Supporting Information

Hypervalent iodine catalysis enabled iterative multi-fluorination: not just a simple alternative for the electrochemical approach

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1. General Information

All reactions were performed under an atmosphere of nitrogen using standard Schlenk techniques unless otherwise indicated. All commercial reagents were used without further purification unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC) analysis. TLC plates were viewed under UV light and stained with potassium permanganate. Yields refer to products isolated after purification by column chromatography unless otherwise stated. Proton nuclear magnetic resonance (^{1}H NMR) spectra, carbon nuclear magnetic resonance (^{13}C NMR) spectra, and fluorine nuclear magnetic resonance (^{19}F NMR) were recorded on Bruker AV-400 (400 MHz) and JEOL-500 (500 MHz) spectrometers. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$ = δ 7.26). Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances IR spectra obtained from Thermo Scientific NICOLET 380 FT-IR (KCl card). HRMS were obtained on an Exactive Plus LC-MS (ESI) mass spectrometer with the use of a quadrupole analyzer or an Agilent 1290-6545XT mass spectrometer with a QTOF analyzer. All chemicals were purchased from *Innochem*, *Sigma-Aldrich* or *Energy Chemical* and used as received.

2. HF Sources

$Et_3N{\cdot}3HF$ = amine:HF / 1:3

$Pyr{\cdot}(HF)_x$ (Olah's reagent) = amine:HF / 1: 9.23 (calculated based on the physical data provided by the supplier, Sigma-Aldrich)

A mixture of amine:HF / 1:3.5 was obtained by mixing 0.057 mL of Pyr•(HF)x and 0.443 mL of $Et_3N{\cdot}3HF$.

A mixture of amine:HF / 1:5.0 was obtained by mixing 0.205 mL of Pyr•(HF)x and 0.295 mL of $Et_3N{\cdot}3HF$.

A mixture of amine:HF / 1:7.5 was obtained by mixing 0.780 mL of Pyr•(HF)x and 0.220 mL of $Et_3N{\cdot}3HF$.

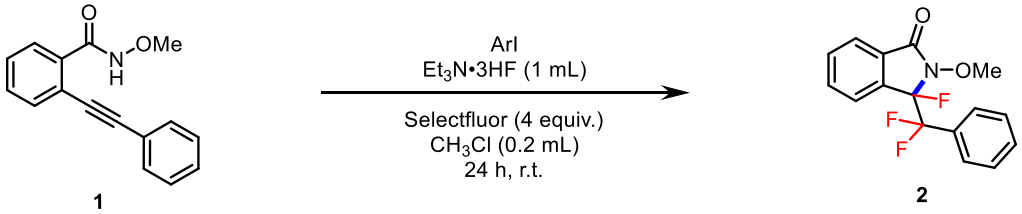
$Et_3N{\cdot}3HF$ Safety Statements: May be corrosive to metals. Fatal by inhalation, in contact with skin and if swallowed. Causes severe skin burns and eye damage. Suspected of causing genetic defects. Causes damage to organs: Respiratory system Central nervous system Pancreas. Causes damage to organs through prolonged or repeated exposure: Pituitary gland Liver Thyroid gland

Respiratory system Bone Nervous system Kidney Testis Central nervous system Teeth. Harmful to aquatic life. Harmful to aquatic life with long lasting effects. **Prevention**: Obtain special instructions before use. Do not handle until all safety precautions have been read and understood. Keep only in original container. Do not breathe mist, vapors, or spray. Do not get in eyes, on skin, or on clothing. Use only outdoors or in a well-ventilated area. Avoid release to the environment. Do not eat, drink, or smoke when using this product. Wash hands and face thoroughly after handling. Wear respiratory protection. Wear protective gloves, protective clothing, face protection.

Pyr·9HF Safety Statements: Pyr·9HF is a corrosive and toxic substance that will corrode glassware. Safe handling can be conducted with plastic syringes and metal needles, with $NaHCO_3$ (aq.) or NaOH (aq.) employed to quench excess HF. Though reactions should not be conducted in glassware when employing Pyr·9HF, glassware may be used to quench reactions provided sufficient quantities of base are present. Always handle Pyr·9HF while wearing gloves and in a fumehood. As a precautionary measure, have calcium gluconate gel nearby and applyimmediately and liberally on skin exposed to HF.

3. Optimization of the Reaction Conditions

Screening of catalyst types and amounts



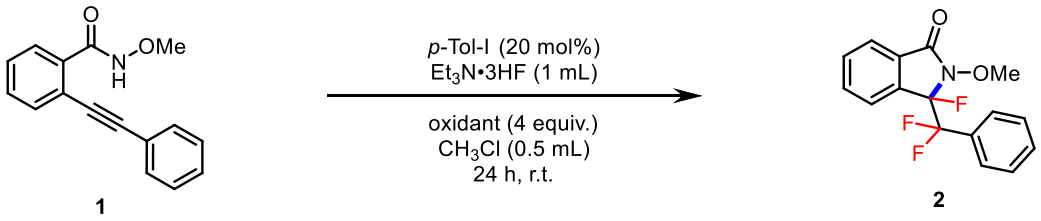
1 **2**

entry	ArI	**2** (%)[a]
1	4-OMeC_6H_4**I** (20 mol%)	12
2	4-$CF_3C_6H_4$**I** (20 mol%)	17
3	C_6H_5**I** (20 mol%)	64
4	4-^{t}BuC_6H_4**I** (20 mol%)	67
5	4-BrC_6H_4**I** (20 mol%)	56
6	*p*-Tol-I (20 mol%)	85(82[b])
7	*p*-Tol-I (10 mol%)	52

[a] Yields were determined by ^{19}F *NMR* with $C_6H_5OCF_3$ as the internal standard.
[b] Isolated yield N.D. (not detected)

Using strongly electron-withdrawing -OMe (entry 1) and strongly electron-donating -CF3 (entry 2) substituted iodobenzene catalysts resulted in a substantial decrease in yield. In contrast, compared to 4-methyliodobenzene (entry 6), iodobenzene, 4-bromoiodobenzene, and 4-tert-butyliodobenzene exhibited lower catalytic activity (entry 3-5). Reducing the amount of 4-methyliodobenzene resulted in a significant reduction in yield (entry 7).

Screening of oxidizing agents



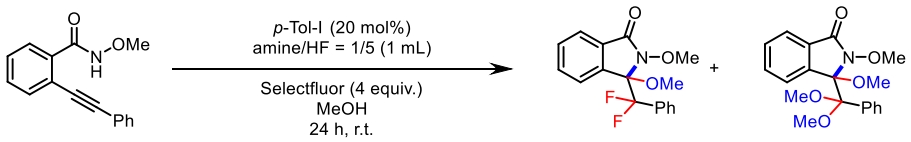
1 **2**

entry	oxidant (4 equiv.)	**2** (%)[a]
1	Selectfluor	85
2	*m*CPBA	N.D.
3	H_2O_2	N.D.
4	PIDA	N.D.
5	PIFA	N.D.
6	no *p*-Tol-I, PIFA	N.D.
7	no *p*-Tol-I, PIDA	N.D.

[a] Yields were determined by ^{19}F *NMR* with $C_6H_5OCF_3$ as the internal standard.
[b] Isolated yield N.D. (not detected)

We tried common oxidizing agents used to generate difluoroaryl iodine (III) and the reaction could not occur (entry 2-3). In addition to this, commercially available highvalent iodine (III) reagent reagents are not effective oxidizing agents (entry 4-7).

Conditional screening on 24 and 25



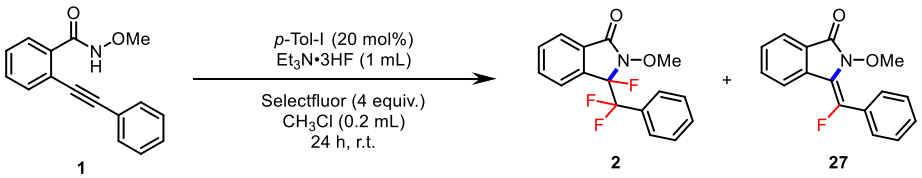
1 **24** **25**

entry	variation	**24**[a]	**25**[a]
1	MeOH 1.0 mL	15%	21%
2	MeOH 0.5 mL	40%	31%
3	MeOH 0.1 mL	68%	N.D.
4	amine/HF = 1/5 (0.5 mL)	20%	37%
5	no F source	-	N.D.

[a] *Yields were determined by ^1H NMR with CH_2Br_2 as the internal standard.*

Increasing the amount of methanol (entry 1) or decreasing the amount of fluorine source (entry 4) can slightly increase the ratio of product 25/24, but it is not possible to control the reaction to produce only 25. The reaction requires the presence of a fluorine source for the reaction to occur (entry 5), and therefore the production of the fluorinated product 24 is unavoidable.

Conditional screening on 1 and 27



1 **2** **27**

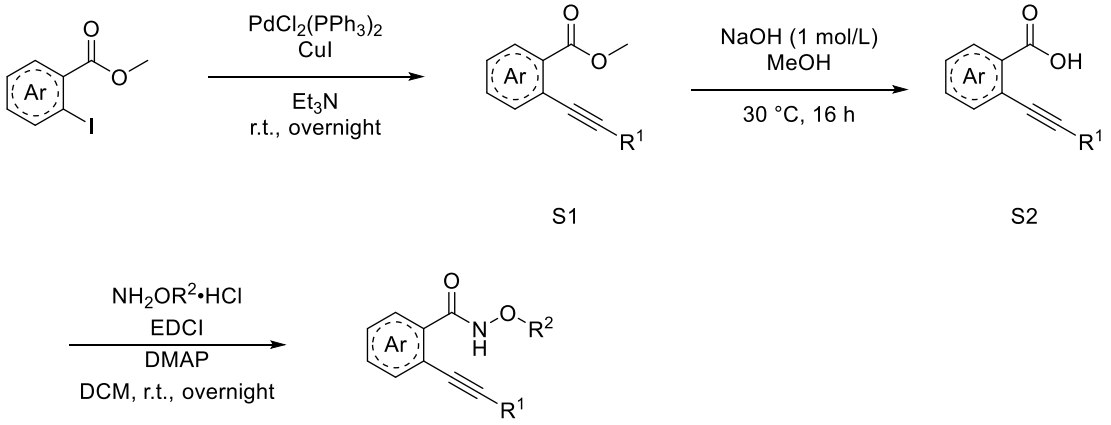
entry	variation	**2** (%)[a]	**27** (%)[a]
1	none	85	N.D.
2	Selectfluor (3 equiv.)	70	N.D.
3	Selectfluor (2 equiv.)	54	<5%
4	Selectfluor (1 equiv.)	35	<5%
5	18 h	67	N.D.
6	12 h	42	<5%
7	6 h	23	<5%

[a] Yields were determined by ^{19}F *NMR* with $C_6H_5OCF_3$ as the internal standard.
N.D. (not detected)

We have tried decreasing the amount of oxidizing agent (entry2-4) or reducing the reaction time (entry5-7), but only trace amounts of 27 were obtained.

4. General Procedures

General procedure for the synthesis of 2-alkynylbenzamides[1]

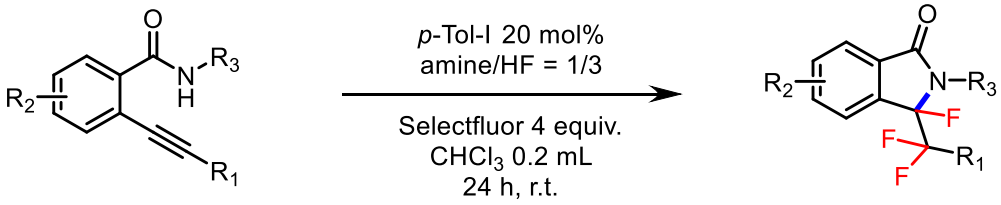


Step 1: To a solution of the methyl 2-iodobenzoate (10.0 mmol, 1.0 equiv.) in Et_3N (30 mL), a terminal alkyne (12.0 mmol, 1.2 equiv.) and $Pd(PPh_3)_2Cl_2$ (0.1 mmol, 70 mg, 1 mol%) were added. After 5 min stirring at room temperature, CuI (0.2 mmol, 38 mg, 2 mol%) was added and the reaction mixture was stirred overnight. The reaction mixture was then filtered. The solvent was removed in vacuo and the crude residue was purified by flash chromatography (EtOAc/Petroleum ether mixtures) on silica gel (300-400 mesh) to give S1.

Step 2: A 100 mL reaction flask was equipped with a magnetic stirring bar and charged with S1 (5.0 mmol, 1.0 equiv.) in 30 mL MeOH. NaOH (1 M, 10 mL) was dropwise added to the solution through a dropping funnel. The reaction mixture was stirred at 30 °C for 16 h, then acidified by HCl (1 M). The resulting mixture was extracted by EtOAc (3 x 20 mL) and the combined organic layer was dried by Na_2SO_4 and then filtered. The solvent was removed in vacuo to afford S2, which was used without further purification.

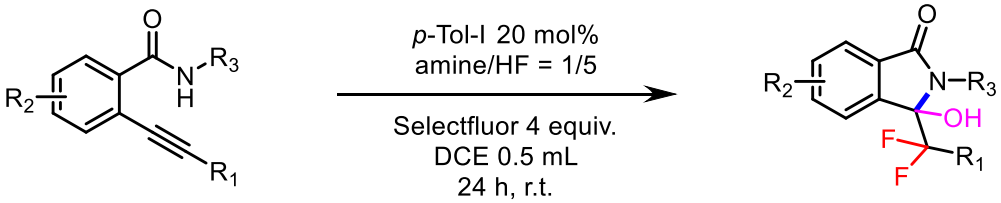
Step 3: To a mixture of acid (5.0 mmol, 1.0 equiv.) and $NH_2OR{\cdot}HCl$ (7.5 mmol, 1.5 equiv.) in dry DCM (15.0 mL) was added EDCI (7.5 mmol, 1.5 equiv.). After DMAP (15.0 mmol, 3.0 equiv.) was added, the reaction was allowed to stir overnight. Then the reaction was quenched with water and extracted with EtOAc. The organic layer was combined and dried over anhydrous sodium sulfate. After filtration and concentration, the residue was applied to flash column chromatography (EtOAc/Petroleum ether mixtures) for separation.

Method A: Procedure for the synthesis of 3-difluoromethyl-3-fluoroisoindolin-1-ones



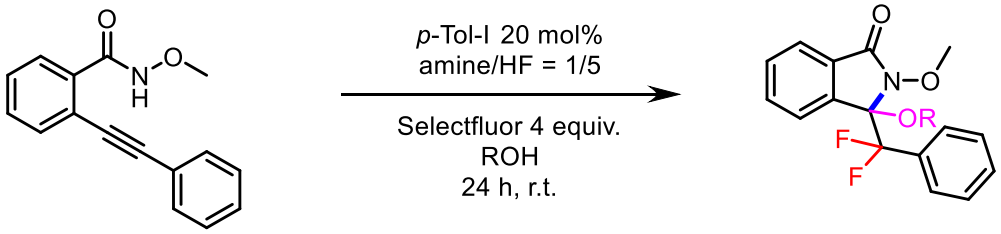
A PE centrifugal tube was charged with 2-alkynylbenzamides (0.2 mmol, 1.0 eq.), *p*-iodotoluene (9 mg, 20 mol%) and chloroform (0.2 mL). To this solution was added $Et_3N{\cdot}3HF$ (1 mL) via syringe. The mixture was stirred for 2 min before Selectfluor (0.8 mmol, 283.4 mg, 4.0 equiv.) was added. The reaction mixture was stirred at ambient temperature for 24 h. The mixture was extracted with dichloromethane (3 x 10 mL) and the combined organic phases were dried over Na_2SO_4. The crude residue was subjected to flash column chromatography on silica gel to yield the desired product.

Method B: Procedure for the synthesis of 3-difluoromethyl-3-hydroxylisoindolin-1-ones



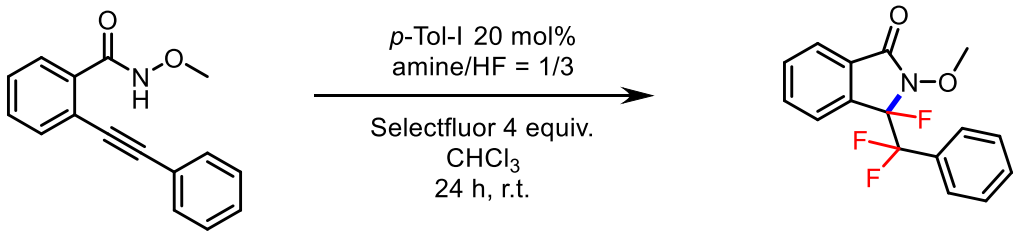
A PE centrifugal tube was charged with 2-alkynylbenzamides (0.2 mmol, 1.0 eq.), *p*-iodotoluene (9 mg, 20 mol%) and 1,2-dichloroethane (0.5 mL). To this solution was added amine:HF, 1:5.0 source (1 mL) via syringe. The mixture was stirred for 2 min before Selectfluor (0.8 mmol, 283.4 mg, 4.0 eq.) was added. The reaction mixture was stirred at ambient temperature for 24 h. The reaction was diluted with dichloromethane (2 mL). The diluted solution was slowly poured into a saturated aqueous solution of $NaHCO_3$ (20 mL) in a separation funnel (CAUTION, strong generation of CO2!). The mixture was extracted with dichloromethane (3 x 10 mL) and the combined organic phases were dried over Na_2SO_4. The crude residue was subjected to flash column chromatography on silica gel to yield the desired product.

Method C: Procedure for the synthesis of 3-difluoromethyl-3-alkoxyisoindolin-1-ones



A PE centrifugal tube was charged with *N*-methoxy-2-(phenylethynyl)benzamide (0.2 mmol, 50.3 mg, 1.0 eq.), *p*-iodotoluene (9 mg, 20 mol%) and ROH (0.1 mL). To this solution was added amine:HF, 1:5.0 source (1 mL) via syringe. The mixture was stirred for 2 min before Selectfluor (0.8 mmol, 283.4 mg, 4.0 eq.) was added. The reaction mixture was stirred at ambient temperature for 24 h. The reaction was diluted with dichloromethane (2 mL). The diluted solution was slowly poured into a saturated aqueous solution of $NaHCO_3$ (20 mL) in a separation funnel (CAUTION, strong generation of CO2!). The mixture was extracted with dichloromethane (3 x 10 mL) and the combined organic phases were dried over Na_2SO_4. The crude residue was subjected to flash column chromatography on silica gel to yield the desired product.

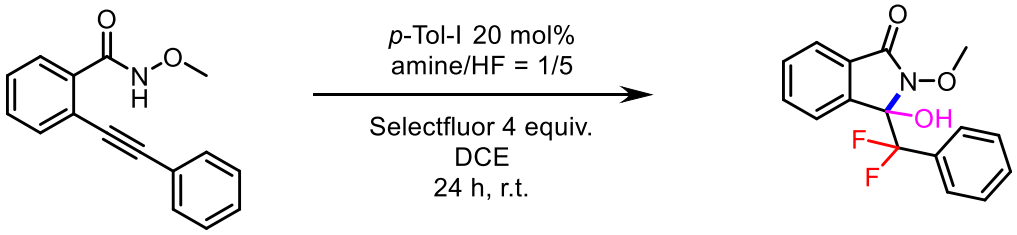
Method D: Gram-scale reaction



8 mmol, 2.0 g

1.6 g, 65%

A PE centrifugal tube was charged with *N*-methoxy-2-(phenylethynyl)benzamide (8.0 mmol, 2.0 g, 1.0 eq.), *p*-iodotoluene (360 mg, 20 mol%) and chloroform (8 mL). To this solution was added $Et_3N{\cdot}3HF$ (40 mL) via syringe. The mixture was stirred for 2 min before Selectfluor (32 mmol, 1.1 g, 4.0 eq.) was added. The reaction mixture was stirred at ambient temperature for 24 h. The mixture was extracted with dichloromethane (3 x 10 mL) and the combined organic phases were dried over Na_2SO_4. The crude residue was subjected to flash column chromatography on silica gel to yield the desired product (1.6 g, 65%).



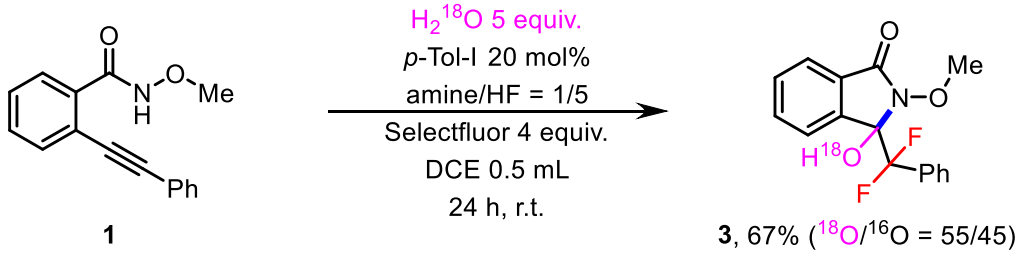
8 mmol, 2.0 g

1.7 g, 69%

A PE centrifugal tube was charged with *N*-methoxy-2-(phenylethynyl)benzamide (8.0 mmol, 2.0 g, 1.0 eq.), *p*-iodotoluene (360 mg, 20 mol%) and 1,2-dichloroethane (20 mL). To this solution was added amine:HF, 1:5.0 source (40 mL) via syringe. The mixture was stirred for 2 min before Selectfluor (32 mmol, 1.1 g, 4.0 eq.) was added. The reaction mixture was stirred at ambient temperature for 24 h. The reaction was diluted with dichloromethane. The diluted solution was slowly poured into a saturated aqueous solution of $NaHCO_3$ in a separation funnel (CAUTION, strong generation of CO2!). The mixture was extracted with dichloromethane (3 x 50 mL) and the combined organic phases were dried over Na_2SO_4. The crude residue was subjected to flash column chromatography on silica gel to yield the desired product (1.7 g, 69%).

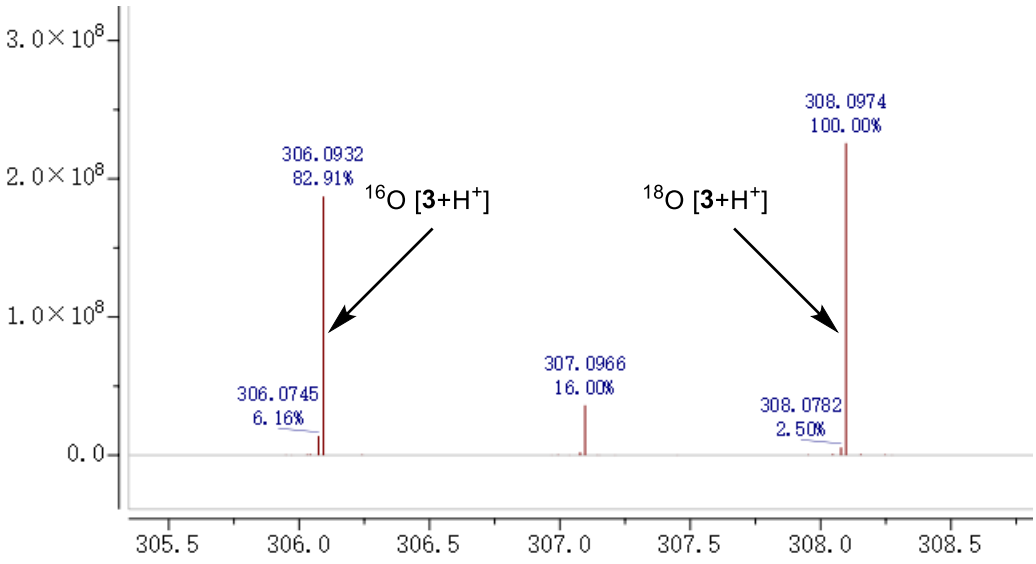
5. Mechanistic Experiments

5.1. ^{18}O Labeling experiment

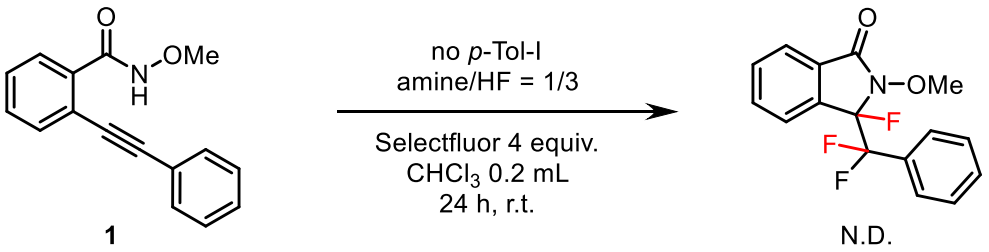


A PE centrifugal tube was charged with *N*-methoxy-2-(phenylethynyl)benzamide (0.2 mmol, 50.3 mg, 1.0 eq.), *p*-iodotoluene (9 mg, 20 mol%), $H_2{}^{18}O$ (20.0 mg 5.0 equiv.) and 1,2-dichloroethane (0.5 mL). To this solution was added amine:HF, 1:5.0 source (1 mL) via syringe. The mixture was stirred for 2 min before Selectfluor (0.8 mmol, 283.4 mg, 4.0 eq.) was added. The reaction mixture was stirred at ambient temperature for 24 h. The reaction was diluted with dichloromethane (2 mL). The diluted solution was slowly poured into a saturated aqueous solution of $NaHCO_3$ (20 mL) in a separation funnel (CAUTION, strong generation of CO2!). The mixture was extracted with dichloromethane (3 x 10 mL) and the combined organic phases were dried over Na_2SO_4. The crude residue was subjected to flash column chromatography on silica gel to yield the desired product.

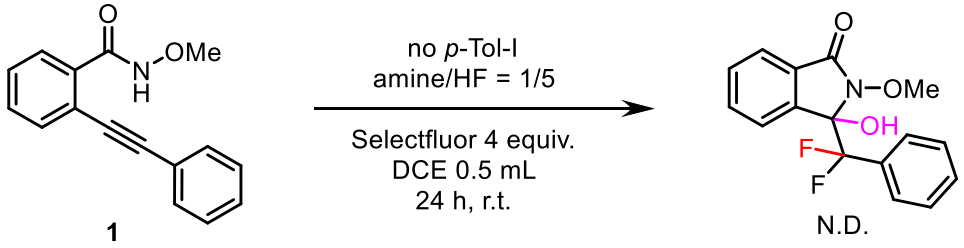
The ESI-MS spectra of **3** when 5.0 equiv. of $H_2{}^{18}O$ was used:



5.2. Controlled experiment

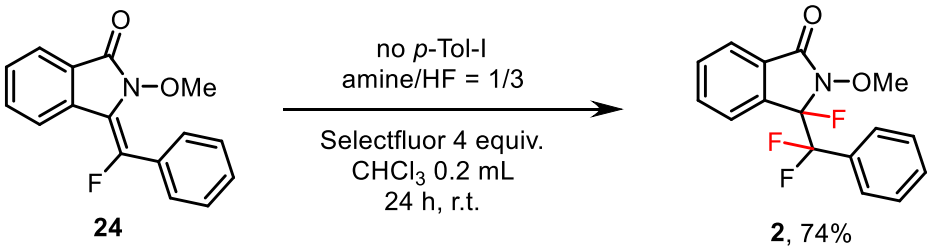


A PE centrifugal tube was charged with *N*-methoxy-2-(phenylethynyl)benzamide (0.2 mmol, 50.3 mg, 1.0 eq.) and chloroform (0.2 mL). To this solution was added $Et_3N{\cdot}3HF$ (1 mL) via syringe. The mixture was stirred for 2 min before Selectfluor (0.8 mmol, 283.4 mg, 4.0 eq.) was added. The reaction mixture was stirred at ambient temperature for 24 h. The mixture was extracted with dichloromethane (3 x 10 mL) and the combined organic phases were dried over Na_2SO_4. Reactions were monitored by ^{19}F NMR and thin-layer chromatography (TLC) analysis.

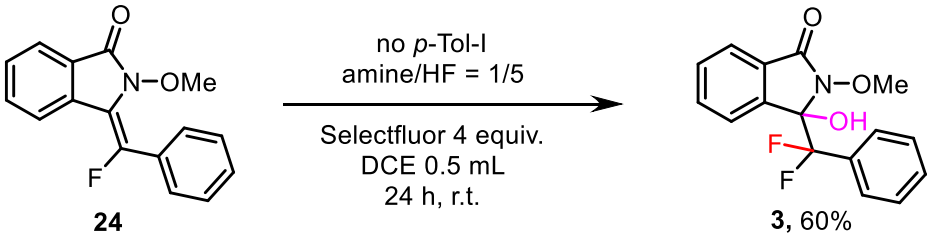


A PE centrifugal tube was charged with *N*-methoxy-2-(phenylethynyl)benzamide (0.2 mmol, 50.3 mg, 1.0 eq.) and 1,2-dichloroethane (0.5 mL). To this solution was added amine:HF, 1:5.0 source (1 mL) via syringe. The mixture was stirred for 2 min before Selectfluor (0.8 mmol, 283.4 mg, 4.0 eq.) was added. The reaction mixture was stirred at ambient temperature for 24 h. The reaction was diluted with dichloromethane (2 mL). The diluted solution was slowly poured into a saturated aqueous solution of $NaHCO_3$ (20 mL) in a separation funnel (CAUTION, strong generation of CO2!). The mixture was extracted with dichloromethane (3 x 10 mL) and the combined organic phases were dried over Na_2SO_4. Reactions were monitored by ^{19}F NMR and thin-layer chromatography (TLC) analysis.

5.3. Intermediate experiments

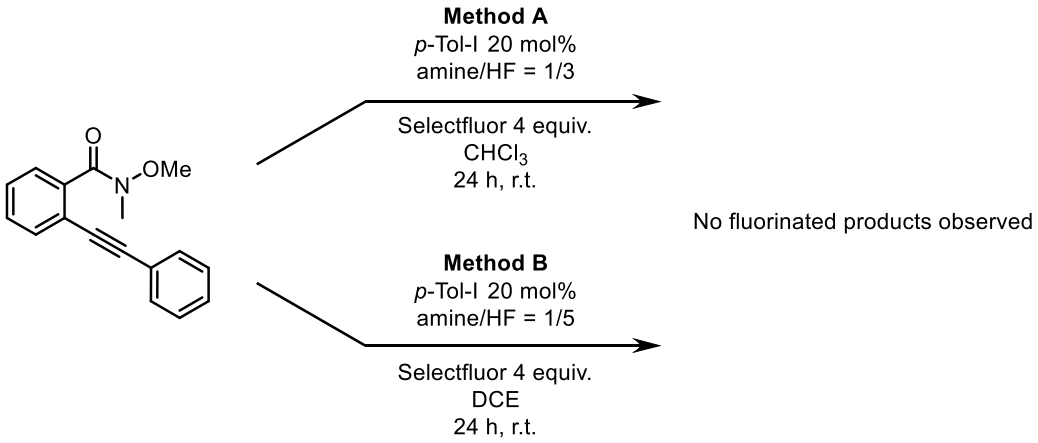


A PE centrifugal tube was charged with (*E*)-3-(fluoro(phenyl)methylene)-2-methoxyisoindolin-1-one (0.2 mmol, 53.9 mg, 1.0 eq.) and chloroform (0.2 mL). To this solution was added $Et_3N{\cdot}3HF$ (1 mL) via syringe. The mixture was stirred for 2 min before Selectfluor (0.8 mmol, 283.4 mg, 4.0 eq.) was added. The reaction mixture was stirred at ambient temperature for 24 h. The mixture was extracted with dichloromethane (3 x 10 mL) and the combined organic phases were dried over Na_2SO_4. The crude residue was subjected to flash column chromatography on silica gel to yield the desired product.



