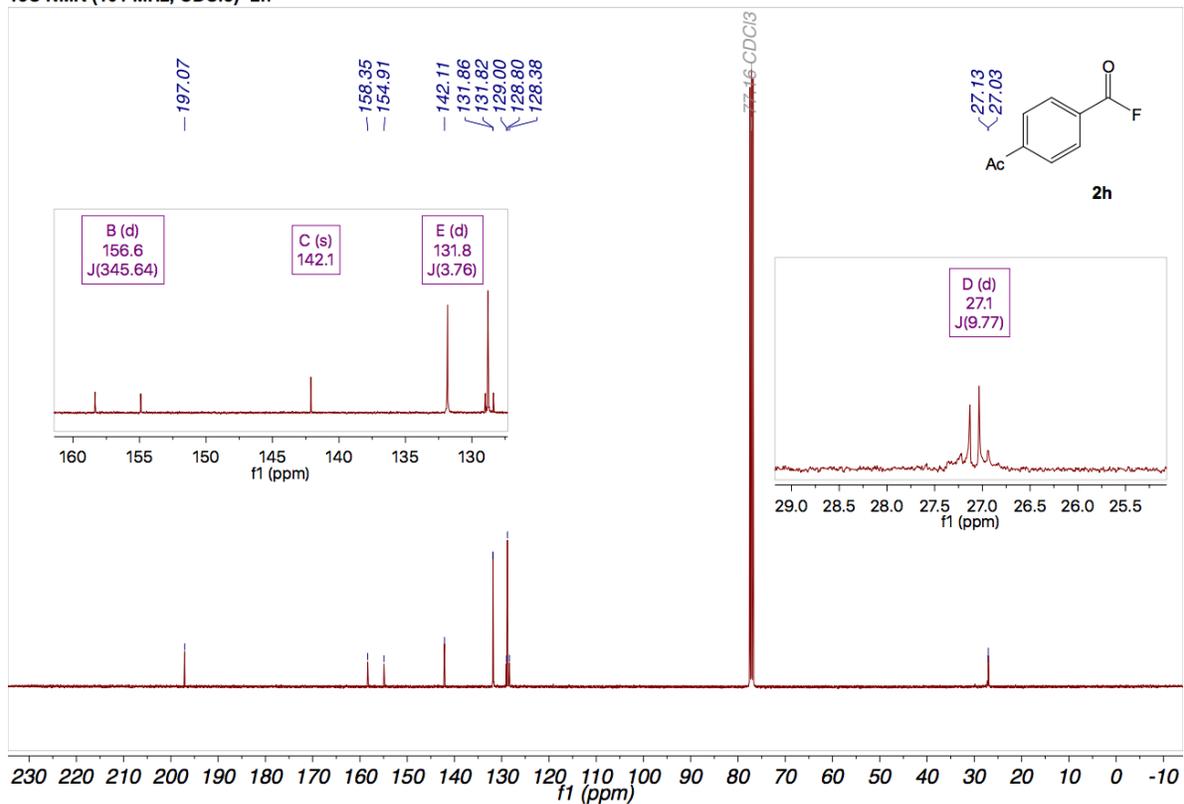
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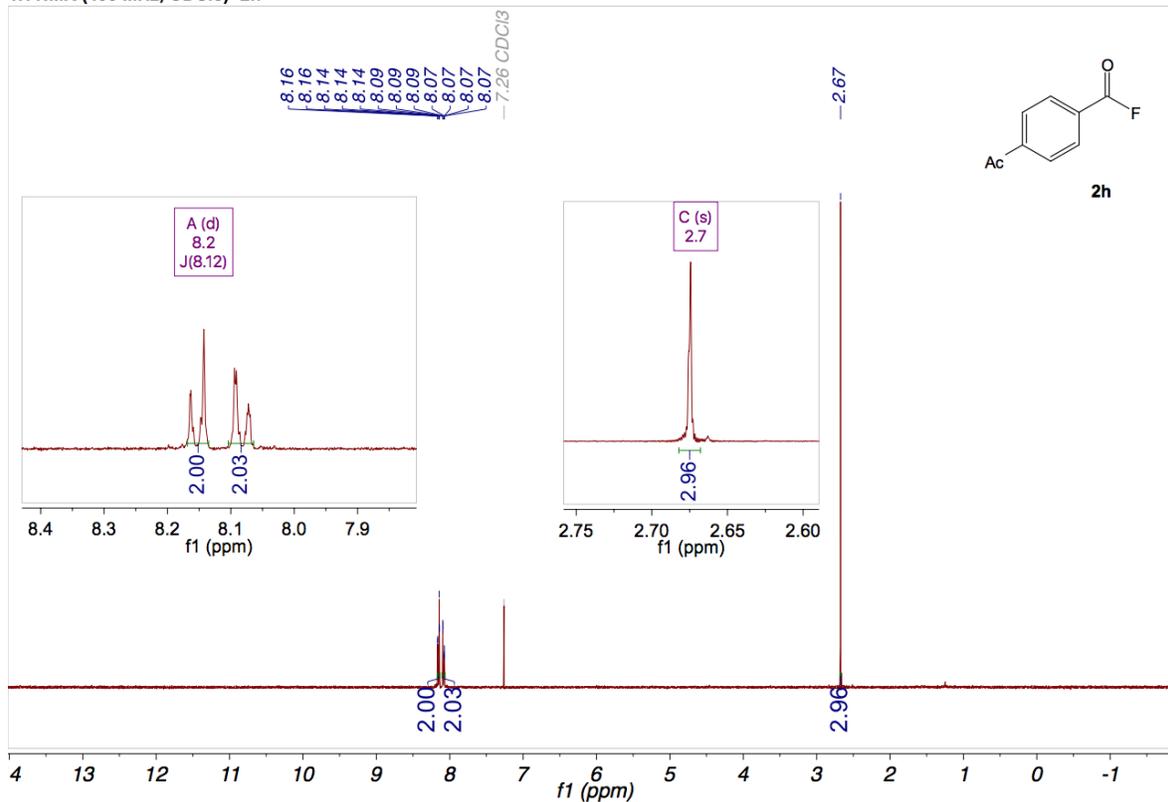
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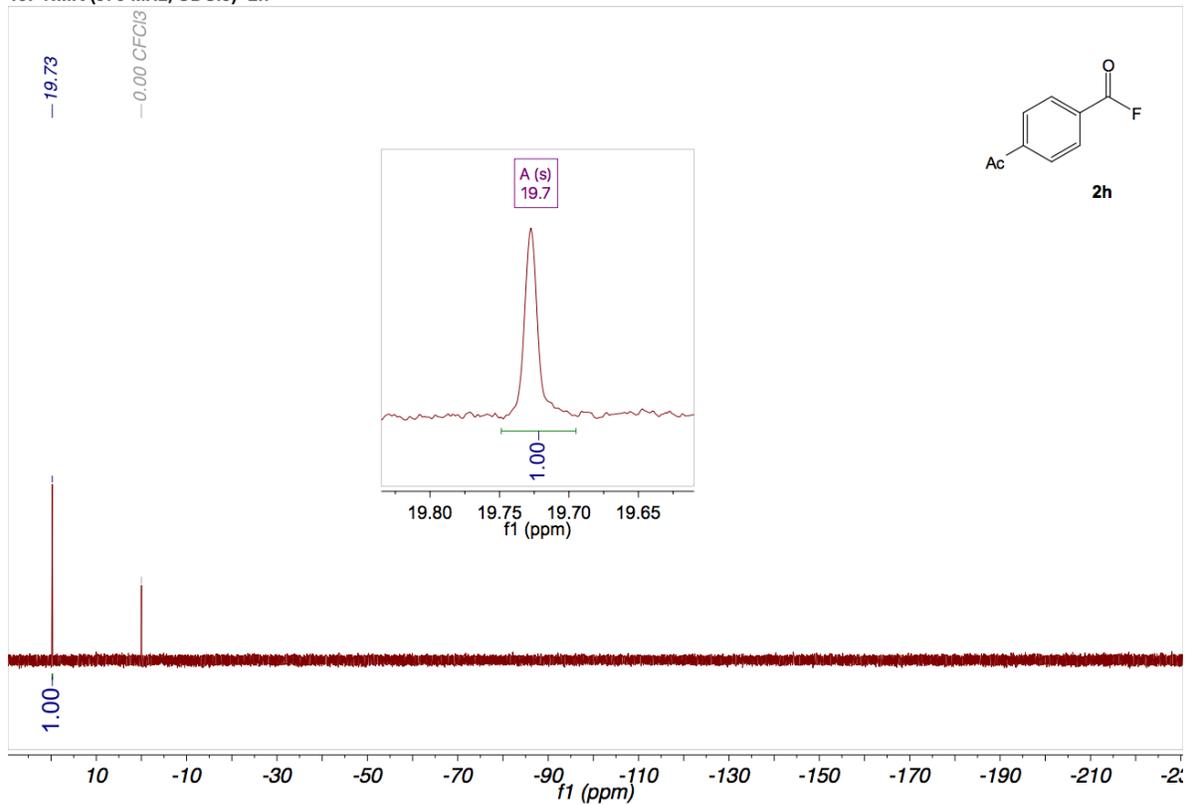
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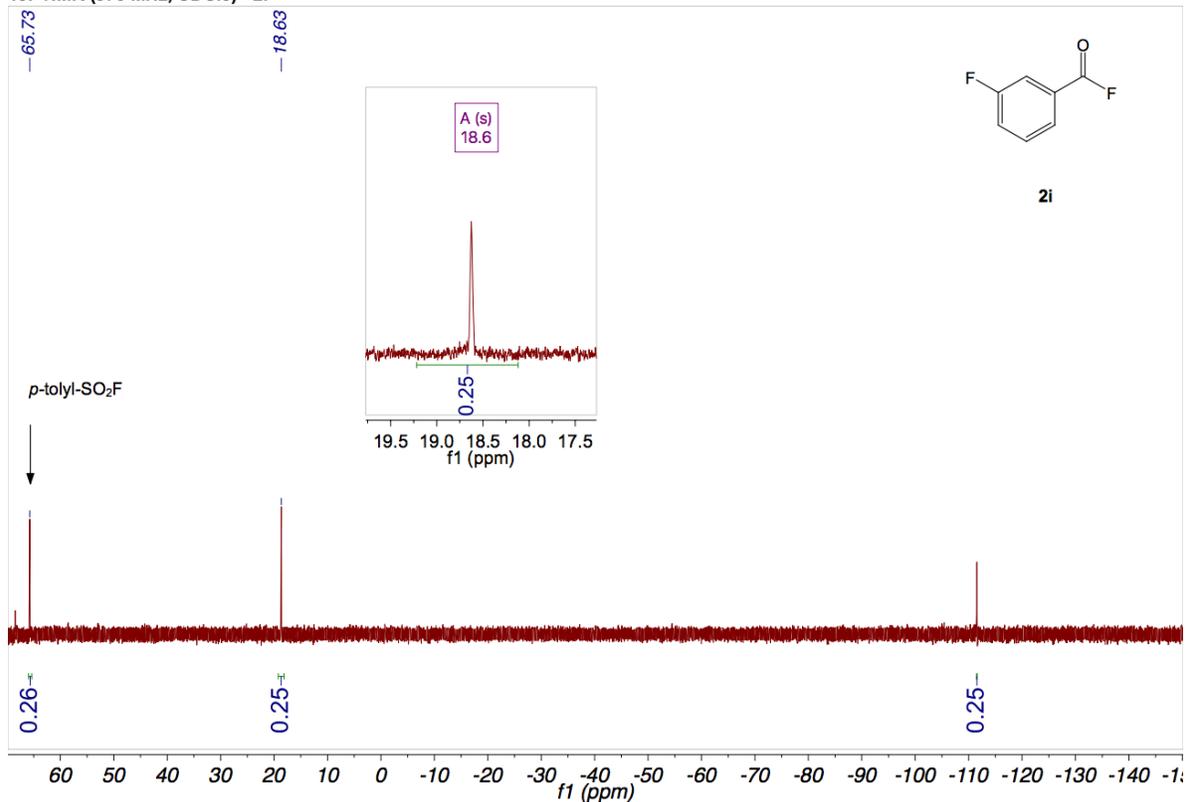
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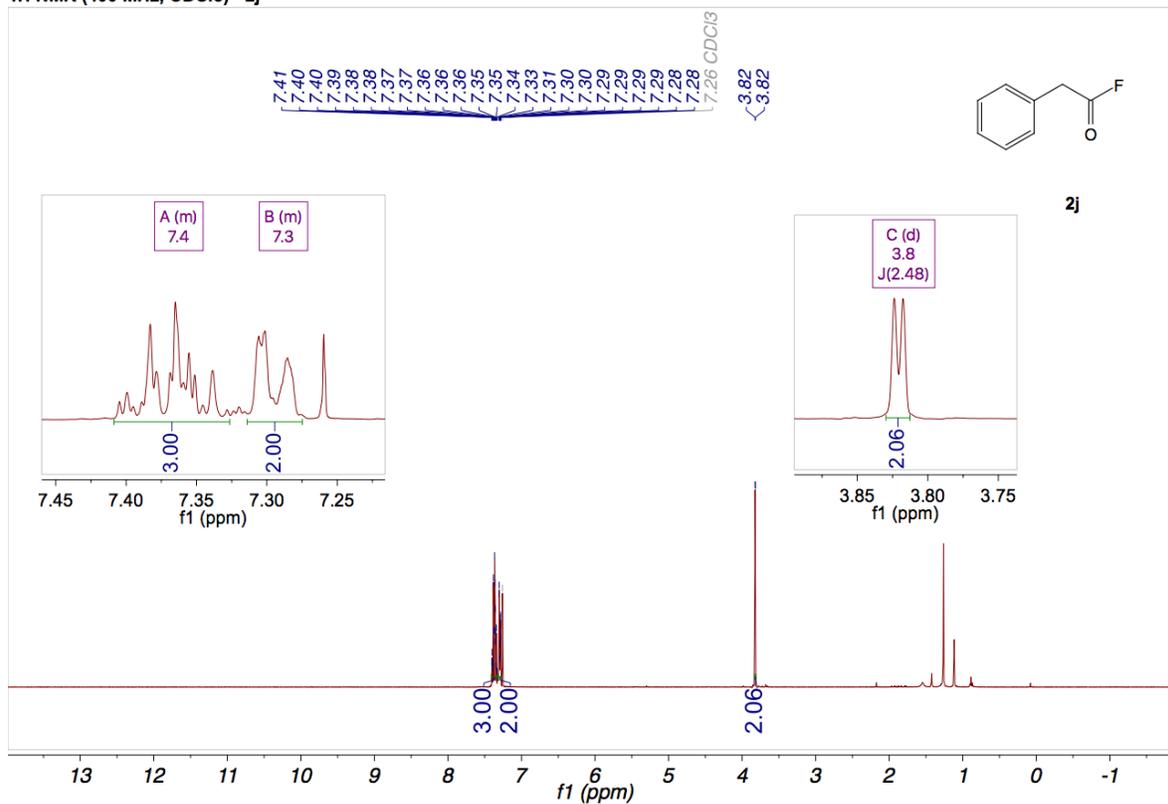
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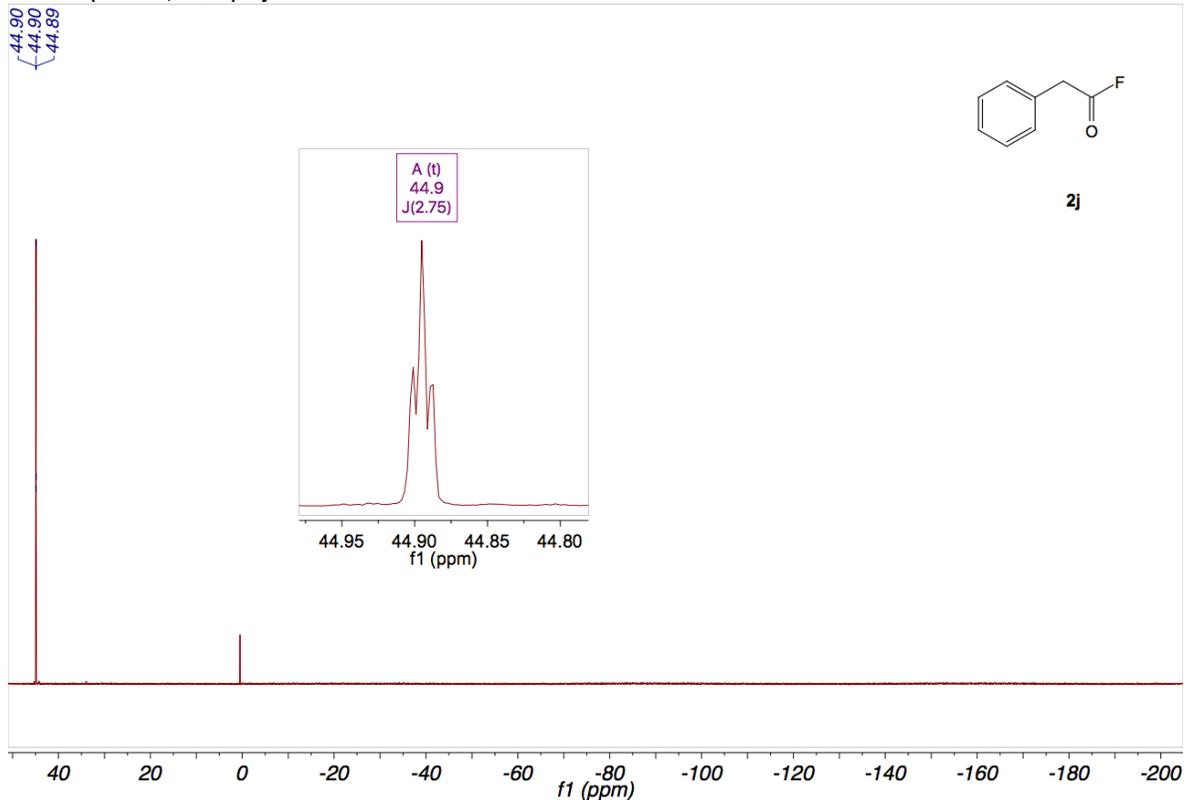
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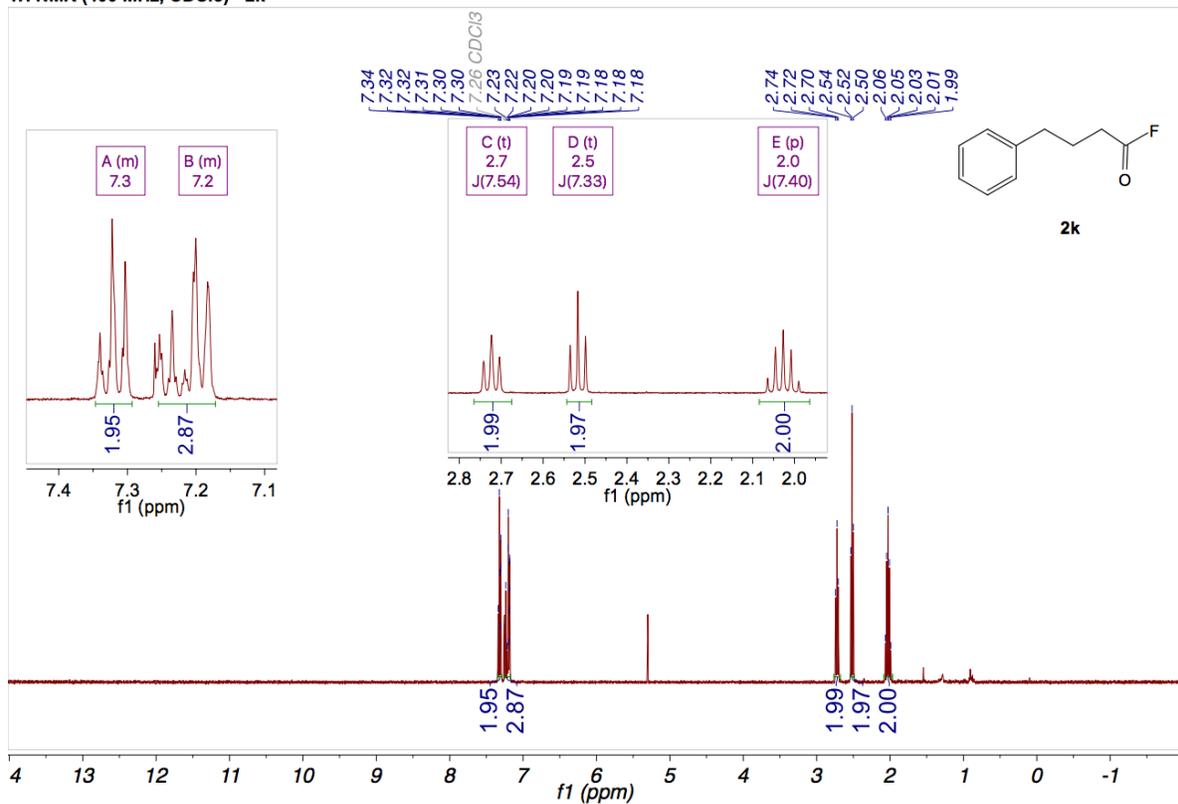
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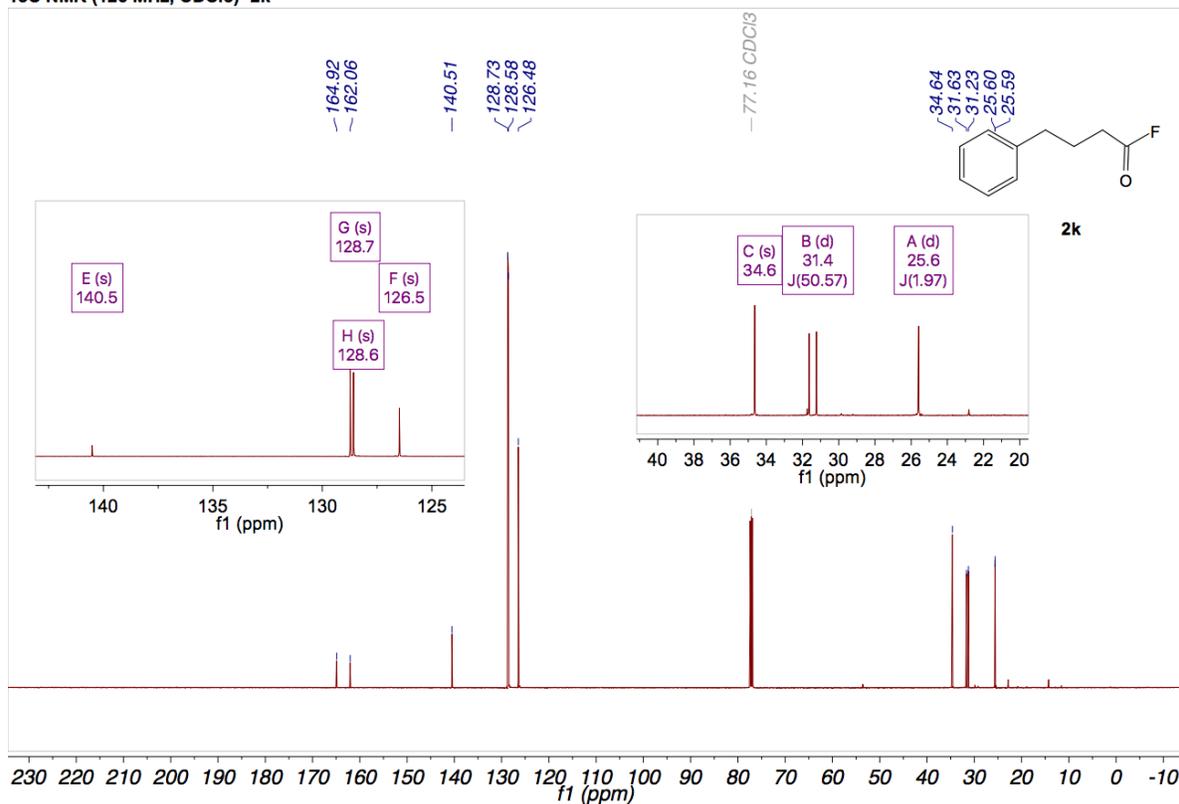