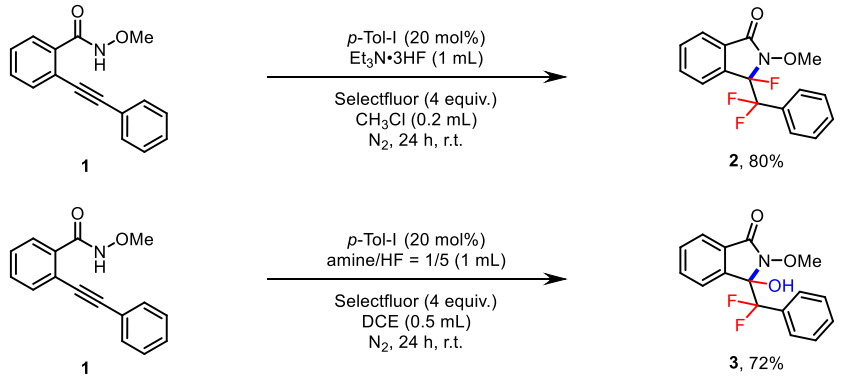
A PE centrifugal tube was charged with (*E*)-3-(fluoro(phenyl)methylene)-2-methoxyisoindolin-1-one (0.2 mmol, 53.9 mg, 1.0 eq.) and 1,2-dichloroethane (0.5 mL). To this solution was added amine:HF, 1:5.0 source (1 mL) via syringe. The mixture was stirred for 2 min before Selectfluor (0.8 mmol, 283.4 mg, 4.0 eq.) was added. The reaction mixture was stirred at ambient temperature for 24 h. The reaction was diluted with dichloromethane (2 mL). The diluted solution was slowly poured into a saturated aqueous solution of $NaHCO_3$ (20 mL) in a separation funnel (CAUTION, strong generation of CO2!). The mixture was extracted with dichloromethane (3 x 10 mL) and the combined organic phases were dried over Na_2SO_4. The crude residue was subjected to flash column chromatography on silica gel to yield the desired product.

5.4. Mechanism verification experiment



The reaction was carried out using *N*-methoxy-*N*-methyl-2-(phenylethynyl)benzamide as the reactant, and no fluorinated product was observed at the end of the reaction under either **method A** or **method B**.

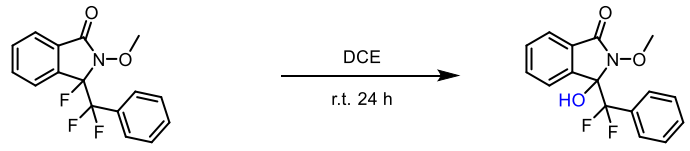
5.5. Experiments under nitrogen atmosphere



The reaction was carried out under a nitrogen atmosphere, and the yield was hardly affected, indicating that oxygen was not involved in the reaction.

6. Trifluorinated isoindolin-1-ones converted to 3-hydroxyisoindolin-1-ones

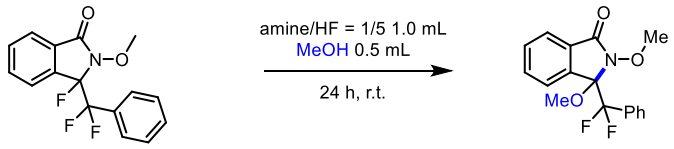
Trifluorinated isoindolin-1-ones converted to 3-hydroxyisoindolin-1-ones under some acidic conditions.



2 **3**

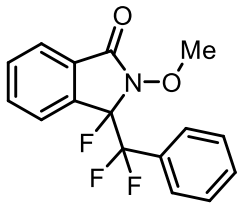
entry	additive	**3**
1	amine/HF = 1/5 (1 mL)	73%
2	CH_3COOH (1 mL)	15%
3	HCl (4.0 mol/L in 1,4-Dioxane, 1 mL)	trace
4	Et_3N (1 mL)	N.D.
5	^{t}BuOK (10 equiv.)	N.D.

[a] Reaction conditions: **2** (0.2 mmol) in DCE (0.5 mL) under air at r.t. for 24 h.

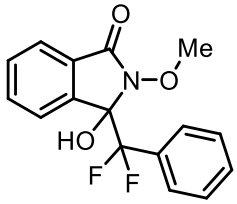


2 **21**, 78%

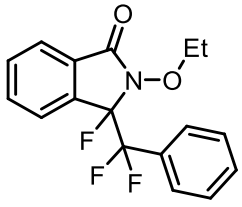
7. Characterization of Products



Compound 2: 3-(difluoro(phenyl)methyl)-3-fluoro-2-methoxyisoindolin-1-one[1]
Followed **Method A**, the desired product was isolated by silica gel chromatography (5% of EtOAc in petroleum ether as the eluent) as a yellow liquid (50.4 mg) in 82% yield.
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.69 (d, 1H), 7.68 – 7.61 (m, 2H), 7.61 – 7.54 (m, 1H), 7.43 – 7.35 (m, 3H), 7.32 – 7.26 (m, 2H), 3.95 (s, 3H). **^{19}F NMR (471 MHz, Chloroform-*d*)** δ -105.3 – -107.9 (m, 2F), -147.0 (t, *J* = 17.4 Hz, 1F).

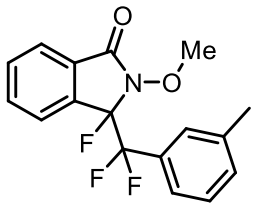


Compound 3: 3-(difluoro(phenyl)methyl)-3-hydroxy-2-methoxyisoindolin-1-one
Followed **Method B**, the desired product was isolated by silica gel chromatography (40% of EtOAc in petroleum ether as the eluent) as a white solid (44.6 mg) in 73% yield.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.58 – 7.49 (m, 2H), 7.48 – 7.32 (m, 3H), 7.33 – 7.19 (m, 4H), 4.92 (s, 1H), 3.99 (s, 3H). **^{13}C NMR (126 MHz, Chloroform-*d*)** δ 164.3, 139.0, 132.9, 132.0 (t, *J* = 25.4 Hz), 130.9, 130.7, 129.4, 127.8, 126.8 (t, *J* = 6.3 Hz), 124.3, 123.5, 120.2 (t, *J* = 257.0 Hz), 90.2 (t, *J* = 30.7 Hz), 65.7. **^{19}F NMR (471 MHz, Chloroform-*d*)** δ -103.4 (d, *J* = 250.7 Hz, 1F), -107.0 (d, *J* = 250.7 Hz, 1F).
IR (neat, cm^{-1}): 3281 (br), 2925 (m), 2853 (w), 1709 (s), 1469 (w), 1280 (w), 1110 (w), 1063 (m), 1003 (m), 857 (w), 756 (s), 700 (s), 664 (w).
HRMS (ESI) m/z: [M+H$^+$] Calcd. for $C_{16}H_{14}F_2NO_3^+$: 306.0937; found: 306.0933.

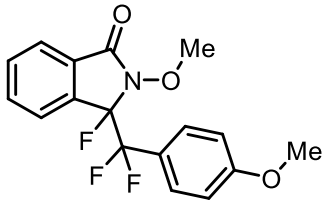


Compound 4: 3-(difluoro(phenyl)methyl)-2-ethoxy-3-fluoroisoindolin-1-one[1]
Followed **Method A**, the desired product was isolated by silica gel chromatography (5% of EtOAc in petroleum ether as the eluent) as a yellow liquid (45.0 mg) in 70% yield.
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.70 (d, *J* = 7.5 Hz, 1H), 7.68 – 7.62 (m, 2H), 7.61 – 7.55 (m, 1H), 7.43 (d, *J* = 7.9 Hz, 2H), 7.41 – 7.36 (m, 1H), 7.34 – 7.28 (m, 2H), 4.19 (dq, *J* = 9.1, 7.1

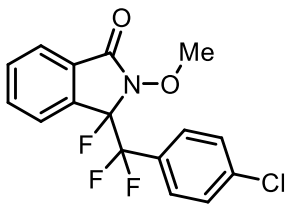
Hz, 1H), 4.08 (dq, *J* = 9.1, 7.1 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H). **^{19}F NMR (471 MHz, Chloroform-*d*)** δ -103.9 (dd, *J* = 259.2, 18.3 Hz, 1F), -106.2 (dd, *J* = 258.9, 12.2 Hz, 1F), -145.0 (t, *J* = 15.3 Hz, 1F).



Compound 5: 3-(difluoro(*m*-tolyl)methyl)-3-fluoro-2-methoxyisoindolin-1-one[1]
Followed **Method A**, the desired product was isolated by silica gel chromatography (5% of EtOAc in petroleum ether as the eluent) as a colorless liquid (48.2 mg) in 75% yield.
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.70 (dd, *J* = 7.2, 0.8 Hz, 1H), 7.68 – 7.62 (m, 1H), 7.62 – 7.53 (m, 2H), 7.20 – 7.09 (m, 4H), 3.95 (s, 3H), 2.27 (s, 3H). **^{19}F NMR (471 MHz, Chloroform-*d*)** δ -106.6 (d, *J* = 16.5 Hz, 2F), -147.1 (t, *J* = 15.8 Hz, 1F).



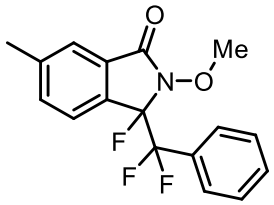
Compound 6: 3-(difluoro(4-methoxyphenyl)methyl)-3-fluoro-2-methoxyisoindolin-1-one
Followed **Method A**, the desired product was isolated by silica gel chromatography (10% of EtOAc in petroleum ether as the eluent) as a white solid (45.9 mg) in 68% yield.
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.69 (d, *J* = 7.5 Hz, 1H), 7.67 – 7.62 (m, 2H), 7.61 – 7.54 (m, 1H), 7.28 (d, *J* = 9.0 Hz, 2H), 6.77 (d, *J* = 8.9 Hz, 2H), 3.98 (s, 3H), 3.76 (s, 3H). **^{13}C NMR (126 MHz, Chloroform-*d*)** δ 163.4, 161.5, 135.7 (d, *J* = 18.7 Hz), 133.5, 131.9, 128.9, 128.3 (t, *J* = 6.3 Hz), 124.6, 123.9, 123.3 (t, *J* = 25.4 Hz), 119.0 (td, *J* = 256.1, 35.0 Hz), 113.4, 102.1 (dt, *J* = 227.3, 33.4 Hz), 66.0, 55.3. **^{19}F NMR (471 MHz, Chloroform-*d*)** δ -104.7 – -106.1 (m, 2F), -147.3 (t, *J* = 18.1 Hz, 1F).
IR (neat, cm^{-1}): 1751 (s), 1614 (w), 1517 (m), 1469 (w), 1257 (s), 1181 (m), 1151 (m), 1086 (m), 1027 (m), 913 (m), 833 (m), 759 (m), 687 (w).
HRMS (ESI) m/z: [M+H^{+}] Calcd. for $C_{17}H_{15}F_3NO_3^{+}$: 338.0999; found: 338.0996.



Compound 7: 3-((4-chlorophenyl)difluoromethyl)-3-fluoro-2-methoxyisoindolin-1-one[1]

Followed **Method A**, the desired product was isolated by silica gel chromatography (5% of EtOAc in petroleum ether as the eluent) as a white solid (53.3 mg) in 78% yield.

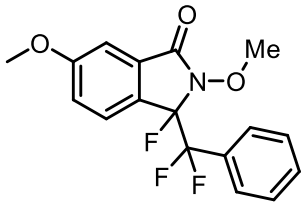
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.76 – 7.69 (m, 1H), 7.70 – 7.64 (m, 2H), 7.63 – 7.55 (m, 1H), 7.38 – 7.31 (m, 2H), 7.30 – 7.26 (m, 2H), 3.93 (s, 3H). **^{19}F NMR (471 MHz, Chloroform-*d*)** δ -104.5 (dd, *J* = 260.2, 18.0 Hz, 1F), -105.8 (dd, *J* = 259.9, 13.5 Hz, 1F), -145.8 (t, *J* = 15.7 Hz, 1F).



Compound 8: 3-(difluoro(phenyl)methyl)-3-fluoro-2-methoxy-6-methylisoindolin-1-one[1]

Followed **Method A**, the desired product was isolated by silica gel chromatography (5% of EtOAc in petroleum ether as the eluent) as a white solid (43.7 mg) in 68% yield.

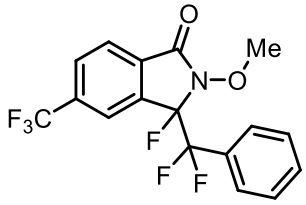
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.48 (dd, *J* = 10.5, 1.2 Hz, 2H), 7.45 – 7.42 (m, 1H), 7.41 – 7.36 (m, 3H), 7.32 – 7.27 (m, 2H), 3.94 (s, 3H), 2.42 (s, 3H). **^{19}F NMR (471 MHz, Chloroform-*d*)** δ -104.8 – -106.5 (m, 2F), -145.2 (t, *J* = 16.1 Hz, 1F).



Compound 9: 3-(difluoro(phenyl)methyl)-3-fluoro-2,6-dimethoxyisoindolin-1-one[1]

Followed **Method A**, the desired product was isolated by silica gel chromatography (10% of EtOAc in petroleum ether as the eluent) as a white solid (37.8 mg) in 56% yield.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.47 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.42 – 7.36 (m, 3H), 7.31 – 7.27 (m, 2H), 7.19 – 7.07 (m, 2H), 3.95 (s, 3H), 3.83 (s, 3H). **^{19}F NMR (471 MHz, Chloroform-*d*)** δ -104.6 – -107.0 (m, 2F), -145.1 (t, *J* = 16.6 Hz, 1F).



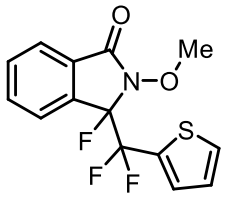
Compound 10: 3-(difluoro(phenyl)methyl)-3-fluoro-2-methoxy-5-(trifluoromethyl)isoindolin-1-one

Followed **Method A**, the desired product was isolated by silica gel chromatography (5% of EtOAc in petroleum ether as the eluent) as a white solid (32.3 mg) in 43% yield.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.91 – 7.82 (m, 2H), 7.81 (s, 1H), 7.47 – 7.38 (m, 3H), 7.37 – 7.30 (m, 2H), 3.93 (s, 3H). **^{13}C NMR (101 MHz, Chloroform-*d*)** δ 161.9, 136.3 (d, *J* = 18.2 Hz), 135.5 (q, *J* = 33.2 Hz), 132.2, 131.4, 131.0 (t, *J* = 24.7 Hz), 129.2 (qd, *J* = 3.7, 1.5 Hz), 128.3, 126.8 (td, *J* = 6.3, 1.6 Hz), 124.6, 123.2 (q, *J* = 274.7 Hz), 122.1, 118.4 (td, *J* = 254.5, 36.4 Hz), 101.6 (dt, *J* = 231.3, 32.3 Hz), 66.1. **^{19}F NMR (471 MHz, Chloroform-*d*)** δ -63.9 (s, 3F), -105.5 (dd, *J* = 260.4, 16.3 Hz, 1F), -107.9 (dd, *J* = 259.0, 13.2 Hz, 1F), -147.0 (t, *J* = 14.6 Hz, 1F).

IR (neat, cm^{-1}): 2955 (m), 2922 (s), 2851 (m), 1762 (w), 1461 (m), 1377 (m), 1141 (m), 1019 (w), 856 (s), 761 (m), 700 (w).

HRMS (ESI) m/z: [M+H$^+$] Calcd. for $C_{17}H_{12}F_6NO_2^+$: 376.0767; found: 376.0767.



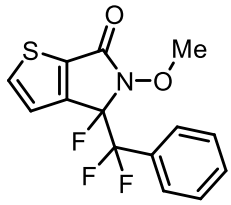
Compound 11: 3-(difluoro(thiophen-2-yl)methyl)-3-fluoro-2-methoxyisoindolin-1-one

Followed **Method A**, the desired product was isolated by silica gel chromatography (5% of EtOAc in petroleum ether as the eluent) as a yellow liquid (45.1 mg) in 72% yield.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.74 (d, *J* = 7.5 Hz, 1H), 7.67 (d, *J* = 4.1 Hz, 2H), 7.64 – 7.56 (m, 1H), 7.38 – 7.32 (m, 1H), 7.23 – 7.17 (m, 1H), 6.98 – 6.86 (m, 1H), 4.00 (s, 3H). **^{13}C NMR (126 MHz, Chloroform-*d*)** δ 163.8, 135.4 (d, *J* = 18.7 Hz), 133.8, 132.6 (t, *J* = 29.1 Hz), 132.2, 129.4 (t, *J* = 5.6 Hz), 129.1, 129.0, 127.0, 124.7, 124.1, 117.7 (td, *J* = 255.8, 36.5 Hz), 101.8 (dt, *J* = 228.1, 31.5 Hz), 66.1. **^{19}F NMR (471 MHz, Chloroform-*d*)** δ -95.7 (dd, *J* = 265.3, 17.2 Hz, 1F), -96.8 (dd, *J* = 265.3, 20.2 Hz, 1F), -146.6 (t, *J* = 18.4 Hz, 1F).

IR (neat, cm^{-1}): 2924 (m), 1752 (s), 1469 (w), 1255 (m), 1146 (m), 1096 (w), 1028 (m), 1003 (m), 898 (w), 836 (m), 759 (m), 716 (m), 686 (w).

HRMS (ESI) m/z: [M+H$^+$] Calcd. for $C_{14}H_{11}F_3NO_2S^+$: 314.0458; found: 314.0455.

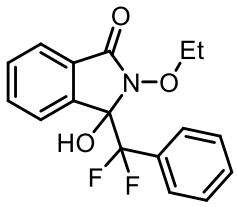


Compound 12: 4-(difluoro(phenyl)methyl)-4-fluoro-5-methoxy-4,5-dihydro-6*H*-thieno[2,3-*c*]pyrrol-6-one

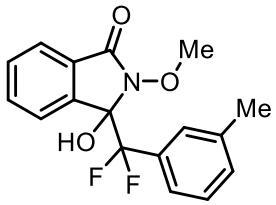
Followed **Method A**, the desired product was isolated by silica gel chromatography (5% of EtOAc in petroleum ether as the eluent) as a yellow liquid (20.1 mg) in 32% yield.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 4.8 Hz, 1H), 7.50 – 7.40 (m, 3H), 7.41 – 7.32 (m, 2H), 7.05 (dd, *J* = 4.8, 0.9 Hz, 1H), 3.89 (s, 3H). **^{13}C NMR (101 MHz, Chloroform-*d*)** δ 160.3, 145.6 (d, *J* = 20.0 Hz), 137.0, 134.2, 131.4, 131.1, 128.1, 126.78 (td, *J* = 6.5, 1.8 Hz), 122.5 (d, *J* = 1.4 Hz), 118.1 (td, *J* = 255.3, 35.6 Hz), 101.2 (dt, *J* = 226.7, 34.7 Hz), 66.0. **^{19}F NMR (376 MHz, Chloroform-*d*)** δ -96.1 – -121.9 (m, 2F), -144.7 (t, *J* = 14.2 Hz, 1F).

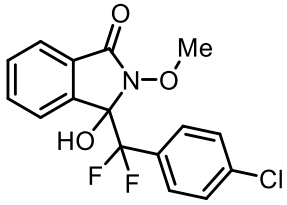
IR (neat, cm^{-1}): 2925 (w), 1750 (s), 1452 (w), 1279 (m), 1143 (m), 1123 (m), 1066 (m), 1008 (m), 957 (m), 854 (w), 816 (m), 755 (m), 699 (s).
HRMS (ESI) m/z: [M+H$^+$] Calcd. for $C_{14}H_{11}F_3NO_2S^+$: 314.0458; found: 314.0448.



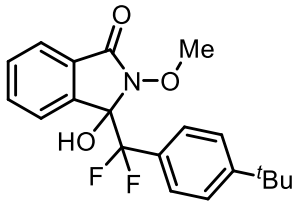
Compound 13: 3-(difluoro(phenyl)methyl)-2-ethoxy-3-hydroxyisoindolin-1-one
Followed **Method B**, the desired product was isolated by silica gel chromatography (40% of EtOAc in petroleum ether as the eluent) as a white solid (38.3 mg) in 60% yield.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.65 – 7.54 (m, 2H), 7.53 – 7.46 (m, 2H), 7.44 – 7.32 (m, 3H), 7.30 – 7.27 (m, 2H), 4.44 (s, 1H), 4.28 (qd, *J* = 7.0, 4.7 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (126 MHz, Chloroform-*d*)** δ 164.6, 139.0, 132.9, 132.0 (t, *J* = 25.1 Hz), 130.9, 130.7, 129.6, 127.8, 126.9 (t, *J* = 6.3 Hz), 124.3, 123.6, 120.1 (t, *J* = 195.3 Hz), 90.1 (t, *J* = 30.2 Hz), 73.8, 13.9. **^{19}F NMR (471 MHz, Chloroform-*d*)** δ -103.6 (d, *J* = 250.3 Hz, 1F), -106.1 (d, *J* = 251.8 Hz, 1F).
IR (neat, cm^{-1}): 3281 (br), 2936 (w), 1708 (s), 1470 (w), 1451 (w), 1234 (w), 1146 (m), 1120 (m), 1076 (m), 1063 (m), 1019 (m), 756 (s), 692 (m).
HRMS (ESI) m/z: [M+H$^+$] Calcd. for $C_{17}H_{16}F_2NO_3^+$: 320.1093; found: 320.1087.



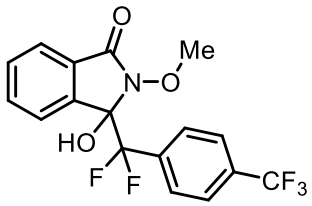
Compound 14: 3-(difluoro(*m*-tolyl)methyl)-3-hydroxy-2-methoxyisoindolin-1-one
Followed **Method B**, the desired product was isolated by silica gel chromatography (40% of EtOAc in petroleum ether as the eluent) as a white solid (40.2 mg) in 63% yield.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.64 – 7.51 (m, 2H), 7.51 – 7.44 (m, 1H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.21 – 6.97 (m, 4H), 4.50 (s, 1H), 4.03 (s, 3H), 2.24 (s, 3H). **^{13}C NMR (126 MHz, Chloroform-*d*)** δ 164.5, 139.0, 137.6, 132.9, 131.8 (t, *J* = 25.0 Hz), 131.5, 130.9, 129.5, 127.8, 124.3, 124.3, 123.9 (t, *J* = 6.3 Hz), 123.6, 119.3 (t, *J* = 270.9 Hz), 90.1 (dd, *J* = 32.2, 29.5 Hz), 65.7, 21.4. **^{19}F NMR (471 MHz, Chloroform-*d*)** δ -104.3 (d, *J* = 249.0 Hz, 1F), -108.4 (d, *J* = 249.0 Hz, 1F).
IR (neat, cm^{-1}): 3359 (br), 2925 (m), 2854 (w), 1710 (s), 1469 (w), 1194 (w), 1146 (w), 1120 (m), 1002 (m), 868 (w), 757 (m), 692 (m).
HRMS (ESI) m/z: [M+H$^+$] Calcd. for $C_{17}H_{16}F_2NO_3^+$: 320.1093; found: 320.1086.



Compound 15: 3-((4-chlorophenyl)difluoromethyl)-3-hydroxy-2-methoxyisoindolin-1-one
Followed **Method B**, the desired product was isolated by silica gel chromatography (40% of EtOAc in petroleum ether as the eluent) as a white solid (45.5 mg) in 67% yield.
^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 8.22 (s, 1H), 7.75 – 7.67 (m, 1H), 7.65 – 7.55 (m, 2H), 7.44 (d, *J* = 8.0 Hz, 3H), 7.28 (d, *J* = 8.4 Hz, 2H), 3.86 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d*$_6$)** δ 162.2, 139.6, 135.5, 133.1, 131.6 (t, *J* = 30.2 Hz), 131.0, 129.1, 128.7, 128.0, 124.5, 122.8, 119.6 (t, *J* = 269.6 Hz), 89.7 (t, *J* = 29.8 Hz), 65.2. **^{19}F NMR (471 MHz, DMSO-*d*$_6$)** δ -104.5 (d, *J* = 251.6 Hz, 1F), -107.8 (d, *J* = 251.3 Hz, 1F).
IR (neat, cm^{-1}): 3281 (br), 2925 (m), 2854 (w), 1709 (s), 1469 (w), 1235 (w), 1147 (m), 1079 (s), 1003 (m), 827 (m), 760 (m), 740 (w), 691 (m).
HRMS (ESI) m/z: [M+H$^+$] Calcd. for $C_{16}H_{13}ClF_2NO_3^+$: 340.0547; found: 340.0543.



Compound 16: 3-((4-(*tert*-butyl)phenyl)difluoromethyl)-3-hydroxy-2-methoxyisoindolin-1-one
Followed **Method B**, the desired product was isolated by silica gel chromatography (30% of EtOAc in petroleum ether as the eluent) as a white solid (49.9 mg) in 69% yield.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.64 – 7.52 (m, 2H), 7.51 – 7.44 (m, 1H), 7.41 (d, *J* = 7.5 Hz, 1H), 7.33 – 7.15 (m, 4H), 4.61 (d, *J* = 12.8 Hz, 1H), 4.02 (s, 3H), 1.26 (s, 9H). **^{13}C NMR (101 MHz, Chloroform-*d*)** δ 164.7, 154.0, 139.1, 132.9, 130.9, 129.5, 129.0 (t, *J* = 25.3 Hz), 126.6 (t, *J* = 6.2 Hz), 124.8, 124.3, 123.6, 120.4 (t, *J* = 255.5 Hz), 90.2 (t, *J* = 31.3 Hz), 65.7, 34.8, 31.2. **^{19}F NMR (376 MHz, Chloroform-*d*)** δ -102.6 (d, *J* = 251.0 Hz, 1F), -106.6 (d, *J* = 250.9 Hz, 1F).
IR (neat, cm^{-1}): 3318 (br), 2960 (m), 2870 (w), 1711 (s), 1469 (m), 1365 (w), 1272 (m), 1111 (w), 1078 (m), 1001 (m), 831 (w), 761 (m), 691 (m).
HRMS (ESI) m/z: [M+H$^+$] Calcd. for $C_{20}H_{22}F_2NO_3^+$: 362.1563; found: 362.1558.



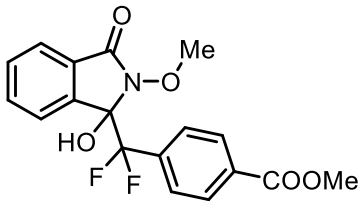
Compound 17: 3-(difluoro(4-(trifluoromethyl)phenyl)methyl)-3-hydroxy-2-methoxyisoindolin-1-one

Followed **Method B**, the desired product was isolated by silica gel chromatography (40% of EtOAc in petroleum ether as the eluent) as a white solid (44.8 mg) in 60% yield.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 (s, 1H), 7.79 – 7.69 (m, 3H), 7.68 – 7.53 (m, 4H), 7.50 – 7.36 (m, 1H), 3.85 (s, 3H). **^{13}C NMR (101 MHz, DMSO-d_6)** δ 162.3, 139.5, 136.9 (t, J = 25.3 Hz), 133.1, 131.0, 130.8, 129.1, 127.9 (t, J = 6.3 Hz), 124.8 (q, J = 4.1 Hz), 124.5, 122.8, 123.9 (q, J = 273.7 Hz), 119.4 (t, J = 255.5 Hz), 89.8 (t, J = 30.1 Hz), 65.2. **^{19}F NMR (471 MHz, DMSO-d_6)** δ -62.0 (s, 3F), -104.0 (d, J = 250.1 Hz, 1F), -105.9 (d, J = 249.3 Hz, 1F).

IR (neat, cm^{-1}): 3300 (br), 2946 (w), 2030 (w), 1710 (m), 1327 (s), 1170 (m), 1133 (m), 1070 (m), 837 (w), 760 (w), 692 (w), 532 (w).

HRMS (ESI) m/z: [M+H$^+$] Calcd. for $C_{17}H_{13}F_5NO_3^+$: 374.0811; found: 374.0808.



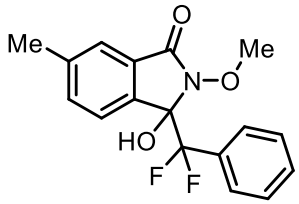
Compound 18: methyl 4-(difluoro(1-hydroxy-2-methoxy-3-oxoisoindolin-1-yl)methyl)benzoate

Followed **Method B**, the desired product was isolated by silica gel chromatography (40% of EtOAc in petroleum ether as the eluent) as a white solid (48.0 mg) in 66% yield.

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.47 – 8.17 (m, 1H), 7.92 (d, J = 8.1 Hz, 2H), 7.77 – 7.66 (m, 1H), 7.66 – 7.52 (m, 2H), 7.51 – 7.27 (m, 3H), 3.85 (s, 6H). **^{13}C NMR (126 MHz, DMSO-d_6)** δ 165.7, 162.3, 139.6, 137.2 (t, J = 25.1 Hz), 133.1, 131.5, 131.0, 129.1, 128.6, 127.3 (t, J = 6.2 Hz), 124.5, 122.8, 119.7 (t, J = 255.2 Hz), 89.8 (t, J = 30.1 Hz), 65.2, 52.5. **^{19}F NMR (471 MHz, DMSO-d_6)** δ -104.1 (d, J = 249.8 Hz, 1F), -105.1 (d, J = 249.4 Hz, 1F).

IR (neat, cm^{-1}): 3283 (br), 2954(m), 2922 (s), 2852 (m), 1725 (s), 1464 (m), 1280 (m), 1113 (m), 1004 (w), 854 (w), 760 (w), 693 (w).

HRMS (ESI) m/z: [M+H$^+$] Calcd. for $C_{18}H_{16}F_2NO_5^+$: 364.0992; found: 364.0990.

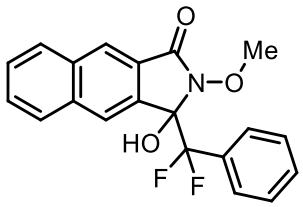


Compound 19: 3-(difluoro(phenyl)methyl)-3-hydroxy-2-methoxy-6-methylisoindolin-1-one

Followed **Method B**, the desired product was isolated by silica gel chromatography (40% of EtOAc in petroleum ether as the eluent) as a white solid (40.9 mg) in 64% yield.

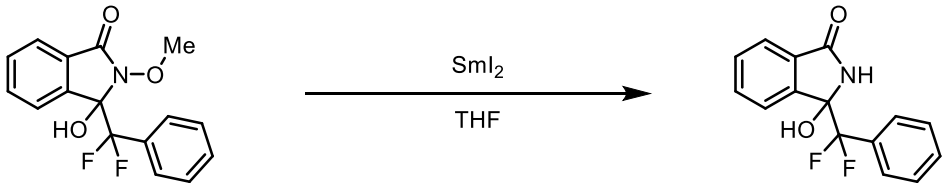
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.42 – 7.39 (m, 1H), 7.39 – 7.31 (m, 4H), 7.30 – 7.27 (m, 3H), 4.62 – 4.43 (m, 1H), 4.05 – 4.03 (m, 3H), 2.39 (s, 3H). **^{13}C NMR (126 MHz, Chloroform-*d*)** δ 164.7, 141.5, 136.1 (d, J = 1.6 Hz), 133.8, 132.1 (t, J = 25.3 Hz), 130.7, 129.5, 127.8, 126.9 (t, J = 6.4 Hz), 124.1 (d, J = 2.7 Hz), 124.0, 120.3 (t, J = 255.8 Hz), 90.1 (t, J = 30.2 Hz), 65.7, 21.6. **^{19}F NMR (471 MHz, Chloroform-*d*)** δ -104.7 (dd, J = 251.0, 13.3 Hz, 1F), -108.4 (d, J = 250.1 Hz, 1F).

IR (neat, cm^{-1}): 3289 (br), 2925 (s), 2854 (m), 1709 (s), 1452 (m), 1281 (s), 1154 (m), 1082 (m), 1063 (m), 825 (w), 760 (m), 701 (s), 626 (w).
HRMS (ESI) m/z: [M+H$^+$] Calcd. for $C_{17}H_{16}F_2NO_3^+$: 320.1093; found: 320.1089.



Compound 20: 3-(difluoro(phenyl)methyl)-3-hydroxy-2-methoxy-2,3-dihydro-1*H*-benzo[*f*]isoindol-1-one
Followed **Method B**, the desired product was isolated by silica gel chromatography (40% of EtOAc in petroleum ether as the eluent) as a yellow solid (29.8 mg) in 42% yield.
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.22 (d, J = 19.3 Hz, 2H), 8.18 – 8.06 (m, 2H), 7.96 (s, 1H), 7.75 – 7.56 (m, 2H), 7.46 – 7.36 (m, 1H), 7.33 – 7.18 (m, 4H), 3.94 (s, 3H). **^{13}C NMR (126 MHz, DMSO-d_6)** δ 161.7, 135.0, 134.7, 133.4, 132.6 (t, J = 25.1 Hz), 130.6, 129.5, 129.0, 128.5, 127.8, 127.8, 126.6 (t, J = 6.2 Hz), 126.4, 124.2, 123.3, 121.2 (t, J = 255.0 Hz), 89.8 (t, J = 30.1 Hz), 65.3.
^{19}F NMR (471 MHz, DMSO-d_6) δ -104.5 (d, J = 251.6 Hz, 1F), -107.8 (d, J = 251.3 Hz, 1F).
IR (neat, cm^{-1}): 2985 (w), 1735 (s), 1447 (w), 1373 (m), 1236 (s), 1044 (s), 939 (w), 847 (w), 735 (s), 703 (m), 634 (w), 608 (m).
HRMS (ESI) m/z: [M+H$^+$] Calcd. for $C_{20}H_{16}F_2NO_3^+$: 356.1093; found: 356.1093.

8. Derivatization of the products



3 **21**

Under an N_2 atmosphere, SmI_2 (0.1 M in THF) (2.4 mmol, 12.0 equiv) was added to a solution of **3** (0.2 mmol, 1.0 equiv) in THF (6 mL) at room temperature.[2] The reaction was carried out at room temperature and monitored by TLC until the disappearance of **3**. The reaction was quenched with saturated $Na_2S_2O_3$. The biphasic mixture was diluted with ether and washed with brine, then dried over anhydrous Na_2SO_4. After removal of the organic solvent under reduced pressure, the resulting residue was purified by flash column chromatography to give **21**.

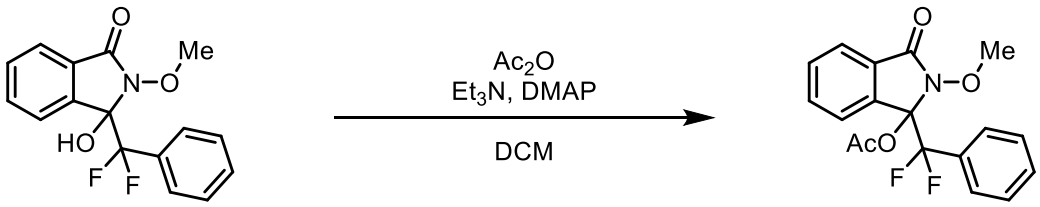
Compound 21: 3-(difluoro(phenyl)methyl)-3-hydroxyisoindolin-1-one

The desired product was isolated by silica gel chromatography (50% of EtOAc in petroleum ether as the eluent) as a white solid (45.1 mg) in 82% yield.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.28 (s, 1H), 7.61 (dt, *J* = 7.5, 4.3 Hz, 1H), 7.52 (d, *J* = 4.2 Hz, 2H), 7.45 – 7.24 (m, 7H). **^{13}C NMR (101 MHz, DMSO-*d*$_6$)** δ 168.3, 144.1, 132.9 (t, *J* = 25.5 Hz), 132.5, 132.2, 130.3, 130.2, 127.7, 127.0 (t, *J* = 6.2 Hz), 124.1, 122.6, 120.5 (t, *J* = 253.5 Hz), 87.9 (t, *J* = 30.7 Hz). **^{19}F NMR (471 MHz, DMSO-*d*$_6$)** δ -108.5 (d, *J* = 249.0 Hz, 1F), -110.0 (d, *J* = 248.4 Hz, 1F).

IR (neat, cm^{-1}): 3202 (br), 2922 (m), 2852 (m), 1708 (s), 1467 (w), 1268 (m), 1120 (m), 1060 (m), 1023 (m), 1005 (m), 903 (w), 761 (s), 700 (s).

HRMS (ESI) m/z: [M+H$^+$] Calcd. for $C_{15}H_{12}F_2NO_2^+$: 276.0831; found: 276.0830.



3 **22**

Under an N_2 atmosphere, in a round-bottomed flask, added in turn alcohol **3** (0.2 mmol), dry dichloromethane (0.4 mL) and the mixture was cooled to 0 ºC.[3] Triethylamine (2 equiv., 0.4 mmol), DMAP (1 equiv., 0.2 mmol) was added, followed by anhydride (0.4 mmol), and the reaction mixture was allowed to warm to room temperature and stirred until TLC analysis showed that **3** was completely consumed. After quenched with saturated aqueous NH_4Cl (20 mL), the mixture was then extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography to give **22**.

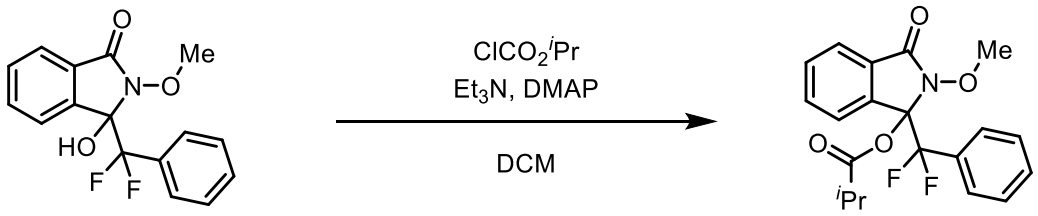
Compound 22: 1-(difluoro(phenyl)methyl)-2-methoxy-3-oxoisoindolin-1-yl acetate

The desired product was isolated by silica gel chromatography (5% of EtOAc in petroleum ether as the eluent) as a white solid (61.8 mg) in 89% yield.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.70 – 7.64 (m, 1H), 7.59 – 7.45 (m, 2H), 7.43 – 7.32 (m, 3H), 7.32 – 7.25 (m, 3H), 3.96 (s, 3H), 2.17 (s, 3H). **^{13}C NMR (126 MHz, Chloroform-*d*)** δ 167.7, 165.3, 137.1, 132.8, 131.5 (t, *J* = 25.1 Hz), 130.9, 130.8, 129.9, 127.9, 127.1 (t, *J* = 6.3 Hz), 123.9, 123.1, 119.2 (t, *J* = 257.0 Hz), 91.3 (t, *J* = 30.3 Hz), 64.9, 21.6. **^{19}F NMR (471 MHz, Chloroform-*d*)** δ -104.5 (d, *J* = 252.4 Hz, 1F), -105.9 (d, *J* = 252.6 Hz, 1F).

IR (neat, cm^{-1}): 2923 (w), 1737 (s), 1370 (w), 1279 (m), 1206 (s), 1139 (m), 1124 (m), 1005 (m), 958 (m), 756 (s), 736 (s), 700 (s).

HRMS (ESI) m/z: [M+H$^+$] Calcd. for $C_{18}H_{16}F_2NO_4^+$: 348.1042; found: 348.1040.



3 **23**

To a solution of propargyl alcohol **3** (0.2 mmol), Et_3N (10 equiv., 2 mmol), and 4-dimethylaminopyridine (5 mol%, 0.01 mmol) in DCM (10 mL) was added isopropyl chloroformate (1.2 equiv., 0.24 mmol) and the mixture was stirred at rt overnight.[4] Then the mixture was quenched with water (10 mL) and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography to give **23**.

Compound 23: 1-(difluoro(phenyl)methyl)-2-methoxy-3-oxoisoindolin-1-yl isobutyrate

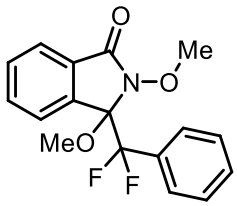
Followed **Method C**, the desired product was isolated by silica gel chromatography (5% of EtOAc in petroleum ether as the eluent) as a white solid (55.6 mg) in 74% yield.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.68 (dt, *J* = 7.3, 1.0 Hz, 1H), 7.57 (td, *J* = 7.6, 1.3 Hz, 1H), 7.51 (td, *J* = 7.5, 1.1 Hz, 1H), 7.41 – 7.33 (m, 4H), 7.30 – 7.22 (m, 2H), 4.73 (hept, *J* = 6.2 Hz, 1H), 3.97 (s, 3H), 1.22 (d, *J* = 6.3 Hz, 3H), 1.18 (d, *J* = 6.2 Hz, 3H). **^{13}C NMR (126 MHz, Chloroform-*d*)** δ 164.9, 150.5, 136.9, 132.9, 131.4 (t, *J* = 25.1 Hz), 131.1, 131.0, 130.0, 127.9, 127.2 (t, *J* = 6.3 Hz), 123.8, 123.3, 119.1 (t, *J* = 260.8 Hz), 92.5 (t, *J* = 31.5 Hz), 73.5, 65.0, 21.6, 21.5. **^{19}F NMR (471 MHz, Chloroform-*d*)** δ -105.3 (d, *J* = 253.1 Hz, 1F), -106.8 (d, *J* = 252.1 Hz, 1F).

IR (neat, cm^{-1}): 2923 (w), 1745 (s), 1467 (w), 1280 (m), 1255 (s), 1142 (m), 1096 (m), 1069 (s), 1001 (s), 913 (m), 758(s), 699 (s).

HRMS (ESI) m/z: [M+K$^+$] Calcd. for $C_{20}H_{19}F_2KNO_4^+$: 414.0914; found:414.0912.

9. Alcohols as nucleophilic reagents



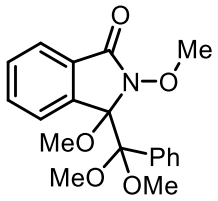
Compound 24: 3-(difluoro(phenyl)methyl)-2,3-dimethoxyisoindolin-1-one

Followed **Method C**, the desired product was isolated by silica gel chromatography (10% of EtOAc in petroleum ether as the eluent) as a white solid (25.5 mg) in 40% yield.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.76 – 7.68 (m, 1H), 7.59 – 7.47 (m, 2H), 7.42 – 7.35 (m, 3H), 7.30 – 7.26 (m, 2H), 7.19 (d, *J* = 7.2 Hz, 1H), 3.98 (s, 3H), 3.14 (s, 3H). **^{13}C NMR (126 MHz, Chloroform-*d*)** δ 164.9, 136.0, 132.7 (t, *J* = 25.2 Hz), 132.7, 131.1, 130.7, 130.6, 127.7, 127.3 (t, *J* = 6.5 Hz), 124.8, 123.9, 119.5 (t, *J* = 255.8 Hz), 95.1 (t, *J* = 30.3 Hz), 64.6, 51.7. **^{19}F NMR (471 MHz, Chloroform-*d*)** δ -103.7 (d, *J* = 251.8 Hz, 1F), -105.2 (d, *J* = 252.2 Hz, 1F).

IR (neat, cm^{-1}): 2954 (m), 2923 (s), 2851 (w), 1736 (s), 1467 (m), 1279 (w), 1200 (w), 1124 (m), 1103 (m), 1064 (m), 1006 (w), 864 (w), 758 (m).

HRMS (ESI) m/z: [M+H$^+$] Calcd. for $C_{17}H_{16}F_2NO_3^+$: 320.1093; found: 320.1087.



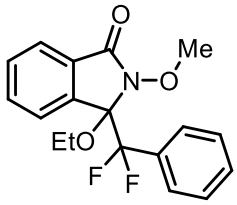
Compound 25: 3-(dimethoxy(phenyl)methyl)-2,3-dimethoxyisoindolin-1-one

Followed **Method C**, the desired product was isolated by silica gel chromatography (20% of EtOAc in petroleum ether as the eluent) as a white solid (21.3 mg) in 31% yield.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.62 (d, *J* = 7.6 Hz, 1H), 7.57 – 7.48 (m, 1H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.38 – 7.31 (m, 1H), 7.15 (d, *J* = 7.6 Hz, 2H), 7.10 – 7.05 (m, 1H), 7.04 – 6.98 (m, 2H), 4.11 (s, 3H), 3.53 (s, 3H), 3.48 (s, 3H), 3.07 (s, 3H). **^{13}C NMR (126 MHz, Chloroform-*d*)** δ 164.8, 138.9, 136.1, 132.0, 130.3, 129.9, 128.6, 128.3, 127.0, 125.0, 123.0, 104.4, 98.7, 64.2, 52.3, 51.8, 51.5.

IR (neat, cm^{-1}): 2926 (m), 1728 (s), 1467 (w), 1198 (w), 1131 (m), 1104 (m), 1061 (s), 991 (w), 846 (w), 754 (m), 707 (m), 692 (w).

HRMS (ESI) m/z: [M+H$^+$] Calcd. for $C_{19}H_{22}NO_5^+$: 344.1493; found: 344.1489.



Compound 26: 3-(difluoro(phenyl)methyl)-3-ethoxy-2-methoxyisoindolin-1-one

Followed **Method C**, the desired product was isolated by silica gel chromatography (10% of EtOAc in petroleum ether as the eluent) as a white solid (38.7 mg) in 58% yield.

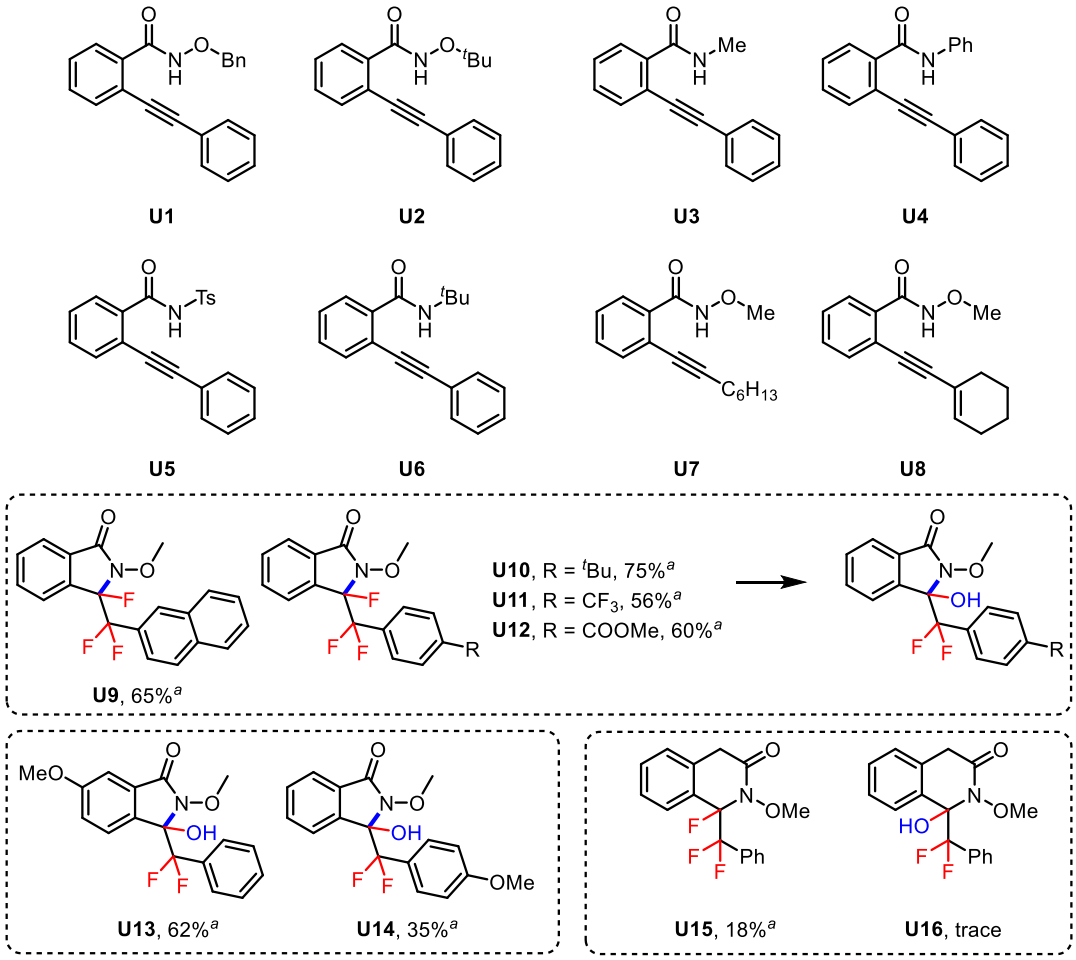
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.83 – 7.65 (m, 1H), 7.59 – 7.46 (m, 2H), 7.44 – 7.35 (m, 3H), 7.28 (t, *J* = 7.3 Hz, 2H), 7.19 – 7.08 (m, 1H), 3.94 (s, 3H), 3.38 (dq, *J* = 9.0, 7.0 Hz, 1H), 3.12 (dq, J = 9.0, 7.0 Hz, 1H), 1.23 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR (126 MHz, Chloroform-*d*)** δ 164.8, 136.6, 132.9 (t, *J* = 25.3 Hz), 132.5, 130.9, 130.5, 130.5, 127.6, 127.3 (t, *J* = 6.5 Hz), 124.8, 123.8, 119.4 (t, *J* = 255.9 Hz), 94.7 (t, *J* = 30.4 Hz), 64.6, 60.0, 14.9. **^{19}F NMR (471 MHz, Chloroform-*d*)** δ -104.1 (d, *J* = 251.3 Hz, 1F), -105.0 (d, *J* = 252.1 Hz, 1F).

IR (neat, cm^{-1}): 2923 (m), 2853 (m), 1734 (s), 1466 (m), 1276 (w), 1233 (w), 1189 (w), 1103 (m), 1076 (m), 1006 (m), 756 (s), 698 (s).

HRMS (ESI) m/z: [M+H$^+$] Calcd. for $C_{18}H_{18}F_2NO_3^+$: 334.1250; found: 334.1246.

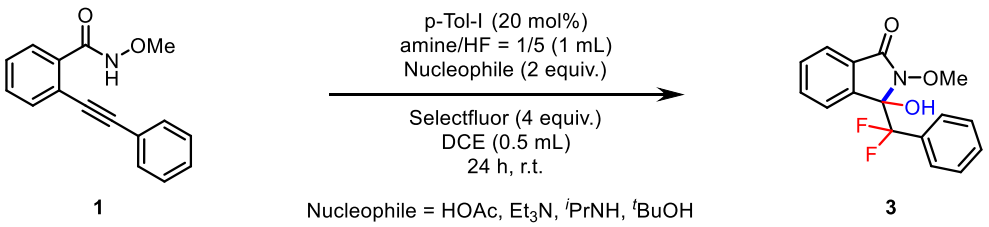
10. Unsuccessful Substrates

Unfortunately, the current protocol is not transferable to these 2-alkynylbenzamides (**U1-U8**). For **U9-U12**, the desired products can be determined by ^{19}F NMR but were converted to the corresponding 3-hydroxyisoindolin-1-ones during column purification. For **U13** and **U14**, attempts to isolate pure products were unsuccessful.



[a] Yield was determined by ^{19}F NMR with $PhOCF_3$ as the internal standard.

We have tried using acids, amines, and large steric hindrance alcohols as nucleophilic reagents, but we end up with 3-hydroxyisoindolin-1-ones. This may be caused by the fact that these molecules are not as nucleophilic as H_2O, or the 3-hydroxy product is more stable.



11. References

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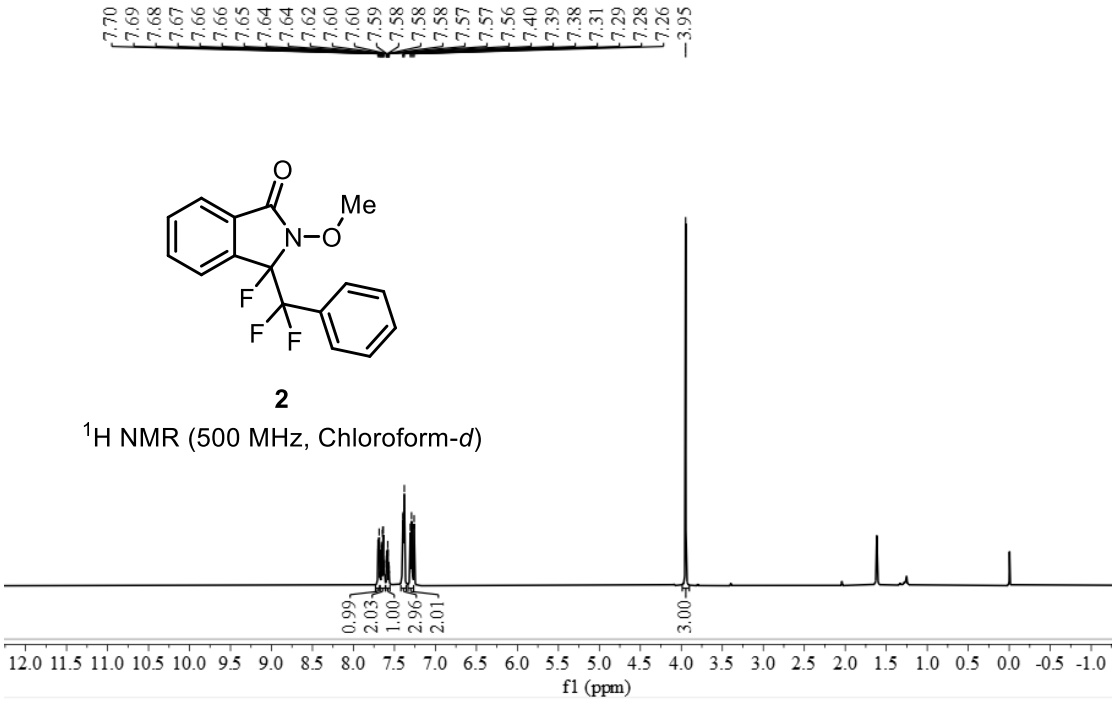
(2) Y. Li, X. Kou, C. Ye, X. Zhang, G. Yang and W. Zhang, Preparation of isoindolinones via a palladium-catalyzed diamination, *Tetrahedron Letters*, 2017, **58**, 285-288.

(3) Z.-F. Xu, J. Liu, X. Chang, T. Chen, H. Xu, S. Duan and C.-Y. Li, Synthesis of Cyclopropanes via 1,3-Migration of Acyloxy Groups Triggered by Formation of α-Imino Rhodium Carbenes, *Organic Letters*, 2020, **22**, 5163-5169.

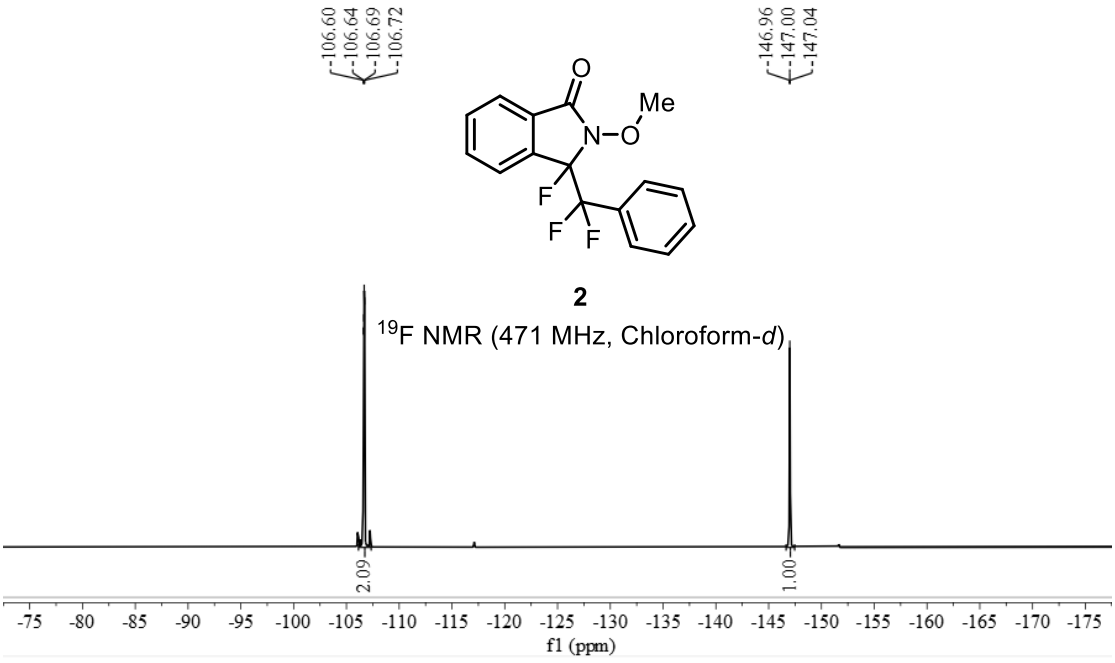
(4) K. Chen, J. Lv, J. Chen, J. Zhang, L. Li, M. Zhao and Y. Jiang, Amine-Release Annulation of Enaminones: Bimetallic Co-Catalytic Synthesis of Cyclopentadienes from Alkynes, Organic Letters, 2023, 25, 4688-4693.