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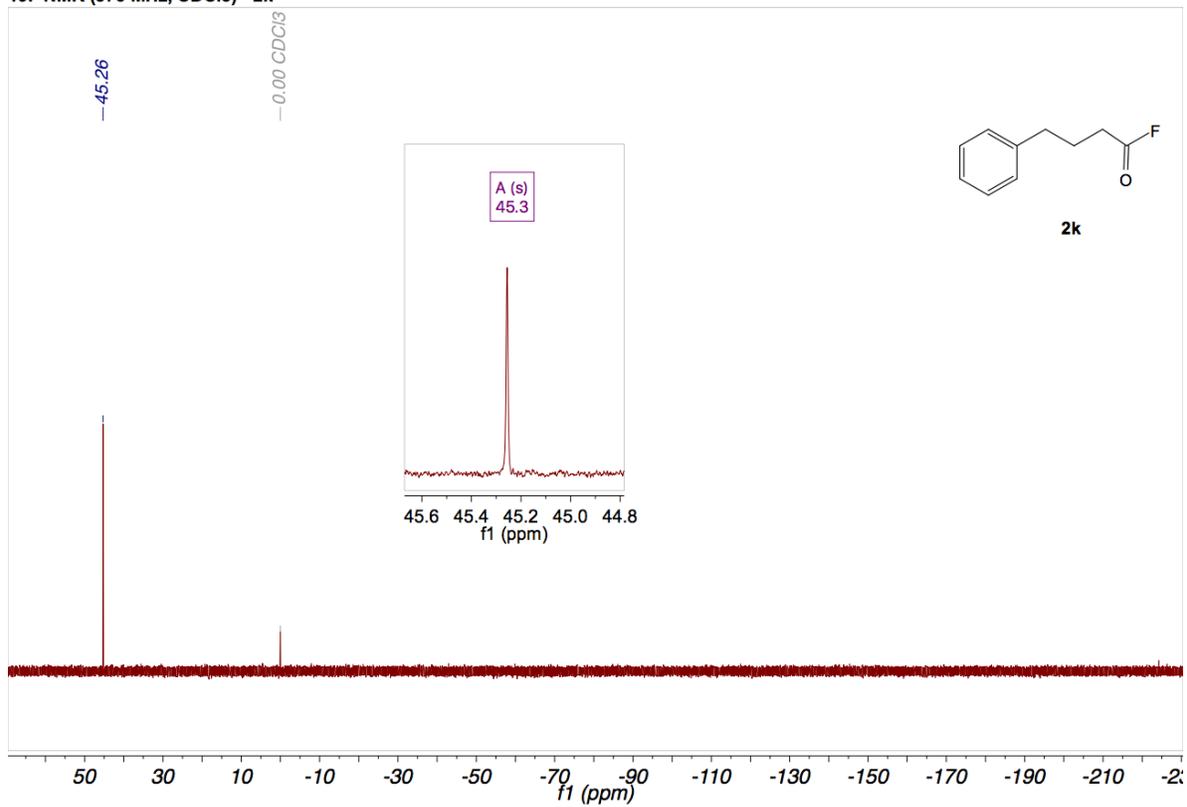
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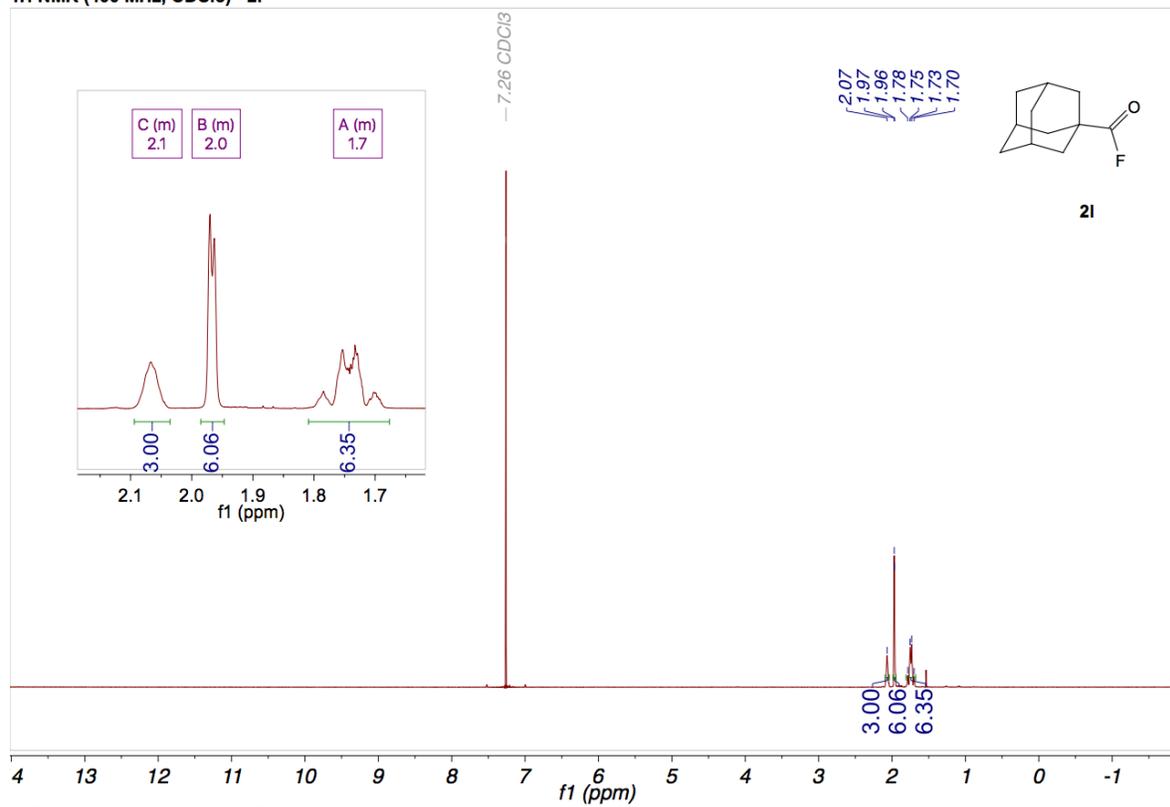
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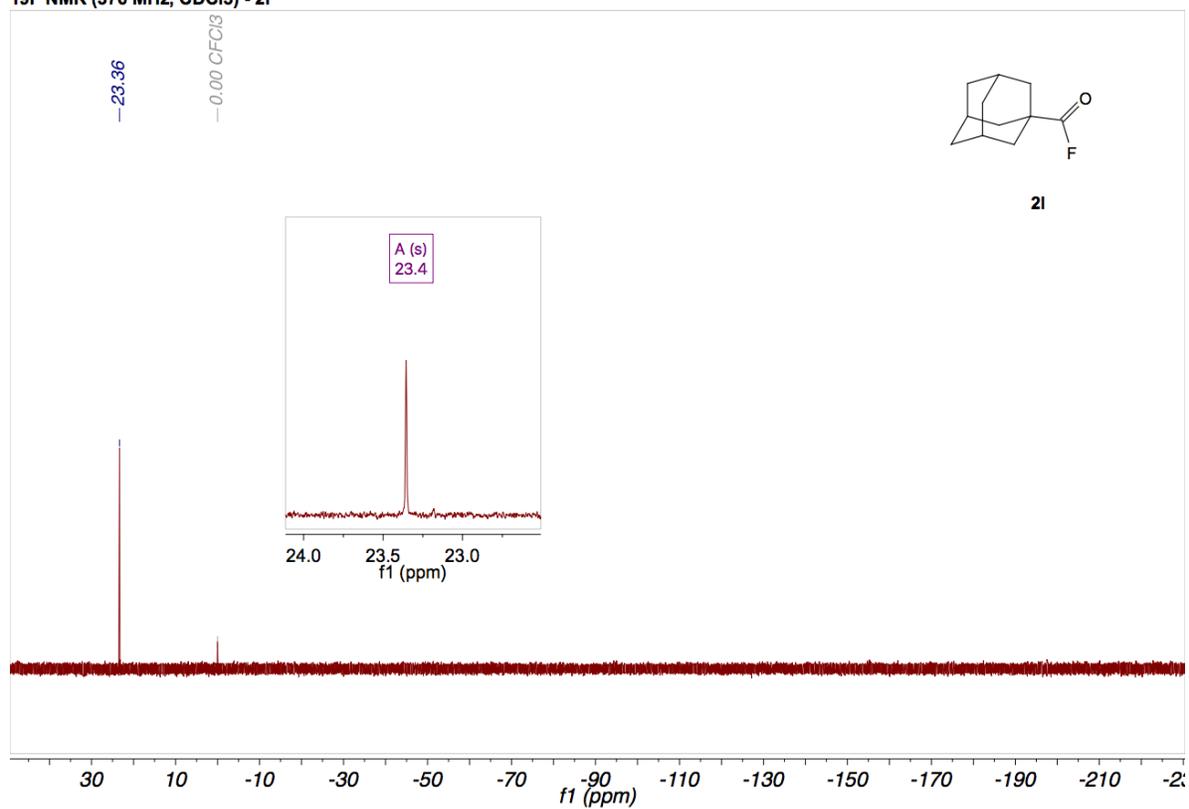
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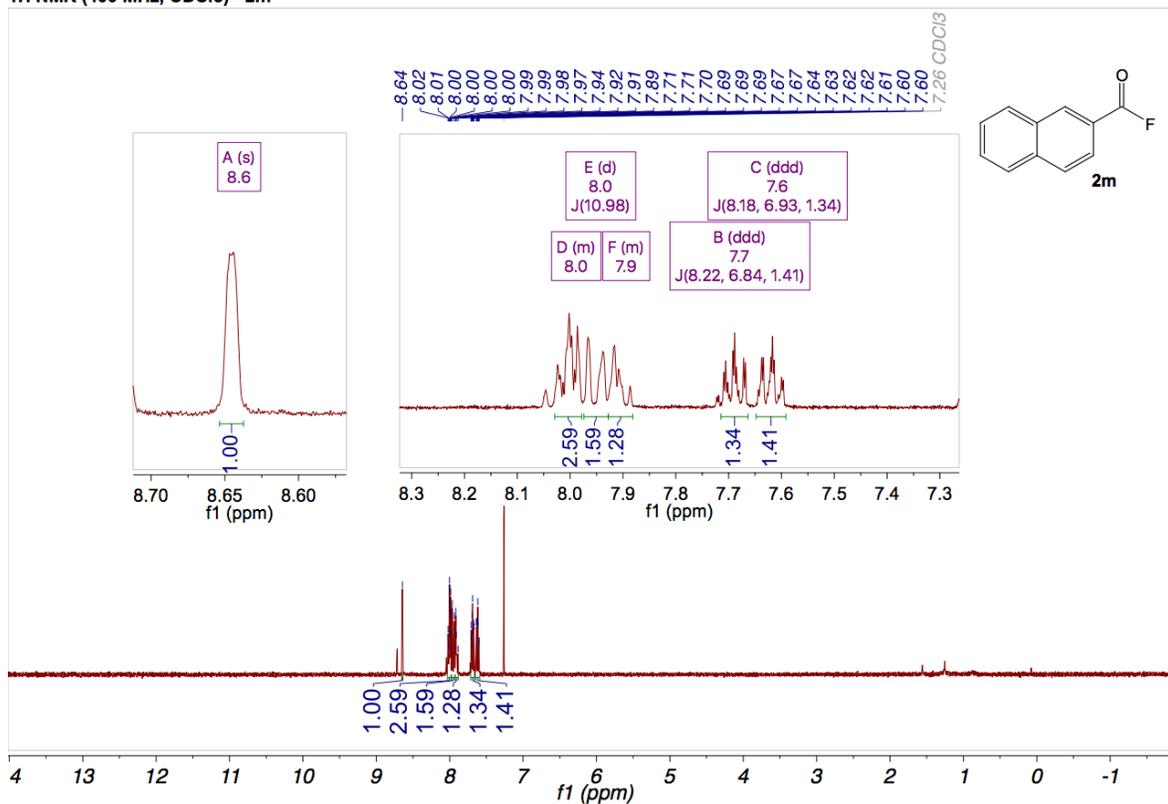
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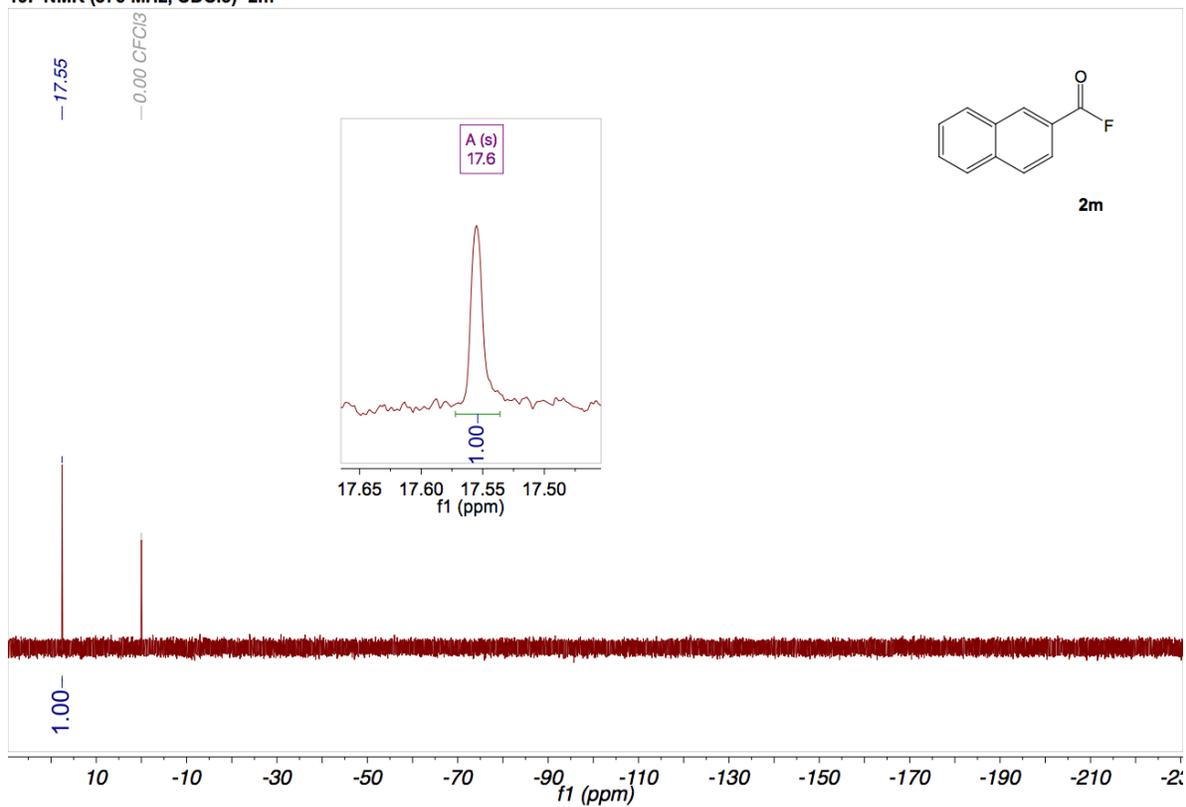
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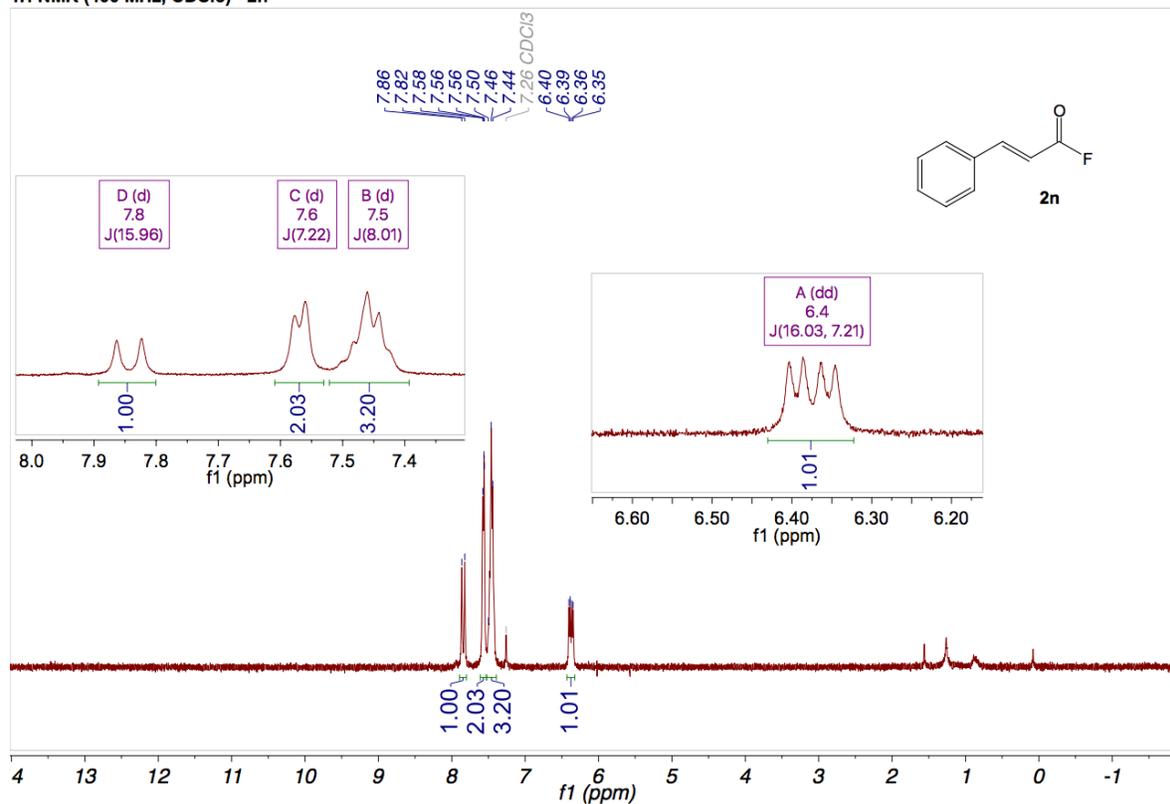
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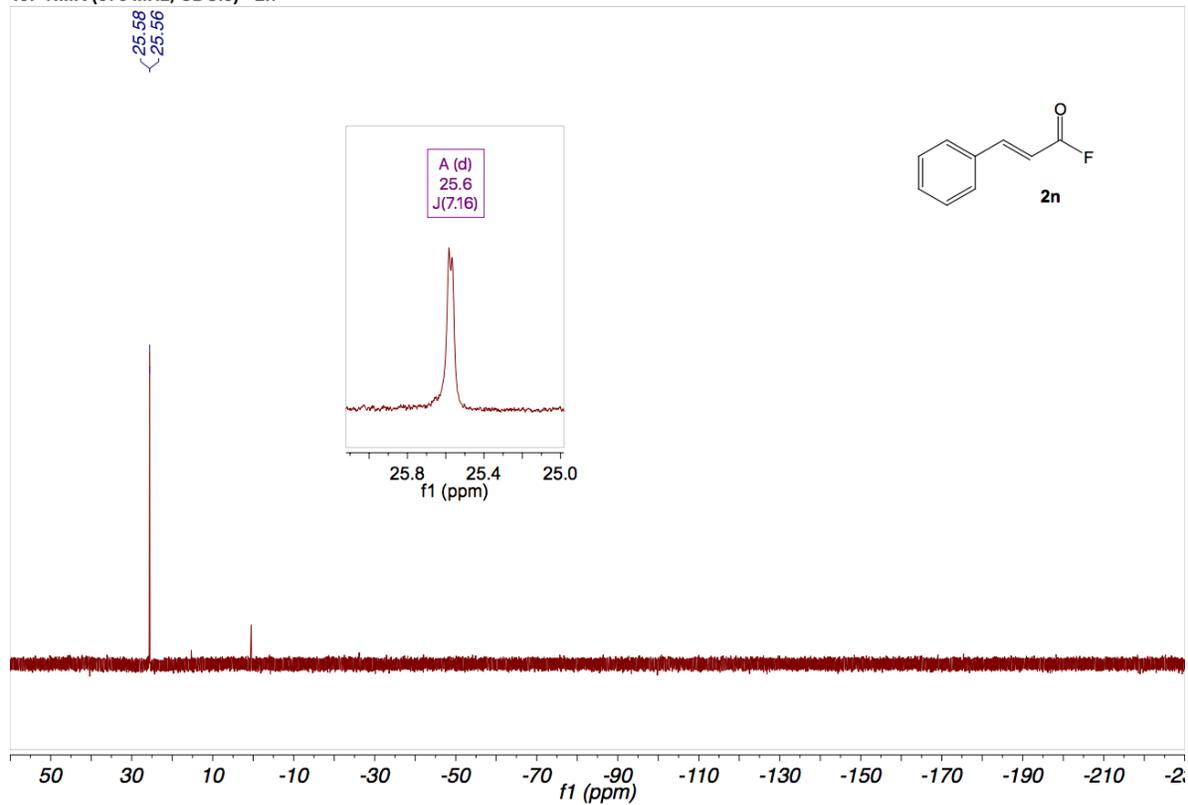
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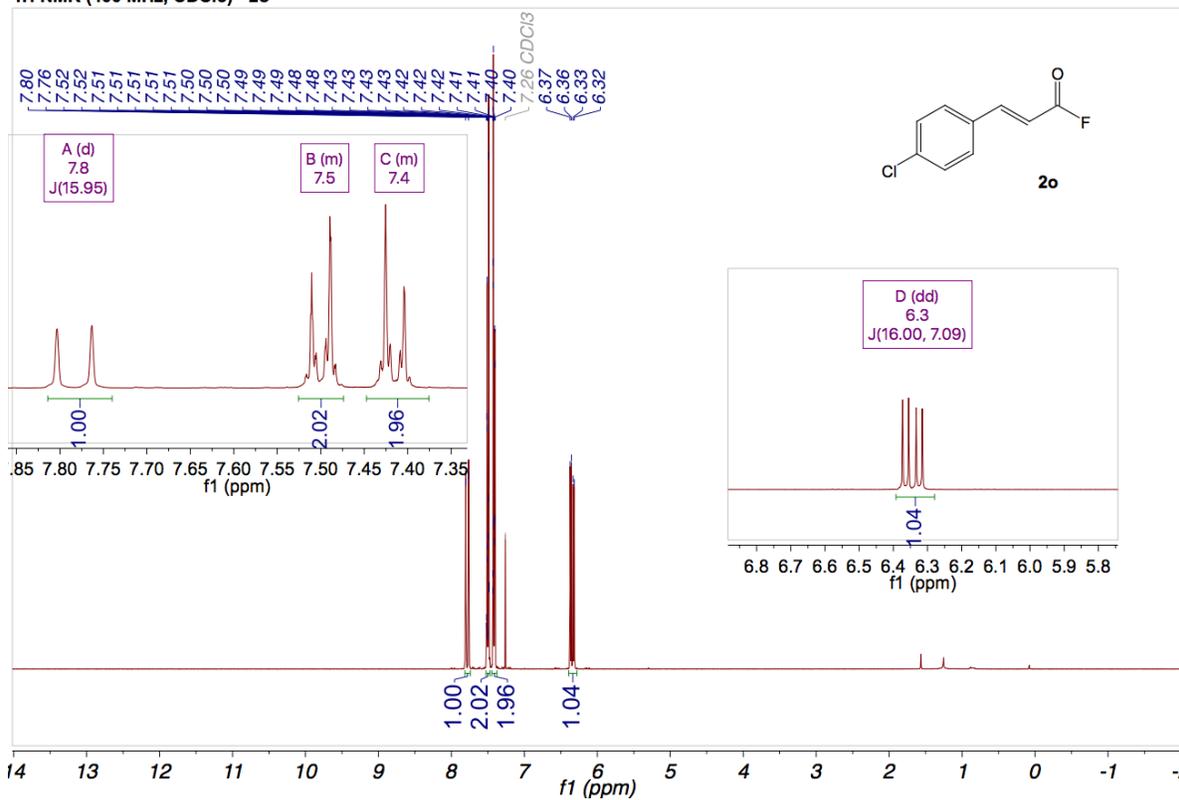
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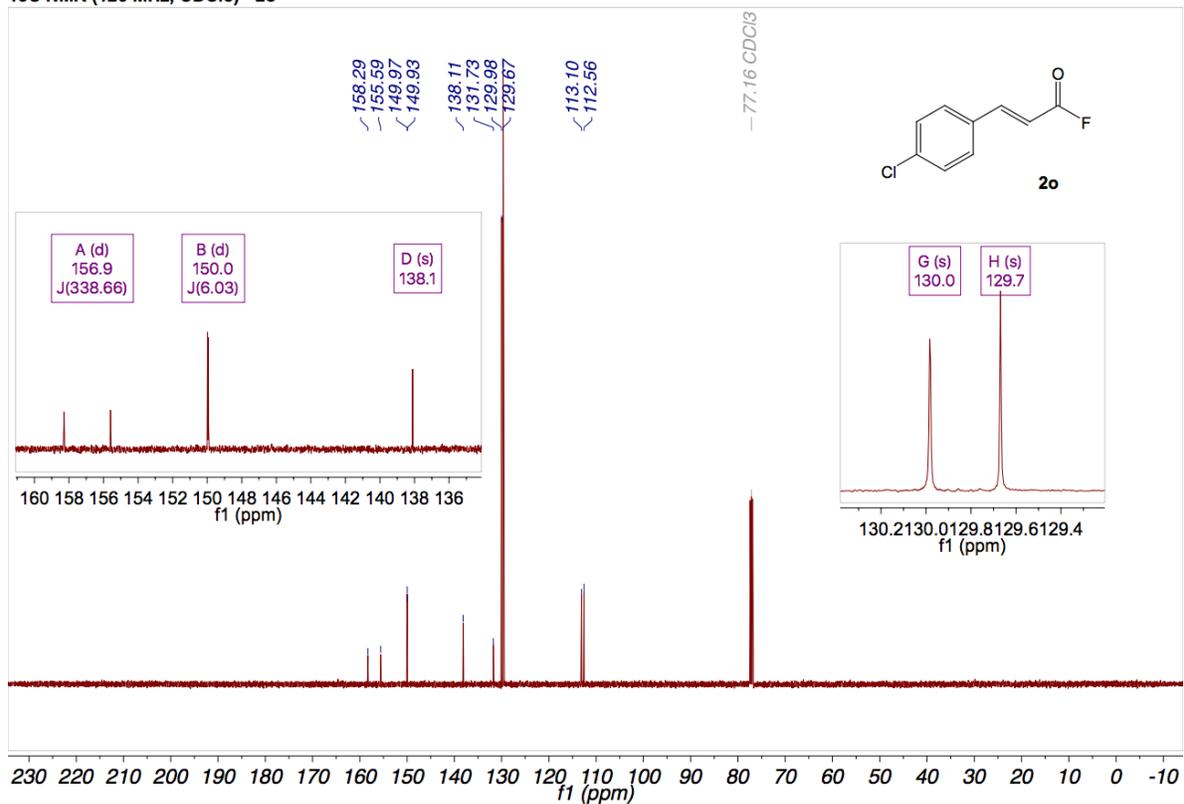
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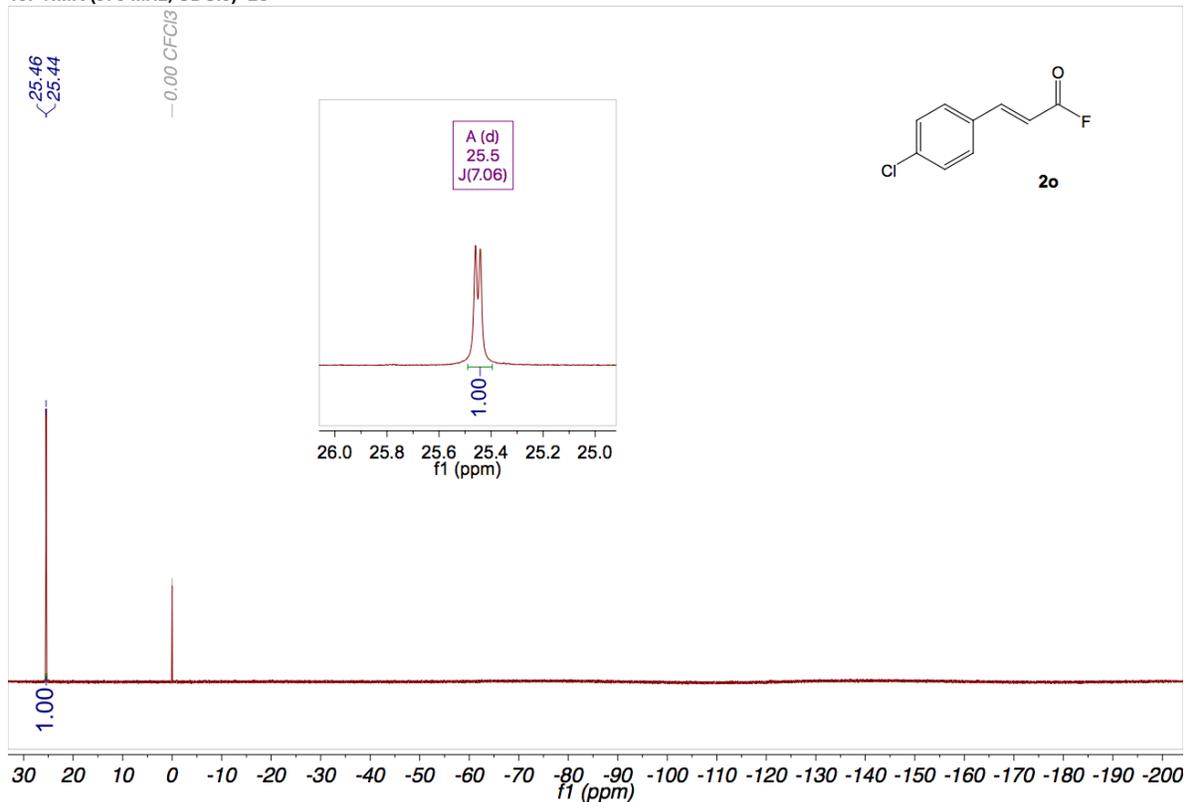
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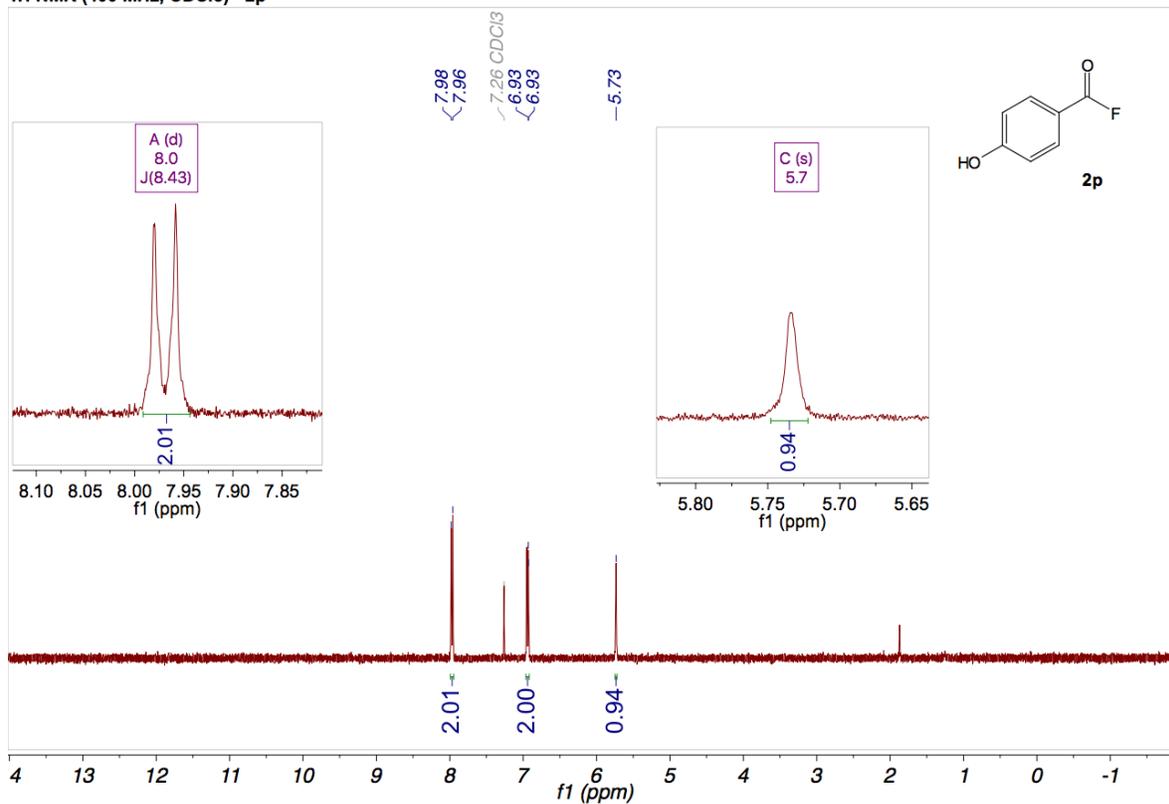
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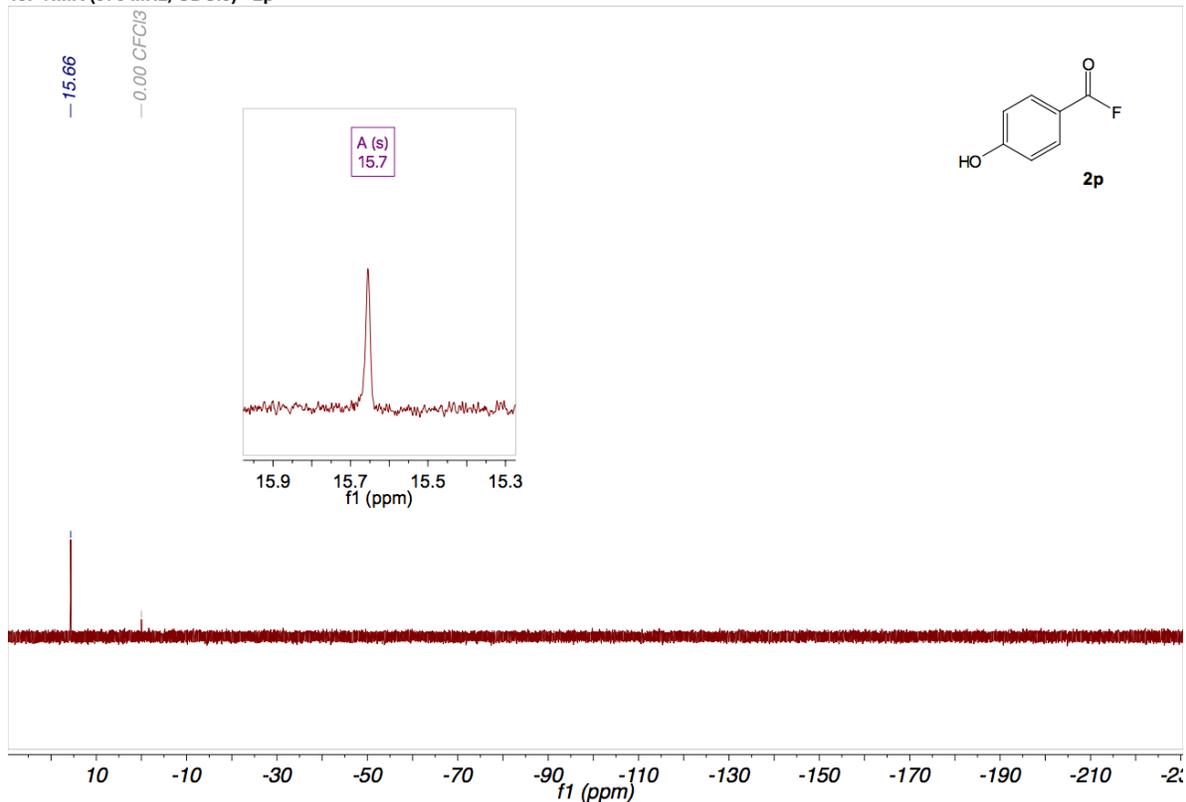
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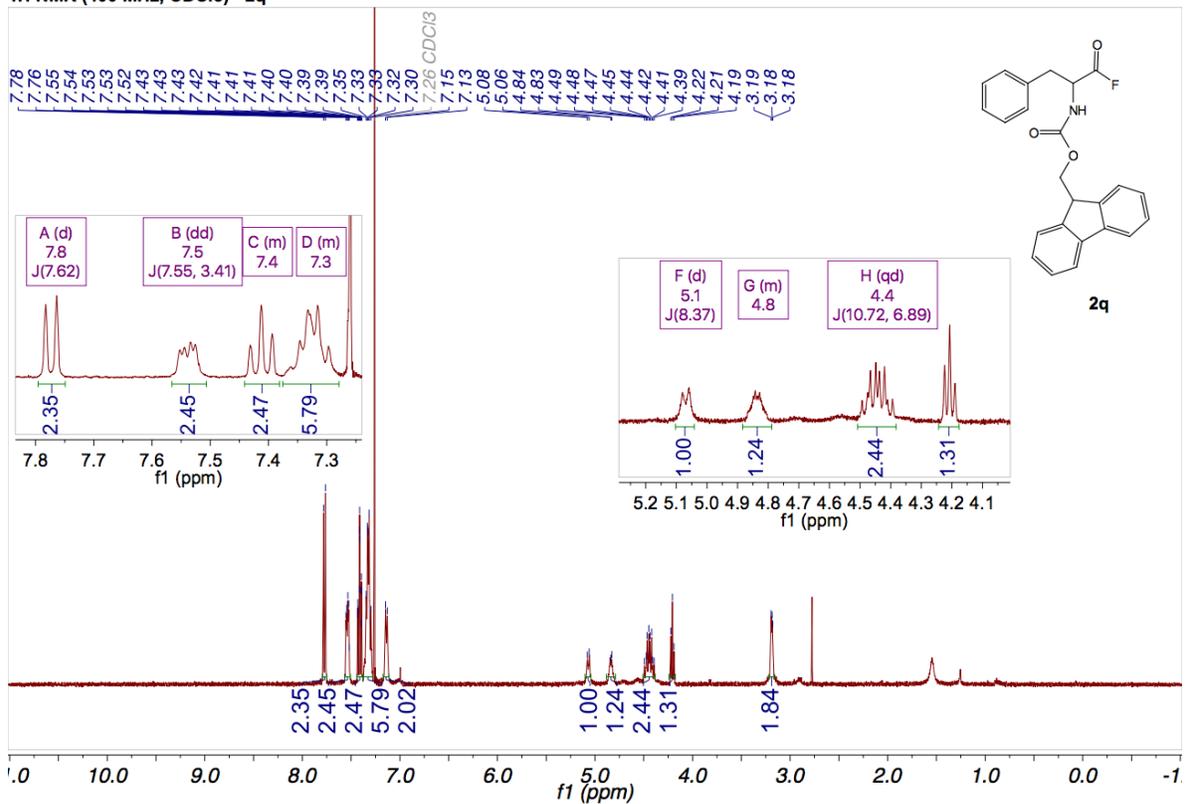
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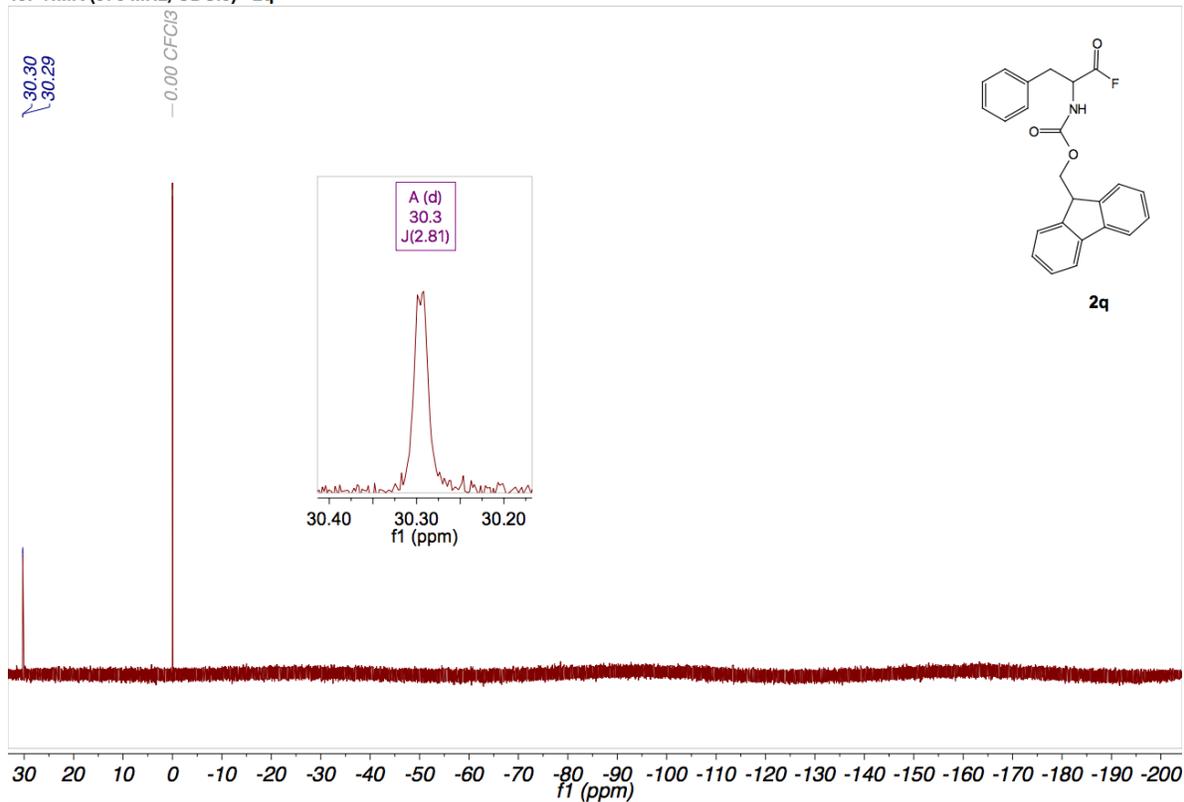
19F NMR (376 MHz, CDCl3) - 2p