12. Copy of NMR spectra



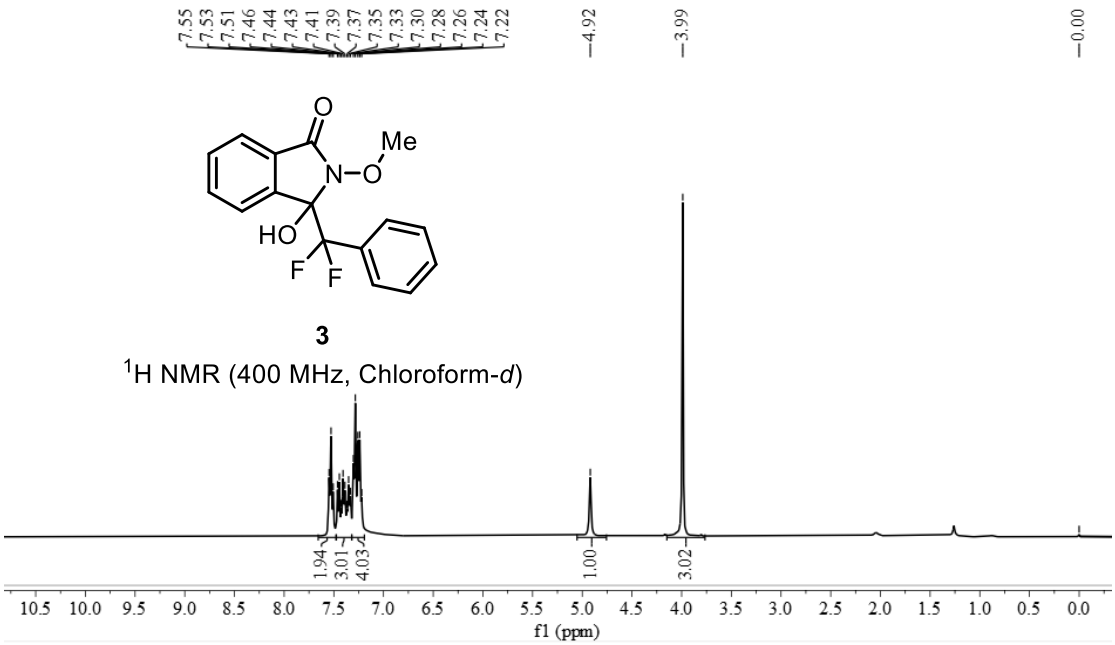
2

^{1}H NMR (500 MHz, Chloroform-*d*)



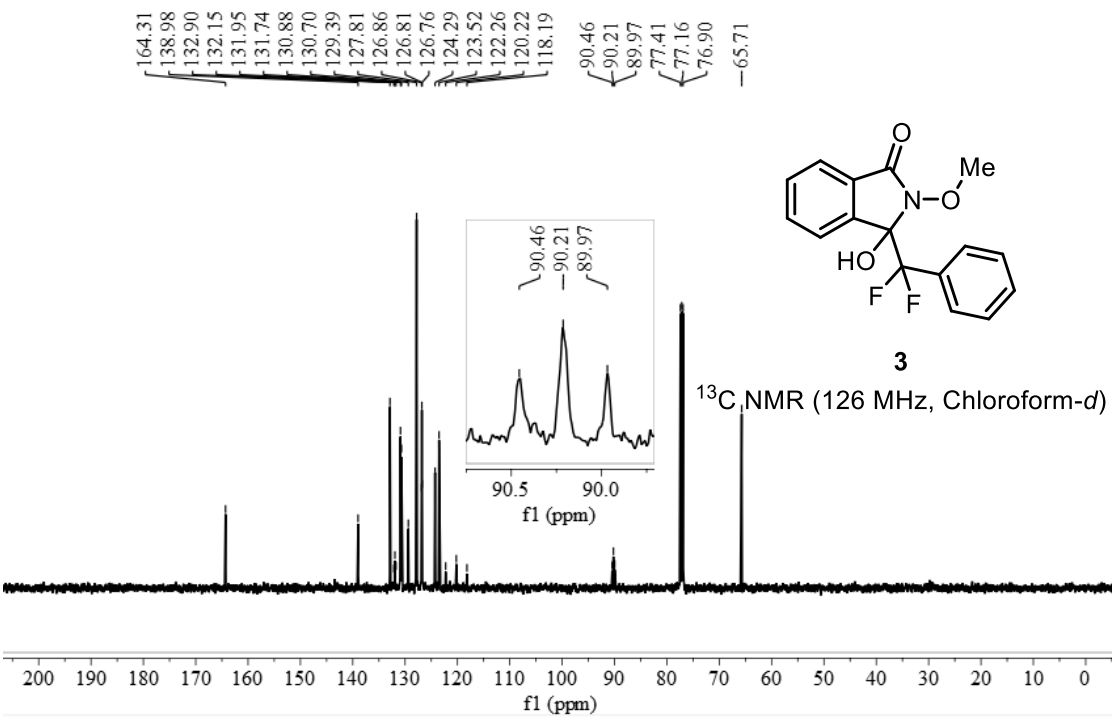
2

^{19}F NMR (471 MHz, Chloroform-*d*)



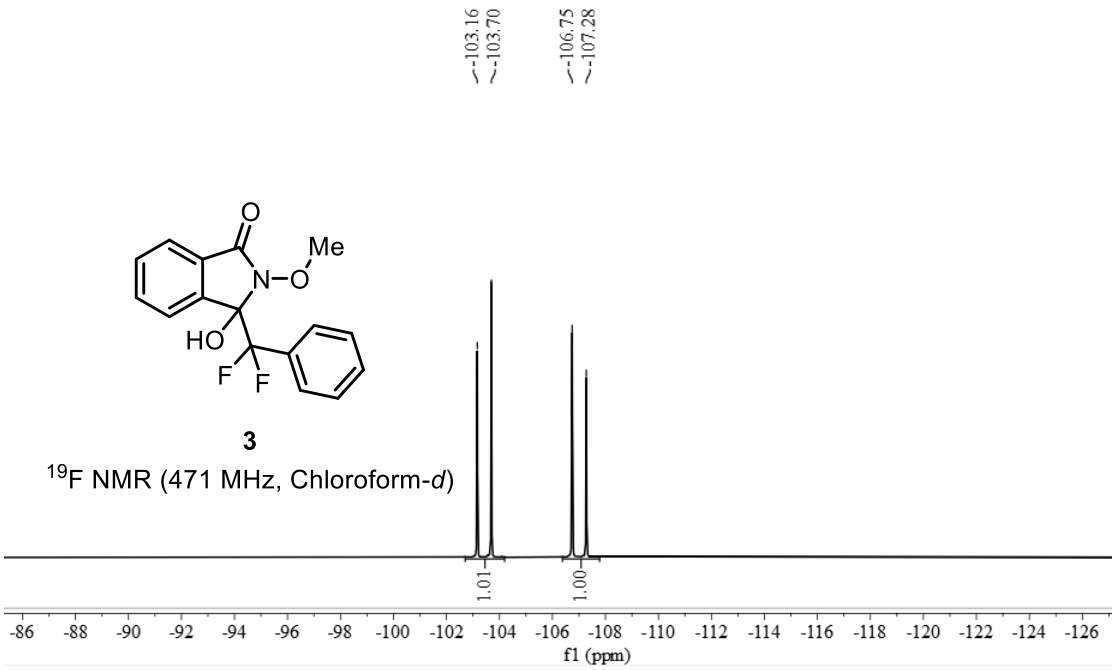
3

^{1}H NMR (400 MHz, Chloroform-*d*)



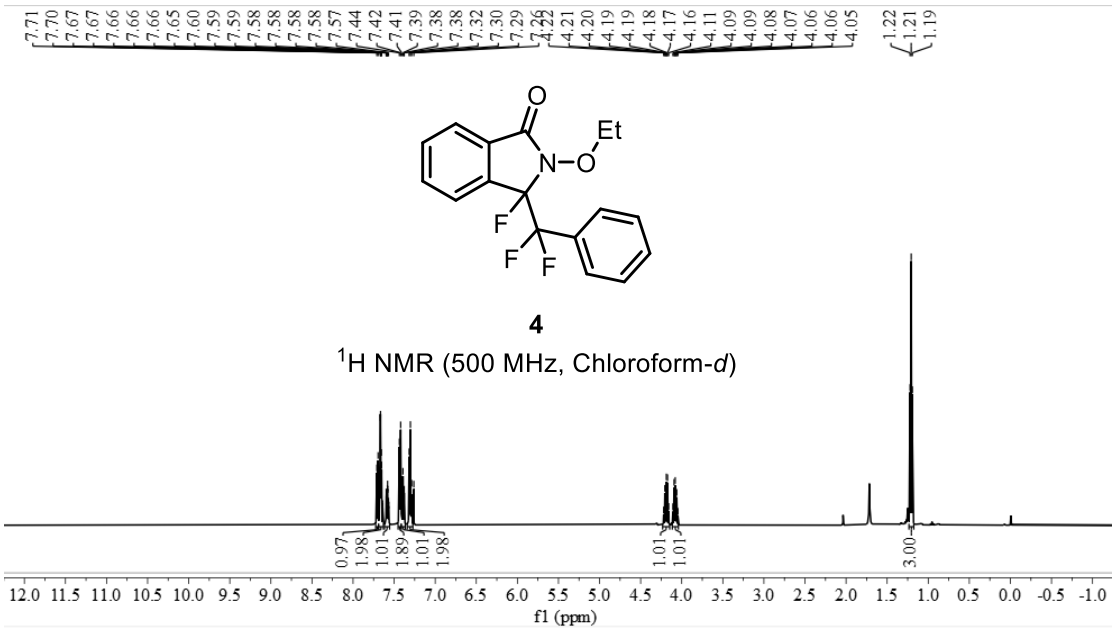
3

^{13}C NMR (126 MHz, Chloroform-*d*)



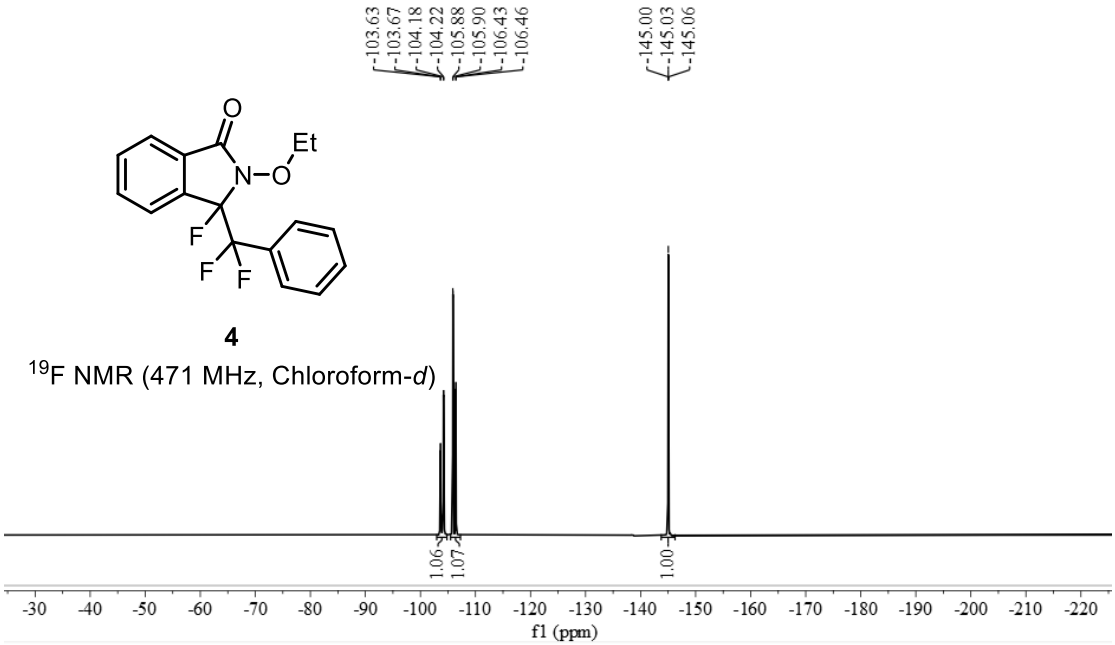
3

^{19}F NMR (471 MHz, Chloroform-*d*)



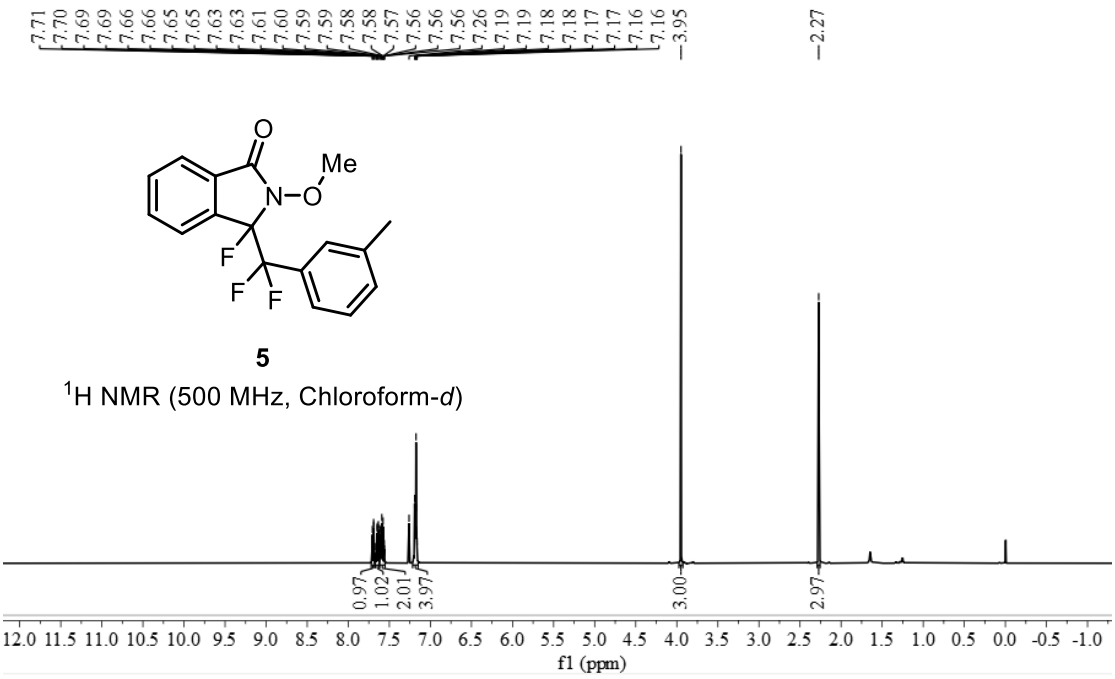
4

^{1}H NMR (500 MHz, Chloroform-*d*)



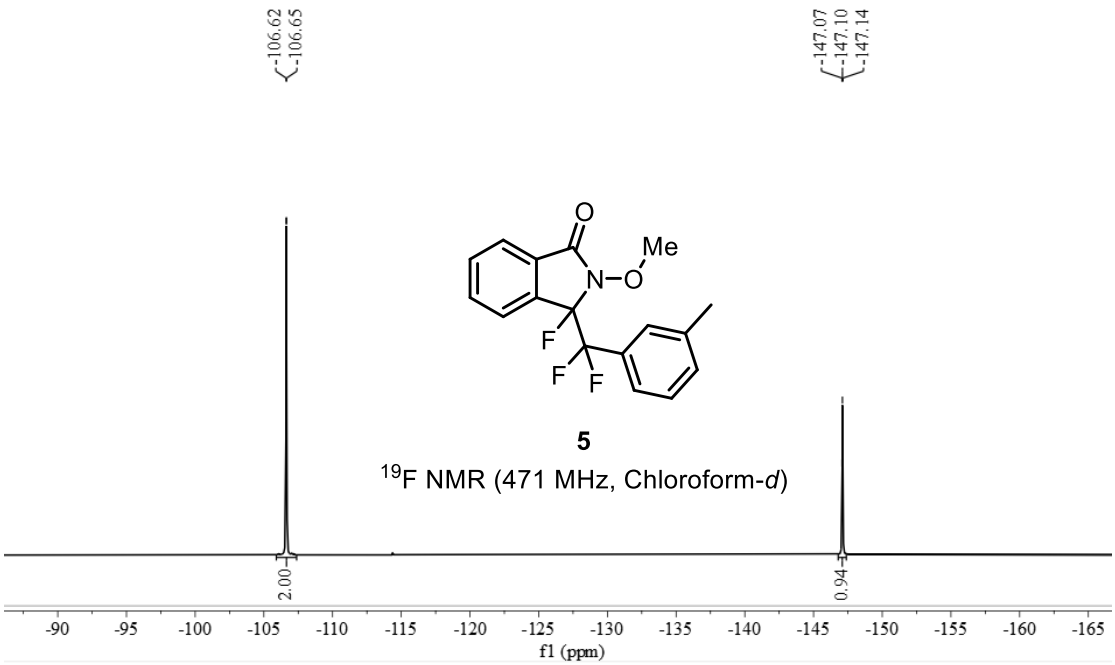
4

^{19}F NMR (471 MHz, Chloroform-*d*)



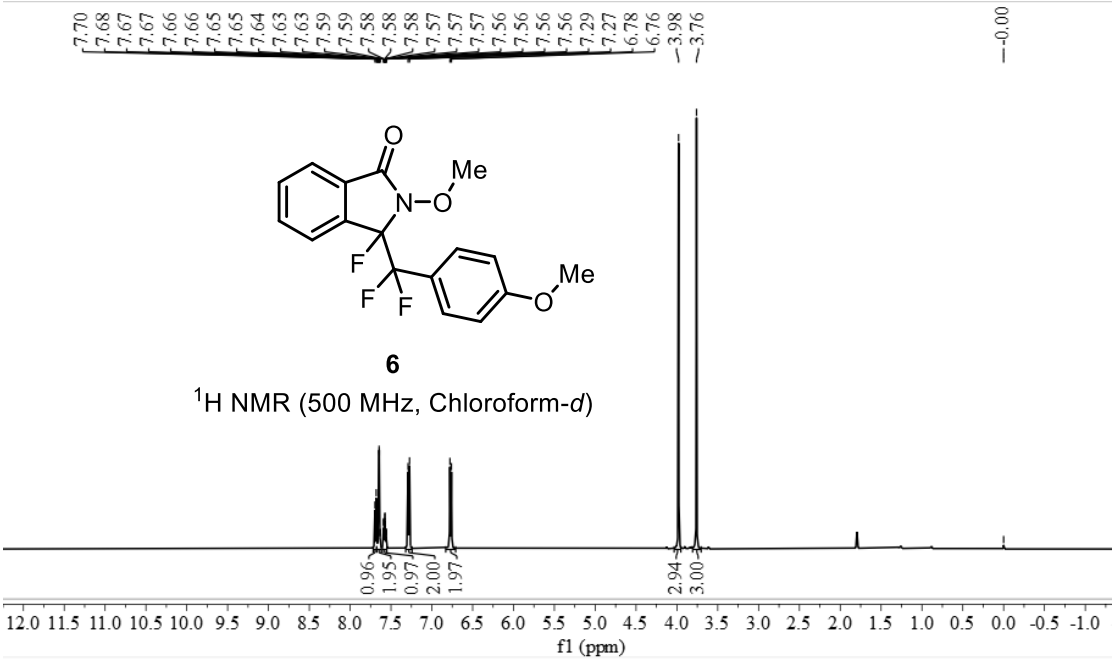
5

^{1}H NMR (500 MHz, Chloroform-*d*)



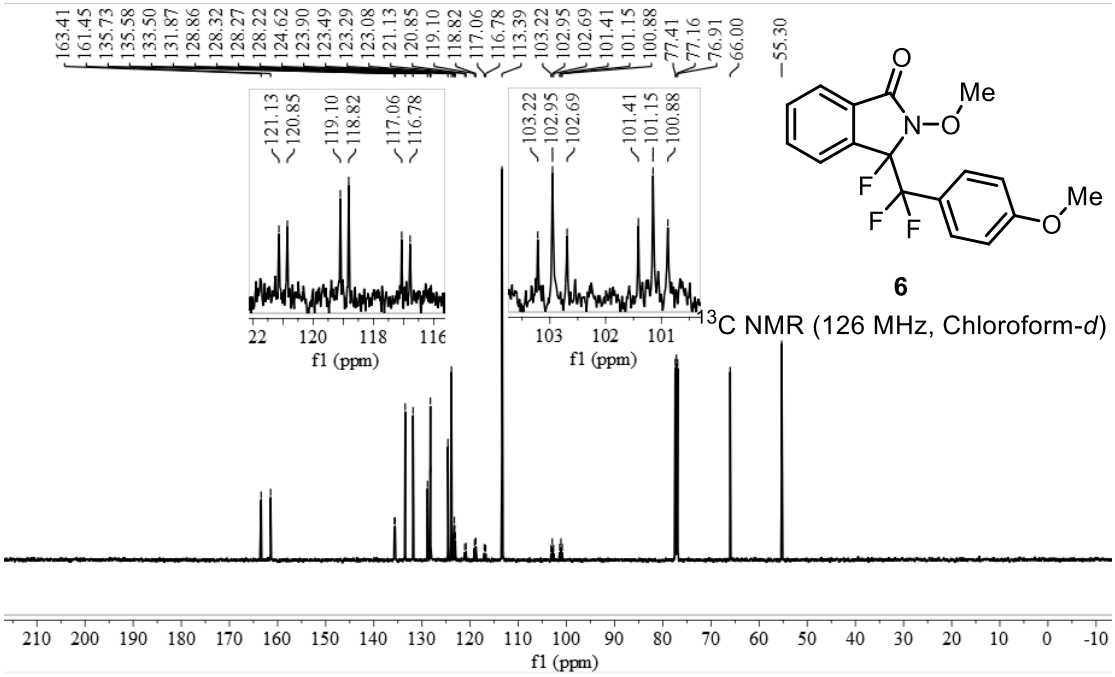
5

^{19}F NMR (471 MHz, Chloroform-*d*)



6

^{1}H NMR (500 MHz, Chloroform-*d*)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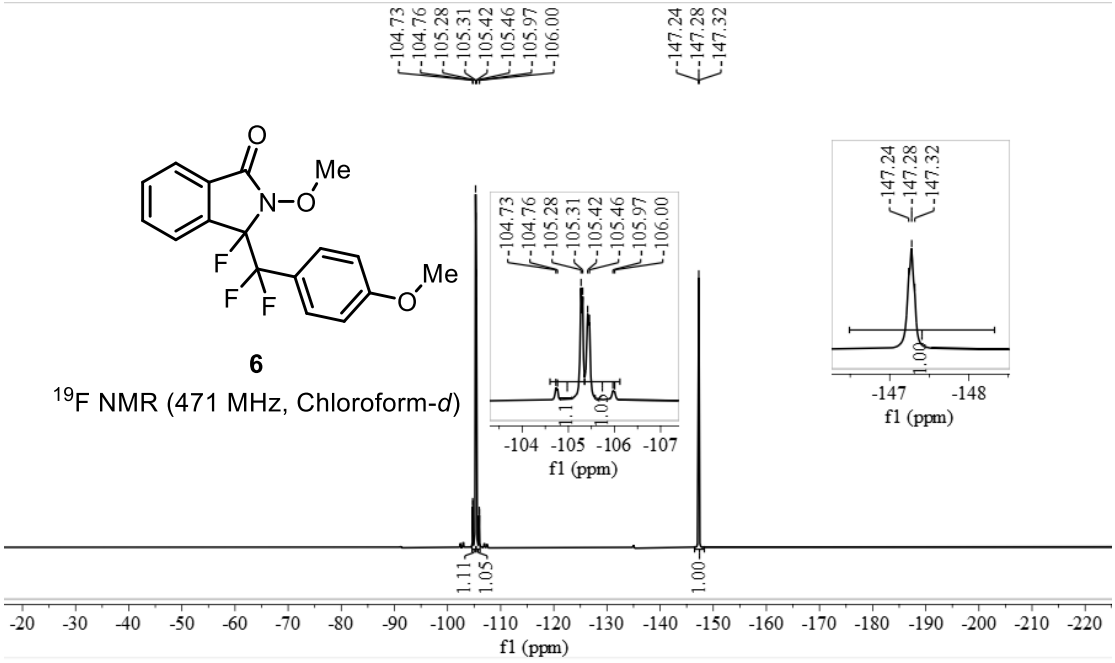
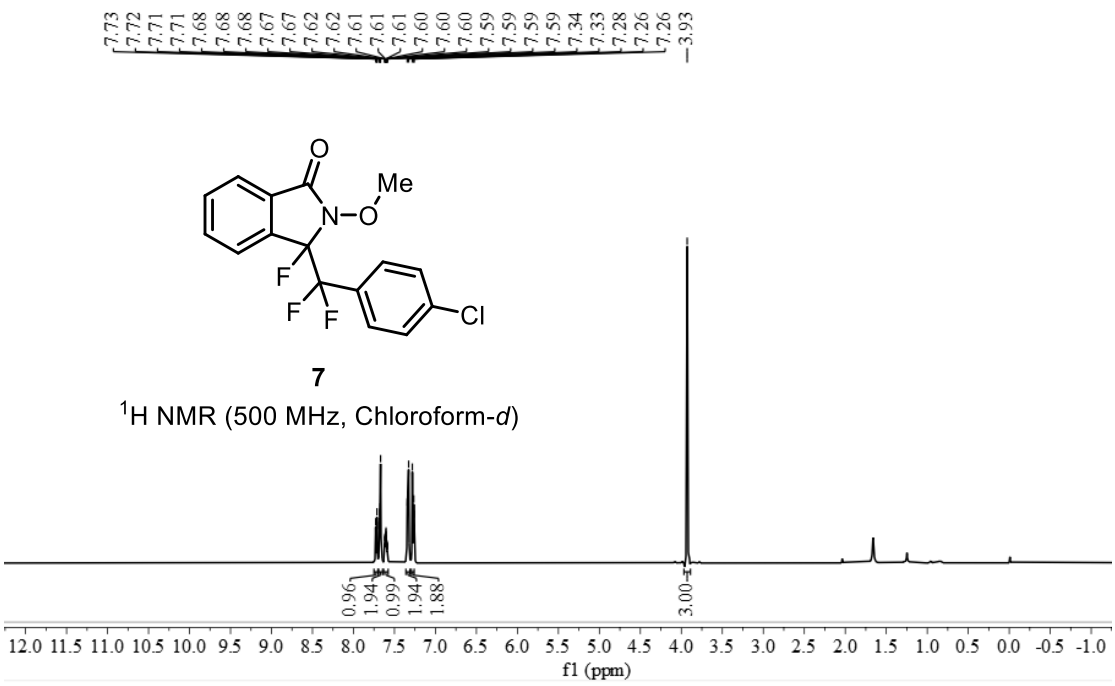
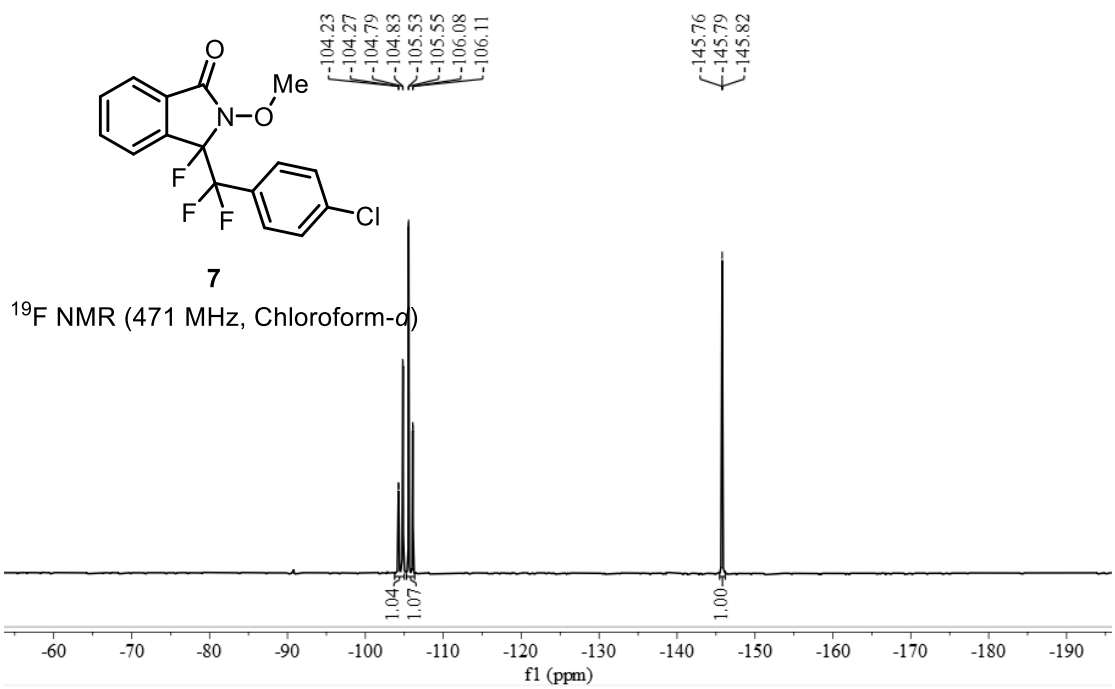
161.45
135.73
135.58
133.50
131.87
128.86
128.32
128.27
128.22
124.62
123.90
123.49
123.29
123.08
121.13
120.85
119.10
118.82
117.06
116.78
113.39
103.22
102.95
102.69
101.41
101.15
100.88
77.41
77.16
76.91
66.00
55.30
O
Me
N–O
F
F
F
Me
O
6
13C NMR (126 MHz, Chloroform-d)
f1 (ppm)


-104.73
-104.76
-105.28
-105.31
-105.42
-105.46
-105.97
-106.00
-147.24
-147.28
-147.32
O
Me
N–O
F
F
F
Me
O
6
19F NMR (471 MHz, Chloroform-d)
1.11
1.05
1.00
f1 (ppm)



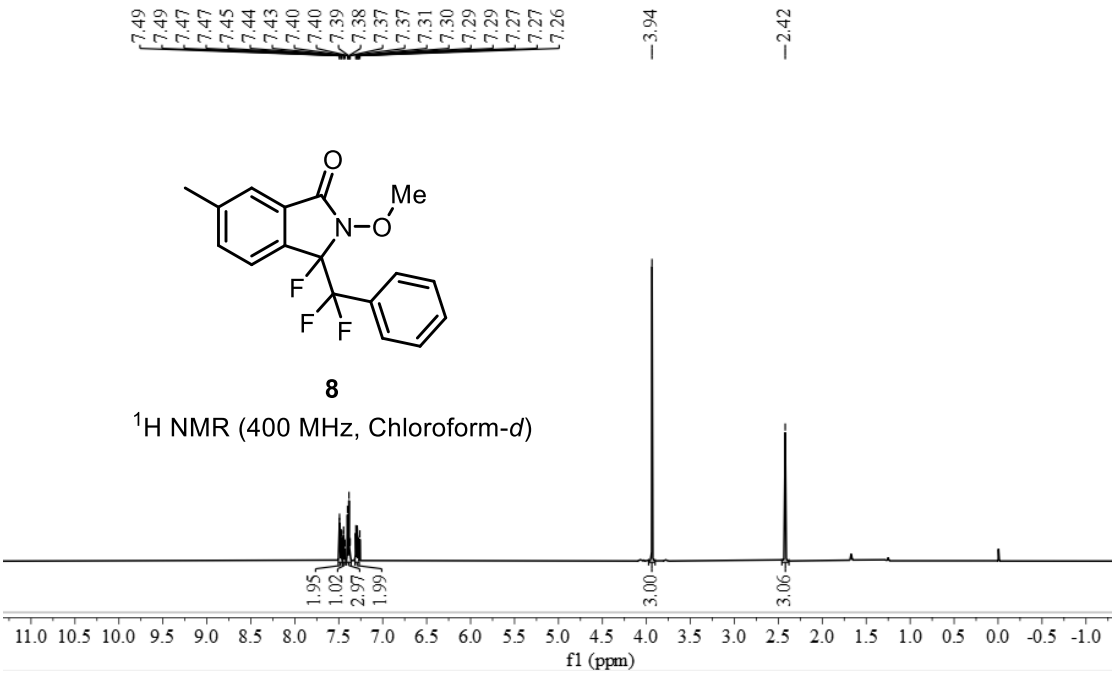
7

^{1}H NMR (500 MHz, Chloroform-*d*)



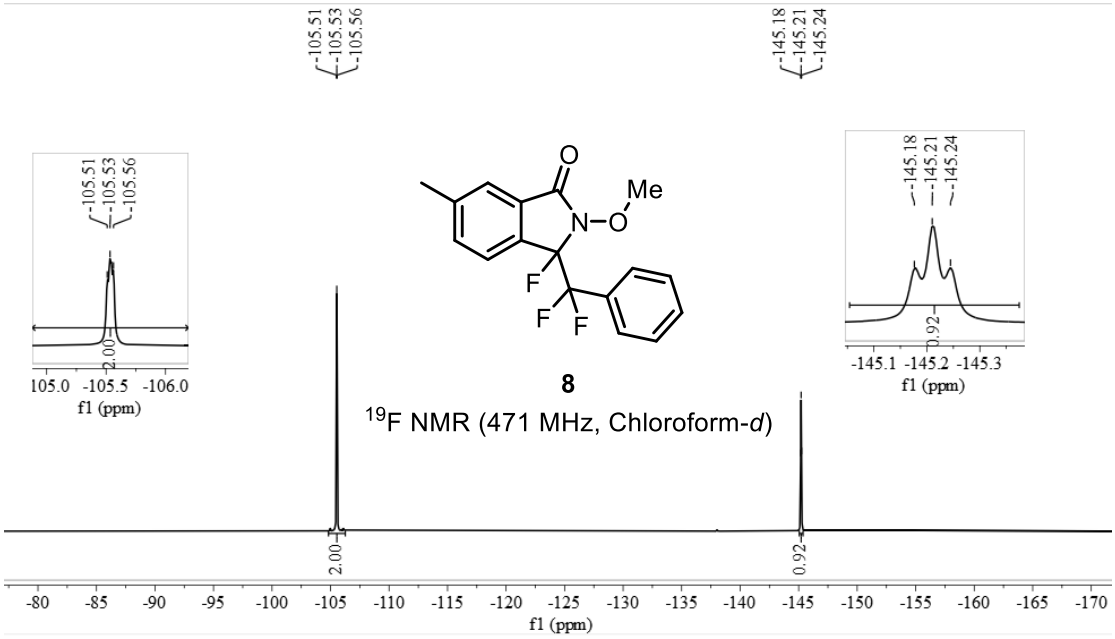
7

^{19}F NMR (471 MHz, Chloroform-*d*)



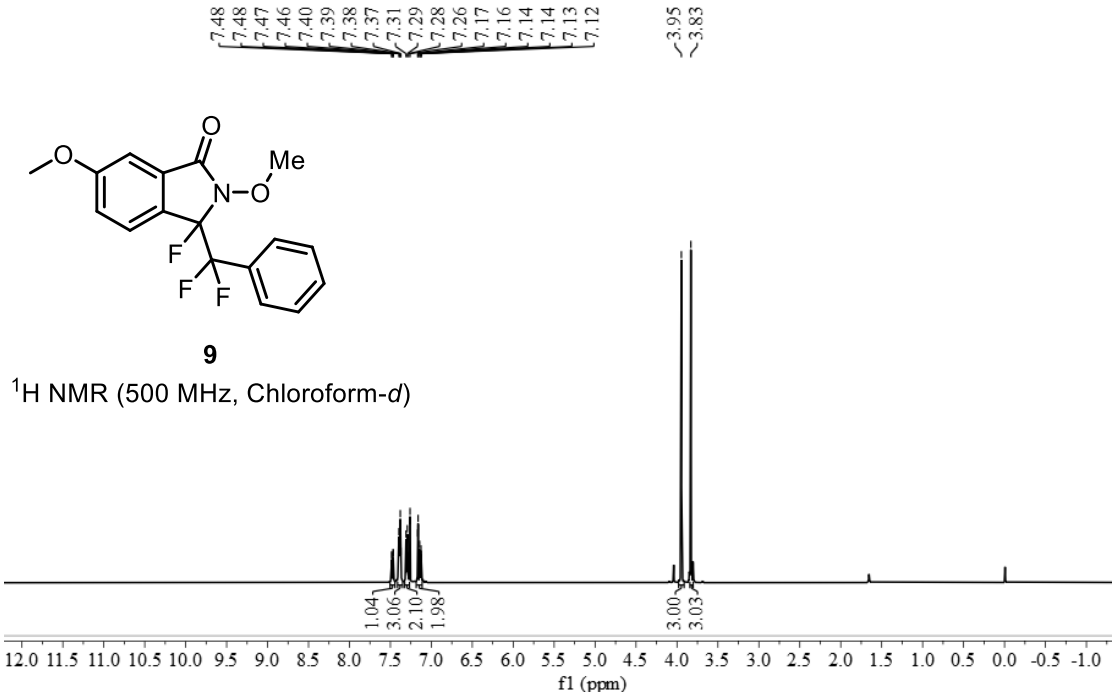
8

^{1}H NMR (400 MHz, Chloroform-*d*)



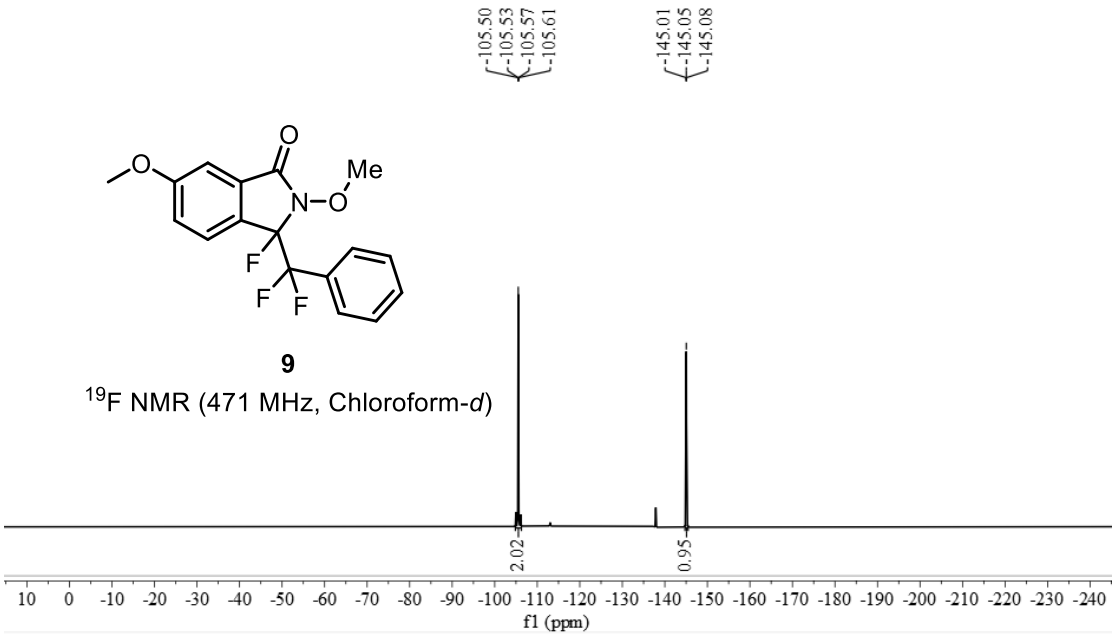
8

^{19}F NMR (471 MHz, Chloroform-*d*)



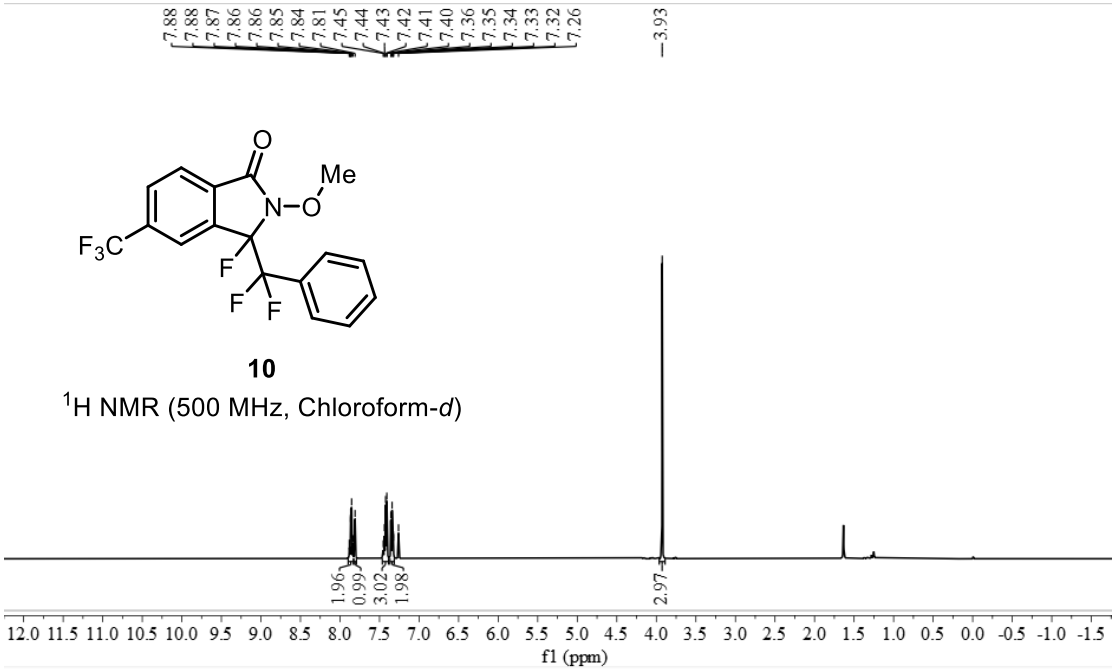
9

^{1}H NMR (500 MHz, Chloroform-*d*)



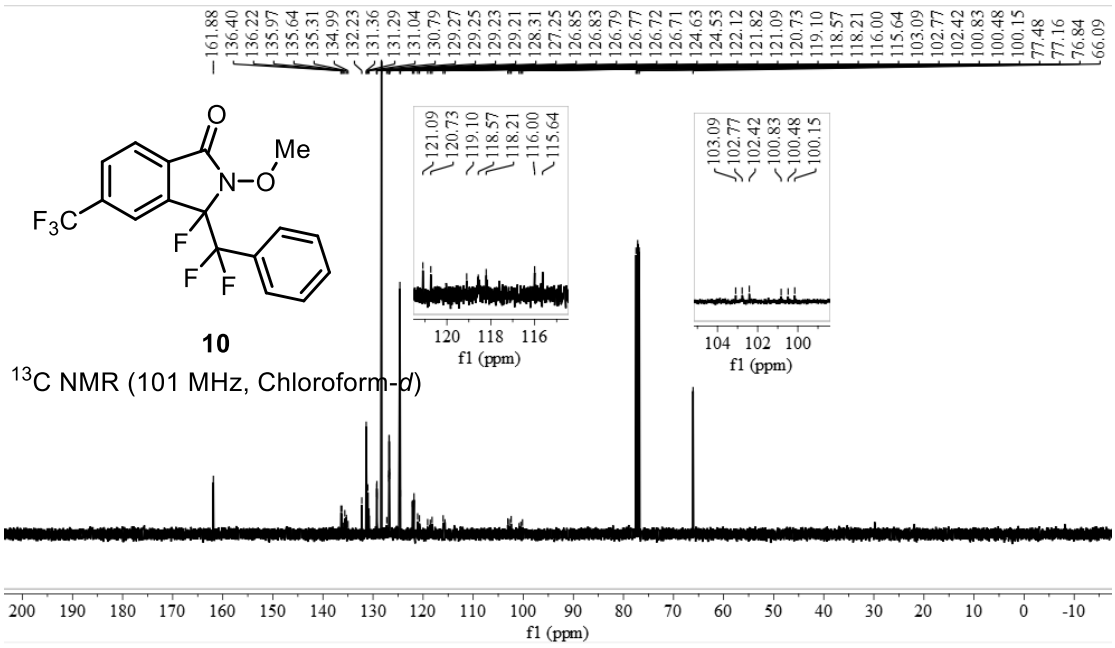
9

^{19}F NMR (471 MHz, Chloroform-*d*)



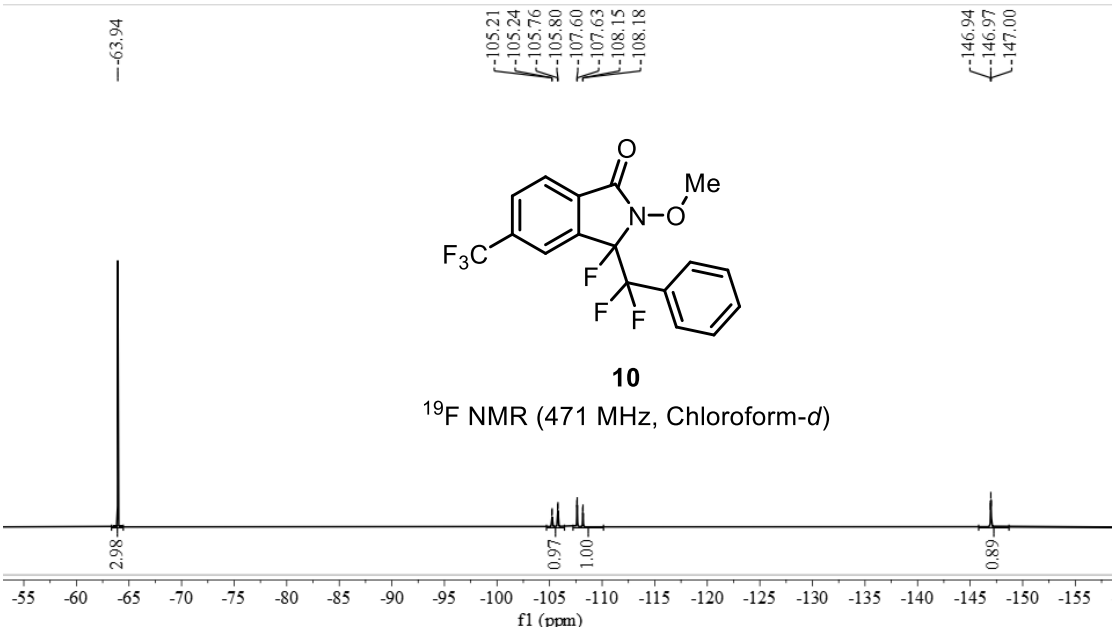
10

^{1}H NMR (500 MHz, Chloroform-*d*)



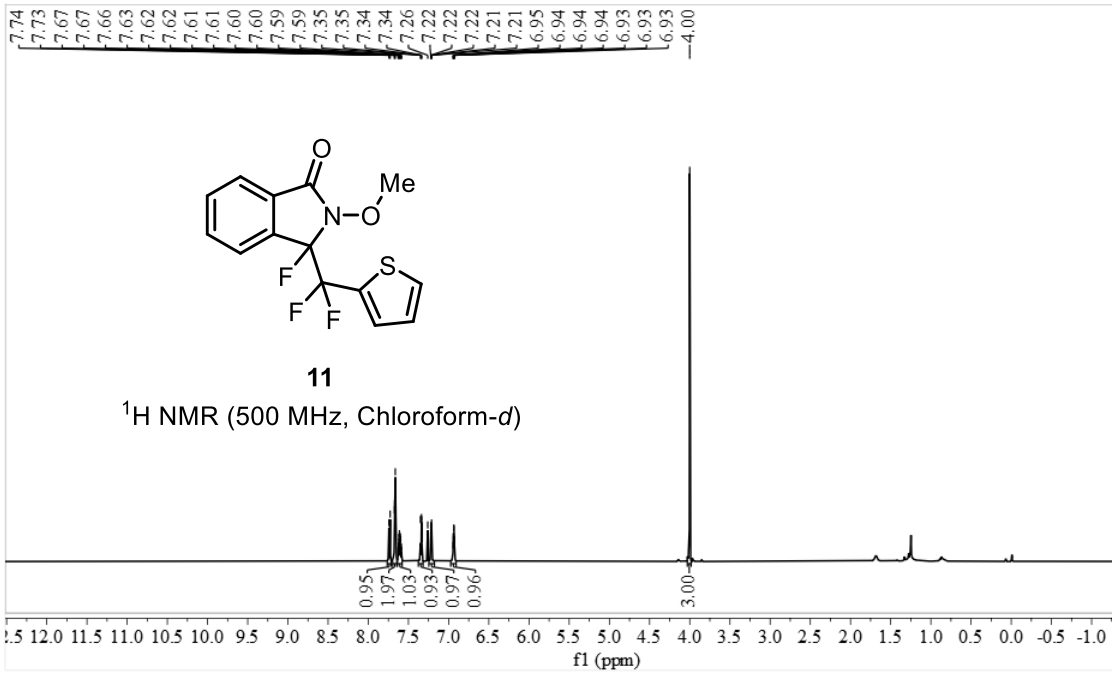
10

^{13}C NMR (101 MHz, Chloroform-*d*)



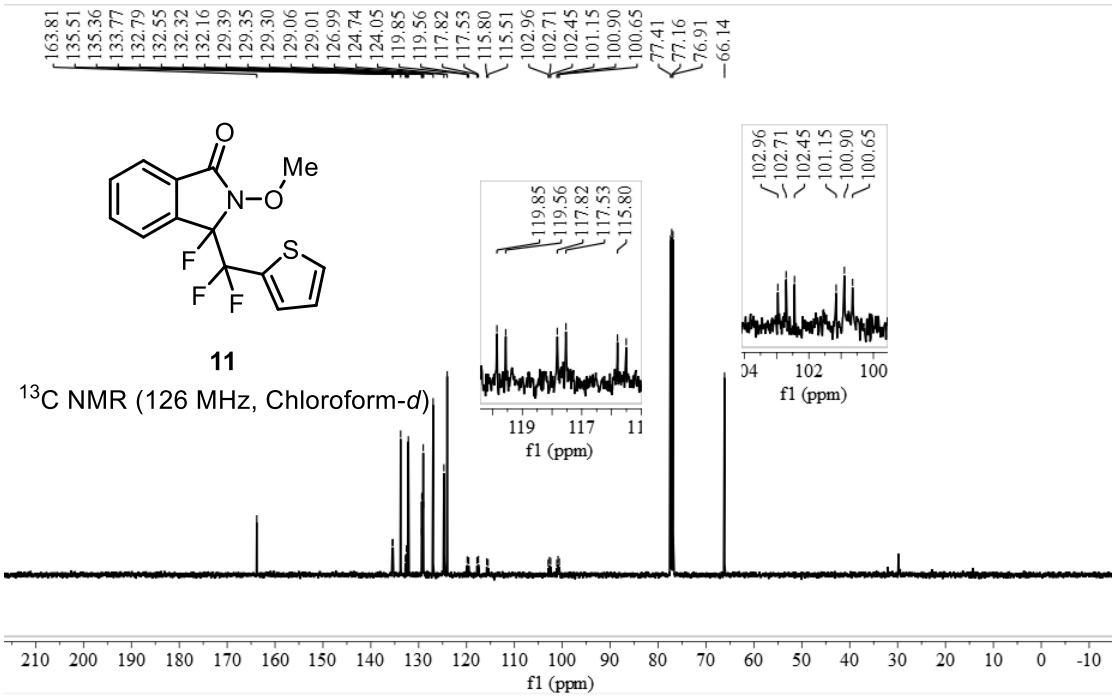
10

^{19}F NMR (471 MHz, Chloroform-*d*)



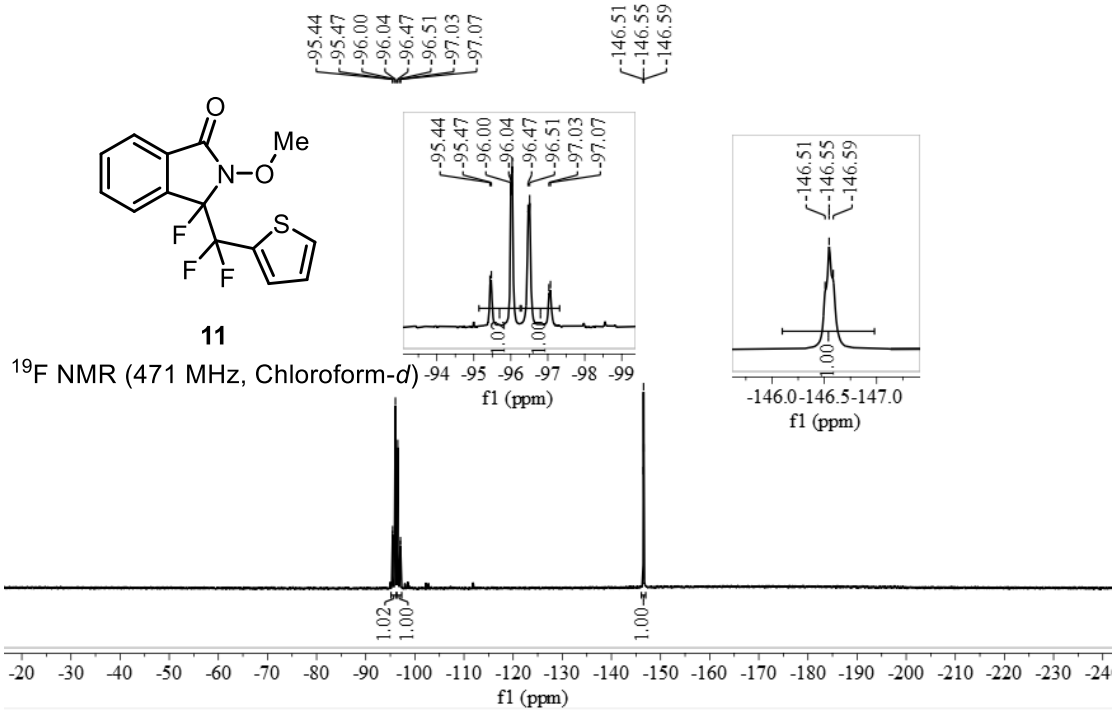
11

^{1}H NMR (500 MHz, Chloroform-*d*)



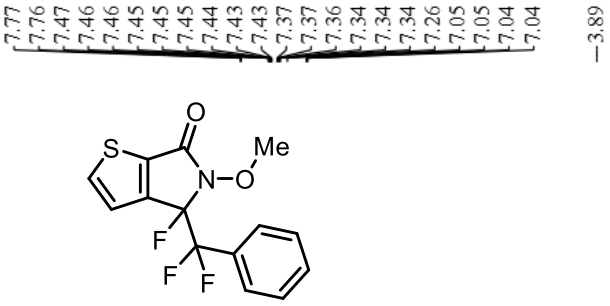
11

^{13}C NMR (126 MHz, Chloroform-*d*)



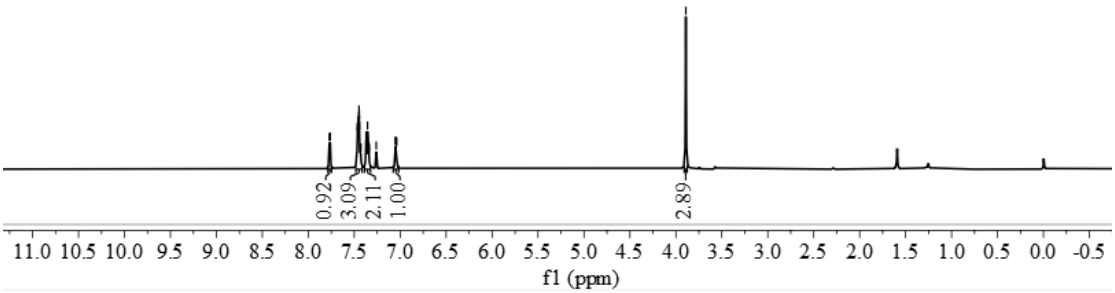
11

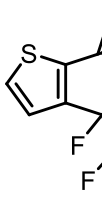
^{19}F NMR (471 MHz, Chloroform-*d*)



12

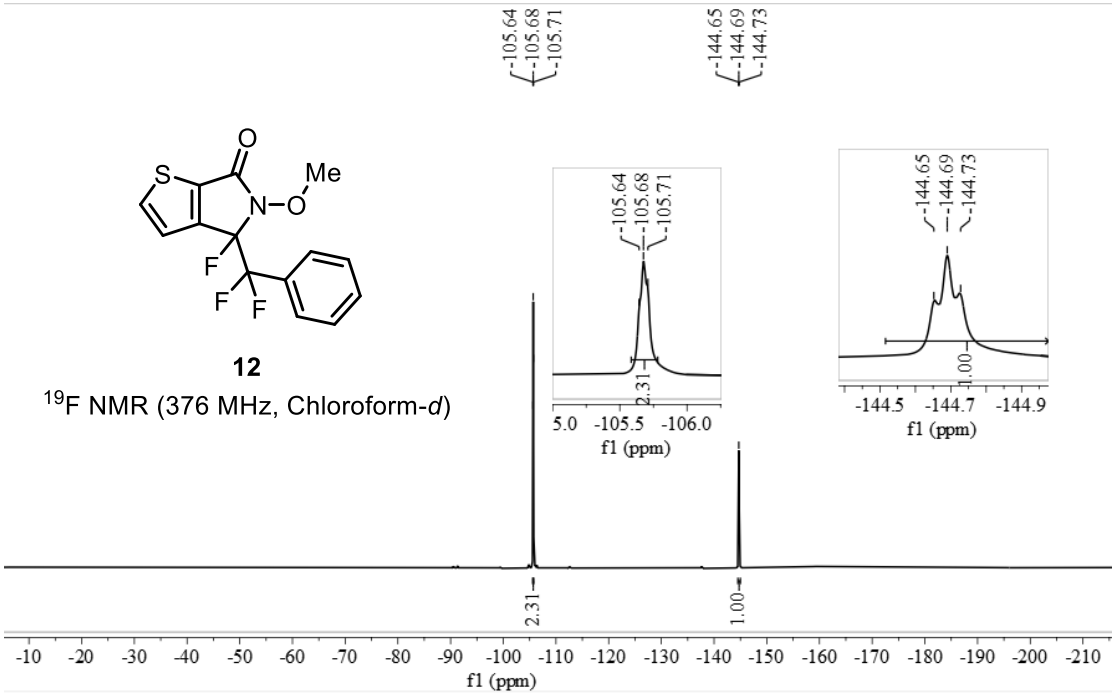
^{1}H NMR (500 MHz, Chloroform-*d*)





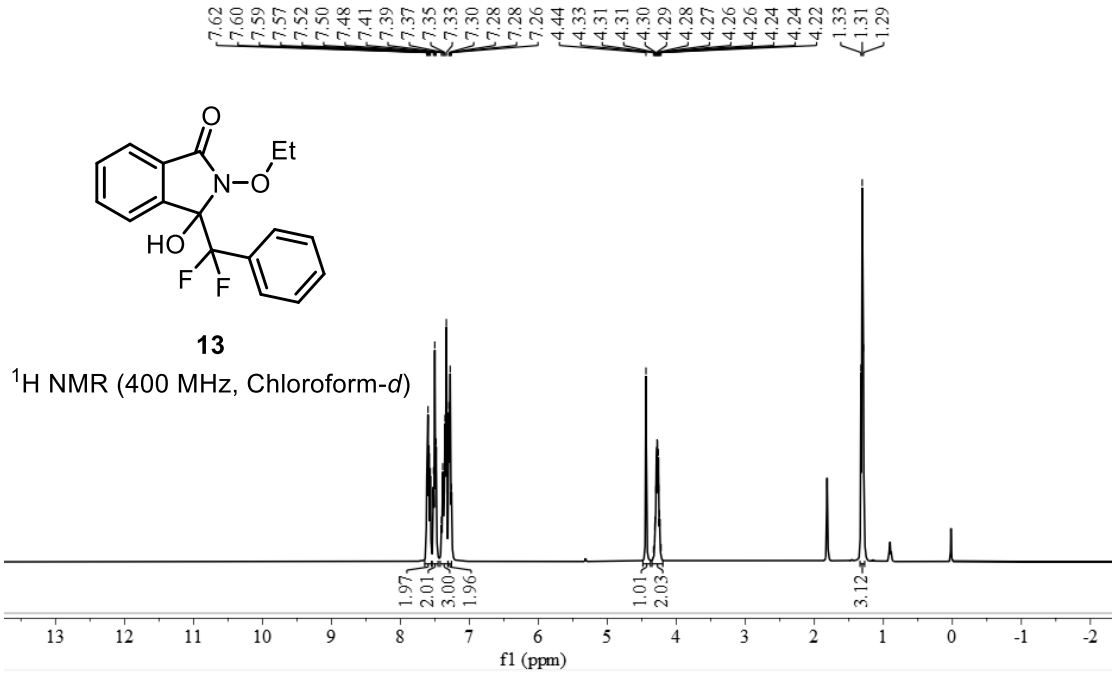
12

^{13}C NMR (101 MHz, Chloroform-*d*)



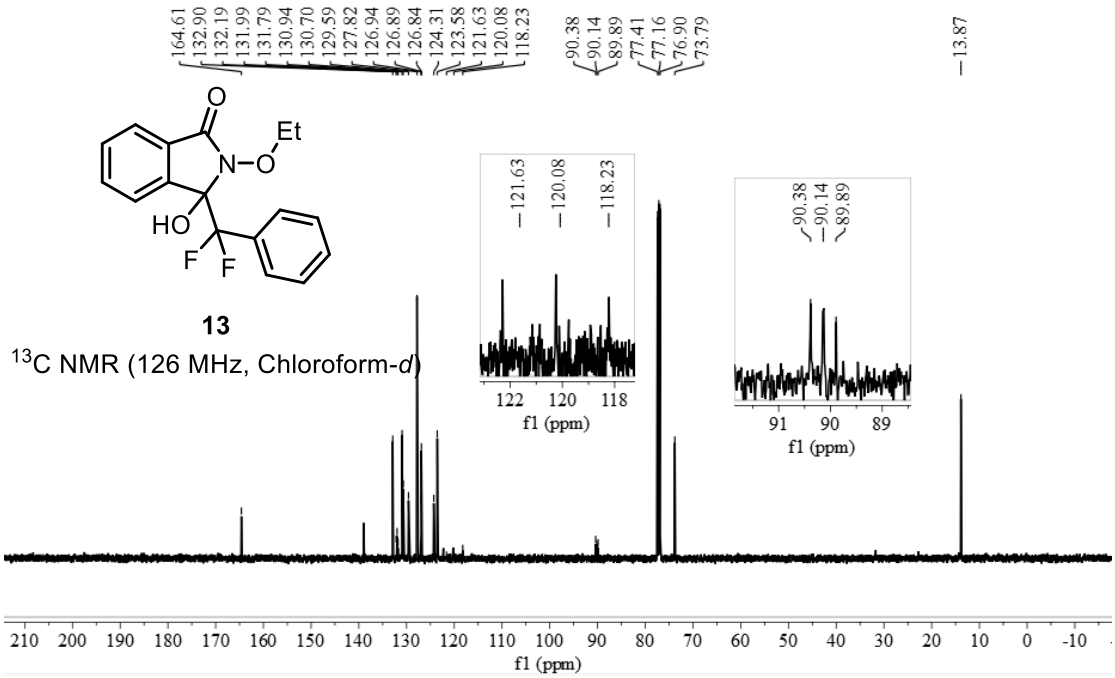
12

^{19}F NMR (376 MHz, Chloroform-*d*)