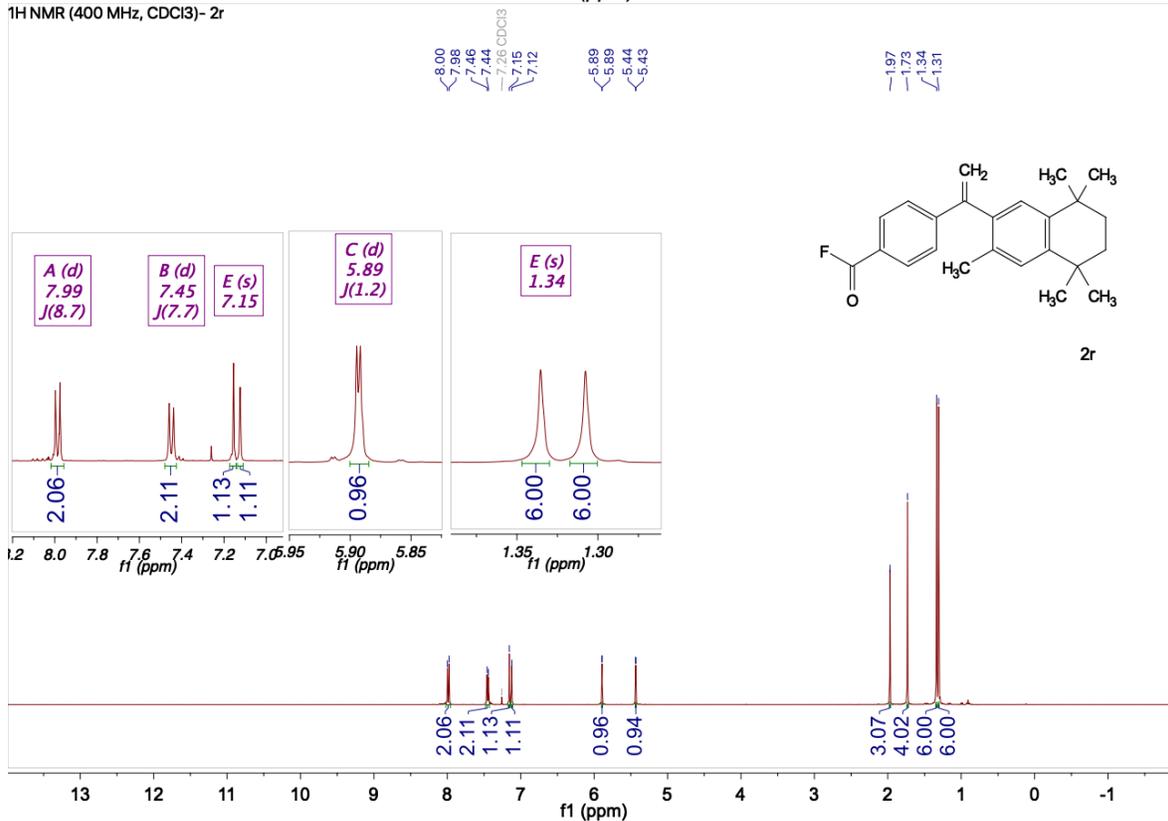
1H NMR (400 MHz, CDCl3) - 2q



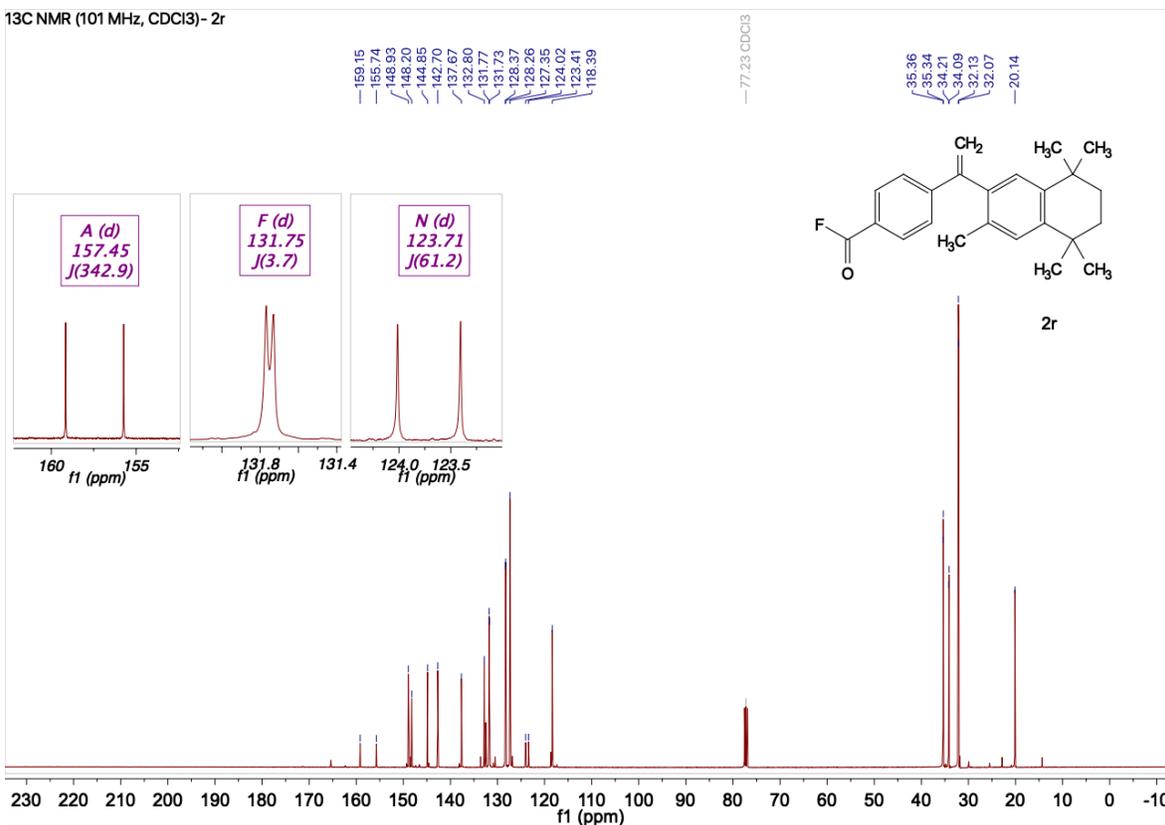
19F NMR (376 MHz, CDCl3) - 2q



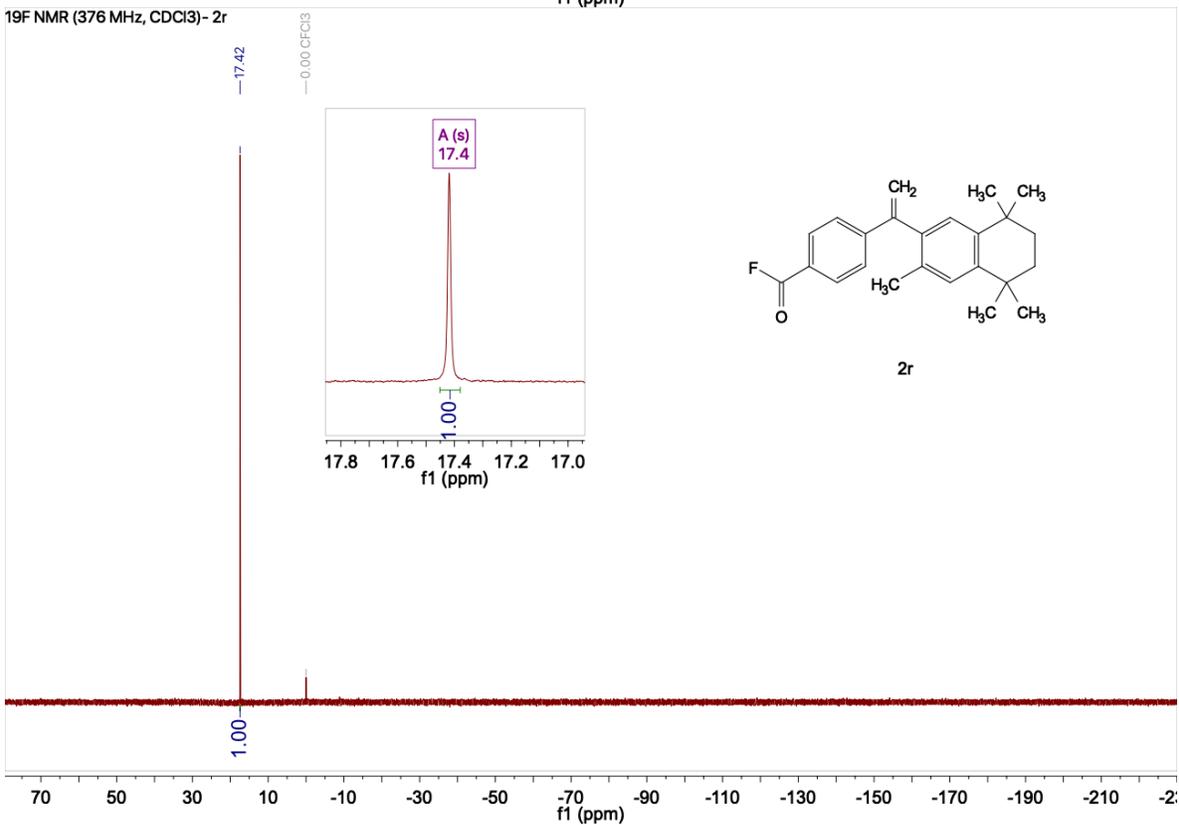
1H NMR (400 MHz, CDCl3) - 2r

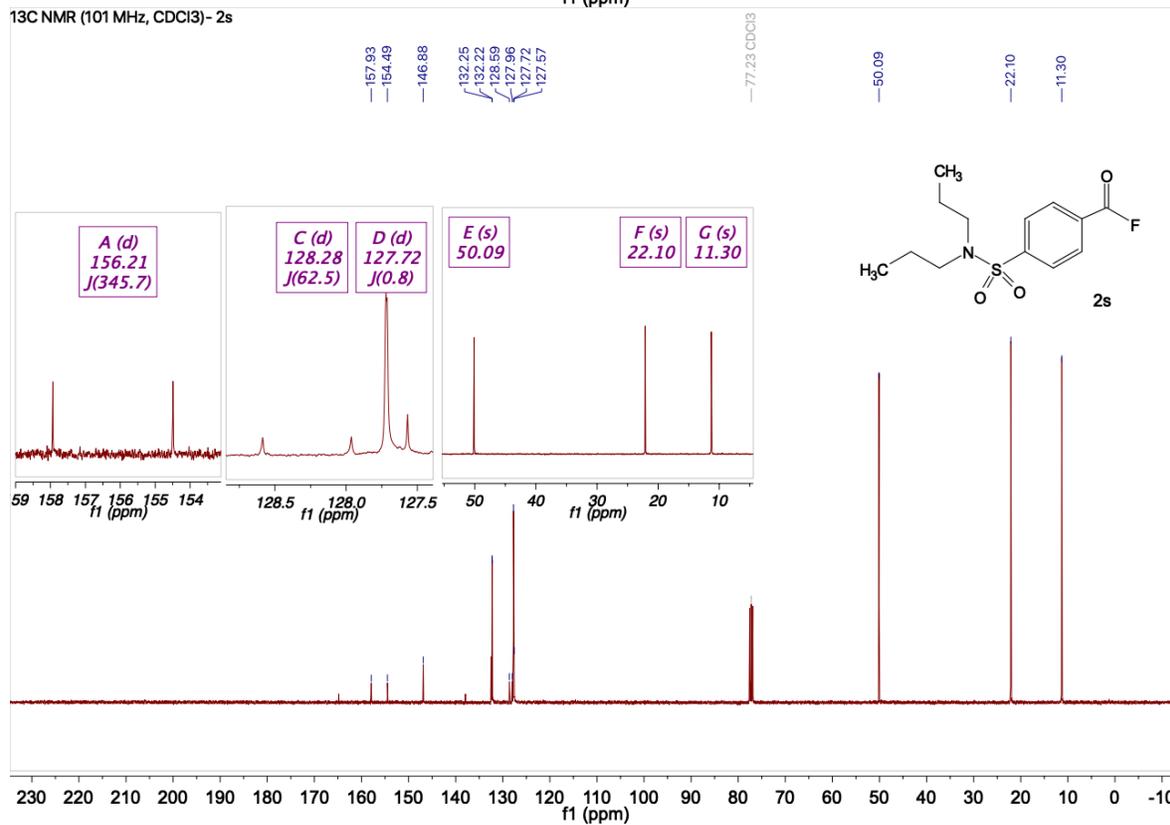
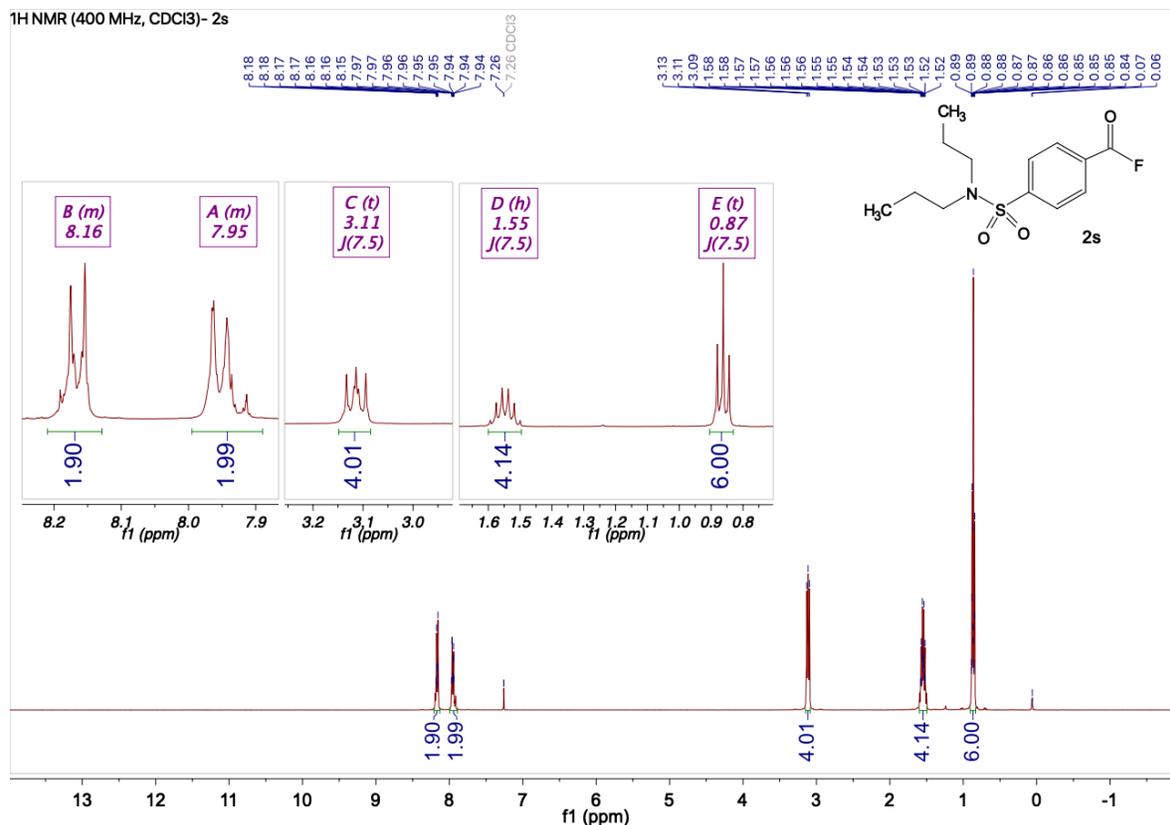