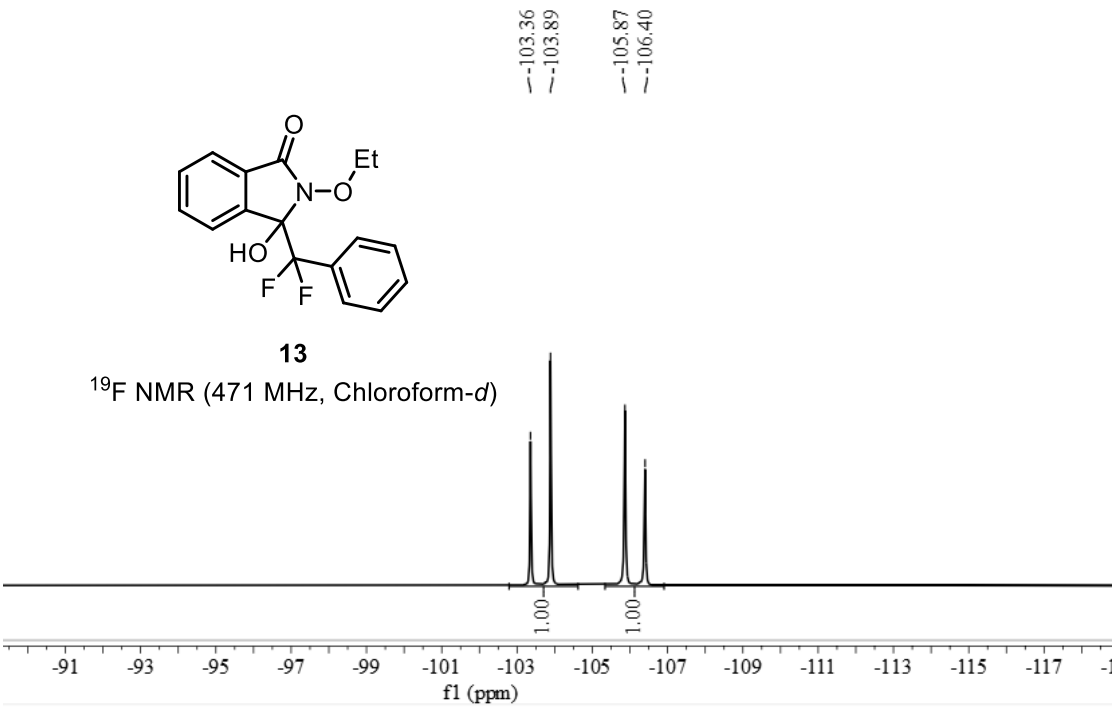
13

^{1}H NMR (400 MHz, Chloroform-*d*)



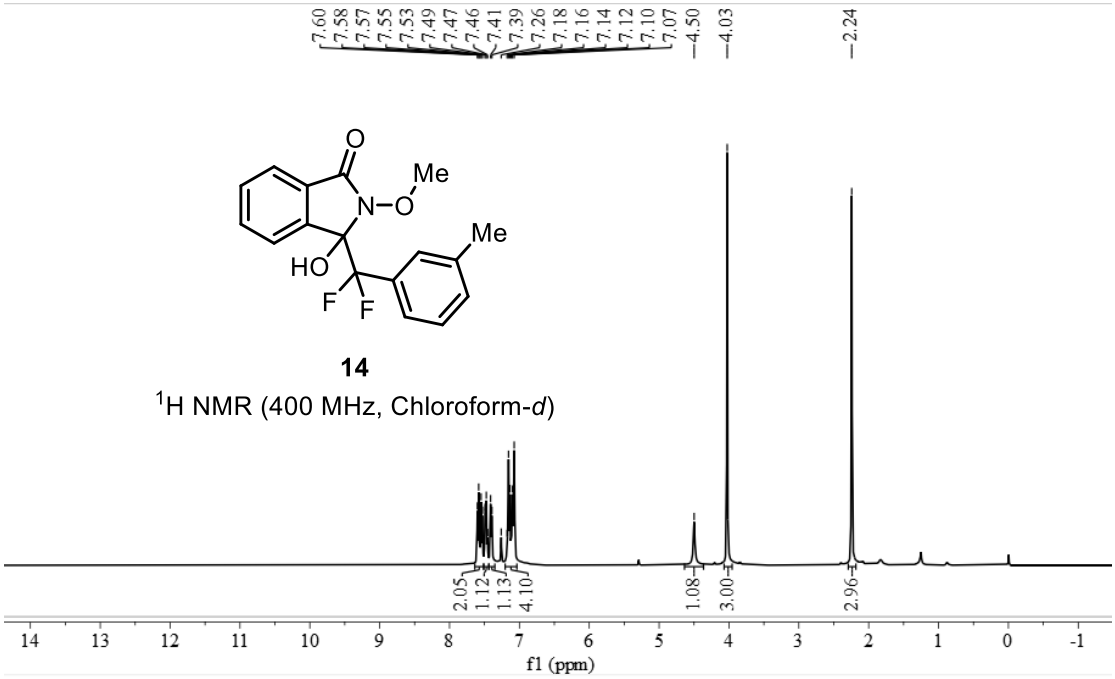
13

^{13}C NMR (126 MHz, Chloroform-*d*)



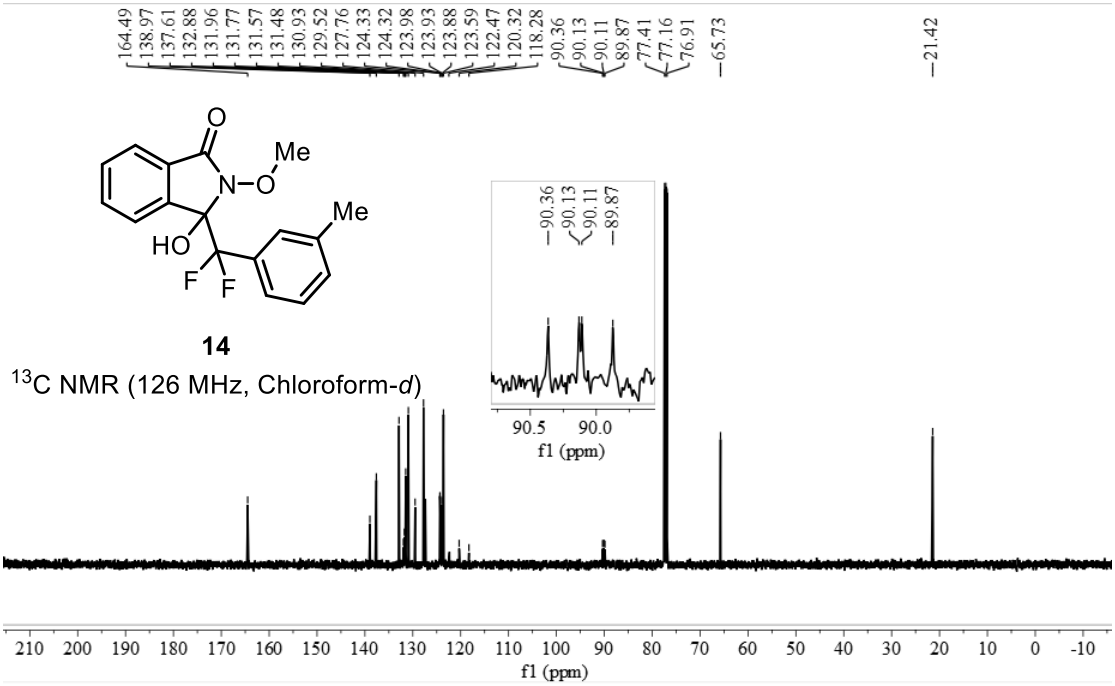
13

^{19}F NMR (471 MHz, Chloroform-*d*)



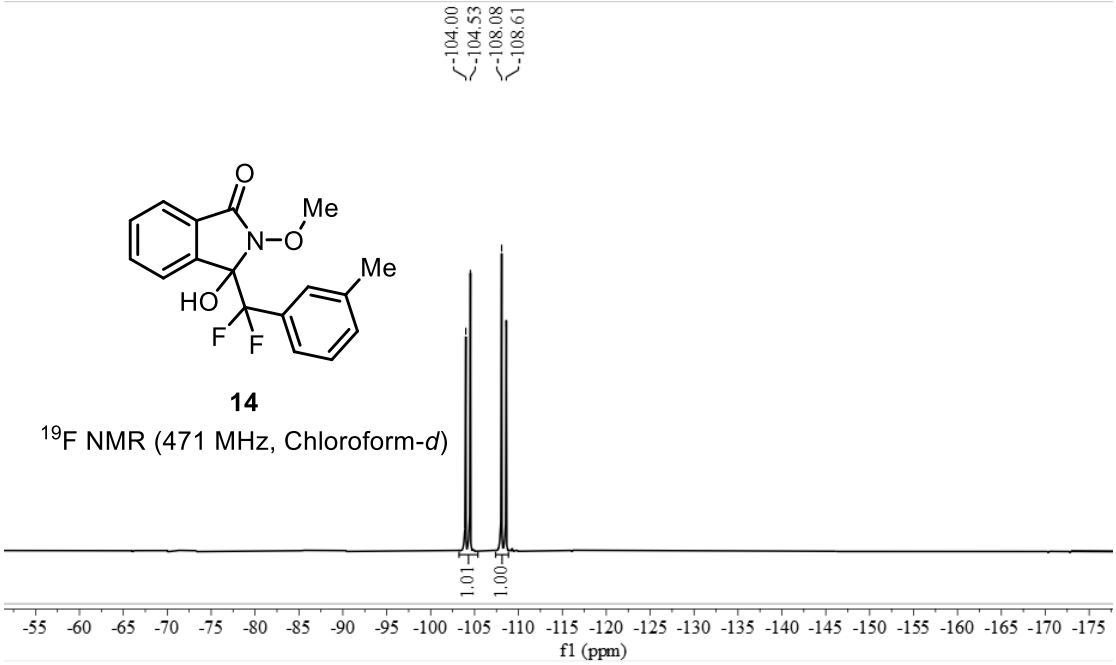
14

^{1}H NMR (400 MHz, Chloroform-*d*)



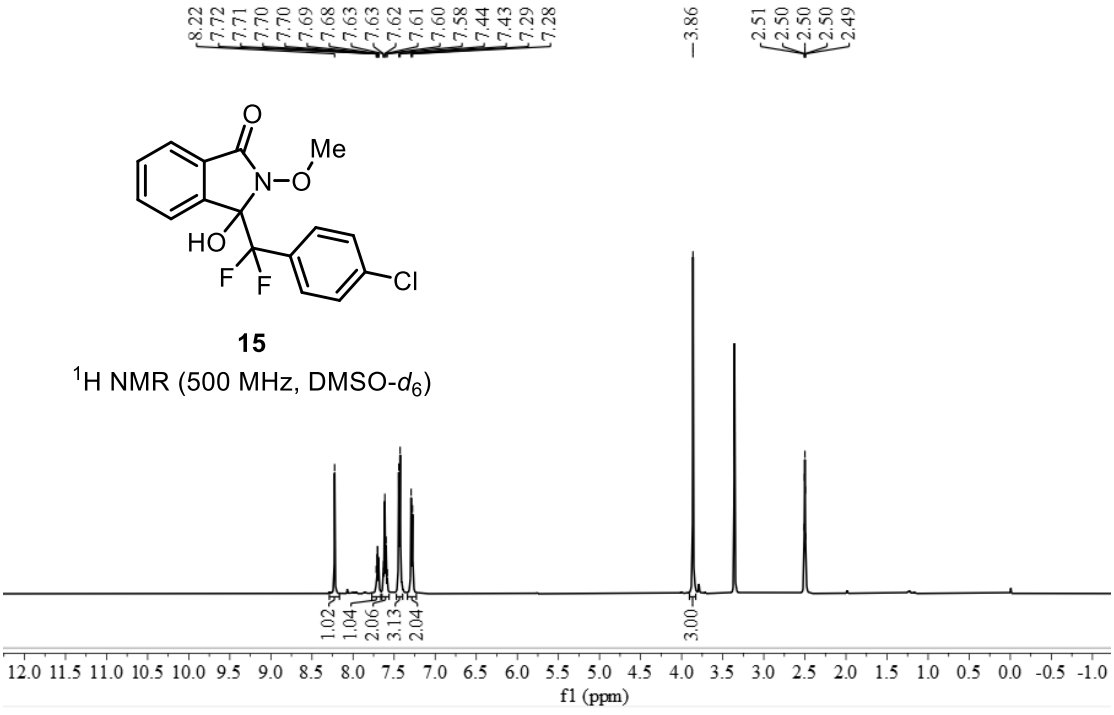
14

^{13}C NMR (126 MHz, Chloroform-*d*)



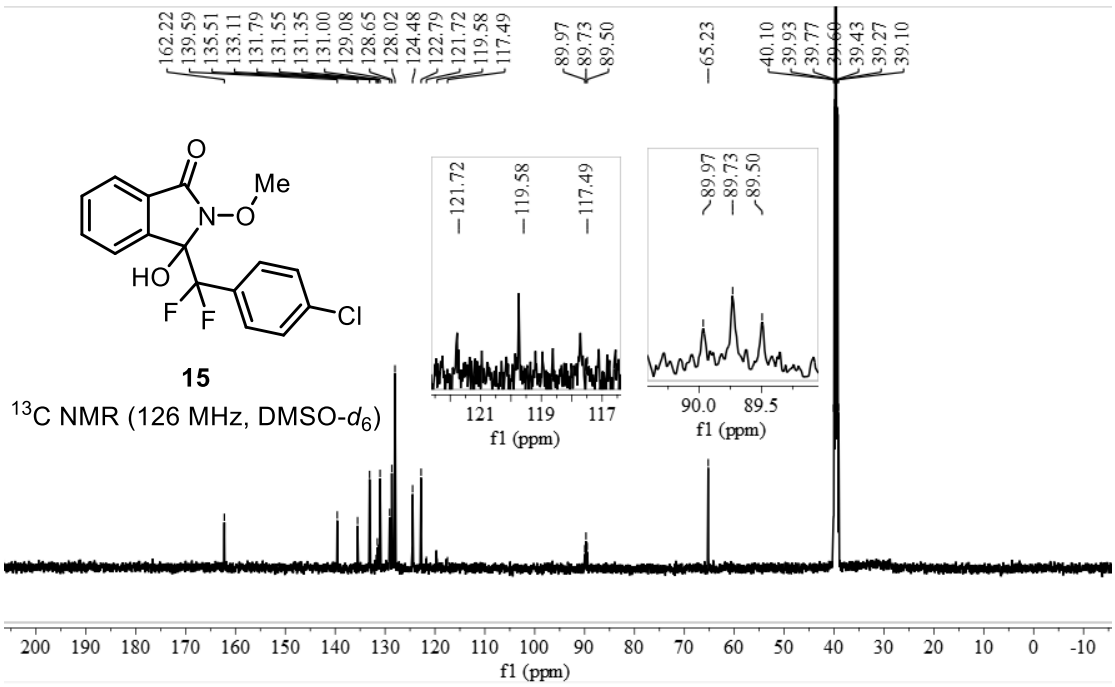
14

^{19}F NMR (471 MHz, Chloroform-*d*)



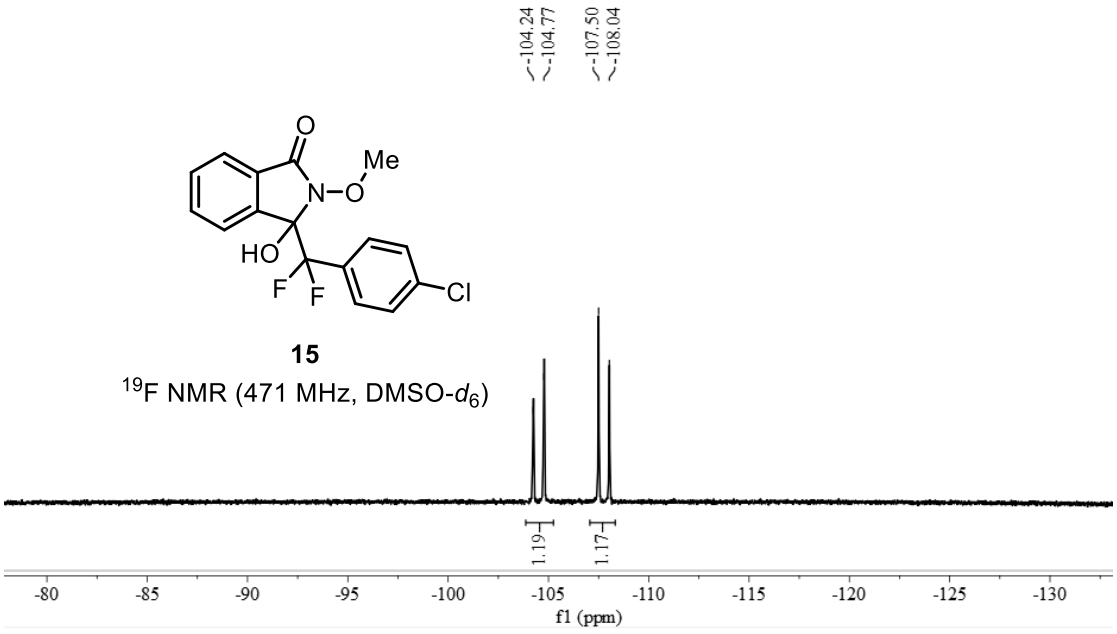
15

^{1}H NMR (500 MHz, DMSO-d_6)



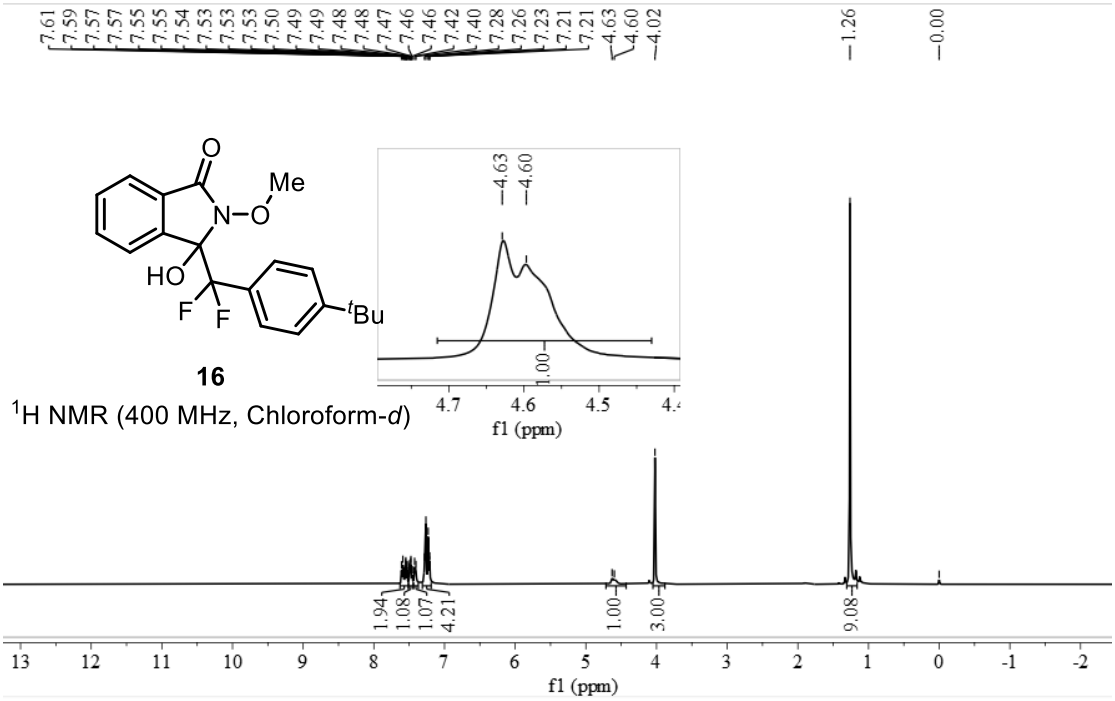
15

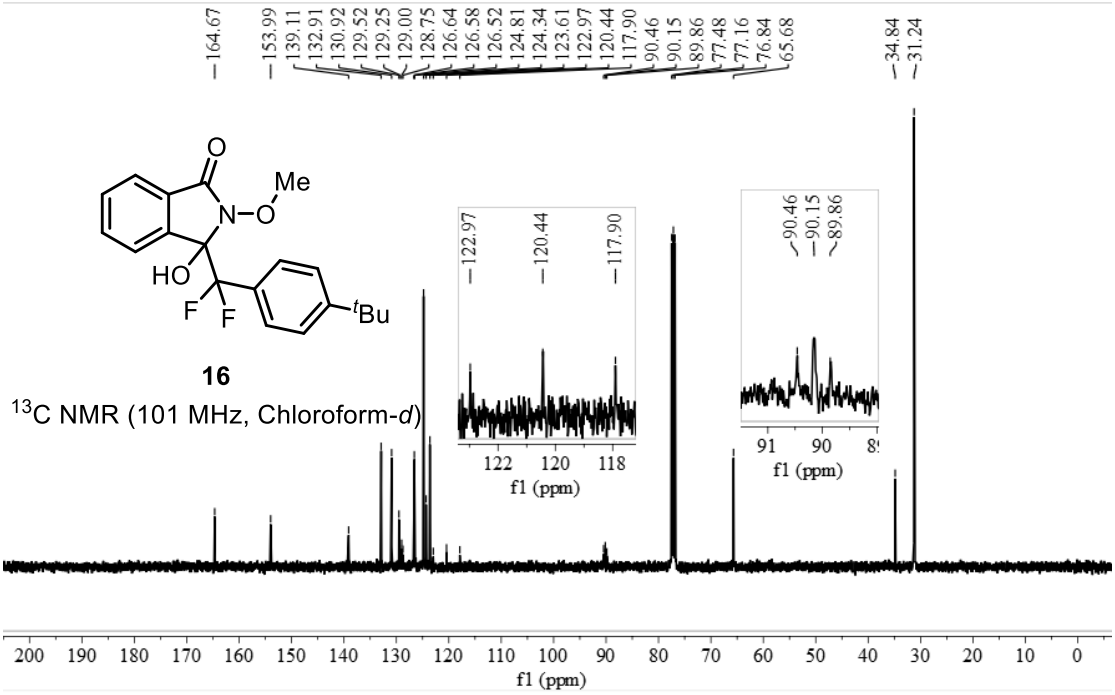
^{13}C NMR (126 MHz, DMSO-d_6)

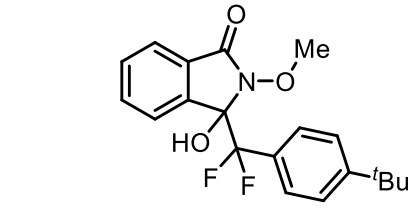


15

^{19}F NMR (471 MHz, DMSO-d_6)

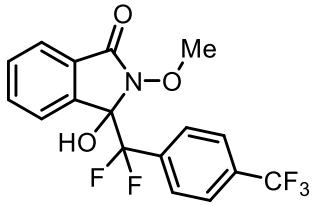

7.61 7.59 7.57 7.57 7.55 7.55 7.54 7.53 7.53 7.53 7.50 7.49 7.49 7.48 7.48 7.47 7.46 7.46 7.42 7.40 7.28 7.26 7.23 7.21 7.21 4.63 4.60 4.02 1.26 0.00
O
Me
N–O
HO
F F
tBu
16
1H NMR (400 MHz, Chloroform-d)
4.63 4.60
1.00
4.7 4.6 4.5
f1 (ppm)
1.94 1.08 1.07 4.21 1.00 3.00 9.08
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
f1 (ppm)


164.67 153.99 139.11 132.91 130.92 129.52 129.25 129.00 128.75 126.64 126.58 126.52 124.81 124.34 123.61 122.97 120.44 117.90 90.46 90.15 89.86 77.48 77.16 76.84 65.68 34.84 31.24
O
Me
N–O
HO
F F
tBu
16
13C NMR (101 MHz, Chloroform-d)
122.97 120.44 117.90
122 120 118
f1 (ppm)
90.46 90.15 89.86
91 90
f1 (ppm)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



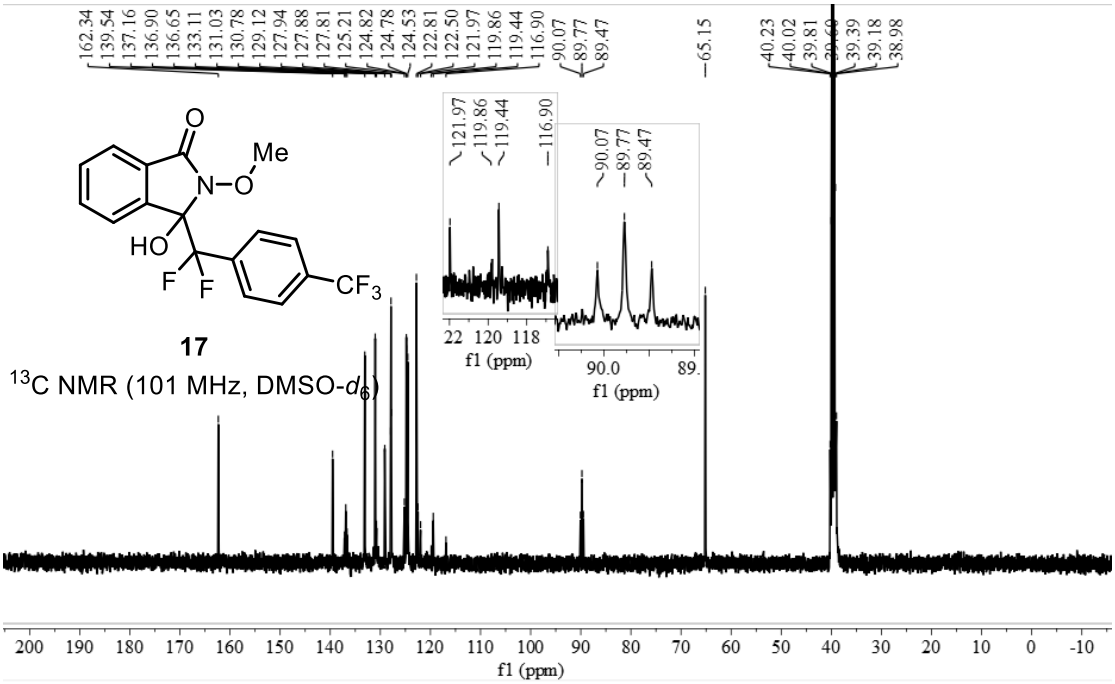
16

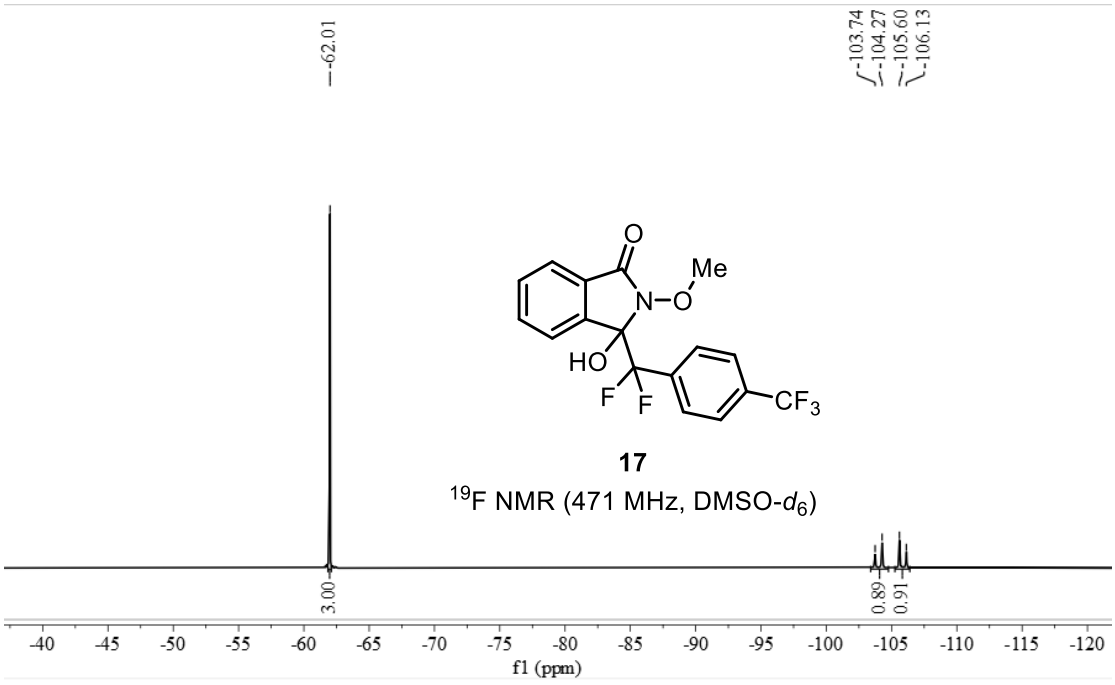
^{19}F NMR (376 MHz, Chloroform-*d*)

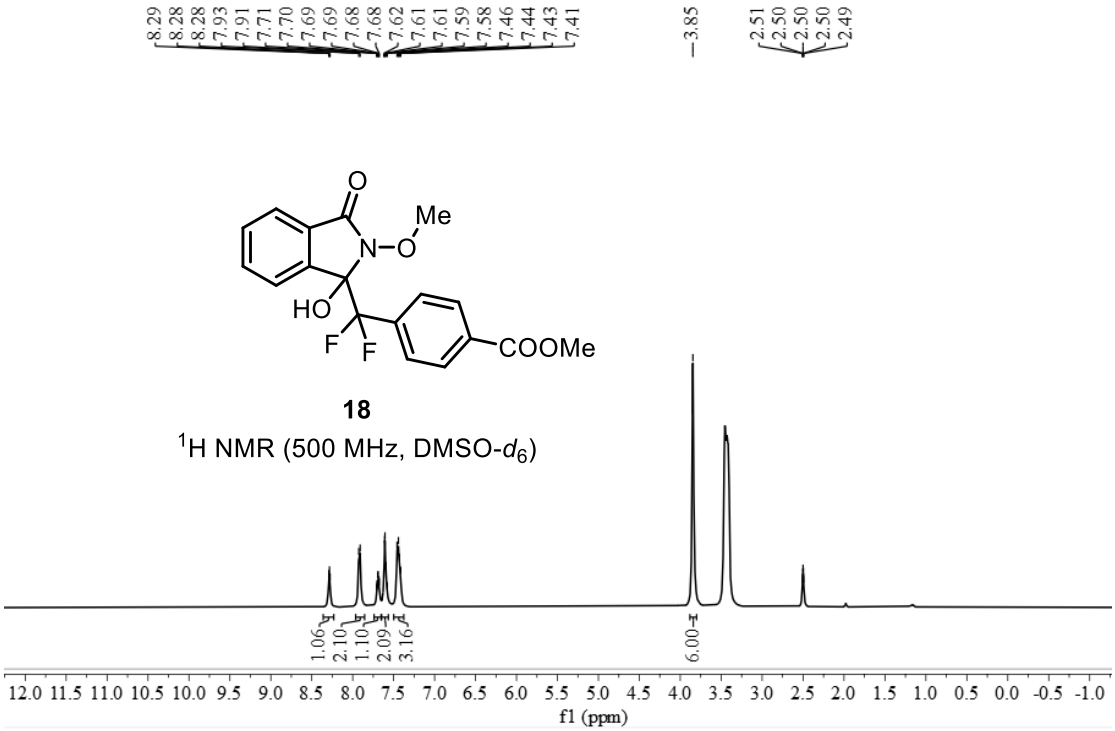


17

^{1}H NMR (400 MHz, DMSO-d_6)

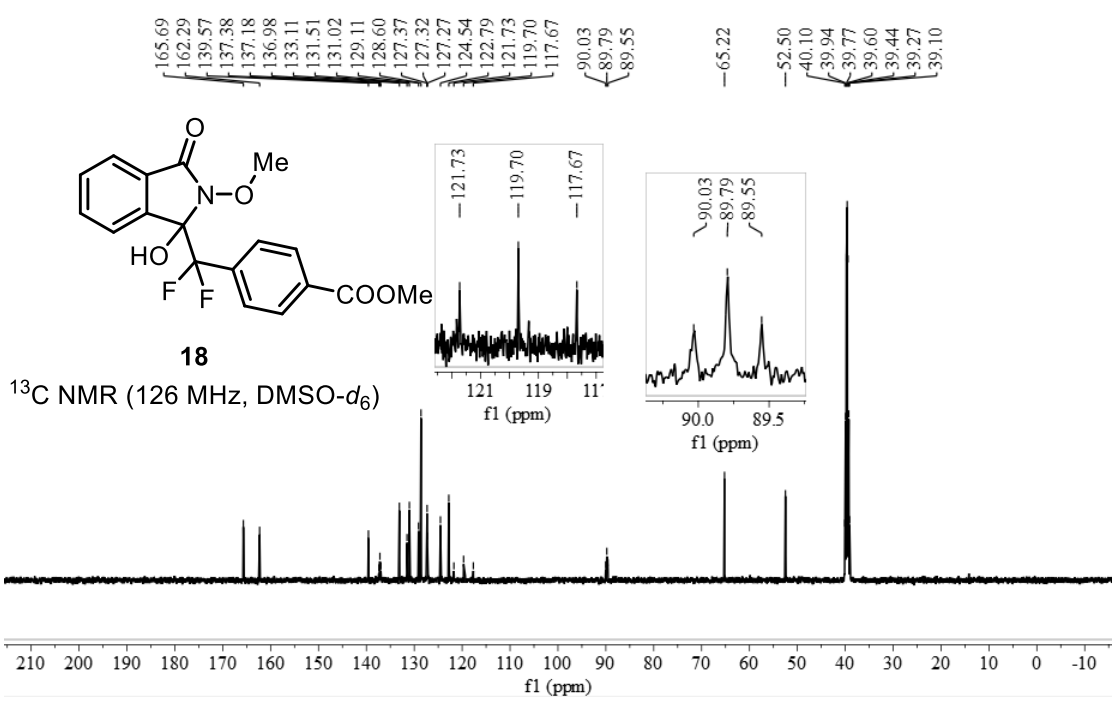

162.34
139.54
137.16
136.90
136.65
133.11
131.03
130.78
129.12
127.94
127.88
127.81
125.21
124.82
124.78
124.53
122.81
122.50
121.97
119.86
119.44
116.90
90.07
89.77
89.47
65.15
40.23
40.02
39.81
39.60
39.39
39.18
38.98
O
Me
N–O
HO
F
F
CF3
17
13C NMR (101 MHz, DMSO-d6)
f1 (ppm)


-62.01
-103.74
-104.27
-105.60
-106.13
O
Me
N–O
HO
F
F
CF3
17
19F NMR (471 MHz, DMSO-d6)
3.00
0.89
0.91
f1 (ppm)



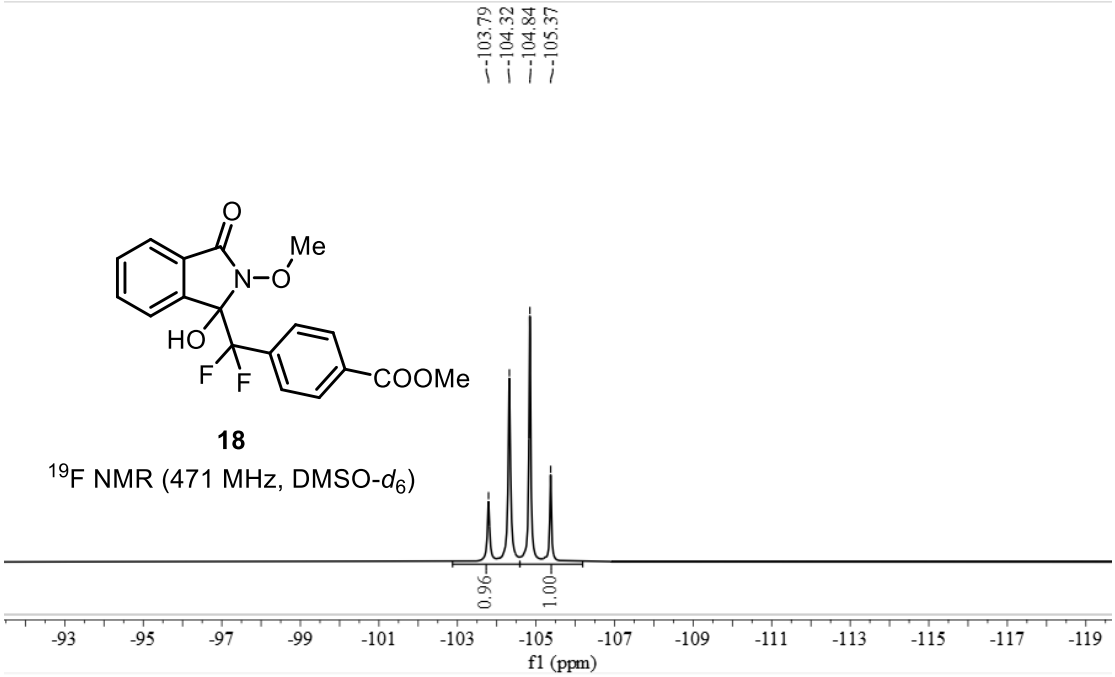
18

^{1}H NMR (500 MHz, DMSO-d_6)



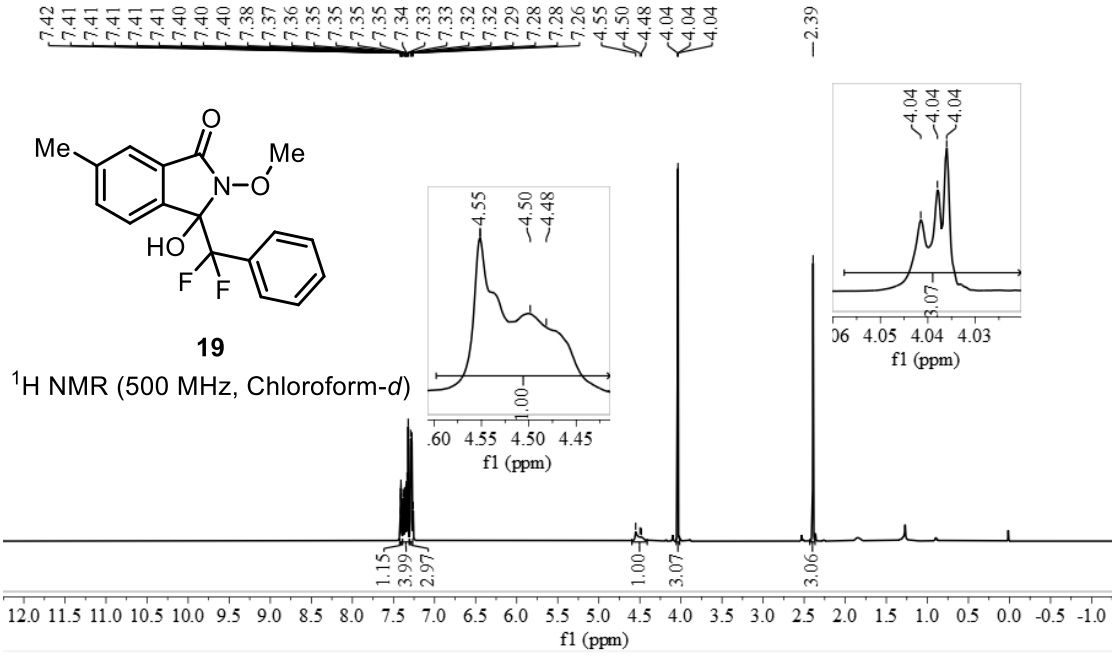
18

^{13}C NMR (126 MHz, DMSO-d_6)



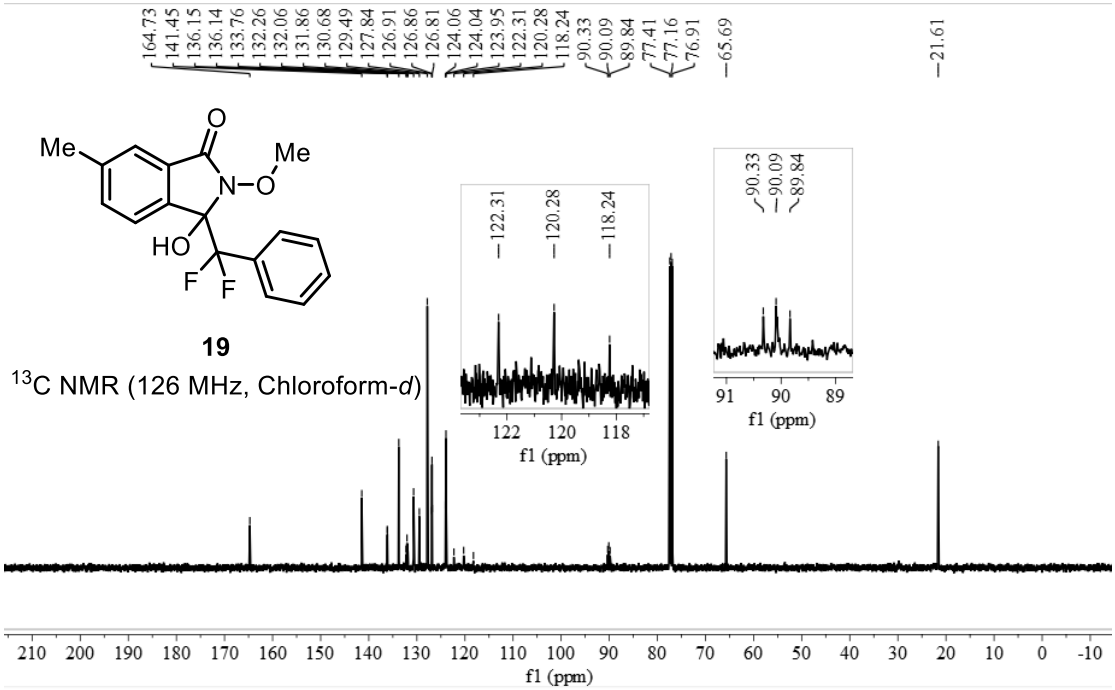
18

^{19}F NMR (471 MHz, DMSO-d_6)



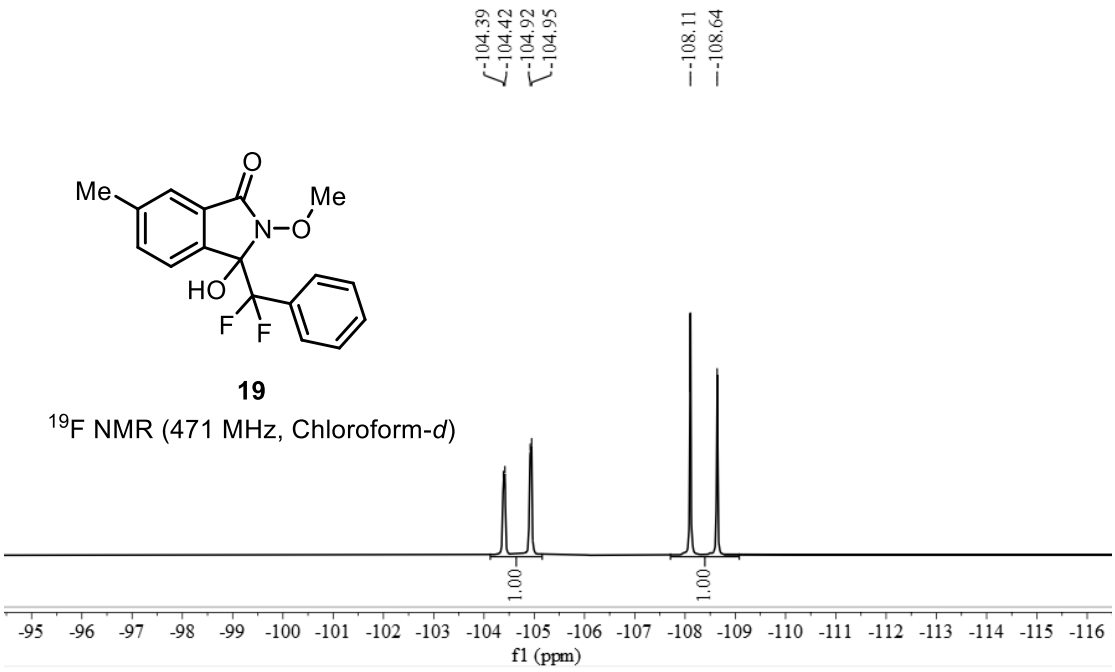
19

^{1}H NMR (500 MHz, Chloroform-*d*)



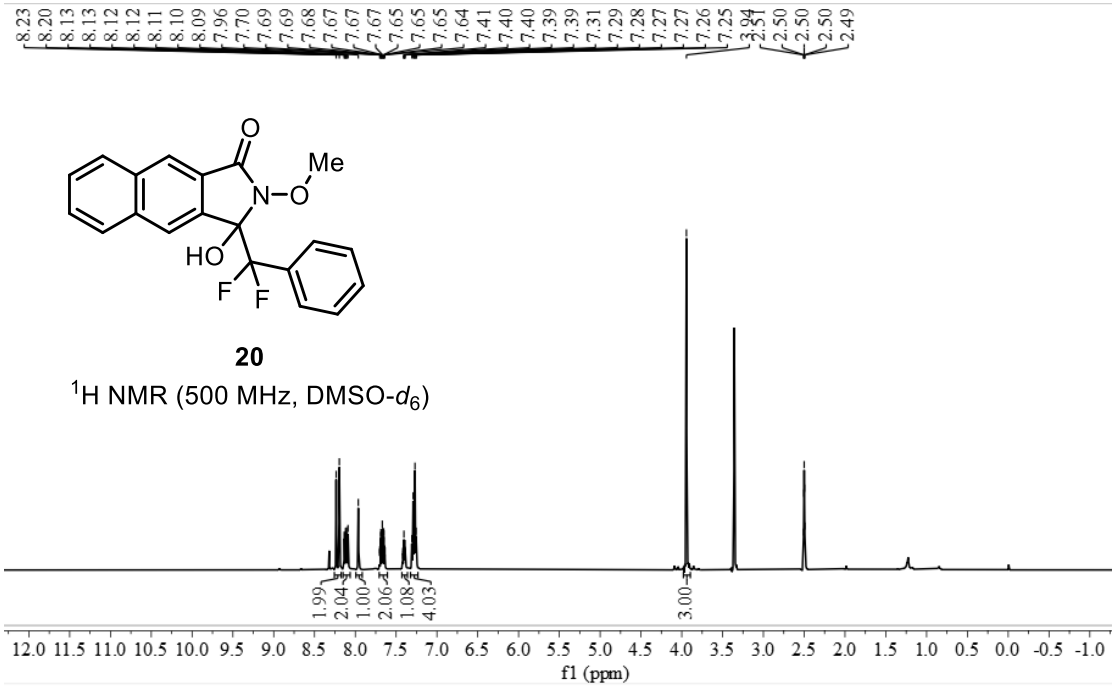
19

^{13}C NMR (126 MHz, Chloroform-*d*)



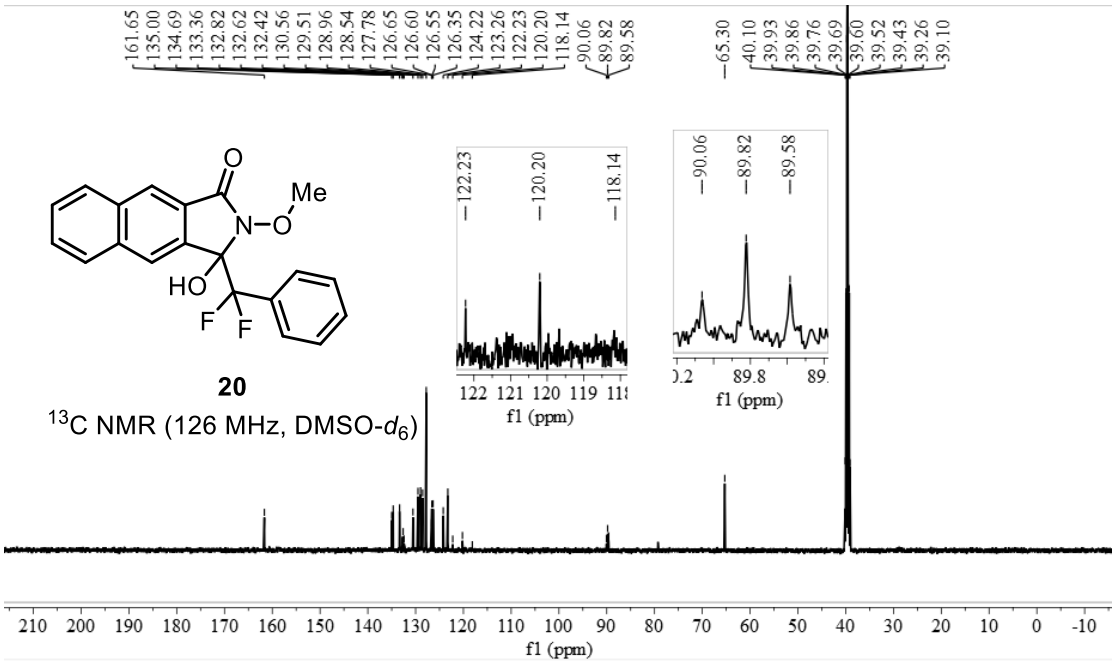
19

^{19}F NMR (471 MHz, Chloroform-*d*)



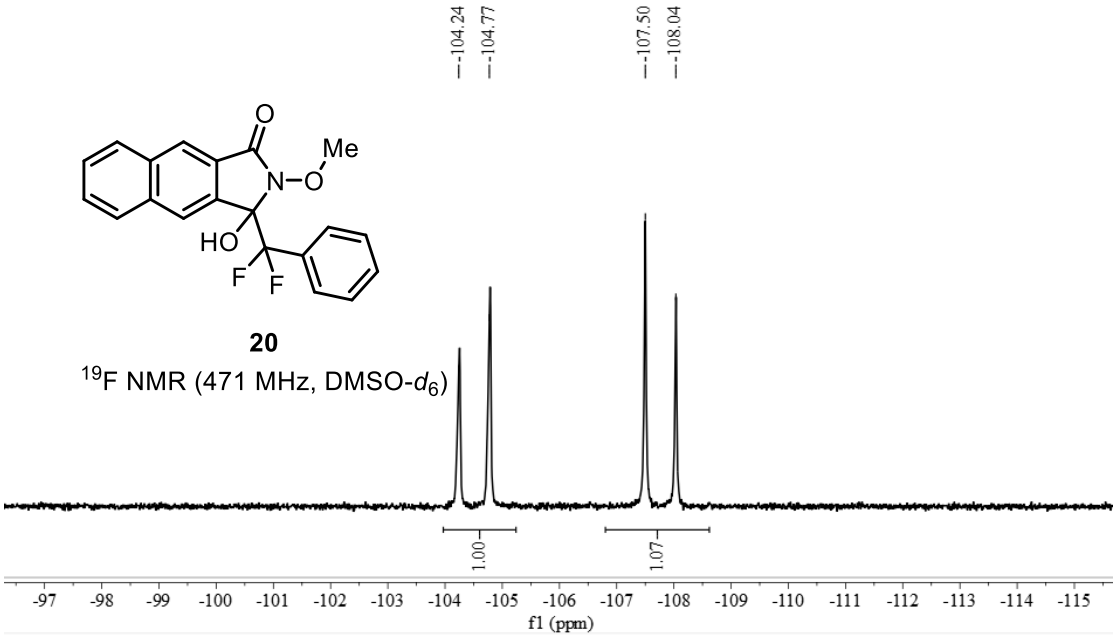
20

^{1}H NMR (500 MHz, DMSO-d_6)



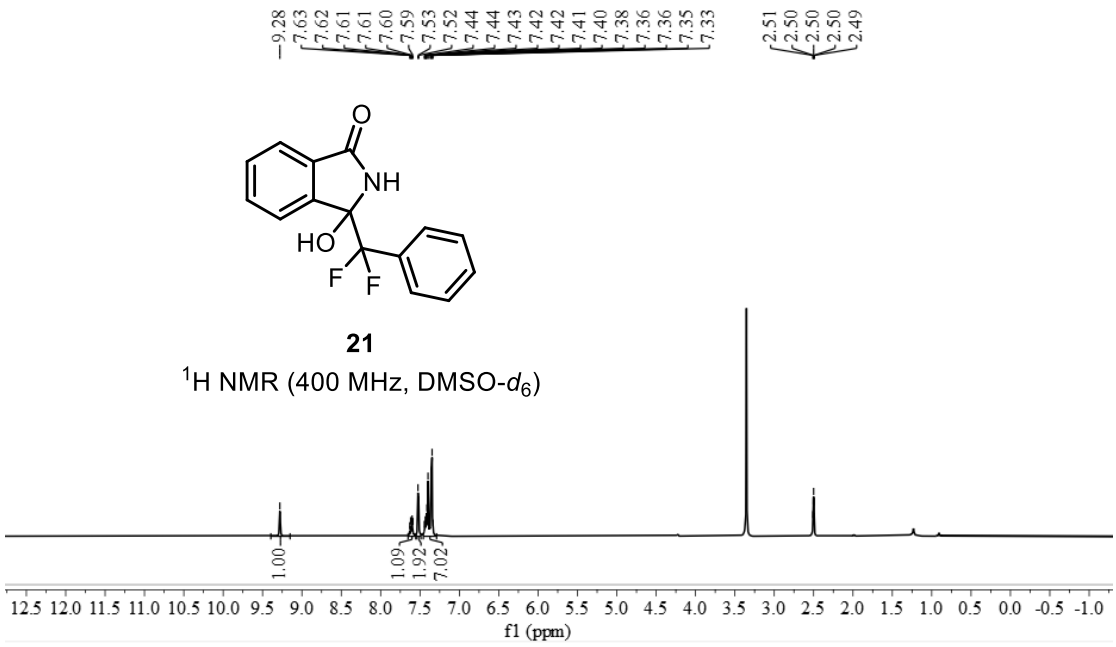
20

^{13}C NMR (126 MHz, DMSO-d_6)



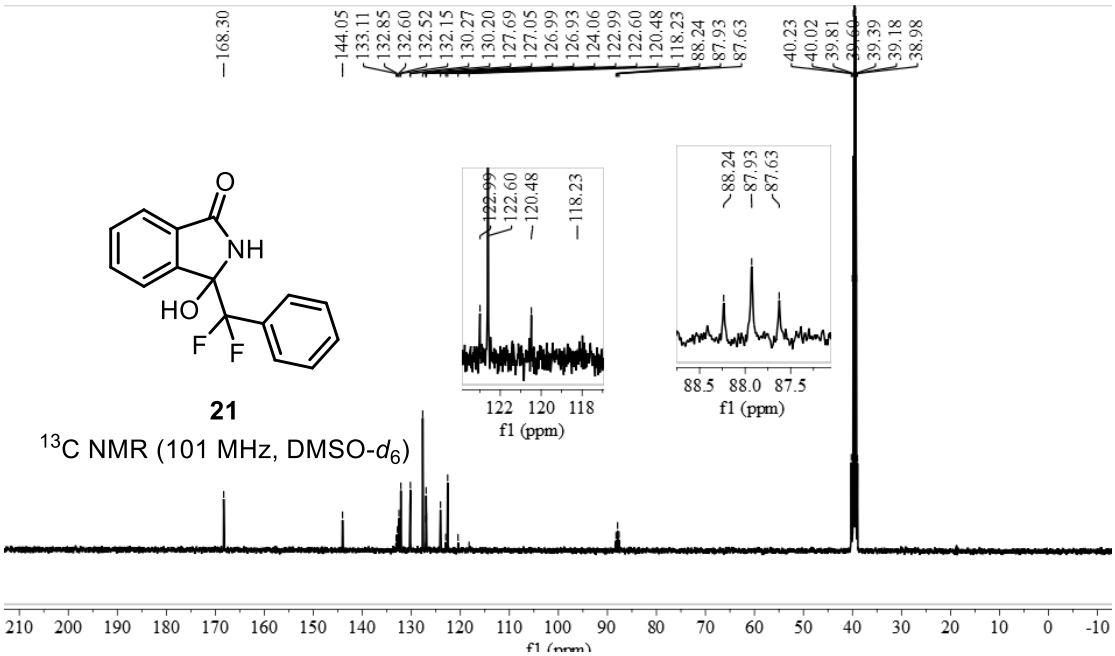
20

^{19}F NMR (471 MHz, DMSO-d_6)



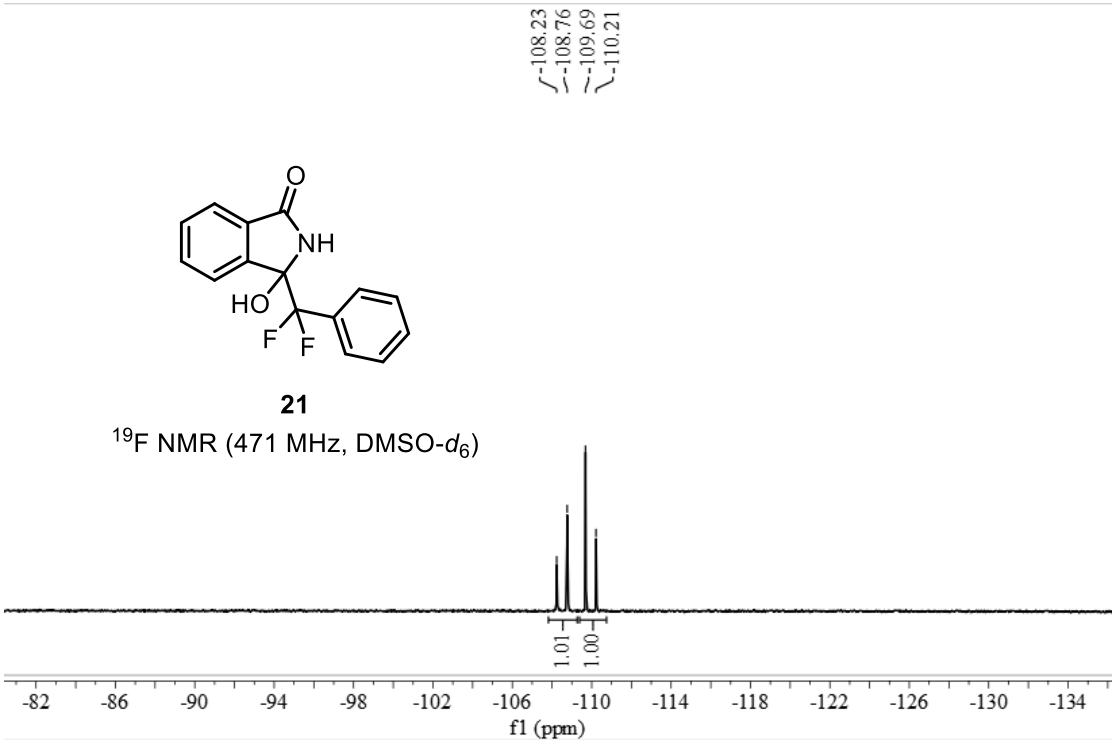
21

^{1}H NMR (400 MHz, DMSO-d_6)



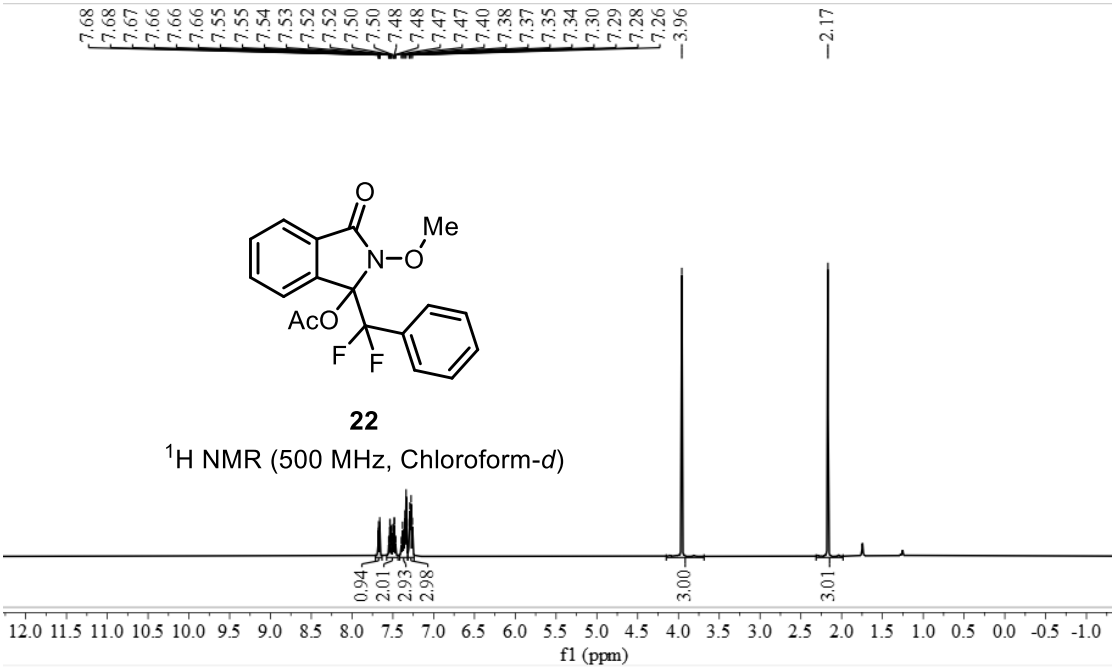
21

^{13}C NMR (101 MHz, DMSO-d_6)