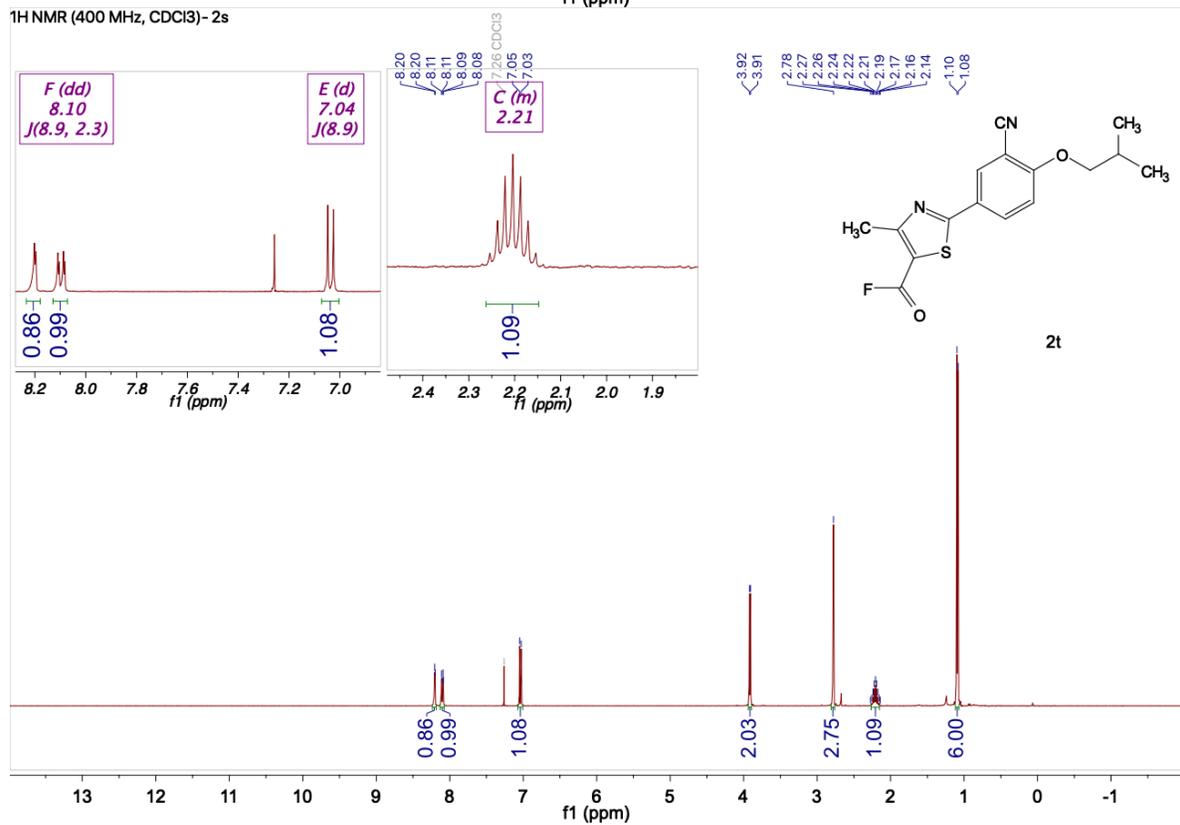
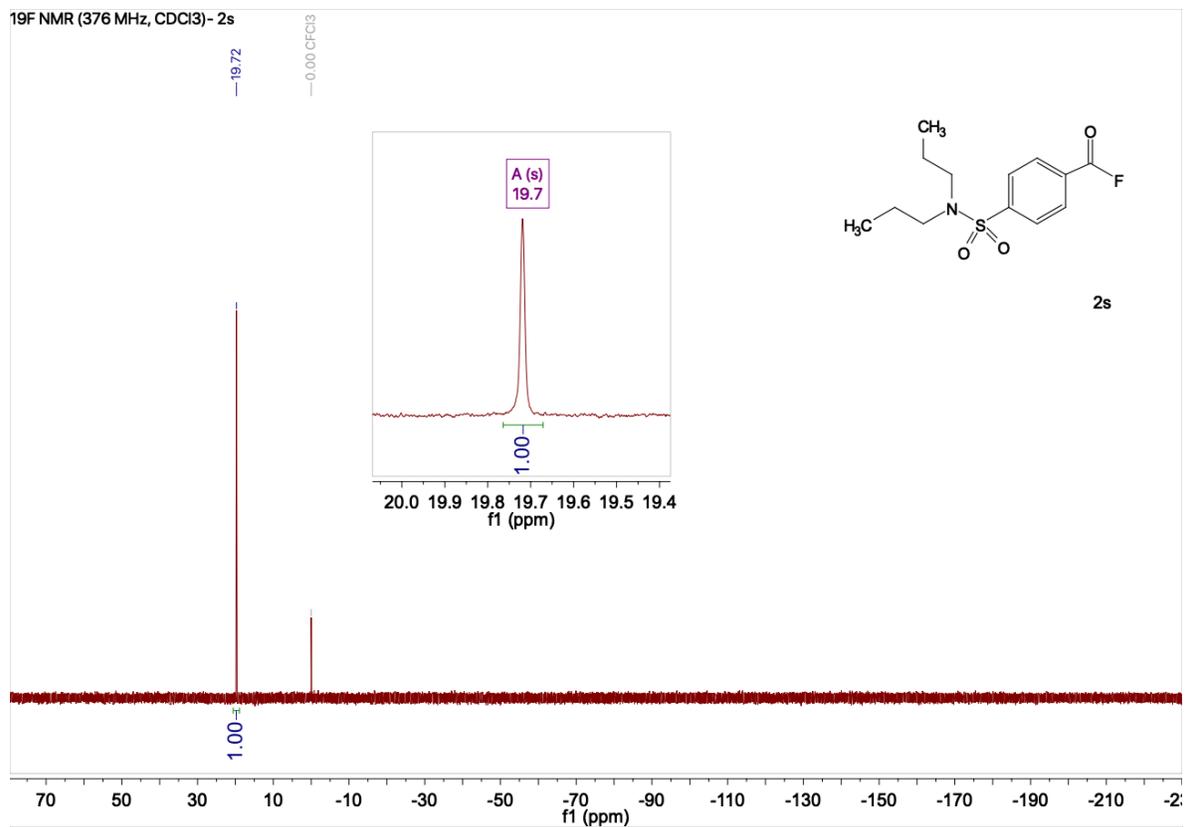
¹³C NMR (101 MHz, CDCl₃)- 2r

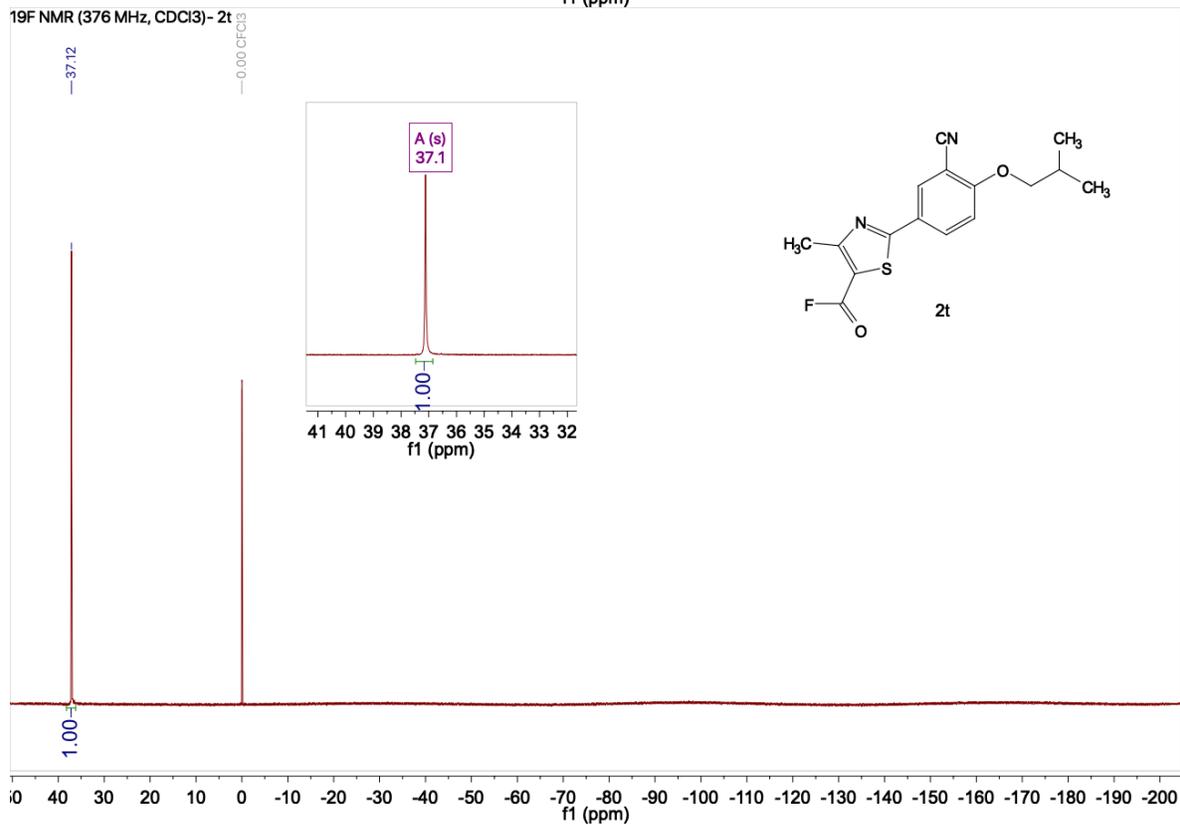
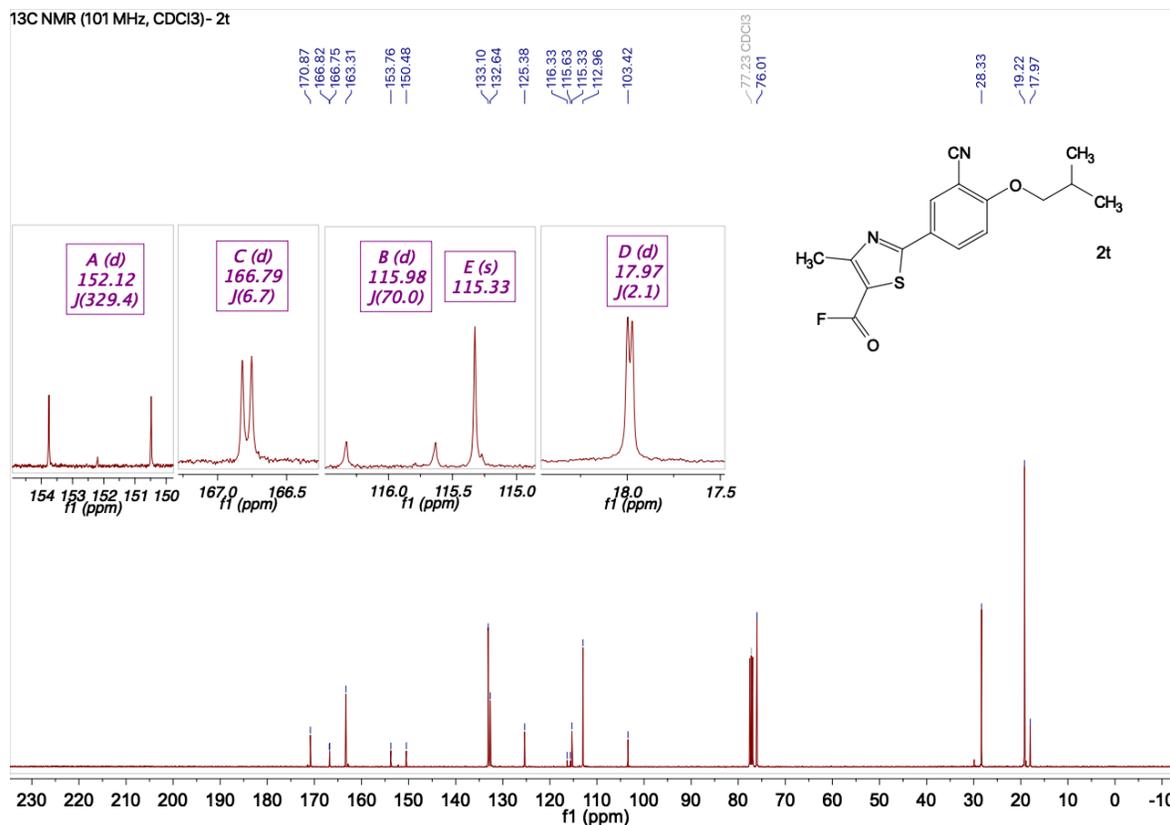


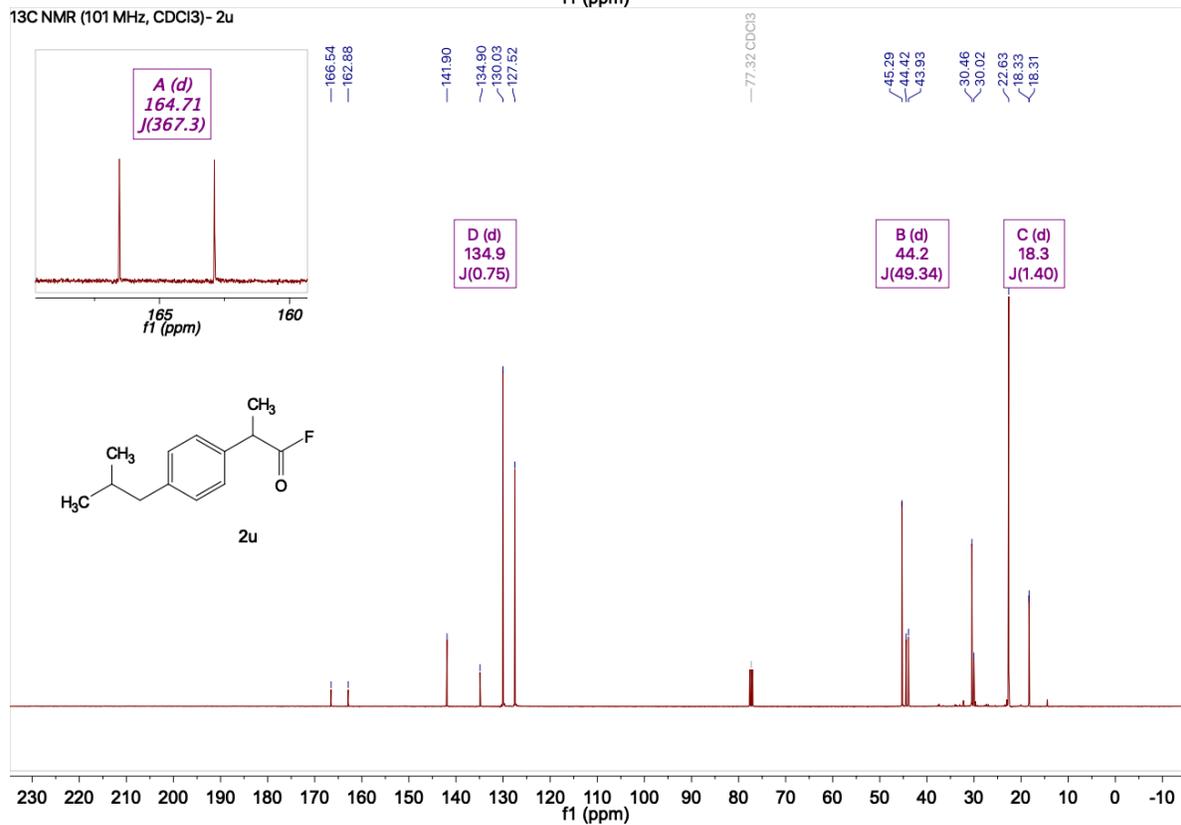
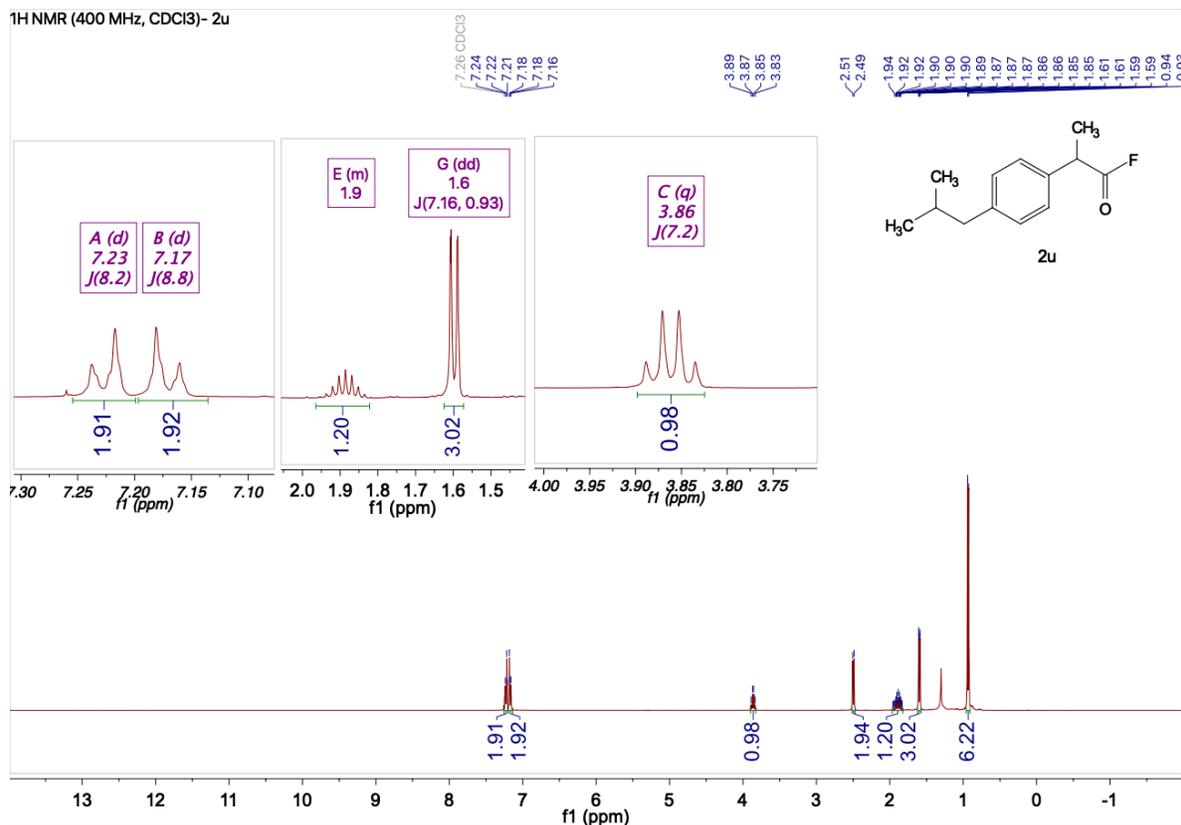
¹⁹F NMR (376 MHz, CDCl₃)- 2r

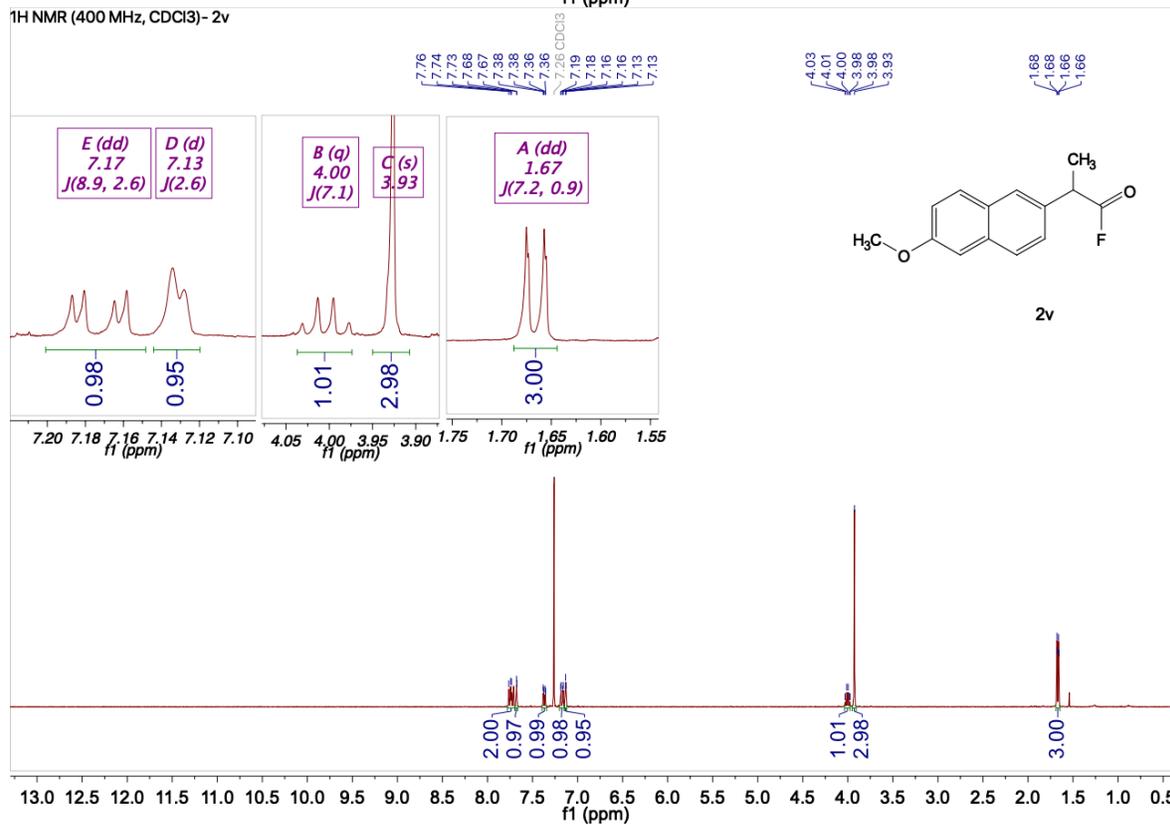
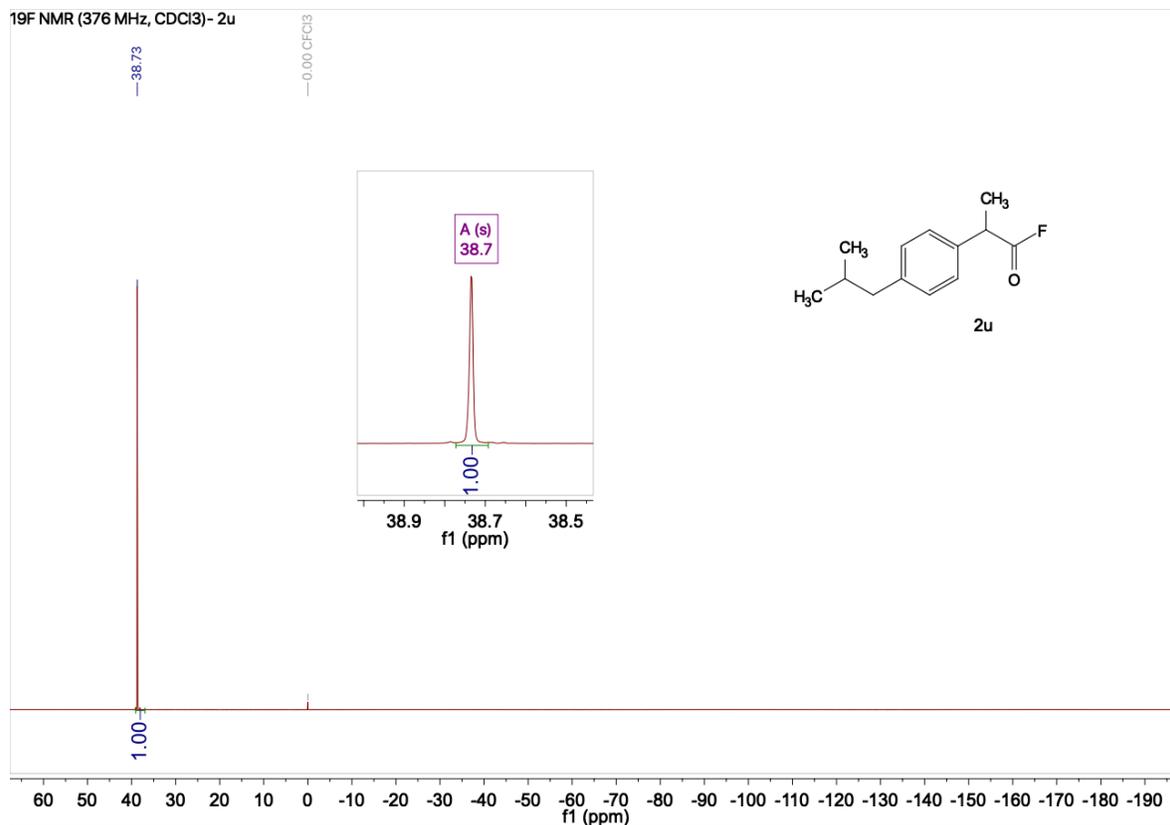


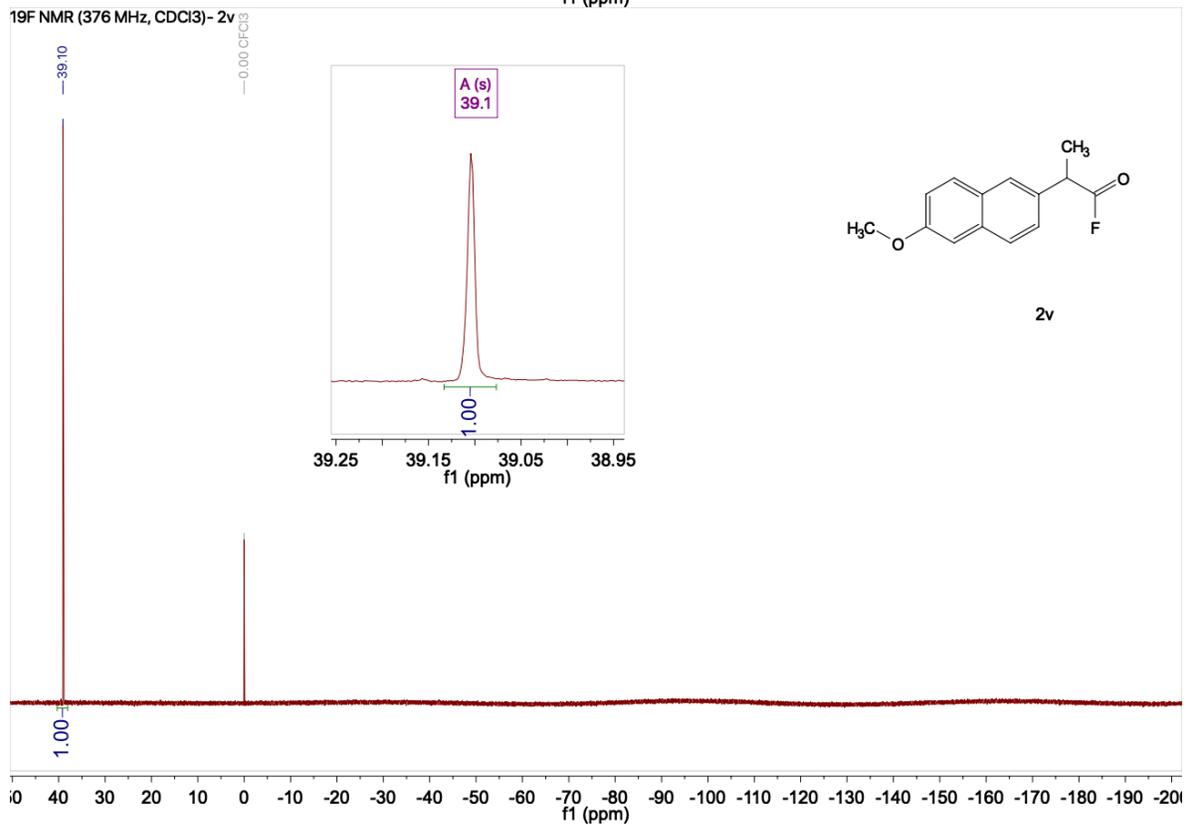
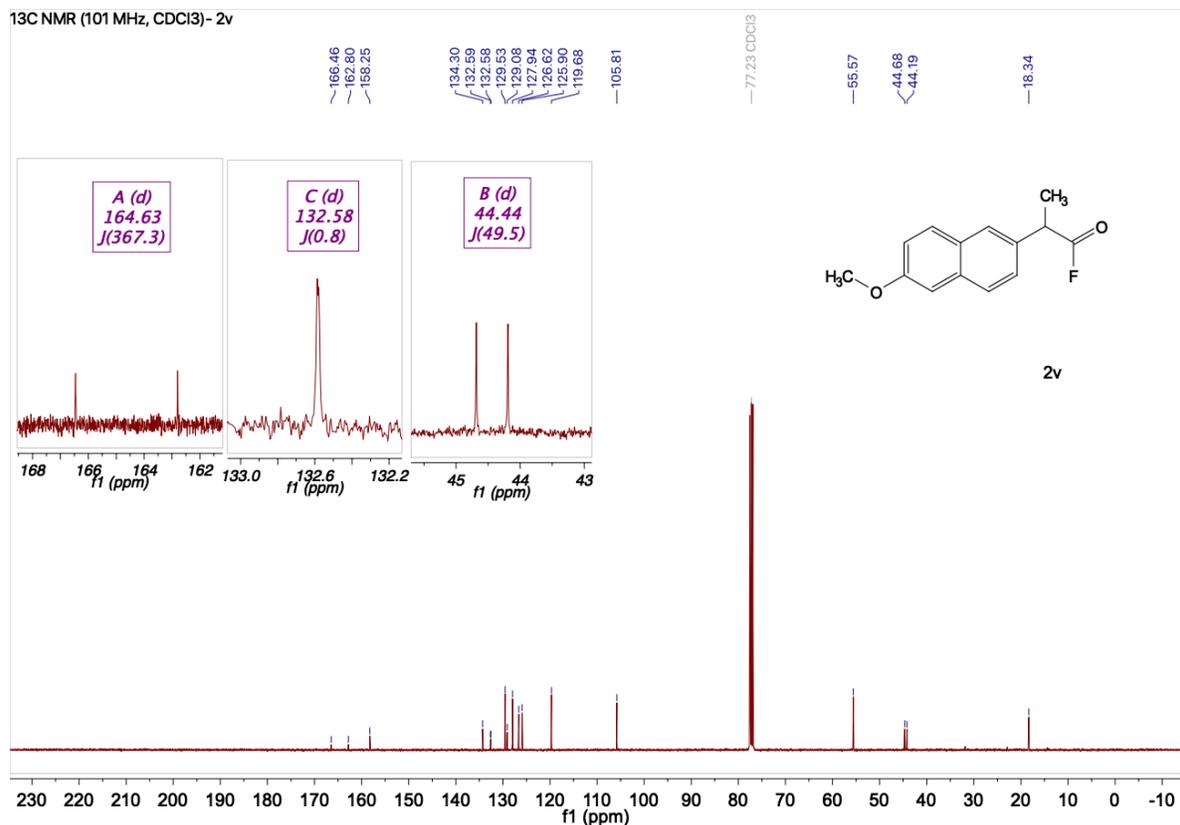




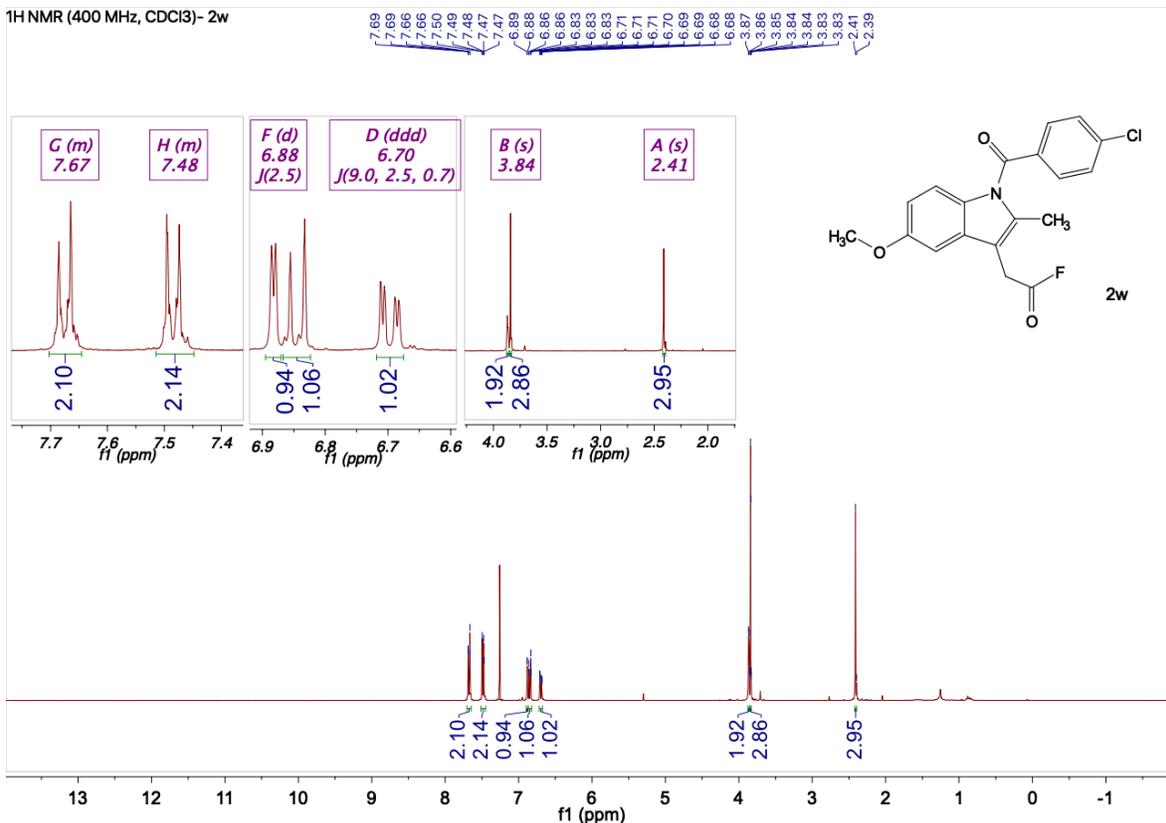




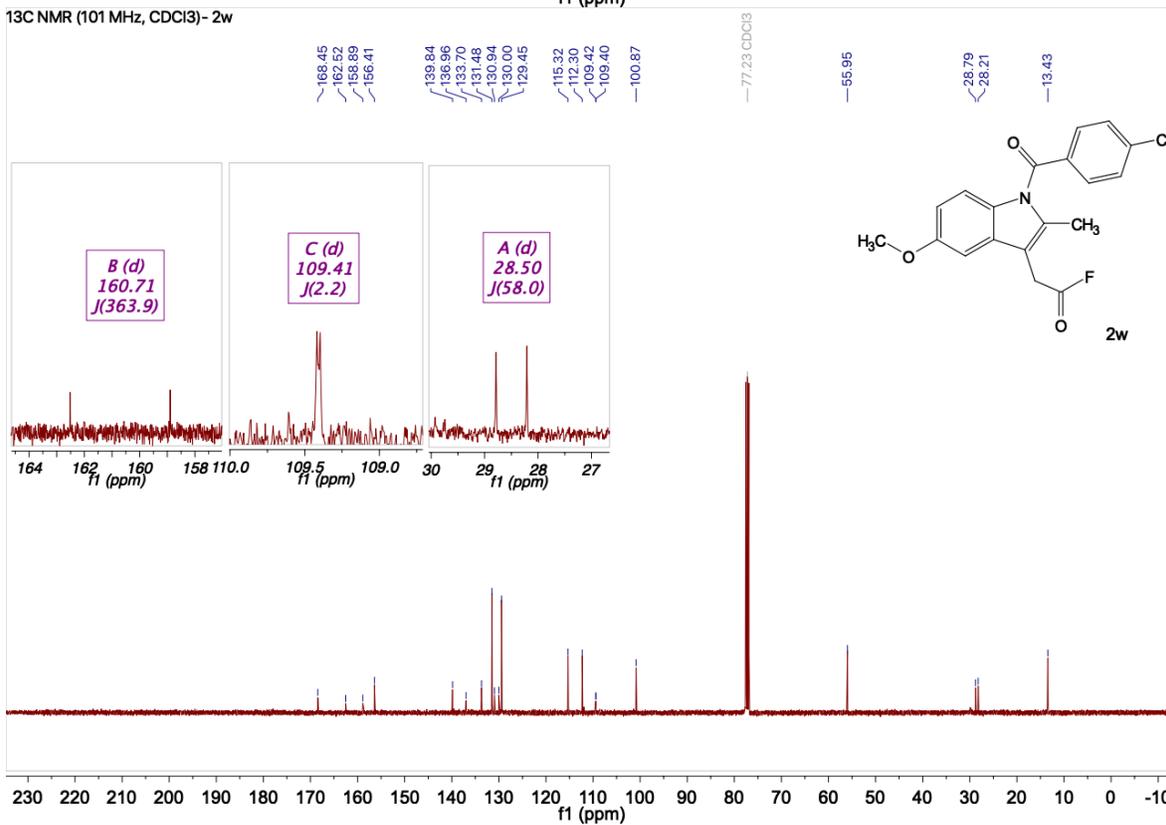


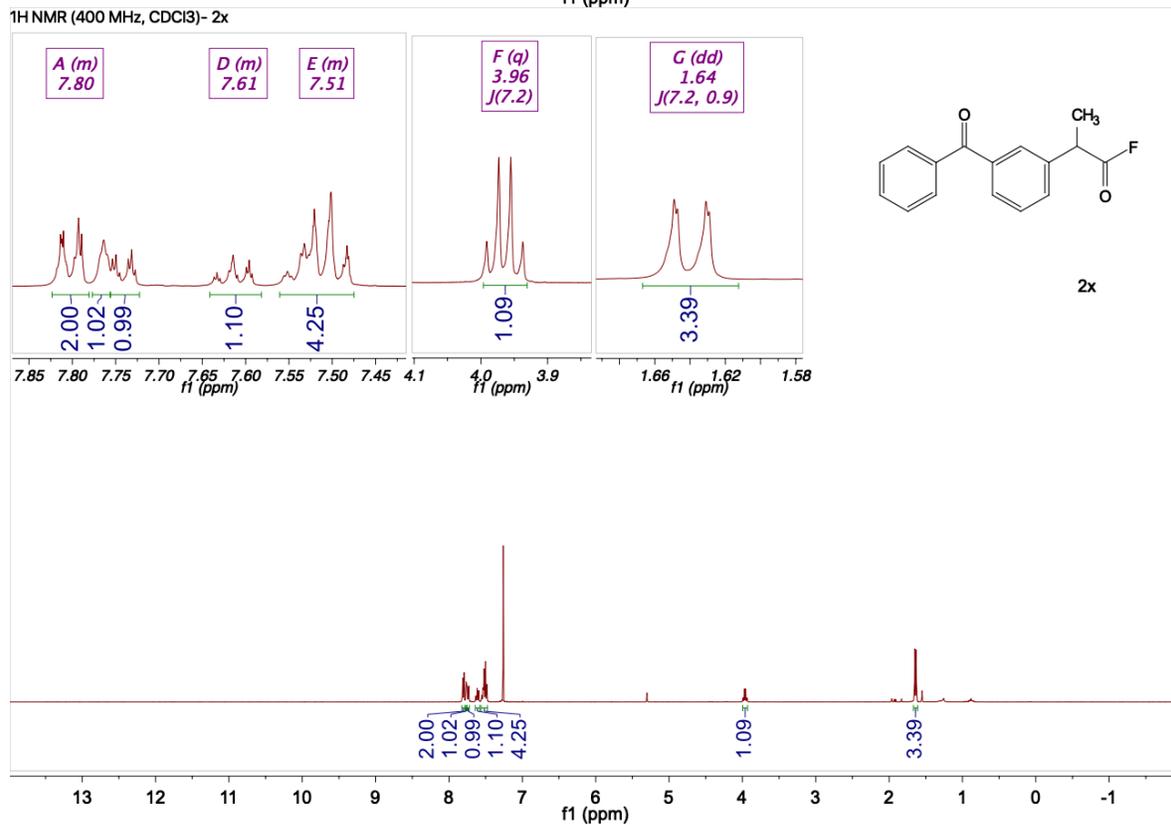
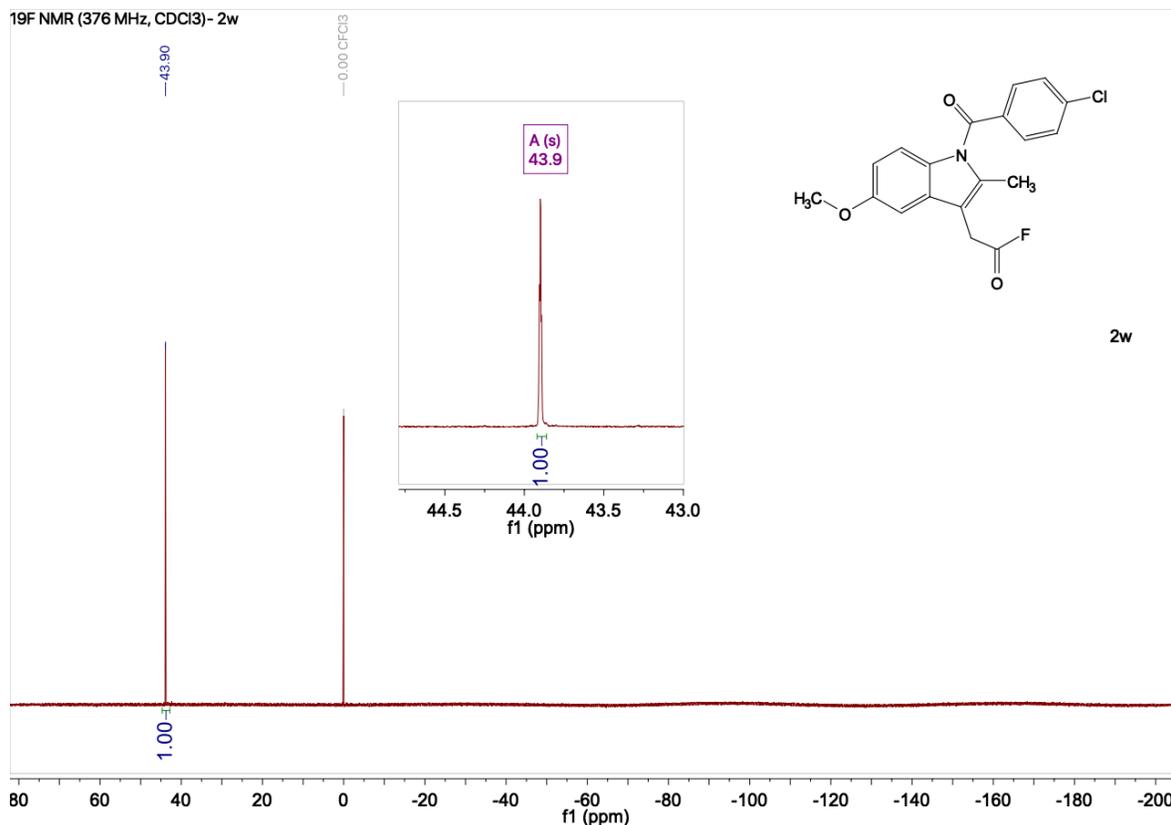