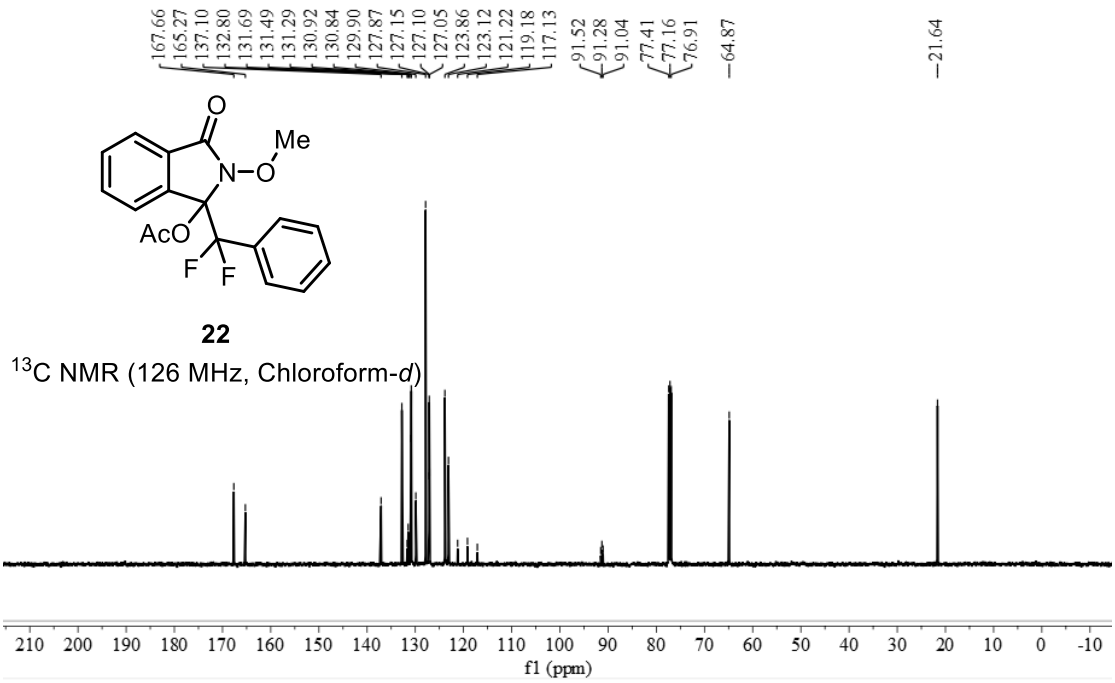
21

^{19}F NMR (471 MHz, DMSO-d_6)



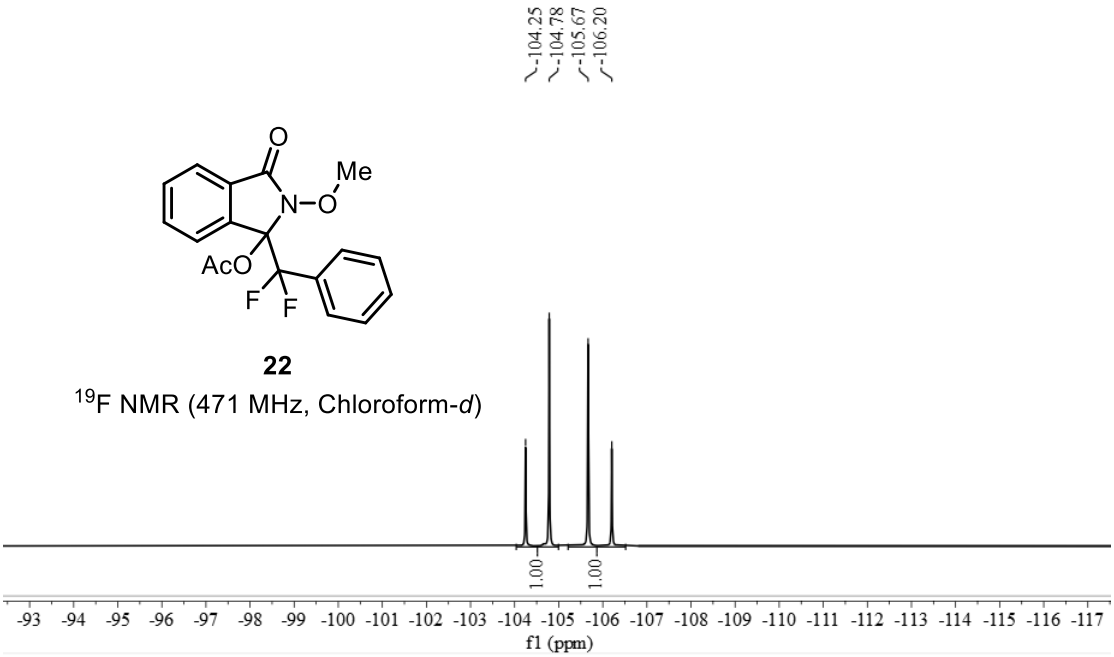
22

^{1}H NMR (500 MHz, Chloroform-*d*)



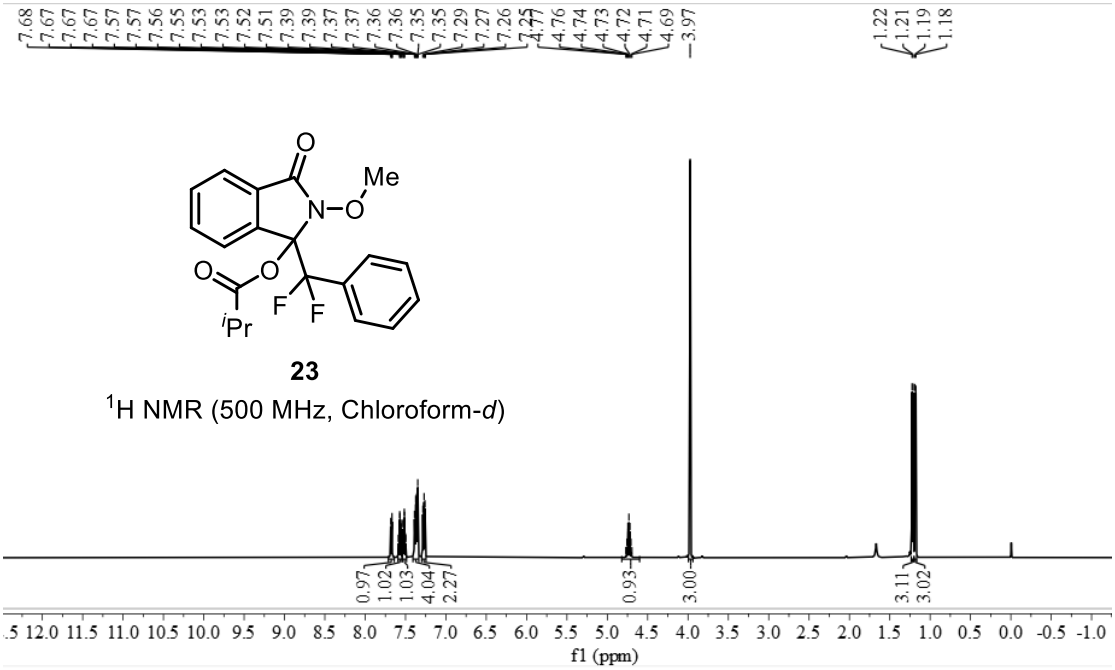
22

^{13}C NMR (126 MHz, Chloroform-*d*)



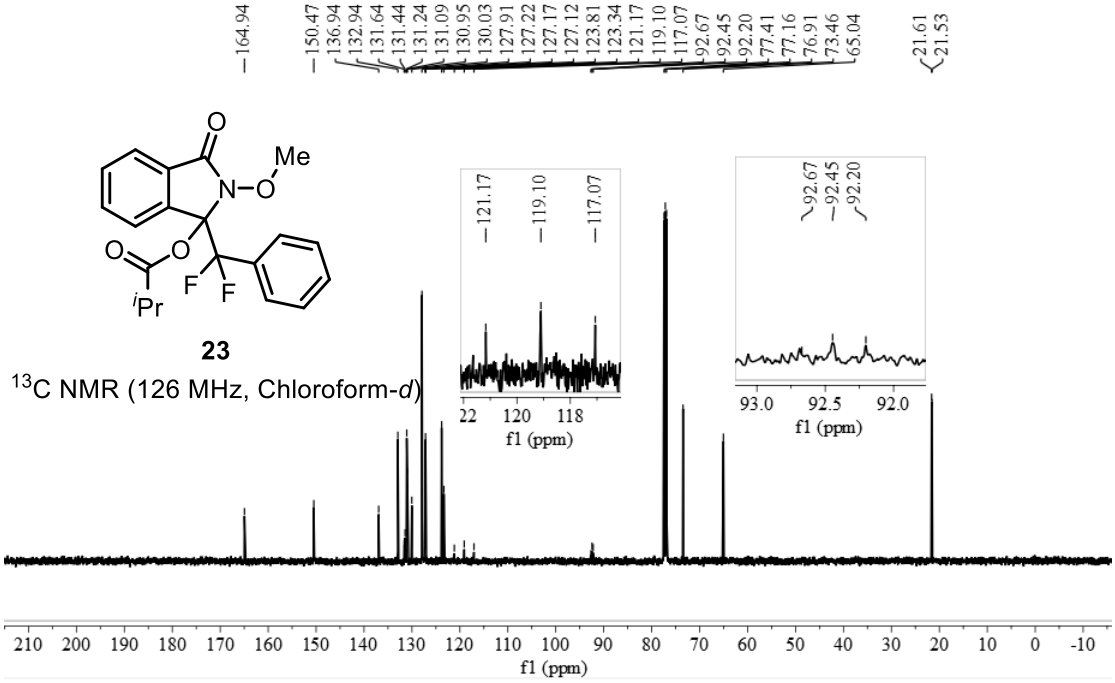
22

^{19}F NMR (471 MHz, Chloroform-*d*)



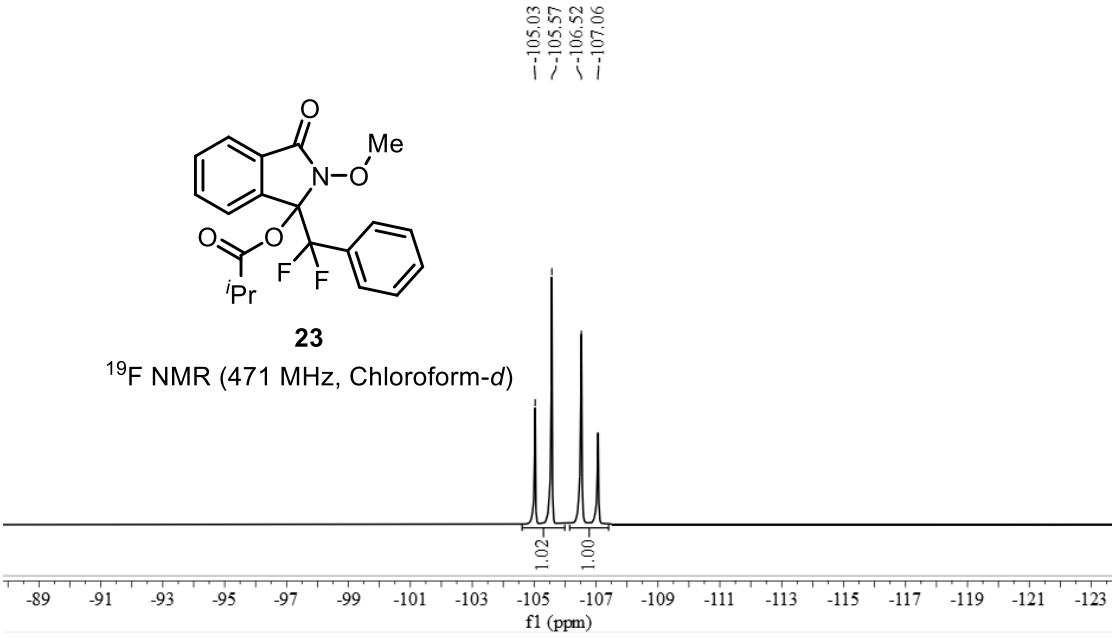
23

^{1}H NMR (500 MHz, Chloroform-*d*)



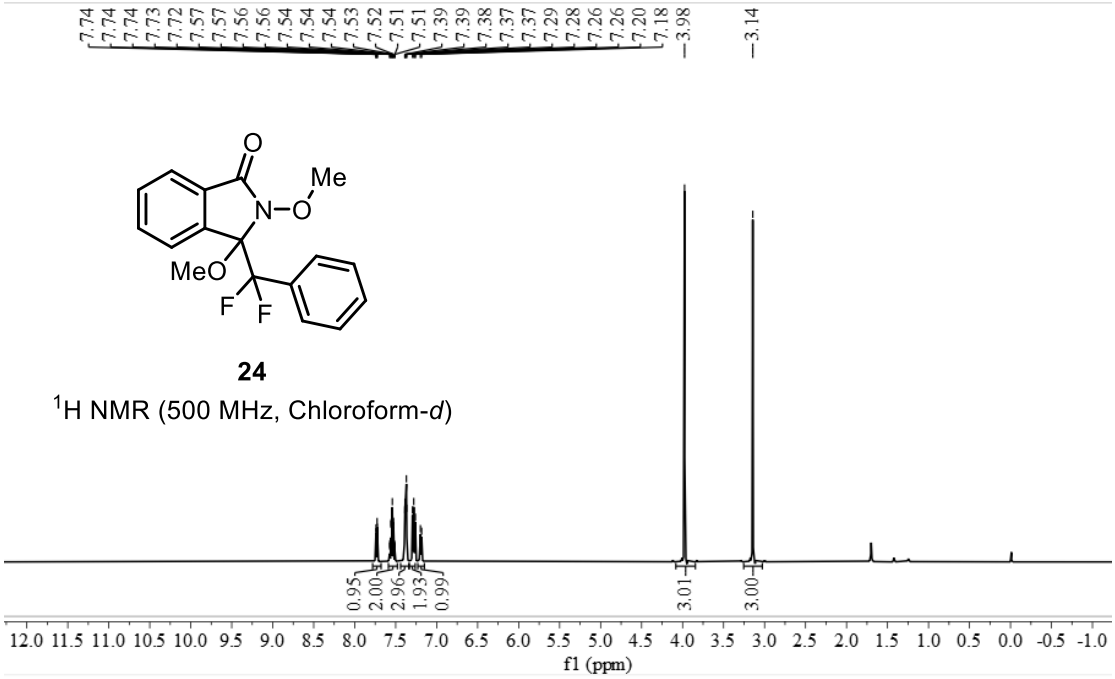
23

^{13}C NMR (126 MHz, Chloroform-*d*)



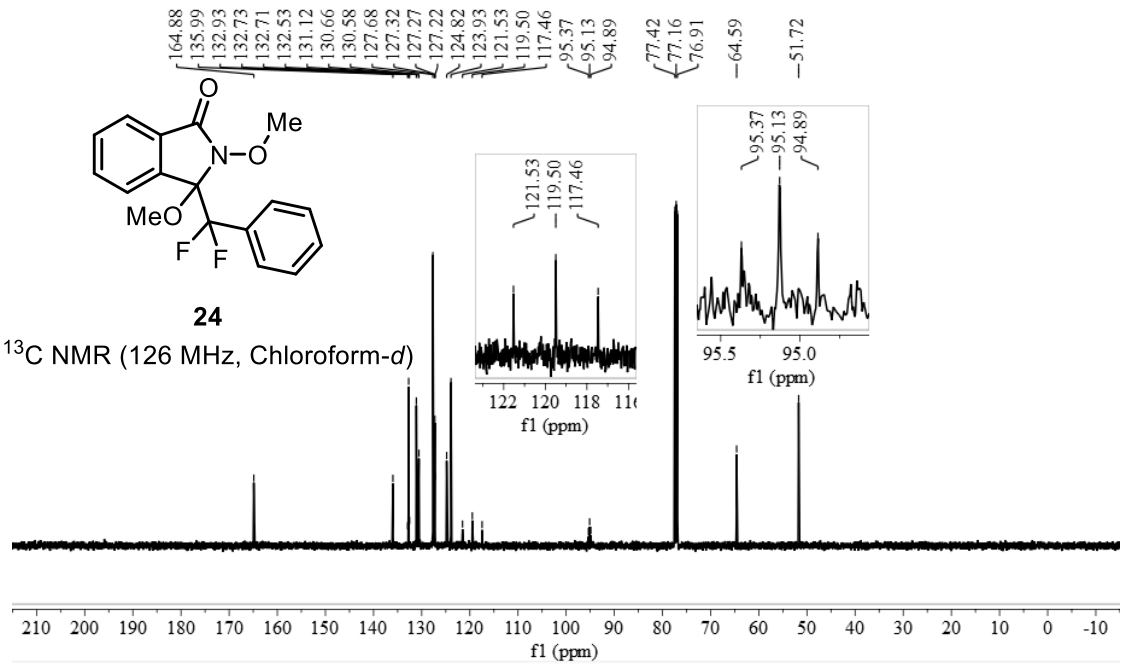
23

^{19}F NMR (471 MHz, Chloroform-*d*)



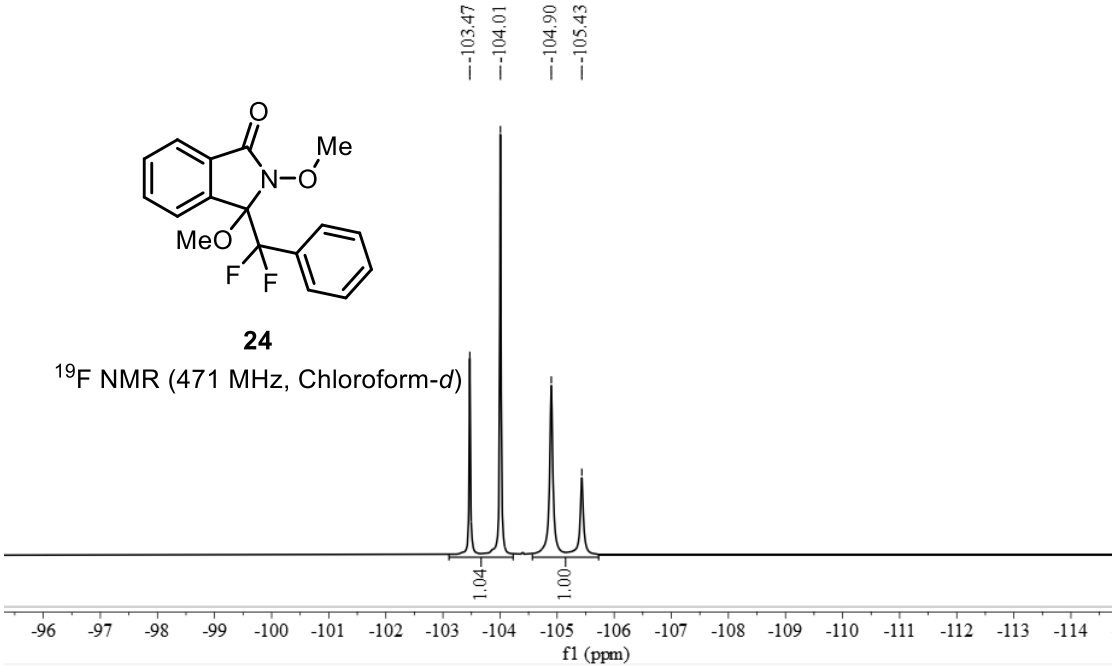
24

^{1}H NMR (500 MHz, Chloroform-*d*)



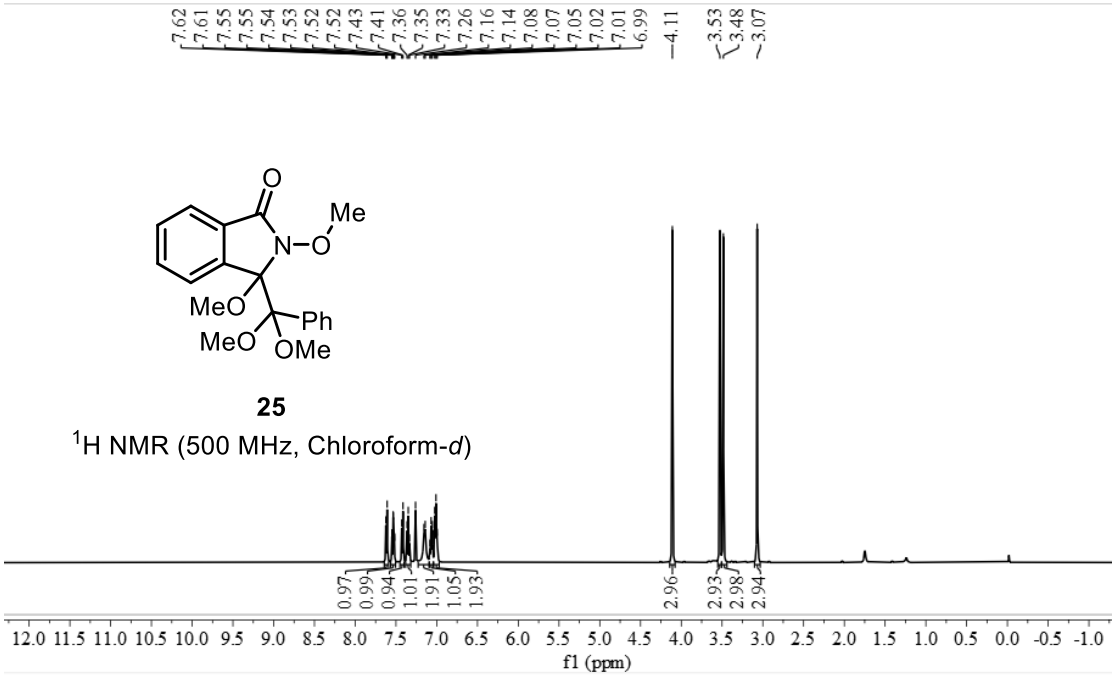
24

^{13}C NMR (126 MHz, Chloroform-*d*)



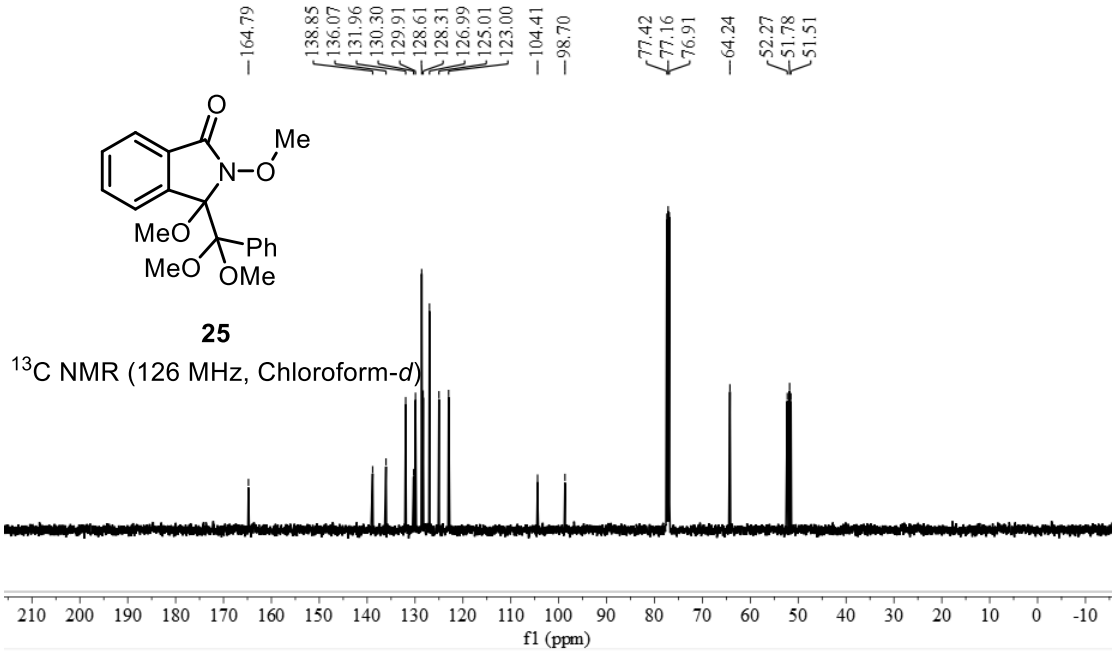
24

^{19}F NMR (471 MHz, Chloroform-*d*)



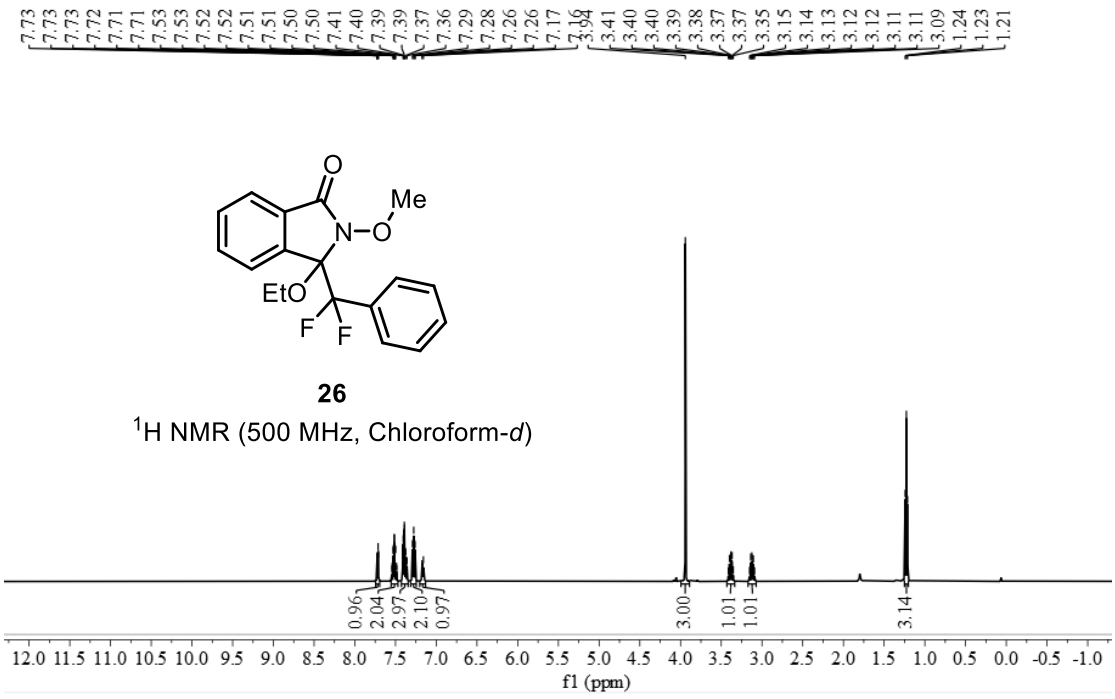
25

^{1}H NMR (500 MHz, Chloroform-*d*)



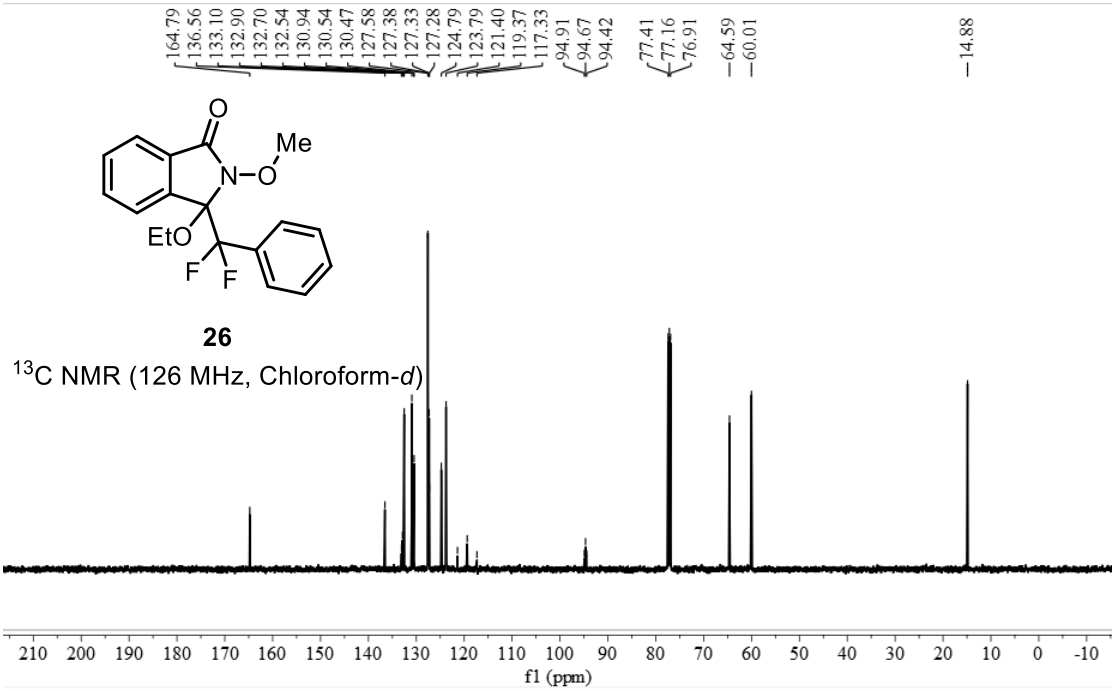
25

^{13}C NMR (126 MHz, Chloroform-*d*)



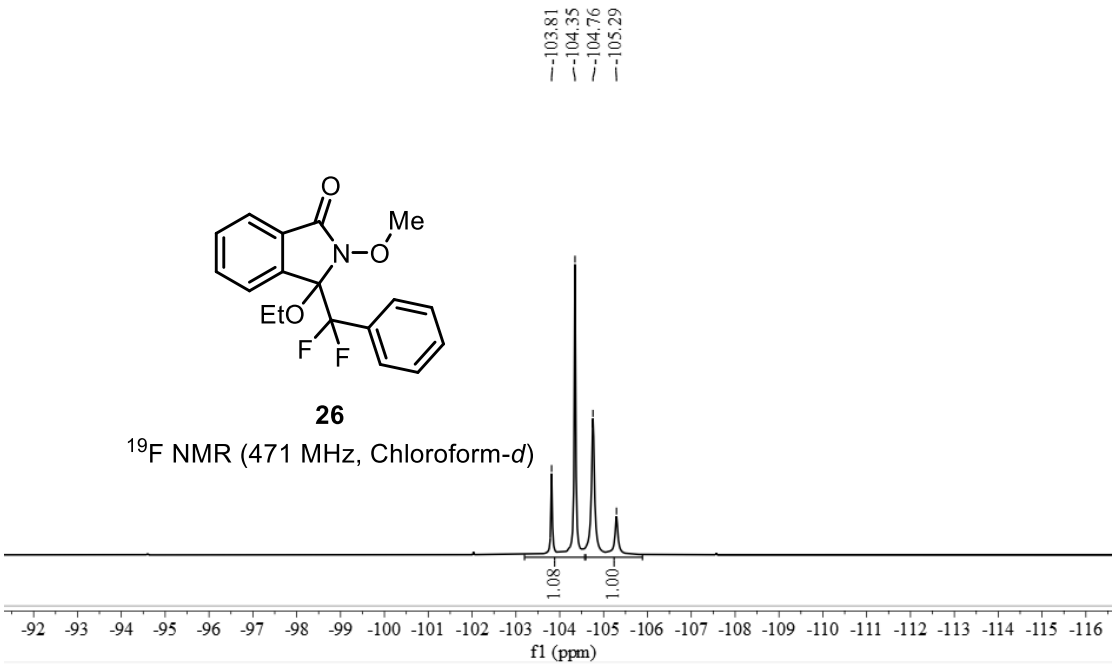
26

^{1}H NMR (500 MHz, Chloroform-*d*)



26

^{13}C NMR (126 MHz, Chloroform-*d*)



26

^{19}F NMR (471 MHz, Chloroform-*d*)