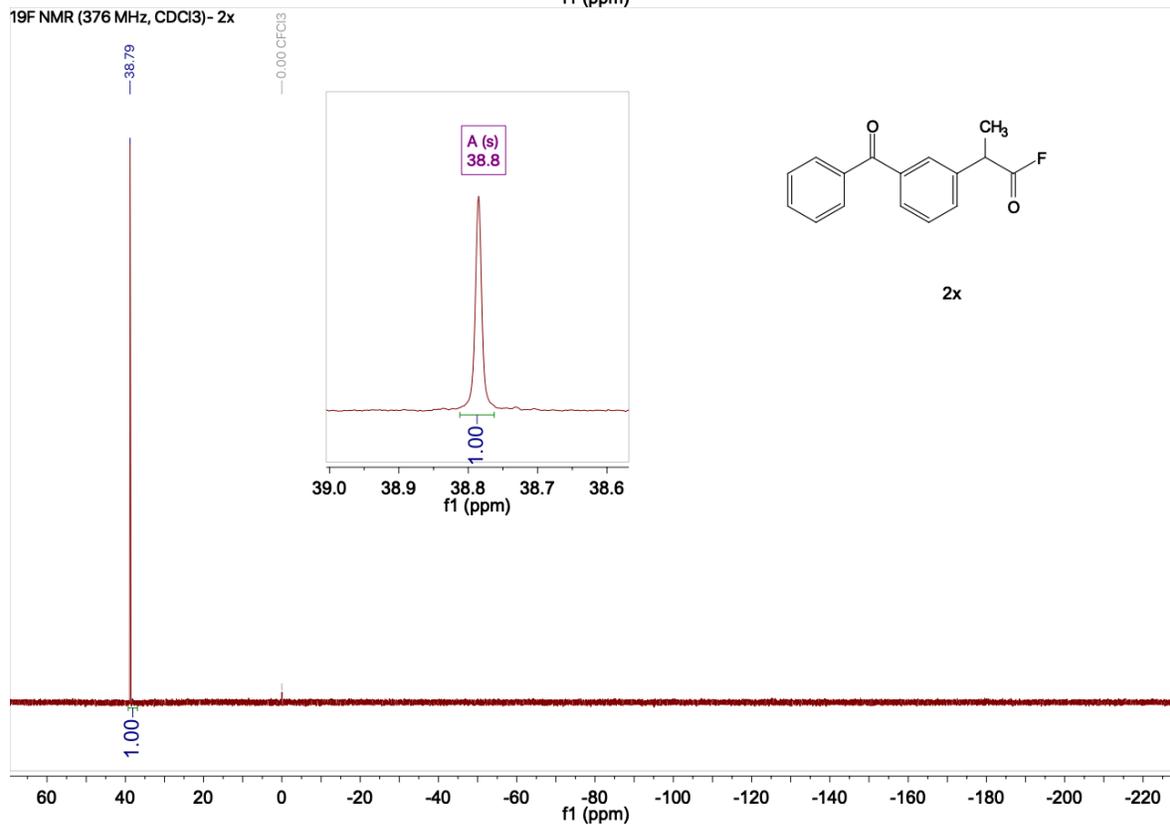
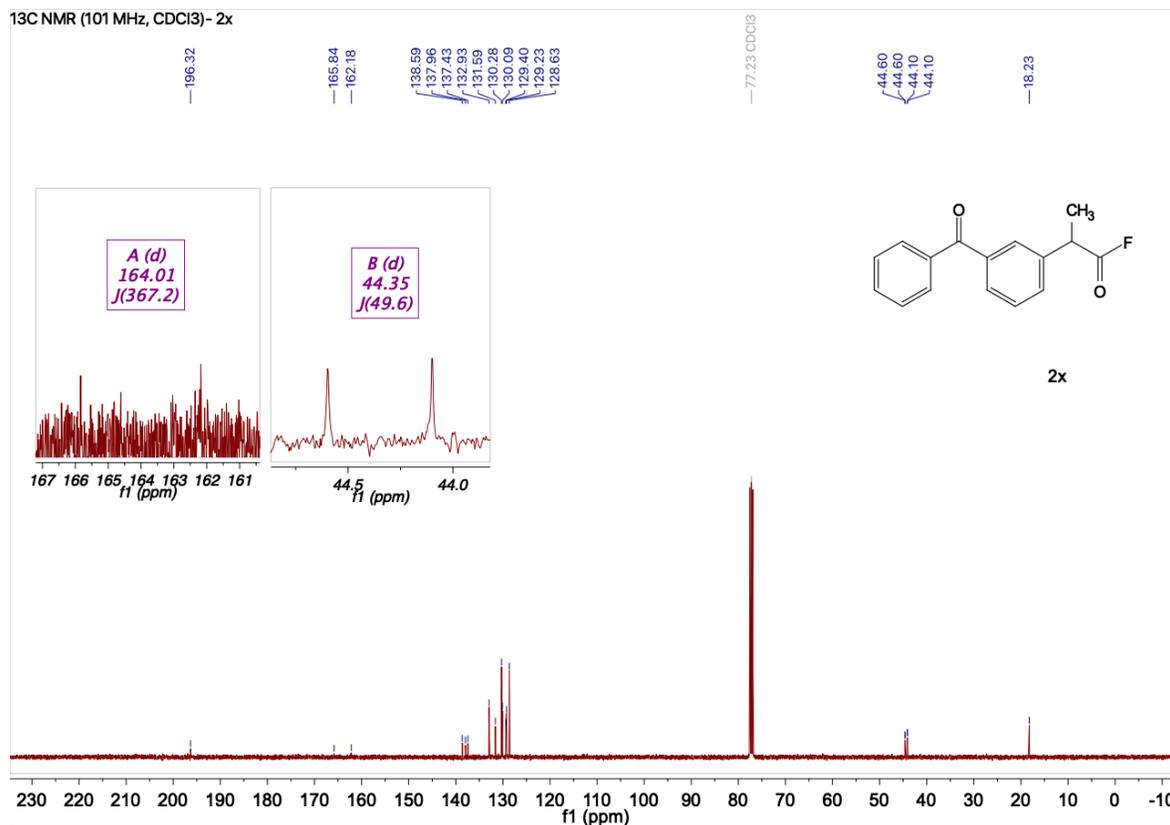
¹H NMR (400 MHz, CDCl₃)- 2w



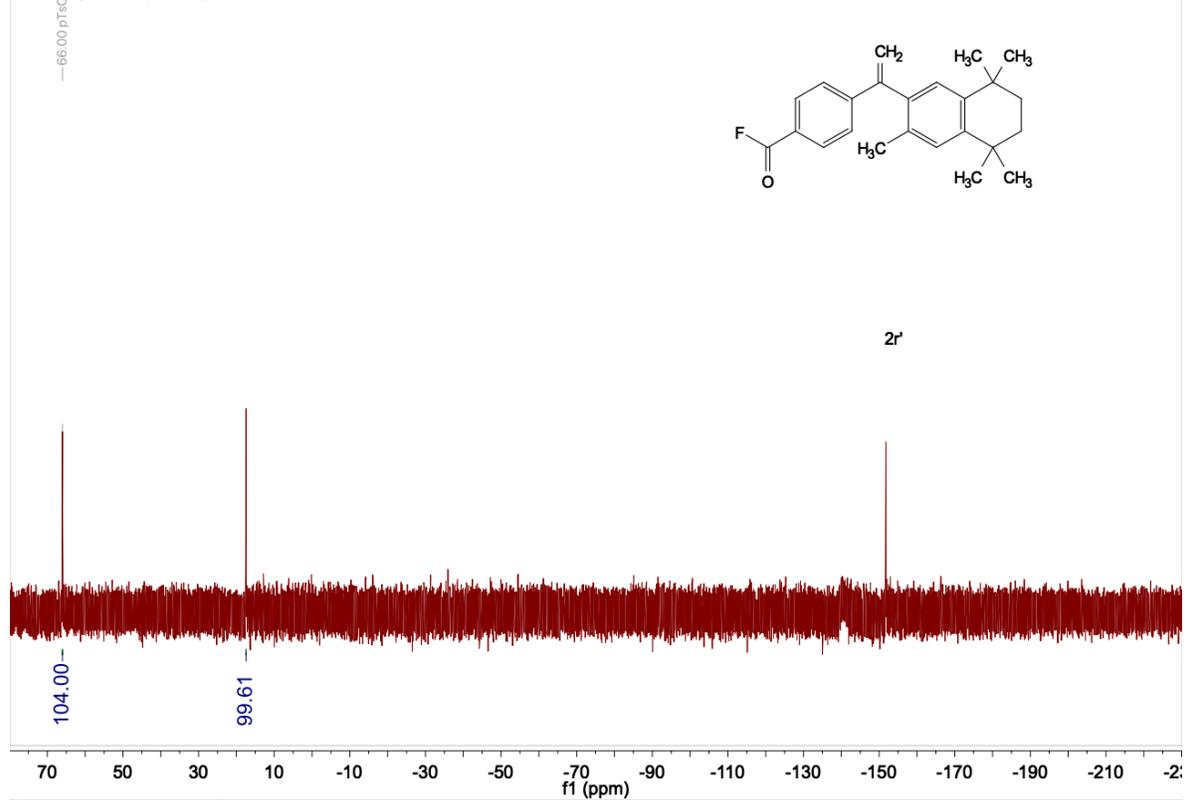
¹³C NMR (101 MHz, CDCl₃)- 2w



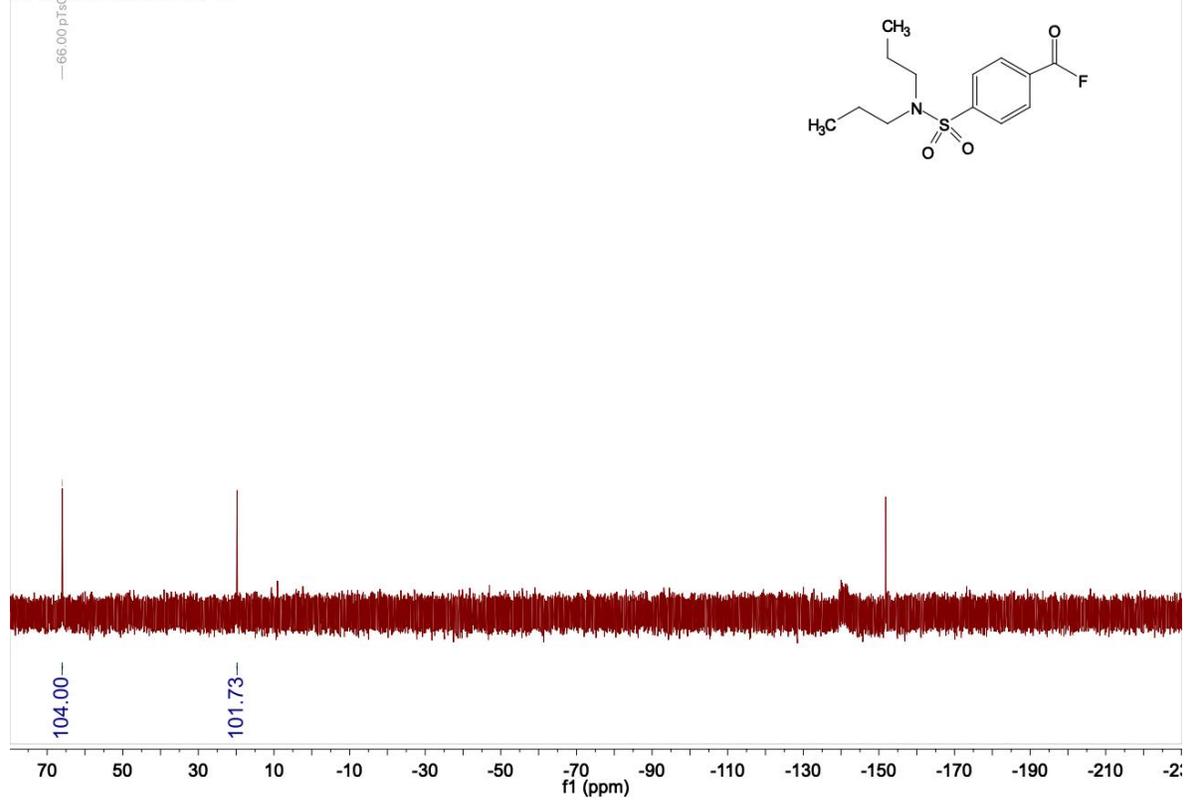




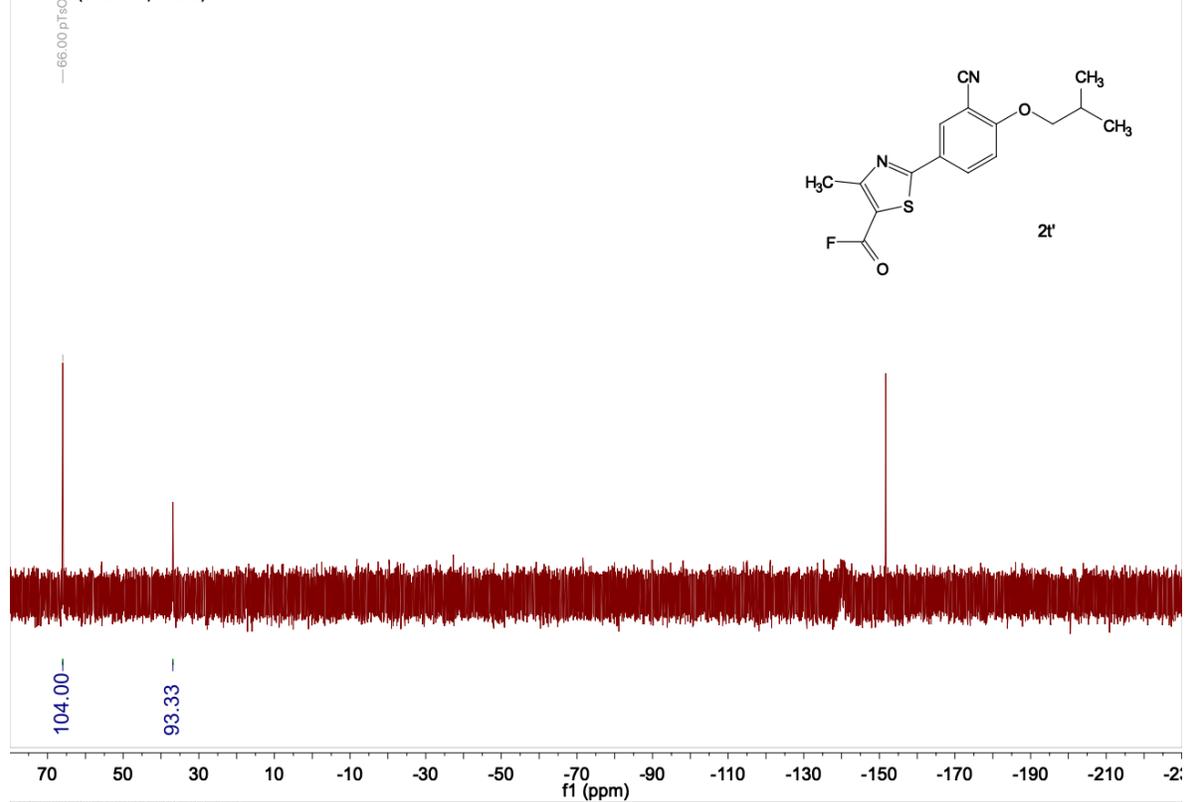
19F NMR (376 MHz, CDCl3)- 2r'



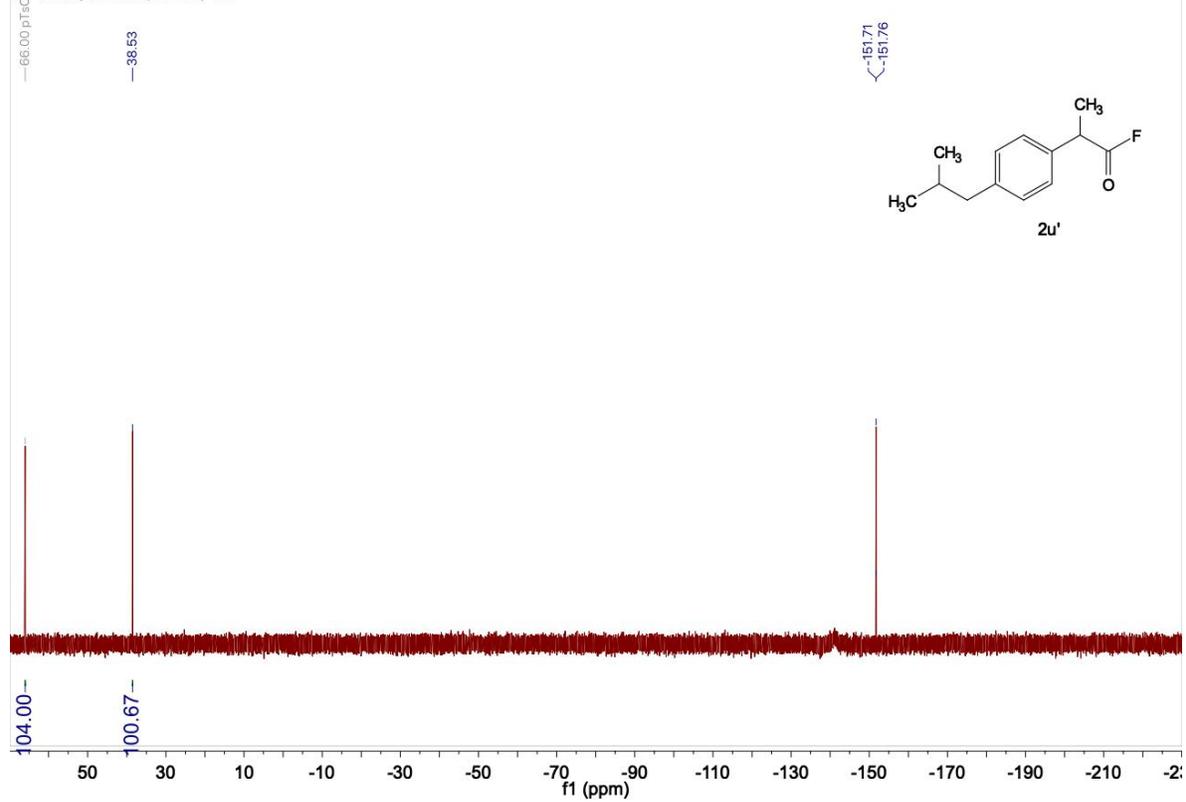
19F NMR (376 MHz, CDCl3)- 2s'



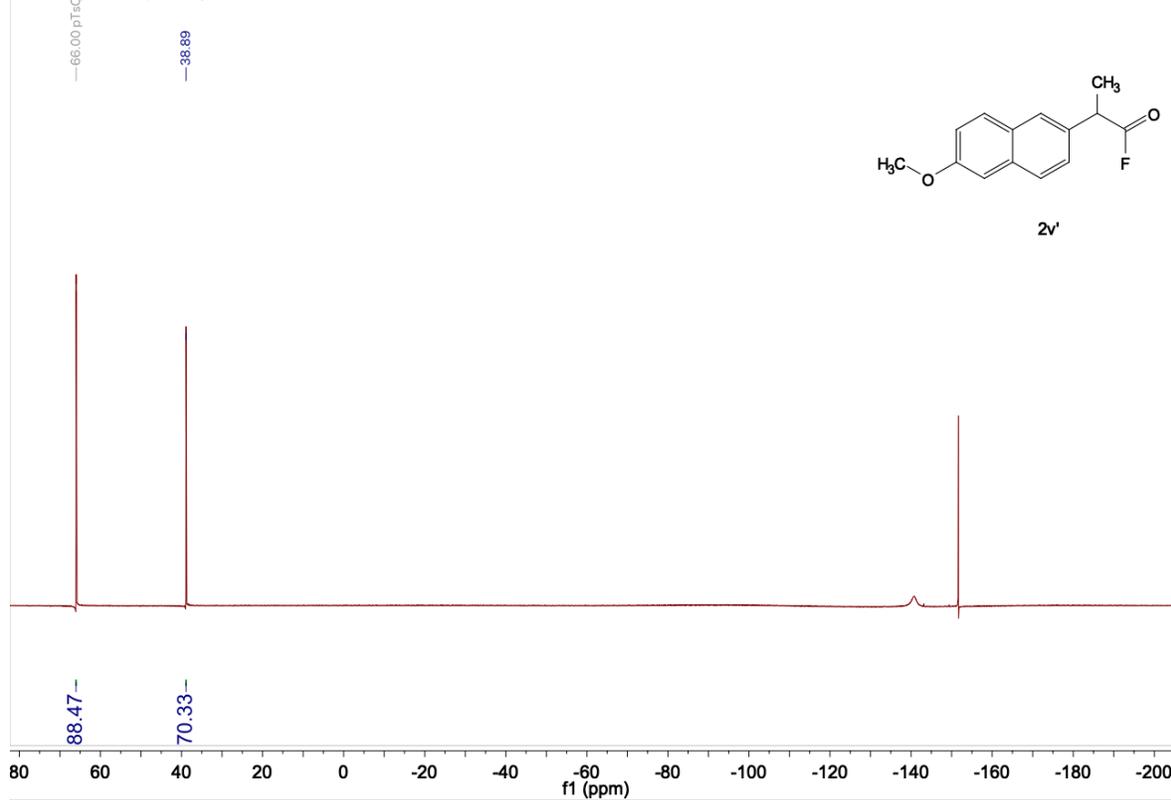
¹⁹F NMR (376 MHz, CDCl₃)- 2t'



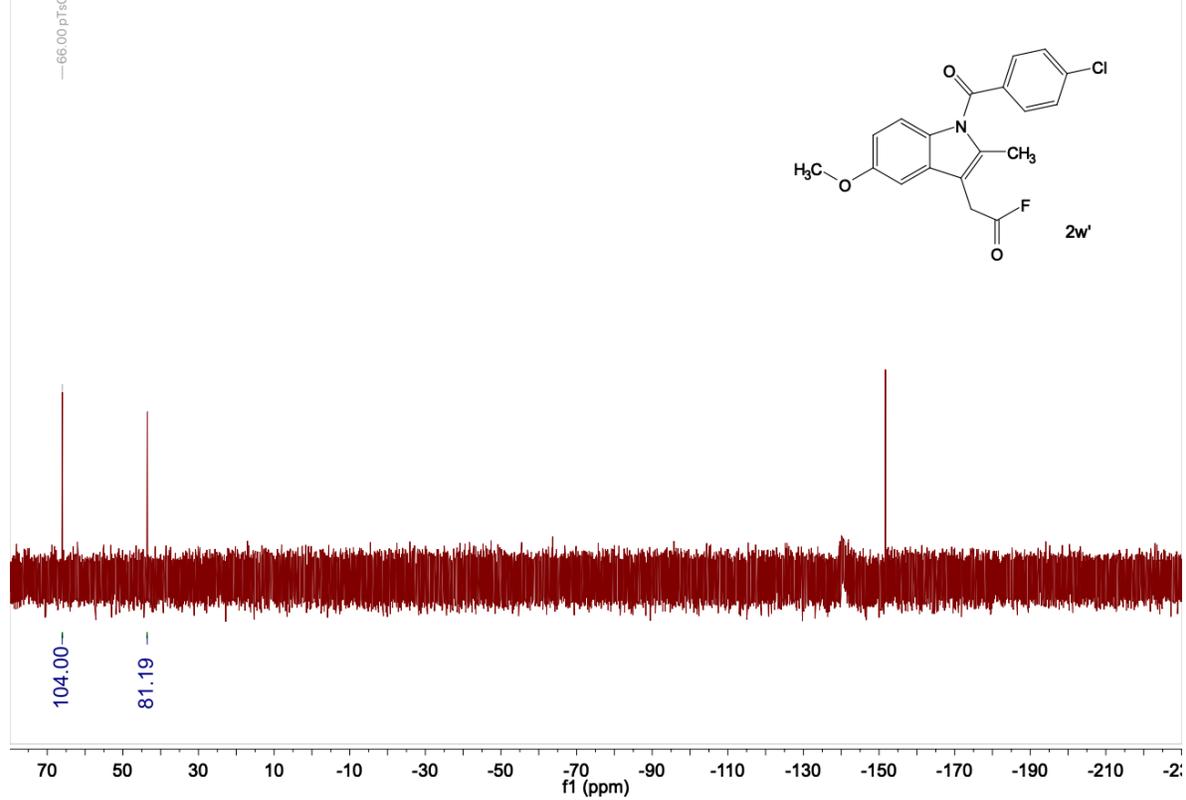
¹⁹F NMR (376 MHz, CDCl₃)- 2u'

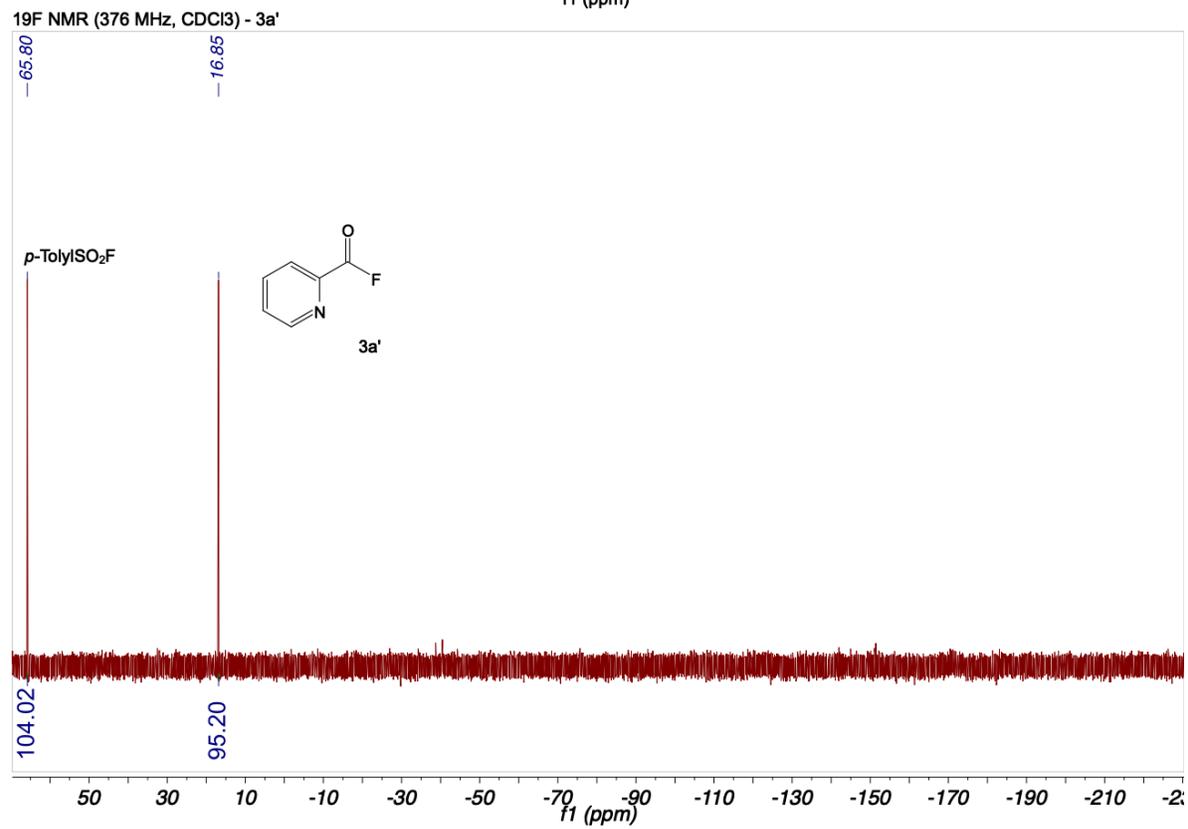
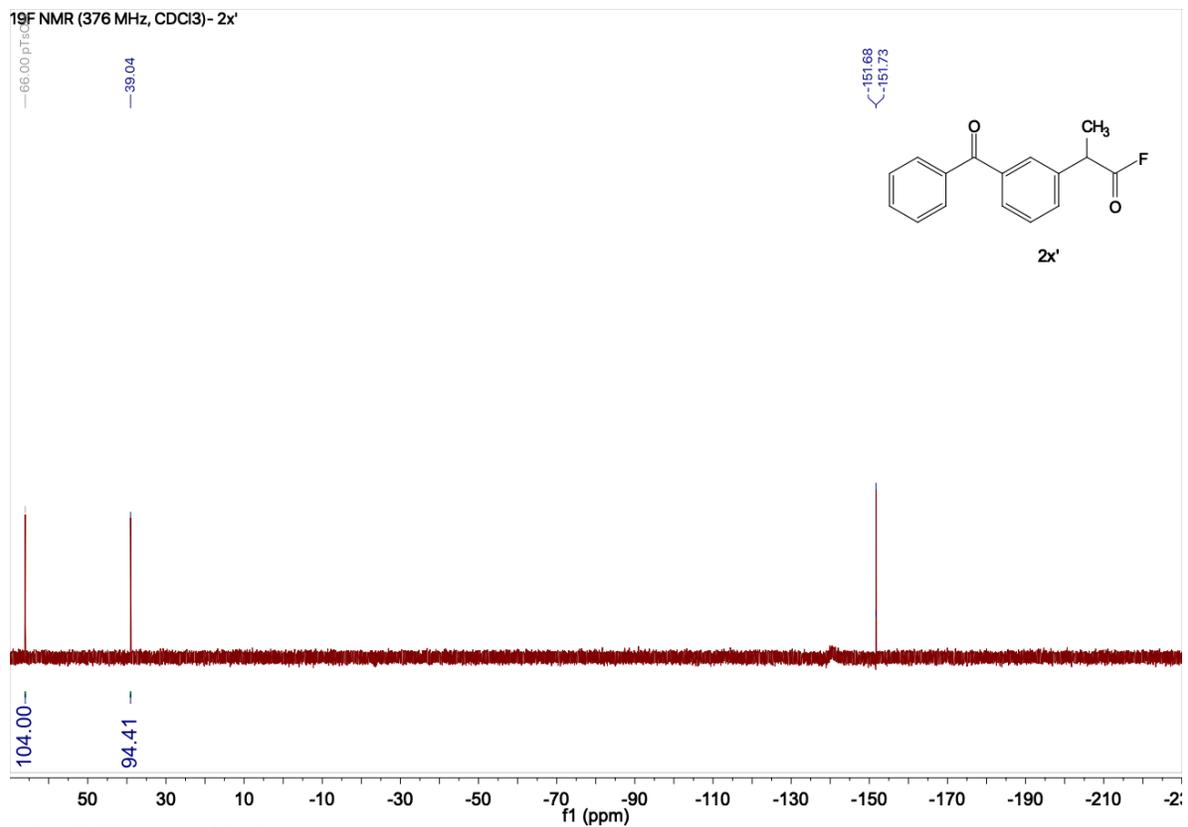


19F NMR (376 MHz, CDCl3)- 2v'

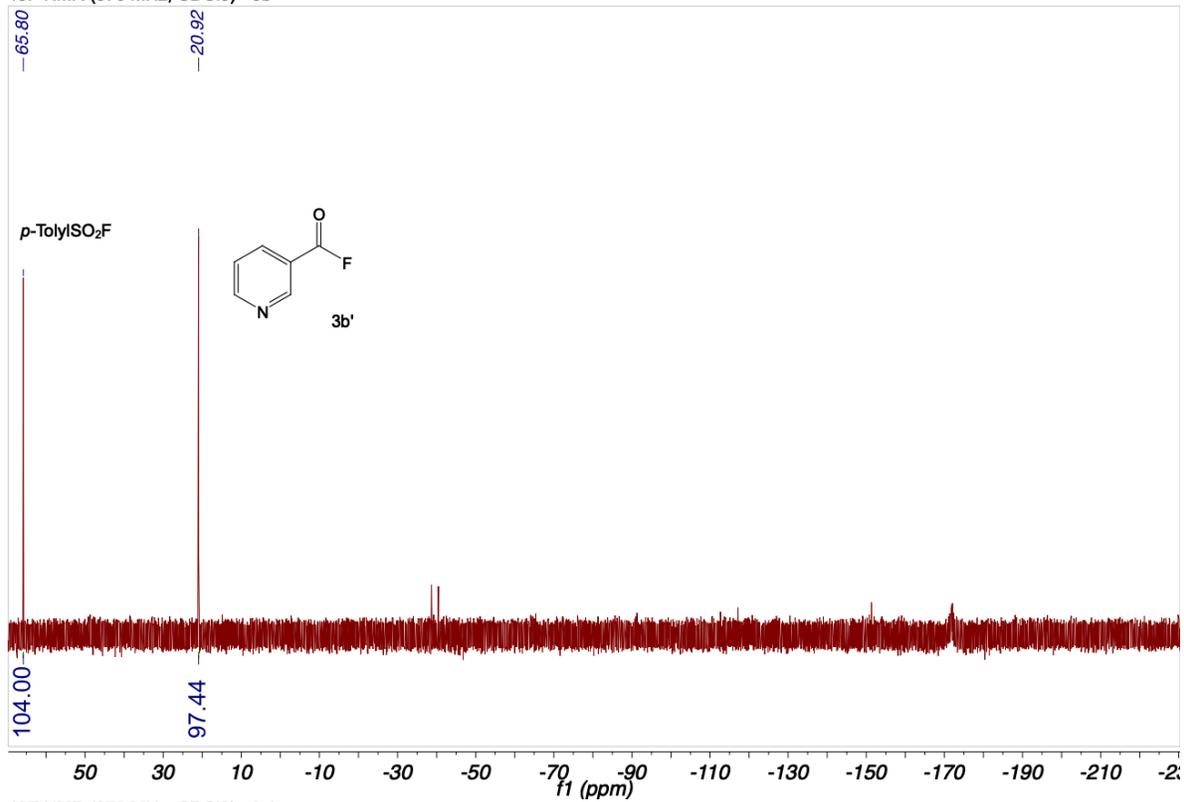


19F NMR (376 MHz, CDCl3)- 2w'

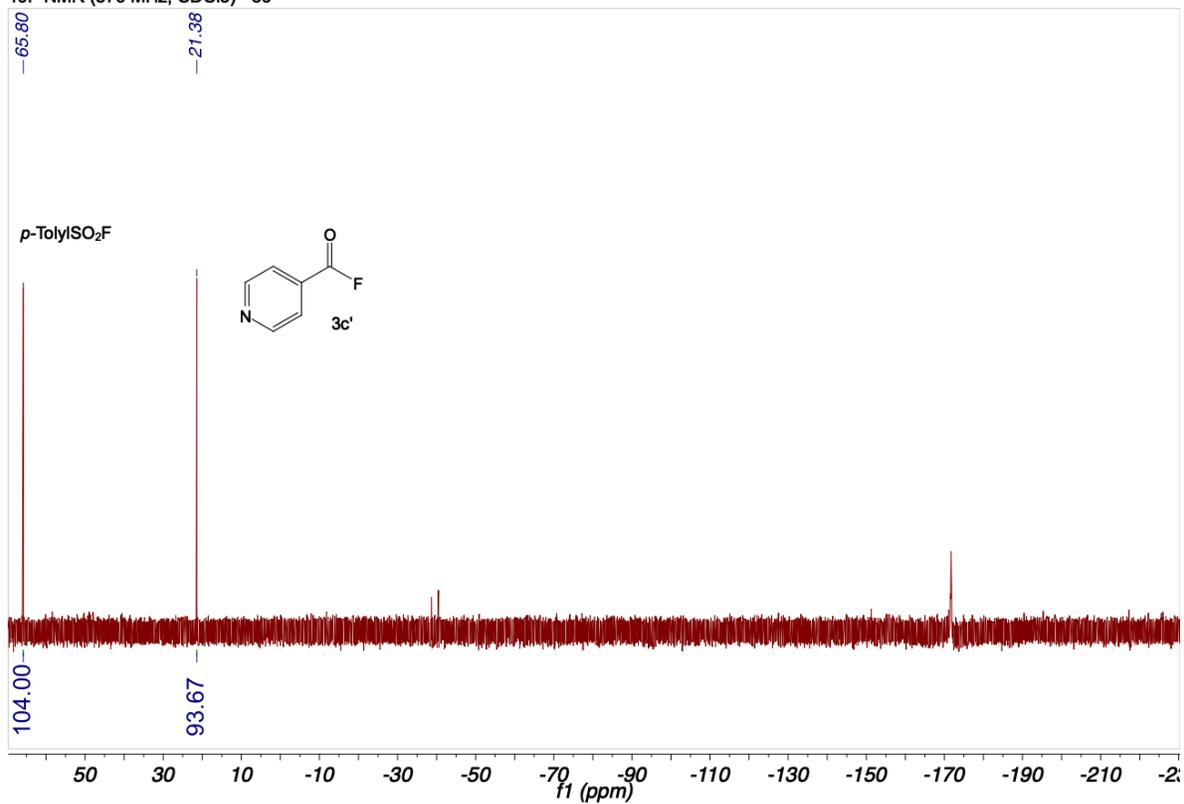




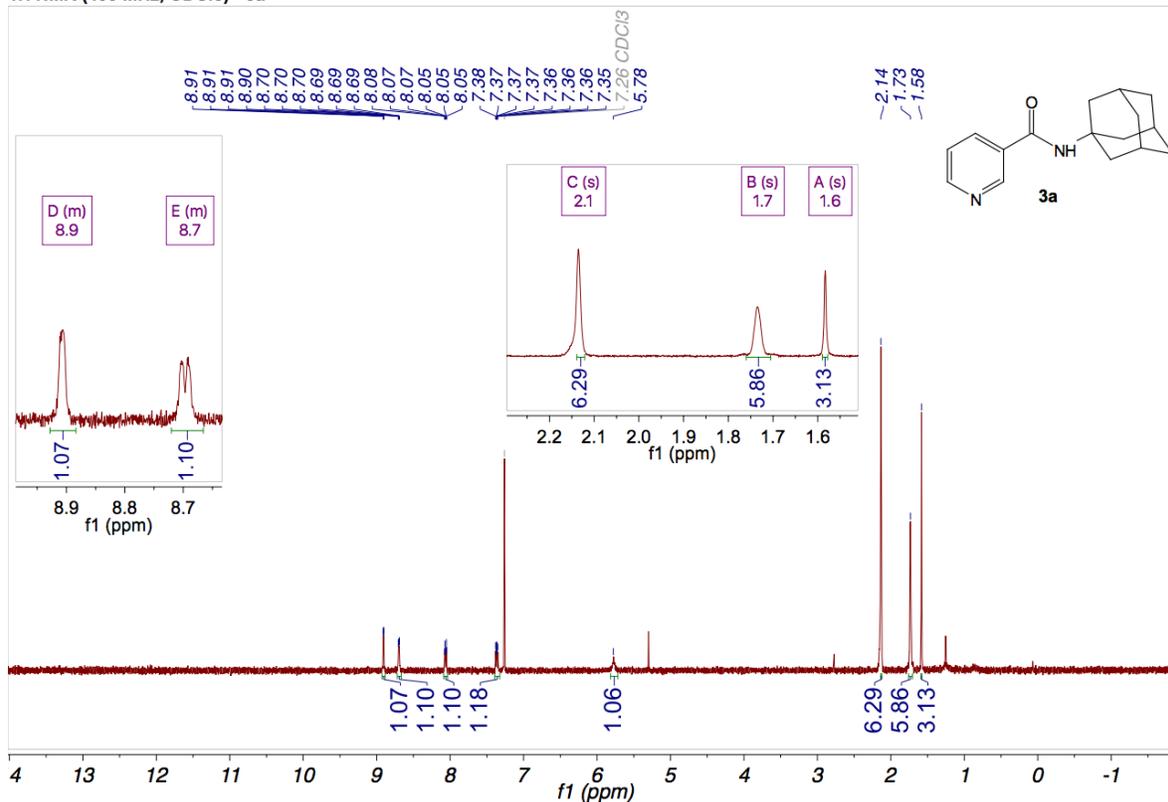
¹⁹F NMR (376 MHz, CDCl₃) - 3b'



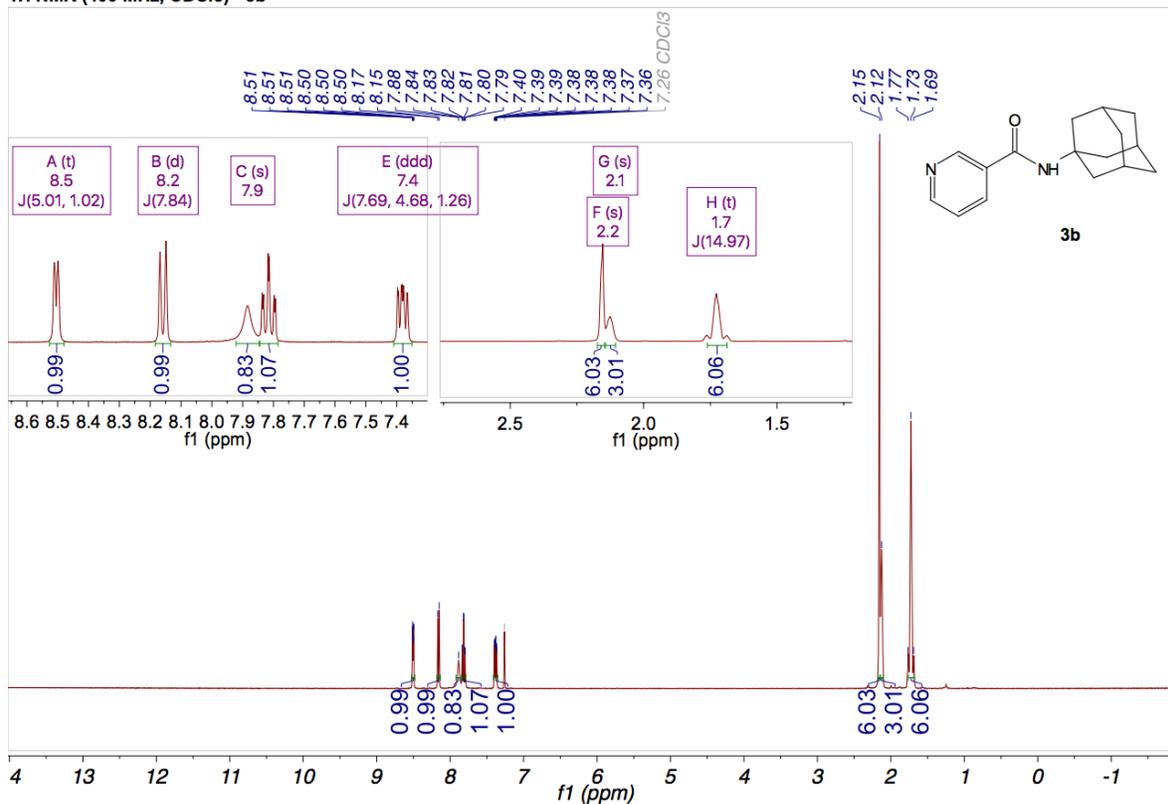
¹⁹F NMR (376 MHz, CDCl₃) - 3c'



1H NMR (400 MHz, CDCl3) - 3a



1H NMR (400 MHz, CDCl3) - 3b



1H NMR (400 MHz, CDCl3) - 3c

